Abstract: In recent years, there have been extraordinary developments of organophosphine-catalyzed reactions. This includes progress in the area of [4C+X] annulations, which are of particular interest due to their potential for the rapid construction of 5–8-membered cyclic products. In this short overview, we summarize the remarkable progress, emphasizing reaction mechanisms and key intermediates involved in the processes. The discussion is classified according to the type of electrophilic reactants that acted as C4 synthons in the annulation process, in the order of α-alkyl allenoates, γ-alkyl allenoates, α-methyl allene ketones, β′-OAc allenoate, δ-OAc allenoate, activated dienes and cyclobutenones.

Keywords: phosphine catalysis; annulation; C4 synthons

1. Introduction

The continuous innovation of synthetic methodologies is one of the sources for sustainable progress in modern organic chemistry. Since the Diels–Alder reaction was reported in 1928, cycloaddition reactions have evolved into one of the most fascinating fields in organic chemistry because of their powerful applications in convergent synthesis of cyclic compounds from simple starting materials. Apart from the electrocyclic reactions, nucleophilic phosphine catalysis, which go through different dipolar cycloaddition modes, also played a significant role in the development of cycloaddition chemistry [1–22]. Those novel annulations provide efficient and powerful approaches to a wide array of carbo- and heterocyclic motifs which are frequently found in natural products as well as biologically active molecules, usually in a regio- and stereoselective manner [1–22]. In addition, due to their merits such as readily availability of starting materials, mild and metal-free reaction conditions, simple post-reaction workup, high atom economy, low environmental pollution, etc., the tertiary phosphine-promoted cycloaddition reactions have received extensive interest from synthetic chemists, and become an important means in sustainable organic synthesis.

In 1995, Lu et al. first reported the PPh3-catalyzed [3+2] cycloaddition reactions of 2,3-butadienoates or 2-butynoates with electron-deficient olefins for the preparation of cyclopentenes [23]. Intrigued by this pioneering work, the potential of allenes acting as a type of C3 synthons were further exploited. Since then, a wide variety of [3+2] annulations together with their asymmetric catalytic versions have been developed. Further studies disclosed that allenes could also play the roles of C4 [24–33] and C1 [34–36] units in various cycloadditions under some circumstances. In addition to allenes, electron-deficient alkynes, and MBHADs (Morita–Baylis–Hillman alcohol derivatives) were often used as C3 synthons in the tertiary phosphine catalyzed [3+2] cycloaddition reactions with electron-poor olefins or imines as well. With the help of newly developed chiral phosphine catalysts, many synthetic
methodologies have been developed for the construction of optically active five-membered ring systems [21].

Thanks to the readily available C₃ synthons (e.g., allenes, electron-deficient alkynes, and MBHADs), phosphine catalyzed [3C+X] cycloadditions have been extensively studied. However, the development of organophosphine-catalyzed [4C+X] cycloadditions is lagging far behind. One of the reasons might be the lack of suitable C₄ synthon. Since Kwon and coworkers reported the innovative finding about the employment of α-substituted allenoates as a novel type of C₄ synthon [37], tremendous progress has been made in the field of organophosphine-catalyzed [4C+X] annulations. Those annulation reactions provide efficient way for the rapid construction of 5–8-membered cyclic products, which are of particular importance in organic synthesis. However, there has been no specific review on this topic. Herein, we present a comprehensive review to summarize the organophosphine-catalyzed [4C+X] annulations as well as to elaborate the mechanisms and key intermediates involved in the process. This overview covers all kinds of nucleophilic phosphine-catalyzed [4C+X] annulations, including [4+1], [4+2], [4+3], and [4+4] cycloadditions and some other miscellaneous [4C+X] annulations. The discussion is organized according to the type of electrophilic reactants that acted as C₄ synthons in the annulation process, in the order of α-alkyl allenoates, δ-aryl allenoates, α-methyl allene ketones, β'-OAc allenoate, δ-OAc allenoate, activated 1,3-dienes and cyclobutenones.

2. [4+X] Annulations of α-Alkyl Allenoates (or 2-Alkyl 2,3-Butadienoates)

Ordinarily, organophosphine-catalyzed reactions of 2,3-butadienoates are initiated by the α-addition of the zwitterionic intermediate 2 to other electrophiles. However, substitution of the hydrogen at the C2 position of 2,3-butadienoates with a methyl group blocked the α-attack of the zwitterionic intermediate. Instead, unprecedented reaction modes initiated by γ- or β'-addition of the zwitterionic intermediate to other electrophiles usually occurred (Scheme 1). Thus, 2-alkyl-2,3-butadienoates act as a type of 1,4-dipole synthon in the annulation with activated imines, electron-deficient olefins, ketones and azomethine imines, rather than the traditional role of 1,3-dipolar synthon in the non-substituted allenoates.

![Scheme 1. Different reaction mode between 2,3-butadienoates and 2-substituted 2,3-butadienoates.](image)

2.1. [4+2] Annulations of α-Alkyl Allenoates with Activated Imines

The [4+2] annulations of α-alkyl allenoates with sulfonimides resulted in the production of highly functionalized tetrahydropyridines [37]. The mechanism of the [4+2] annulation reaction is outlined in Scheme 2: Firstly, nucleophilic addition of PBu₃ to the β-position of α-alkyl allenoates resulted in the formation of zwitterionic intermediate 11, which existed as a resonance-stabilized zwitterionic intermediate 6a. Subsequently, the allylic carbanion 6a underwent a nucleophilic addition
to the imine 9 at the γ-position of the allenoate to produce intermediate 12. It was supposed that the reason for the γ-position selectivity was that the larger steric hindrance of the α-position blocked its corresponding nucleophilic attack. Then, two consecutive proton-transfer processes caused the shift of C-C double bond. Finally, 6-endo ring closure of intermediate 15 accompanied with the release of phosphine catalyst generated the product. The 2-alkyl-2,3-butadienoates played the role of 1,4-dipole synthon throughout the whole reaction process. This important finding extended the scope of phosphine-catalyzed annulations of allenoates from [3C+X] to [4C+X] cycloadditions. It represents the milestone for the role-transformation of allenoates, and lays the foundation for the subsequent similar 1,4-dipolar cycloaddition reactions.

![Proposed mechanism of the [4+2] annulation reaction](image)

Scheme 2. Proposed mechanism of the [4+2] annulation reaction [37].

In 2005, the above phosphine-catalyzed [4+2] cycloaddition of α-alkyl allenoate was successfully applied to the formal synthesis of Alstonia macroline alkaloids, (±)-macroline and (±)-alstonerine by Kwon et al. Under the catalysis of PBu3, [4+2] annulation of diester allene 17a with indoly-substituted imine 16 gave rise to indoly-substituted tetrahydropyridine 18 in 73% yield with 3:1 dr, which was then converted to the key allyl alcohol compound 19 by a sequence of six-step transformations. Since compound 19 was the known key intermediate in the total synthetic route of (±)-macroline (20) and (±)-alstonerine (21) reported by the group of Cook [38–40], Kwon and coworkers’ research work represents formal synthesis of alkaloids (±)-macroline and (±)-alstonerine (Scheme 3) [41]. Besides, a similar [4+2] cycloaddition of ethyl α-methyl allenoate with imine was also applied to the total synthesis of (±)-Hirsutine by the same group in 2012 (Scheme 4) [42].
In 2005, the group of Fu achieved the asymmetric version of Kwon’s [4+2] annulation of α-alkyl allenoates with imines [43]. For most substrates, this reaction has excellent diastereoselectivity, moderate to excellent yields and ee values. However, the electron-rich p-methoxybenzaldehyde-derived imine appears to be relatively unreactive and can only achieve 42% yield of target product 25a, although the ee value is as high as 98%. Besides, imines with electron-poor substituents on the ortho-position of the aromatic groups resulted in unsatisfactory stereoselectivities (e.g., 25b).

### Scheme 3. Formalsynthesis of alkaloids (±)-macroline and (±)-alstonerine [38–41].

![Scheme 3](image3.png)

### Scheme 4. Total synthesis of alkaloids (±)-Hirsutine [42].

![Scheme 4](image4.png)

### Scheme 5. Catalytic asymmetric [4+2] annulation of α-alkyl allenoates with imines [43].

![Scheme 5](image5.png)
The asymmetric [4+2] cycloaddition of α-alkyl allenoates with N-tosyl aldimines were achieved by Zhao et al. as well in 2011 (Scheme 6) [44]. A simple bifunctional N-acyl amino phosphine catalyst TP-2 derived from isoluecine was identified to be the best catalyst for the [4+2] cycloaddition, providing a series of chiral tetrahydropyridines in good to high enantioselectivities whose absolute configuration was just opposite to those reported by the Fu’s group. It is worth noting that the electron-rich 4-anisyl imine 9a which was once a reluctant coupling partner in Fu’s catalytic system worked as well and gave the corresponding product *ent*-25a in an excellent yield and 90% ee. 2-chlorobenzene aldimine 9b, which performed unsatisfactorily previously, also gave an improved result: from 75% to 88% yield and from 60% to 96% ee.

In 2014, the group of Kwon developed a class of *trans*-hydroxy-L-proline (Hyp) derived P-chiral [2.2.1] bicyclic phosphine catalysts, which was named as “HypPhos” ligands [45]. Recently, they applied the HypPhos to the [4+2] annulation of α-alkyl allenoates with imines, and found that *exo*-(p-anisyl)-HypPhos TP-3 was able to effect the above [4+2] annulation to produce tetrahydropyridines in excellent enantioselectivities (Scheme 7) [46]. Although the highly enantioselective synthesis of 2,6-disubstituted guvacines had been achieved by Fu’s and Zhao’s groups, optically active 6-substituted (none substitution at the γ position) guvacines could not be acquired as easy as the former. In Fu’s research, 6-substituted guvacines 26 were formed in moderate enantioselectivities (Scheme 7) [43], and under the catalytic system of Zhao’s amino acid derived bifunctional phosphine TP-2, the 6-phenyl guvacine ester was not obtained [44]. However, Kwon and coworkers’ catalytic system overcame the limitation and achieved the [4+2] annulation of α-methyl allenoates 4 with imines to produce 6-substituted guvacine esters in excellent enantioselectivities [46]. With this method, optically enriched (R)-aplexone 27, which is a promising anti-cholesterol drug, could be quickly synthesized through a two-step, high-yielding sequential transformation of the chiral 6-disubstituted guvacines 26a (Scheme 8).

In 2014, Guo’s group achieved a [4+2] cycloaddition reaction of sulfamate-derived cyclic imines with α-alkyl allenoates (Scheme 9) [47]. For the racemic version, *n*-PrPPh2 was proved as the best catalyst that effected the reaction to provide a variety of sulfamate-fused tetrahydropyridines 30 in high yield with excellent diastereoselectivities. Similar to previous mechanisms proposed by Kwon, Fu, Zhao, the zwitterionic intermediate exhibited normal regioselectivity: nucleophilic attack took place at the γ-position. When a chiral bifunctional tertiary phosphine catalyst TP-4 derived from natural amino acids was employed as the catalyst, the asymmetric [4+2] cycloaddition proceeded smoothly to afford a series of chiral sulfamate-fused tetrahydropyridines 30 in good yields with moderate to excellent enantioselectivities.

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\begin{align*}
\text{Scheme 6. Catalytic asymmetric [4+2] annulation of α-alkyl allenoates with imines (PMP: p-methoxyphenyl).} \quad [44].
\end{align*}
\]
was favored in other \([4+2]\) cycloaddition of \(\alpha\)-methyl allenoates with imines. The electronic property of the phosphine catalyst was conjectured to be the determining factor for the regioselectivity: electron-poor phosphine catalysts are inclined to promote \(\beta\)-addition while electron-rich nucleophilic catalysts usually lead to \(\gamma\)-addition. In 2012, a different \([4+2]\) cycloaddition of 2-methyl-2,3-butadienoate 4 with cyclic saccharin-derived ketimines 31 was reported by the group of Ye (Scheme 10) [48]. Nucleophilic attack of the zwitterionic intermediate exhibited \(\beta\)'-position selectivity rather than the \(\gamma\)-selectivity that was favored in other \([4+2]\) cycloaddition of \(\alpha\)-methyl allenoate with imines. Thus, in the whole reaction process, \(\alpha\)-alkyl allenoate was equal to type-B 1,4-dipole which posed a reversed polarity compared to previously introduced \([4+2]\) annulations. The electronic property of the phosphine catalyst was conjectured to be the determining factor for the regioselectivity: electron-poor phosphine catalysts are inclined to promote \(\beta\)'-addition while electron-rich nucleophilic catalysts usually lead to \(\gamma\)-addition.
Interestingly, a reversal of regioselectivity was found when different organophosphine-phosphonium dienolate-to-phosphorus ylide equilibrium was employed: the stronger nucleophilic hexamethylphosphine triamide (HMPT) effected organophosphine-catalyzed [4+2] cycloaddition of 2-alkyl allenoates with arylidenemalononitrile. The enantioselective [4+2] cycloadditions of 2-methyl-2,3-butadienoate 4 with saccharin-derived ketimines 31 was also realized by Sasai and coworkers in 2014 (Scheme 11) [49]. The highly nucleophilic monoaryl phosphine catalyst (R)-SITCP (TP-5) developed by Zhou’s group catalyzed the enantioselective [4+2] cycloadditions in a normal γ-selective addition pathway, producing kinetically favored multifunctionalized tetrahydropyridines 33 with a hetero-quaternary chiral center in high yields with up to 93% ee and ≥20:1 regioselectivities.

2.2. [4+2] Annulations of α-Alkyl Allenoates with Electron-Deficient Olefins

Under the catalysis of organophosphines, α-alkyl allenoates, as effective novel C4 synthons, reacted not only with activated imines to produce tetrahydropyridines, but could also couple with electron-deficient alkenes to prepare all-carbon cyclohexenes. In 2007, Kwon et al. realized the organophosphine-catalyzed [4+2] cycloaddition of 2-alkyl allenoates with arylidenemalononitrile 34 (Scheme 12) [50]. Interestingly, a reversal of regioselectivity was found when different organophosphine catalysts were employed: the stronger nucleophilic hexamethylphosphine triamide (HMPT) effected the annulation reaction with normal γ-position selectivity while the less nucleophilic triarylpophosphines with electron-deficient aryl groups converted the α-alkyl allenoates to an inverted 1,4-dipole equivalent D (β'-position selectivity). The explanation for this intriguing reversal of regioselectivity was that the phosphonium dienolate-to-phosphorus ylide equilibrium (C to D) favored the ylide D when a more electron-withdrawing triarylpophosphine was utilized.

Scheme 10. Thermodynamically favored [4+2] cycloaddition of α-alkyl allenoates with cyclic ketimines [48].

Scheme 11. Kinetically favored [4+2] cycloaddition of α-alkyl allenoates with cyclic ketimines [49].
Scheme 12. [4+2] cycloaddition of α-alkyl allenoates with arylidenemalononitrile [50].

Later, more extensive electrophilic olefins were used in the [4+2] annulation reaction by Kwon and coworkers (Scheme 13) [51]. Similarly, HMPT was identified as the best nucleophilic phosphine catalyst. Reaction of arylidene cyanoacetates 37 with 2-methyl allenoate 4 afforded the normal γ-position cycloadducts 38. However, when the less-reactive arylidene malonates 39 were employed as the olefin substrates, both cycloadducts 40 and 41 resulted from two different reaction pathways were produced. It was rationalized that there was enough time for the isomerization of phosphonium dienolate 39 when relatively unreactive olefin substrates were used. It should be noted that triarylphosphine or some other electron-rich tertiary phosphines were ineffective at mediating the cycloaddition reactions.

Scheme 13. [4+2] annulations of 2-methyl allenoate with arylidene cyanoacetate or arylidene malonates [51].

In 2012, the group of Lu and Zhao independently realized the first asymmetric [4+2] annulation reaction of α-alkyl allenoates with activated olefins by employing the amino acid-derived LB-BA (short for Lewis base-Brønsted acid) bifunctional chiral tertiary phosphine catalyst.

In the research work of Lu (Scheme 14) [52], two different types of LB-BA bifunctional chiral phosphine catalysts were identified to be suitable for two different types of activated alkene substrates: for the [4+2] cycloaddition of arylidene malononitrile 34, threonine-derived bifunctional chiral tertiary phosphine catalyst TP-6 with a sterically bulky tris(trimethylsilyl)silyl (TTMSS) group on the oxygen atom was found to be the best catalyst, enabling the formation of cyclohexenes 42 in high to excellent yields with excellent enantioselectivities and moderate to good diastereoselectivities, while, for the [4+2] cycloaddition of isatylidenemalononitrile 43, the performance of the chiral tertiary phosphine...
catalyst TP-6 was not ideal as only 17% ee value could be induced, however, the chiral tertiary phosphate catalyst TP-7 based on the skeleton of dipeptide O-TBDPS-L-Thr-L-N-Boc-tert-Leu was adequate to mediate the annulation and provide the desired 3-spirocyclohexene-2-oxidoles 44 and 45 in high yield with excellent enantioselectivities and diastereoselectivities. Due to the ester group at the β′ position of the allenoates, which increases the steric hindrance of the β′ position, γ-addition cycloadducts were formed exclusively for the two types of [4+2] cycloadditions. After replacement of the ester group at the β′ position with electron-poor aromatic rings, the [4+2] annulation could also proceed smoothly to afford cyclization products in moderate yields with good dr and excellent ee. However, β′-substitution of electron neutral phenyl ring was not tolerated in the reaction.

At the same time, by employing L-isoleucine-derived LB-BA bifunctional chiral tertiary phosphate compound TP-8 as the catalyst, Zhao and coworkers successfully achieved the asymmetric [4+2] cycloadditions of 2-alkyl substituted allenoates with 2-cyano acrylate derived activated olefins (Scheme 15) [53]. In addition to the frequently-used aryl aldehydes-derived alkenes, aliphatic aldehyde-derived olefin (46, R = aliphatic) was also applied to such a stereoselective transformation for the first time, and the corresponding isopropyl cyclohexene 47b could be obtained in 92% yield with 97% ee.

In recent years, some electron-deficient olefins that are embodied in novel skeleton scaffolds have been developed as dipolarophiles as well in the phosphine-catalyzed [4+2] cycloadditions with α-alkyl allenoates. To establish an efficient and concise synthetic access to the naturally occurring tricyclic benzopyrone framework, in 2011, Kumar and coworkers applied the electron-deficient 3-formy chromone as the alkene in [4+2] annulations with zwitterion C (γ-addition selectivity) generated by the addition of phosphine catalyst to α-alkyl allenoates (Scheme 16) [54]. A cascade sequence of [4+2] annulation followed by a deformylation that provided the desired tricyclic cyclohexene-fused chromone rings 50 with up to three stereogenic centers as a single diastereoisomer was observed.

Scheme 14. Asymmetric [4+2] cycloaddition of α-alkylallenoates with activated olefins [52].
The exocyclic allenic lactone 51 proved to be a competent 1,4-dipolar C₄ synthon as well in the same [4+2] annulations, smoothly delivering the tetracyclic benzopyrones 52 in high diastereoselectivities.

Scheme 15. Asymmetric [4+2] cycloaddition of α-alkylallenoates with 1-cyano-1-ester olefins [53].

Scheme 16. [4+2] cycloaddition of α-alkyl allenoates with chromone derivatives [54].

In 2016, Kumar et al. realized the asymmetric catalytic version of the above [4+2] annulations (Scheme 17) [55]. Instead of the 3-formychromone, 3-cyano-chromones were employed as the activated alkenes. L-Threonine-derived bifunctional N-acylaminophosphine (TP-9) proved to be the best catalyst, mediating the [4+2] annulations with α-alkyl allenoates 17 to generate tricyclic tetrahydroxanthones 54 containing three continuous chiral centers in high yields with excellent enantioselectivities and moderate to high diastereoselectivities.

Scheme 17. Asymmetric [4+2] cycloaddition of α-alkylallenoates with chromones [55].

In 2015, Guo and coworkers employed the unsaturated pyrazolone 55 as a novel type of activated alkene to examine the similar phoshine-catalyzed [4+2] cycloaddition with α-substituted allenoates
The moderately nucleophilic MePPh₂ was capable of triggering the desired racemic annihilation with diethyl 2-vinylidene succinate to afford the corresponding spiropyrazolone products in 49–99% yields as a single diastereomer. Reaction of β′-aryl-substituted allenoates with the unsaturated pyrazolone resulted in poor diastereoselectivities although the annihilation proceeded smoothly to provide the corresponding cycloadducts in good to excellent yields (75–99%). Utilization of a chiral thiourea-based bifunctional phosphine TP-4 (Scheme 9) as the chiral organocatalyst allowed the formation of a variety of chiral polysubstituted spiropyrazolones in moderate to excellent yields with excellent enantioselectivities and moderate to good diastereoselectivities (Scheme 18).

![Scheme 18. [4+2] cycloadditions of unsaturated pyrazolones with allenoates](image)

In 2016, Guo, Zhou, and co-workers found that the barbiturate-derived alkenes 58 were another type of ideal dipolar olefin in the phosphine-catalyzed asymmetric [4+2] annulation with α-alkyl allenoates (Scheme 19) [57]. The spirocyclic chiral phosphate catalyst TP-10 was capable of inducing high to excellent enantioselectivities. It is noteworthy that, compared to previously reported chiral phosphine-catalyzed [4+2] annulations where only β′-alkoxy carbonyl substituted allenoate were tolerated in most cases, the allenoate scope were quite wide in this work. Not only β′-ethoxy carbonyl substitution, but non-substituted α-methyl allenoate, and α-methyl allenoates with electron-rich, -neutral, and -deficient aromatic moieties (include naphthyl substitution) on the β′-positions were also tolerated in the annihilation reactions. With the adoption of this methodology, a wide variety of pharmaceutically important spirobarbiturate-cyclohexenes 59 were obtained in good to excellent yields with excellent diastereo- and enantioselectivities.

![Scheme 19. Enantioselective [4+2] cycloadditions of barbiturate-derived alkenes with α-substituted allenoates](image)

Although Lu’s group have reported the highly enantioselective [4+2] annulation reactions of β′-alkoxy carbonyl and β′-electron-poor aryl substituted allenoates with isatylidene malononitrile for the synthesis of functionalized chiral 3-spirocyclohexene-2-oxindoles in 2012, reactivities of the simple, non-substituted α-methyl allenoates 4 were not examined. In 2017, Chen, He and co-workers investigated the [4+2] annulations of 2-methyl-2,3-butadienones 4 with isatylidene malononitrile 60 (Scheme 20) [58], and found that the expected spiroannulation could proceed smoothly to deliver two separable regioisomers 61 and 62 derived from γ- and β′-addition, respectively, when conducting the reaction at 80 °C with the use of PPh₃ as the catalyst. Regioselectivities were unsatisfactory in most
cases except for halogen-substituted N-Ac isatin-derived alkenes (R = Ac, 61:62 = 5:95). In addition, indan-1,3-dione-derived alkenes 63 were tested as well, similarly, the [4+2] annulations furnished a corresponding pair of regioisomers 64 and 65 in excellent yields with modest to good regioselectivities (64:65 = 39:61–5:95).

2.3. [4+2] Annulations of α-Alkyl Allenoates with Ketones

In 2010, the group of Ye found that when trifluoromethyl(aryl)ketones 66 or pentafluoroethyl(phenyl)ketone 68 were used as the dipolarophiles, [4+2] annulations occurred to produce highly functionalized fluorinated dihydropyrans (Scheme 21) [59]. Both electron-donating and electron-withdrawing substituents were tolerated on phenyl ring in the [4+2] annulations, furnishing the desired dihydropyrans in good yields with high diastereoselectivities. Heteroaryl trifluoromethyl ketone and pentafluoroethyl(phenyl)ketone also worked to give the corresponding cycloadducts although in a slightly lower yield. However, reactions of α-methyl or α-ethoxyl carbonyl allenoates gave no or only trace corresponding [4+2] annulation product. Furthermore, other activated ketones, such as 2-oxo-2-phenylacetate, benzoyl cyanide and N-methylisatin, did not react with the α-benzyl allenolate under the same reaction conditions.

2.4. [4+3] Annulations of α-Alkyl Allenoates with Azomethine Imines

Due to the intrinsic ring strain and competing cyclization pathways, phosphine-catalyzed cycloaddition of α-alkyl allenoates with other dipolarophiles usually lead to the formation of normal-sized 5- or 6-membered rings. Despite its great efficiency in construction of 5- or 6-membered rings, phosphine-catalyzed preparation of medium-sized rings was elusive until in 2012. Guo, Zhong, Kwon and coworkers described phosphine-catalyzed [3+2] and [4+3] annulation reactions...
of α-substituted allenoates with C,N-cyclic azomethine imines for the synthesis of a variety of pharmaceutically important tetrahydroisoquinoline derivatives (Scheme 22) [60]. Interestingly, they found that the nucleophilic phosphine catalyst together with the allenoate substrates had a great influence on the chemoselectivity of the annulation reaction. Generally, for the β'-aryl allenoates 29, employment of strongly nucleophilic PBu₃ as the catalyst mainly led to [4+3] cyclization pathways, while in the presence of PMe₃ thermodynamically favored [3+2] annulate pathway was predominate (Scheme 22, up). However, under the catalysis of either PBu₃ or PMe₃, the reactions of α-alkyl allenoates 8 underwent the [3+2] cyclization process exclusively, giving only very small amounts (<1% in most cases) of the [4+3] cycloadducts (Scheme 22, bottom).

Based on the previous reported [4+2] annulations of α-substituted allenoates, they depicted the plausible mechanism for the 1,3-dipolar cycloadditions as in Scheme 23: nucleophilic addition of the phosphine catalyst to the β-carbon of the allenoate generated the zwitterionic intermediate C, which subsequently attacked the azomethine imine 70 through the γ-carbon to form the zwitterionic intermediate 74. 5-exo cyclization followed by a β-elimination of the phosphine catalyst afforded the [3+2] annulated product 72 or 73. On the other hand, when R is an aryl group, a favorable sequence of proton transfer and equilibration took place, which led to isomerization of 74 to 75 due to the more acidic nature of the β'-carbon. After a further proton transfer process, 7-endo cyclization occurred. Expulsion of the catalyst PBu₃ furnished the [4+3] cycloaddition product 71.

**Scheme 22.** Phosphine-catalyzed [3+2] and [4+3] annulation reactions of α-substituted allenoates with azomethine imines [60].

**Scheme 23.** Plausible mechanism for the phosphine-catalyzed [3+2] and [4+3] annulation reactions of azomethine imines [60].
Guo and coworkers later found that the PBu₃-catalyzed annulation of α-substituted allenoates with C,N-cyclic aromatic azomethine imines 77, including N-acetyliminoisouquinolinium betaine (77a), N-acetyliminosquinolinium betaine (77b), and N-acetylimiphenanthridinium betaine (77c), exclusively produced the [4+3] cycloadducts 78, providing dinitrogen-fused heterocyclic compounds in moderate to excellent yields (Scheme 24) [61]. Both alkyl and ethoxy carbonyl, and methylene aryl groups with different electronic substitution patterns were compatible at the α-position of the allenoates in the [4+3] annulations. Compared with the initial report, this catalytic [4+3] cycloaddition process was a practical synthetic method for biologically important heterocycles, suggesting immense synthetic utility.

\[
\text{R-CH=CH-CO}_{2}\text{Et} + 77 \overset{\text{BuP (20 mol%), DCM, rt, 48 h}}{\longrightarrow} 78, \text{major}
\]

**Scheme 24.** The [4+3] cycloadditions of α-substituted allenoates with azomethine imines [61].

In their following research, the enantioselective version of the phosphine-catalyzed [4+3] cycloaddition of α-substituted allenoates with C,N-cyclic azomethine imines was realized for the first time (Scheme 25) [62]. The commercially available Kwon phosphine TP-11 was identified as the optimal catalyst, mediating the asymmetric [4+3] cycloaddition to produce the seven-membered ring-fused quinoxoline-based tricyclic heterocycles 80 in high to excellent yields with high to excellent enantioselectivities and mostly excellent diastereoselectivities. The substrate scope of both the allenoate and the azomethine imine was rather wide. Not only various allenoates bearing different electronic properties of substituents on the benzene ring of the β'-aryl allenoates but also β'-carboxylate- or alkyl-substituted allenoates were compatible in the reaction. The obtained chiral tricyclic adducts 80 could be easily transformed into monocyclic diazepines 81 which frequently show significant biological activities in pharmaceutical chemistry by an oxidation-ring opening procedure.

\[
\text{R-CH=CH-CO}_{2}\text{Et} + \text{R'-Ph,48\% yield 1:1 Dr} \quad \text{R = CO}_{2}\text{Et}, 77\%, 2:3 \text{dr} \quad \text{7 examples 80-97\% yield 5:4 - 10:1 dr}
\]

**Scheme 25.** Phosphine-catalyzed enantioselective [4+3] cycloadditions of α-substituted allenoates with azomethine imines [62].
3. [4+2] Annulations of δ-Aryl Allenoates with Activated Olefins

In 2013, the group of Huang disclosed an unprecedented phosphine-catalyzed [4+2] annulation of γ-substituted allenoates 82 with 2-arylidene-1H-indene-1,3(2H)-diones (Scheme 26) [63]. Differently from the previously reported annulation reactions that γ-substituent allenoates had participated in before [64–68], the γ-benzyl allenoates firstly serves as a new type of C₄ synthon in this novel [4+2] cyclization process. With this method, highly substituted spiro-[4.5]-dec-6-ene skeletons 83 could be powerfully constructed in excellent yields with complete regioselectivity and high diastereoselectivity. The mechanism of this [4+2] annulation process was proposed as below in Scheme 27: firstly, nucleophilic addition of the phosphine catalyst on the γ-benzyl allenoate generated a pair of resonant 1,3-dipolar zwitterionic intermediates 84 and 85. A subsequent proton transfer step gave rise to the transient allylic carbanion 86 where the negative charge was located on the δ-position of the allenoate. Michael addition of the allylic carbanion 86 to the alkene substrate 63 afforded intermediate 87. A consecutive proton shift enabled the formation of intermediate 88. Finally, an intramolecular umpolung addition followed by proton transfer and elimination of the phosphine catalyst furnished the desired spirocyclohexene product 83 and regenerated the catalyst.

Scheme 26. [4+2] annulation of γ-benzyl allenoates with indan-1,3-dione-derived alkenes [63].

Scheme 27. Proposed mechanisms for the [4+2] annulation of γ-benzyl allenoates with indan-1,3-dione-derived alkenes [63].
At the same time, a similar phosphine-catalyzed [4+2] cycloadditions of δ-aryl-substituted penta-2,3-dienoates with 3-arylidene oxindoles were also reported by Marinetti, Voituriez and coworkers (Scheme 28) [69]. Under the catalysis of PPh₃, a wide scope of substrates were tolerated in the [4+2] annihilations, providing a broad range of functionalized spiro-cyclohexene oxindoles containing three contiguous stereogenic centres in 48–89% yields with efficient stereoselective control in most cases (dr > 9:1 in most cases). A preliminary asymmetric catalytic study about this reaction revealed that (S,S)-2,4-bis-(diphenylphosphino)pentane ((S,S)-BDPP, TP-12) could promote the cyclization process to afford the expected spirocyclic oxindole in moderate enantioselectivity (60% ee for 93a).

Scheme 28. [4+2] annulation of δ-aryl-substituted penta-2,3-dienoates with 3-arylideneoxindoles [69].

4. [4+4] Annulations of α-Methylallene Ketones with α,β-Unsaturated Imines

In 2017, Lu, Ullah and co-workers disclosed the first example of a phosphine-catalyzed cycloaddition for the synthesis of eight-membered rings, achieving an enantioselective phosphine-catalyzed [4+4] annulation reaction of α-methyl allene ketones with α,β-unsaturated imines (Scheme 29) [70]. The dipeptide L-Thr-L-Thr-derived bifunctional phosphine catalyst TP-13 was found to mediate the asymmetric [4+4] cycloadditions to produce eight-membered azocine in excellent yields with excellent enantioselectivities (>98% ee in most cases). A wide range of aurone- or azaurone-derived α,β-ununsaturated imines bearing different aromatic moieties were compatible in the reactions, affording the corresponding benzofuran- or indole-fused azocines respectively. A strong electron-withdrawing protecting group on the nitrogen atom of the imine was required, as sulfonamides was adequate to involve into the expected [4+4] cycloadditions while imines with an alkyl or aryl group on the N atoms were inert under the same reaction conditions. Employment of terminal α-methyl allene ketones was another crucial point for the success of the reactions because either the similar α-substituted allenoates or γ-substituted allene ketones failed to react with the α,β-ununsaturated imines. The mechanism proposed for the [4+4] cycloaddations was similar to those for the [4C+X] annihilations of α-substituted allenoates: firstly, nucleophilic addition of the phosphine catalyst to the α-methyl allene ketones led to the formation of a pair of resonant zwitterionic intermediates and 98. Then, γ-addition of the phosphonium enolate to the α,β-ununsaturated imines afforded intermediate 99. Subsequently, a proton shift enabled alkeneisomerization to give 100. Finally, cyclization and release of the phosphine catalyst gave rise to the eight-membered product 96. The authors explained that the steric hindrance of the NTs anion avoided the [4+2] annihilation pathways.
Scheme 29. Enantioselective phosphine-catalyzed formal [4+4] annulation reaction [70].

5. [4+X] Annulations of β’-Acetoxy Allenoates

Generally, the zwitterionic intermediates derived from nucleophilic addition of the phosphine catalyst to the allenoates are nucleophilic to react with various electrophiles, but a remarkable reversal of polarity was witnessed after elimination of a negative charged group of the zwitterion. In 2010, Tong’s group innovatively introduced an acetoxy group (−OAc) at the β'-position of 2,3-butadienoate as a leaving group, enabling it to serve as a versatile 1,4-biselectrophilic precursor to produce α-cyanoketones were used as the other coupling reactant, providing functionalized cyclopentenones in good to excellent yields. Other similar one-carbon bisnucleophiles, such as α-cyano ester, malononitrile, α-nitril ketones, 1,3-dicarbonyl compounds, as well as heteroatomatic bisnucleophile, such as tosyl amide, could also be employed in the [4+1] annulations, albeit the 2,5-dihydropyrrole 103i was obtained in a much lower yield (22%) when tosyl amide (TsNH₂) was utilized. N-Ts hydrazide 104 could also serve as a type of two-atomic 1,2-bisnucleophiles, participating in analogous [4+2] annulation with 2-(acetoxyethyl)buta-2,3-dienoate 102a to produce the corresponding tetrahydropyridazine derivative 105 in 81% yield.

Scheme 30. Phosphine-catalyzed [4C+X] annulations of 1,4-biselectrophiles [71].
Taking the [4+1] annulation of 2-(acetoxymethyl)buta-2,3-dienoate 102a with 3-oxo-phenyl-propanenitrile 101a as an example, the proposed mechanism was as depicted in Scheme 31. Firstly, nucleophilic addition of PPh3 to 2-(acetoxymethyl)buta-2,3-dienoate 102a formed the zwitterionic intermediate 106, whose negative charge on the α-position promoted a subsequent 1,2-elimination of an acetate anion (AcO\textsuperscript{-}) to generate the 1,4-biselectrophilic intermediate 107. Then, after deprotonation by the base, the 1,1-bisnucleophile 101a became a carbanionic intermediate 108, which attacked the γ-carbon of 1,4-biselectrophilic intermediate 107 to provide phosphonium ylide 109. Thirdly, the original α-position of 1,4-bisnucleophile underwent a deprotonation again via intramolecular proton shift and thus resulted in the formation of intermediate 110. Finally, conjugate addition and recycling of the phosphine catalyst furnished the [4+1] cycloadduct 103a.

Scheme 31. Proposed mechanism for the [4+1] annulation1,4-biselectrophiles [71].

In 2014, highly enantioselective [4+1] annulation of the 1,4-biselectrophiles with pyrazolone 111 was realized by the group of Lu for the first time (Scheme 32) [72]. L-threonine-derived O-silylated bifunctional phosphine catalyst TP-14 was the optimal catalyst to promote the expected [4+1] annulation reaction to generate a series of chiral spiropyrazolones 112 that have potential biological activity in good yields with good to high enantioselectivities.

Scheme 32. Asymmetric synthesis of functionalized spiropyrazolones [72].
Almost at the same time, the asymmetric [4+1] annulations of \( \beta' \)-acetoxy allenoates were reported by Fu and co-workers (Scheme 33) [73]. The biphenyl-derived axially chiral phosphine was used as the catalyst and a wide array of \( \alpha \)-cyano compounds, such as \( \alpha \)-cyano ketones, amides, esters, sulfones, phosphine oxides and phosphonates, were employed as the nucleophiles. A wide variety of functionalized cyclopentenes 103 bearing non-spirocyclic, fully substituted stereocenters (either all-carbon or heteroatom-substituted (sulfur and phosphorus)) were assembled in high yields with good to high enantiomeric excesses. Cyclopentenes bearing two consecutive stereocenters could also be generated under the catalytic system in good stereoselectivities when \( \beta' \)- or \( \gamma \)-substituted \( \beta' \)-acetoxy allenoates were employed (Scheme 34). Furthermore, a mechanistic study revealed that the turnover-limiting step occurs after the addition of the chiral phosphine to the allenoate, and likely after the addition of the second coupling partner as well.

![Scheme 33. Enantioselective [4+1] annulations to synthesize functionalized cyclopentenes [73].](image)

| Entry | Phos Cat. | E         | Yield (%) | Ee (%) |
|-------|-----------|-----------|-----------|--------|
| 1     | TP-15     | Ph        | 85        | 94     |
| 2     | TP-15     | 2-thienyl | 88        | 90     |
| 3     | TP-15     | NPh₂      | 93        | 91     |
| 4     | TP-15     | OMe       | 61        | 82     |
| 5     | TP-16     | SO₂\(^\text{Bu}^\) | 97        | 94     |
| 6     | TP-16     | PO\(\text{Ph}_2\) | 86        | 84     |
| 7     | TP-16     | PO\(\text{OPh}_2\) | 88        | 87     |

Scheme 34. Enantioselective [4+1] annulations to synthesize functionalized cyclopentenes with two consecutive stereocenters [73].

One example of [4+1] cycloaddition of 2-(acetoxyethyl)buta-2,3-dienoate 102 with nitrogen nucleophile (TsNH₂) was reported in Tong’s work, but the reaction afforded an achiral 2,5-dihydropyrrole 103i in low yield (Scheme 30) [71]. In 2015, the group of Fu disclosed an asymmetric
[4+1] cycloaddition of γ-substituted 2-(acetoxymethyl)buta-2,3-dienoate 102 with sulfonamides (Scheme 35) [74]. With the aid of a novel chiral spirophosphine catalyst TP-17, they achieved the objectives for constructing an array of enantioenriched 2,5-dihydropyrrole products 120 in high yields (67–95%) with excellent enantioselectivities (83–93% ee) in which the newly formed stereocenter emanated from the γ-carbon of the racemic allenes 119. Control experiments proved that both β'- and γ-addition pathways were feasible when the sulfonamide 118 coupled with the 1,4-biselectrophilic intermediates 121.

![Scheme 35. Enantioselective [4+1] annulations of amines with γ-substituted 2-(acetoxymethyl)buta-2,3-dienoate [74].](image)

In 2016, α-aminonitriles 124 were employed as C,N-bisnucleophiles to react with 2-(acetoxymethyl)buta-2,3-dienoates by Liao, Zhang and coworkers (Scheme 36) [75]. Under the catalysis of PPh3, the [4+2] cycloaddition of a wide range of α-aminonitriles 124 proceeded smoothly to furnish the corresponding poly-substituted tetrahydropyridines 125 which include a quaternary carbon stereocenter in moderate to good yields. Although a variety of α-aminonitriles were compatible in the annulation, reaction of N-Ts protected α-aminonitrile did not form the same [4+2] cycloadduct. Concerning the mechanism, the authors proposed a firstly γ-addition of the nucleophilic carbanion to the 1,4-biselectrophile before proton transfer and cyclization.

![Scheme 36. Phosphine-catalyzed [4+2] annulations of α-aminonitriles with 2-(acetoxymethyl)buta-2,3-dienoate [75].](image)

6. [4+2] Annulations of δ-Acetoxy Allenoates

In 2017, the group of Tong disclosed a novel type of phosphine-catalyzed, substrate-dependent [4+2] annulations of δ-acetoxy allenoates with ketones (Scheme 37) [76]. Under the optimized reaction
conditions (running the reaction in MeTHF at 80 °C with the use of PPhMe2 as the catalyst and tPr₂NEt as the base), the [4+2] cycloaditions of δ-acetoxy allenates 129 with 2-substituted cyclic 1,3-diones 130 mainly formed the functional group rich and structurally complex 1,3-cyclohexadiene compounds 131. However, δ-acetoxy allenates bearing an aryl group at the δ-position seemed unsuitable for the above [4+2] annulations, as reaction with the diketone 130 led to formation of a complex mixture under the same reaction conditions. With their continued efforts, soon after, they found that cyclic β-carbonyl amides 137 were suitable annulation partners to react with the allenates 129. Interestingly, with the use of PPh₃ as the catalyst and K₂CO₃ as the base when running the reaction in DCM at room temperature, reaction of the cyclic β-carbonyl amides 137 with δ-aryl-substituted δ-acetoxy allenates involved in a cascade “[4+2] annulation/cyclic imide formation” process, furnishing a novel array of structurally more complicated tricyclic products 138 in good yields (50–94%) (Scheme 38).

Scheme 37. Phosphine-catalyzed [4+2] annulations of δ-acetoxy allenates and cyclic β-carbonyl amides and related mechanisms [76].

Scheme 38. Phosphine-catalyzed [4+2] annulations of δ-acetoxy allenates and cyclic β-carbonyl amides [76].
With regard to mechanisms, initiation of the reaction was very similar to that of the \( \beta^\prime \)-acetoxy allenotes, that is, firstly cationic intermediate 132, which has been proven to be a good 1,4-biselectrophile toward annihilations with bisnucleophiles, was formed through an “addition—elimination” sequence. However, when 2-substituted cyclic 1,3-diones were utilized as the annihilation partner, nucleophilic addition of the corresponding carbanionic diketone intermediate 133 to the 1,4-biselectrophile 132 preferred \( \delta \)-addition, allowing for the formation of phosphonium intermediate 134 (Scheme 37, bottom). Then, intramolecular nucleophilic attacked of the \( \alpha \)-carbanion to the ketone afforded alkoxide intermediate 135. Intramolecular proton transfer and elimination of the phosphine catalyst ultimately led to the production of 1,3-cyclohexadiene cycloadduct 131.

In stark contrast, the enolate of cyclic \( \beta \)-carbonyl amides 139 preferentially attacked the \( \alpha \)-position of 1,4-biselectrophilic intermediate 132 to give the intermediate 140. Then, nucleophilic addition of the \( \delta \)-carbon anion to the ketone resulted in cyclization and the formation of alkoxide intermediate 141, which would abstract proton from the amide. Subsequently, the amide attacked the spatially adjacent ester and kicked away EtO\(^-\), resulting in the formation of cyclic imide 143. Finally, with the assistance of the released strong base EtO\(^-\), deprotonation, proton transfer and elimination of the phosphine catalyst successively happened, thus yielding the tricyclic 1,3-cyclohexadiene products 138 (Scheme 38, bottom).

Preliminary catalytic asymmetric investigation of the two types of [4+2] annihilations of \( \delta \)-acetoxy allenotes was also conducted, and the results indicated that approximately 45% ee were obtained for the two reactions at this stage (Scheme 39).

![Scheme 39](image)

Scheme 39. Asymmetric phosphine-catalyzed [4+2] annihilations of \( \delta \)-acetoxy allenotes [76].

7. [4+X] Annulations of Electron-Deficient 1,3-Dienes

In 2012, a novel phosphine-catalyzed asymmetric [4+1] annulation of MBH carbonates 145 with dicyano-2-methylenebut-3-enoates 144 was developed by Shi and coworkers (Scheme 40) [77]. Catalyst screening and reaction conditions optimization revealed that the multifunctional chiral phosphine catalyst TP-18 bearing an axially chiral binaphthyl scaffold was the most effective catalyst when the reaction was conducted in toluene at room temperature with 4 Å MS as the additive. A wide array of highly functionalized cyclopentenes 146 bearing an all-carbon quaternary stereogenic center was efficiently synthesized in moderate to good yields with excellent enantioselectivities. Based on previous correlative research works, a plausible reaction mechanism was proposed as: initially, an addition–elimination–deprotonation sequential processes resulted in the formation the 1,1-dipolar (or 1,3-dipolar in other transformations) phosphonium ylide 147; conjugate addition of phosphorus ylide 147 to the activated 1,3-dienes 144 at the C\(_1\)-terminal position furnished intermediate 148; then, a consecutive proton transfer took place to cause alkene isomerization; and, finally, an intramolecular Michael addition followed by elimination of the phosphine catalyst gave rise to the [4+1] cycloadduct 146.
Although Diels–Alder reaction are prevalent methods to assemble six-membered cyclohexenes, the sensitivity to steric hindrance and the strict requisite for proper electron-property usually limited the application. Delightedly, triphosphine initiated dipolar cycloadditions can supplement its deficiency. In 2018, Zhang’s group firstly developed a phosphine-catalyzed [4+2] annulation of electron-deficient diene with the alkyl vinyl ketone that hardly occur in Diels–Alder reactions (Scheme 41) [78]. The [4+2] cycloaddition of a series of β,δ-diaryl-substituted electron-deficient dienes 151 with alkyl vinyl ketones 150 were carried out in THF at room temperature with the use of Ph₂PMe (10 mol%) as the catalyst, which proceeded smoothly to produce functionalized cyclohexenes 152 in moderate to good yields with excellent diastereoselectivities. However, β-alkyl-substituted electron-deficient dienes and other electron-deficient olefins except alkyl vinyl ketone, such as acrolein and phenyl ketone, were incompatible in the [4+2] cycloadditions. Preliminary catalytic asymmetric investigation revealed that the use of Peng-Phos (TP-19) developed by their group afforded the chiral product 152a in 70% yield with 75% ee.

Scheme 40. [4+1] annulation of electron-deficient 1,3-diene with MBH carbonates [77].

Scheme 41. [4+2] annulation of electron-deficient 1,3-diene with alkyl vinyl ketone [78].
8. [4+2] Spiroannulations of Cyclobutenones

In 2015, the group of Zhang firstly exploited cyclobutenones as a novel type of 1,4-dipolar precursor in phosphine catalysis (Scheme 42) [79]. Under the catalysis of phenylanine-derived LB-BA bifunctional chiral phosphine catalyst TP-20, the enantioselective 1,4-dipolar spiroannulations of cyclobutenones 153 with isatylidenemalononitriles 60 produced the enantioenriched 3-spiro-cyclohexenone-2-oxindoles 154 in good to excellent yields with up to 87% ee. Generally speaking, the organo-phosphine catalyzed reaction processes were usually initiated by the conjugate addition of the strong nucleophilic but weak basic phosphine atom to the C-C multiple bonds, such as alkenes, allenes and alkynes, but Zhang and coworkers proposed another unique and unclassical activation mode, that is, the nucleophilic phosphine catalyst initially chemoselectively attacked the carbonyl group of cyclobutenones to entice the reaction. The subsequently formed oxygen anion of intermediate 155 promoted C-C single bond activation and cleavage of the small ring to furnish a novel type of vinyl-enolate-based 1,4-dipoles 156 and 157. Nucleophilic addition of the 1,4-dipoles to the isatylidenemalononitrile 60 formed intermediate 158. Finally, cyclization accompanied with the regeneration of phosphine catalyst produced the spirocyclic products 154.

![Scheme 42. Enantioselective [4+2] cycloaddition of cyclobutenones with isatylidenemalononitriles [79].](image)

9. Other Miscellaneous [4C+X] Annulations

Usually, allenoates serve as C₂ or C₃ synthons in the phosphine-catalyzed cycloadditions, but in 2005, Kwon and coworkers demonstrated that the reaction of allenoates with aldehydes could also proceed via [4+2] cycloaddition process when bulky trialkylphosphine catalysts were employed (Scheme 43) [80]. The subtlety of this unique chemoselectivity is that, when an allenoate was added by a phosphine catalyst, the use of sterically hindered trialkylphosphines, such as tricyclopentyl phosphine, facilitated the shift of equilibrium from the Z- toward E-isomeric zwitterionic intermediate to minimize the steric interaction between the phosphonium moiety and the ethoxy carbonyl group. Upon addition to the other aldehyde at the γ-carbon, the consequently formed alkoxide was in close proximity to the ester group, which would promote intramolecular nucleophilic attack of the alkoxide to the ester to furnish the lactone intermediate 166. The ejected ethoxide (EtO⁻) then acts as a base to abstract proton from the lactone intermediate, which subsequently induce a successive proton-transfer processes. Elimination of the triphosphine catalyst released the final 2-pyrone products 160.
In 2010, Shi, Wei and coworkers reported a highly enantioselective phosphine-catalyzed formal [4+2] tandem cyclizations between isatylidenemalononitriles 60 and 1,4-dien-3-one 169 to synthesize multi-stereogenic spirocyclic oxindoles 170 (Scheme 42) [79]. The LB-BA bifunctional chiral tertiary phosphine catalyst TP-21 derived from an axially chiral binaphthyl skeleton was able to achieve the asymmetric synthesis of the multi-stereogenic spirocyclic oxindoles 170 in high yields along with excellent enantioselectivities and diastereoselectivities. The whole reaction process progressed through a tandem “Rauhut–Currier/Michael/Rauhut–Currier” reaction sequence, where two molecules of 1,4-dien-3-one 169 were involved into the reaction and were embedded in the final product 170. Detailed reaction mechanism was proposed as below in Scheme 45: firstly, nucleophilic addition of the chiral phosphine catalyst TP-21 to the vinyl ketone 169 initiated the reaction. Then, the resulted zwitterionic intermediate 171 underwent a nucleophilic attack to the isatylidenemalonitrile to produce intermediate 172. Subsequently, an intramolecular Michael addition, followed by proton transfer and elimination of the phosphine catalyst, yielded the electronically neutral molecular intermediate 174. As the intermediate 174 still contained an activated C-C double bond, it was hard for reaction to cease at this step, thus, another Rauhut–Currier reaction took place in the presence of the active phosphine catalyst to give the cascade product 170.

Scheme 43. Phosphine-catalyzed [4+2] cycloaddition of allenoles with aldehydes [80].

Scheme 44. Asymmetric synthesis of functionalized spirocyclohexanoneoxindoles [81].
Scheme 45. Proposed mechanism for the [4+2] tandem cyclization of 1,4-dien-3-one with isatylidenemalononitriles [81].

Most recently, the group of Jiang developed an efficient, chiral phosphine-triggered synthetic route to access functionalized cyclohexenes via a cascade [4+2] cycloaddition/semipinacol-type rearrangement (Scheme 46) [82]. In the presence of (+)-Duanphos (TP-22), a series of 2-(acyl)but-2-enenitriles 176 were treated with MBH (Morita–Baylis–Hillman) carbonates 175 in DCE, affording the desired cyclohexene derivatives 177 in high levels of enantio- and diastereoselectivities (up to 98% ee and >20:1 dr). This reaction was initiated by the nucleophilic addition of the chiral phosphine catalyst to the MBH carbonates and a subsequent ejection of CO2 and tBuO– to give the phosphonium intermediate 178, which would be attacked by the incoming nucleophiles 179 that were deprotonated from the (E)-2-benzoyl-3-phenylbut-2-enenitriles 176. Subsequent cyclization via intramolecular nucleophilic addition to the ketones formed the six-membered zwitterionic intermediate 181. Finally, semipinacol-type sigmatropic 1,3-hydrogen shift occurred leading to ring-opening, which was followed by intramolecular SN2 substitution to regenerate the phosphine catalyst to complete the catalytic cycle and deliver the cyclohexene product 177.
In summary, with the continuous efforts to explore novel C₄ annulation partners in the area of phosphine catalysis, many types of substrates have been successfully introduced into the [4C+X] cycloadditions. Except electron-deficient dienes and cyclobutenones, almost all others types of substrates are based on the skeleton of allenenes, namely α-substituted allenoates, δ-substituted allenoates, α-methyl allene ketones, β'-acetoxy allenoates and δ-acetoxy allenoates. Despite these great studies together with the corresponding asymmetric [4C+X] annihilations have been performed, there is still much to be discovered. Except for α-substituted allenoates, there are very few types of [4C+X] annihilations based on the already known C₄ synthons. Searching for even more extensive suitable coupling partners to cyclize with them is always highly desirable. On the other hand, finding novel C₄ synthetic blocks and relevant novel annulation patterns as well as the development of the corresponding asymmetric catalytic forms are undoubtedly the permanent goals in this field due to its great efficiency to construct enantioenriched functionalized cyclic compounds. Meanwhile, some of the methodologies posed very obvious drawbacks, such as limited substrates compatibility and poor stereoselectivity, thus deep theoretical studies as well as appropriate catalyst design are also desired to address these issues. Nevertheless, with the increasing research interests thrown into the field of phosphine catalysis, we are confident that much more meaningful phosphine-catalyzed [4C+X] annihilations will spring up in the next decade. We especially expect wonderful applications of these methodologies into the synthesis of natural products or the preparations of biologically important molecules in the future.
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