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Phosphine Catalysis of Allenes with Electrophiles

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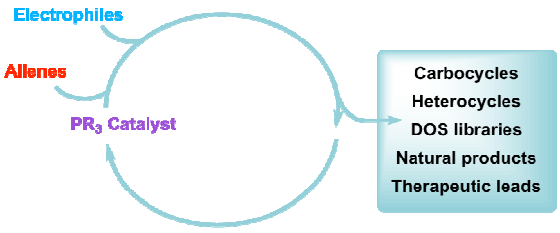


Abstract: Nucleophilic phosphine catalysis of allenes with electrophiles is one of the most powerful and straightforward synthetic strategies for the generation of highly functionalized carbocycle or heterocycle structural motifs, which are present in a wide range of bioactive natural products and medicinally important substances. The reaction topologies can be controlled through judicious choice of the phosphine catalyst and the structural variations of starting materials. This Tutorial Review presents selected examples of nucleophilic phosphine catalysis using allenes and electrophiles.

Key learning points

1. An overview of the main history of nucleophilic phosphine catalysis.

2. Electron-deficient allenes can be used as three- or four-carbon synthons in phosphine-catalyzed annulations.

3. A diverse range of electrophiles—including olefins, imines, aldehydes, ketones, aziridines, and azomethine imines—can be coupled with allenes in phosphine-catalyzed annulations.

4. Reaction topologies of nucleophilic phosphine catalysis can be controlled through judicious choice of the catalyst.

5. Reaction outcomes of nucleophilic phosphine catalysis can be controlled through structural variations of the starting materials.

1. Introduction

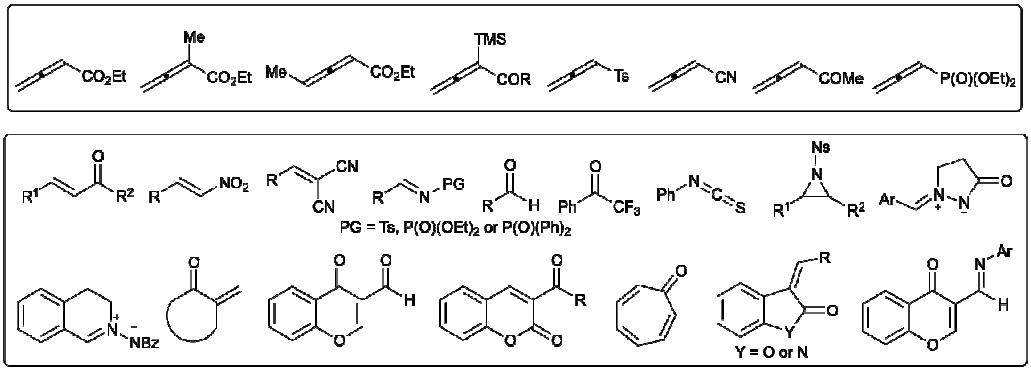
Trivalent phosphines and their derivatives are used widely in organic synthesis. Traditionally, they are applied as stoichiometric reagents in several name reactions, including the Wittig, Staudinger, and Mitsunobu reactions.[1] In modern organic chemistry, organophosphorus compounds are often employed as ligands for transition metal–catalyzed processes.[2] Although the use of phosphines as catalysts for organic reactions can be traced back to the 1960s, reports of nucleophilic phosphines as organocatalysts are relatively rare in the second half of the last century. In 1963, and Currier reported one of the first phosphine-catalyzed reactions: the dimerization electron-deficient olefins.[3] In 1966, Winterfeldt and Dillinger discovered triphenylphosphine-catalyzed annulation for the synthesis of γ-butenolides when

acetylenedicarboxylates and aldehydes as substrates.[4] Two years later, Morita *et al*. described a reaction of an activated olefin and an aldehyde catalyzed by a phosphine.[5] This phosphine-catalyzed transformation, together with the similar amine-catalyzed reaction discovered by Baylis and Hillman in 1972, is known as the Morita–Baylis–Hillman (MBH) reaction; it has become one of the most useful and popular methodologies in organic synthesis.

In recent years, recognition of the huge potential of and the determined scientific interest in Lewis base catalysis has led to nucleophilic phosphine catalysis receiving considerable attention.[6] Because the catalytic behavior and unique properties of trivalent phosphines differ from those of amines, many novel annulations of electron-deficient alkynes, alkenes, and allenes have been discovered in laboratories worldwide, as described in several recent reviews.[7–9] In general, the significant growth of nucleophilic phosphine catalysis can be attributed to several important features: (1) the reactions are highly atom-economical and usually do not produce any by-products; (2) the catalytic system is metal-free, allowing the reactions to performed readily on large scales—a feature that is especially attractive for pharmaceutical applications; and (3) the reaction topologies can be controlled through judicious choice of the phosphine catalyst (i.e., varying its substituents) as well as structural variations of the starting materials.

The main purpose of this Tutorial Review is to present key developments in nucleophilic phosphine catalysis between allenes and electrophiles for application in organic synthesis. Scheme 1 summarizes the diverse range of allenes and electrophiles

that can be used in this catalytic reaction. Because of space limitations, this Tutorial Review emphasizes the different kinds of novel reaction types in nucleophilic phosphine catalysis of allenes with electrophiles, rather than providing a comprehensive list of examples. Nevertheless, for certain novel reactions, such as the [3+2] allene–olefin annulation, relatively detailed accounts are presented. some important modifications of the reactions are discussed and very recent progress mentioned. Some important applications of these methodologies in the construction of combinatorial libraries and the total syntheses of natural products are also highlighted. The literature related to theoretical studies of nucleophilic phosphine catalysis is beyond the scope of this Tutorial Review.



Scheme 1 Typical allenes and electrophiles used in nucleophilic phosphine catalysis

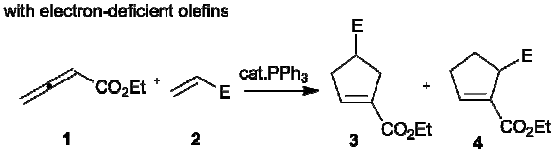
2. Nucleophilic phosphine catalysis of allenes with electrophiles

2.1. [3+2] Annulation with electron-deficient olefins

In 1995, Lu discovered a novel phosphine-catalyzed [3+2] annulation of ethyl 2,3-butadienoate (**1**) with electron-deficient olefins **2** to form the cyclopentene derivatives **3** and **4** (Table 1).[10] Although the regioselectivity governing the product distribution was not great, this transformation is the first example of

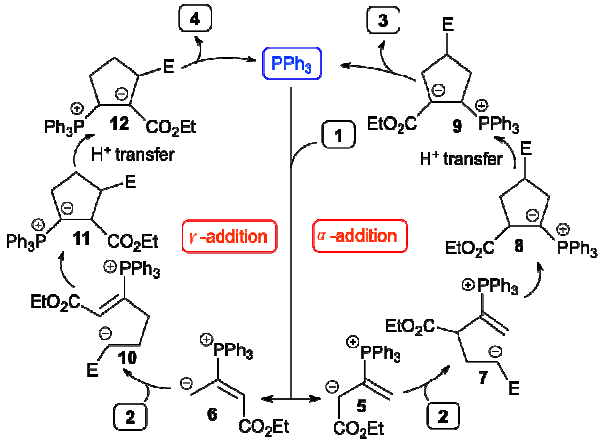
phosphine-catalyzed annulation of an allene. Enlightened by Lu's pioneering work, reaction has been investigated by over 20 different research groups, with applications the syntheses of medicinally important agents and bioactive natural products, including the total syntheses of iridoid β-glucoside-(+)-geniposide and (–)-hinesol.[11,12] In the mechanism proposed (Scheme 2), the catalytic cycle is initiated by nucleophilic addition of triphenylphosphine to ethyl 2,3-butadienoate (**1**), leading to the formation of the resonance-stabilized phosphonium dienolates **5**↔**6**. The nucleophilic addition the α-carbon atom in **5** to the electron-deficient olefin **2** forms the intermediate **7**, undergoes intramolecular cyclization, proton transfer, and phosphine elimination to yield the α-addition product **3**. Alternatively, the γ-addition product **4** can be generated through the γ-addition pathway of **6** to **2**. Ethyl 2,3-butadienoate readily serves as a three-carbon synthon in this transformation.

Table 1 Phosphine-catalyzed [3+2] annulation of ethyl 2,3-butadienoate with electron-deficient olefins



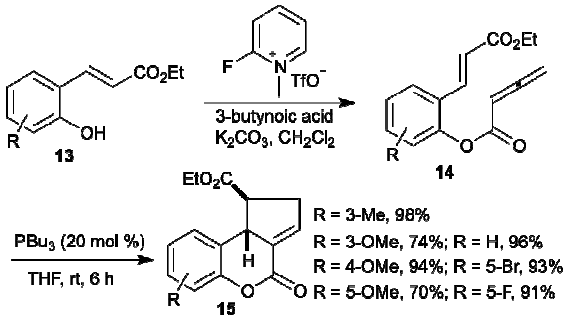
1 2 3 4

entry	E	yield (%)	3 : 4
1	CO_2Et	76	75 : 25
2	CO_2Me	81	80 : 20
3	COMe	55	63 : 37
4	CN	79	83 : 17



Scheme 2 Mechanism of allene–olefin [3+2] annulation

The first intramolecular allene–olefin [3+2] annulation was reported by Kwon in 2007 (Scheme 3).[13] The reaction starting materials **14** were synthesized from salicylaldehydes through Wittig reactions to form **13**, followed by esterification with 3-butynoic acid under the influence of Mukaiyama's reagent. The geometric constraint inherent in the substrates can control the reaction pathway so that only the α-addition product is obtained. In this reaction, 2-styrenyl allenoates featuring either electron-donating or -withdrawing substituents on the aromatic ring were readily converted into cyclopentene-fused dihydrocoumarins **15** in excellent to good yields with exclusive diastereoselectivity.

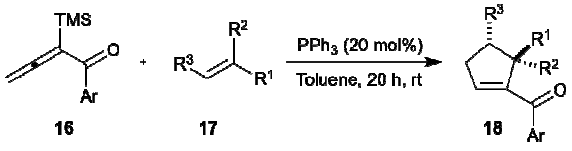


Scheme 3 Intramolecular allene–olefin [3+2] annulation

In 2009, Loh reported a highly regioselective synthesis of functionalized cyclopentenes **18** through phosphine-catalyzed [3+2] annulations between

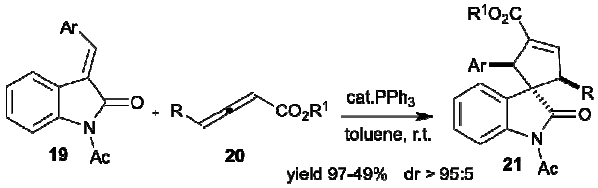
α-silyl-substituted allenones **16** and electron-deficient olefins **17** (Table 2).[14] The bulk of the silyl substituent at the α-position leads to preferential addition at the γ-position, yielding the γ-addition product **18**. This method works well with both phenyl and 2-furanyl allenones and a range of electron-deficient olefins, including chalcones, methyl acrylate, diethyl maleate, diethyl fumarate, and ethyl-4,4,4-trifluorocrotonoate. Notably, the trimethylsilyl group in the starting material is not retained in the final product.

Table 2 Phosphine-catalyzed olefin [3+2] annulation of α-silylallenones



16 17 18

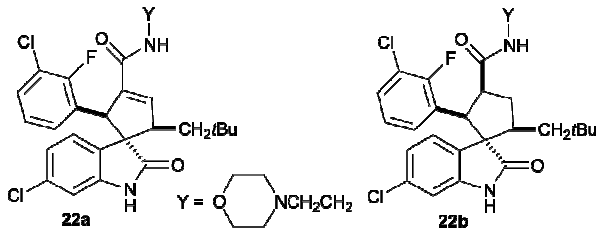
entry	Ar	R^1	R^2	R^3	yield (%)
1	phenyl	COC_6H_5	H	C_6H_5	84
2	phenyl	CO_2Et	H	CO_2Et	82
3	phenyl	CF_3	H	CO_2Et	63
4	2-furanyl	4-$MeOC_6H_4$	H	4-$EtOC_6H_4$	80
5	2-furanyl	H	CO_2Et	CO_2Et	83
6	2-furanyl	CO_2Me	H	H	83



19 20 21

yield 97-49% dr > 95:5

R = *n*-Pr, *i*-Pr, CH_2CH_2Ph, CH_2-*t*-Bu, CH_2-*cyclo*-C_5H_9, or $CH_2CH_2CO_2Me$



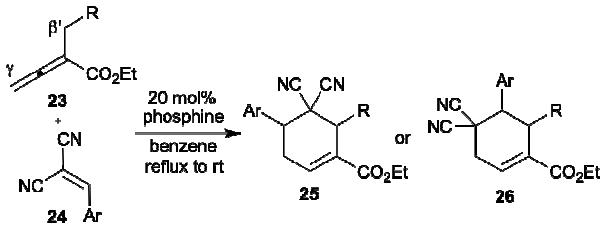
Scheme 4 Synthesis of spiro(cyclopenten)oxindoles through allene–olefin [3+2] annulation

Interestingly, a range of polyfunctionalized fused- and spiro-cyclopentenes can besynthesized through Lu's allene–olefin [3+2] annulation of some designed

electron-deficient olefins. A very recent example was reported by the Marinetti group (Scheme 4).[15] Several spiro(cyclopentene)oxindoles **21** with trisubstituted cyclopentene units were obtained by using arylideneoxindoles **19** as starting materials. In particular, this synthetic strategy is a straightforward means of synthesizing carbocyclic analogues (**22**) of an important series of anticancer agents inhibiting MDM2–p53 interactions.

2.2. [4+2] Annulation with electron-deficient olefins

Table 3 Phosphine-catalyzed [4+2] annulation of α-alkylallenoates with electron-deficient olefins

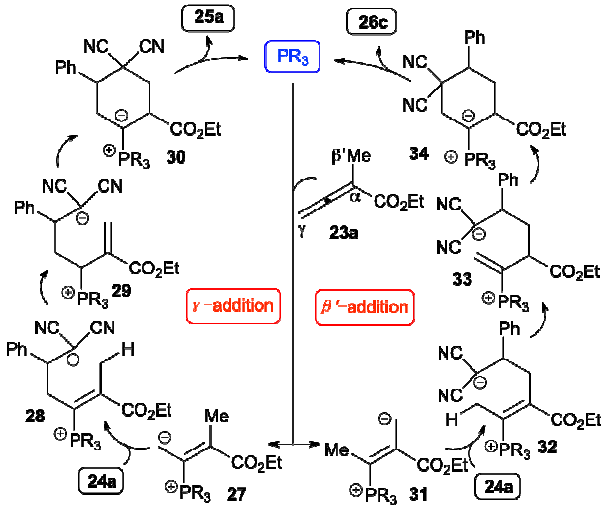


entry	R	Ar	phosphine	product	yield (%)	*cis* : *trans*
1	H	Ph	HMPT	**25a**	98	-
2	H	4-OMe-Ph	HMPT	**25b**	94	-
3	Ph	Ph	HMPT	**25c**	93	82 : 18
4	Et	Ph	HMPT	**25d**	98	92 : 8
5	H	4-Br-Ph	$P(4\text{-F-Ph})_3$	**26a**	86	-
6	H	*N*-Me-2-indolyl	$P(4\text{-F-Ph})_3$	**26b**	91	-
7	H	Ph	$P(4\text{-F-Ph})_3$	**26c**	93	-

Inspired by the robust Lu's [3+2] annulation for the synthesis of functionalized cyclopentenes, Kwon disclosed an unprecedented [4+2] annulation of α-substituted allenoates **23** and arylidenemalononitriles **24** (Table 3).[16] In this case, the reaction regioselectivity is controlled by the electronic nature of the phosphine catalyst. When hexamethylphosphorous triamide (HMPT) was used as the catalyst, the reaction produced the cyclohexene **25**. On the other hand, when a more electron-withdrawing triarylphosphine, such as *tris*(*p*-fluorophenyl)phosphine, was used as the catalyst, the

reaction provided the alternative regioisomeric cyclohexene **26**.

In the mechanism proposed (Scheme 5), the γ-addition reaction pathway begins with conjugate addition of the phosphonium dienolate intermediate **27** to the benzylidenemalononitrile **24a**, producing the vinylphosphonium species **28**, which undergoes two proton transfer steps to form the allylic phosphonium species **29**. Intramolecular cyclization of the intermediate **29** followed by the release of the phosphine catalyst gives the final product **25a**. Alternatively, the phosphonium dienolate **27** isomerizes into the vinylogous ylide intermediate **31**, leading to the reaction producing the cyclohexene **26c** through the β'-addition pathway. The α-substituted allenoate readily serves as a four-carbon synthon in this transformation.

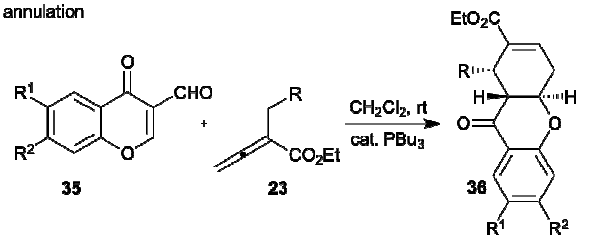


Scheme 5 Mechanism of allene–alkene [4+2] annulation

Recently, Kumar expanded the allene–olefin [4+2] annulation to the stereoselective synthesis of common tricyclic benzopyrone compounds **36**, which were then transformed into a diverse range of naturally occurring scaffolds and related compounds (Table 4).[17] With n-Bu_3P as the phosphine catalyst, the tricyclic benzopyrone derivatives can be prepared, in moderate to good yields and with good

diastereoselectivities, from 3-formylchromones **35** and allenoates **23** through a reaction sequence of [4+2] annulation followed by deformylation. Notably, the presence of the formyl group in the chromenone starting materials **35** activates the chromenone double bond and allows the reaction to take place smoothly.

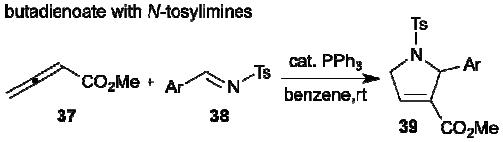
Table 4 Synthesis of tricyclic benzopyrones through allene–olefin [4+2] annulation



entry	R^1	R^2	R	yield (%)
1	H	H	CO_2Et	83
2	Cl	Me	CO_2Et	60
3	Me	H	Ph	80
4	H	H	Me	67
5	Br	H	Me	60

2.3. [3+2] Annulation with imines

Table 5 Phosphine-catalyzed [3+2] annulation of methyl 2,3-butadienoate with *N*-tosylimines



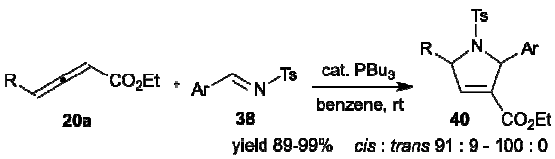
entry	R	yield (%)
1	phenyl	98
2	*o*-methoxyphenyl	96
3	*p*-chlorophenyl	97
4	1-naphthyl	98
5	2-furyl	83[a]

[a] Another adduct, methyl 4,5-dihydro-5-furyl-*N*-tosyl-1*H*-pyrrole-2-carboxylate, was isolated in 15% yield.

In allene–alkene [3+2] annulations, allenoates react with a variety of electron-deficient olefinic electrophiles to form multiply substituted cyclopentenes. To expand the utility of the [3+2] annulation, Lu developed the phosphine-catalyzed allene–imine [3+2] annulation in 1997 (Table 5).[18] They obtained excellent yields of 2-substituted pyrrolines **39** as single annulation products from reactions of methyl

2,3-butadienoate **37** with *N*-tosyl imines **38** when employing triphenylphosphine as catalyst. Unlike the allene–alkene [3+2] annulation (Scheme 2), for most aryl imines this reaction proceeds mainly through the α-addition pathway to generate the α-adduct products **39**. When 2-furylimine was used as the reaction partner, however, the γ-addition product, methyl 4,5-dihydro-5-furyl-1-tosyl-1*H*-pyrrole-2-carboxylate, was isolated in 15% yield as a minor product.

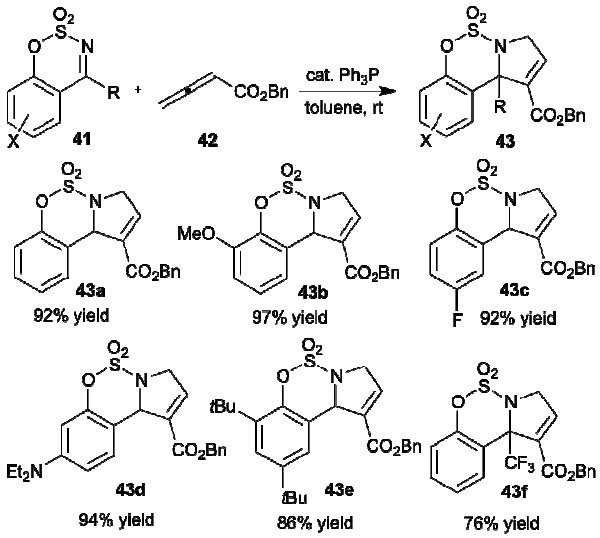
In 2005, Kwon described the highly diastereoselective syntheses of highly substituted pyrrolines **40** through use of Lu's allene–imine [3+2] annulation (Scheme 6).[19] In this reaction, tributylphosphine was used as the nucleophilic catalyst to improve the reaction efficiency and diastereoselectivity. When γ-substituted allenoates **20a** were used as the imine reaction partner, 2,5-*cis*-substituted pyrrolines **40** were produced exclusively in high yield. The reaction efficiency and selectivity can meet the high standards of diversity-oriented synthesis (DOS) for library construction. A DOS library containing a variety of fused heterocyclic compounds possessing distinctive frameworks was constructed through a sequence of phosphine-catalyzed imine annulation, Tebbe reaction, Diels–Alder reaction, and, in some cases, hydrolysis. From this library, several molecules were identified as antimigratory agents of human breast cancer cells.[20]



R = methyl, ethyl, propyl, isopropyl, *tert*-butyl, or phenyl
Ar = Ph, 2-FC_6H_4, 3-BrC_6H_4, 4-$CF_3C_6H_4$, 4-(*i*-Pr)C_6H_4, 2-ClC_6H_4,3-ClC_6H_4, 4-FC_6H_4, 4-$MeOC_6H_4$, 4-CNC_6H_4, 3,4-$Cl_2C_6H_3$, 4-MeC_6H_4, or 1-Naphthyl

Scheme 6 Phosphine-catalyzed imine [3+2] annulation of γ-substituted allenoates

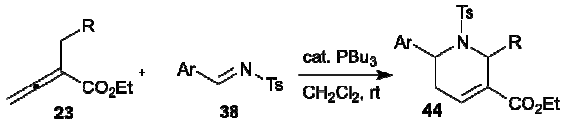
Since the first report of Lu's allene–imine [3+2] annulation, several research groups have applied the reaction in the syntheses of various aza-heterocycles possessing distinctive frameworks. In a very recent example, Wang reported the synthesis of benzo-fused cyclic sulfamidate heterocycles **43** through phosphine-catalyzed [3+2] annulation between the allenoate **42** and the cyclic aldimine/ketimines **41** (Scheme 7).[21] This approach allows benzo-fused cyclic sulfamidate heterocycles **43** featuring a variety of substituents at various positions on the aromatic ring to be prepared readily with high isolated yields. Furthermore, these reactions can also be performed conveniently on the gram scale.



Scheme 7 Synthesis of benzo-fused cyclic sulfamide heterocycles through allene–imine [3+2] annulation

2.4. [4+2] Annulation with imines

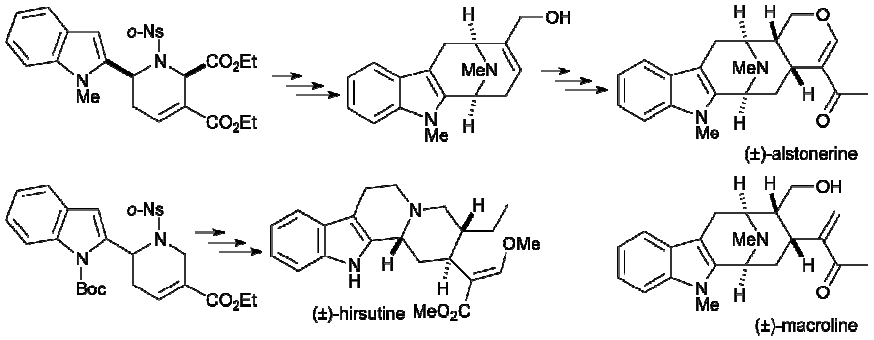
Table 6 Phosphine-catalyzed [4+2] annulation of α-substituted allenoates with imines



entry	R	Ar	yield (%)	*cis* : *trans*
1	H	Ph	98	-
2	H	4-MeC_6H_4	95	-
3	H	4-FC_6H_4	95	-
4	H	2-furyl	97	-
5	H	*N*-Boc-2-pyrroyl	99	-
6	3-$MeOC_6H_4$	Ph	99	98 : 2
7	Ph	4-$NO_2C_6H_4$	90	95 : 5
8	4-CNC_6H_4	2-$CF_3C_6H_4$	80	90 : 10

In the imine [3+2] annulation described above, unsubstituted or γ-substituted allenoates react readily with *N*-sulfonylimines in the presence of a phosphine to generate functionalized pyrrolines. With the vision of exploiting the potential of phosphine catalysis of allenes, in 2003 Kwon disclosed an unprecedented [4+2] annulation to produce highly functionalized tetrahydropyridines **44** (Table 6).[22] variety of *N*-tosylimines **38** and α-substituted allenoates **23** are suitable for this When 2-benzyl-2,3-butadienoates **23** are used as starting materials, 2,6-diaryltetrahydropyridines **44** are obtained in excellent yields with good diastereoselectivities favoring the *cis* isomer. This robust allene–imine [4+2] annulation can be employed to generate tetrahydropyridines **44** on large scales.[23] The application of this reaction to natural product syntheses, such as the formal syntheses (±)-alstonerine and (±)-macroline (2005) and the total synthesis of (±)-hirsutine (2012), was reported by the same group (Scheme 8).[24,25] Unlike the allene–alkene [4+2] annulation (Scheme 5), this reaction proceeds through the γ-addition pathway to generate γ-addition products **44** as single products. Surprisingly, no β′-addition

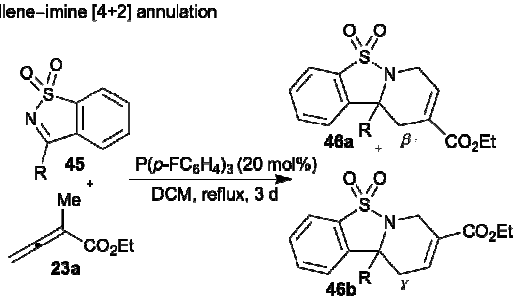
products were isolated in this case.



Scheme 8 Synthesis of (±)-alstonerine, (±)-macroline, and (±)-hirsutine through allene–imine [4+2] annulation

Recently, Ye discovered the phosphine-catalyzed [4+2] annulation of α-substituted allenoate **23a** and cyclic ketimines **45** (Table 7).[26] This reaction can produce corresponding sultam-fused tetrahydropyridines **46** in good yields and with moderate to excellent regioselectivities. The use of triarylphosphines featuring electron-withdrawing groups, such as tris(4-fluorophenyl)phosphine and tris(4-chlorophenyl)phosphine, can increase the reaction efficiency. Interestingly, in contrast to the annulation with aldimines described above, the ketimine [4+2] annulation proceeds mainly through the β'-addition pathway to generate the β'-adducts **46a** as major products.

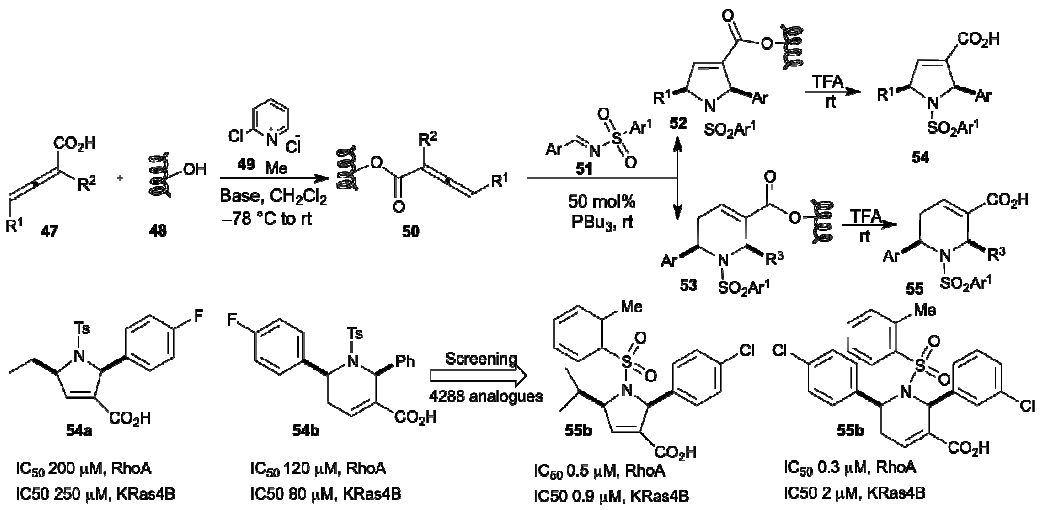
Table 7 Synthesis of sultam-fused tetrahydropyridines through allene–imine [4+2] annulation



entry	R	yield(%)	46a:46b
1	Ph	65	5:1
2	4-MeC_6H_4	68	6:1
3	4-$MeOC_6H_4$	73	21:1
4	3-BrC_6H_4	69	9:1
5	3-CNC_6H_4	72	5:1

One of the merits of the robust allene–imine [3+2]/[4+2] annulation is that the reaction is extremely compatible with reactions performed in the solid phase, thereby allowing efficient construction of aza-heterocyclic compound libraries for biological screening. In 2007, Kwon described the first solid phase phosphine catalysis of resin-bound allenoates with imines to generate dihydropyrrole and tetrahydropyrodine libraries (Scheme 9).[27] The resin-bound allenoates **50** were prepared from SynPhase lanterns of Wang resin **48** and allenoic acid in the presence of Mukaiyama's reagent. A library of 4288 carboxylic acids **54** and **55** was obtained, with good to excellent yields and high diastereoselectivities, through phosphine-catalyzed [3+2]/[4+2] annulations of the resin-bound allenoates with the *N*-sulfonylimines and subsequent cleavage of the resins **52** and **53** using 2.5% trifluoroacetic acid in CH_2Cl_2. After biological screening of the 4288 analogues, two potent inhibitors of protein geranylgeranyltransferase type I with submicromolar IC_{50} values were identified. An octahydro-1,6-naphthyridin-4-one library was reported by the same group in 2011. The library was built through a sequence of phosphine- catalyzed imine [4+2]

annulation, Tebbe reaction, Diels–Alder reaction, and hydrolysis, using the solid phase split-and-pool technique; this approach led to the identification of octahydro-1,6-naphthyridin-4-ones as activators of endothelium-driven immunity.[28]

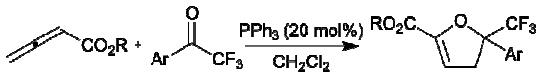


Schema 9 Construction of nitrogen heterocycle libraries through phosphine-catalyzed allene–imine [3+2] and [4+2] annulations

2.5. [3+2]/[4+2] Annulation with ketones

Inspired by the robust allene–olefin/imine [3+2] and [4+2] annulations pioneered by Lu and Kwon, Ye reported the [3+2] and [4+2] annulations between allenoates and ketones in 2010 and 2011 (Tables 8 and 9).[29,30] The use of trifluoromethyl ketones was key for the success of these transformations. Various dihydrofurans **58** were generated through phosphine-catalyzed [3+2] annulation of 2,3-butadienoates **56** and trifluoromethyl ketones **57** in good yields with excellent γ-regioselectivities (Table 8).[29] Furthermore, hydrogenation of the dihydrofurans produced the corresponding 2,5,5-trisubstituted tetrahydrofurans in good yields and with exclusive *cis*-selectivities.

Table 8 Phosphine-catalyzed [3+2] annulation of allenoates with trifluoromethyl ketones

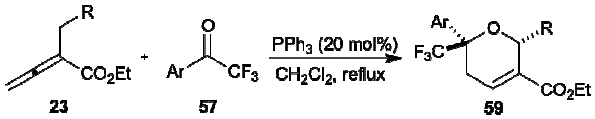


56 57 58

entry	R	Ar	yield(%)
1	Et	Ph	72
2	Et	4-MeC_6H_4	79
3	Et	4-ClC_6H_4	99
4	Cy	4-$MeOC_6H_4$	61
5	Cy	2-thienyl	54

Moreover, when ethyl α-benzylallenoates **23** were used as the allene reaction partners, [4+2] annulation occurred through a γ-addition pathway, very similar to the catalytic cycle proposed by Kwon. This transformation provided a straightforward means for the highly diastereoselective synthesis of 6-trifluoromethyl-5,6-dihydropyrans **59**, reduction of which with H_2 gave the corresponding tetrahydropyrans in high yields and with exclusive diastereoselectivity (Table 9).[30]

Table 9 Phosphine-catalyzed [4+2] annulation of allenoates with trifluoromethyl ketones



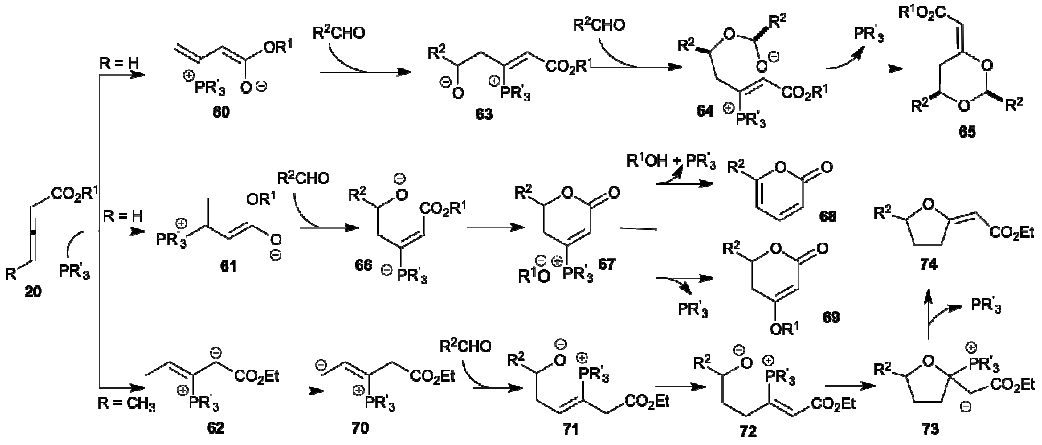
23 57 59

entry	R	Ar	yield (%)	dr
1	Ph	Ph	76	14:1
2	4-$MeOC_6H_4$	Ph	67	14:1
3	2-BrC_6H_4	Ph	85	14:1
4	2-MeC_6H_4	Ph	68	12:1
5	Ph	4-ClC_6H_4	85	>25:1
6	Ph	2-thienyl	58	13:1

2.6. Annulations with aldehydes

In contrast to the successful transformations observed when using electron-deficient olefins, imines, and trifluoromethyl ketones as electrophiles, subjecting aldehydes to the reaction did not result in any corresponding [3+2] and [4+2] annulations, but rather in interesting alternative transformations. Indeed, the reaction topologies are

controlled by the nature of the phosphine catalyst, the reaction conditions, as well as structural variations of the starting materials (Scheme 10).[31–34] When a small tertiary phosphine (e.g., trimethylphosphine) was employed in the reaction, the dioxanes **65** were produced through the intermediate **60** having *s-trans* geometry, due to electrostatic association of the dienolate oxygen anion with the phosphonium cation. When a bulky tertiary phosphine or a hydrogen-bond donor was present, the pyrones (in presence of tricyclopentylphosphine) or dihydropyrones (in presence of MeOH) were generated through the *s-cis*-phosphonium dienolate intermediate **61**. When γ-methyl allenoate was used as the reaction partner instead of an unsubstituted allenoate, the tetrahydrofurans **74** were obtained through the phosphorus ylide **70**, which was generated from the phosphonium dienoate **62** by an overall 1,4-hydrogen shift.

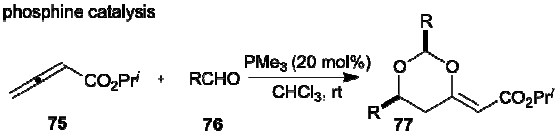


Scheme 10 Nucleophilic phosphine catalysis of allenes with aldehydes

In 2005, Kwon reported the first phosphine-catalyzed reaction of aldehydes **76** with allenoates **75** to generate 2,6-disubstituted-1,3-dioxan-4-ylidene-acetates **77** (Table 10).[31] Pyridine aldehydes and benzaldehydes with electron-withdrawing groups both afforded the corresponding 1,3-dioxan-4-ylidenes **77** in excellent yields and with

good stereoselectivities favoring the *E* isomers. Less-reactive benzaldehydes bearing electron-donating substituents, however, afforded their products in moderate yields. Furthermore, some ubiquitous δ-hydroxyl-β-ketoesters were synthesized from the 1,3-dioxan-4-ylidenes through acid-mediated hydrolysis of the acetal functionality.

Table 10 Synthesis of 1,3-dioxan-4-ylidenes through nucleophilic phosphine catalysis

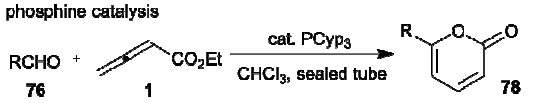


75 76 77

entry	R	yield(%)	*E*/*Z* ratio
1	4-pyridyl	99	8:1
2	4-$CF_3C_6H_4$	99	7:1
3	2-$CF_3C_6H_4$	65	6:1
4	3-$NO_2C_6H_4$	97	7:1
5	Ph	54	only *E*
6	3-$MeOC_6H_4$	47	only *E*

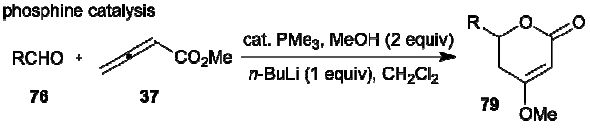
On the other hand, when bulky tricyclopentylphosphine was used as the catalyst, the 2-pyrones **78** were isolated from the same starting materials (Table 11).[32] Various aromatic aldehydes **76**, including benzaldehyde, 2-naphthaldehyde, and 2-furaldehyde, gave the 6-aryl-2-pyrones **78** in good yields. Although the reaction yields were not satisfactory when using aliphatic aldehydes as reaction partners, the reaction afforded a valuable compound, 6-propyl-2-pyrone, which possesses a sweet, creamy, coumarin-like herbal flavor, in one step from a commercially available aldehyde.

Table 11 Synthesis of 6-aryl-2-pyrones through nucleophilic phosphine catalysis



entry	R	$PCyp_3$ (mol%)	yield (%)
1	Ph	10	60
2	3-ClC_6H_4	10	91
3	2-ClC_6H_4	10	73
4	2-$CF_3C_8H_4$	20	71
5	2-naphthyl	30	66
6	2-furyl	30	61
7	*n*-propyl	30	34

Table 12 Synthesis of disubstituted dihydropyrones through nucleophilic phosphine catalysis



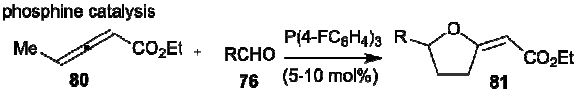
entry	R	yield (%)
1	4-NCC_6H_4	58
2	3-NCC_6H_4	83
3	3-$NO_2C_8H_4$	74
4	2-$CF_3C_6H_4$	58
5	Ph	37
6	3-MeC_6H_4	36

In 2008, Kwon also described the alcohol-assisted phosphine-catalyzed reaction of aldehydes **76** and allenoates **37** to provide disubstituted dihydropyrones **79** in moderate to good yields (Table 12).[33] They found that the addition of a base, such as *n*-BuLi, allowed generation of methoxide *in situ* and led to the promising formation of the dihydropyrones **79** in good yields, without any undesired products. Benzaldehydes possessing a variety of electron-withdrawing or -donating groups provided the desired dihydropyrones **79** in moderate to good yields.

Recently, He disclosed the phosphine-catalyzed [3+2] annulation of allenoates **80** with aldehydes **76** as a simple and efficient pathway for the synthesis of 2-arylidenetetrahydrofurans **81** (Table 13).[34] The presence of the γ-methyl group on

the allenoates **80** changed the regioselectivity of the addition of the aldehyde to the non-substituted allenoates and played a critical role in the occurrence of the [3+2] annulation with aldehydes. The reaction conditions (i.e., catalyst, solvent, and temperature) significantly influence the chemoselectivity and efficiency of the [3+2] annulations.

Table 13 Synthesis of 2-arylidenetetrahydrofurans through nucleophilic phosphine catalysis

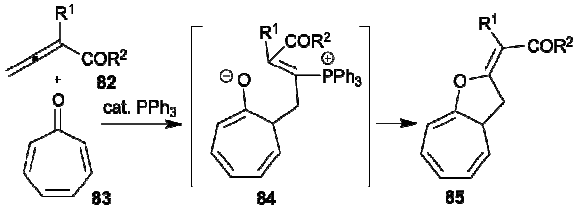


entry	R	**80** (equiv)	t (h)	yield (%)	*E*/*Z* ratio
1	2-ClC_6H_4	2.4	18	94	4:1
2	2-FC_6H_4	1.8	24	81	4:1
3	2,4-$Cl_2C_6H_3$	1.8	22	98	6:1
4	4-$NO_2C_6H_4$	1.8	5	84	5:1
5	4-$CF_3C_6H_4$	2.0	17	81	4:1
6	3-pyridyl	1.8	5	81	20:1
7	2-furyl	2.0	24	72	2:1

2.7. Miscellaneous

Since Lu's initial discovery of phosphine-catalyzed allene–alkene [3+2] annulation, many research groups have expanded the substrate scope of the electrophiles, increasing the molecular complexity and structural variety of the products. Currently, more than eight allenes (shown in Scheme 1) with different substituents are known to be suitable substrates for nucleophilic phosphine catalysis with various electrophiles containing carbon, oxygen, nitrogen, sulfur, phosphorus, and fluorine atoms (Scheme 1). Several unusual reaction types of allenes with electrophiles, such as [8+2], [4+3], [3+3], and [3+2+3] annulations, have also been discovered in this research area. Some of the most interesting examples are outlined below (for more details, see ref. 35 and references therein).

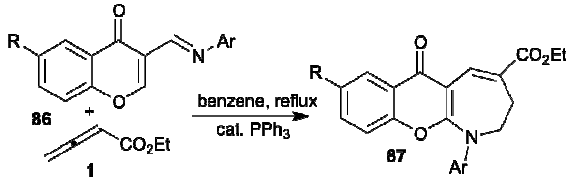
Table 14 Phosphine-catalyzed [8+2] annulation of allenes with tropone



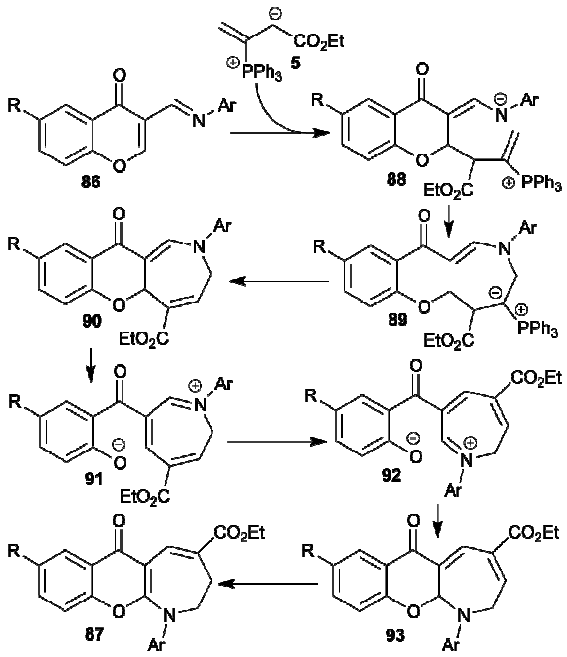
entry	R^1	R^2	t (h)	yield (%)
1	H	OEt	3.5	82
2	H	Me	3.0	95
3	H	Ph	5.0	90
4	H	CH_2Ph	8.0	90
5	Me	OEt	14	70

In 2000, Ishar reported phosphine-catalyzed [8+2] annulation of allenic esters/ketones **82** with tropone **83**, leading to the 8-oxa-9-(ethoxycarbonyl/acylalkyl-idene)-bicylo[5.3.0]deca-1,3,5-trienes **85** (Table 14).[36] Notably, the [8+2] cycloadducts **85** were obtained as the only products in excellent yields; the normal electron-deficient allene–olefin [3+2]/[4+2] annulation products were not observed. Mechanistically, γ-addition of the phosphonium dienolate at the C2 atom of tropone formed the intermediate **84**; subsequent intramolecular cyclization and elimination of phosphine provided the desired product **85**.

Table 15 Phosphine-catalyzed [4+3] annulation of allenes with 3-(*N*-aryliminomethyl)chromones



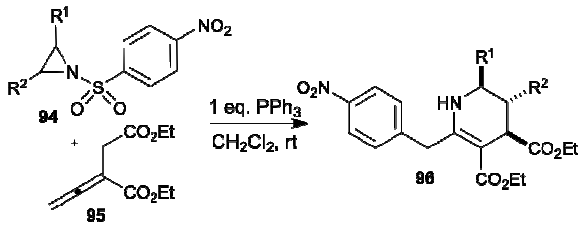
entry	R	Ar	t (h)	yield (%)
1	H	*p*-anisyl	80	55
2	H	*p*-chlorophenyl	90	57
3	Me	*p*-anisyl	85	64
4	Cl	*p*-chlorophenyl	80	64



Scheme 11 Mechanism of chromone–allene [4+3] annulation

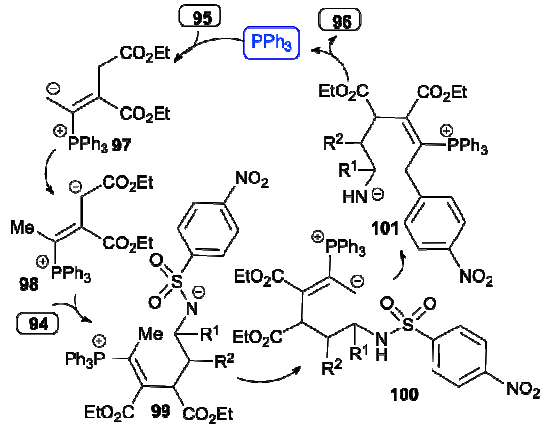
In the same year, Ishar also described the synthesis of novel *N*-aryl-2,3-dihydro-4-ethoxycarbonylchromano[2,3-*b*]azepine-6-ones **87** from 3-(*N*-arylimino-methyl)chromones **86** through phosphine-catalyzed [4+3] annulation followed by tandem rearrangement (Table 15).[37] In the mechanism proposed (Scheme 11), α-addition of the phosphonium dienolate **5** to the chromon **86** forms the intermediate **88**, which undergoes intramolecular cyclization and phosphine elimination to afford the [4+3] annulation product **90**. Thermal opening of the chromone ring in compound **90** generates the intermediate **91**; subsequent rotation around a C–C single bond, recyclization of the chromone ring, and a 1,5-H shift in **93** affords the final product **87**.

Table 16 Phosphine-catalyzed [3+3] annulation of allenes with aziridines



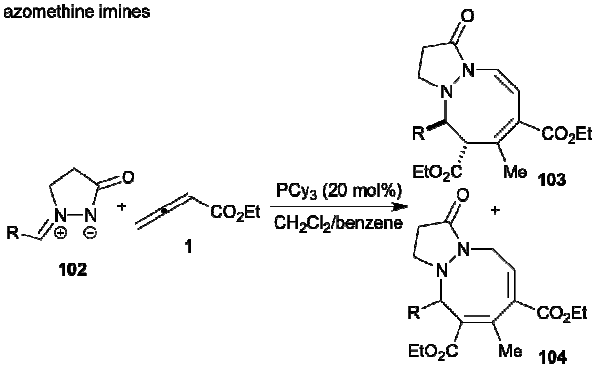
entry	R^1	R^2	yield (%)	dr (*trans*:*cis*)
1	H	2-MeC_6H_4	88	90:10
2	H	4-FC_6H_4	76	88:12
3	H	3-ClC_6H_4	86	83:17
4	H	2-naphthyl	58	85:15
5	Me	H	66	41:59
6	H	Ph	73	9:1

In 2009, Kwon disclosed a novel [3+3] annulation of allenoates **95** with aziridines **94** to generate highly functionalized tetrahydropyridines **96** (Table 16).[38] Aryl aziridines **94** featuring both electron-rich and -deficient substituents are suitable for this reaction, giving the desired products **96** in good to excellent yields. In the mechanism proposed (Scheme 12), *β′*-addition of the vinylogous ylide **98** to the phenyl aziridine **94** occurs to form the intermediate **99**, which is converted to the phosphonium dienolate **100** through proton transfer. Intramolecular nucleophilic aromatic substitution and desulfonylation of **100** affords **101**; subsequent intramolecular conjugate addition and phosphine elimination afford the final product **96**. Although the reaction is catalytic, one equivalent of triphenylphosphine was used to expedite the reaction.



Scheme 12 Mechanism of allene–aziridine [3+3] annulation

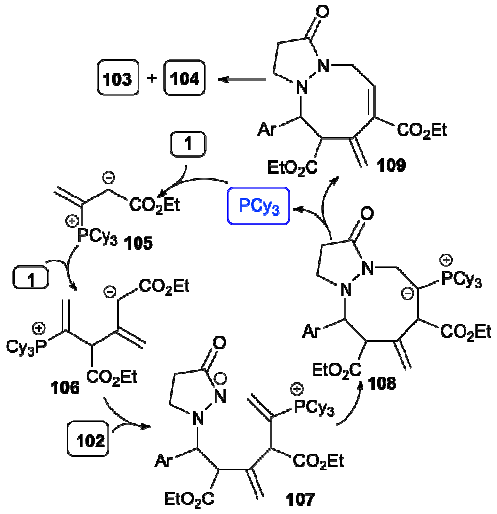
Table 17 Phosphine-catalyzed [3+2+3] annulation of allenes with azomethine imines



entry	R^1	yield (%)	ratio of **103**:**104**
1	Ph	81	34:66
2	4-*i*-PrC_6H_4	67	42:58
3	4-MeOC_6H_4	76	44:56
4	4-BrC_6H_4	77	29:71
5	4-ClC_6H_4	90	24:76
6	4-FC_6H_4	88	25:75
7	2-naphthyl	76	32:68

Recently, Guo and Kwon reported a phosphine-catalyzed [3+2+3] annulation of two molecules of an allenoate **1** and an azomethine imine **102**, leading to the tetrahydropyrazolo-diazocinone products **103** and **104** (Table 17).[35] Both electron-rich and -deficient aryl azomethine imines, as well as a polyaromatic azomethine imine, are compatible substrates. Mechanistically, the key event is the formation of the trimeric zwitterionic intermediate **106**, which gives the intermediate **107** after addition to the azomethine imine **102** (Scheme 13). Intramolecular cyclization of **107** generates

108, which gives the final products **103** and **104** as a mixture of tautomers after proton transfer, phosphine elimination, and olefin isomerization.

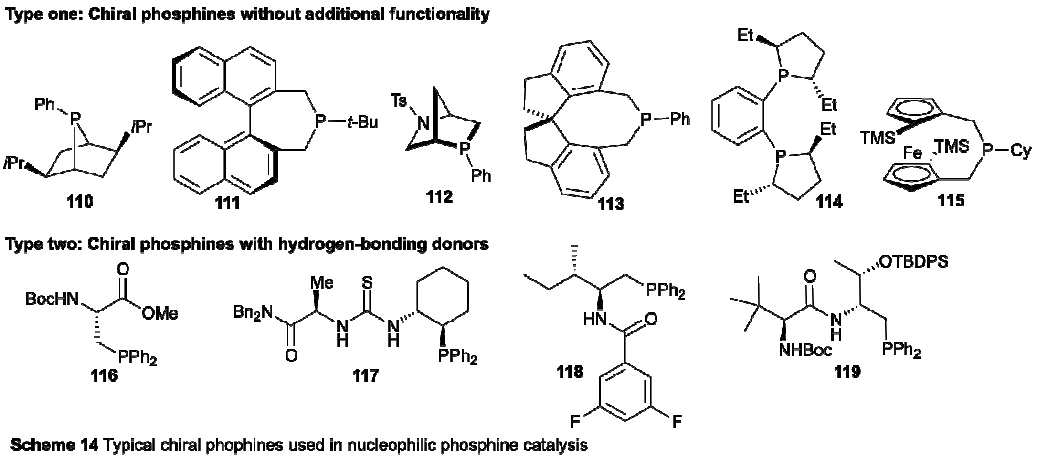


Scheme 13 Mechanism of allene–allene–azomethine imine [3+2+3] annulation

3. Enantioselective nucleophilic phosphine catalysis of allenes with electrophiles

Since Lu reported the first phosphine-catalyzed allene–alkene [3+2] annulation in 1995, the nucleophilic phosphine catalysis of allenes with electrophiles has become one of the most powerful and straightforward synthetic strategies for generation of the highly functionalized carbocyclic and heterocyclic structural motifs found widely in bioactive natural products and medicinally important substances. Despite the many very promising results that have been achieved in phosphine catalysis of allenes with electrophiles, enantioselective variants of these transformations has, however, remained relatively rare. A handful of chiral phosphine organocatalysts, which can be divided into two categories (chiral phosphines without additional functionalities and chiral phosphines with hydrogen bond donors), have been found to be effective for these reactions (Scheme 14). In this Section, we provide a brief overview of these enantioselective nucleophilic phosphine-catalyzed reactions of allenes with

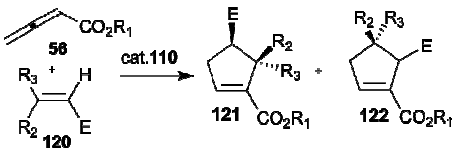
electrophiles and also point the reader to several comprehensive reviews for more details.[9,39–41]



Scheme 14 Typical chiral phophines used in nucleophilic phosphine catalysis

3.1. Chiral phosphines without additional functionality

Table 18 Enantioselective allene–olefin [3+2] annulation reported by Zhang

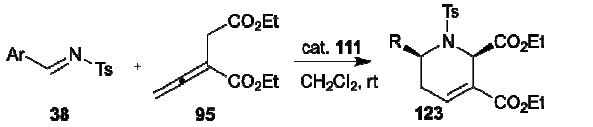


entry	E	R_1	R_2	R_3	yield (%)	121:122	% ee of 121
1	CO_2Me	Et	H	H	87	96 : 4	79
2	$CO_2{}^tBu$	Et	H	H	88	100 : 0	93
3	CO_2Et	^tBu	H	H	84	94 : 6	69
4	CO_2Et	Et	CO_2Et	H	49		79
5	CO_2Me	Et	H	CO_2Me	84		36

In 1997, Zhang reported the first enantioselective phosphine-catalyzed [3+2] annulation of 2,3-butadienoates **56** with electron-deficient olefins **120**, affording the cyclopentene products **121** and **122** with excellent regioselectivity and good enantioselectivity (Table 18).[42] After initial screening of known and new chiral phosphines, they found that the newly designed bicyclic monodentate chiral phosphine **110** was most suitable for this reaction. Furthermore, using acrylates with bulky ester substituents (e.g., *tert*-butyl) improved the regio- and enantioselectivity.

Despite the great synthetic potential of the results described above, no further progress was made in enantioselective nucleophilic phosphine catalysis of allenes with electrophiles until 2005, when Fu demonstrated the asymmetric allene–imine [4+2] annulation to give the piperidine derivatives **123** when employing Gladiali's phosphine **111** as the catalyst (Table 19).[43] Under the optimized conditions, they obtained a range of useful functionalized tetrahydropyridines **123** in high yields and enantioselectivities. This asymmetric [4+2] reaction is a novel and efficient means of access to a common framework found in several important natural products, including 6-oxoalstophyllal and 6-oxoalstophylline.

Table 19 Enantioselective allene–imine [4+2] annulation reported by Fu

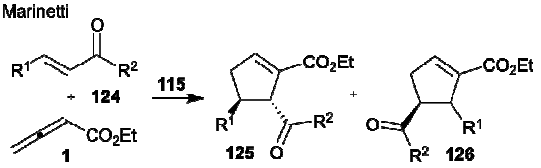


38 **95** **123**

entry	Ar	ee (%)	*cis*:*trans*	yield (%)
1	Pr	98	91:9	93
2	3-MeC_6H_4	98	93:7	98
3	2-$NO_2C_6H_4$	68	96:4	98
4	2-naphthyl	99	93:7	96
5	2-furyl	97	87:13	98
6	3-pyridyl	97	91:9	76

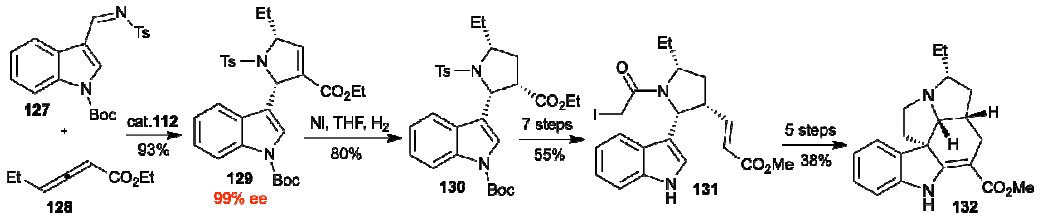
In 2008, Marinetti reported the enantioselective allene–alkene [3+2] annulation by using the phosphine **115**, exhibiting planar chirality, as the catalyst (Table 20).[44] When using the chalcones **124** as reaction partners, the γ-addition products **125** were afforded in moderate to good yields, with excellent enantioselectivities favoring the *trans* isomers. Very recently, the same group employed this chiral phosphine as the catalyst for the enantioselective syntheses of spirocyclic compounds.[45]

Table 20 Enantioselective allene–alkene [3+2] annulation reported by Marinetti



entry	R^1	R^2	**125 : 126** ratio	yield (%)	ee (%)
1	H	OEt	1 : 1.5	53	88/84
2	Ph	Ph	20 : 1	65	92
3	1-naphthyl	Ph	>20 : 1	87	96
4	4-$MeOC_6H_4$	Ph	>20 : 1	71	93
5	4-$NO_2C_6H_4$	Ph	10 : 1	63	92
6	2-furyl	Ph	8 : 1	71	93

In 2012, Kwon demonstrated the first enantioselective total synthesis of the monoterpene indole alkaloid (+)-ibophyllidine **132**, featuring an asymmetric phosphine-catalyzed allene–imine [3+2] annulation as the key reaction step (Scheme 15).[46] Using their P-chiral [2.2.1]bicyclic phosphine **112** as the catalyst, they obtained the *syn*-pyrrolidine **129** as a synthetic intermediate from 4-ethyl-2,3-butadienoate and *N*-tosylbenzaldimine in 93% yield and with 99% ee. Hydrogenation of **129** afforded the stereochemically dense pyrrolidine ring compound **130** in excellent yield with exceptionally high degrees of both diastereo- and enantioselectivity. A subsequent 12-step sequence of chemical manipulations provided the target natural product (+)-ibophyllidine **132**.



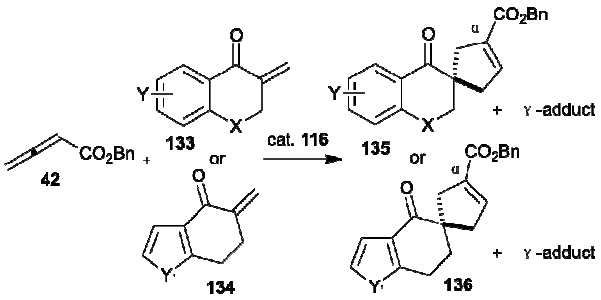
Scheme15 Enantioselective total synthesis of (+)-ibophyllidine through asymmetric phosphine-catalyzed allene–imine [3+2] annulation

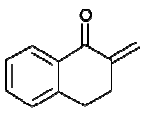
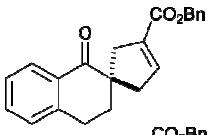
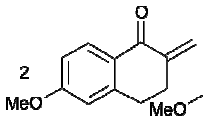
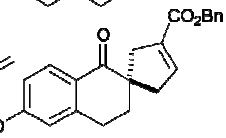
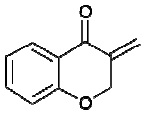
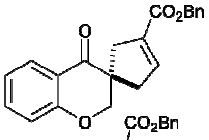
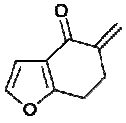
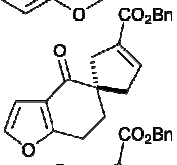
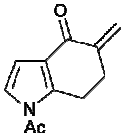
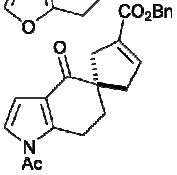
3.2. Chiral phosphines with hydrogen-bond donors

In contrast to chiral phosphines lacking additional functionality, which induce

asymmetry through steric interactions, chiral phosphines with hydrogen-bonding donors instigate high enantioselectivity through hydrogen bonding. The first example of asymmetric allene–olefin [3+2] annulation employing the multifunctional chiral phosphine **116** as the catalyst was reported by Miller in 2007 (Table 21).[47] When using benzyl 2,3-budienoate **42** as the reaction partner, they obtained various spirocyclic compounds **135** and **136** from corresponding electron-deficient olefins in good yields with good to moderate enantioselectivities. The presence of a heteroatom-substituted ring system in the starting material resulted in significantly lower yields and enantioselectivities.

Table 21 Enantioselective allene–olefin [3+2] annulation reported by Miller

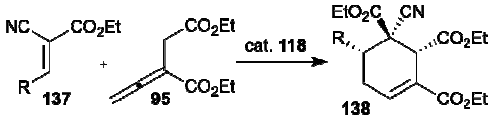


entry	substrate	product()	yield +(%)	α :	ee(%)
1			95	> 99 : 1	80
2			95	> 99 : 1	84
3			68	94 : 6	65
4			75	> 99 : 1	76
5			53	> 99 : 1	71

Encouraged by Miller's pioneering work, Zhao and Lu independently developed their amino acid–derived bifunctional chiral phosphines in 2010 and 2011, respectively.[48,49] Zhao reported the highly enantioselective [4+2] annulation of the allenoate **95** with the alkylidene cyanoacetate **137** catalyzed by his *N*-acyl aminophosphine **118** (Table 22);[48] a range of highly functionalized cyclohexene derivatives **138**, bearing three contiguous chiral centers, were synthesized with good to excellent diastereoselectivities and enantioselectivities. On the other hand, Lu described versatile enantioselective [3+2] annulations of imines and allenoates

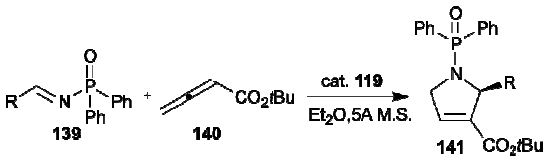
catalyzed by his dipeptide-based chiral phosphine **119** (Table 23).[49] Notably, this reaction is the first example of aliphatic imines **139** being applied successfully in phosphine-catalyzed [3+2] annulation. Moreover, this transformation was applied as a key step in the concise formal synthesis of (+)-trachelanthamidine.

Table 22 Enantioselective allene–olefin [4+2] annulation reported by Zhao



entry	R	t (h)	yield (%)	ee (%)
1	Ph	4	94	96
2	isopropyl	3	92	97
3	2-naphthyl	3	95	95
4	4-ClC_6H_4	6	99	97
5	3-$MeOC_6H_4$	6	88	96
6	2-thienyl	4	87	93

Table 23 Enantioselective allene–imine [3+2] annulation reported by Lu

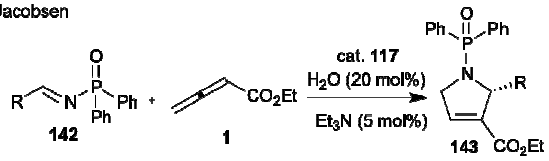


entry	R	yield (%)	ee (%)
1	methyl	75	95
2	ethyl	78	96
3	*n*-hexyl	84	97
4	*iso*-propyl	81	99
5	$PhCH_2CH_2$	81	95
6	cyclohexyl	83	99

Another significant example of asymmetric allene–imine [3+2] annulation catalyzed by a chiral phosphine featuring a hydrogen-bonding donor was discovered by Jacobsen *et al*. in 2008 (Table 24).[50] They developed a new family of chiral phosphinothiourea derivatives **117** for highly enantioselective syntheses of disubstituted dihydropyrroles **143**. Notably, the use of diphenylphosphinoyl (DPP) imines **142** and the addition of 0.2 equiv of H_2O and 0.05 equiv of Et_3N improved the

reaction efficiency.

Table 24 Enantioselective allene–imine [3+2] annulation reported by Jacobsen



entry	R	7a (mol%)	yield (%)	ee (%)
1	Ph	10	84	98
2	*p*-FC_6H_4	10	72	95
3	*p*-$MeOC_6H_4$	20	80	97
4	*m*-$NO_2C_6H_4$	10	70	95
5	o-BrC_6H_4	10	90	95
6	4-pyridyl	10	70	94
7	3-furyl	20	68	94
8	2-thienyl	20	77	97

4. Conclusions

The use of nucleophilic phosphines as Lewis base catalysts for organic reactions has grown over the last decade and is now an active area of organocatalysis. Ten modes of nucleophilic phosphine catalysis with allenes and electrophiles have been demonstrated in this Tutorial Review; these transformations take advantage of the unique and highly tunable properties of trivalent phosphine. A variety of unique carbo/heterocyclic frameworks, some of which are present in a wide range of bioactive natural products and medicinally important substances, can be obtained through these transformations. Some examples of asymmetric nucleophilic phosphine catalysis with high enantioselectivities have also been developed, with promising applications in the total synthesis of natural products. Future advances in phosphine catalysis are likely to occur along a number of lines, including the development of novel reaction modes and the synthesis of novel chiral phosphines that perform their catalytic functions with high efficiency. In addition, much work remains to develop

asymmetric variants of several recently discovered transformations.

Acknowledgements

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References

1 D. H. Valentine and J. H. Hillhouse, *Synthesis*, 2003, 317.

2 *A Guide to Organophosphorus Chemistry*, ed. L. D. Quin, Wiley, New York, 2000.

3 M. M. Rauhut and H Currier, *U. S. Patent* 3 074 999, 1963; *Chem. Abstr.* 1963, **58**, 11224a.

4 E. Winterfeldt and H. J. Dillinger, *Chem. Ber.*, 1966, **99**, 1558.

5 K. Morita, Z. Suzuki and H. Hirose, *Bull. Chem. Soc. Jpn.*, 1968, **41**, 2815.

6 S. E. Denmark and G. L. Beutner, *Angew. Chem. Int. Ed.*, 2008, **47**, 1560.

7 L.-W. Ye, J. Zhou and Y. Tang, *Chem. Soc. Rev.*, 2008, **37**, 1140.

8 B. J. Cowen and S. J. Miller, *Chem. Soc. Rev.*, 2009, **38**, 3102.

9 Y. C. Fan and O. Kwon, *Chem. Commun.*, 2013, **49**, 11588 and references therein.

10 C. Zhang and X. Lu, *J. Org. Chem.*, 1995, **60**, 2906.

11 R. A. Jones and M. J. Krische, *Org. Lett.*, 2009, **11**, 1849.

12 Y. Du and X. Lu, *J. Org. Chem*., 2003, **68**, 6463.

13 C. E. Henry and O. Kwon, *Org. Lett*., 2007, **9**, 3069.

14 M. Sampath and T. Loh, *Chem. Commun*., 2009, 1568.

15 C. Gomez, M. Gicquel, J. Carry, L. Schio, P. Retailleau, A. Voituriez and A. Marinetti, *J. Org. Chem*., 2013, **78**, 1488.

16 Y. S. Tran and O. Kwon, *J. Am. Chem. Soc*., 2007, **129**, 12632.

17 B. Baskar, P. Dakas and K. Kumar, *Org. Lett*., 2011, **13**, 1988.

18 Z. Xu and X. Lu, *Tetrahedron Lett*., 1997, **38**, 3461.

19 X. Zhu, C. E. Henry and O. Kwon, *Tetrahedron*., 2005, **61**, 6276.

20 Z. Wang, S. Castellano, S. S. Kinderman, C. E. Argueta, A. B. Beshir, G. Fenteany and O. Kwon, *Chem. Eur. J*., 2011, **17**, 649.

21 Y. Wang, Y. Zhang, H. Dong, J. Zhang and J. Zhao, *Eur. J. Org. Chem*., 2013, 3764.

22 X. Zhu, J. Lan and O. Kwon, *J. Am. Chem. Soc*., 2003, **125**, 4716.

23 K. Lu, O. Kwon, K. M. Brummond and M. M. Davis, *Org. Synth*., 2009, **86**, 212.

24 Y. S. Tran and O. Kwon, *Org. Lett.*, 2005, **7**, 4289.

25 R. A. Villa, Q. Xu and O. Kwon, *Org. Lett.*, 2012, **14**, 4634.

26 X. Chen and S. Ye, *Eur. J. Org. Chem*., 2012, 5723.

27 S. Castellano, H. D. G. Fiji, S. S. Kinderman, M. Watanabe, P. Leon, F. Tamanoi and O. Kwon, *J. Am. Chem. Soc*., 2007, **129**, 5843.

28 C. Daniel, Z. Wang, J. Kibbie, R. Modlin and O. Kwon, *Proc. Nat. Acad. Sci. U.S.A.*, 2011, **108**, 6769.

29 T. Wang and S. Ye, *Org. Biomol. Chem*., 2011, **9**, 5260.

30 T. Wang and S. Ye, *Org. Lett*., 2010, **12**, 4168.

31 X. Zhu, C. E. Henry, J. Wang, T. Dudding and O. Kwon, *Org. Lett*., 2005, **7**, 1387.

32 X. Zhu, A. Schaffner, R. C. Li and O. Kwon, *Org. Lett*., 2005, **7**, 2977.

33 G. S. Creech and O. Kwon, *Org. Lett*., 2008, **10**, 429.

34 S. Xu, L. Zhou, R. Ma, H. Song and Z. He, *Chem. Eur. J*., 2009, **15**, 8698.

35 R. Na, C. Jing, Q. Xu, H. Jiang, X. Wu, J. Shi, J. Zhong, M. Wang, D. Benitez, E. Tkatchouk, W. A. Goddard, III, H. Guo and O. Kwon, *J. Am. Chem. Soc*., 2011, **133**, 13337.

36 K. Kumar, A. Kapur and M. S. Ishar, *Org. Lett*., 2000, **2**, 787.

37 K. Kumar, R. Kapoor, A. Kapur and M. S. Ishar, *Org. Lett*., 2000, **2**, 2023.

38 H. Guo, Q. Xu and O. Kwon, *J. Am. Chem. Soc*., 2009, **131**, 6318.

39 Z. Zhou, Y. Wang and C. Tang, *Curr. Org. Chem.* 2011, **15**, 4083.

40 S. –X. Wang, X. Han, F. Zhong, Y. Wang and Y. Lu, *Synlett*, 2011, 2766.

41 Q. –Y. Zhao, Z. Lian, Y. Wei and M. Shi, *Chem. Commun*., 2012, **48**, 1724.

42 G. Zhu, Z. Chen, Q. Jiang, D. Xiao, P. Cao and X. Zhang, *J. Am. Chem. Soc*., 1997, **119**, 3836.

43 R. P. Wurz and G. C. Fu, *J. Am. Chem. Soc*., 2005, **127**, 12234.

44 A. Voituriez, A. Panossian, N. Fleury-Brégeot, P. Retailleau and A. Marinetti, *J. Am. Chem. Soc*., 2008, **130**, 14030.

45 D. Duvvuru, N. Pinto, C. Gomez, J. F. Betzer, P. Retailleau, A. Voituriez and A. Marinetti, *Adv. Synth. Catal*., 2012, **354**, 408.

46 I. P. Andrews and O. Kwon, *Chem. Sci*., 2012, **3**, 2510.

47 B. J. Cowen and S. J. Miller, *J. Am. Chem. Soc*., 2007, **129**, 10988.

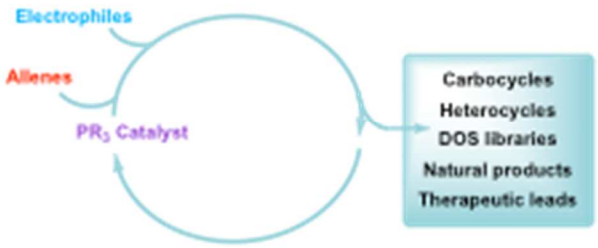
48 H. Xiao, Z. Chai, D. Cao, H. Wang, J. Chen and G. Zhao, *Org. Biomol. Chem*., 2012, **10**, 3195.

49 X. Han, F. Zhong, Y. Wang and Y. Lu, *Angew. Chem. Int. Ed*., 2012, **51**, 767.

50 Y. Fang and E. N. Jacobsen, *J. Am. Chem. Soc*., 2008, **130**, 5660.

Table of Contents

This Article compiles the most representative examples of phosphine-catalyzed annulations between allenes and electrophiles to form various carbo- and heterocycles.



Zhiming Wang

Zhiming Wang, Professor of Chemistry at Changzhou University (China), received his BS and PhD degrees from Zhejiang University (China) in 2002 and 2007, respectively. After three years of postdoctoral research on phosphine catalysis and its applications in biochemistry, at UCLA with Prof. Ohyun Kwon, he started his independent career at Changzhou University in 2010. His research focuses on the development of phosphine catalysis and Lewis acid–catalyzed reactions for the synthesis of heterocycles, and their biochemical applications.

Xingzhu Xu

Xingzhu Xu received his BS in Applied Chemistry at Changzhou University (China) in 2012. Currently, he is pursuing his MS in Organic Chemistry at Changzhou University under the guidance of Prof. Zhiming Wang. His research focuses on the synthesis of novel chiral phosphines for application in asymmetric reactions.

Ohyun Kwon

Ohyun Kwon, Professor of Chemistry and Biochemistry at UCLA, received her BS and MS degrees from Seoul National University in 1991 and 1993, respectively. After her PhD at Columbia University in 1998 and a postdoctoral stint at Harvard University, Kwon started her independent career at UCLA in 2001. She has played key roles in establishing phosphinocatalysis as one of the main areas of organocatalysis research. She is recognized as one of the key leaders in the field.