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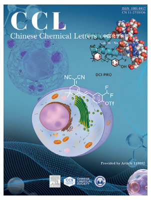

Recent advances in phosphine-mediated sequential annulations

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ABSTRACT

Polycyclic compounds are widely found in natural products and drug molecules with important biological activities, which attracted the attention of many chemists. Phosphine-catalyzed nucleophilic addition is one of the most powerful tools for the construction of various cyclic compounds with the advantages of atom economy, mild reaction conditions and simplicity of operation. Allenolates, Morita–Baylis–Hillman (MBH) alcohols and their derivatives (MBHADs), electron-deficient olefins and alkynes are very efficient substrates in phosphine mediated annulations, which formed many phosphonium species such as β-phosphonium enolates, β-phosphonium dienolates and vinyl phosphonium ylides as intermediates. This review describes the reactivities of these phosphonium zwitterions and summarizes the synthesis of polycycle compounds through phosphine-mediated intramolecular and intermolecular sequential annulations. Thus, a systematic summary of the research process based on the phosphine-mediated sequential annulations of allenolates, MBH alcohols and MBHADs, electron-deficient olefins and alkynes are presented in Chapters 2–6, respectively.

1. Introduction

Polycyclic compound structures are widely found among natural products, biologically active products and drug molecules [1–5]. Given their biological activities, several successful methodologies have been developed and the most accessible routes involved transition-metal-catalyzed annulation reactions [6–8]. In addition, organo-catalyzed, catalyst-free protocols have also developed in recent years [9]. Nevertheless, these reactions always rely on the use of non-commercially available or complex ligands, and has limited. Therefore, building polycycle products in one pot from readily available starting material remains a consistent topic. Sequential annulation approach then was developed, which is one of the most powerful methods to synthesis polycyclic compounds [10]. While sequential, domino and tandem reactions are known [11], the sequential annulations have not been defined. In this review, we define the construction of two or more rings in one-step as sequential annulations.

Organo-phosphine catalysis is widely used in synthesis of carbon-carbon and carbon-hetero bonds [12–18]. On the one hand, it has been employed as reagents to develop a variety of classical name reactions, such as Wittig [19], Staudinger [20], Appel [21] and Mitsunobu reactions [22]. On the other hand, they also have been widely used as ligands in metal-catalyzed reactions [23,24]. The use of organo-phosphines as small organic molecules to catalyze some organic synthesis reactions was reported sporadically from the 1960s to the 1980s. After the 1990s, the organo-phosphine-catalyzed organic synthesis reactions began to develop rapidly.

Phosphine-catalyzed annulations has been of great interest since the pioneering [3 + 2] annulation developed by Lu in 1995, which has been widely used in the construction of five-membered carbocyclic and heterocycle skeletons [25]. Later, the Kwon group developed the [4 + 2] annulations to construct six-membered rings [26]. In 2010, Tong and co-workers designed novel [4 + 1] annulations to build five-membered rings [27]. Three years later, Huang reported another [4 + 2] annulations with γ-benzyl allenoates to construct six-membered rings [28]. Phosphine-catalyzed [3 + 2] and [4 + 2] annulations have been shown to be a key step in total synthesis of natural products such as (±)-hirsutene, (+)-geniposide, (+)-ibophyllidine, (-)-physostigmine, longeracinphyllin A and daphenylline, which have anticancer and other bioactivities (Scheme 1) [29–41]. Compared with phosphine-catalyzed annulations toward monocycles, sequential annulations are superior in constructing of polycycles. Thus, development phosphine-mediated sequential annulations are urgently required.

Among these phosphine catalysis systems, phosphine acceptors such as allenoates, MBHADs, electron-deficient olefins and alkynes are attacked by a phosphine catalyst to give phosphine ylides as reactive intermediates, which play a key role in hundreds of phosphine-catalyzed reactions [42–60]. As a result, a wide range of

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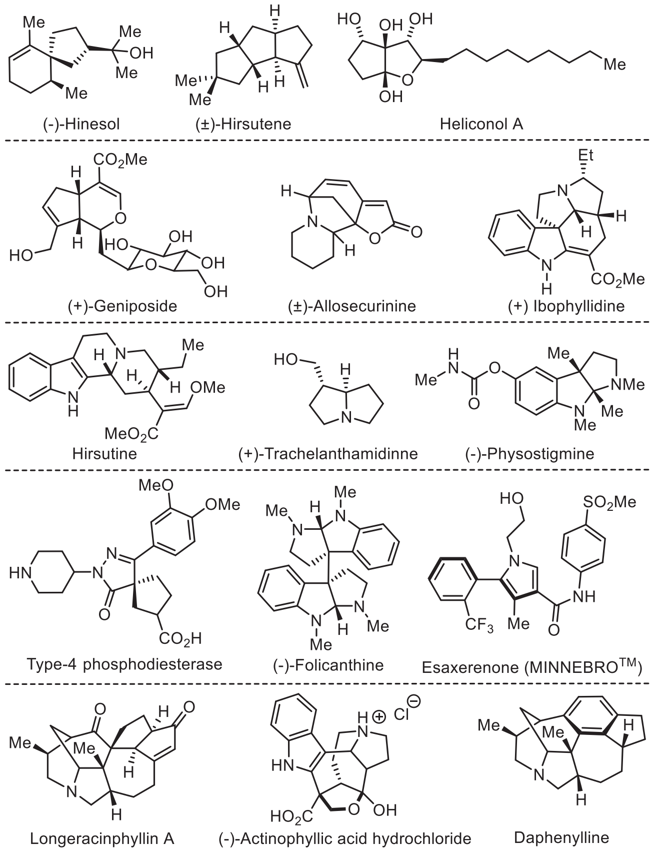


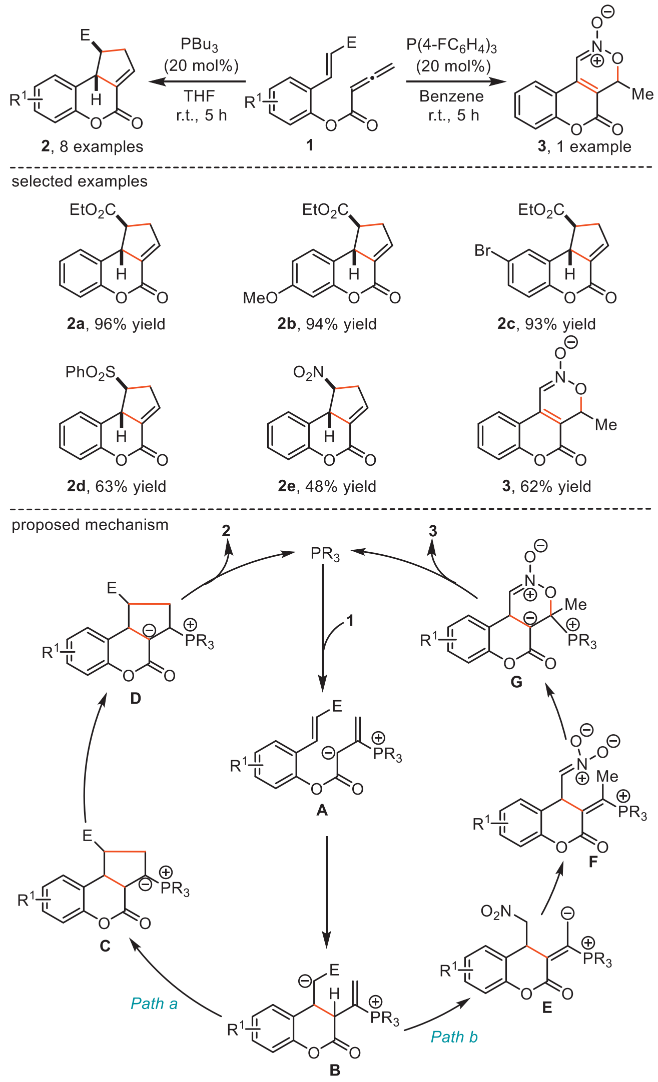
Scheme 1. Natural products synthesized *via* phosphine-catalyzed sequential annulations.

polycycle compounds were synthesized by phosphine-mediated sequential annulations, and applied in the synthesis of complex compounds.

There are a rich variety of reactions for the phosphine-mediated synthesis of polycyclic compounds, and in previous reviews, only partial applications of polycycle compounds had been summarized [51–56]. As a large number of studies have been reported in the recent twenty years, a comprehensive review on this topic is highly desirable and thus the current review is timely. In this review, we will introduce the organo-phosphine-mediated/catalyzed sequential annulations of allenoates, MBH alcohols and their derivatives (MBHADs), electron-deficient olefins and alkynes, respectively.

2. Sequential annulations of allenoates

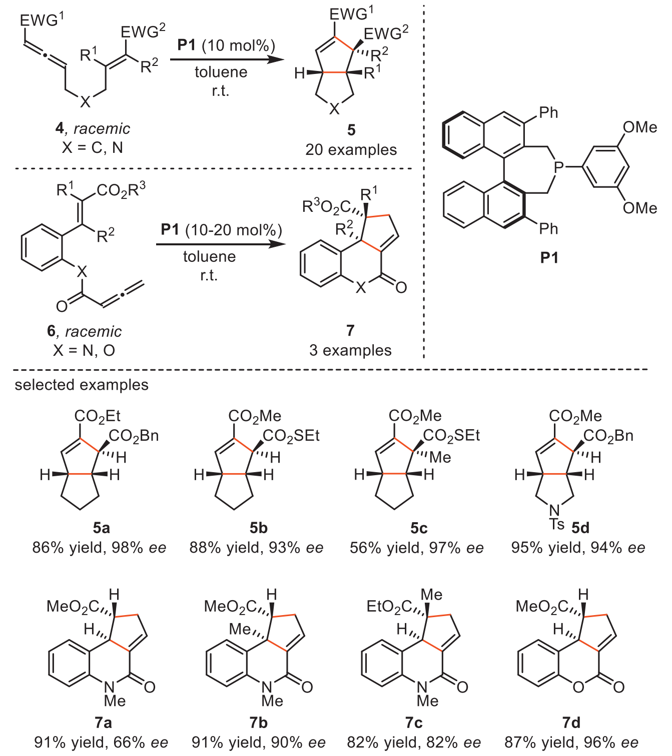
When allenoates are treated with phosphine catalysts, the formation of the phosphonium dienolate leads to the activation of the pronucleophiles, electrophiles, dinucleophiles and electrophile-nucleophile to undergo a general addition. A wide range of reactions occur when electrophiles are used as reaction partners with allenoates, annulation processes such as Lu's [3 + 2] [25], Kwon's [4 + 2] [26] and Huang's [4 + 2] [28] reactions can occur. Although kwon reported a Michael-Michael reaction between allenoates and dinucleophiles [61], the classical reaction sequence occurring between allenoates and dinucleophile are the domino γ-umpolung-Michael processes. A different type of annulations occurs when electrophile-nucleophile partners are present in the mixtures of allenoates. Arguably, allenoates have countless diverse reactivity, providing a wide range of phosphine catalyzed products, which also features prominently in phosphine-catalyzed sequential annulations.



Scheme 2. Phosphine-catalyzed sequential annulation of 2-styrenyl allenoates.

2.1. Intramolecular sequential annulations of allenoates

Since Lu reported the pioneering phosphine-catalyzed [3 + 2] annulation of allenoates in 1995 [25], various annulations of allenoates have begun to attract the attention of chemists [62]. In 2007, Kwon and co-workers developed two different reaction modalities for the phosphine-catalyzed sequential annulations of 2-styrenyl allenoates **1**, providing efficient methods to synthesize cyclopentene-fused dihydrocoumarins **2** and a tricyclic nitronate compound **3** respectively (Scheme 2) [63]. The reaction was conducted under room temperature in the presence of a simple phosphine as the catalyst, and the coumarins derivatives were obtained in good yield. In the proposed mechanism, the phosphine catalyst reacted with **1** to generating the phosphonium dienolate **A**, which underwent intramolecular nucleophilic addition to give the intermediate **B**. Subsequently, an intramolecular [3 + 2] reaction *via* pathway a gave intermediate **C**, proton migration followed by β-elimination of the phosphine catalyst to afford the target product **2**. In addition, When the electron-withdrawing group is nitro-substituted, intermediate **B** underwent proton transfer *via* pathway b to give intermediate **E**, followed by nucleophilic addition to the nitro group to give intermediate **F**, and further annulation reaction of [4 + 2] to produce intermediate **G**, which provided the final

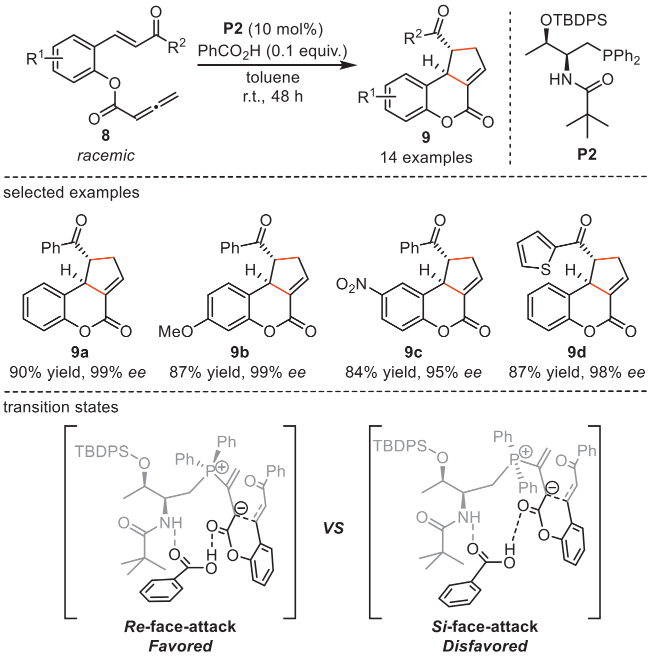


Scheme 3. Chiral phosphine-catalyzed sequential annulation of allenes with olefins.

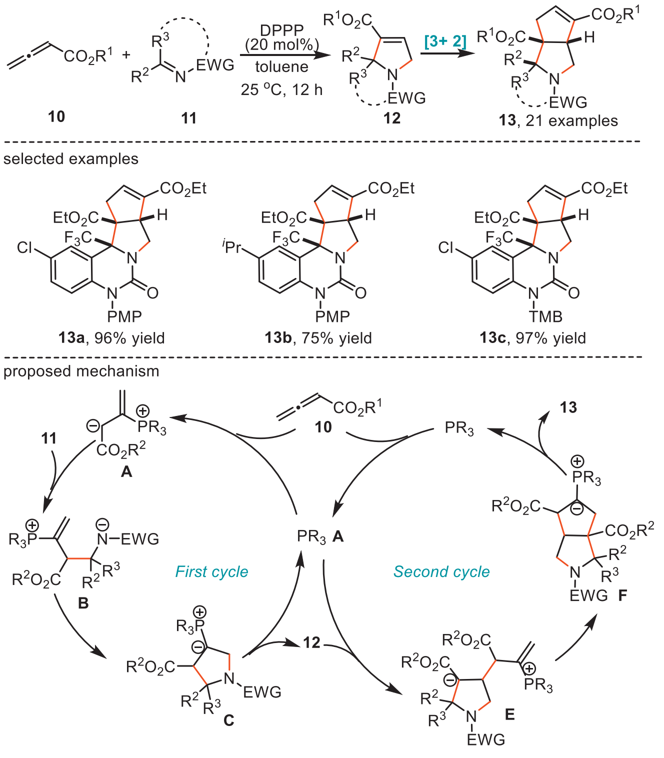
product **3** after β-elimination of the phosphine catalyst and isomerization processes.

Until 2015, the Fu group described the first phosphine-catalyzed enantioselective intramolecular [3 + 2] cycloaddition of allenes with olefins (Scheme 3) [64]. The reaction was carried out under room temperature in the presence of chiral spirophosphine **P1** as the catalyst, both of carbon and nitrogen atoms of substituted 5-allenic olefins proceeded smoothly, giving the corresponding cycloadducts in good yields with excellent enantioselectivities. Notably, a wide range of 6-allenic olefins underwent [3 + 2] annulation reaction in the presence of **P1** in the toluene to afford quinolin-2-one derivatives in good yields along with good enantioselectivities. This strategy resulted in the formation of two new rings and multiple stereogenic centers in one step.

Shortly, based on the recent success of phosphine catalysis for intramolecular sequential annulations of allenoates, the Lu, Lan and Ullah developed a highly enantioselective intramolecular [3 + 2] annulation of chalcones bearing an allene moiety for synthesis of dihydrocoumarin architectures (Scheme 4) [65]. Using amino acid-derived chiral phosphine **P2** as the catalyst and benzoic acid as an additive, both electron-withdrawing and electron-donating groups on the benzene rings worked well to give dihydrocoumarin scaffolds **9** in high yields and with excellent enantiomeric excesses. Furthermore, their DFT calculations revealed that the key hydrogen bonding network introduced by the achiral Brønsted acid additives was crucial for the observed enantioselectivity.



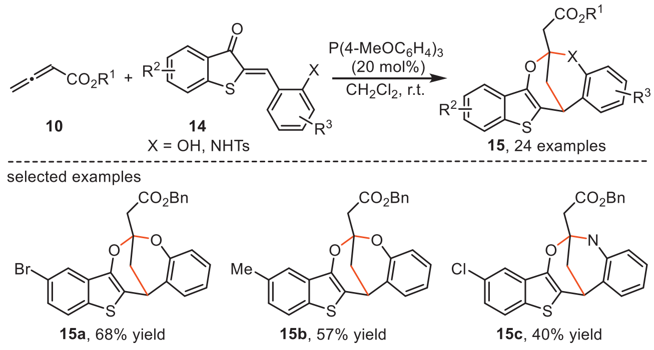
Scheme 4. Chiral phosphine-catalyzed sequential annulation of chalcones bearing an allene moiety.



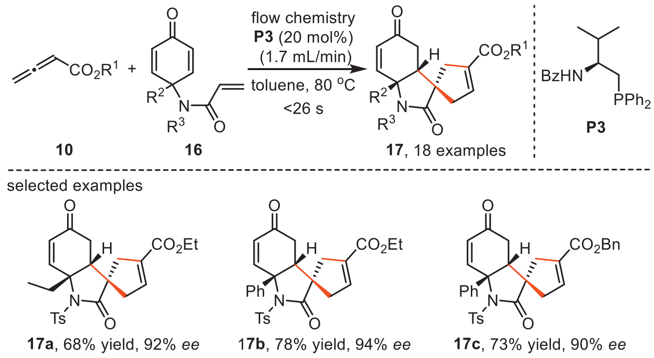
Scheme 5. Phosphine-catalyzed sequential annulation of unsubstituted allenoates with cyclic ketimines.

2.2. Intermolecular sequential annulations of unsubstituted allenoates

In 2013, the Ma group developed an novel and efficient bisphosphine-triggered one pot sequential [3 + 2]/[3 + 2] annulation of unsubstituted allenoates with cyclic ketimines (Scheme 5) [66]. In this reaction, the products of the first [3 + 2] annulation was the electron-deficient substrate for the second [3 + 2] annulation reaction. During this transformation, highly functionalized *N*-fused polycyclic compounds with three contiguous stereogenic centers **13** were obtained in moderate to excellent yields and with excellent diastereoselectives. Mechanistic studies revealed that the reaction proceeded *via* a sequential [3 + 2]/[3 + 2] annulation, which could involve two catalytic cycles. In the first cycle, the nucleophilic bis-phosphine catalyst initially attacked the β-carbon atom of allenoates **10** to yield zwitterion **A**. The α-carbon atom of anionic allylic **A** was added to the C=N group of cyclic ketimines **11**



Scheme 6. Phosphine-catalyzed sequential annulation reaction of unsubstituted allenoates with thioaurones.

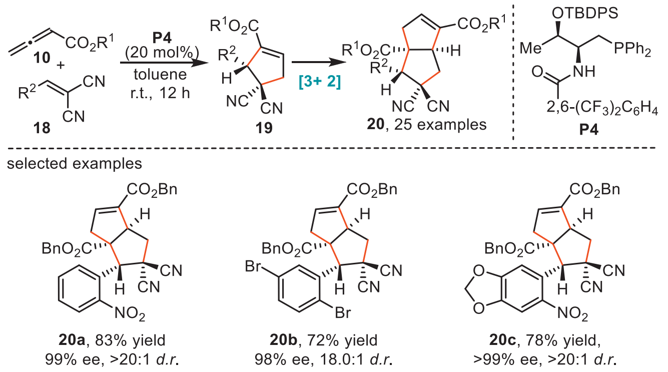


Scheme 7. Chiral phosphine-catalyzed sequential annulation of unsubstituted allenoates with dienones in a flow system.

to give the intermediate **B**, and then a subsequent intramolecular Michael addition afforded the cycloadduct **C**, which provided the [3 + 2] product **12** after β-elimination of the phosphine catalyst. In the second cycle, an intermolecular Michael addition of anionic allylic **A** to the cycloadduct **12** provided the addition intermediate **E**, which underwent an intramolecular Michael addition to form **F**. Finally, the desired products were formed through proton transfer and elimination of the phosphine catalyst.

In 2018, Meng and co-workers presented a phosphine-catalyzed domino reaction of unsubstituted allenoates and thioaurones for synthesis of benzothiophene-fused dioxabicyclo[3.3.1]nonane derivatives (Scheme 6) [67]. This methodology enabled the introduction of different substituents on aryl groups of thioaurones to form bridged bicyclic rings in moderate to good yields in a single step. The asymmetric reaction catalyzed by several chiral phosphines were attempted when using model substrates, resulting the corresponding product in 45% yield with 13% *ee* value by using bifunctional chiral phosphine catalysts. Preliminary mechanistic studies were investigated and supported by DFT calculations.

Although phosphonium dienolate have been used as key catalytic intermediates in many transformations including [3 + 2] annulations, the generation of phosphonium dienolate in a flow system was rarely reported. In 2020, Sasai and co-workers demonstrated a highly atom-economical enantioselective domino reaction initiated by Rauhut-Currier and [3 + 2] annulation sequence using an organo-phosphine catalyst in a flow system (Scheme 7) [68]. Suitable flow conditions were explored through reaction screening of multiple parameters using machine learning. Using chiral phosphine **P3** as the catalyst, functionalized chiral spirooxindole analogue bearing different functional groups were obtained in high yields with good *ee* values as a single diastereomer within one minute.



Scheme 8. Chiral phosphine-catalyzed sequential annulation of unsubstituted allenoates with arylidenemalononitriles.

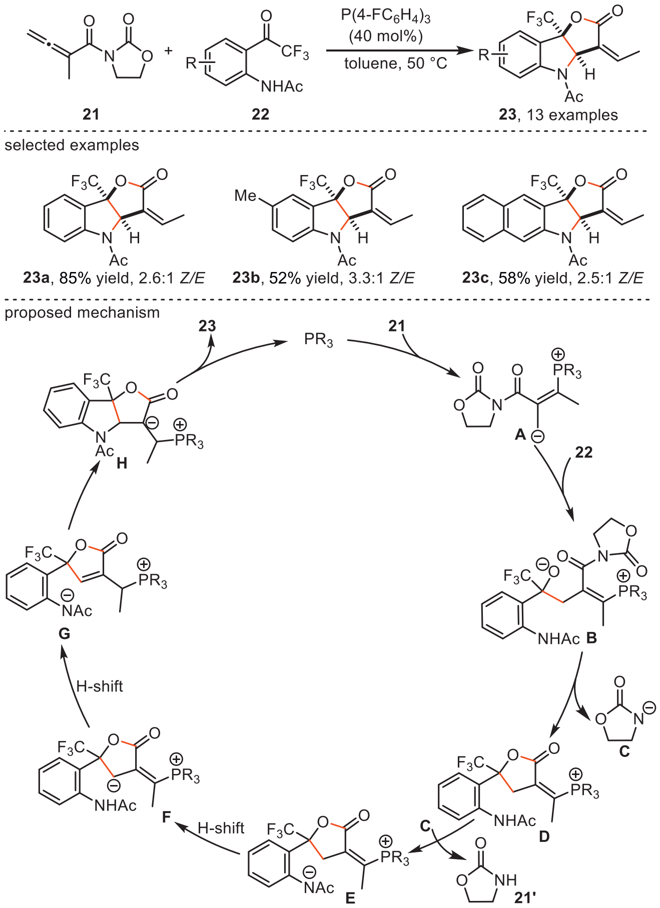
In Ma's work, only racemic products were formed for the sequential [3 + 2]/[3 + 2] annulation of unsubstituted allenoates with cyclic ketimines. By using amino acid-derived chiral phosphine **P4** as the catalyst, in 2022, Lu and co-workers disclosed a highly diastereo- and enantioselective phosphine-catalyzed sequential [3 + 2/[3 + 2] annulation between unsubstituted allenoates and arylidenemalononitriles (Scheme 8) [69]. This strategy allowed for the facile construction of multifunctionalized *cis*-fused bicyclic[3,3,0]octene and cyclopenta[*c*]quinolinones scaffolds, encompassing three consecutive stereogenic centers with one quaternary carbon center, in a one-step operation from readily available materials.

2.3. Intermolecular sequential annulations of α-methyl substituted allenoates

In 2022, Huang and co-workers successfully presented a phosphine-promoted domino annulation of α-methyl substituted allenyl imide and *o*-aminotrifluoroacetophenones (Scheme 9) [70]. This reaction had broad scope and high functional group compatibility, allowing the rapid synthesis furo[3,2-*b*]indol-2-ones bearing a CF_3-substituted quaternary stereogenic center in moderate to good yields. Based on their mechanistic studies, they proposed the intermediate **A** attacked the electrophilic C=O group of **22** to generate the intermediate **B**, which eventually underwent intramolecular cyclization followed by the elimination of 2-oxazolidinyl anion **C** to give the intermediate **D**. Subsequently, the 2-oxazolidinyl anion **C** abstracted the amide proton to give the 2-oxazolidone **21′** and intermediate **E**. After two H-shift processes, intermediate **E** was converted to **F**, which was followed by the intramolecular Michael cyclization and regeneration of phosphine catalyst to deliver the desired product **23**.

2.4. Intermolecular sequential annulations of β'-acetoxy substituted allenoates

In 2010, Tong and co-workers designed a novel β'-acetoxy substituted allenoates, which were reacted with bisnucleophiles to synthesize cyclopentene and tetrahydropyridazine derivatives *via* phosphine-catalyzed [4 + 1] and [4 + 2] annulations, respectively [27]. And in 2015, they documented a β'-acetoxy substituted allenoates **24** to synthesis 2-oxabicyclo[3.3.1]nonane **27** and cyclopenta[*a*]*p*-yrrolizine skeletons **28** (Scheme 10) [71]. The reaction of 2-acetoxymethyl-2,3-butadienoate with 2-carbonyl-3-methyl-acrylonitriles bearing aryl or alkyl substituents readily generated substituted 2-oxabicyclo[3.3.1]nonanes in moderate to good yields. When the reaction partner was switched to 2-acyl-3-(2-pyrrole)-acrylonitrile under similar conditions, the cyclopenta[*a*]pyrro-lizines was delivered in good to excellent

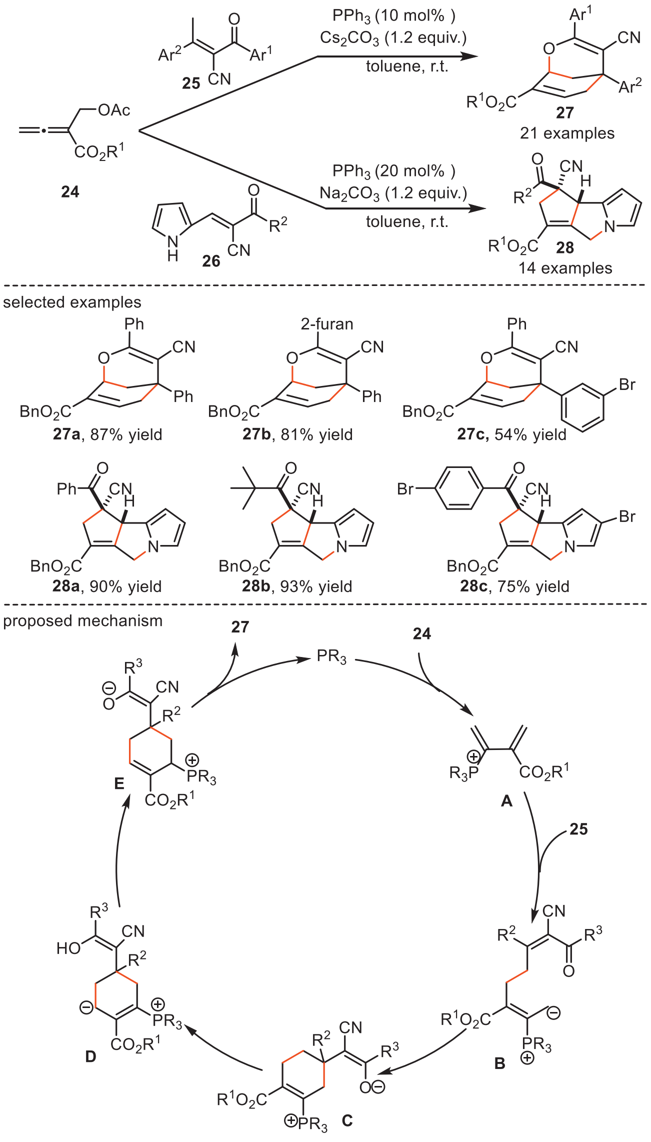


Scheme 9. Phosphine-mediated sequential annulation of α-methyl substituted allenyl imide and *o*-aminotrifluoroacetophenones.

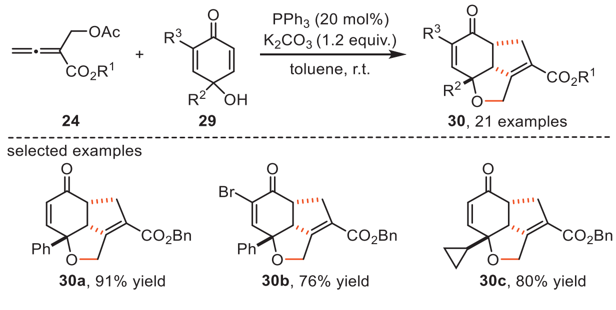
yields. Additionally, the asymmetric variants of these two reactions has also been realized to give enantioenriched 2-oxabicyclo[3.3.1]-nonanes and cyclopenta[*a*]pyrrolizines with up to 93% *ee* using Kwon's chiral phosphine as the catalyst. According to the mechanistic studies, the addition of β'-acetoxy allenoates to phosphine followed by 1,2-elimination of acetate group generated the electrophilic intermediate **A**, which was attacked by the carbanion of **25** at the β'C position to form the zwitterionic intermediate **B**. Then, the γ-carbanion of **B** underwent an intramolecular addition to yield the enolate intermediate **C**. The resulting enolate served as a base to abstract a β'H to produce intermediate **D**, after an H-shift process, **D** was converted to **E**, which was followed by a S_N2'-type process to release product **27** and regenerate phosphine catalyst.

In 2018, the Shi group reported a phosphine-initiated sequential annulation of β'-acetoxy allenoates and *p*-quinols (Scheme 11) [72]. The reaction was performed in the presence of PPh_3 and K_2CO_3 in toluene at room temperature, generating an efficient access to highly functionalized multiple ring-fused hexahydroindeno furan derivatives **30** with excellent functional group tolerance. Using Kwon's chiral phosphine as the catalyst, enantioselective variant of this transformations, under otherwise identical conditions, was also investigated to give desired cycloadduct in 39% yield along with 55% *ee* value.

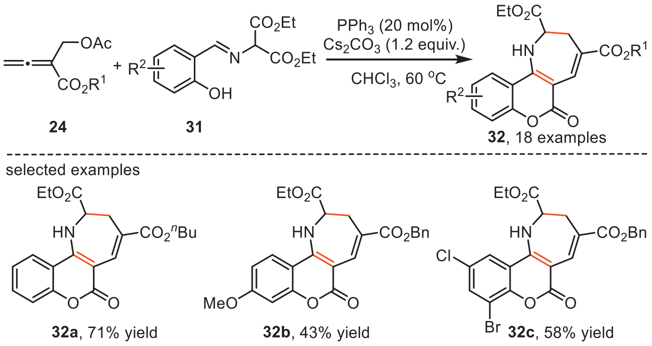
In 2020, by replacing the nucleophilic substrate with alminine esters substrate, the Zhou and co-workers realized a phosphine-catalysed chemoselective [4+3] cycloaddition to synthesize azepines from β'-acetoxy allenoates and alminine esters (Scheme 12) [73]. Under phosphine catalysis, resulting a series of 1,3-dihydro-2*H*-azepine-2,2,4-tricarboxylates showed moderate to good yields and they were converted to the corresponding 2,3-dihydrochromeno[4,3-*b*]azepin-6(1*H*)-ones **32** when the reaction was performed in the presence of Cs_2CO_3 and PPh_3. Based on their mechanistic studies, the authors proposed a sequential [4+3]/ester group migration/lactonization to account the formation of 2,3-dihydrochromeno[4,3-*b*]azepin-6(1*H*)-ones.



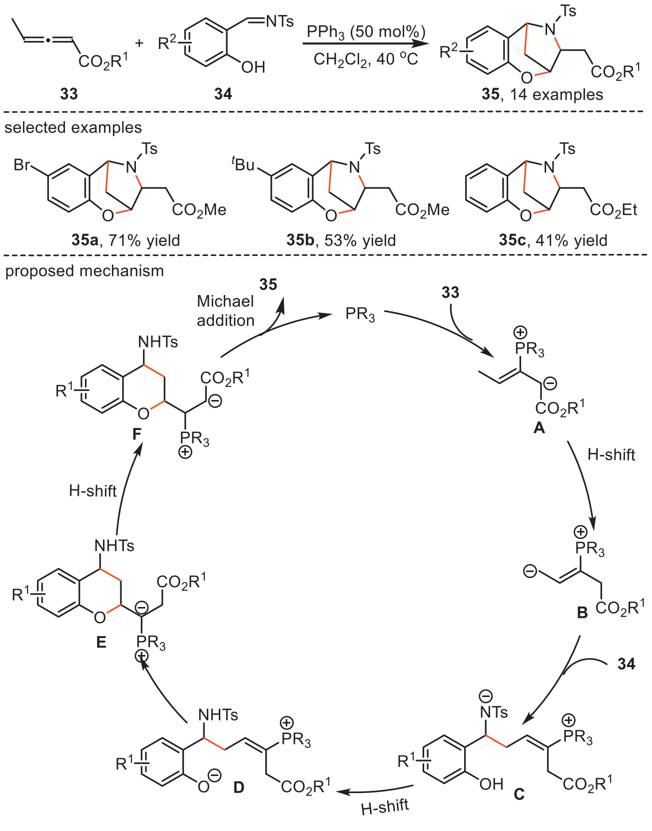
Scheme 10. Phosphine-catalyzed sequential annulation of β'-acetoxy substituted allenoates and the proposed mechanism.



Scheme 11. Phosphine-catalyzed sequential annulation of β'-acetoxy substituted allenoates with *p*-quinols.



Scheme 12. Phosphine-catalyzed sequential annulation of β'-substituted acetoxy allenoates with alminine esters.

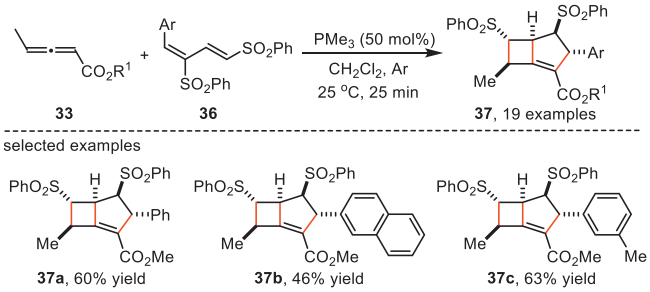


Scheme 13. Phosphine-mediated sequential annulation of γ-methyl substituted allenoates with salicyl N-tosylimines.

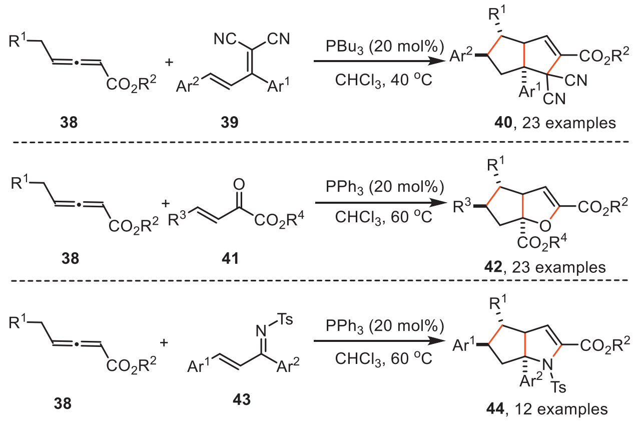
2.5. Intermolecular sequential annulations of γ-substituted allenoates

Benzoxazepine derivatives are the core substructures that are often found in natural products and bioactive molecules [74,75]. By employing the protecting group of the salicylaldimine from a thiophosphinyl to a tosyl group, in 2013, the Huang group developed a phosphine-mediated aza-MBH domino [2 + 4]/[2 + 3] annulation between γ-methyl substituted allenoates **33** and salicyl N-tosylimines **34**, forming a direct way to synthesize a lot of benzoxazepine derivatives which are versatile synthetic building blocks (Scheme 13) [76]. This was the first example of the γ-methyl substituted allenoate which was used as this kind of C3 synthon in organic synthesis.

The mechanistic studies indicated that the reaction involved initial generation of the intermediate **B**, subsequently underwent an aza-MBH reaction with **34** to afford intermediate **C**, followed by intramolecular proton transfer and umpolung addition to produce intermediate **E**. After an H-shift process, intermediate **E** was converted to **F**, which was followed by intramolecular Michael addition to give the desired product **35**.



Scheme 14. Phosphine-mediated sequential annulation of γ-methyl substituted allenoates with 1,3-bis(sulfonyl)butadienes.

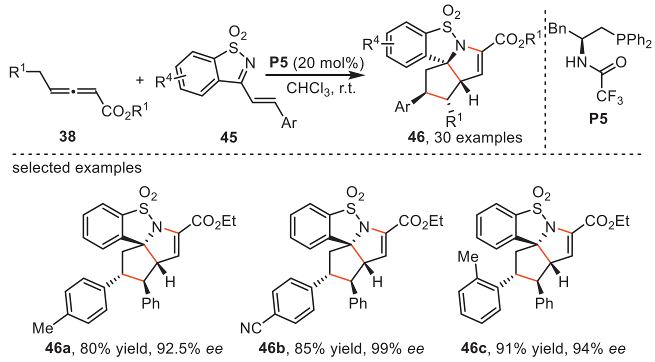


Scheme 15. Phosphine-catalyzed sequential annulation of γ-benzyl substituted allenoates with activated dienes.

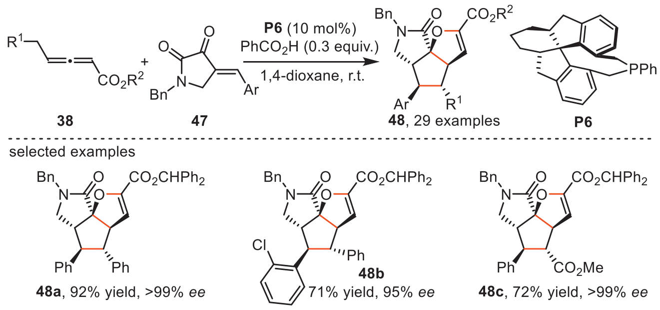
Shortly, the same group disclosed an interesting phosphine-mediated sequential annulation of γ-methyl substituted allenoates with 1,3-bis(sulfonyl)butadienes for synthesis of a multifunctionalized bicyclo[3.2.0]heptene skeleton (Scheme 14) [77]. Both of aryl-substituents, electron-donating groups and electron-withdrawing groups worked well to give bicyclo[3.2.0]heptane skeleton derivatives in good yields in the presence of PMe_3 as the catalyst. According to mechanistic studies and literature precedents on phosphine-catalyzed annulations, they proposed that this reaction proceeded with a [4 + 3] annulation and a further intramolecular cyclization to provide the target products.

In 2014, the Huang group showcased a related transformation that provided bicyclic[3,3,0]octene skeletons with good to excellent yields from γ-benzyl substituted allenoates **38** and activated dienes **39** *via* phosphine-catalyzed sequential [2 + 3] and [3 + 2] annulation (Scheme 15) [78–80]. Later, they also reported that β,γ-unsaturated α-ketoesters **41** and α,β-unsaturated ketimines **43** were used as electrophiles, giving cyclopenta[*b*]dihydrofuran and aza-bicyclo[3,3,0]octane derivatives in good yield in the presence of PPh_3 as the catalyst, respectively. These reactions were very efficient at building molecular complexity rapidly, which was forged C–C, C–O and C–N bonds in one process.

A chiral difunctional phosphine-catalyzed highly enantioselective sequential [2 + 3]/[3 + 2] annulation between γ-benzyl substituted allenoates and ketimines derived from saccharin was later reported by the same group in 2016 (Scheme 16) [81]. The desired poly-heterocycle rings with four contiguous stereogenic centers were obtained in moderated to excellent yields and with good to excellent enantioselectivities, using **P5** as the catalytic system.



Scheme 16. Chiral phosphine-catalyzed sequential annulation of γ-benzyl substituted allenoates with ketimines.



Scheme 17. Chiral phosphine-catalyzed sequential annulation of γ-benzyl substituted allenoates with pyrrolidine-2,3-diones.

Three years after Huang's publication of the chiral phosphine-catalyzed sequential [2 + 3]/[3 + 2] annulation, Lu and co-workers also documented an enantioselective domino reaction between γ-benzyl substituted allenoates and pyrrolidine-2,3-diones for the formation of polycyclic γ-lactams by using chiral phosphine NUSIOC-Phos **P6** as the chiral catalyst (Scheme 17) [82]. This reaction gave its products containing five contiguous stereogenic centers in high yields and with nearly perfect enantioselectivities. Furthermore, the authors also showed that the kinetic resolution process of racemic γ-benzyl substituted allenoates led to the generation of optically enriched chiral allenes.

By exploring the reactivities of γ-benzyl substituted allenoates, in 2019, Huang and co-workers then designed a novel and efficient phosphine-catalyzed [3 + 2]/[2 + 3] sequential annulation involving a triple nucleophilic addition reaction of γ-vinyl allenoates (Scheme 18) [83]. The resulting functionalized hydropyrroloimidazolones showed moderate to excellent yields under mild reaction conditions, displaying great tolerance of the reaction to a wide variety of functional groups. Mechanistic studies supported that the nucleophilic addition of vinyl allenoates **49** by phosphine catalyst afforded zwitterionic intermediate **A**, which then acted as a base to deprotonate the pro-nucleophile **50** and underwent nucleophilic attack of the vinyl group to produce the intermediate **B**. Subsequently, two proton transfers of the intermediate **B** to obtain intermediate **D**, which underwent intramolecular Michael addition to provide the intermediate **E**. After an H-shift process, intermediate **E** was converted to **F**, which was followed by the nucleophilic addition and elimination of phosphine catalyst to generate the desired compounds **51** and **52**.

Shortly, the same group described an interesting reaction of the phosphine-catalyzed [3 + 2]/[3 + 2] sequential annulation employing γ-vinyl substituted allenoates and alkylidenemalononitriles as the substrates (Scheme 19) [84]. Using this approach, they received a broad range of structurally dense tetra- and penta-substituted bicyclic[3.3.0]octene derivatives containing a quaternary center and three sequential stereogenic centers in good to excellent yields. Mechanistic experiments indicated that the annulation process included an intermolecular 1,7-addition reaction, an intramolecular 1,4-addition reaction and an intramolecular umpolung addition to form three new C−C bonds.

In 2021, they also presented the sequential [2 + 3]/[2 + 4] annulation of γ-vinyl substituted allenoates and aldimine esters *via* nucleophilic catalysis with a phosphine, adding a novel pathway to achieve the chromeno[4,3-*b*]pyrroles (Scheme 20) [85]. This procedure constructs three σ-bonds and three contiguous stereogenic centers in a one-step to assemble chromeno[4,3-*b*]pyrrole derivatives directly in good yields with excellent chemoselectivity and diastereoselectivity under mild conditions. In the proposed mechanism, an intramolecular hydrogen bond was used as a crucial for the reaction to run smoothly.

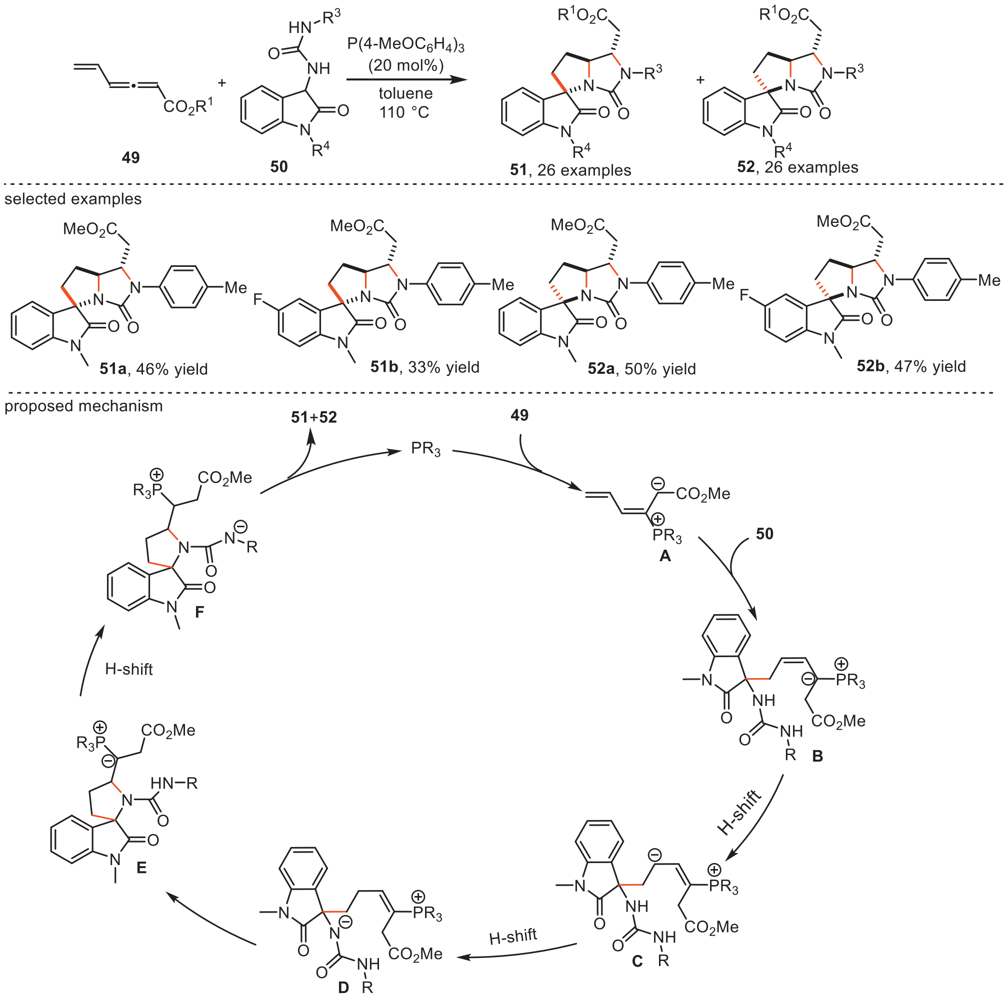
Very recently, Huang and co-workers elegantly developed a phosphine-catalyzed process for synthesis of tetrahydrofuro[3,2-*c*]quinoline derivatives by domino annulation reaction of γ-vinyl substituted allenoates and *o*-aminotrifluoacetophenones (Scheme 21) [86]. The reaction took place under phosphine catalysis without any ligands and base, delivering a series of substituted tetrahydrofuro[3,2-*c*]quinoline derivatives in good yields with moderate to excellent diastereoselectivities. In addition, the asymmetric variant also examined, by using chiral spirophosphine (*R*)-SITCP as the catalyst, giving the desired tetrahydrofuro[3,2-*c*]quinoline in 20% yield with 65% *ee*. The reaction mechanism had been proposed on the basis of control experiments, and was also supported by DFT calculations.

2.6. Intermolecular sequential annulations of δ-substituted allenoates

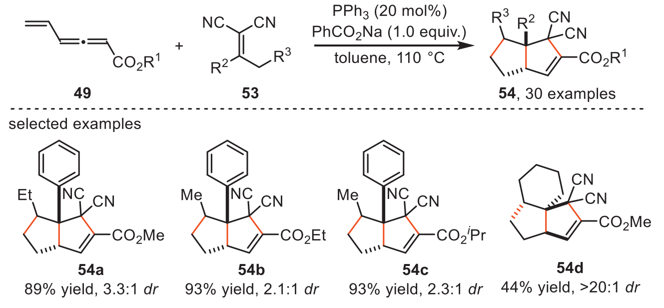
Following their previous work on sequential annulation of allenoates, in 2019, Huang and co-workers designed a newly substrate, namely, δ-sulfonamido-allenoates **59**, which were served as 5 atom synthons for phosphine-catalyzed domino [3 + 3]/[3 + 3] annulation (Scheme 22) [87]. Diverse range of activated dienes, including mono-substituted, di-substituted and even heterocyclic substituted on the benzene rings proceeded well to give the functionalized hydroisoquinoline derivatives in medium to good yields with moderate diastereoselectivity. Based on their mechanistic studies, the authors proposed a cascade process for the reaction, as shown in Scheme 22. Initially, the phosphonium dienoate **A** was formed from δ-sulfonamido-allenoates **59** and phosphine catalyst. Then a Michael addition of phosphonium dienoate **A** toward activated dienes **39** produced a new intermediate **B**. Next, the first [3 + 3] annulation intermediate **D** was obtained by a H-shift and subsequent Michael addition driven by the enamine anion from **C**. The authors thought that another H-shift and imine–enamine tautomerism of **E** made the subsequent aza-intramolecular nucleophilic addition to the cyano group, which completed the second [3 + 3] annulation process. Finally, the intermediate **F** performed a H-shift to afford the intermediate **G**, which eliminated the phosphine catalyst and the following isomerization to give the final product **60**.

Shortly, the same group reported an unprecedented sequential [3 + 3]/aza-6π-electrocyclization between δ-sulfonamido-allenoates and cross-conjugated azatrienes, providing efficient and facile access to highly functionalized tetrahydroisoquinoline derivatives (Scheme 23) [88]. The protocol was formed two new cycles and three bonds in a one-step process. In addition, the utility of this methodology has been demonstrated by facile transformation of tetrahydroisoquinoline skeletons into fused tetra- and pentacyclic molecules.

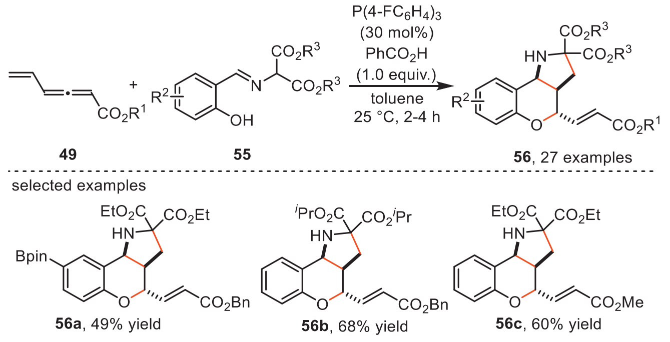
By using δ-acetoxy substituted allenoates as the substrates, in 2020, the Zhou group demonstrated a phosphine-catalyzed cascade



Scheme 18. Phosphine-catalyzed sequential annulation reaction of γ-vinyl substituted allenoates with urea derivatives.



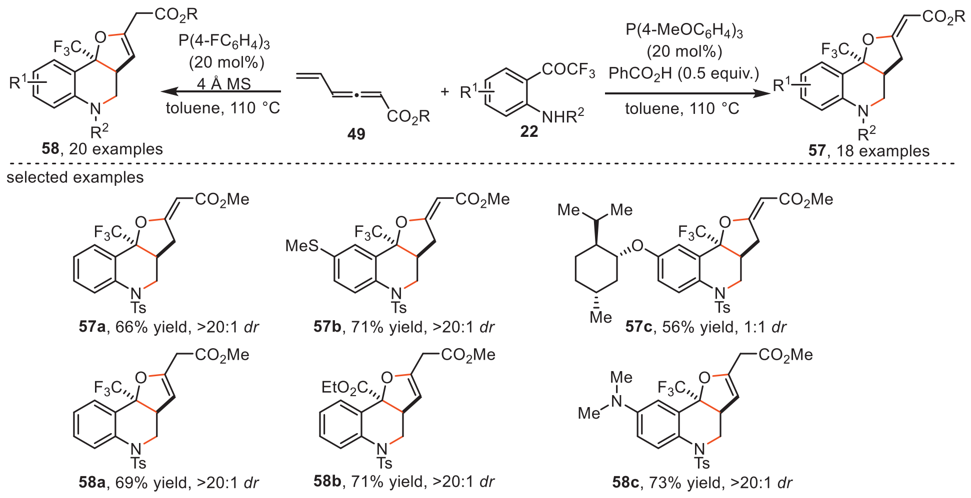
Scheme 19. Phosphine-catalyzed sequential annulation of γ-vinyl substituted allenoates with alkylidenemalononitriles.



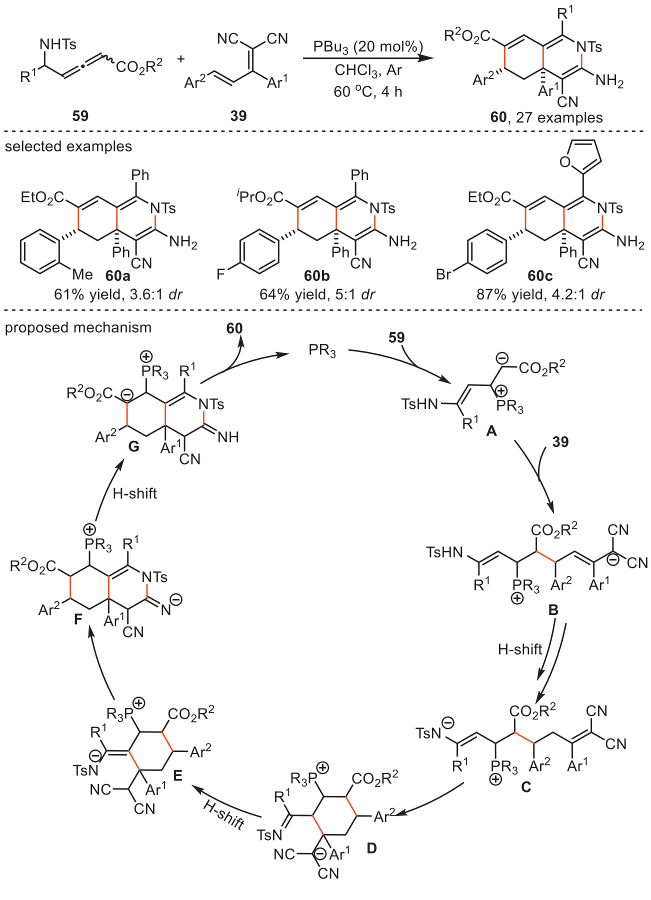
Scheme 20. Phosphine-catalyzed sequential annulation reaction of γ-vinyl substituted allenoates with aldimine esters.

annulation of δ-acetoxy substituted allenoates and aldimine esters (Scheme 24) [89]. This method enabled tandem annulation of different substituents on the benzene rings of the two substrates to form a series of chromeno[4,3-*b*]pyrrole derivatives, which were obtained in generally good yields with excellent diastereoselectivities. In particular, by using a chiral phosphine **P7** as the catalyst, the cycloaddition reaction can also initially realize the asymmetric synthesis of chromeno[4,3-*b*]pyrrole in medium to good yields with good enantioselectivities. In their proposed mechanism, the cationic intermediate **31′** attacked **B** to generate zwitterionic intermediate **C**, which eventually allowed for intramolecular addition of the carbon anion to vinyl phosphonium to afford intermediate **D**. The intermediate **E** were obtained after a H-shift process, which subsequently underwent an intramolecular nucleophilic attack and regenerated the phosphine catalyst to produce the desired product **64**.

In 2023, Guo and co-workers designed a novel phosphine-catalyzed tandem annulation of δ–hydroxyl substituted allenoates with 1,1-dicyanoalkenes (Scheme 25) [90]. Interestingly, this method provided a various of tetrahydrocyclopentafuran derivatives in 40%–89% yields with moderate to excellent diastereoselectivities. The authors postulated a mechanism for this transformation was showed in Scheme 25. The phosphonium zwitterion

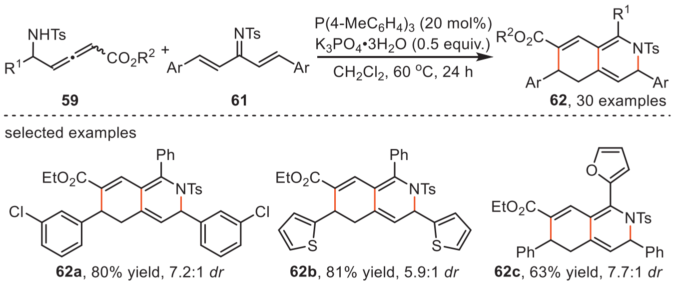


Scheme 21. Phosphine-catalyzed sequential annulation of γ-vinyl substituted allenoates and *o*-aminotrifluoacetophenones.



Scheme 22. Phosphine-catalyzed sequential annulation of δ-sulfonamido substituted allenoates with activated dienes.

A performed conjugate addition to the alkene **18** to generate the intermediate **B**, which underwent intramolecular nucleophilic addition and a proton shift to form the intermediate **D**. Subsequent unusual nucleophilic addition of the alkoxide ion of intermediate **D** to the cyano group led to the bicyclic intermediate **E** having an imino substituent. After intermediate **E** performed a proton shift to produce the intermediate **F**, which eliminated the phosphine catalyst to afford the product **66**.



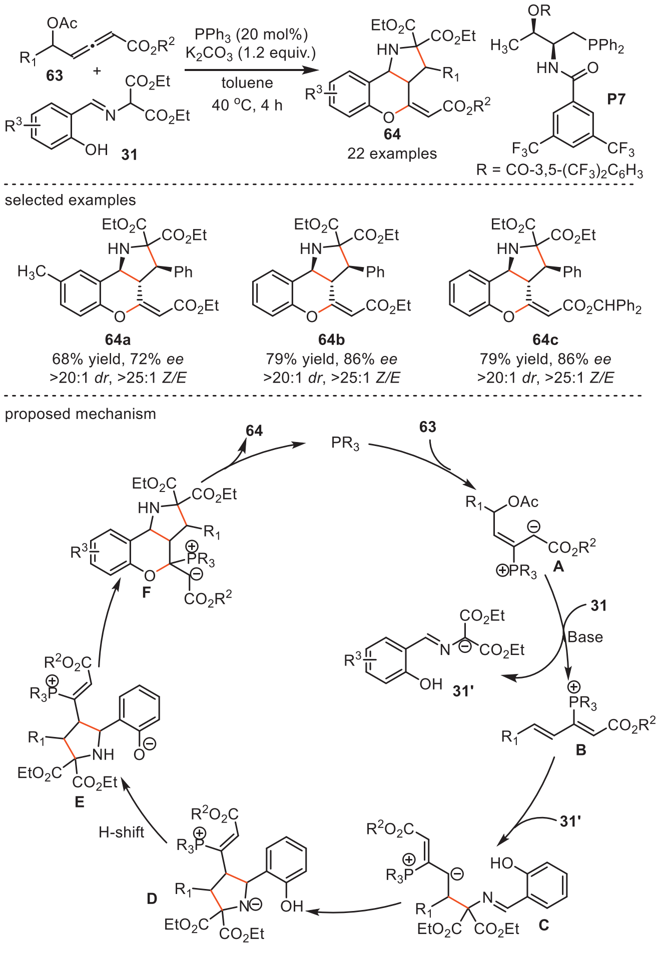
Scheme 23. Phosphine-catalyzed sequential annulation of δ-sulfonamido substituted allenoates with cross-conjugated azatrienes.

3. Sequential annulations of MBH alcohol and their derivatives (MBHADs)

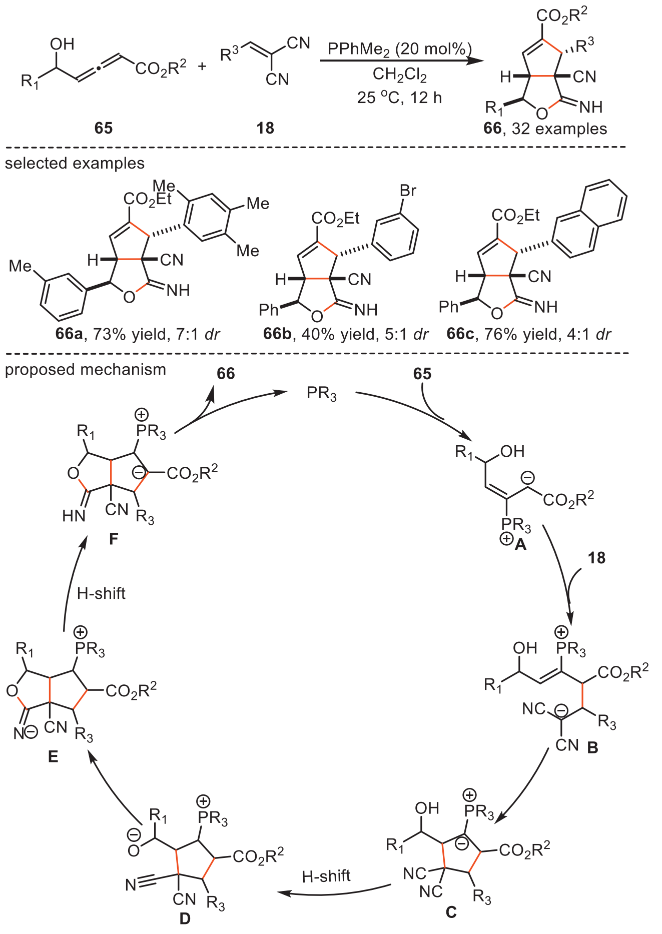
An emerging field in phosphine catalysis is the use of Morita–Baylis–Hillman alcohol and their derivatives (MBHADs), which install a leaving group at the β'-hydroxyacrylates to introduce a novel phosphonium species [91]. Similar to phosphine catalysis of allenoates, the new phosphonium species provide access to new reaction pathways with nucleophiles, electrophiles, dinucleophiles and electrophile–nucleophiles. More importantly, the new phosphonium species are also suitable for the sequential annulations to give the polycycle compounds and describe in detail in this section.

3.1. Intramolecular sequential annulations of MBHADs

By installing a leaving group, in 2003, Lu and co-workers discovered a novel phosphine-catalyzed MBH alcohol derivatives (MBHADs) to produce a newly phosphonium species, which opened the door to several new annulations [91]. In 2007, Tang and co-workers showcased a phosphine-catalyzed intramolecular ylide annulation (Scheme 26) [92–94]. This work provided an efficient way to construct bicyclo[n.3.0] ring systems with three continuous stereogenic centers. Interestingly, the use of Na_2CO_3 as an additional additive with PPh_3 catalyst was found to be crucial to obtain the products in good yields. According to mechanistic studies, they proposed phosphine catalyst reacted with bromide **67** to form phosphonium salt **A**, which was deprotonated by Na_2CO_3 to generate the corresponding phosphonium ylide **B** *in situ*. An intramolecular Michael addition of the ylide, followed by a Michael addition



Scheme 24. Phosphine-catalyzed sequential annulation of δ-acetoxy substituted allenoates and aldimine esters.



Scheme 25. Phosphine-catalyzed sequential annulation of δ–hydroxyl substituted allenoates with 1,1-dicyanoalkenes.

of phosphonium salt **C** and then β-elimination of phosphine catalyst, which gave the final products and completed the catalytic cycle.

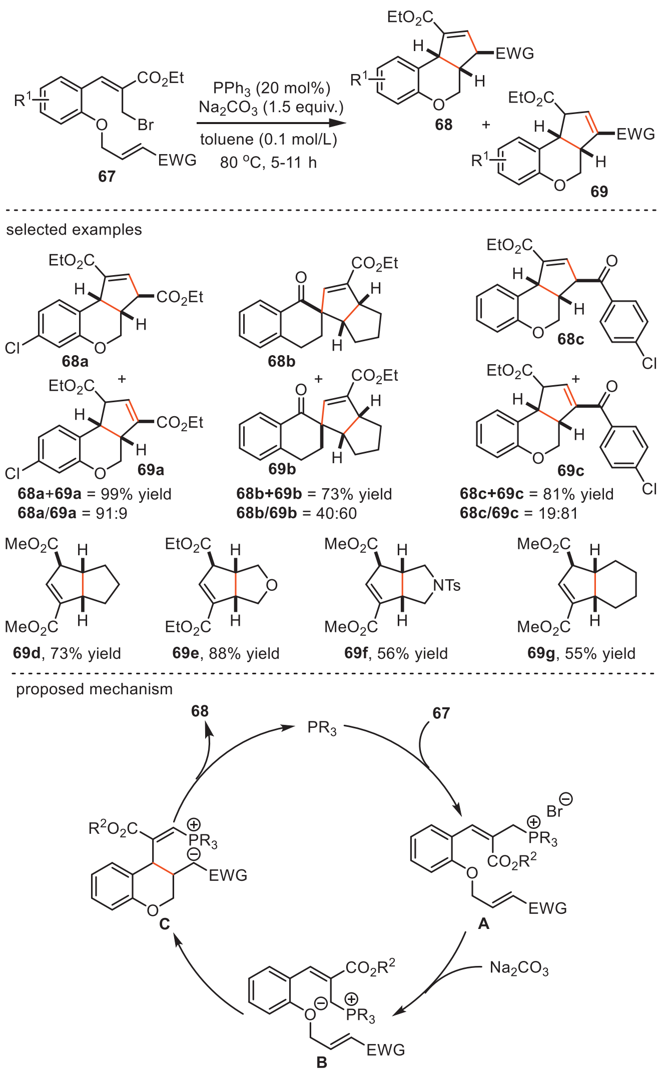
In 2010, Tang and Zhou reported an asymmetric version of the intramolecular [3 + 2] annulation of MBHADs with alkenes by using a chiral spirocyclic phosphine **P8** as the catalyst (Scheme 27) [95]. The resulting tricyclic skeletons showed excellent yields and high enantioselectivities, which could be transformed to the corresponding derivative with four contiguous stereocenters. Interestingly, the use of titanium(IV) isopropoxide as an additional additive was found to be crucial to obtain the product, which prohibited the isomerization and greatly improved the selectivity of the reaction due to the MBHAD−allene intramolecular [3 + 2] annulation was olefin isomerization of the byproducts.

3.2. Intermolecular sequential annulations of MBHADs

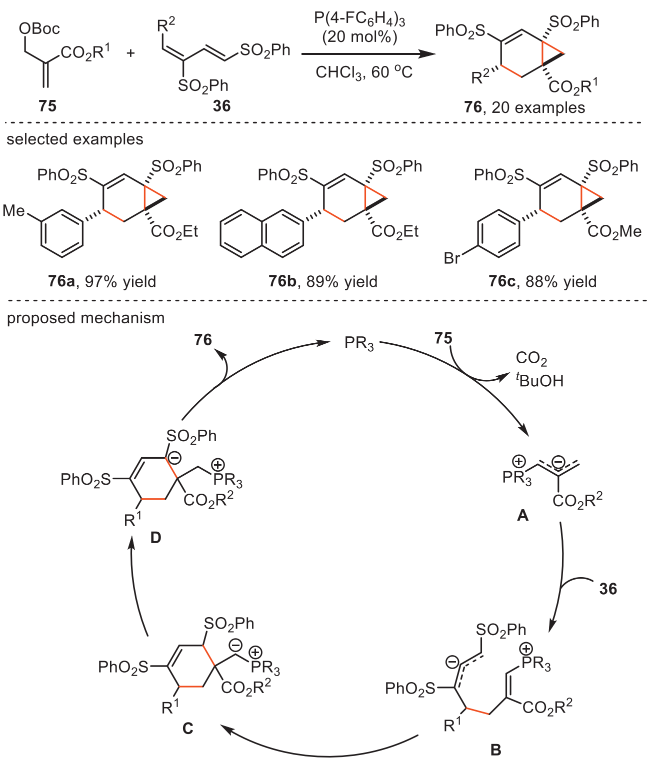
As a rare class of key building blocks, bicyclo[4.1.0]heptane ring systems have attracted growing interest in their synthesis but they are usually required special starting material [96–99]. In 2014, the Huang group disclosed the synthesis of bicyclo[4.1.0]heptane skeletons *via* phosphine-catalyzed sequential annulation (Scheme 28) [100]. Treatment of MBH carbonates with 1,3-bis(sulfonyl)butadienes bearing aryl or alkyl substituents in the presence of $P(4\text{-}FC_6H_4)_3$ in $CHCl_3$ at 60 °C provided a range of substituted bicyclo[4.1.0]heptenes in high yields. The reaction was, nevertheless, tolerating only unsubstituted MBHADs due to the sensitive to steric effects. According to the mechanistic studies, the author proposed the zwitterion **A** was generated from the MBHADs. Then Nucleophilic addition between the diene sulfone **36** and the zwitterion **A** produced the intermediate **B**, which underwent intramolecular cyclization, proton transfers, and catalyst displacement, the corresponding bicyclo[4.1.0]heptene product **76** were obtained.

Shortly, based on the recent success of phosphine catalysis for annulation of MBHADs [101–119], the same group developed a phosphine-mediated sequential annulation process of MBH carbonates with 2-tosylaminochalcones to construct functionalized aza-benzobicyclo[4.3.0] derivatives (Scheme 29) [120]. Under PPh_3 catalysis, both of aryl and alkyl substituents of 2-tosylaminochalcones worked well to give aza-benzobicyclo[4.3.0] derivatives **78** in moderate to excellent yields and high diastereoselectivity. Additionally, the reaction was tolerated when substituted MBHADs were employed. In this reaction, MBH carbonates acted as 1,2,3-C3 synthons. Based on the mechanistic observation, the reaction process involved allyl alkylation, intramolecular nucleophilic attack, proton migration and Wittig reaction to obtain the target compounds.

In 2017, the Meng group documented a phosphine-mediated domino reaction between MBH carbonates with 2-alkylidenebenzothiophene-3(2*H*)-ones (Scheme 30) [121]. By using MOTPP as the catalyst, several functionalized benzothiophene-fused oxatricyclodecene derivatives had been prepared through this strategy, resulting in medium conversions to the products. The control experiments showed that the strong polarity solvent DEF/H_2O and high reaction temperature might be helpful for the



Scheme 26. Phosphine-catalyzed sequential annulation of intramolecular ylide.

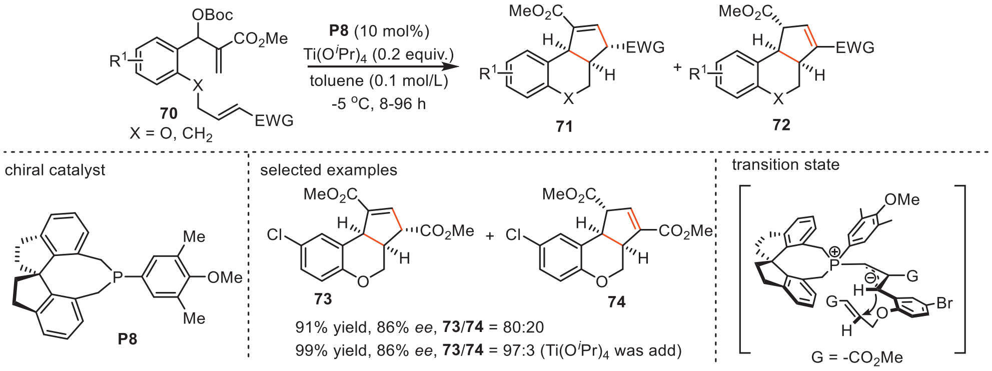


Scheme 28. Phosphine-catalyzed sequential annulation of MBH carbonates with 1,3-bis(sulfonyl)butadienes.

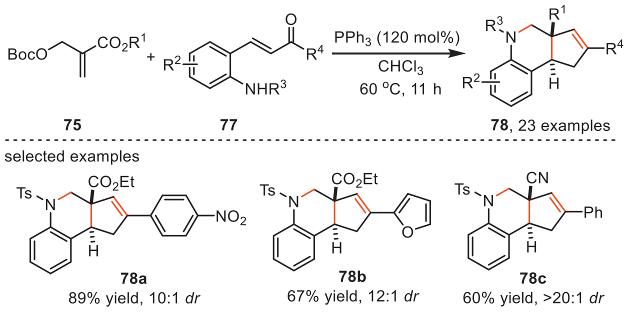
formation of benzothiophene-fused oxatricyclodecene derivatives **80**.

In 2020, another novel synthetic strategy was disclosed by Meng and co-workers, further demonstrating the versatility of MBH carbonates in the preparation of [6–5–5–6–6] pentacyclic compounds containing benzothiophene and tetrahydroquinoline skeletons (Scheme 31) [122]. Interestingly, the authors founded that the stereoselectivity was affected by the sulfur or oxygen atom in the substrates. Moreover, the reaction mechanism was explored by density functional calculations, which identified the 1,4-hydrogen-shift step to be the selectivity-determining step.

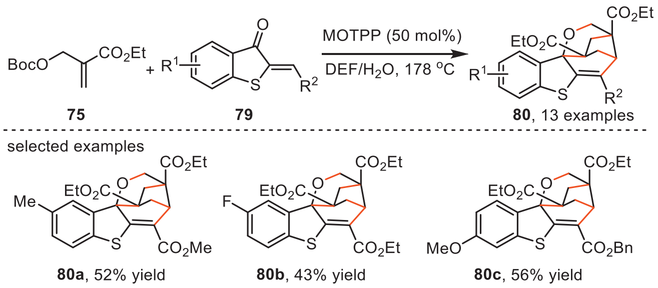
A phosphine-catalyzed cascade annulation of MBH carbonates with diazenes was achieved under mild reaction conditions by Guo and co-workers in 2021 (Scheme 32) [123]. The desired hexahydrocyclopenta[*c*]pyrazole derivatives were obtained in moderate to excellent yields using PPh_2Cy as the catalytic system. Various functional groups such as aryl- and aromatic ring substituents of diazenes were tolerated, and substituted MBH carbonates were all suitable partners. The reaction path way was proposed that the intermediate **A** attacked the diazenes **83** to finish the ylide **B**, and then reacted with another molecule of MBH carbonates **75** to generate the intermediate **C**. Subsequent deprotonation of the intermediate **C** led to the ylide **D**, which performed an isomerization to afford the intermediate **E.** After intramolecular nucleophilic addition triggered cascade annulation to furnish the intermediate **F**,



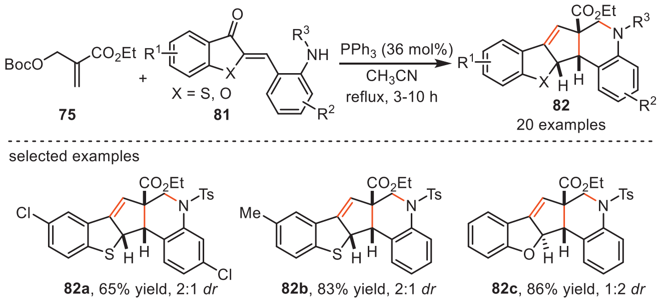
Scheme 27. Chiral phosphine-catalyzed intramolecular [3 + 2] sequential annulation of MBHADs with alkenes.



Scheme 29. Phosphine-mediated sequential annulation of MBH carbonates with 2-tosylaminochalcones.



Scheme 30. Phosphine-mediated sequential annulation of MBH carbonates with 2-alkylidenebenzothiophene-3(2*H*)-ones.

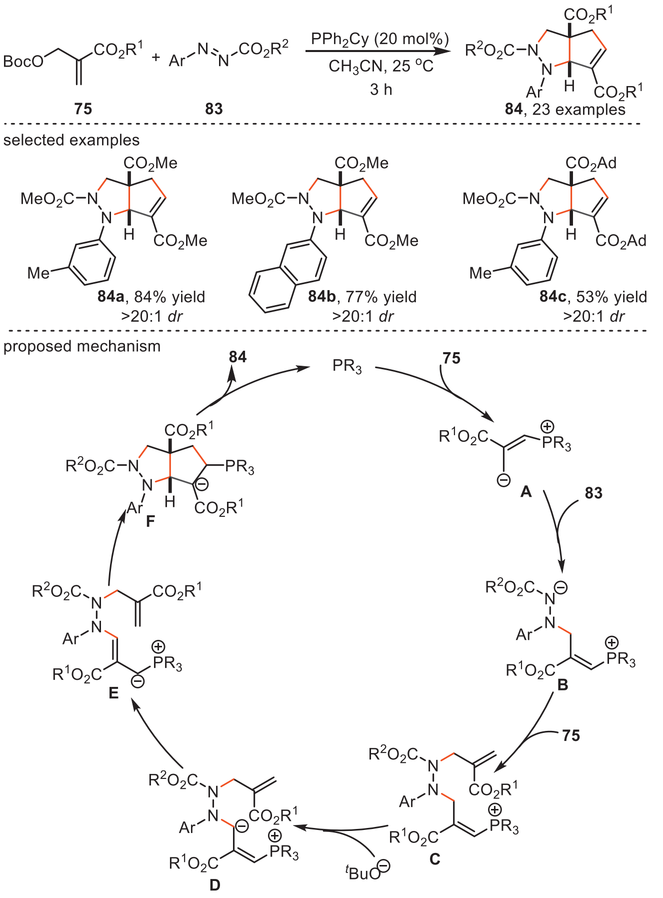


Scheme 31. Phosphine-catalyzed sequential annulation reaction of MBH carbonates with thioaurone or aurone derivatives.

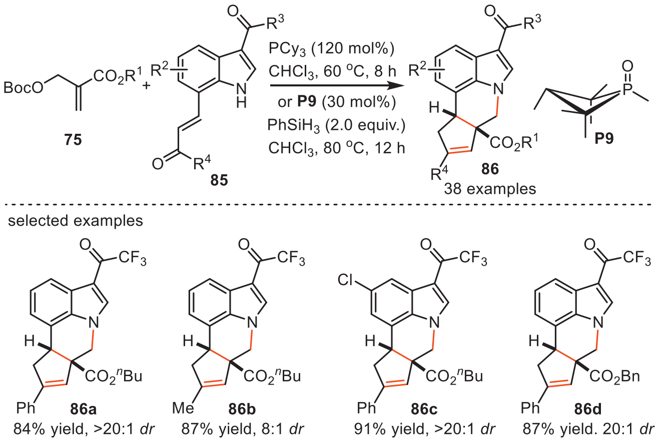
followed by β-elimination of phosphine catalyst, giving the final product **84**.

In 2022, Huang and co-workers described an efficient phosphine-mediated sequential [2+4]/[2+3] annulation of MBH carbonates with *N*-unprotected indoles, which resulted in the successful synthesis of pyrroloquinoline derivatives in moderate to excellent yields and good diastereoselectivities (Scheme 33) [124]. The reaction could be either mediated by stoichiometric PCy_3 or catalyzed by R_3PO *via* $P^{III}/P^{V}=O$ redox cycling in the presence of phenylsilane. In addition, the utility of the methodology was further demonstrated by various transformations of the pyrroloquinoline.

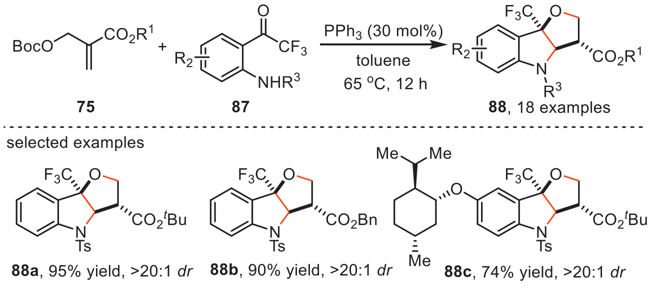
o-Aminotrifluoroacetophenone derivatives could also be used in the domino annulations with MBH carbonates, in 2024, as demonstrated by Zhu and co-workers in the construction of functionalized tetrahydrofuro[3,2-*b*]indolines (Scheme 34) [125]. In the presence of PPh_3, the reactions of MBH carbonates and *o*-aminotrifluoroacetophenone derivatives provided their corresponding products in moderate to excellent yields and with excellent diastereoselectivities. The reaction was, nevertheless, tolerating only substituted group at the 5-position in *o*-aminotrifluoroacetophenone.



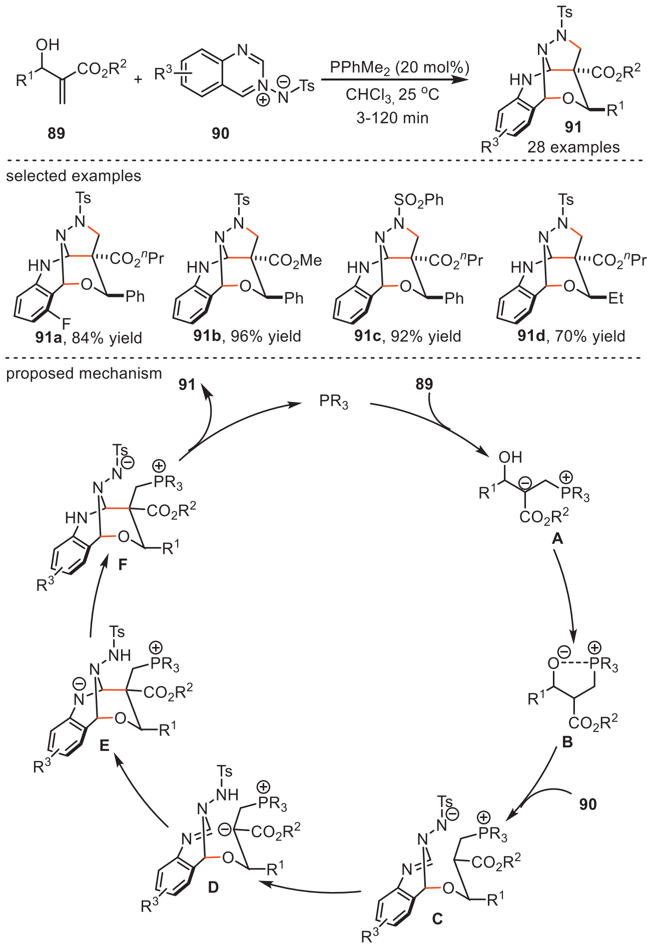
Scheme 32. Phosphine-catalyzed sequential annulation of MBH carbonates with diazenes.



Scheme 33. Phosphine-mediated sequential annulation of MBH carbonates with *N*-unprotected indoles.



Scheme 34. Phosphine-catalyzed sequential annulation of MBH carbonates with *o*-aminotrifluoroacetophenones.



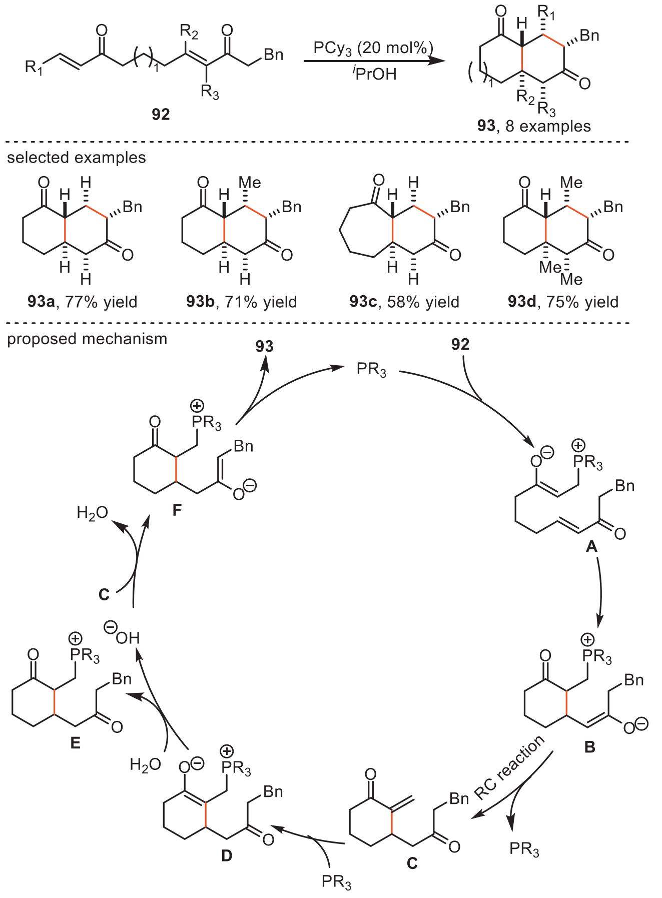
Scheme 35. Phosphine-catalyzed sequential annulation of MBH alcohols with azomethine imines.

3.3. Intermolecular sequential annulation of MBH alcohols

In 2019, Guo and co-workers explored the phosphine-catalyzed tandem annulation of MBH alcohols with azomethine imines, which was discovered a different mode of reactivity of MBHADs in the reaction (Scheme 35) [126]. With $PPhMe_2$ as the catalyst, they examined the scope of the MBH alcohols and azomethine imines in $CHCl_3$ at 25 °C, yielding a variety of three-dimensional heterocyclic compounds in high yields with excellent diastereoselectivities.

It was the first time the direct activation of unmodified MBH alcohols acting as new oxa-synthons has been achieved. Using a chiral spirocyclic phosphine as the catalyst, they investigated the asymmetric version of this tandem annulation, delivering chiral products in high yields with excellent diastereoselectivities and up to 21% *ee*. Initially, in their proposed mechanism, the zwitterionic intermediate **A** isomerized to the zwitterionic intermediate **B** *via* a proton transfer. The oxygen anion then underwent a nucleophilic addition of **90** to generate intermediate **C**, followed by a proton shift and an intramolecular Mannich-type process to give the intermediate **E**. Finally, the proton shift and intramolecular nucleophilic substitution reaction resulted in the final product **91** with the simultaneous regeneration of phosphine catalyst.

4. Sequential annulations of electron deficient olefins



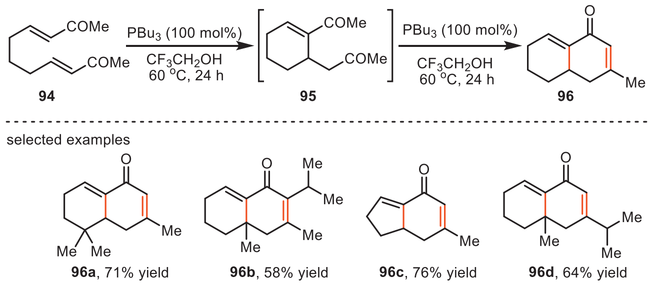
Scheme 36. Phosphine-catalyzed intramolecular sequential annulation of bis(enones).

One of the oldest phosphine-catalyzed reactions with an electron deficient olefins and nucleophiles is the conjugate addition, which forms the Horner's zwitterionic adduct [127]. The phosphonium enolate leads to the activation of the pronucleophiles to undergo a formal base-catalyzed Michael addition or the conjugated addition towards electrophiles. The different reaction pathways depend on the nature of the second reaction partner. The progress of electron deficient olefins in sequential annulations are detailed in this section.

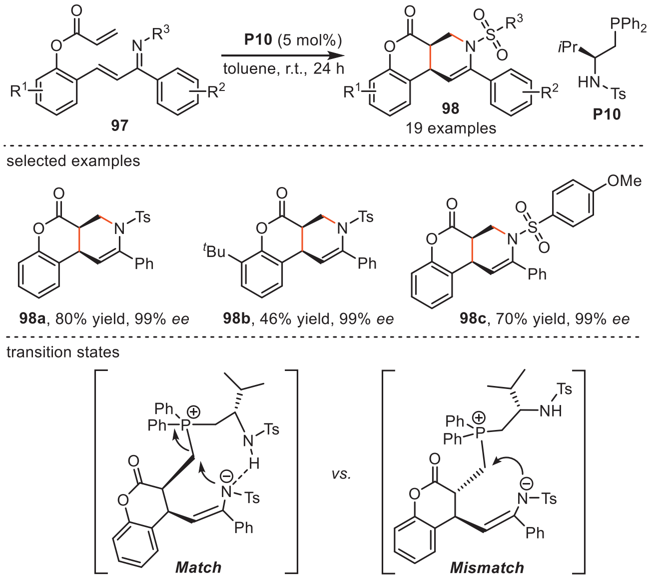
4.1. Intramolecular sequential annulation of electron deficient olefins

The generation of zwitterionic species from tertiary phosphines was first evidenced by Horner and co-workers in 1955, he isolated the crystalline zwitterionic adducts between triethyl- and triphenylphosphine and ethylenemalononitrile [127]. Until in 1963, Rauhut and Currier demonstrated the first tributylphosphine in the reactions with acrylates, where α-methylene succinates demonstrated as the reaction dimer product [128]. Five years later, the Morita group reported a tricyclohexylphosphine-catalyzed addition reaction of electron deficient olefins and aldehyde to form α-hydroxymethylated acrylates, which namely Morita reaction [129]. Based on these publications, nucleophilic phosphine catalysis attracted a great deal of attention from researchers.

In 2004, Couturier and co-workers disclosed a phosphine-catalyzed intramolecular [4+2] sequential annulation of bis(enones) to synthesis functionalized bicyclic products (Scheme 36) [130]. In this process, addition of water or alcohol solvent was beneficial, facilitating the proton transfer process. The corresponding products were obtained in medium yields under adjust conditions. Nevertheless, the bis(enones) with n=0 did not give its desired product under the standard conditions. According to the proposed mechanism, the reaction was initiated by the addition of



Scheme 37. Phosphine-mediated intramolecular sequential annulation of unsaturated diketones.

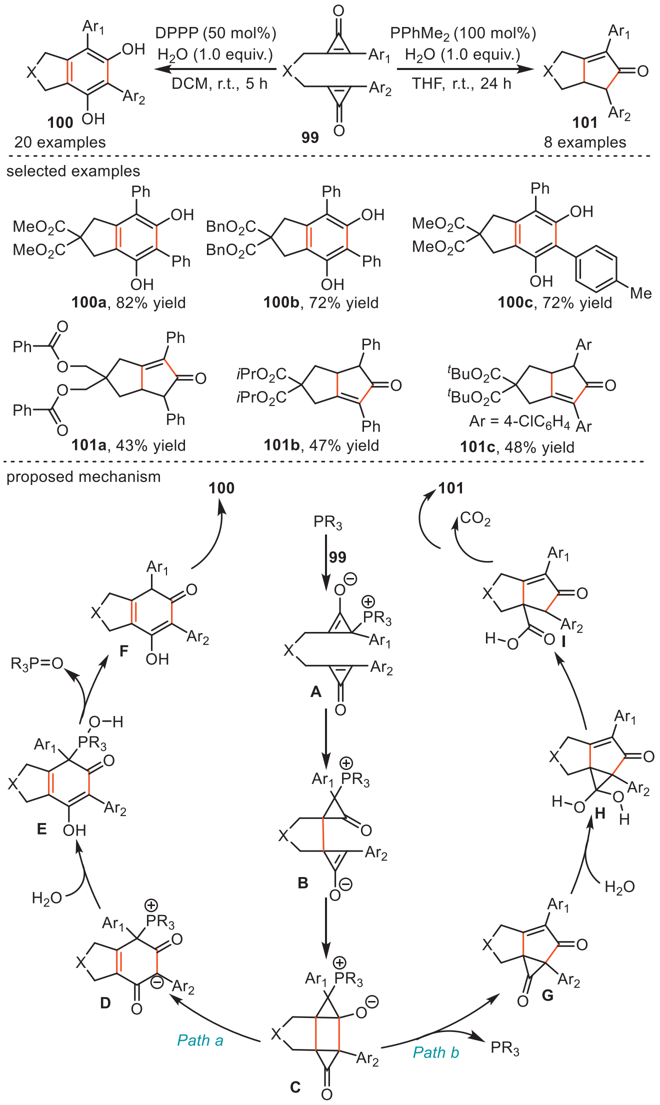


Scheme 38. Chiral phosphine-catalyzed intramolecular sequential annulation of acrylates and α,β-unsaturated imines.

phosphine catalyst onto the bis-enone **92** to give the phosphonium enolate **A**, which proceeded through an intramolecular RC reaction to produce the enone **C** after elimination of the phosphine catalyst. Subsequent Michael addition process between phosphine catalyst and enone **C** afforded the intermediate **D**, which underwent proton transfers with the mediation of water, the intermediate **D** and hydroxide ion pair were produced. Finally, hydroxide ion pair served as the base for the second cycloisomerization.

In 2005, Roush discovered a phosphine-mediated intramolecular tandem annulation of unsaturated diketones, providing an efficient method to synthesize cross conjugated bicyclic dienone products from readily available starting materials (Scheme 37) [131]. Both of bisenone bearing a shorter tether as well as sterically differentiated bisenones containing β,β-disubstituted enone were suitable for this transformation to afford the dienones in good yields with good regioselectivity. The authors postulated that the high degree of selectivity derives from an interaction between the phosphonium unit and the adjacent carbonyl, which could increase the acidity of the β-phosphonium-substituted methyl ketone such that it is deprotonated regioselectively by the alkoxide.

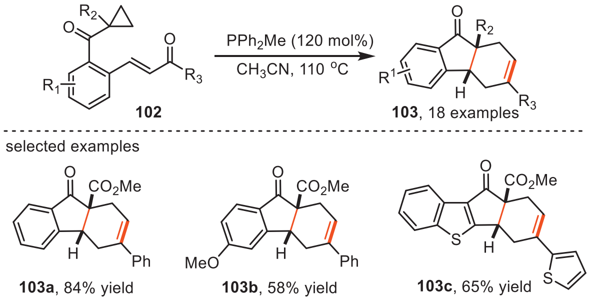
Compared to polycyclic ring structures, enantiomerically pure synthesis such compounds are more difficult, due to the difficulty in controlling stereoselectivity. In 2012, Chi and co-workers reported an enantioselective intramolecular [2 + 4] annulation of acrylates and α,β-unsaturated imines (Scheme 38) [132]. This method employed amino acid derived phosphine **P10** as the catalyst to overcome the intrinsic limitations of enantioselectivities, and allowed two heterocyclic rings with exceptionally high diastereo- and enantioselectivities. Various substituent patterns on the aromatic rings, such as alkyl, halogen and allyl were all applicable, while β-substituent (-Me, -Ph, -vinyl) to the acrylate moieties of the substrates led to no formation of the products.



Scheme 39. Phosphine-mediated intramolecular sequential annulation of dicyclopropenones.

In the following year, the Shi group discovered a novel phosphine-promoted intramolecular annulation of dicyclopropenones (Scheme 39) [133]. A variety of 2,3-dihydro-1*H*-indene-4,6-diol derivatives **100** and hexahydropentalen-2-one derivatives **101** were obtained selectively in moderate to good yields under modified reaction conditions. The reaction mechanism had been proposed on the basis of isotopic labeling and control experiments, and was also supported by DFT calculations.

Mechanistic studies revealed that the reactions proceeded *via* aldol-intervened RC reaction, which could involve two pathways (path a and b). Initially, nucleophilic addition of the phosphine catalyst to bis-cyclopropenone **99** produced the phosphonium enolate **A**, followed by [2 + 2] addition to form intermediate **C** stepwise *via* intermediate **B**. In the pathway a, ring opening occurred to generate intermediate **D**. In the presence of water, addition to the phosphine occurred, leading to extrusion of the phosphine oxide and production of intermediate **F**. Finally, **F** underwent aromatization, leading to **100**. In the pathway b, the highly strained intermedi-



Scheme 40. Phosphine-mediated intramolecular sequential annulation of cyclopropyl ketones.

ate **C** underwent skeletal rearrangement to give the intermediate **H** with the addition of water. After rearrangement and decarboxylation afforded **101**.

Very recently, Ramasastry described a phosphine-promoted ring opening/recyclization of cyclopropyl ketones to access hydrofluorenones (Scheme 40) [134]. This reaction was performed at 110 °C in the presence of commercially available PPh_2Me as the catalyst and acetonitrile as the solvent. Various functional groups such as aryl and alkyl were tolerated, and heterocycle as well as other ester groups were all suitable partners, where the group on the substrate was aldehyde substituted gave no desired products under the optimized conditions. In addition, the utility of the method was further demonstrated by various transformations of the hydrofluorenones. The authors postulated a mechanism for the transformations involving a cascade ring opening/Michael addition/Wittig reaction sequence of enone-tethered cyclopropyl ketones to generate tetrahydrofluorenones.

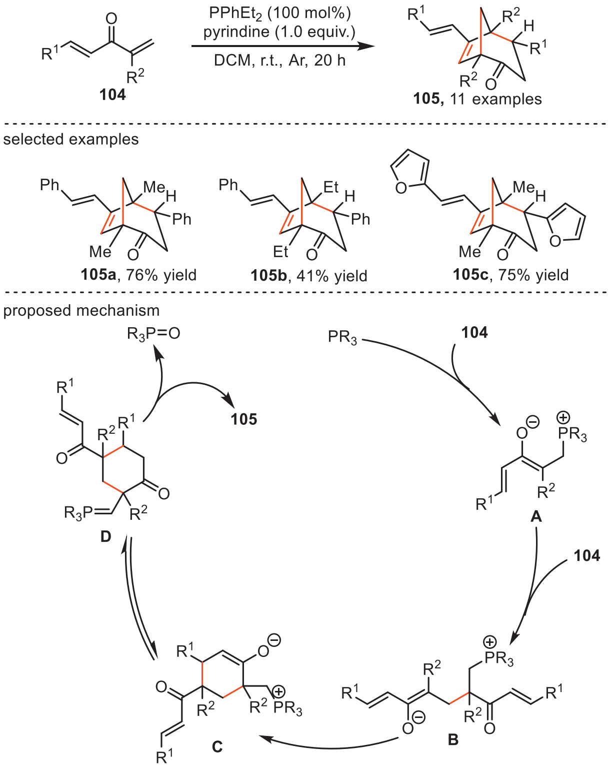
4.2. Intermolecular sequential annulation of electron deficient olefins

Carbocycles with defined quaternary centers can be synthetically challenging for the synthetic area. In 2006, Schaus and co-workers reported highly diastereoselective synthesis of bicyclo[3.2.1]octenones that contain two quaternary carbon centers by a formal [4 + 2] domino annulation and Wittig reaction process (Scheme 41) [135]. In this reaction, the authors proposed that the phosphine catalyst acted as both a nucleophilic promoter to generate a 1,3-diene and a mediator of intramolecular olefination, which was shown in Scheme 41. Initially, the nucleophilic addition of the phosphine catalyst to the 1,4-dienone **104** afforded the intermediate **A**. Subsequently, a formal [4 + 2] cycloaddition of another 1 equiv. of **104** in an endo fashion produced the zwitterionic species **C**. After proton transfer and the intramolecular Wittig reaction process, the bicyclo[3.2.1]octane **105** was obtained.

In 2011, Huang and Chen discovered an unprecedented substrate-controlled and phosphine-mediated domino reaction between conjugated dienes and β,γ-unsaturated-α-ketoester in a more elaborate system (Scheme 42) [136]. Treatment of conjugated dienes **106** with β,γ-unsaturated-α-ketoesters bearing aryl substituents in the presence of catalytic amount of tributylphosphine prepared substituted tetrahydrocyclopentafuran derivatives **108** in good yields. The authors postulated a mechanism for the transformations involving an RC–aldol–S_N2' cascade pathway. A variety of bicyclic phosphorane derivatives **107** were also prepared in high yields in the presence of a stoichiometric amount of tributylphosphine.

5. Sequential annulations of electron deficient alkynes

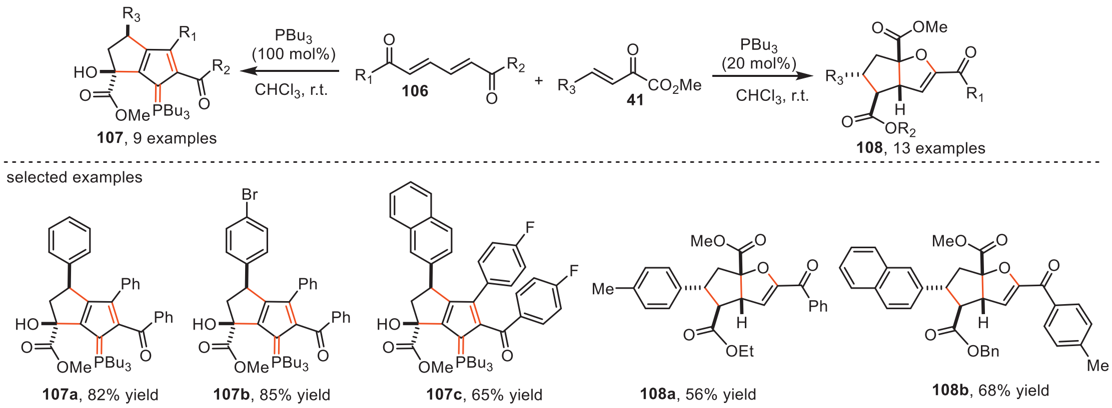
When treating electron deficient alkynes with phosphine catalysts, the formation of the phosphonium species reacts with the nucleophile, electrophiles, dinucleophiles, or nucleophile–electrophiles to prompt a wide variety of reactions. These reactions can be triggered by the phosphine interacting with the electron deficient alkynes alone, resulting in rapid isomerization to the diene. Michael addition and α-umpolung addition are the two major reaction pathways in the presence of a nucleophile. A wide variety of annulations occurs when dinucleophiles, electrophiles and nucleophile–electrophiles are incorporated. in the mixtures of electron deficient alkynes. It is also prominently characteristics in the synthesis of polycyclic compounds by phosphine-catalyzed sequential annulations, which are described in detail in this section.



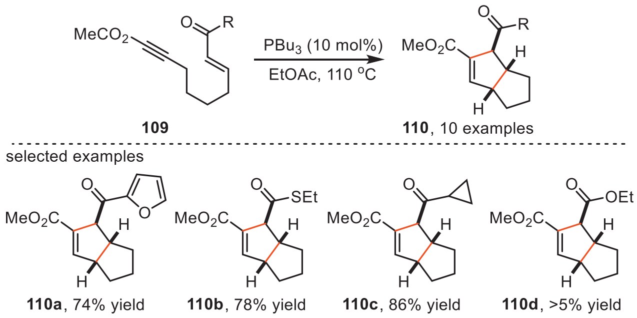
Scheme 41. Phosphine-mediated sequential annulation of 1,4-dienone.

5.1. Intramolecular sequential annulations of electron deficient alkynes

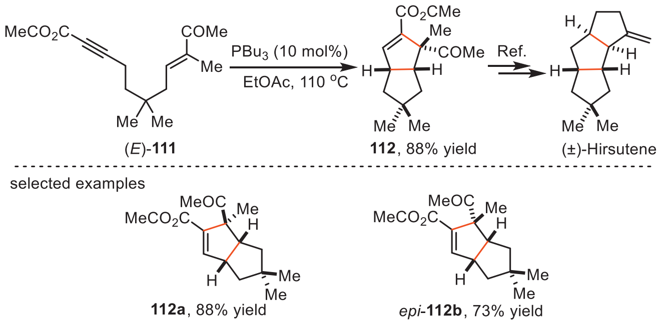
In 1966, Winterfeldt reported the first phosphine-catalyzed annulation between dimethyl acetylenedicarboxylate (DMAD) and aldehydes to form functionalized butanolide from a novel phosphonium species [137]. The field of research on phosphine-catalyzed alkynes with electrophiles has not progressed significantly for several years, since Winterfeldt presented a single example. It was only in 1996 that Nozaki and Takaya documented a phosphine-catalyzed cyclization of DMAD with α-keto esters, which broadened the scope of DMAD [138]. To overcome the issues of regio- and diastereoselectivity, in 2003, Krische designed that electron-deficient 1,7-enynes smoothly engage in intramolecular [3 + 2] annulation upon exposure to substoichiometric quantities of tributylphosphine, giving functionalized diquinanes in good yields (Scheme 43) [139]. The reaction of 1,7-enynes containing aryl, alkyl and hetero groups proceeded well to obtain their corresponding products, whereas a less electrophilic enoate–ynoate substrate was tested to produce the desired products in a poor result.



Scheme 42. Phosphine-mediated sequential annulation of conjugated dienes and β,γ-unsaturated-α-ketoester.

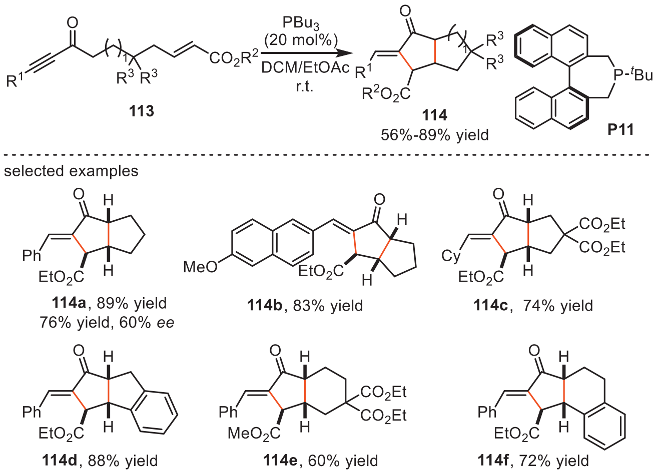


Scheme 43. Phosphine-catalyzed intramolecular sequential annulation of enone−ynoate to the synthesis of diquinanes.



Scheme 44. Phosphine-catalyzed intramolecular sequential annulation of enone−ynoate to the synthesis of (±)-hirsutene.

Krische also presented a concise and stereocontrolled approach to the total synthesis of (±)-hirsutene based on phosphine-catalyzed intramolecular enone−ynoate [3 + 2] annulation (Scheme 44) [140]. Treatment of (*E*)−**111** in the presence of PBu$_3$ gave access to diquinane **112** in 88% yield, and obtained (±)-hirsutene according to known methods. The authors employed (*Z*)−**111** to probe the stereospecificity of the cycloaddition under identical conditions, producing the epimeric diquinane *epi*−**112b** in 73% yield and without any detectable formation of the cycloadduct derived from (*Z*)−**111**. These results firmly established the intramolecular phosphine-catalyzed [3 + 2] dipolar cycloaddition as a stereospecific process. Furthermore, it also showcased the utility of Lu's allene−alkene [3 + 2] annulation.



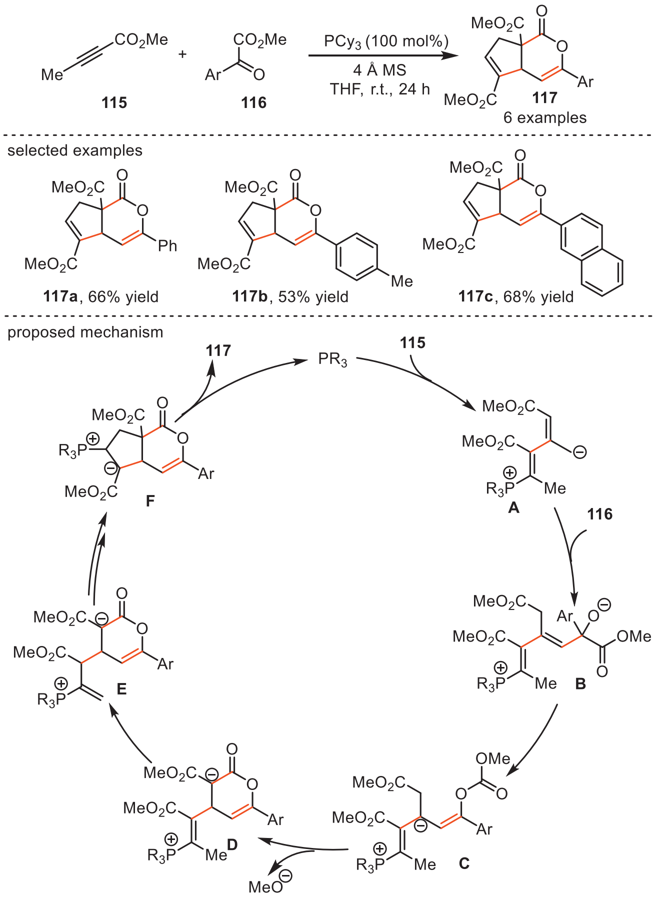
Scheme 45. Phosphine-catalyzed intramolecular sequential annulation of enone−ynoate.

In 2010, the Fu group exhibited a stereoselective phosphine-catalyzed synthesis of highly functionalized diquinanes (Scheme 45) [141]. The reaction was carried out in the presence of tributylphosphine as the catalyst, various functional groups such as aromatic, alkenyl and alkyl were tolerated. In addition, the linker between the ynone and the enoate can bear substituents or even include an aromatic ring. The authors also investigated the variant of this phosphine-catalyzed diquinane synthesis, resulting the corresponding product in 76% yield with 60% *ee* value by using chiral spirocyclic phosphine catalyst **P11**. Preliminary mechanistic studies indicated that the catalytic cycle normally involved nucleophilic addition/Michael addition/α-umpolung addition steps *via* a [3 + 2] annulation process.

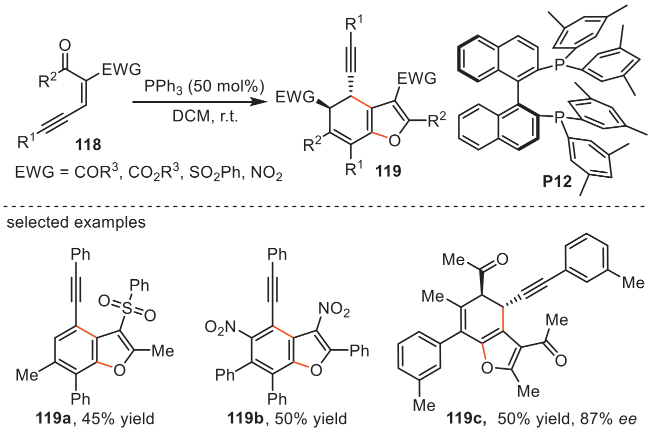
5.2. Intermolecular sequential annulations of electron deficient alkynes

In 2014, the Miller group explored a phosphine-mediated annulation of 2–butynoate and α–keto esters (Scheme 46) [142]. This reaction provided highly substituted cyclopentene derivatives in moderate yields under mild conditions in the presence of PCy$_3$ as the catalyst and 4 Å MS as the additive.

In the proposed mechanism, the zwitterion **A** was generated through phosphine-catalyzed dimerization of the butynoate **115** and a proton transfer. Addition to the **116** then gave the intermediate **B**, which underwent a rearrangement reaction involving C—C bond cleavage to produce the intermediate **C**. The transfer of a proton to intermediate **C** followed by a concerted ester group transfer and cyclization reaction resulted in intermediate **D**. Isomerization to **E** and subsequent deprotonation, a second annulation reaction and proton transfer led to intermediate **F**. After an elimination sequence, the final product **117** was obtained.

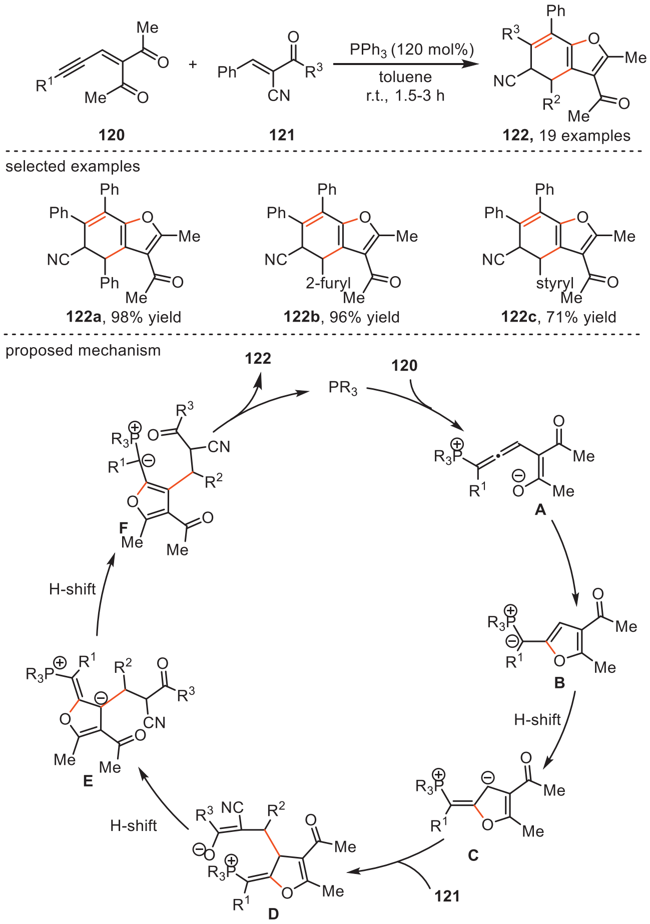


Scheme 46. Phosphine-mediated intramolecular sequential annulation of 2–butynoate and α–keto esters.



Scheme 47. Phosphine-mediated sequential annulation of conjugated ene–yne ketones.

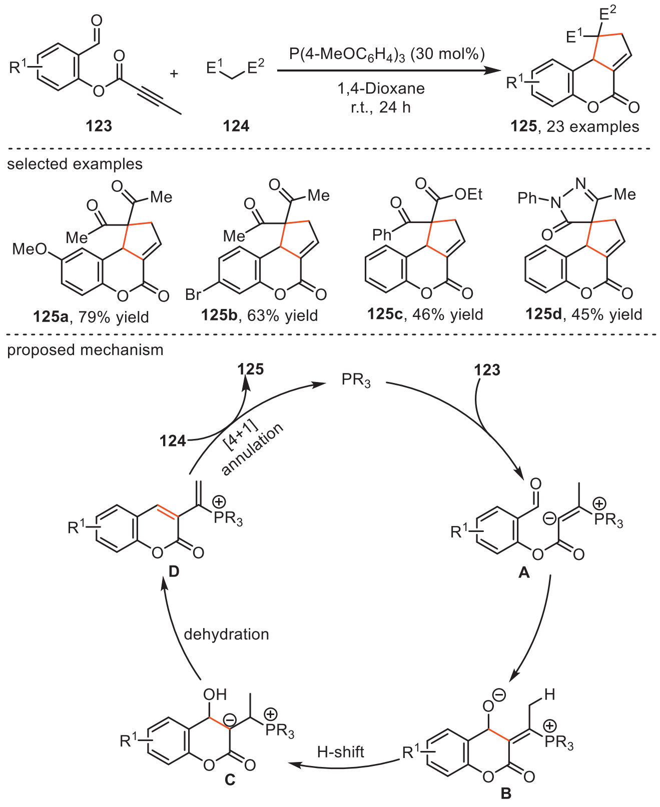
Thus far, successful examples for the construction of functionalized furans by isomerization of carbonyl group-containing ene-ynes have been extensively explored. In 2017, Shi and coworkers also developed a related transformation that provided functionalized dihydrobenzofurans in moderate to excellent yields with high diastereoselectivities *via* phosphine-catalyzed dimerization (Scheme 47) [143]. The reaction of conjugated ene–yne ketones bearing aryl and alkyl substituents were suitable to furnish their corresponding products, whereas the ene–yne ketone substituted with a sterically bulky 1-naphthyl group gave no desired products under the standard conditions. The asymmetric variant also examined, by using a xyl-BINAP **P12** as the chiral catalyst, giving the desired dihydrobenzofurans in good *ee* values. A mechanistic investigation involving the NMR spectroscopic tracing experiments revealed that this transformation proceeds through an isomerization/Michael addition/Wittig reaction cascade.



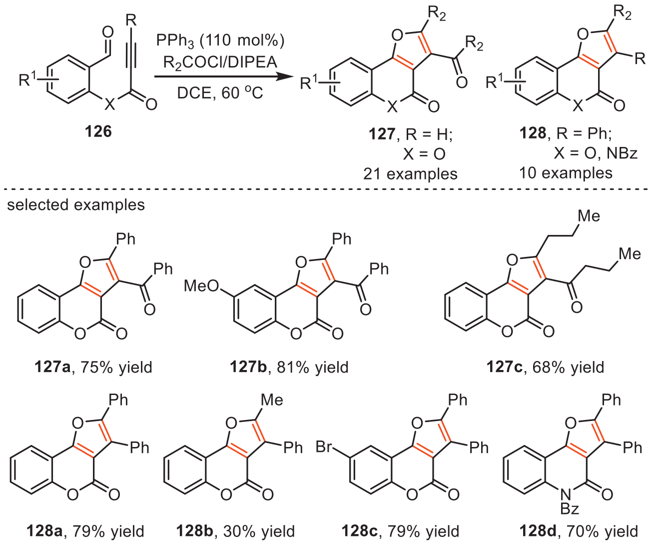
Scheme 48. Phosphine-mediated sequential annulation of enynones and a-cyano-a,β-unsaturated ketones.

In 2017, Huang group established a novel methodology for the facile access to multifunctionalized 4,5-dihydrobenzofurans *via* phosphine catalysis (Scheme 48) [144]. Various substituents 4,5-dihydrobenzofurans were smoothly produced in excellent yields from enynones and a-cyano-a,β-unsaturated ketones by using PPh_3 as the catalyst. Furthermore, the incorporation of a vinyl substituent on the benzenes rings of **121** showed only marginal effect on the efficiency, resulting in the corresponding product in satisfactory yield under the optimized condition. Mechanistic experiments indicated that the transformation started with the 1,6-addition of phosphine to **120** and gave the enolate intermediate, then underwent cyclization to afford intermediate **B**. Subsequent H-shift process gave intermediate **C**. The conjugate addition of **C** to **121** generated intermediate **D**. Further intramolecular proton transfer and a Wittig reaction furnished the product **122**.

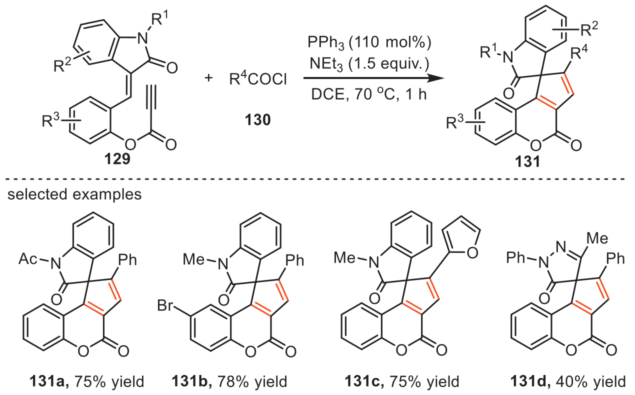
Remarkably, phosphine-catalyzed intramolecular [3 + 2] annulations of chalcones and allenes represented a distinguished approach to construct cyclopentene-fused dihydrocoumarins [63–65]. In 2021, Yang and co-workers also showcased a phosphine-catalyzed domino annulation between 2-formylphenyl alkynoates with activated methylene compounds, providing cyclopentene-fused coumarins in moderate to good yields with high diastereoselectivity (Scheme 49) [145]. Based on the control experiments,



Scheme 49. Phosphine-catalyzed sequential annulation of alkynoates and activated methylenes.



Scheme 50. Phosphine-mediated sequential annulation of alkynoates and acyl chlorides.



Scheme 51. Phosphine-mediated sequential annulation of alkynoates and activated methylenes.

they proposed that the reaction involved tandem Knoevenagel condensation and [3 + 2] annulation. However, they studied the mechanism of the phosphine-catalyzed domino sequence of alkynoates and activated methylenes *via* DFT calculations [146]. The computational results revealed that the [3 + 2] annulation sequence could be ruled out, due to a difficult Knoevenagel condensation of aromatic aldehydes and active methylenes. The authors thought that the reaction proceeded through a [4 + 1] annulation pathway, which involved a phosphine-catalyzed MBH-type reaction to give intermediate **B** followed by a [1,5]-proton shift and dehydration to afford vinyl phosphonium intermediates **D**. Then 1,3-dicarbonyls **124** acted as nucleophiles to attack vinyl phosphonium intermediates, subsequently leading to a stepwise [1,3]-proton shift and an intramolecular nucleophilic attack to finish the final product **125**.

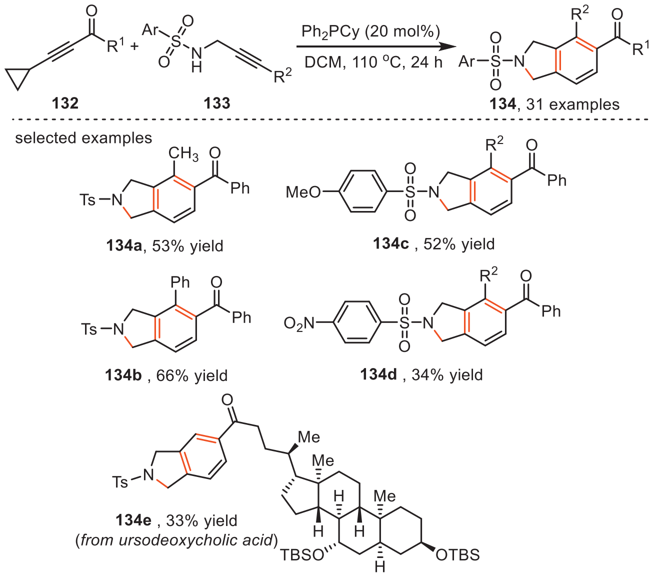
In 2021, employing the alkynoates, Lin and co-workers demonstrated a new approach for the construction of furo[3,2-*c*]coumarins and furo[3,2-*c*]quinolinones in the presence of a phosphine catalyst (Scheme 50) [147]. Treatment of terminal or internal alkynoates with acyl chlorides in the presence of triphenylphosphine in 1,2-dichloroethane at 60 °C for 2–8 h gave substituted furo[3,2-*c*]coumarins in moderate to good yields. When treated with *N*-substituents alkynoates, these substituted furo[3,2-*c*]quinolinones were obtained in a good yields. According to mechanistic studies and literature precedents on phosphine-mediated reactions, they proposed the reaction process involved MBH-type/acyl-transfer/Wittig reaction.

Shortly, a phosphine-mediated sequential annulation of oxindoles bearing alkyonate and acyl chlorides was achieved under controlling conditions by the same group (Scheme 51) [148]. The reactions of a series of alkynones bearing different substituents with several acyl chlorides provided substituted spirocyclopenta[*c*]chromene-indolinones in moderate to good yields, and regardless of the electronic and steric effects of the substituents. Based on the results and control experiments, the authors proposed the plausible mechanism involved a Rauhut-Currier (RC)-type/acyl transfer/Wittig strategy progress.

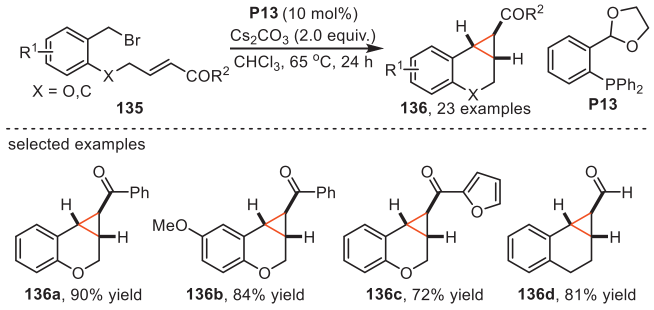
Recently, Ye and co-workers documented an effective phosphine-catalyzed sequential annulation of the ring-opening/elaboration of cyclopropanes, providing the 2,4-pentadiene sulfonamides and isoindolines in moderate to good yields (Scheme 52) [149]. Diverse range of cyclopropyl alkynoates and propargyl sulfonamides proceeded well to give the products in good yields. Satisfyingly, this protocol was also suitable for the late-stage modification of some bioactive molecules and were carried out to prepare various structurally diverse organic compounds. The authors proposed that the key to the success of this reaction was phosphine-catalyzed *in situ* formation of higher ring strain cyclopropylidenemethyl phosphonium salt. Based on the mechanism studies, they thought that the possibility of the domino reaction process involved opening amination/isomerization/Diels–Alder reaction/aromatization.

6. Other sequential annulation

In 2014, Tang and Li realized the first phosphine-catalyzed cyclopropanation reaction of α,β-unsaturated carbonyl compounds *via* covalent ylide catalysis in the presence of sidearm-assisted phosphine catalyst **P13** (Scheme 53) [150]. The desired [n.1.0] bi-



Scheme 52. Phosphine-catalyzed sequential annulation of cyclopropyl alkynoates and propargyl sulfonamides.



Scheme 53. Phosphine-catalyzed intramolecular sequential annulation of α,β-unsaturated carbonyl compounds.

cycloalkanes were obtained from α,β-unsaturated carbonyl compounds in good to excellent yields. Additionally, enals and α,β-unsaturated esters were also worked well for this reaction, giving their corresponding products in good yields.

Mechanistic studies indicated an interaction between the ether oxygen and the phosphonium atom, which was believed to be crucial for switching the phosphine reactivity from a typical ylide route to an unprecedented catalytic cyclopropanation pathway. Finally, DFT calculations also rationalized the insight of the sidearm effects.

7. Summary and outlook

As illustrated in this review, by using phosphine as the catalyst, the main features of such reactions are simple and mild reaction conditions, environmentally friendly, no metal residues, high catalytic activity, controllable enantioselectivity and stereoselectivity, and broad application prospects. Developments in this field have provided more effective methods for the synthesis of polycyclic compounds and further explored the interesting reaction mechanisms by efficiently constructing multiple chemical bonds through phosphine-mediated sequential annulations. In addition, there is still much room for development in the design of new efficient chiral phosphine catalysts, the development of new reaction substrates and synthetic methodologies.

Design of chiral catalysts: From the above reactions, chiral phosphine catalysts include a large class of phosphine catalysts derived from amino acids, spirocyclic skeletons and binaphthyl skeletons. Comparatively, there are fewer types of chiral phosphine catalysts available for the synthesis of polycyclic compounds. In the future, we expect to develop available and more efficient chiral phosphine catalysts and catalytic systems with high universality and apply them to the synthesis of drug molecules and natural products.

Types of substrates: The substrates for the synthesis of chiral phosphine-catalyzed polycyclic compounds can be broadly divided into the following categories: electron-deficient olefins, alkynes, bis-enolates, MBH alcohols and their derivatives. The substrates are relatively limited to various types of electron-deficient compounds, and the development of rich substrate types is also an important direction of development.

Synthesis of methods: A number of polycyclic compounds have been synthesized based on organo-phosphine catalysis, and further synthesis of natural products has been achieved. Although there are problems of difficult catalyst recycling and relatively limited substrates for the reaction, we aim to overcome these problems by designing catalytic systems for redox cycling, reducing catalyst dosage and developing co-catalytic systems. The development of different catalytic systems to synthesis of polycyclic compounds will provide a new green, simple and efficient method for the synthesis of more drug molecules.

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.

CRediT authorship contribution statement

Xuling Pan: Writing – original draft. **Wei Cai:** Writing – original draft. **You Huang:** Writing – review & editing, Supervision, Project administration.

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