Phosphine-triggered synthesis of functionalized cyclic compounds

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Nucleophilic phosphine catalysis has proven to be a powerful tool in organic synthesis, which can provide easy access to cyclic, bicyclic or polycyclic carbocycles and heterocycles. Owing to their comparatively strong and readily tunable nucleophilicity, phosphines can be easily tailored to efficient annulation reactions with good control over reaction selectivity. This has resulted in a tremendous increase in their scope and in a concomitant number of reports where phosphine-triggered annulation reactions occur. This *tutorial review* summarizes the recent achievements in this area.

1 Introduction

Efficient construction of highly functionalized carbocycles and heterocycles with a defined configuration is of significant importance in the synthesis of many natural products, pharmaceutically active products, perfumes and dyes.[1] Much effort has been devoted to this area of research, and cycloadditions such as the (hetero) Diels–Alder reaction, transition-metal-catalyzed ring-closing metathesis (RCM), and cycloisomerizations are already well established as powerful ring-forming tools.

Nucleophilic phosphine organocatalysis has also emerged as a versatile method for the synthesis of cyclic and heterocyclic compounds. Generally, tertiary phosphine-mediated annulations start *via* nucleophilic addition of phosphines to activated olefins, allenes and alkynes. The resultant zwitterionic intermediates react with electrophiles to furnish cyclic compounds. Based on this mechanistic insight, nucleophilic phosphine organocatalysis has the following important features: (1) the nucleophilicity of phosphines may be easily tuned by varying the substituents, ranging from the trialkylphosphines to aryl substitution, in order to obtain a suitable catalyst for a given reaction. Furthermore, both steric and electronic properties of the phosphines may be altered, which sometimes enables fine tuning of the reaction regioselectivity; (2) in addition to intramolecular annulation *via* pre-organized acyclic substrates, one-pot analogous intermolecular variants may be accomplished from easily available starting materials with high selectivity; (3) chiral acyclic and cyclic phosphine ligands are readily available for screening to tackle enantioselective synthesis; (4) another important aspect of this methodology is that it is completely free from contamination by heavy metals, which is an especially attractive feature for industrial synthesis.[2]

The employment of nucleophilic phosphine organocatalysis for ring construction can be traced back to Fráter's intramolecular Mortita–Baylis–Hillman to synthesize five- and six-membered carbocycles,[3] Trost's intramolecular γ-addition of oxygen nucleophiles to 2-alkynoates,[4] Lu's [3 + 2] annulation reaction[5] and the groups of Krische and Roush's independent intramolecular Rauhut–Currier reaction.[6] Inspired by the aforementioned pioneering work, this methodology received increasing attention and developed rapidly, especially in the asymmetric catalysis area where significant progress has been made. The aim of this review is to focus on the latest development of phosphine-catalyzed ring construction reactions since the comprehensive review on nucleophilic phosphine organocatalysis by Methot and Roush in 2004[7] and elucidate plausible mechanisms when necessary.

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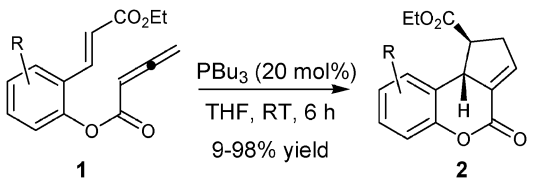
Yong Tang's current research interests are the development of new synthetic methodology, and the design and synthesis of olefin polymerization catalysts. Long-Wu Ye (left) is currently conducting PhD research in the group of Prof. Yong Tang (right) while Jian Zhou (middle) is now working as a postdoctoral fellow with Prof. Benjamin List at the Max-Planck-Institut für Kohlenforschung.

2 Annulation of allenes with electron-deficient alkenes

2.1 Intramolecular allene/alkene [3 + 2] cycloaddition

Phosphine-catalyzed [3 + 2] cycloaddition of allenoates with α,β-unsaturated carbonyl compounds has been established as a promising method for the preparation of a variety of carbocycles from readily available starting materials.[8] Pioneered by Lu, this annulation reaction has been successfully applied to synthesize some natural products.[9] Thorough mechanistic studies have been recently reported by Yu and by Kwon.[10] Especially, intramolecular versions of this process enable a facile construction of polycyclic compounds with exclusive regioselectivity.

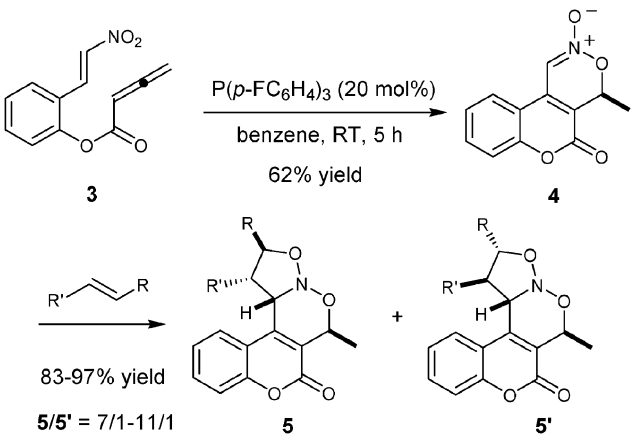


Scheme 1 Phosphine-catalyzed intramolecular [3 + 2] cycloaddition.

Recently, Kwon *et al*. reported an intramolecular variant of this [3 + 2] cycloaddition. For substrate **1**, the phosphine-catalyzed regio- and diastereo-selective [3 + 2] cycloadditions gave the cyclopentene-fused dihydrocoumarins **2** in good to excellent yields, providing a simple and efficient approach to the synthesis of structurally complex coumarins (Scheme 1).[11]

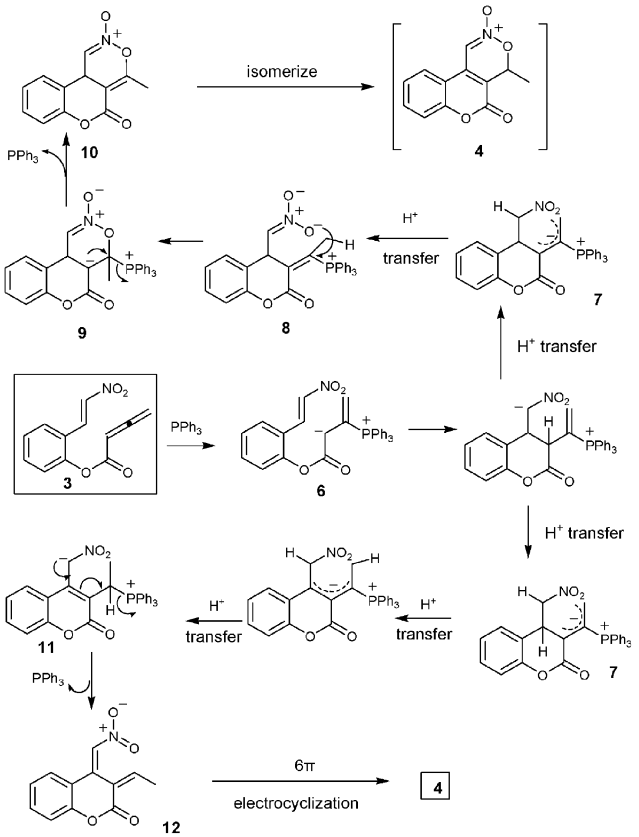
They also found that the reaction of 2-(2-nitrostrenyl) allenoate **3** in the presence of tris(*p*-fluorophenyl)phosphine in benzene led to the formation of the tricyclic nitronate **4** (Scheme 2), possibly through an unprecedented pathway. The thus formed nitronate **4** could undergo efficient face-, regio-, and exo-selective 1,3-dipolar cycloadditions with a number of dipolarophiles to provide tetracyclic coumarin derivatives **5** as shown in Scheme 2. Notably, *cis*-disubstituted alkenes were recalcitrant to this annulation reaction.

Based on the observation that no reaction takes place in the absence of phosphine, two possible mechanisms are proposed



Scheme 2 Phosphine-catalyzed synthesis of tetracyclic coumarin derivatives **5**.

involving phosphine as a catalyst. Nucleophilic addition of triphenylphosphine to allenoate **3** results in the formation of the zwitterionic intermediate **6**. An intramolecular Michael addition, followed by a proton transfer of the most acidic proton, yields the allylic anion **7**. 1,5-Proton transfer in **7** furnishes **8**, which undergoes 6-endo cyclization to form **9**. Then **9** is transformed to nitronate **10** and regenerates the phosphine catalyst. **10** further isomerizes to the final product nitronate **4**. The other possible pathway differs from the above one in that, intermediate **11** formed from **7** *via* 1,4-proton transfer generates nitrodiene **12** and releases catalyst. Finally, 6π electrocyclic ring closure of nitrodiene **12** provides the final product **4** (Scheme 3).



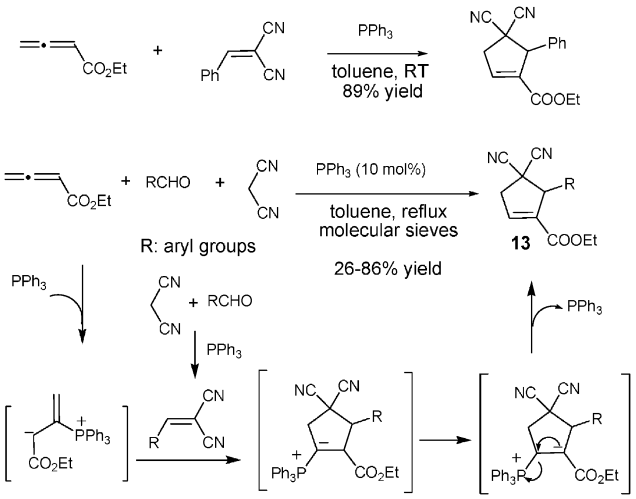
Scheme 3 Mechanistic proposal for the formation of **4**.

Interestingly, Krische reported an elegant phosphine-mediated intramolecular heteroaromatization reaction, leading to multisubstituted furans.[8g]

2.2 Intermolecular allene/alkene [3 + 2] cycloaddition

Unlike the intramolecular counterpart, intermolecular annulation of allenoates with terminal electron-deficient alkenes generally furnishes a mixture of regioisomeric cyclopentenes.[12] Furthermore, β-substituted olefins are rarely employed except double-activated olefins such as diethyl fumarate and diethyl maleate. To address this problem, Lu *et al*. recently examined β-substituted olefins with two electron-withdrawing groups at the α-olefin carbon atom, and found that the reaction worked well and afforded one regioisomer exclusively in excellent

yield.[13] Considering that PPh_3 could also promote a Knoevenagel condensation, they also developed an elegant one-pot three-component annulation reaction from aryl aldehydes, malononitrile and ethyl 2,3-butadienoate, as shown in Scheme 4.

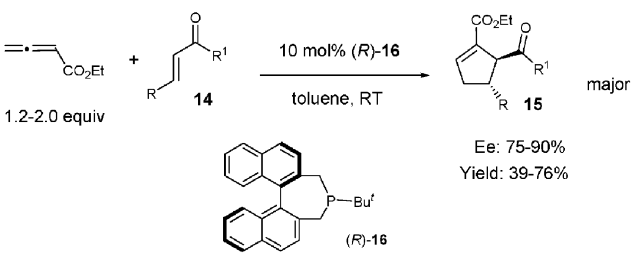


Scheme 4 Phosphine-catalyzed one-pot synthesis of cyclopentenes **13**.

Yamamoto *et al*. also documented a remarkable phosphine-mediated condensation of activated alkynes with isocyanides. This intermolecular [3 + 2] cycloaddition protocol provides an easy access to substituted pyrroles.[8f]

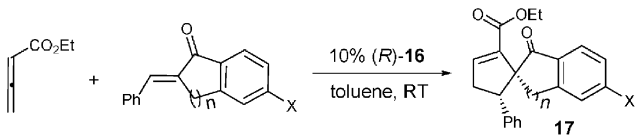
2.3 Asymmetric allene/alkene [3 + 2] cycloaddition

Pioneering work of catalytic asymmetric of Lu's [3 + 2] cycloaddition of allenes with olefins was reported by Zhang in 1997.[14] Although good enantioselectivity has been achieved, the range of olefins is limited to unsubstituted acrylate esters and diethyl maleate. Recently, Fu and co-workers re-examined this reaction using phosphine (*R*)-**16**. With this aid, the scope of activated olefins was broadened to include α,β-unsaturated enones **14**, and functionalized cyclopentenes **15** were obtained in high enantioselectivity (Scheme 5).[15]



Scheme 5 Chiral phosphine-catalyzed annulation of allenes with enones **14**.

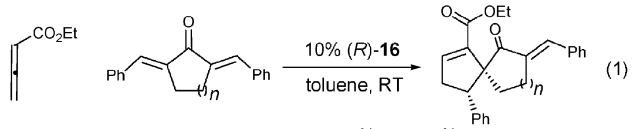
These chiral phosphine-catalyzed annulation reactions could also furnish spirocyclic compounds **17** with adjacent quaternary and tertiary stereocenters.[15] The structure of the trisubstituted enones is found to influence the reaction efficiency. For example, cycloaddition of an indanone proceeded in excellent yield with high enantioselectivity, while the reaction of a closely related tetralone was considerably less efficient but highly enantioselective (Scheme 6).



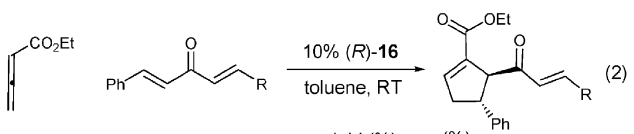
n	X	yield (%)	*ee* (%)
1	Br	97	89
2	H	32	95

Scheme 6 Chiral phosphine-catalyzed synthesis of spirocyclic compounds **17**.

Moreover, Fu *et al*. found that dienones are also suitable substrates. Notably, only one regioisomer was observed in this annulation. Interestingly, phosphepine **16** could achieve enantioselective cycloadditions with complete site selectivity for unsymmetrical compounds **18b** (Scheme 7).



n	yield (%)	*ee* (%)
1	81	89
2	57	93

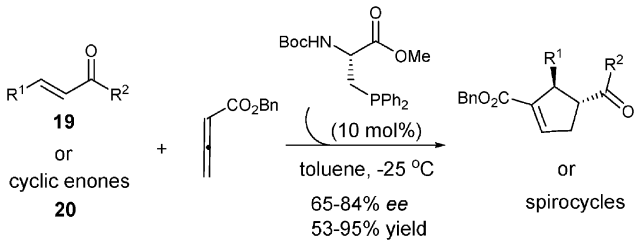


	R	yield (%)	*ee* (%)
18a	Ph	75	89
18b	2,6-dichlorophenyl	68	73

Scheme 7 Chiral phosphine-catalyzed annulation of allenes with dienones.

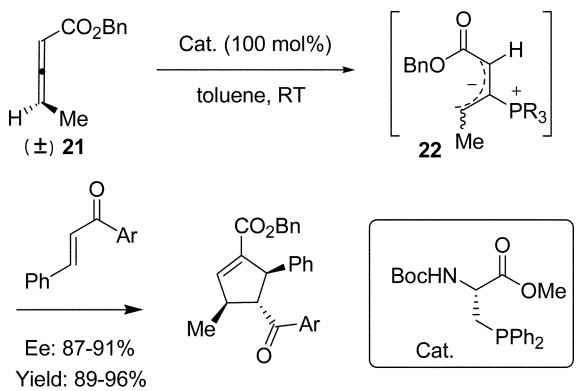
Although chirality at the phosphine atom of the catalyst was expected to be capable of a direct and strong influence on the stereochemical outcome of nucleophilic phosphine-catalyzed processes, it is not a prerequisite. Fu's report showed that axial chirality adjacent to the phosphine center could induce high enantioselectivity. Very recently, Cowen and Miller also demonstrated that a chiral center separated by a methylene group from the phosphine atom, could still achieve high enantiofacial control. They described a protected, multifunctional phosphine-containing α-amino acid catalyzed asymmetric [3 + 2] cycloaddition of allenes with enones **19** and cyclic enones **20**. Under optimized reaction conditions, this novel chiral phosphine-catalyzed annulation could furnish functionalized cyclopentenes and the corresponding spirocycles, respectively, with high diastereoselectivity and enantioselectivity (Scheme 8).[16]

Based on the fact that the addition of a phosphine to an allene will form adducts, such as **22** which erases the element



Scheme 8 Protected, multifunctional phosphine-catalyzed annulation of allenes with enones.

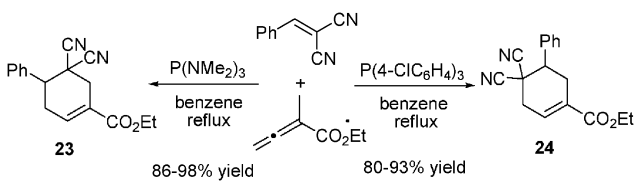
of planar chirality, Miller and his co-workers[16] developed a "dynamic kinetic asymmetric transformation" using γ-substituted racemic allene substrates. They found that a stoichiometric amount of the catalyst could promote the reaction to full conversion, affording highly substituted cycloadducts in excellent yields as single regio- and dia-stereomers. On decreasing catalyst loading to 20 mol%, the reaction was greatly slowed down but the high enantioselectivity was retained. These examples constitute unique cases of allenoate deracemizations *via* chiral phosphine-catalyzed [3 + 2] cycloadditions (Scheme 9).



Scheme 9 Protected multifunctional phosphine-catalyzed annulation of allenes **21** with chalcones.

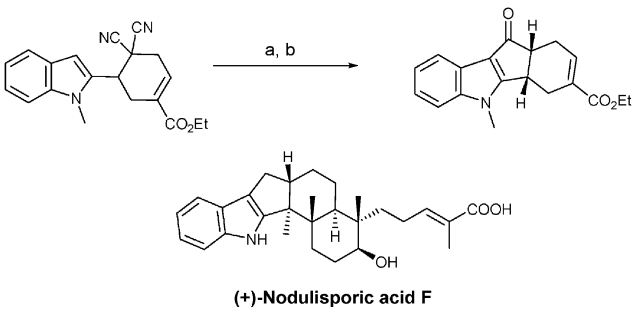
2.4 Intermolecular allene/alkene [4 + 2] cycloaddition

Compared with [3 + 2] annulation of allenes and activated alkenes, [4 + 2] annulation is less developed. Very recently, the Kwon group successfully utilized nucleophilic phosphine catalysis for the highly regioselective synthesis of cyclohexenes from activated allenes and alkenes *via* intermolecular [4 + 2] annulation (Scheme 10).[17] An interesting finding in this work is that changing substitutents in the phosphines leads to complete regioselectivity control while the use of hexamethylphosphorus(III) triamide (HMPT) exclusively afforded cyclohexenes **23**, and the more electron-deficient (4-$ClC_6H_4)_3P$ gave cyclohexenes **24**. This finding further demonstrated one of the versatilities of nucleophilic phosphine catalysis: namely the easily varied donor capacity for the control of reaction selectivity.



Scheme 10 Phosphine-catalyzed [4 + 2] annulation for the synthesis of cyclohexenes.

The potential utility of this [4 + 2] annulation was demonstrated by the construction of the tetracyclic framework of biologically active natural nodulisporic acid F as depicted in Scheme 11.[17]

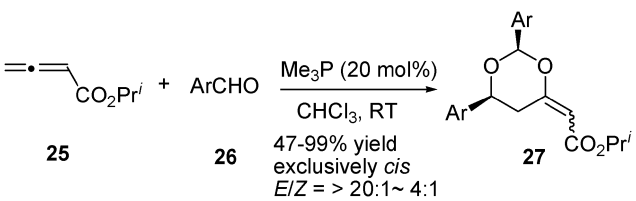


Scheme 11 Potential application of allene/alkene [4 + 2] cycloaddition.

3 Annulation of allenes with aldehydes and imines

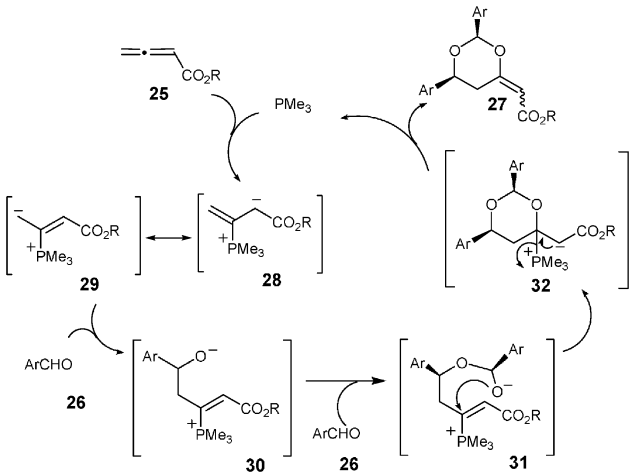
3.1 Annulation of allenes with aldehydes

Despite the abundance of coupling reactions between allenes and various electrophiles under nucleophilic catalysis, the employment of aldehydes as substrates in [3 + 2] annulation was reported for the first time in 2005. Kwon and co-workers demonstrated that allenoate **25** and aldehyde **26**, in the presence of 20 mol% Me_3P, can afford the (2,6-diaryl[1,3]dioxan-4-ylidene)acetates **27** in moderate to excellent yields with complete diastereoselectivity and high *E*/*Z*-selectivities (Scheme 12).[18]



Scheme 12 Phosphine-catalyzed synthesis of 1,3-dioxan-4-ylidenes **27**.

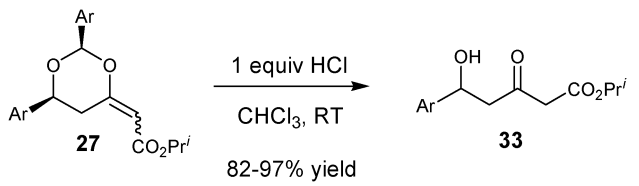
Kown *et al.* gave a plausible mechanism for the formation of compounds **27**, as shown in Scheme 13. γ-Addition of the vinylphosphonium salt **29** to an aldehyde results in the formation of **30**. Adduct **30** incorporates another equivalent of aldehyde to produce **31**. An intramolecular Michael addition, followed by a β-elimination of trimethylphosphine, completes the catalytic cycle. The overall reaction is reminiscent of the reported three-component Baylis–Hillman reaction in which



Scheme 13 Proposed mechanism for the formation of compounds **27**.

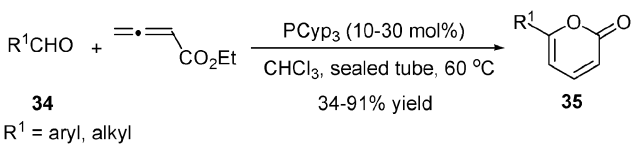
the coupling of 2 equivalents of aldehyde and 1 equivalent of acrylate afforded 5-methylene-1,3-dioxan-4-ones.[19]

When dioxanylidenes **27** were treated with 1 equivalent of HCl, δ-hydroxy-β-ketoesters **33** were obtained in 82–97% yield (Scheme 14). As a result, allenoate could be regarded as a masked precursor for the acetoacetate unit, providing an alternative to construct ubiquitous δ-hydroxy-β-ketoesters.

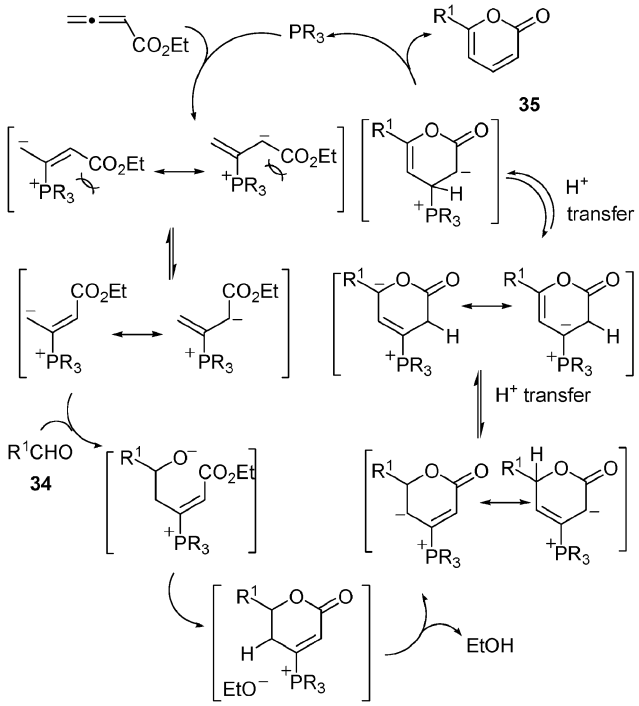


Scheme 14 Acid-mediated synthesis of δ-hydroxy-β-ketoesters **33**.

The formation of *Z*-isomeric zwitterionic intermediate **29** ↔ **28**, as shown in Scheme 13, is crucial for the formation of product **27**, because the *in situ* generated alkoxide **30** could not undergo an intramolecular lactonization due to the disfavoured geometry. On the contrary, the formation of *E*-isomeric zwitterionic intermediate should favour the synthesis of pyrones *via* the intramolecular lactonization. Based on this analysis, Kwon and co-workers further developed a one-step synthesis of 6-substituted 2-pyrones from one equivalent of aldehydes and allenoate. It was found that the use of the bulky tricyclopentylphosphine favoured the formation of the *E*-isomeric zwitterionic intermediate shown in Scheme 16, and thus readily transformed to pyrone **35**. They found that various aromatic as well as aliphatic aldehydes underwent the transformation in moderate to excellent yields (Scheme 15).[20]



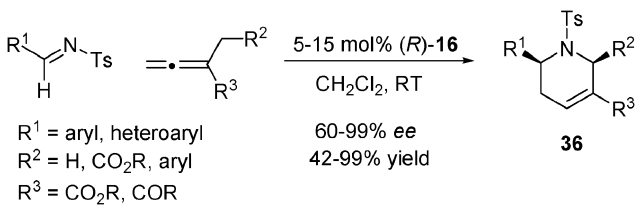
Scheme 15 Phosphine-catalyzed synthesis of 6-substituted 2-pyrones **35**.



Scheme 16 Mechanistic proposal for the formation of **35**.

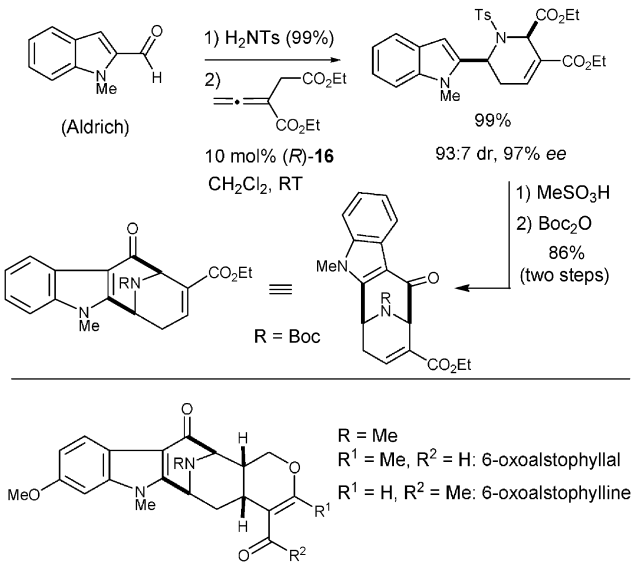
3.2 Annulation of allenes with imines using chiral phosphines

Phosphine-catalyzed annulation between allenes and imines readily afforded highly valuable functionalized pyrrolines and piperidines.[21] The [4 + 2] annulation of allenes with imines to afford piperidines was first reported by Kwon and co-workers in 2003,[22] and has been applied successfully for the synthesis of indole alkaloids[21b] and a potent inhibitors of the protein geranylgeranyltransferase type I (GGTase-I).[21a] Later on, Fu *et al*. developed it into a highly enantioselective version using binaphthyl-based C_2-symmetric phosphepines (*R*)-**16**. The enantioselectivity of this annulation was independent of amine structures, and all the aromatic imines afforded excellent enantioselectivity. However, the allene substituent influenced the enantioselectivity, that is only allenes bearing an R^2 group that can stabilize an anion (*e.g.*, carbonyl or aryl) work well, whereas the unsubstituted allene (R^2 = H) could only achieve moderate enantioselectivity (Scheme 17).[23]



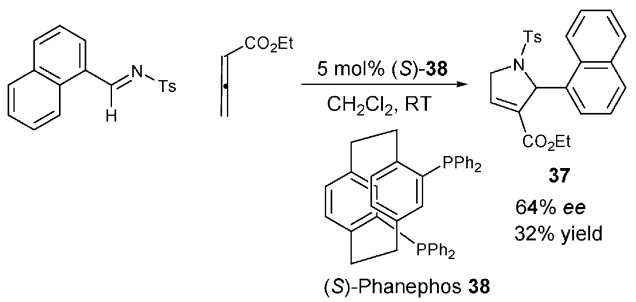
Scheme 17 Chiral phosphine-catalyzed annulation of allenes with imines.

The utility of this method was demonstrated by facile transformation of the product to a framework common to some important natural products (Scheme 18).



Scheme 18 Potential application to the synthesis of an array of important natural products.

The [3 + 2] annulation of allenes with *N*-tosylimines was first reported by Xu and Lu.[24] Jean and Marinetti recently systematically screened commercially available phosphines in the cycloaddition reaction between 2,3-butadienoates and arylimines. They found that 2-aryl-3-pyrrolines **37** could be obtained with enantiomeric excesses up to 64%, using (*S*) phanephos **38** as a catalyst (Scheme 19).[25]



Scheme 19 Chiral phosphine-catalyzed annulation of 2,3-butadienoates with imines.

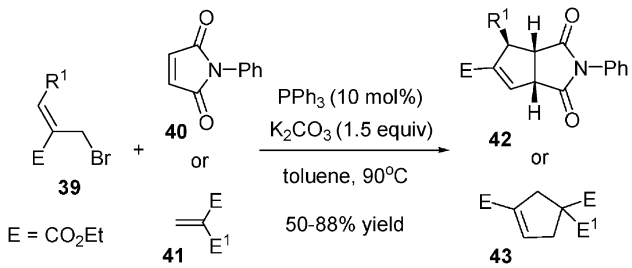
It seems that the specific use of phosphines as nucleophilic catalysts was required for this annulation, because when nucleophilic amine catalysts such as DMAP and DABCO were used, the same starting materials afforded either azetidines or dihydropyridine derivatives, respectively.[26] This further demonstrated the difference between nucleophilic amine catalysis and phosphine catalysis.

4 Formal [3 + 2] and [3 + 6] ylide cycloaddition reactions

4.1 Formal [3 + 2] ylide cycloaddition reactions

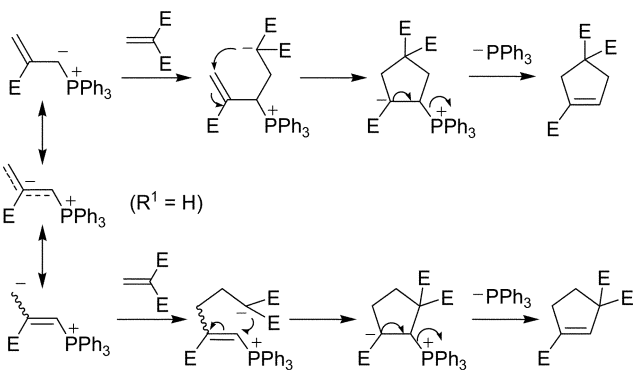
As shown in the previous examples, a phosphorus ylide intermediate might be involved in the nucleophilic phosphine-catalyzed [3 + 2] cycloadditions of electron-deficient allenes, which can also be expected in phosphine catalyzed isomerizations, α and γ-additions. Therefore, a phosphine-catalyzed annulation reaction might be realized with a modified allylic phosphorus ylide with electron-deficient alkenes.

Lu and co-workers reported the first phosphine-catalyzed allylic ylide annulation reaction. In the presence of a catalytic amount of PPh_3, [3 + 2] cycloaddition reactions of modified allylic compounds **39** with dually activated olefins **40** and **41** afford different cyclopentenes **42** and **43**, respectively, in moderate to good yields with high diastereoselectivity (Scheme 20).[27]



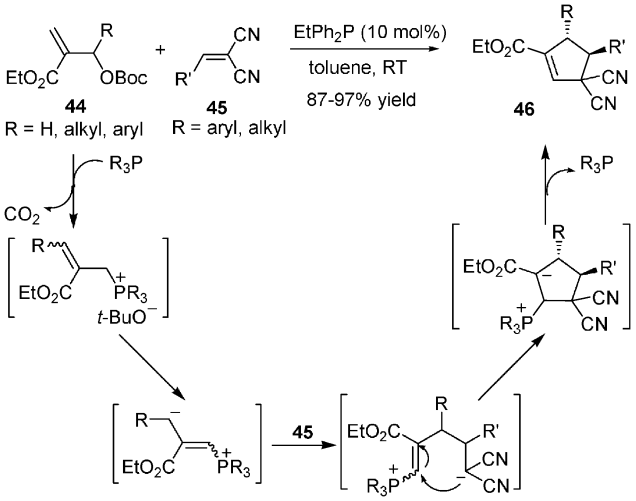
Scheme 20 Phosphine-catalyzed ylide annulation reaction of allylic bromide **39** with dually activated olefins **40** and **41**.

The authors gave the following rationalization to explain this ylide annulation. Triphenylphosphine reacts with bromide **39** to form a phosphonium salt, which is deprotonated by K_2CO_3 to generate the corresponding phosphonium ylide *in situ*. A Michael addition of the ylide, followed by another intramolecular Michael addition of phosphonium salt and then β-elimination of triphenylphosphine, completes the catalytic cycle (Scheme 21). The formation of the two isomers can be explained by α- or γ-attack of ylide to dually activated olefins **41**. Of course, the possibility of migration of the double bond in cyclopentene products under the reaction conditions cannot be excluded.



Scheme 21 Proposed mechanism of the phosphine-catalyzed ylide annulation reaction.

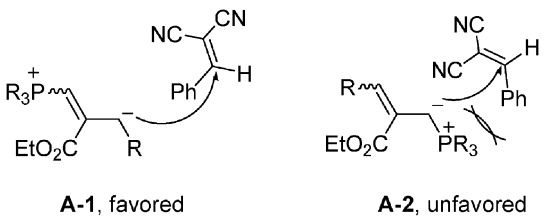
Subsequently, Lu and co-workers extended the allylic ylide annulation reaction to 2-substituted 1,1-dicyanoalkene substrates. In the presence of 10 mol% $EtPh_2P$, the reaction of allylic carbonate **44** with 2-substituted 1,1-dicyanoalkenes **45** furnished various cyclopentenes **46** in excellent yields with high stereoselectivity in most cases (Scheme 22).[28] The use of Boc-substituted substrate **44** obviates the use of K_2CO_3,



Scheme 22 Phosphine-catalyzed ylide annulation reaction of allylic carbonate **44** with 2-substituted 1,1-dicyanoalkenes **45**.

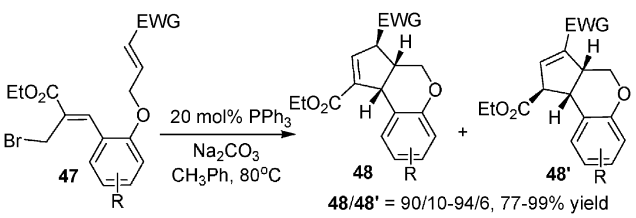
because the *in situ* generated *tert*-butoxide anion contributes to the formation of ylide.

The regioselectivity is different from the [3 + 2] annulation of allenoates and 2-substituted 1,1-dicyanoalkenes shown in Scheme 4, probably owning to the fact that addition of the α-position of the ylide **A-2** to **45** was unfavorable due to the steric hindrance of the bulky phosphine group and the substituents at the 2-position of **45** (Scheme 23).



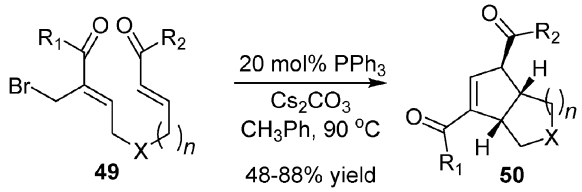
Scheme 23 Regioselectively favored reaction path.

Very recently, Tang and co-workers developed an intramolecular formal [3 + 2] cycloaddition reaction. In the presence of 20 mol% of PPh_3 and 1.5 equiv of Na_2CO_3 and using toluene as solvent at 80 °C, the reaction of preorganized acyclic bromides **47** furnished the benzobicyclo[4.3.0] compounds **48** and **48′** with excellent diastereoselectivities in good to excellent yields (Scheme 24).[29]



Scheme 24 Intramolecular phosphine-catalyzed ylide annulation reaction of aromatic substrates **47**.

In addition, aliphatic substrates **49** also gave the corresponding bicyclo[3.3.0] compounds **50** with high diastereoselectivities in moderate to good yields, which complements the excellent methodology for the synthesis of bicyclo[3.3.0] ring

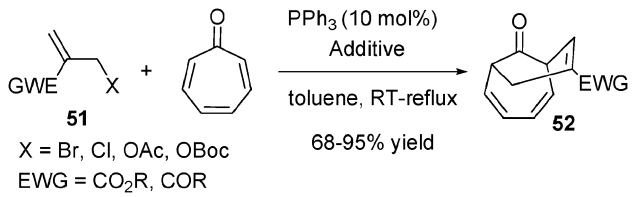


Scheme 25 Intramolecular phosphine-catalyzed ylide annulation reaction of aliphatic substrates **49**.

compounds developed by Krische and co-workers (Scheme 25).[30]

4.2 Formal [3 + 6] ylide cycloaddition reactions

Besides electron-deficient olefins, Lu and co-workers also examined other kinds of dipolarophiles in phosphine-catalyzed allylic ylide annulation. Recently, they reported that tropone worked well with allylic compounds **51**, including acetates, bromides, chlorides, and *tert*-butyl carbonates derived from Morita–Baylis–Hillman (MBH) reactions, to yield formal [3 + 6] annulation products **52** in excellent yields (Scheme 26).[31] This novel ylide annulation offers a simple and convenient method for the construction of bridged nine-membered carbocycles.

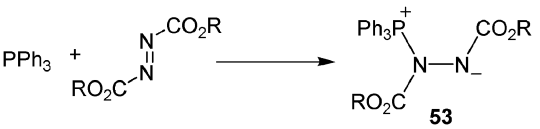


Scheme 26 Phosphine-catalyzed [3 + 6] annulation reaction of modified allylic compounds **51** and tropone.

It should be pointed out that under the catalysis of Ph_3P, tropone prefers to react with allenic ketones/esters in a [2 + 8] cycloaddition manner, and the [3 + 6] cycloadducts could only be isolated as a minor product in the case of allenic ester.[32] In this light, from the same dipolarophile tropone, one can easily control the reaction pathway ([2 + 8] *vs.* [3 + 6]) to obtain different cyclic compounds, by changing the way to prepare the allylic ylide (nucleophilic addition of phosphine to allenic ketone and esters *vs.* nucleophilic attack of phosphine to allylic compounds).

5 Annulations *via* the "Huisgen Zwitterion"

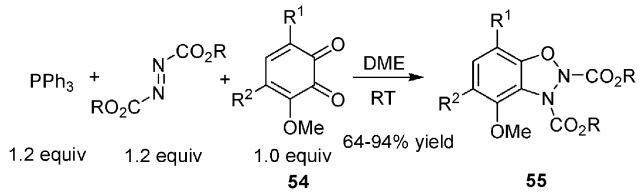
Phosphines are known to readily react with azodicarboxylates to afford the zwitterion **53** (eqn (1)), and the nucleophilic reactivity of the latter was established by Huisgen *et al.*[33] Although this zwitterion **53** was recognized as the nucleophilic trigger in the Mitsunobu reaction,[34] it received limited attention.[35] Recently, it was systematically studied by Nair's group, which led to fruitful construction of heterocyclic compounds.



(1)

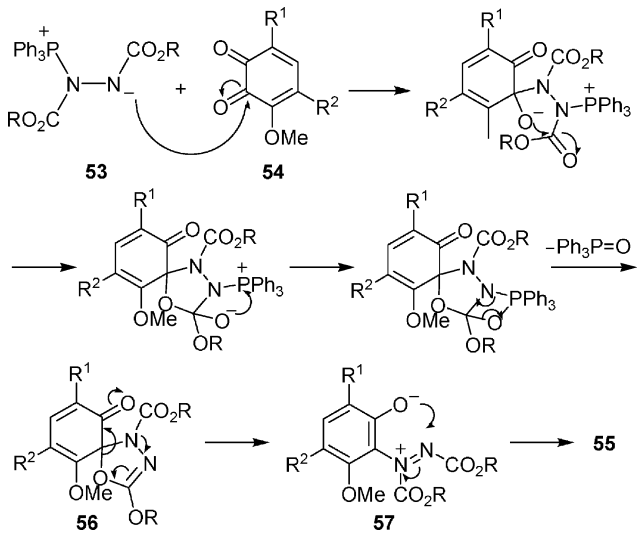
5.1 Annulation of phosphine-DIAD with 1,2-benzoquinone and isatins

In 2005, Nair *et al*. reported that in the presence of 1.2 equiv. of triphenylphosphine, the reaction of diisopropyl azodicarboxylate (DIAD) with 1,2-benzoquinone **54** could afford dihydro-1,2,3-benzoxadiazole **55** in moderate to good yields (Scheme 27). The product **55** could be transformed to hydrazino phenols by hydrogenolysis using Pd/C.[36]



Scheme 27 Phosphine-mediated annulation of DEAD with quinones **54**.

The authors rationalize the reaction by the following mechanism. The Huisgen zwitterion **53** formed from triphenylphosphine and the diisopropyl azoester could add to the quinone carbonyl group to give the spirooxadiazoline **56**, with the elimination of triphenylphosphine oxide in a process resembling the Wittig reaction. This spirooxadiazoline then transforms to the final product (Scheme 28).

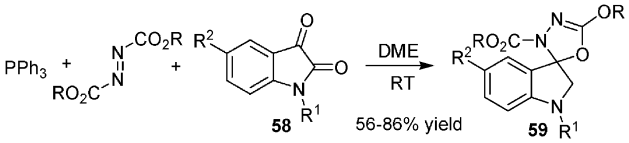


Scheme 28 Mechanistic proposal for the reaction of Huisgen zwitterion **53** with quinones **54**.

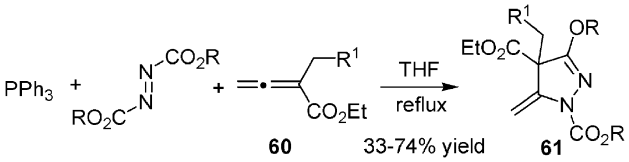
The same reaction can also be extended to *N*-substituted isatins **58**, which react with Huisgen zwitterion **53** to afford spiro-oxadiazoles **59** in moderate to good yields (Scheme 29).

5.2 Annulation of phosphine-DIAD with allene esters

Subsequently, Nair *et al*. further demonstrated that the reaction of Huisgen zwitterion **53** with allenic esters **60** could afford highly functionalized pyrazoles **61** in moderate to good yields (Scheme 30).[37]

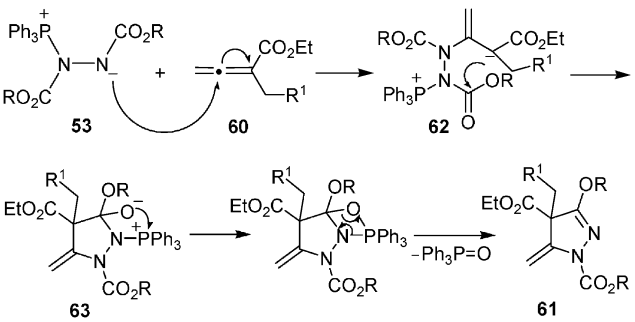


Scheme 29 Phosphine-mediated annulation of DEAD with isatins **58**.



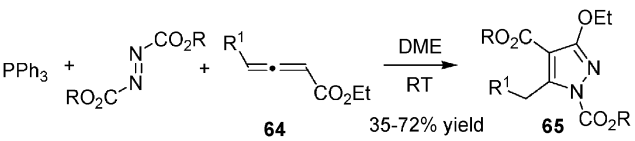
Scheme 30 Phosphine-mediated annulation of DEAD with allenic esters **60**.

The possible mechanism of this reaction is rationalized as in Scheme 31. Huisgen zwitterion **53** could add to the electron-deficient double bond of the allenic ester to give a tetrahedral intermediate **62**, which gives the functionalized pyrazole **61**, presumably by elimination of triphenylphosphine oxide *via* a process resembling the Wittig reaction.



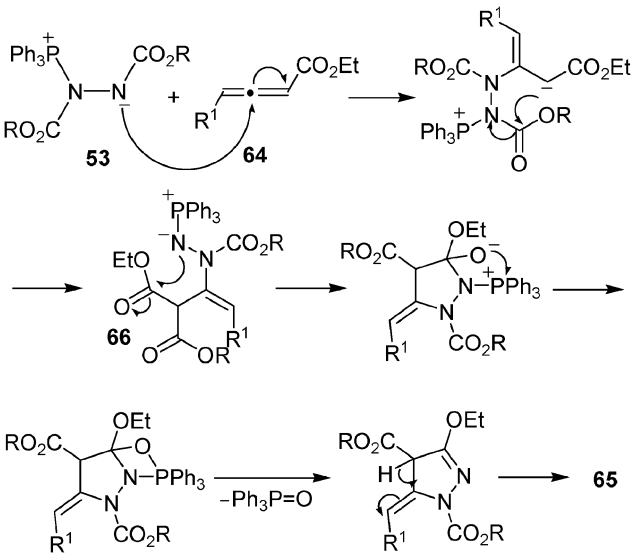
Scheme 31 Mechanistic proposal for the reaction of the Huisgen zwitterion with allenic esters **60**.

Interestingly, 3-substituted allenoates **64** could also react with Huisgen zwitterion **53** to furnish highly functionalized pyrazole derivatives **65**, which are often found useful as pharmaceuticals and agrochemicals (Scheme 32).



Scheme 32 Phosphine-mediated annulation of DEAD with allenic esters **64**.

Here it should be especially mentioned that the novel nitrogen to carbon migration of the ester group is the key step in this annulation. Huisgen zwitterion **53** adds to the electron-deficient double bond of the allenic ester to give a tetrahedral intermediate, which undergoes a nucleophilic attack on the ester group of the azoester to deliver ylide **66**.

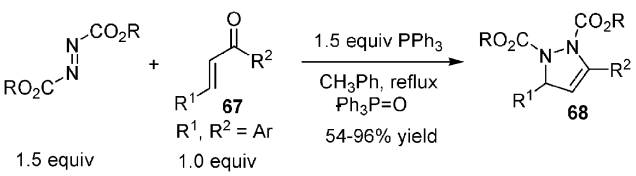


Scheme 33 Mechanistic proposal for the reaction of the Huisgen zwitterion with allenic esters **65**.

Ring closure of ylide **66**, followed by elimination of triphenylphosphine oxide and double-bond isomerization leads to the final product **65** (Scheme 33).

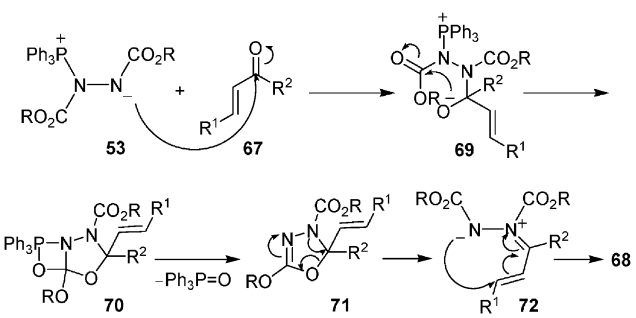
5.3 Annulation of phosphine-DIAD with electron-deficient alkenes

Very recently, Nair and co-workers observed that in the presence of 1.5 equiv. triphenylphosphine, the reaction of DIAD with simple electron-deficient alkenes could afford pyrazolines **68** in moderate to good yields, which opens a new route to pyrazolines (Scheme 34).[38]



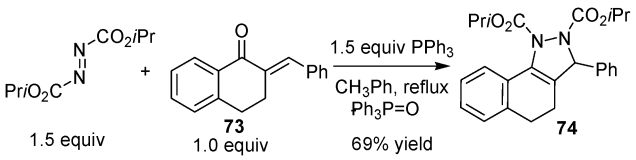
Scheme 34 Phosphine-mediated synthesis of functionalized pyrazolines **68**.

The formation of the pyrazoline could be explained as follows. The addition of Huisgen zwitterion **53** to the carbonyl group of the chalcone, followed by elimination of triphenylphosphine oxide generates oxadiazoline **70**. This oxadiazoline then undergoes ring fragmentation to form **72**, which is further transformed to the final product **68** (Scheme 35).



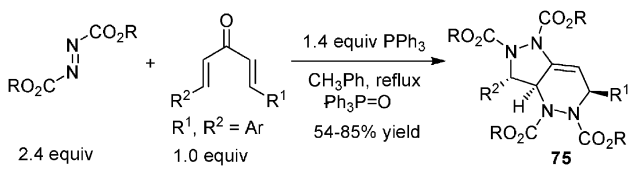
Scheme 35 Mechanistic proposal for the reaction of the Huisgen zwitterion with chalcone **67**.

When benzylidene tetralone **73** was used instead, tricyclic pyrazoline derivative **74** could be obtained in 69% yield (Scheme 36).



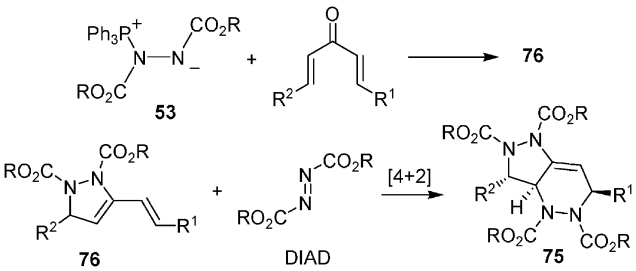
Scheme 36 Phosphine-mediated synthesis of a polycyclic pyrazoline **73**.

Moreover, Nair *et al*. extended the scope of the reaction to a number of dienone substrates, and the reaction furnished the corresponding pyrazolopyrazoline derivatives **75** in good yields (Scheme 37).



Scheme 37 Phosphine-mediated synthesis of pyrazolopyridazines.

The formation of pyrazolopyrazoline derivatives **75** could be explained by an intermolecular Diels–Alder reaction of dienophile DIAD with the initially generated vinyl pyrazoline **76**, which contains a diene moiety (Scheme 38). It should be mentioned that the regioselectivity depends on their relative electronegativities if R^1 and R^2 are not identical.



Scheme 38 Mechanistic proposal for the reaction of the Huisgen zwitterion with a dienone.

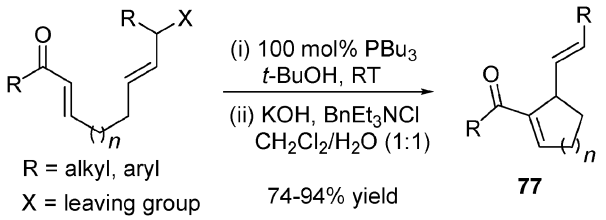
6 Morita–Baylis–Hillman (MBH) type reactions

6.1 Intramolecular S_N2 reactions

Nucleophilic phosphine-catalyzed intramolecular Morita–Baylis–Hillman reactions also provide a good method for construction of cyclic compounds.[39] Early excellent examples include Roush's synthesis of functionalized cyclopentenes and cyclohexenes *via* the vinylogous intramolecular MBH reaction,[40] Krische's combination of the nucleophilic features of the MBH reaction[41] and the electrophilic features of the Trost–Tsuji π-allyl-palladium intermediates.[42] Recently, this

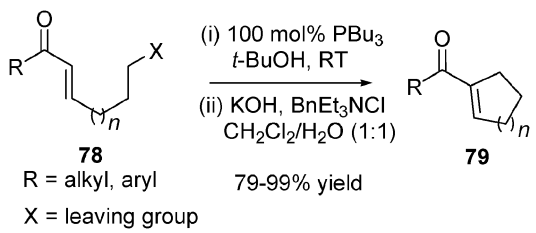
strategy received more attention for the construction of cyclic and polycyclic compounds.

In 2005, Krafft and Haxell reported for the first time that allylic leaving groups could be installed as the electrophilic partner in a completely organocatalytic intramolecular variant of the Morita–Baylis–Hillman reaction (Scheme 39).[43] This novel reaction allows one to use primary and secondary allylic chlorides generating both five- and six-membered cyclic compounds **77** in good to excellent yields. In addition, the reaction furnishes both mono- and di-substituted alkenes with excellent selectivity in the absence of a transition metal catalyst.



Scheme 39 Phosphine-mediated synthesis of cyclic enones **77**.

Usually, only highly reactive sp^2 hybridized electrophiles are effective in the MBH reactions, and the less reactive sp^3 hybridized electrophiles have never been utilized in the MBH reaction. Inspired by the above finding that allylic leaving groups can be applied in the intramolecular MBH reaction as the electrophilic partner, Krafft *et al.* demonstrated for the first time that the sp^3 hybridized electrophiles could work well in the intramolecular MBH reaction. As a result, acyclic substrate **78** was transformed to five- and six-membered enone cycloalkylation products **79** in good to excellent yields (Scheme 40) under the catalysis of nBu$_3$P.[44] NMR studies suggest that cyclization had occurred prior to the addition of base, which serves only to promote elimination to the enone.

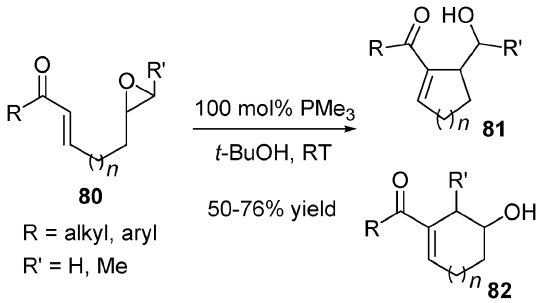


Scheme 40 Phosphine-mediated cycloalkylation reaction.

Besides allylic halides and alkyl halides, epoxides can also serve as electrophile in the intramolecular MBH reaction to generate a chain extended homologous Aldol product. Krafft and Wright found that, under catalysis by trimethylphosphine, the intramolecular Morita–Baylis–Hillman cyclization of **80** furnished homologous Aldol adducts **81** and **82** in moderate to good yields (Scheme 41).[45] This nucleophilic epoxide opening provides a new way to construct carbon skeletons and extends the synthetic utility of epoxides in organic synthesis.

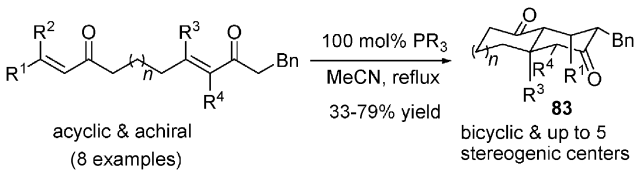
6.2 Formal [4 + 2] cycloaddition reactions

Nucleophilic phosphine-catalyzed formal [4 + 2] cycloaddition reactions provide an alternative to Diels–Alder cycloaddition, for the formation of several carbon–carbon bonds and contiguous stereogenic centers in a single-pot operation.



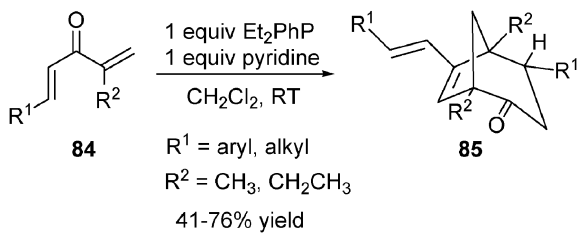
Scheme 41 Phosphine-mediated epoxide opening.

A trialkylphosphine-catalyzed annulation reaction to form the bicyclic compounds **83** was reported by Couturier *et al.* (Scheme 42).[46] They found that the single-pot operation could generate two carbon–carbon bonds and up to five contiguous stereocenters in one step, starting from achiral aliphatic substrates.



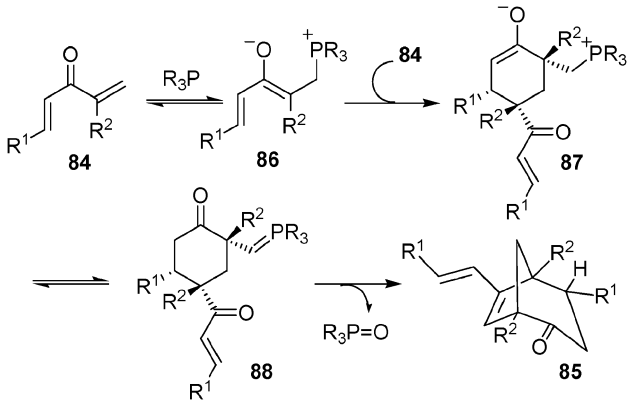
Scheme 42 Phosphine-mediated [4 + 2] annulation of bis(enones).

Recently, McDougal and Schaus reported a phosphine-mediated highly diastereoselective synthesis of bicyclo[3.2.1]octenones **85** that contain two quaternary carbon centres by a formal [4 + 2] cycloaddition–Wittig reaction process (Scheme 43).[47] It should be mentioned that the phosphine acts as both a nucleophilic trigger to generate a 1,3-diene and a mediator of intramolecular olefination in this process.



Scheme 43 Phosphine-mediated synthesis of bicyclo[3.2.1]octenones **85**.

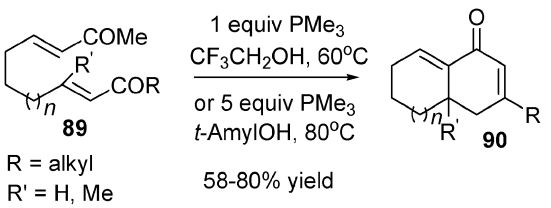
Based on NMR studies, the authors explained the possible mechanism of this transformation as shown in Scheme 44. Nucleophilic addition of the phosphine to **84** affords diene **86**. A formal [4 + 2] cycloaddition of **86** with a further equivalent of **84** furnishes *endo* cycloadduct **87** as one diastereomer. Subsequent intramolecular Wittig olefination of **88** and the α,β-unsaturated carbonyl group located on the same face of the cyclohexanone ring provides the bicyclo[3.2.1]octenone **85** and phosphine oxide.



Scheme 44 Proposed mechanism for the phosphine-mediated reactions of 1,4-dien-3-ones **84**.

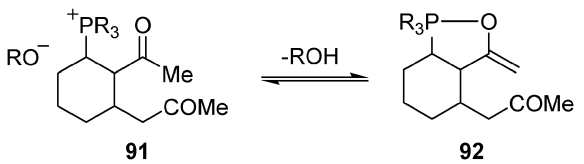
6.3 MBH initiated tandem reactions

In 2005, Thalji and Roush demonstrated an interesting type of phosphine-mediated intramolecular annulation reaction. They discovered a phosphine-mediated intramolecular MBH/aldol tandem cyclization of unsaturated diketones **89** that proceeded with extremely high levels of regioselectivity for the cross conjugated bicyclic dienone products **90** (Scheme 45).[48]



Scheme 45 Phosphine-mediated synthesis of the cross-conjugated bicyclic dienone products **90**.

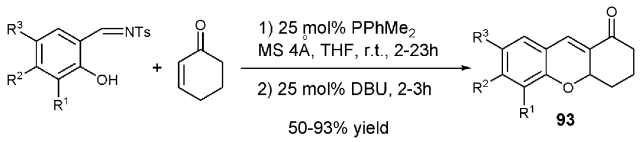
The sense of regioselectivity observed in this reaction is unattainable using traditional aldol conditions and is governed by the chemistry of the phosphine-Michael adduct **91**. This would increase the acidity of the β-phosphonium-substituted methyl ketone and promote the deprotonation regioselectively by the alkoxide (**91** to **92**, Scheme 46).



Scheme 46 Possible interaction between the phosphonium unit and the adjacent carbonyl in intermediate **91**.

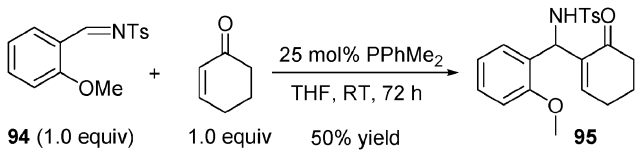
Shi and Shi reported another interesting type of phosphine-mediated intermolecular MBH/Michael addition tandem annulation reaction. In the presence of 25 mol% of $PPhMe_2$, the reaction of salicyl *N*-tosylimines with 2-cyclohexenone affords tetrahydroxanthenones **93** within a few hours in most cases, providing a facile access to xanthone compounds (Scheme 47).[49]

Since weak nucleophilic catalysts, such as DABCO, DMAP and DBU, failed to catalyze this transformation, the authors



Scheme 47 Phosphine-catalyzed synthesis of the tetrahydroxanthenones **93**.

suggest that the reaction is initiated by an aza-Baylis–Hillman reaction, followed by intramolecular Michael addition to give the product **93**. This was further supported by a control experiment. The *N*-tosylimine of more sterically hindered 2-methoxybenzaldehyde **94** reacted with 2-cyclohexen-1-one much more slowly to afford the aza-Baylis–Hillman product **95** in only 50% yield even after 72 h (Scheme 48).

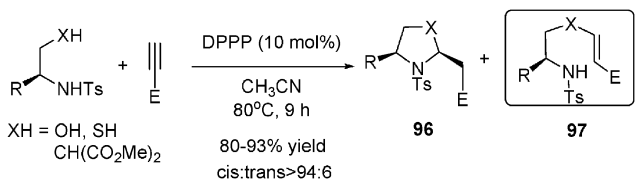


Scheme 48 Mechanistic experiment.

6 Michael addition reactions of activated alkynes

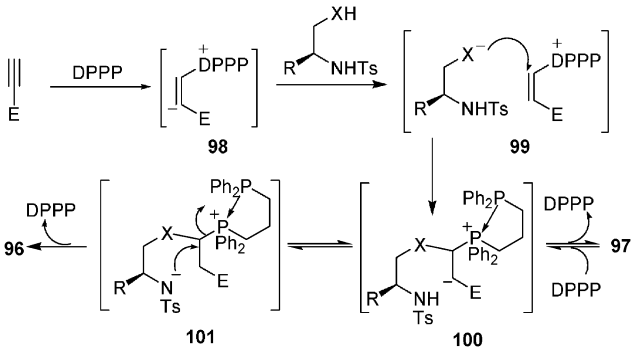
Phosphine-catalyzed tandem addition of a bifunctional nucleophile to electron-deficient alkyne also provides a facile method for construction of useful heterocycles under neutral conditions. Early examples of this strategy include the formation of γ-butyrolactone from the ring-opening product of the γ-adduct of Meldrum's acid and alkynone,[4,50] substituted thiazolines from thioamides, 2-alkynoates and 2,3-dienoates,[51] and a series of oxygen and nitrogen-containing heterocycles from α,β-unsaturated alkynes.[52]

Very recently, Kwon and co-workers reported a bisphosphine-catalyzed mixed double-Michael reaction for the asymmetric synthesis of an array of heterocycles **96**. Oxazolidines, thiazolidines, pyrrolidines and octahydroindoles could be readily synthesized in high *cis* selectivity from electron-deficient alkynes and suitable bifunctional nucleophiles (Scheme 49).[53] It was found that the use of bisphosphine other than DPPM was crucial for suppressing side acyclic product **97**. This finding cast some light on the reaction mechanism.



Scheme 49 Bisphosphine-catalyzed mixed double-Michael reactions for the asymmetric synthesis of an array of heterocycles.

The reaction was initiated by the nucleophilic addition of the phosphine to the electron-deficient alkynes. The resulting anion **98** deprotonates the pronucleophile to accelerate the first Michael addition. The presence of an additional phosphine moiety at a suitable distance could stabilize the



Scheme 50 Proposed mechanism for the reaction.

intermediate phosphonium ions **100** and **101**, so that β-elimination of the phosphine from **100** to afford mono-Michael product **97** was suppressed. Intermediate **101** undergoes an S_N2 displacement to produce the final heterocycles **96** (Scheme 50).

7 Conclusions

In conclusion, phosphine-triggered annulation reactions have already become a powerful tool in organic chemistry. New reactions are continuing to be developed in this area and a series of heterocyclic and polycyclic compounds could be easily synthesized from readily available materials. In many cases, the reaction selectivities are excellent. Furthermore, the regioselectivity of the reaction could be readily tuned in some cases by changing the nucleophilic phosphine catalyst. These advantages, together with the metal-free conditions, make this strategy valuable from an economical and environmental point of view. Currently, most of these annulations need at least 10 mol% of catalyst loading and the enantioselective examples are still limited. In this light, how to increase the catalytic efficiency and how to develop a catalytic asymmetric annulation will be the aim of further investigations. In addition, the pioneering work of achiral phosphine catalysis, in combination with chiral BINOL derivatives in asymmetric Morita–Baylis–Hillman reactions[54] and the combination of nucleophilic phosphine catalysis with transition metal catalysis by Krische,[41] promise opportunities in blending the best of nucleophilic phosphine catalysis with other catalysts for efficient ring construction. We believe that nucleophilic phosphine catalysis will make significant contribution to synthetic organic chemistry.

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