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Recent advances in stoichiometric phosphine-mediated organic synthetic reactions

Silong Xu[a] and Zhengjie He*[b]

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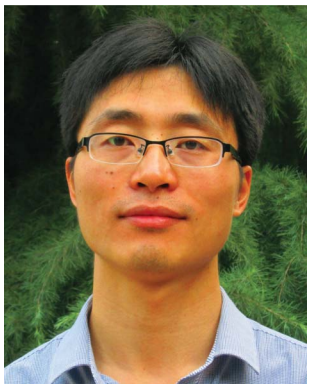
Organic synthetic reactions mediated by tertiary phosphines have attracted much attention in the organic chemistry community in the past two decades. These reactions can be divided into two categories: phosphine-catalyzed and stoichiometric phosphine-mediated transformations. While the phosphine-catalyzed reactions mechanistically rely on the unique properties of tertiary phosphines such as excellent nucleophilicity and good leaving group ability, the stoichiometric transformations are usually driven by nucleophilicity and strong oxyphilicity of tertiary phosphines. Since tertiary phosphines represent an important class of versatile chemical reagents in organic synthesis, stoichiometric phosphine-mediated reactions have recently demonstrated their uniqueness and high efficiency in organic synthesis, particularly with respect to the construction of carbon–carbon and carbon–heteroatom bonds, and therefore have stimulated much research interest. In this review, recent advances in stoichiometric phosphine-mediated reactions primarily including olefinations and annulations are summarized.

1. Introduction

Tertiary phosphines have been widely used in organic syntheses due to their unique and diverse properties.[1] The non-bond lone pair of electrons of the highly polarizable phosphorus atom renders strong nucleophilicity but weak basicity. Phosphines also possess strong oxyphilicity and act as good reducing agents by forming a high energy phosphorus–oxygen bond (*ca.* 130 kcal mol^{-1}). Moreover, an ability to stabilize ylide structures and to serve as good leaving groups allow phosphines to be versatile catalysts in organic reactions. Zwitterionic species and phosphonium ylides are thus common intermediates in phosphine-mediated organic reac-

[a]*Department of Chemistry, School of Science, Xi'an Jiaotong University, Xi'an 710049, P. R. China*
[b]*The State Key Laboratory of Elemento-Organic Chemistry and Department of Chemistry, Nankai University, Tianjin 300071, P. R. China.*
E-mail: zhengjiehe@nankai.edu.cn

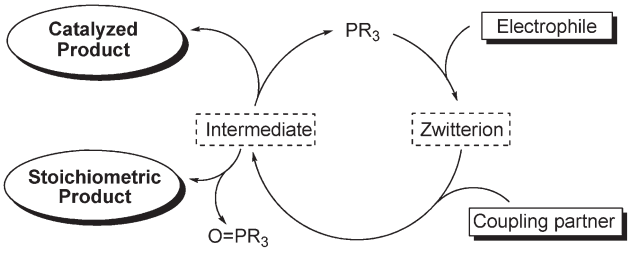


Silong Xu

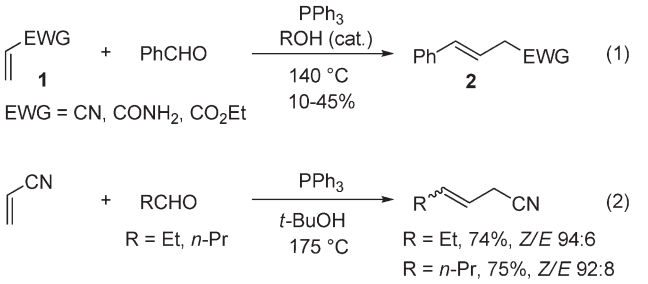
Silong Xu was born in 1982 in Hunan province, China. He received his B.S. degree in Chemistry from Hunan Normal University in 2004. After working for two years as a middle school teacher, he joined the research group of Prof. Zhengjie He at Nankai University, Tianjin, China, where he obtained his MSc (2009) and PhD (2012) in Organic Chemistry. Now he is employed as a Lecturer at Xi'an Jiaotong University, Xi'an, China. His current research is focused on the development of new synthetic reactions promoted by tertiary phosphines.

Zhengjie He

Zhengjie He received his B.S. degree in 1989 from Central China Normal University and his Ph.D. degree from Nankai University in 1994. He began his career at the Institute of Elemento-Organic Chemistry, Nankai University as a lecturer (1994–1996) and an Associate professor (1996–1998). In early 1998, he moved overseas to pursue his postdoctoral training at Pretoria University, SA (1998–1999), Marquette University (1999–2002) and Purdue University, USA (2003–2004). In November 2004, he joined the faculty at Nankai University as a full professor of organic chemistry. His current research interests include development of phosphorus reagent-mediated organic synthetic reactions and development of imaging agents for PET and SPECT.



Scheme 1 Two pathways of phosphine-mediated reactions.



Scheme 2 PPh_3-mediated olefinations between alkenes **1** and aldehydes.

tions. Nowadays, popular applications of phosphines in organic synthesis include the stoichiometric use of phosphines in the well-known Wittig,[2] Mitsunobu,[3] Staudinger[4] and Appel[5] reactions, and their catalytic use as ligands in transition-metal catalysis[6] and as catalysts in newly emerging organocatalysis.[7]

Nucleophilic phosphine organocatalysis has recently emerged as a powerful tool for the construction of carbon–carbon and carbon–heteroatom bonds.[7] Synthetically important phosphine-catalyzed reactions include the Morita–Baylis–Hillman reaction,[8] the Rauhut–Currier reaction,[9] isomerization of alkynes,[10] and allene-based annulation reactions *etc.*[7c,f] Mechanistically, a phosphine-catalyzed chemical transformation generally begins with nucleophilic addition of a phosphine to electrophilic unsaturated species (*e.g.* electron-deficient olefins, allenes or alkynes) to form a zwitterionic intermediate (Scheme 1). The reactive zwitterion is then intercepted by an appropriate coupling partner to give a tetrahedronal intermediate, which leads to formation of the final product by elimination of the phosphine catalyst, usually in a domino fashion. The pronounced nucleophilicity and good leaving group ability of phosphines both play crucial roles in the catalytic cycle. In another scenario, when the oxyphilicity of a phosphine takes effect over its leaving group ability with aid of other functional groups like carbonyl in the transformation, the reaction will alternatively give rise to a deoxygenated product by elimination of a byproduct phosphine oxide in a chemical stoichiometric manner (Scheme 1). These two kinds of transformations constitute the overwhelming majority of the phosphine-involved reactions. As evidenced by the classical Wittig, Mitsunobu, and Staudinger reactions, the stoichiometric phosphine-mediated reactions possess enormous potential in organic synthesis. While the rapid development of nucleophilic phosphine catalysis has been witnessed in the past two decades, a myriad of new stoichiometric phosphine-mediated synthetic reactions have also emerged and have attracted a great deal of interest from the chemistry community. This review aims to summarize the recent advances in stoichiometric phosphine-mediated reactions beyond the traditional Mitsunobu and Staudinger type reactions, with an emphasis on direct phosphine-mediated olefination and annulation reactions. Mechanisms of relevant reactions are also discussed when necessary. To offer readers a clear spectrum of the substrates present in the stoichiometric phosphine-mediated reactions, this review is mainly organized by type of substrate.

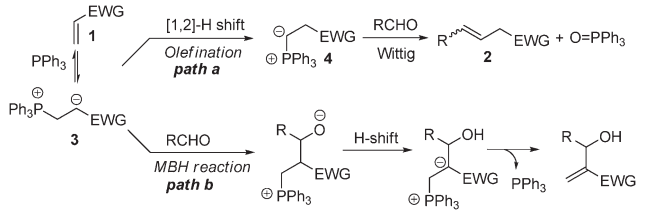
2. Phosphine-mediated olefinations

The Wittig reaction using phosphorus ylides to build alkenes with carbonyl compounds occupies the central position in the construction of carbon–carbon double bonds in organic synthesis. Phosphorus ylides, also known as Wittig reagents, are traditionally prepared from phosphonium salts by deprotonation with bases. Thus, the traditional Wittig reaction is usually carried out under basic and salt-present conditions. Recently, direct tertiary phosphine-mediated olefination reactions between apt Michael acceptors and carbonyl compounds have been successfully realized under neutral and salt-free conditions. These reactions provide a convenient and efficient protocol to build carbon–carbon double bonds, and thus have attracted considerable attention from synthetic organic chemists.

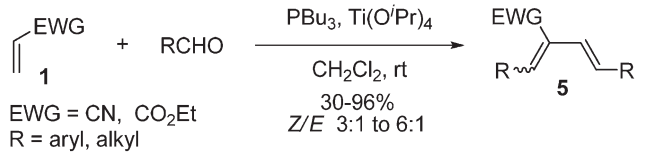
2.1 Based on electron-deficient alkene substrates

The history of direct phosphine-mediated olefination reactions can be traced back to 1964, when Oda and co-workers[11] reported the PPh_3-mediated olefination of electron-deficient terminal alkenes (*e.g.* acrylonitrile, ethyl acrylate) with benzaldehydes in the presence of alcohol, to yield β,γ-unsaturated compounds **2** with exclusive *E*-selectivity (Scheme 2, eqn 1). McClure[12] subsequently disclosed that the reaction with aliphatic aldehydes exhibited an interesting *Z*-selectivity (Scheme 2, eqn 2). Besides the terminal alkenes, doubly-activated olefins such as diethyl fumarate, diethyl maleate, maleic anhydride and maleimide were also effective in olefination reactions with aldehydes under similar conditions.[13]

It was proposed that the olefination was initiated by the nucleophilic addition of phosphine to alkene **1** to form a zwitterionic intermediate **3**, followed by an alcohol-assisted 1,2-proton shift to generate *in situ* a phosphorus ylide **4**, which was intercepted by aldehydes *via* a Wittig reaction to produce the olefination products **2** and phosphine oxide (Scheme 3, path a). The olefination reaction is reminiscent of the Morita–Baylis–Hillman (MBH) reaction[8] between electron-deficient olefins and aldehydes under similar conditions (Scheme 3, path b). The divergent olefination may mechanistically arise



Scheme 3 Possible mechanism of PPh_3-mediated olefination between alkenes **1** and aldehydes.

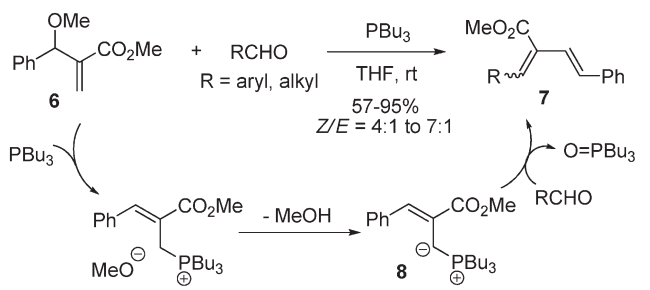


Scheme 4 PBu_3-mediated synthesis of dienes **5** from alkenes **1** and aldehydes.

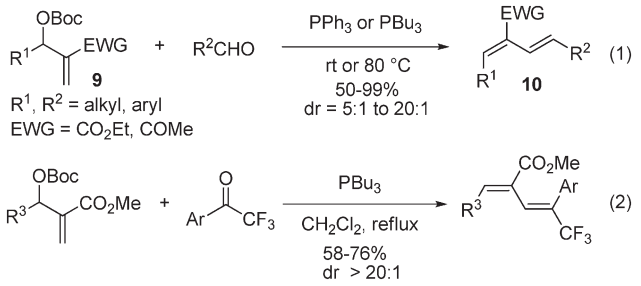
from the preferential 1,2-proton shift of intermediate **3** to form the phosphorus ylide intermediate in the presence of an alcohol.

An innovative extension of the above phosphine-mediated olefination to the synthesis of dienes was reported by Aggarwal in 2007.[14] Under the mediation of stoichiometric PBu_3 and $Ti(O^iPr)_4$, one molecule of terminal alkenes **1** and two molecules of aldehydes were incorporated to generate trisubstituted conjugated dienes **5** with two identical substituents at 1,4-positions (Scheme 4). An attempt to synthesize dienes with different substituents at 1,4-positions proved to be feasible by using methylated MBH adducts **6** instead of terminal alkenes **1**. Under the mediation of PBu_3, **6** and aldehydes readily gave dienes **7** in good yields and moderate stereoselectivity (Scheme 5). The mechanism for the formation of dienes **7** is postulated to encompass an addition-elimination-deprotonation process, in which an allylic phosphorus ylide **8** as a key intermediate is generated *in situ* (Scheme 5).

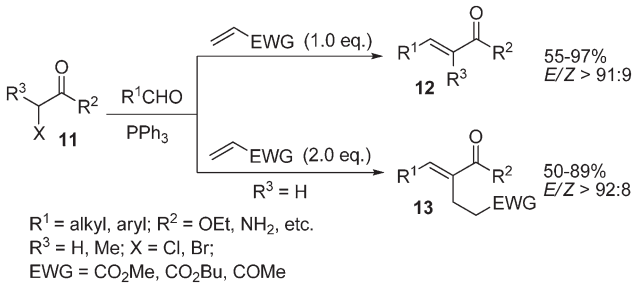
He *et al.*[15] recently developed this protocol to be a general method for stereoselective synthesis of 1,2,4-trisubstituted 1,3-dienes **10** by employing MBH carbonates **9** as the alkene precursor (Scheme 6, eqn 1). Compared to MBH methyl ethers or MBH acetates, the olefination of MBH carbonates **9** could readily proceed with high yield, good stereoselectivity and wide substrate scope. This method was successfully expanded by



Scheme 5 PBu_3-mediated synthesis of dienes **7** from MBH adducts.



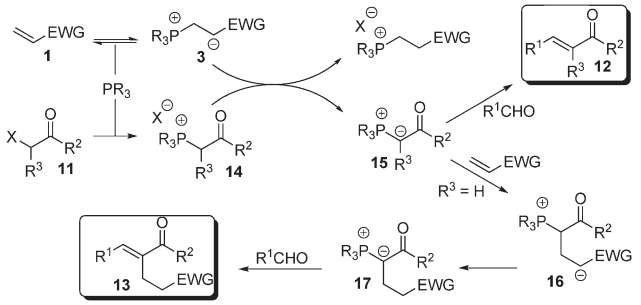
Scheme 6 Phosphine-mediated synthesis of dienes from MBH carbonates.



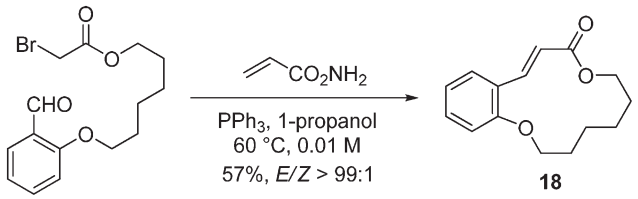
Scheme 7 Phosphine-mediated synthesis of alkenes **12** and **13**.

Ye[16] in the stereoselective synthesis of trifluoromethyl-substituted dienes (Scheme 6, eqn 2).

The active phosphorus ylide intermediates could also be *in situ* generated from α-halo carbonyl compounds. Recently, Tian and co-workers[17] reported a one-pot four-component olefination reaction between α-halo carbonyl compounds **11**, aldehydes, phosphines, and electron-deficient terminal alkenes **1** to efficiently synthesize alkenes **12** and **13** (Scheme 7). The reaction exhibited a wide substrate scope and excellent stereoselectivity. It is believed that the zwitterion **3**, derived from the phosphine and the electron-deficient alkene, serves as a general base in the deprotonation of the phosphonium salt **14** (Scheme 8). The resulting phosphorus ylide **15** could either condense with aldehydes to give alkenes **12** or undergo Michael addition to electron-deficient alkene **1** to form intermediate **16**, depending on the ratio and addition sequence of the reactants. Subsequent proton transfer of intermediate **16** gives phosphorus ylide **17**, which incorporates



Scheme 8 Proposed mechanism for the formation of alkenes **12** and **13**.



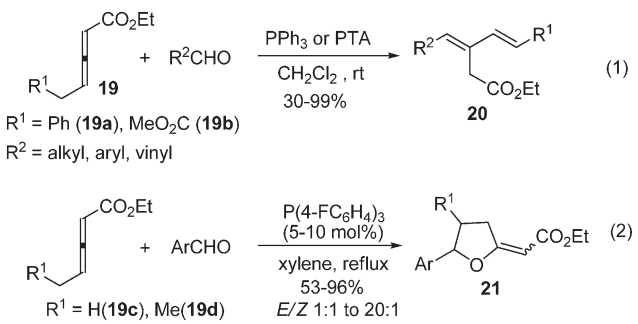
Scheme 9 Intramolecular olefination for synthesis of macrolide **18**.

an aldehyde to produce the alkene **13**. The synthetic utility of this protocol was also demonstrated in the highly *E* selective construction of α,β-unsaturated macrolide **18** *via* an intramolecular olefination (Scheme 9).

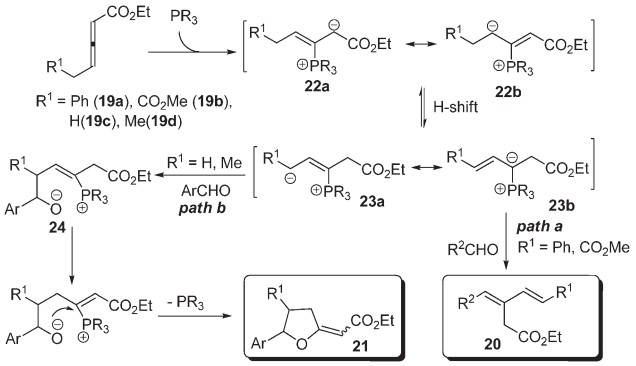
2.2 Based on electron-deficient allene or alkyne substrates

Electron-deficient allenes and alkynes such as allenoates and alkynoates have become a class of popular and versatile substrates in the nucleophilic Lewis base catalyzed reactions.[7b,c,f] The pioneering work by He and other researchers has demonstrated that allenoates and alkynoates also possess decent reactivity in stoichiometric phosphine-mediated olefination reactions with carbonyls.[18] In 2009, He and co-workers[19] disclosed a novel olefination reaction between γ-substituted allenoates **19** and aldehydes under the mediation of phosphines such as PPh_3 or 1,3,5-triaza-7-phosphaadamantane (PTA), that provided trisubstituted 1,3-dienes **20** in high yields with exclusive *E*,*E*-selectivity (Scheme 10, eqn 1). Results indicated that the chemoselectivity was highly dependent on the nature of the γ-substituent of the allenoates. While γ-benzyl allenoate (**19a**) or γ-(methoxycarbonyl)methyl allenoate (**19b**) preferentially underwent olefination reaction with aldehydes, other allenoates bearing a non-conjugative substituent at the *δ* carbon (R^1 in **19** is H or methyl) predominantly undertook a divergent phosphine-catalyzed [3 + 2] annulation reaction with aldehydes to yield 2-alkylidene tetrahydrofurans **21** (Scheme 10, eqn 2).[20]

Isotopic labeling studies provide supportive evidence based on a plausible mechanism as depicted in Scheme 11.[20] Initial nucleophilic attack of the phosphine at the *β* carbon of allenoates forms a resonance-stabilized zwitterionic intermediate **22**, which subsequently undergoes water-assisted stepwise [1,4]-H shift to generate an allylic phosphorus ylide



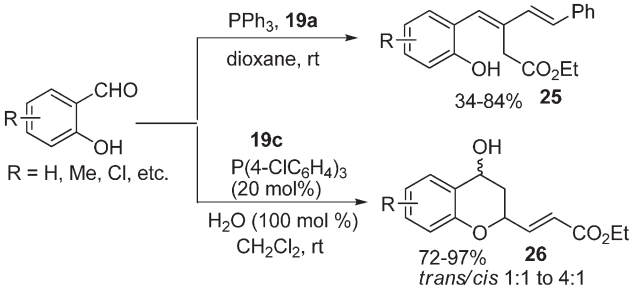
Scheme 10 Phosphine-mediated reactions between γ-substituted allenoates **19** and aldehydes.



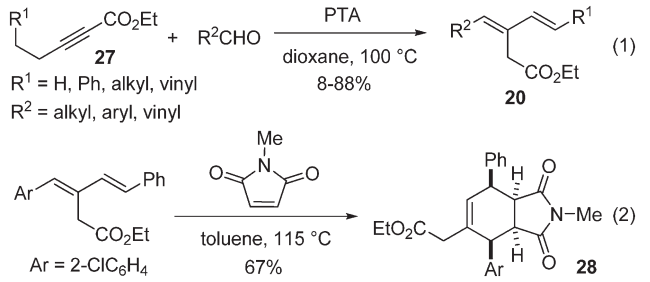
Scheme 11 Possible mechanism for the formation of **20** and **21**.

23. When the substituent R^1 in **23** is a conjugative phenyl or methoxycarbonyl, the more stable resonance form **23b** (R^1 = Ph, CO_2Me) represents the major contributor to the intermediate **23**, which favors the Wittig reaction with aldehydes to produce diene products **20** (path a). In contrast, when R^1 = H or methyl, the ylide **23** preferentially undertakes an addition to aldehydes in the form of the allylic carbanion **23a** probably due to less steric hindrance. Upon double bond migration, the resulting phosphonium salt intermediate **24** undergoes an intramolecular Michael cyclization, followed by elimination of the phosphine, leading to the [3 + 2] annulation product **21**. This kind of substituent-controlling chemoselectivity was further observed in the phosphine-mediated reactions of γ-substituted allenoates with dual-functional salicylaldehydes (Scheme 12). It was found that γ-benzyl allenoate **19a** tended to react by olefination with salicylaldehydes to form the diene products **25**, while γ-methyl allenoate **19c** underwent a distinct phosphine-catalyzed [4 + 2] annulation reaction with salicylaldehydes giving the functionalized chromans **26**.[21]

Under the mediation of tertiary phosphines, alkynoates often exhibit similar reactivity to that of allenoates. Recently, Gothelf *et al.*[22] illustrated that readily available 2-alkynoates **27** could be used as the equivalent of γ-substituted allenoates in the phosphine-mediated olefination reaction with aldehydes to synthesize trisubstituted dienes **20**. The olefination reaction of 2-alkynoates **27** was best mediated by PTA in dioxane at 100 °C, resulting in dienes **20** in good yields and excellent *E*,*E*-selectivity (Scheme 13, eqn 1). The prospective synthetic



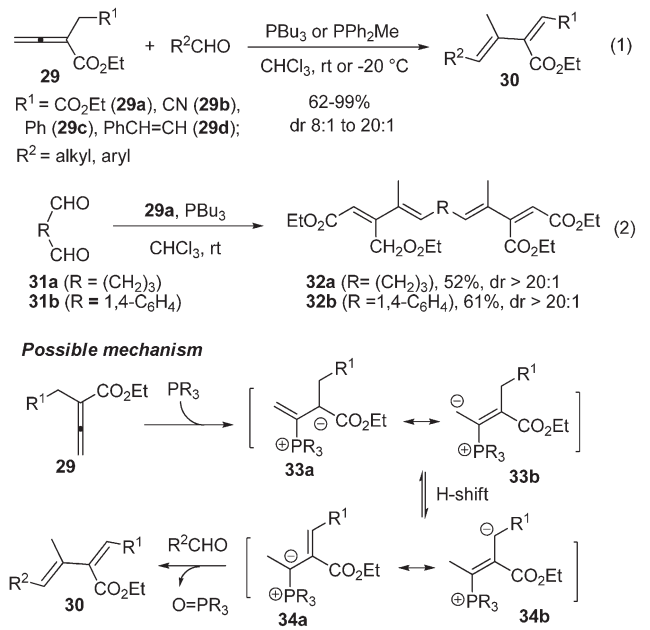
Scheme 12 Phosphine-mediated reactions between salicylaldehydes and allenoates **19**.



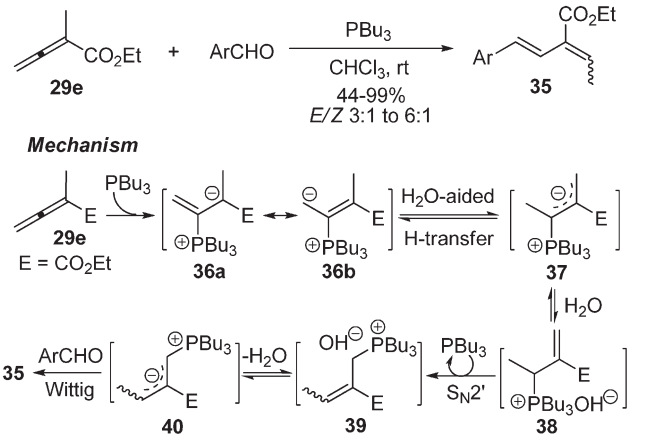
Scheme 13 PTA-mediated olefination of alkynoates **27** and aldehydes.

utility of the dienes **20** was also exemplified in the Diels–Alder reaction with *N*-methylmaleimide to afford *endo*-selective cyclohexenes **28** (Scheme 13, eqn 2).

The phosphine-mediated olefination reactions of α-substituted allenoates with aldehydes was recently developed by He and co-workers.[23] Under the mediation of stoichiometric PBu_3 or PPh_2Me, α-substituted allenoates **29**, *e.g.* α-(ethoxycarbonyl)methyl, α-benzyl allenoates, readily underwent olefinations with various aldehydes, to deliver 1,2,3,4-tetrasubstituted conjugated dienes **30** in excellent yields and with high levels of chemo- and stereoselectivities (Scheme 14, eqn 1). Dialdehydes **31** like glutaraldehyde (**31a**) and terephthalic aldehyde (**31b**) could incorporate two molecules of allenoates to offer the corresponding tetraenes **32** (Scheme 14, eqn 2). Based on ^{31}P NMR tracking and deuterium-labeling experiments, the authors propose a possible mechanism. Presumably, the nucleophilic attack of the phosphine at the allenoate leads to a resonance-stabilized zwitterion **33**, which undergoes a water-assisted stepwise [1,4]-H shift to give an allylic phosphorus ylide **34**. Finally, the Wittig reaction of the



Scheme 14 Phosphine-mediated olefination between allenoates **29** and aldehydes.



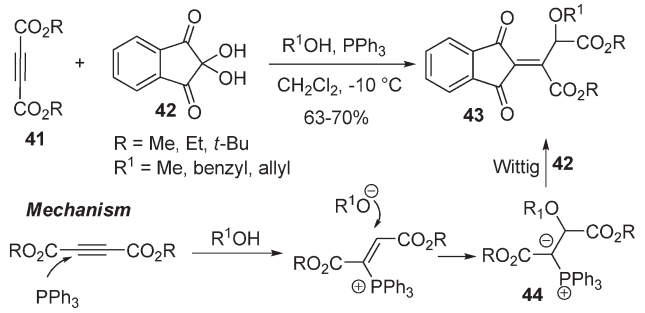
Scheme 15 PBu_3-mediated vinylogous Wittig reaction between allenoate **29e** and aldehydes.

in situ generated phosphorus ylide **34** with aldehydes results in the formation of the dienes **30** (Scheme 14).

Interestingly, when a simple α-methyl allenoate **29e** was subjected to similar reaction conditions, a divergent olefination reaction with aromatic aldehydes occurred, producing regio-differentiated 1,2,4-trisubstituted 1,3-dienes **35** (Scheme 15). In the reaction, the α-methyl group of the allenoate was directly involved in the C=C bond formation. It constitutes a unique example of a vinylogous Wittig reaction. This reaction was previously observed independently by He[24] and Kwon[25] with triarylphosphines used as the mediator. Further studies by He[26] disclosed that the vinylogous Wittig reaction mediated by strongly nucleophilic PBu_3 was superior to the precedents with regard to yield, stereoselectivity and substrate scope, providing an efficient synthesis of trisubstituted 1,3-dienes.

Based on a series of in-depth mechanistic studies including deuterium-labeling, intermediate entrapment, and NMR monitoring, a novel mechanism was proposed to rationalize the vinylogous Wittig reaction (Scheme 15).[26] Initially, the nucleophilic attack of PBu_3 at allenoate **29e** forms a zwitterionic intermediate **36**, which converts into allylic phosphorus ylide **37** through a water-aided stepwise hydrogen shift. Subsequent protonation with adventitious water yields an allylic phosphonium salt **38**. An allylic phosphonium 1,3-rearrangement of **38** *via* a PBu_3-involved S_N2' process generates another phosphonium salt **39**, which undergoes deprotonation by hydroxyl anion to produce a ''rearranged'' allylic phosphorus ylide **40**. Finally, Wittig olefination of the ylide **40** with aldehyde results in the formation of dienes **35**. It should be mentioned that this mechanism is in sharp contrast with the previous mechanism of the vinylogous Wittig reaction involving a key step of retro-Diels–Alder reaction.[27]

Electron-deficient alkynes may be effective substrates in the stoichiometric phosphine-mediated olefination reactions. Ramazani[28] reported that, in the presence of stoichiometric PPh_3 and alcohol, acetylenedicarboxylates **41** and ninhydrin **42** readily delivered highly functionalized alkenes **43** in good yields (Scheme 16). Presumably, the reaction proceeds through



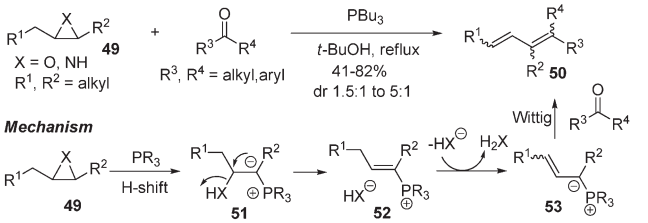
Scheme 16 Condensation between alkynes **41**, ninhydrin **42**, alcohol and PPh_3.

a Wittig reaction of the *in situ* generated phosphorus ylide **44** with ninhydrin. The alcohol acts as a pronucleophile to assist the formation of phosphorus ylide **44**.

Another phosphine-mediated deoxygenative isomerization reaction of propargyl alcohols **45** may also be classified as an olefination reaction (Scheme 17).[29] The treatment with stoichiometric triphenylphosphine, propargyl alcohols **45** gave rise to (*E*,*E*)-dienes **46** in high yields with exclusive *E* selectivity. This reaction was proposed to proceed through a deoxygenation-isomerization process *via* a key intermediate allenone **48**. Typically, it takes full advantage of both strong oxyphilicity and nucleophilicity of the tertiary phosphines. Given its synthetic merits including mild conditions, high yield and exclusive (*E*,*E*)-selectivity, this reaction has been recently applied in total syntheses of several natural products.[30]

2.3 Reactions based on other substrates

In 2004, Hou and co-workers[31] reported a PBu_3-mediated diene synthesis from *N*-Ts aziridines or epoxides and carbonyl compounds (Scheme 18). Aliphatic and aromatic aldehydes or ketones worked well in the olefinations, giving diene products **50** in good yields and moderate *E*/*Z*-selectivity. In-depth mechanistic investigations revealed that the nucleophilic phosphine ring-opening of aziridines or epoxides followed by proton transfers gives rise to the ylide intermediate **51**. A retro-Michael addition of the ylide **51** produces a vinylphosphonium salt **52**, which is subjected to deprotonation to form an allylic phosphorus ylide **53**. The Wittig reaction of the ylide **53** with

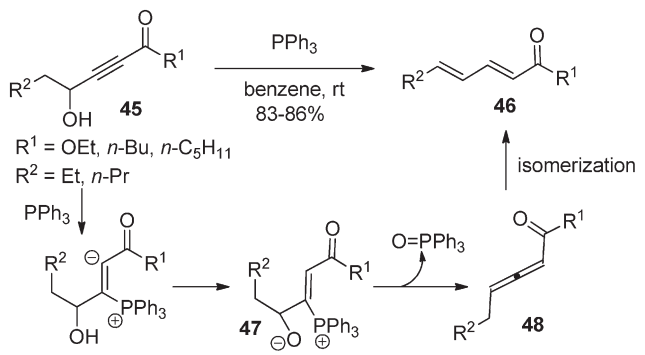


Scheme 18 PBu_3-mediated olefinations of aziridines or epoxides with ketones.

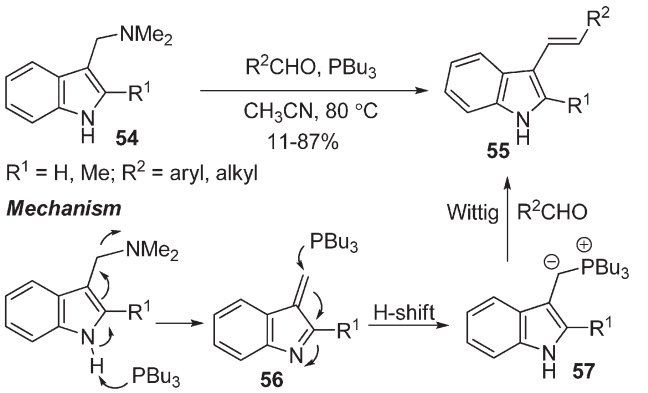
aldehydes or ketones finally accomplishes formation of the conjugated dienes. Given that independently prepared allylic alcohols or amines failed to give the corresponding dienes under the reaction conditions, another alternative pathway consisting of a Wittig olefination of ylide **51** with aldehyde or ketone followed by subsequent elimination of H_2O or $TsNH_2$ to give the diene product has been ruled out.

A facile PBu_3-mediated olefination between gramines **54** and aldehydes was developed by Magomedov and co-workers[32] for the construction of synthetically versatile 3-vinylindoles **55** with excellent *E*-selectivity (Scheme 19). Aromatic aldehydes provided good to excellent yields while aliphatic aldehydes gave low yields, presumably due to the diminished stability of the alkyl-substituted vinylindole products. Compared to traditional methods for preparing vinylindoles, this protocol is certainly attractive with the merits of metal-free and neutral reaction conditions, easy availability of starting materials and no necessity of protection groups on the indole nitrogen. Mechanistically, PBu_3 first acts as a base to deprotonate the indole unit to facilitate elimination of the amine moiety. The resulting azadiene intermediate **56**, upon the conjugate addition of the phosphine followed by a prototropic shift then gives a phosphorus ylide **57**, which undergoes the Wittig reaction with aldehydes to complete the formation of 3-vinylindoles **55** (Scheme 19).

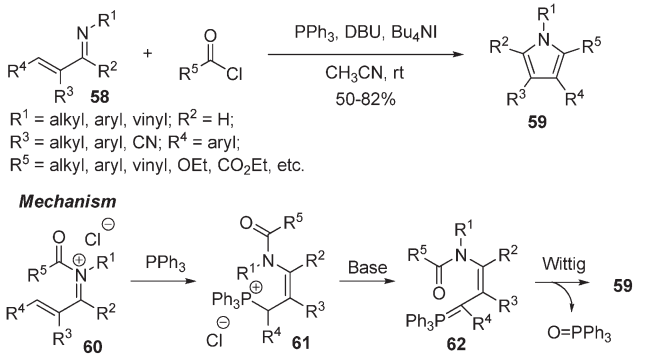
As is clearly demonstrated in the above examples, direct phosphine-mediated olefination reactions featuring *in situ* generation of phosphorus ylides show significant synthetic advantages in the construction of C=C double bonds, and represent a valuable complement to the traditional Wittig



Scheme 17 PPh_3-mediated deoxygenative isomerization of propargyl alcohols **45**.



Scheme 19 Phosphine-mediated synthesis of 3-vinylindoles **55**.



Scheme 20 Phosphine-mediated synthesis of polysubstituted pyrroles.

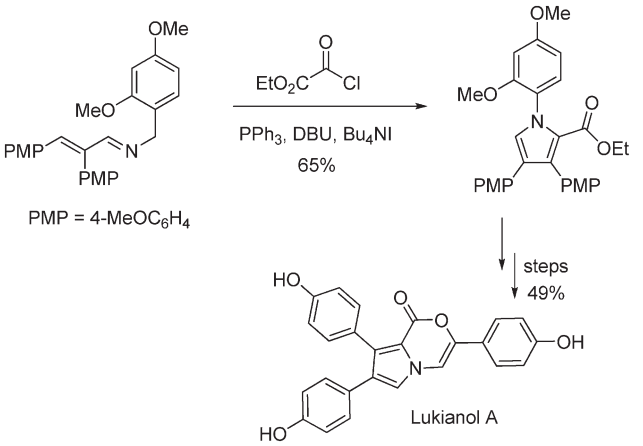
reaction. This methodology is particularly superior in the stereoselective syntheses of conjugated dienes over the classical Wittig olefination reaction of allylic phosphorus ylides which usually suffers from severe side reactions and low stereoselectivity.

3. Phosphine-mediated annulations

Stoichiometric phosphine-mediated annulation reactions have emerged as a versatile toolbox for the construction of carbo- and heterocycles. In the annulations, the phosphines often convert to phosphine oxides. Various electrophilic substrates such as electron-deficient alkenes, alkynes, allenes, and azo compounds are most often used in these transformations. Accordingly, phosphine-mediated annulations will be discussed in this section by the type of electrophilic substrates. It should be mentioned that phosphine-mediated annulations involving Staudinger reactions are not discussed herein because a comprehensive review by de los Santos *et al.* has recently addressed various aspects of the Staudinger reaction.[33]

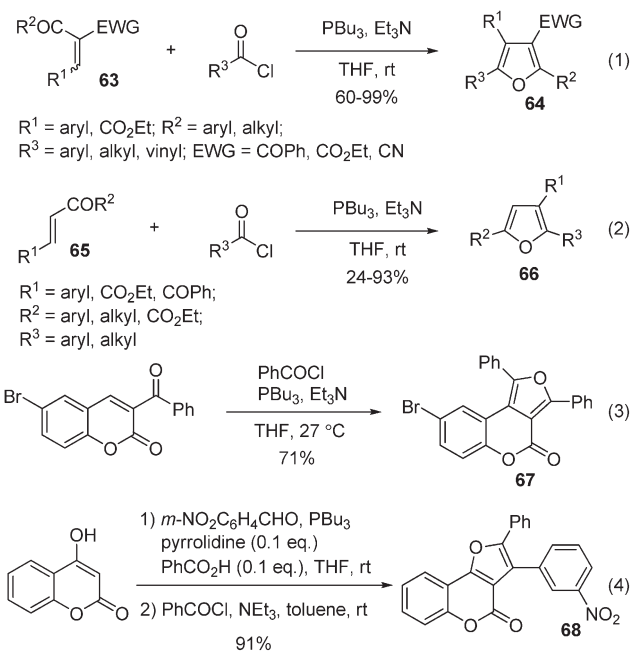
3.1 Based on electron-deficient alkene substrates

In 2009, Arndtsen and co-workers[34] successfully devised a facile synthesis of important polysubstituted pyrroles from α,β-unsaturated imines **58** and acid chlorides under the mediation of stoichiometric phosphines and bases (Scheme 20). A soft halide additive Bu_4NI was found to be good for suppressing byproducts. A diverse and wide range of pyrroles **59** could be accessed in good to excellent yields through modulation of the two building blocks. The authors postulated a mechanism as follows: the phosphine undergoes a Michael-type 1,4-addition to the α,β-unsaturated iminium salt **60** that is generated from acid chloride and imine; the resulting phosphonium salt **61** is then deprotonated by the base DBU, leading to the formation of the phosphorus ylide **62**; an intramolecular Wittig reaction of **62** completes synthesis of the pyrrole **59**. The synthetic utility of this annulation reaction was also illustrated in the total synthesis of Lukianol A, an important compound possessing activity against human epidermoid carcinoma (Scheme 21).

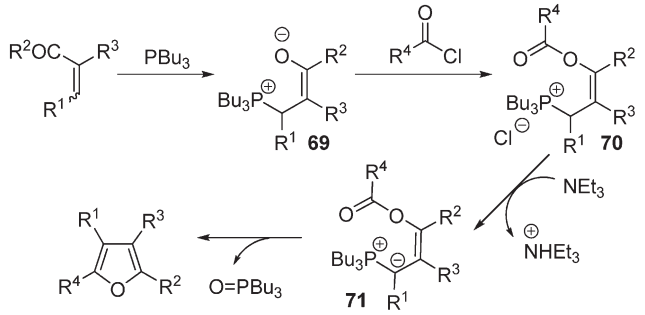


Scheme 21 Synthesis of Lukianol A.

By a similar strategy, Lin and co-workers[35] have recently developed a series of phosphine-mediated annulations from different enones and acid chlorides to construct furan structures. From doubly activated enones **63** and acid chlorides, tetrasubstituted furans **64** were readily prepared in good yields under the treatment of PBu_3 and triethylamine (Scheme 22, eqn 1). Simple α,β-unsaturated ketones **65** afforded trisubstituted furans **66** under the similar conditions (Scheme 22, eqn 2).[36] These two annulation methods are also useful in the construction of furan-fused cyclic structures like furo[3,4-*c*]coumarins **67** and furo[3,2-*c*]coumarins **68** (Scheme 22, eqn 3 and 4).[37] It is proposed that formation of the furans from enones and acid chlorides proceeds through a double domino sequence of *O*-acylation/intramolecular Wittig



Scheme 22 Phosphine-mediated syntheses of furans from enones and acid chlorides.

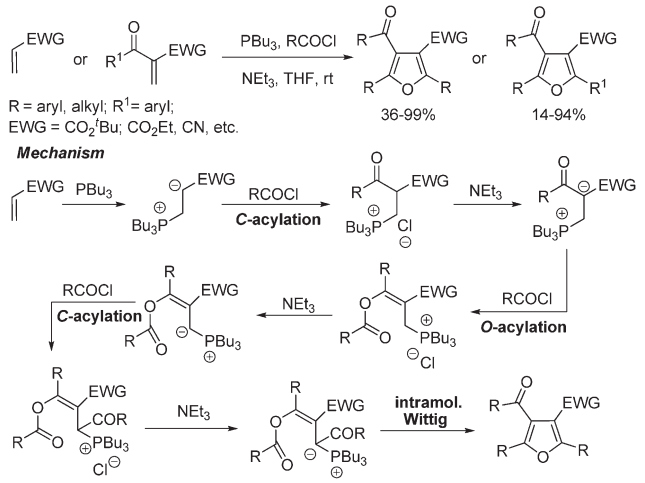


Scheme 23 Rationale for the phosphine-mediated formation of furans from enones.

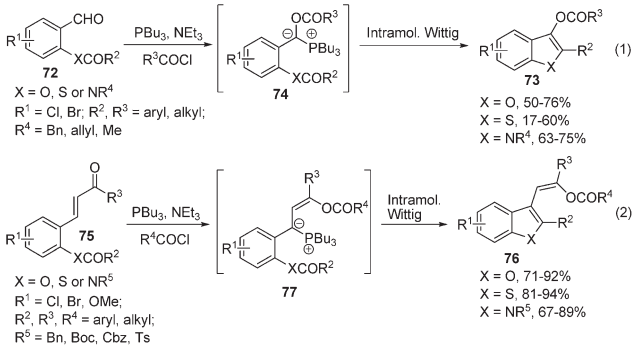
reaction. Initially, Michael addition of the phosphine to the enone generates a zwitteronic intermediate **69**, which undergoes *O*-acylation with acid chloride giving phosphonium salt **70**. Upon treatment of the base triethylamine, phosphonium salt **70** gives out the phosphorus ylide **71**. Ylide **71** finally undertakes an intramolecular Wittig reaction to accomplish formation of the furan structures (Scheme 23).

Recently, He and co-workers[38] expanded this synthetic methodology by employing more readily available terminal olefins (Scheme 24). Under the mediation of stoichiometric PBu_3, simple terminal activated alkenes like acrylates, acrylonitrile, and 2-acylacrylates with acid chlorides or anhydrides provided tetrasubstituted furans in moderate to excellent yields. This reaction is proposed to proceed through a highly efficient multiple domino process like *C*-acylation/*O*-acylation/*C*-acylation/intramolecular Wittig reaction sequence (Scheme 24).

The phosphine-mediated synthetic methodology for furans can be further extended to the syntheses of benzo heterocycles. A facile phosphine-mediated synthesis of benzofurans, benzothiophenes and indoles from salicylic aldehyde derivatives and acid chlorides was developed by Lin and co-workers (Scheme 25).[39] Benzaldehydes **72** with a functionality of ester,



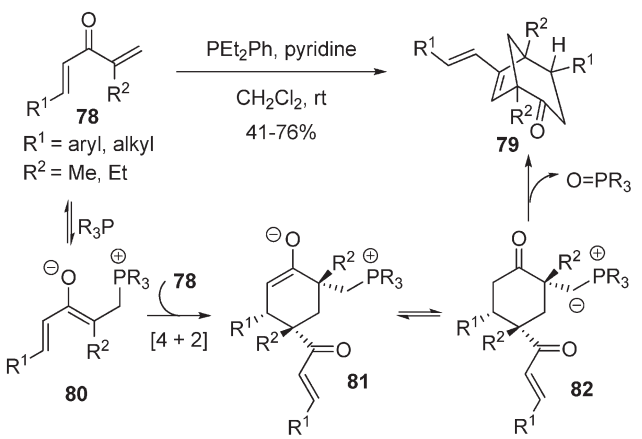
Scheme 24 Phosphine-mediated domino synthesis of furans from terminal alkenes.



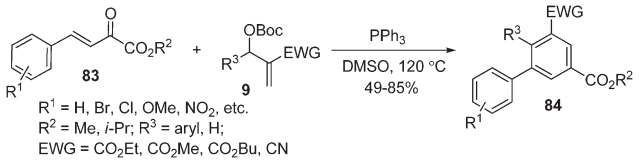
Scheme 25 Phosphine-mediated syntheses of benzofurans, benzothiophenes and indoles.

thioester or amide group readily underwent an annulation with acid chlorides under the mediation of PBu_3 and NEt_3 to produce benzofurans, benzothiophenes and indoles, respectively. Subsequently, the authors also reported that the aromatic enones **75** undertook a similar annulation under the same conditions to deliver benzofurans, benzothiophenes and indoles, respectively.[40] The phosphorus ylides **74** and **77** were verified as the key intermediates in the annulations. It is noteworthy that the intramolecular Wittig reaction of the ylide **77** regioselectively took place between the ylide and the carbonyl linked to benzene ring to form benzo heterocycles **76**.

In addition to the synthesis of heterocycles, stoichiometric phosphine-mediated annulations of electron-deficient alkenes are also applied in the construction of carbocycles. In 2006, Schaus and co-workers[41] demonstrated a highly stereoselective phosphine-mediated tandem cyclization of 1,4-dien-3-ones **78** for the construction of bicyclo[3.2.1]octenones (Scheme 26). On the basis of deuterium-labeling and ^{31}P NMR experiments, the authors proposed a mechanism with the phosphine acting as both a nucleophilic trigger and a Wittig mediator (Scheme 26). Initially, nucleophilic addition of the phosphine to the terminal alkene unit of **78** leads to a diene intermediate **80**, which then undergoes an *endo*-selective [4 + 2] cycloaddition with one molecule of **78** to give cycloadduct **81**. A



Scheme 26 Phosphine-mediated construction of bicyclo-[3.2.1]octenones **79**.

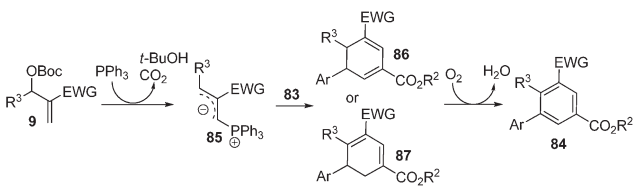


Scheme 27 Phosphine-mediated benzannulation reaction.

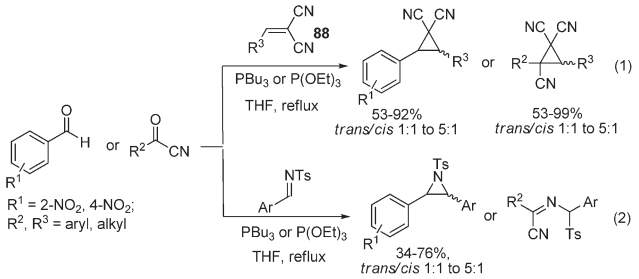
reversible proton transfer is necessary to produce the ylide intermediate **82**, which undertakes an intramolecular Wittig reaction between the ylide and the exocyclic carbonyl of the enone moiety to complete the construction of bicyclo[3.2.1]octenone **79**.

Recently, Huang and co-workers[42] developed an efficient phosphine-mediated benzannulation reaction of MBH allylic carbonates **9** with β,γ-unsaturated α-ketoesters **83** to produce polysubstituted benzenes **84** (Scheme 27). Multi-aryl compounds bearing different substituents including halogens could be accessible by this approach. Those halo multi-aryls are generally difficult to synthesize by metal-catalyzed aryl–aryl cross coupling reactions. In a plausible mechanism, the benzannulation reaction involves an air oxidation of cyclohexadiene intermediates **86** or **87** (Scheme 28). These intermediates may be generated from a common intermediate allylic phosphorus ylide **85** with β,γ-unsaturated α-ketoesters **83** in a domino process.

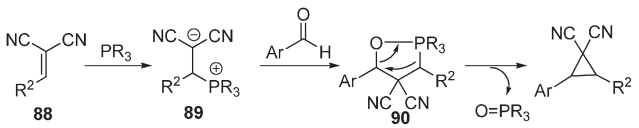
Highly strained cyclopropanes are also accessible by the phosphine-mediated annulation strategy. Shi and co-workers[43] disclosed an interesting cyclopropanation reaction between doubly activated alkenes methylidenemalononitriles **88** and carbonyl compounds under the treatment of stoichiometric phosphites or phosphines (Scheme 29, eqn 1). Although the carbonyl compounds were limited to reactive 2- or 4-nitrobenzaldehydes and α-keto nitriles, various aryl- and alkyl-substituted methylidenemalononitriles were effective in the reaction to give functionalized cyclopropanes in good yields and moderate diastereoselectivity. Interestingly, using *N*-Ts imines instead of methylidenemalononitriles, the corresponding aziridines were also prepared from nitrobenzaldehydes in modest yields but failed with α-keto nitriles (Scheme 29, eqn 2). Regarding the cyclopropanation mechanism, initial nucleophilic addition of phosphine/phosphite to the activated alkene **88** forms a carbanion intermediate **89**, which in turn undergoes another nucleophilic addition to the carbonyl compound, generating a five-membered oxaphospholane intermediate **90**. Decomposition of the oxaphospholane **90** brings about cyclopropane and phosphine oxide (Scheme 30).



Scheme 28 A plausible mechanism for formation of **84**.



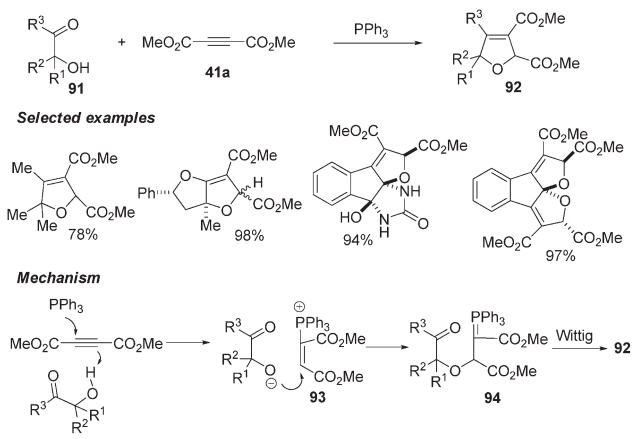
Scheme 29 Phosphine-mediated annulations for three-membered rings.



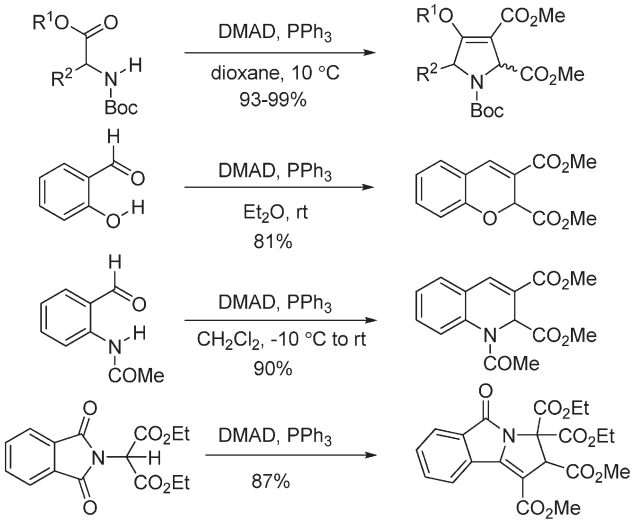
Scheme 30 Proposed mechanism for the phosphine-mediated cyclopropanation.

3.2 Based on electron-deficient alkyne and allene substrates

Electron-deficient alkynes and allenes are also prevalent substrates in phosphine-mediated annulation reactions. A number of efficient synthetic methods for carbo- and heterocycles have been recently developed from these two kinds of substrates. In particular, acetylenedicarboxylates **41**, featuring a triple bond functionality flanked with two ester groups, are widely used in many phosphine-mediated annulation reactions to provide efficient syntheses of carbo- and heterocycles. Yavari *et al.*[44] first reported that dimethyl acetylenedicarboxylate (DMAD) **41a** and dual-functional α-hydroxy carbonyl compounds afforded highly functionalized dihydrofuran products **92** under the mediation of stoichiometric PPh_3 (Scheme 31). Using cyclic α-hydroxy carbonyl compounds, the corresponding bicyclic or polycyclic dihydrofuran structures could be readily prepared.[45] Mechanistically, formation of the dihydrofuran structure by this reaction is pretty straightforward. Nucleophilic addition of the phosphine to DMAD and



Scheme 31 Phosphine-mediated synthesis of dihydrofurans.



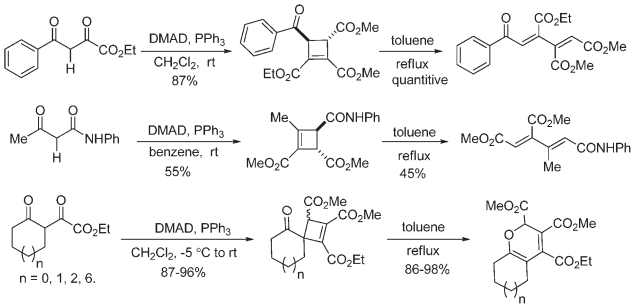
Scheme 32 Phosphine-mediated annulations between DMAD and dual-functional carbonyl compounds.

subsequent deprotonation of α-hydroxy carbonyl compound **91** associatively generates an ion pair intermediate **93**. A Michael addition of the ion pair **93** followed by an intramolecular Wittig reaction readily accomplishes the formation of the dihydrofuran **92** (Scheme 31).

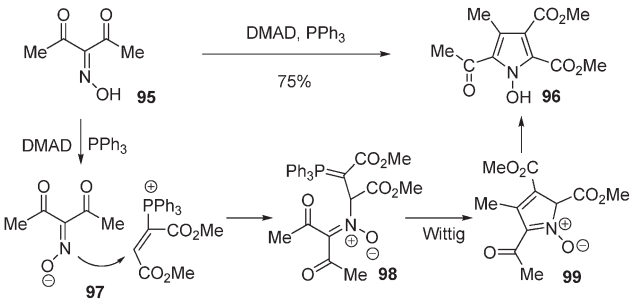
A series of similar dual-functional carbonyl compounds bearing adjacent acidic hydrogen such as α-amino esters, salicylaldehydes, *etc.* have the same reactivity with DMAD and PPh_3, delivering various cyclic products (Scheme 32).[46]

Under similar conditions, 1,3-dicarbonyl compounds with an acidic α-CH and DMAD readily afforded four-membered cyclobutenes in good to excellent yields. In boiling toluene, the cyclobutenes could undergo electrocyclic ring-opening reactions to deliver highly functionalized 1,3-dienes or 2*H*-pyran derivatives (Scheme 33).[47]

Hekmatshoar[48] reported that pentan-2,3,4-trione 3-oxime **95** could also serve as a dual-functional partner in the PPh_3-mediated annulation reaction with DMAD, giving an annulation product *N*-hydroxypyrrole **96** in 75% yield. A plausible mechanism involves a sequence of the following steps: initial formation of the vinylphosphonium salt **97**, generation of the phosphorus ylide **98**, ring closure by an intramolecular Wittig



Scheme 33 Phosphine-mediated synthesis of cyclobutenes from DMAD.



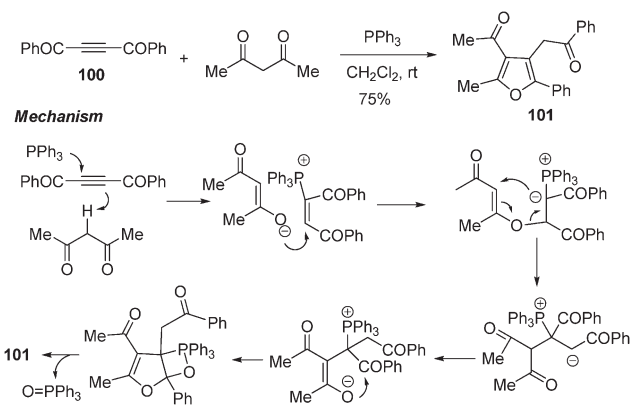
Scheme 34 Phosphine-mediated synthesis of *N*-hydroxypyrrole **96** from DMAD.

reaction, and tautomerization to the *N*-hydroxypyrrole **96** (Scheme 34).

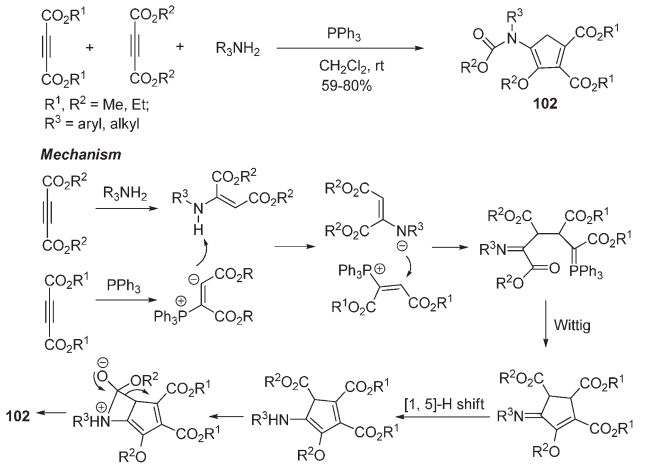
1,4-Butynediones exhibit a different annulation mode under similar conditions. Yavari and co-workers[49] reported, under the mediation of stoichiometric PPh_3, dibenzoylacetylene **100** and acetylacetone gave out tetrasubstituted furan **101** (Scheme 35). Other enol-like substrates like 5,5-dimethylcyclohexane-1,3-dione, 1-naphthol, 2-naphthol, 2,7-dihydroxynaphthalene, or 8-hydroxyquinoline could undertake the annulation reaction to generate the corresponding furans. As depicted in Scheme 35, the authors proposed a distinct mechanism to rationalize formation of the furan product **101**.

A novel tandem PPh_3-mediated annulation reaction between primary amines and two molecules of acetylenedicarboxylates was observed by Yavari and co-workers, which delivered highly functionalized cyclopentadienes **102** in good yields (Scheme 36).[50] When two kinds of different acetylenedicarboxylates were used, the cross-condensation reaction could be readily realized by adjusting the addition sequence of acetylenedicarboxylates to obtain a single product. For example, when ethyl and methyl acetylenedicarboxylates were added sequentially or in a reversed order, two different products were obtained respectively. This observation provides supportive information for the putative mechanism depicted in Scheme 36.

Kumar and co-workers[51] recently reported a rare annulation of acetylenedicarboxylates with *N*-phenyl-*C*-chromonyl



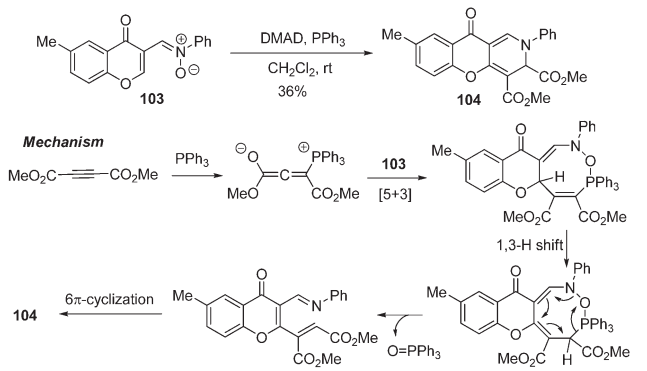
Scheme 35 Phosphine-mediated annulation of alkynediones and acetylacetone.



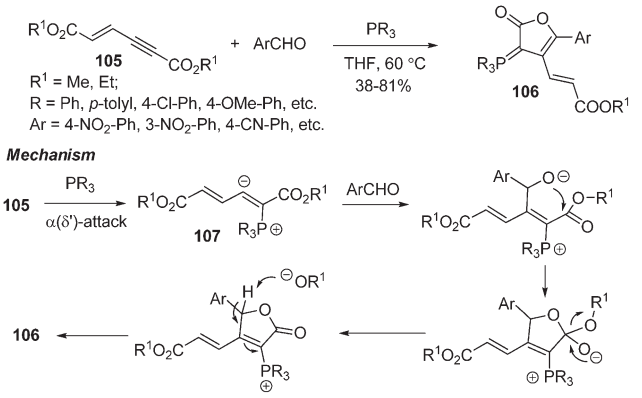
Scheme 36 Phosphine-mediated synthesis of cyclopentadienes **102**.

nitrones **103** in the presence of PPh_3, producing dihydropyridine-fused benzopyrones **104** in moderate yields. Presumably, the reaction mechanism encompasses a novel [5 + 3] annulation step and a following deoxygenative rearrangement process, as shown in Scheme 37. It is noteworthy that the corresponding *N*-alkyl nitrones only underwent a distinct [3 + 2] cycloaddition with acetylenedicarboxylates in the presence or absence of phosphines. This chemoselectivity may be attributed to the difference in the configuration of the nitrones: *N*-phenyl-*C*-chromonyl nitrone **103** prefers to adopt a Z-configuration which facilitates the initial [5 + 3] annulation with DMAD; while the corresponding *N*-alkyl nitrone prefers to adopt an *E*-configuration, leading to the [3 + 2] cycloaddition with acetylenedicarboxylates.

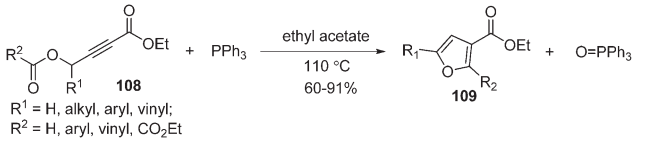
Deng and Chuang[52] recently reported a stoichiometric phosphine-mediated annulation reaction of enynoates **105** with aldehydes. A three-component reaction readily occurred between enynoates, aldehydes and phosphines, leading to the formation of γ-lactones **106** bearing a phosphorus ylide moiety (Scheme 38). The reaction features a non-classical Michael addition of the phosphine to the α(δ′)-position of the enynoates producing the zwitterionic intermediates **107**, which subsequently react with aldehydes to form γ-lactones.



Scheme 37 Phosphine-mediated annulation of unsaturated nitrones.



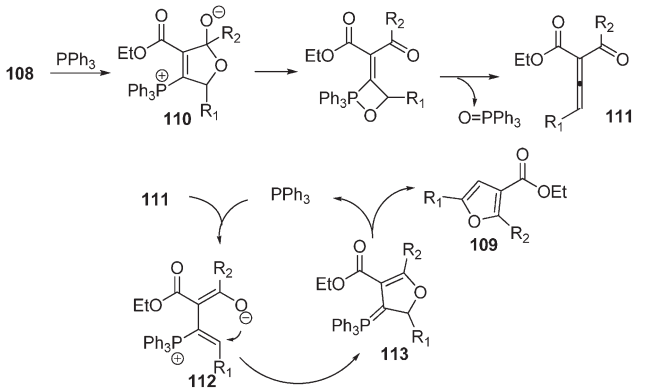
Scheme 38 Phosphine-mediated annulation of enynoates and aldehydes.



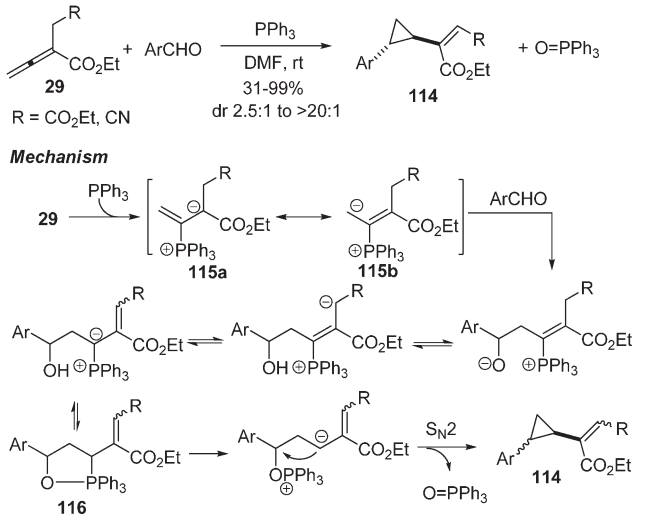
Scheme 39 Phosphine-mediated synthesis of furans from γ-acyloxy butynoates.

A highly efficient and convergent synthesis of substituted furans **109** was developed by Krische and co-workers from γ-acyloxy butynoates **108** (Scheme 39).[53] The precursor γ-acyloxy butynoates **108** can be readily prepared by the condensation of propiolates with aldehydes followed by acylation with acid chlorides. By this method, 2,3- and 2,4-disubstituted and 2,3,5-trisubstituted furans could be assembled under the mediation of stoichiometric PPh_3 with good tolerance to functional groups.

In the formation of furans, the phosphine plays a dual-functional role as both a reducing agent and a nucleophilic catalyst (Scheme 40). Exposure of γ-acyloxy butynoate **108** to PPh_3 results in a tandem sequence of conjugated addition/acyl substitution, affording a betaine intermediate **110**. Extrusion of triphenylphosphine oxide leads to the intermediate allene **111**. Under the catalysis of the phosphine, the electron-



Scheme 40 A possible mechanism for the formation of furans **109**.



Scheme 41 Phosphine-mediated cyclopropanation between α-substituted allenoates and aldehydes.

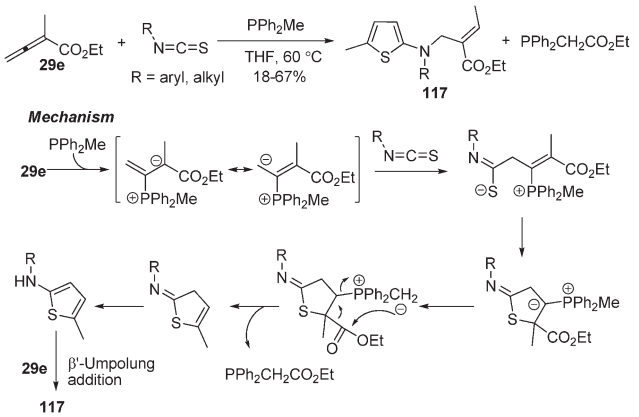
deficient allene **111** then accomplishes an intramolecular ring closure to bring about the furan product **109**.

In addition to electron-deficient alkynes, allenoates were also good candidates in the stoichiometric phosphine-mediated annulation reactions. An interesting cyclopropanation reaction between α-substituted allenoates, aldehydes and PPh_3 was recently reported by He and co-workers, delivering functionalized vinyl cyclopropanes **114** (Scheme 41).[54] This reaction constitutes the first example of the smallest carbocycles prepared from allenoates under the mediation of phosphines. Mechanistically, the phosphine first adds to the allenoate to form a zwitterionic intermediate **115**, which is intercepted by an aldehyde and subsequently subjected to a series of reversible proton transfers to generate an oxaphospholane **116**. A C–P bond cleavage followed by an intramolecular S_N2 displacement then finishes the formation of cyclopropane **114**. Deuterium-labeling and ^{31}P NMR monitoring experiments have provided supportive evidence for the above putative mechanism.

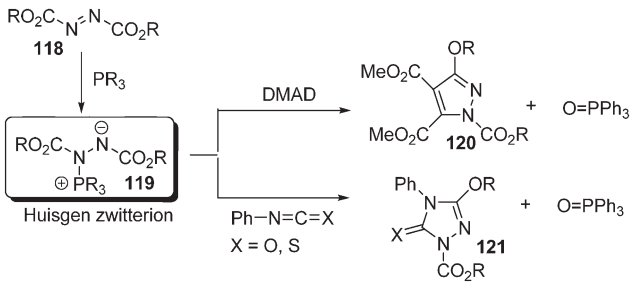
Recently, Shi and co-workers[55] disclosed a rare phosphine-mediated annulation reaction to give thiophenes. Thus, under the mediation of stoichiometric PPh_2Me, two molecules of α-methyl allenoate **29e** and one molecule of isothiocyanate formed 2-aminothiophene derivative **117** in moderate yield (Scheme 42). Interestingly, at the completion of the reaction, the phosphine PPh_2Me was converted into $PPh_2CH_2CO_2R$ by a possible migration of an ester group from the allenoate (Scheme 42).

3.3 Based on dialkyl azodicarboxylates substrates

It is well known that dialkyl azodicarboxylates **118** are able to form zwitterionic species **119** with phosphines (Scheme 43). Such a zwitterion is called as the Huisgen zwitterion since Huisgen first established its structure.[56] Traditionally, the Huisgen zwitterion is known as a key intermediate in the important Mitsunobu reaction.[3] In fact, Huisgen zwitterions are very often involved in many annulation reactions to



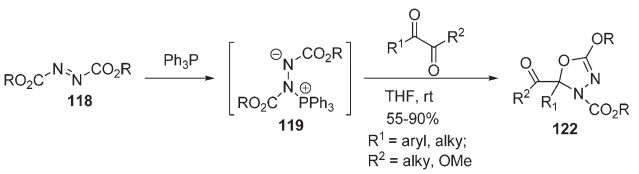
Scheme 42 PPh_2Me-mediated formation of thiophenes from allenoates and isothiocyanates.



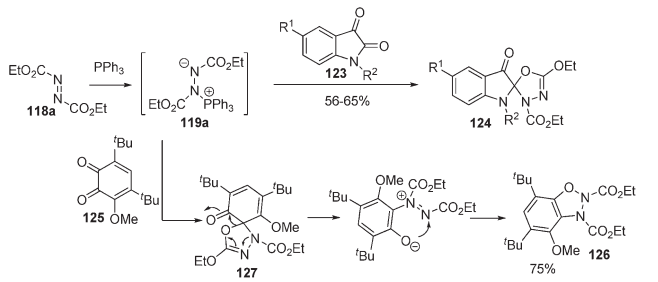
Scheme 43 Early reports on the annulations of Huisgen zwitterions.

construct heterocycles. Early reports about the annulations of Huisgen zwitterions can be traced back to 1960s when Cookson[57] first reported its cyclization with dimethyl acetylenedicarboxylate (DMAD) to form pyrazoles **120**, and Huisgen[56] reported its annulations with isocyanates or isothiocyanates to produce triazole products **121** (Scheme 43).

However, little attention had been paid to the annulations of the Huisgen zwitterions during the following several decades until the annulation reactions of Huisgen zwitterions with α-ketoesters or α-diketones was disclosed by Lee and co-workers in 2005, leading to the synthesis of the oxadiazole compounds **122** (Scheme 44).[58] The simple alkyl ketones and aldehydes failed to give the annulation products, but afforded acyclic hydrazine derivatives. In the same year, Nair[59] performed a similar annulation by employing *N*-substituted isatins **123** as the electrophiles, producing spiro-oxadiazoles **124** in moderate yields (Scheme 45). However, the structurally similar 1,2-benzoquinone **125** and Huisgen zwitterions deliv-



Scheme 44 Synthesis of oxadiazoles from Huisgen zwitterions.



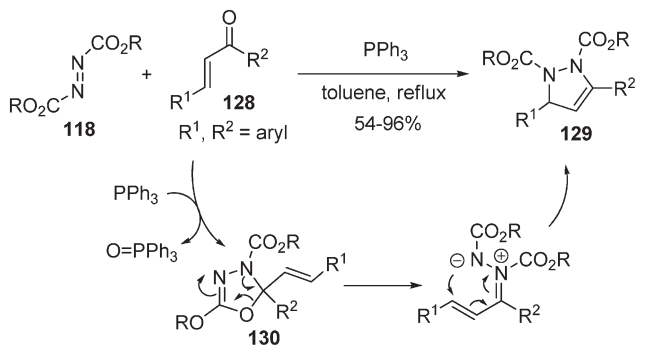
Scheme 45 Annulations of Huisgen zwitterions with isatins **123** and 1,2-benzoquinone **125**.

ered dihydro-1,2,3-benzoxadiazole **126** in a good yield. Generation of **126** was ascribed to a spontaneous rearrangement of the corresponding spiro-oxadiazole intermediate **127**.

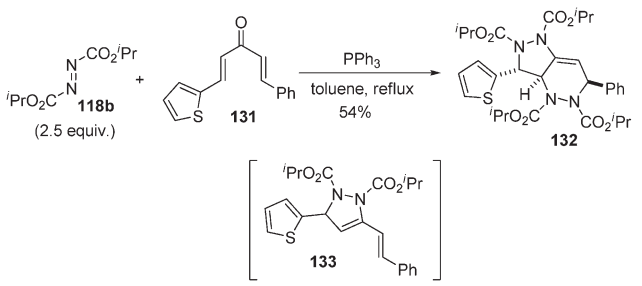
Nair and co-workers[60] further developed an interesting annulation of Huisgen zwitterions with α,β-unsaturated ketones like chalcones **128**, which furnished pyrazolines **129** in good yields (Scheme 46). The reaction is believed to proceed through the initial annulation of the Huisgen zwitterions with the carbonyl of chalcones to generate an intermediate vinyl oxadiazole **130**. Subsequent ring rearrangement produces the final pyrazolines. Interestingly, treatment of dienone **131** with diisopropyl azodicarboxylate (DIAD, **118b**) and PPh_3 afforded highly functionalized pyrazolopyridazine **132**, which was presumably resulted from the follow-up Diels–Alder reaction of the initially generated vinyl pyrazolines **133** with excessive DIAD (Scheme 47).

Wang and co-workers[61] also developed an alternative annulation of Huisgen zwitterions with acyl aziridines **134** to afford pyrazolines **135** in excellent yields (Scheme 48). Mechanistically, this reaction was proposed to proceed through initial formation of intermediate oxadiazoline **136** and subsequent aziridine moiety-triggered rearrangement to finish the synthesis of pyrazolines **135**.

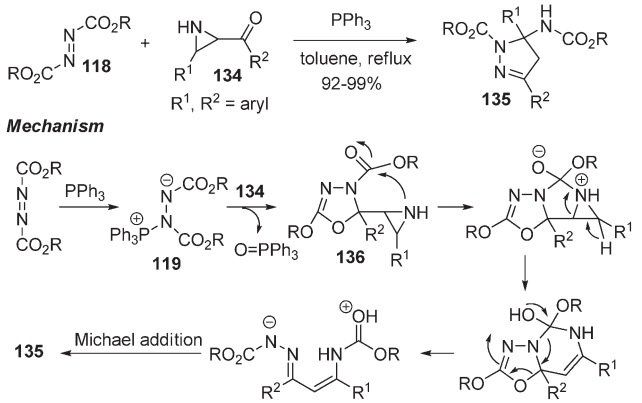
Similar to carbonyl compounds, imines are also effective electrophiles in the annulations with Huisgen zwitterions. Very recently, an annulation reaction of *N*-protected imine **137** with Huisgen zwitterions leading to the formation of triazole **138** in a quantitative yield was reported by Shi and co-workers (Scheme 49).[62] Using its precursor **139** instead of the imine,



Scheme 46 The annulation of Huisgen zwitterions with chalcones.



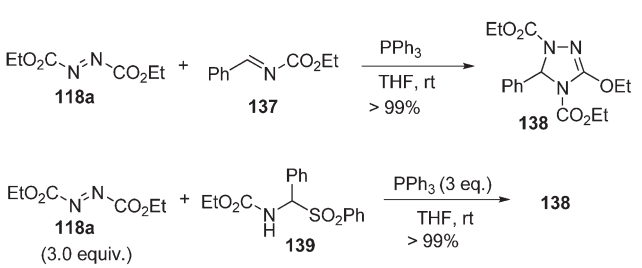
Scheme 47 Formation of pyrazolopyridazine **132**.



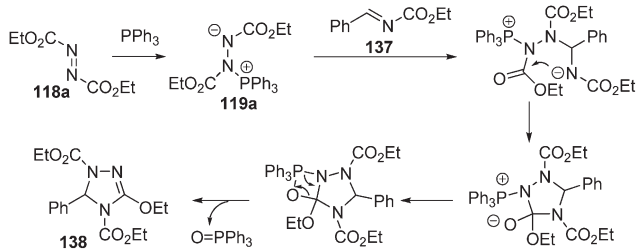
Scheme 48 The annulation reaction of Huisgen zwitterions with acyl aziridines.

the annulation reaction also took place with three equivalents of diethyl azodicarboxylate and PPh_3 used. Presumably, the precursor **139** was converted *in situ* into the imine **137** with Huisgen zwitterions acting as a base. It was observed that the mismatched imines and azoesters with different ester groups resulted in a mixture of substituted triazoles. A plausible mechanism of this annulation reaction is depicted in Scheme 50.

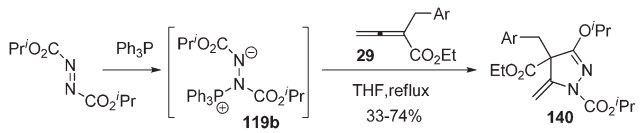
It is well known that electron-deficient allenes like allenoates can readily form reactive zwitterionic intermediates upon nucleophilic attack of phosphines.[7c] However, results from Nair group[63] showed that, in the presence of azodicarboxylates, phosphines like PPh_3 preferentially formed Huisgen zwitterions instead. Thus, upon the treatment of PPh_3, α-substituted allenoates **29** and DIAD afforded pyrazolines **140** in good yields (Scheme 51).



Scheme 49 The annulation of Huisgen zwitterions with imines.



Scheme 50 Proposed mechanism for the formation of **138**.

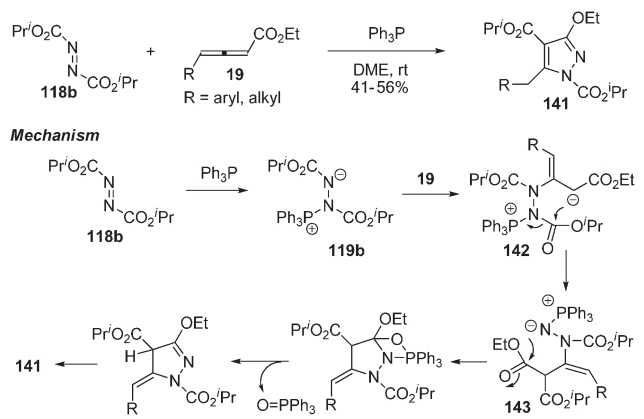


Scheme 51 The annulation of Huisgen zwitterions with α-substituted allenoates.

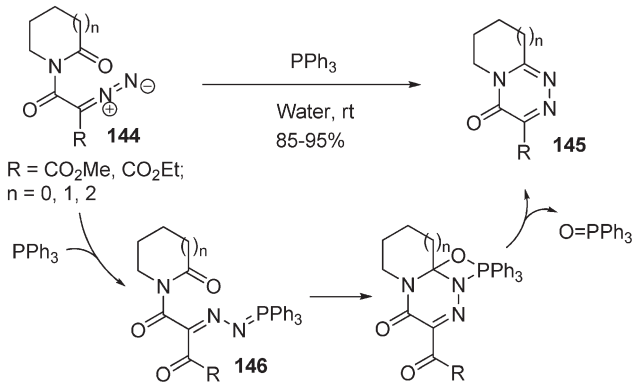
Interestingly, γ-substituted allenoates **19** undertook a distinct annulation mode with Huisgen zwitterions and afforded fully substituted pyrazoles **141**. Apparently, a unique migration of ester group from nitrogen to carbon is involved in the reaction (Scheme 52). In a plausible mechanism, Huisgen zwitterions **119b** initially adds to the allenoates **19** to give zwitterionic intermediate **142** which undertakes an intramolecular nucleophilic attack at an ester group of azoester, leading to the formation of aza-ylide intermediate **143**. An intramolecular aza-Wittig reaction, followed by a double bond migration, accomplishes the formation of pyrazoles **141**.

3.4 Based on other substrates

Besides the above mentioned popular substrates including electron-deficient alkenes, alkynes, allenes, and azodicarboxylates, other substrates have also been sporadically used in stoichiometric phosphine-mediated annulation reactions. For example, in 2009, Muthusamy and Srinivasan[64] reported that diazoimides **144** readily cyclized in the presence of phosphines



Scheme 52 The annulation of Huisgen zwitterions with γ-substituted allenoates.



Scheme 53 Phosphine-mediated synthesis of bicyclic triazines.

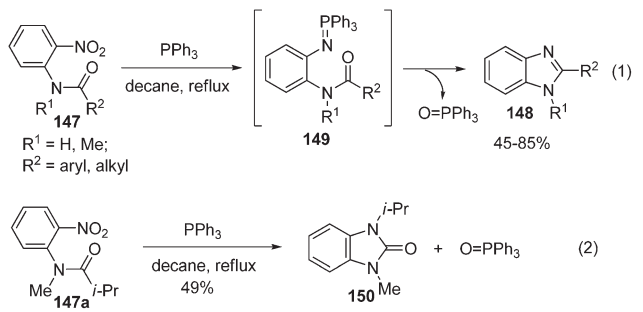
to afford bicyclic 1,2,4-triazines **145** (Scheme 53). The reaction when performed in water was better in obtaining triazines **145** in good to excellent yields, thus providing an easy and green procedure for synthesis of 1,2,4-triazines. Mechanistically, the reaction is proposed to proceed through the initial formation of the aza phosphorus ylide **146**, followed by an intramolecular aza-Wittig reaction to lead to the formation of the triazines.

Another effective reductive cyclization of 2-nitroanilides **147** to generate 2-substituted benzimidazoles **148** under the treatment of PPh_3 was recently realized by Vasella *et al.* (Scheme 54, eqn 1).[65] The cyclization reaction presumably proceeds through an intramolecular aza-Wittig reaction *via* the *in situ* generated aza phosphorus ylide intermediate **149**. Both aliphatic and aromatic acyl-derived 2-nitroanilides are effective in the reaction. However, an exceptional cyclization reaction was observed in the case of *N*-methyl isobutyranilide **147a**, resulting in the formation of benzimidazole **150** under identical conditions (Scheme 54, eqn 2). This divergent cyclization mode was speculated to result from the bulkiness of *i*-Pr group.

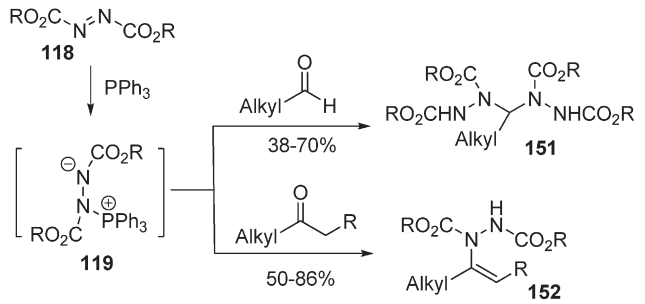
4. Miscellaneous reactions

4.1 Synthesis of hydrazone/hydrazine derivatives

As illustrated in section 3.3, the Huisgen zwitterions, generated from azodicarboxylates and triphenylphosphine,



Scheme 54 Phosphine-mediated cyclizations of 2-nitroanilides **147**.



Scheme 55 Reactions of Huisgen zwitterions with alkyl aldehydes and ketones.

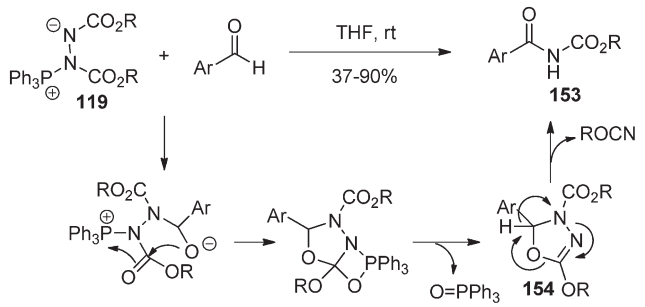
have displayed rich and diverse annulation reactivity with multi-functional carbonyl compounds such as α-ketoesters, α-diketones, 1,2-benzoquinones, and chalcones *etc.*, leading to a variety of nitrogen heterocycles. Conversely, the reactions of Huisgen zwitterions and simple carbonyl compounds are able to provide acyclic nitrogen-containing compounds such as hydrazones and hydrazines. The seminal report by Lee[58] disclosed that Huisgen zwitterions reacted with alkyl aldehydes and ketones to afford acyclic hydrazines **151** and vinyl hydrazones **152**, respectively (Scheme 55).

In contrast to alkyl aldehydes, Nair[66] demonstrated that aromatic aldehydes and Huisgen zwitterions produced acyl carbamates **153**. It is conceivable that an oxadiazoline intermediate **154** is initially formed, which subsequently undergoes ring fragmentation and concomitant hydride transfer to deliver the product acyl carbamates with release of by-product alkyl cyanate (Scheme 56).

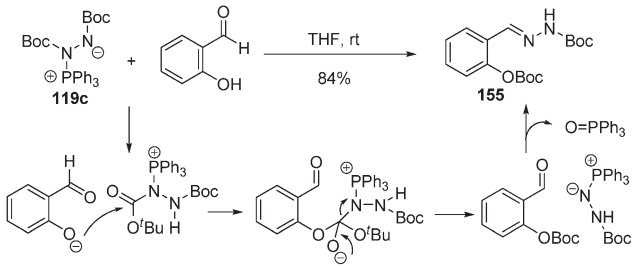
Girard *et al.*[67] reported that dual-functional salicylaldehyde exhibited a distinct reactivity with Huisgen zwitterion **119c**, producing Boc-protected hydrazone **155** (Scheme 57).

In a related work,[68] Nair examined the reactivity of aryl ketones with Huisgen zwitterions. The reaction of diaryl-1,2-dione **156** with Huisgen zwitterions **119a** produced dicarboethoxy monohydrazone **157** through a migration of carboethoxy group *via* intermediates **158** and **159** (Scheme 58).

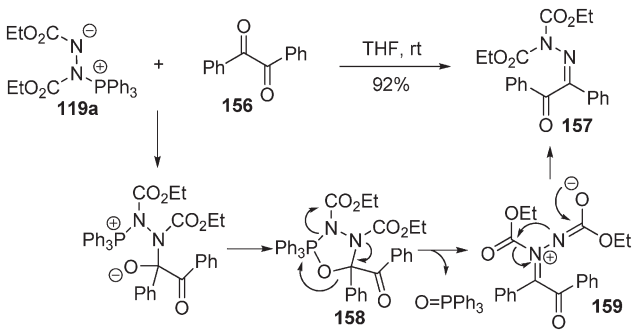
Recently, Shi and co-workers[69] reported that acyl cyanides and Huisgen zwitterions could produce the corresponding hydrazones **160** at 90 °C in toluene. At room temperature, however, the reaction gave azines **161** chemoselectively. Azines **161** were able to be converted into hydrazones **160** at an elevated temperature in toluene (Scheme 59). This temperature-dependent chemoselectivity is presumably ascribed to a reversible nitrogen-to-oxygen migration of alkoxycarbonyl group.



Scheme 56 Synthesis of acyl carbamates from Huisgen zwitterions and aromatic aldehydes.



Scheme 57 Reaction of Huisgen zwitterions with salicylaldehyde.



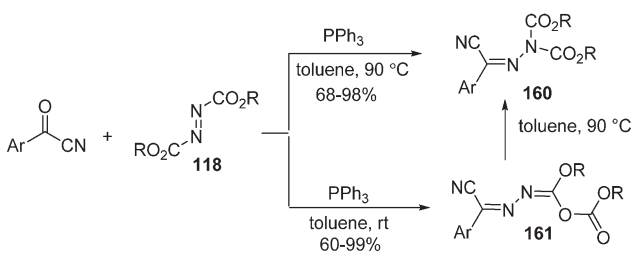
Scheme 58 Reactions of Huisgen zwitterions with aryl ketones.

4.2 Synthesis of enamides

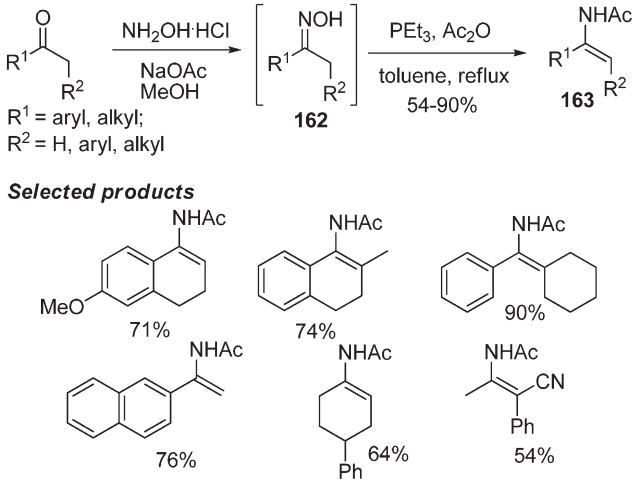
An efficient phosphine-mediated reductive acylation of oximes **162** with acetic anhydride to give enamides **163** was developed by Singh and co-workers (Scheme 60).[70] Since the oximes are easily accessible from the corresponding ketones, this reaction thus constitutes a valuable protocol for the transformation of ketones to enamides.

4.3 Synthesis of acylated cyanohydrins

Trialkyl phosphines can be used as an efficient reducing agent in organic syntheses. Shi and co-workers[71] demonstrated that activated carbonyl groups in α-keto esters, benzils, 1,2-cyclohexanedione, and α-ketophosphonates could be reduced



Scheme 59 Temperature-dependent syntheses of hydrazones **160** and azines **161**.

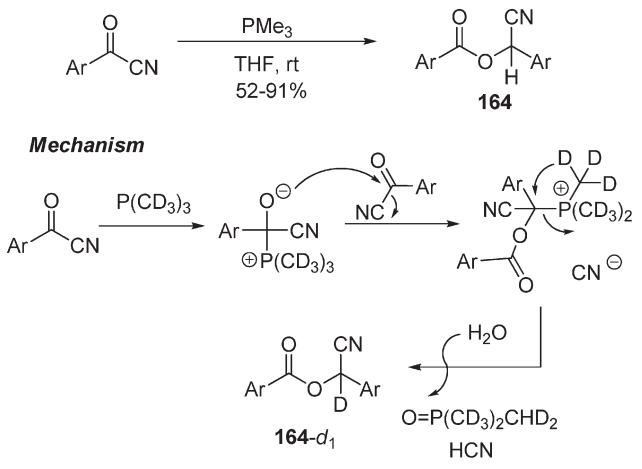


Scheme 60 Phosphine-mediated synthesis of enamides.

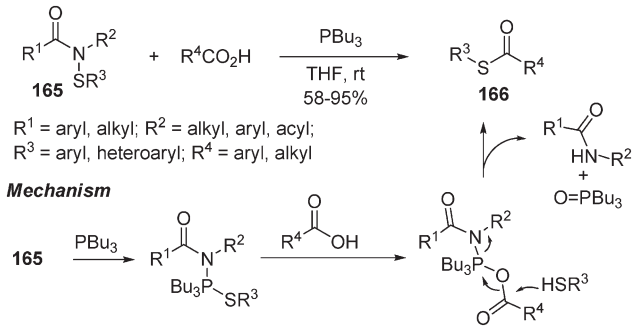
into the corresponding hydroxyl compounds by alkyl phosphines. Recently, the same authors described an interesting reductive coupling of two molecules of acyl cyanides to produce *O*-acyl cyanohydrins **164** under the mediation of trimethylphosphine (Scheme 61).[72] The possible mechanism involves a rare hydride transfer from alkyl phosphine to the carbonyl group, which is strongly supported by the formation of deuterated *O*-acyl cyanohydrin **164**-d_1 in a deuterium-labeling experiment with deuterated trimethylphosphine-d_9 used.

4.4 Synthesis of thioesters

The phosphine-mediated reaction of disulfides and carboxylic acids is a well-known synthetic route for thioesters. However, in this method, only half of the sulfur moieties in disulfides are incorporated into the desired thioesters. Recently, a more efficient synthetic method for thioesters was successfully developed by Srogl and Henke from thioimides **165** and carboxylic acids (Scheme 62).[73] Under the mediation of



Scheme 61 Phosphine-mediated synthesis of *O*-acyl cyanohydrins from acyl cyanides.



Scheme 62 Phosphine-mediated synthesis of thioesters from thioimides.

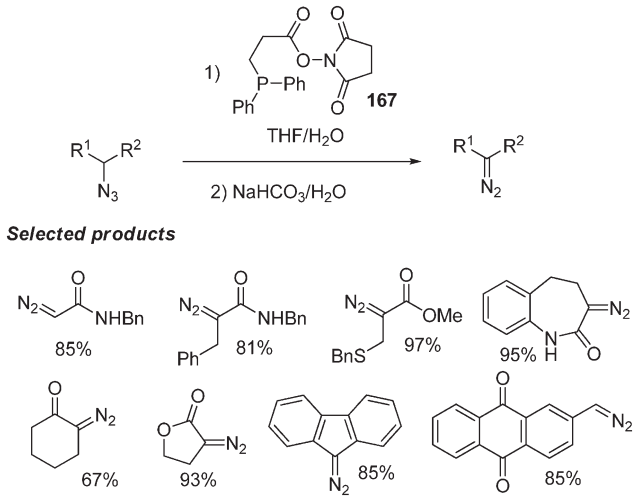
stoichiometric phosphine PBu_3, both cyclic and acyclic thioimides readily furnished the thioesters **166** in good to excellent yields with a good tolerance to various functional groups. In a postulated mechanism, initial insertion of the phosphine into the S–N bond of the thioimide results in a pentavalent phosphorus intermediate, which then interacts with carboxylic acid to eventually form the desired thioesters **166** and by-products amide and phosphine oxide.

4.5 Synthesis of diazo compounds

Phosphines and azides can readily react to generate iminophosphoranes by extrusion of N_2, as is well known in the Staudinger reaction.[4] However, a recent work by Raines *et al.*[74] found that the reaction between phosphines and azides could be induced into a divergent pathway by introducing special functional group into the phosphines. They found that the treatment of a phosphine **167** possessing a proximate *N*-hydroxysuccinimyl ester group, a wide range of azides could be converted into the corresponding diazo compounds in high yields. This phosphine-mediated reaction thus provides an attractive method to synthesize diazo compounds (Scheme 63). A rationale about this reaction is illustrated in Scheme 64. The strongly electrophilic *N*-hydroxysuccinimyl ester group readily traps the phosphazide intermediate **168** to generate a triazenophosphonium species **169** before it decomposes into iminophosphorane as in the Staudinger reaction. Upon hydrolysis and a follow-up base-catalyzed fragmentation, the triazenophosphonium species **169** converts to diazo compounds.

5. Phosphine-economical organic synthetic reactions

Stoichiometric phosphine-mediated reactions have enormous potential in organic synthesis as testified by the traditional Wittig, Mitsunobu, Staudinger and Appel reactions and those newly discovered phosphine-mediated olefinations, annulations and other reactions summarized in this review. As a common feature of the stoichiometric phosphine-mediated reactions, the formation of phosphine oxide as a concomitant byproduct, however, represents a drawback which impacts on the atom economy and large-scale applicability of these

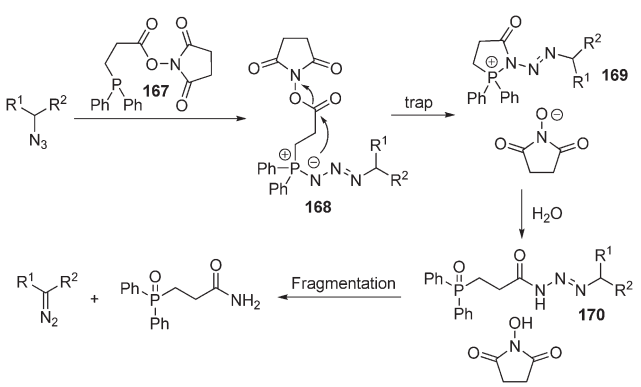


Scheme 63 Phosphine-mediated synthesis of diazo compounds from azides.

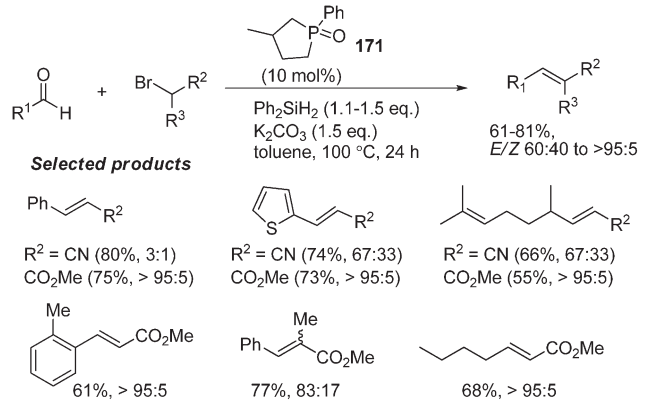
reactions. To tackle this ''phosphine-oxide'' issue, considerable efforts have recently been engaged in how to convert a stoichiometric phosphine-mediated reaction into a catalytic phosphine-mediated one, and encouraging progress has been witnessed in this area.

In situ reduction of phosphine oxides with reducing agents represents a reasonable strategy for the development of phosphine-economical organic reactions. However, owing to the high energy of P=O bond, the chemoselective reduction of phosphine oxides to phosphines in the presence of other functionalities from starting materials and products remains a formidable challenge. Identifying a compatible reducing agent and a suitable phosphine to fulfill this purpose has proved elusive for many years.

It was in 2009 when O'Brien and co-workers[75] reported the discovery of a viable combination of diphenylsilane (Ph_2SiH_2) as the reducing agent and a cyclic phosphine oxide **171** as the precatalyst, that provided the first catalytic Wittig reaction at a higher temperature (100 °C) (Scheme 65). The catalytic Wittig reaction manifested a generally wide substrate scope and produced the alkenes in good yields and high *E*-selectivity. In a



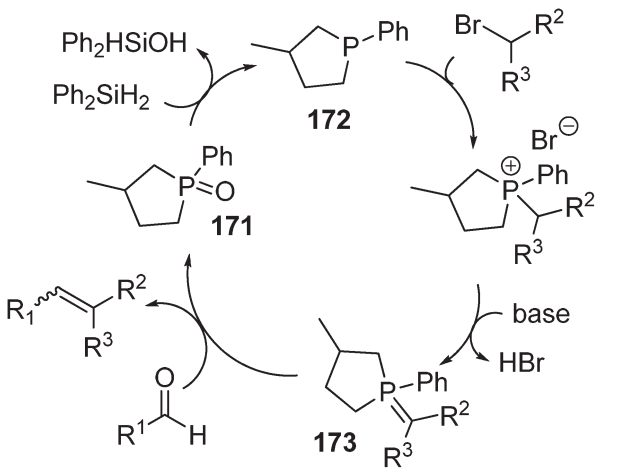
Scheme 64 Rationale for the formation of diazo compounds from azides.



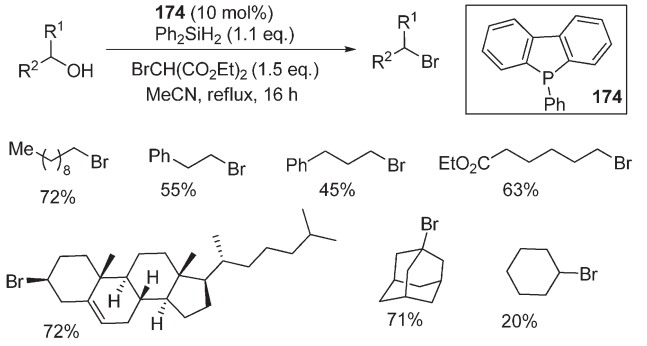
Scheme 65 The first catalytic Wittig reaction.

possible catalytic cycle (Scheme 66), phosphine oxide **171** is reduced *in situ* to the corresponding phosphine **172**, which is converted into the ylide **173** with alkyl bromide in the presence of a base; the subsequent Wittig reaction of the ylide and aldehydes produces the alkene product and releases the phosphine oxide into the catalytic cycle. Remarkably, diphenylsilane (Ph_2SiH_2) reduced the phosphine oxide **171** selectively in the presence of aldehydes and other reagents. It is noteworthy that $O{=}PPh_3$ was less efficient in the catalytic Wittig reaction than cyclic phosphine oxide **171**. Very recently, O'Brien[76] demonstrated that a catalytic amount of acid additive *e.g.* 4-nitrobenzoic acid could promote the efficiency of acyclic phosphine oxides such as $O{=}PBu_3$ and $O{=}PPh_3$ as the precatalysts in the catalytic Wittig reaction. Proper acid additives greatly enhanced the reduction rate of phosphine oxides with silanes. By this means, a catalytic Wittig reaction was realized even with cyclic phosphine oxide **171** at room temperature.[76]

In 2011, van Delft and co-workers[77] systematically explored silane reductions of a range of cyclic phosphine oxides and found that phosphines of five-membered rings are preferred



Scheme 66 Mechanism for the catalytic Wittig reaction.

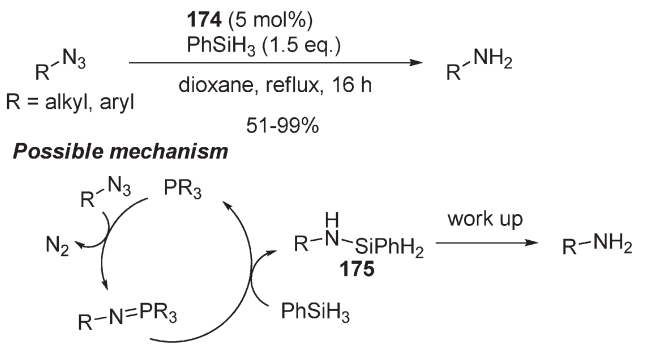


Scheme 67 Phosphine-catalyzed Appel reaction.

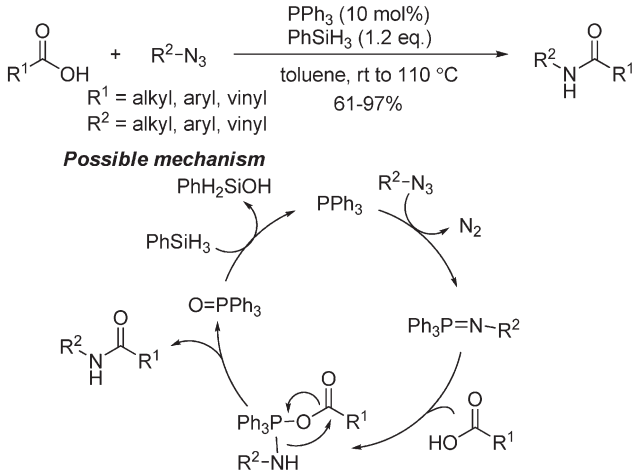
candidates for catalytic applications. A combination of dibenzophosphole **174** and Ph_2SiH_2 could be successfully applied in phosphine catalytic Appel reactions (Scheme 67). A series of primary, secondary and tertiary alcohols were converted to the corresponding bromides in good yields with diethyl bromomalonate used as a bromide source.

A phosphine-catalyzed Staudinger reduction reaction was subsequently developed by van Delft[78] by employing dibenzophosphole **174** and $PhSiH_3$ (Scheme 68). Primary amines were prepared in good to excellent yields with high functional group tolerance from a variety of azides. In contrast with traditional Staudinger reduction, the catalytic variant avoids the use of equivalent water in the reduction step. Mechanistically, the reaction of an azide and phosphine initially forms a iminophosphorane intermediate by extrusion of N_2; subsequent reduction by a silane regenerates the phosphine and produces aminosilane **175** which is hydrolyzed to the amine products during work-up (Scheme 68).

Phosphine-promoted Staudinger ligation of carboxylic acid derivatives and azides represents a pre-eminent strategy for the construction of amide C–N bond. However, the generation of stoichiometric phosphine oxide at the same time plagues this method. Very recently, Ashfeld and co-workers[79] developed the first phosphine-catalyzed Staudinger ligation by applying an *in situ* reduction protocol (Scheme 69). It was found that the combination of PPh_3 (0.1 equiv.) and Ph_2SiH_2 (1.2 equiv.) could efficiently provide the chemoselective



Scheme 68 Phosphine-catalyzed Staudinger reduction.

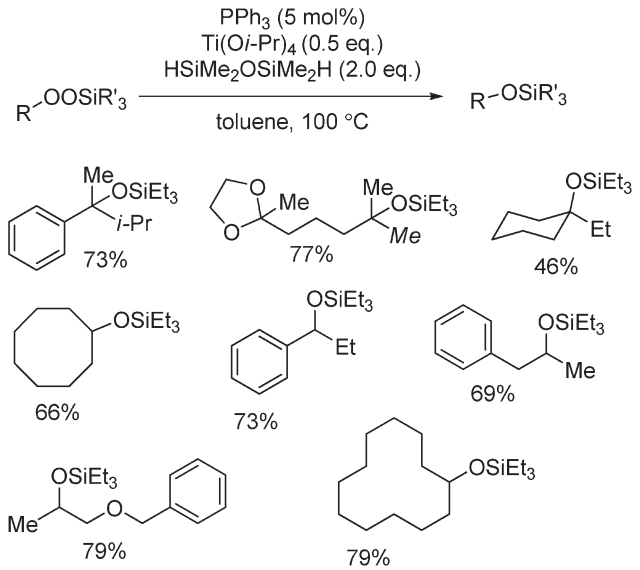


Scheme 69 Phosphine-catalyzed Staudinger ligation.

catalytic Staudinger ligation.[78] Various carboxylic acids and azides underwent the catalytic Staudinger ligation to produce the corresponding amides in excellent yields. Impressively, this catalytic variant is applicable to the assembly of peptides from amino acids without loss of optical purity. Accordingly, it may find further uses in preparing biologically active peptides.

Reduction of peroxides with stoichiometric phosphines provides a useful method for the synthesis of alcohol derivatives. Woerpel and co-workers[80] recently reported a PPh_3-catalyzed reduction of alkyl silylperoxides by using a combination of a titanium(IV) alkoxide and a siloxane as a reducing agent (Scheme 70). Various silylperoxides were effective substrates that provided the corresponding silylated alcohols in acceptable yields.

As illustrated in the above reports, the strategy of *in situ* reduction with the reducing agent silanes has proven success-



Scheme 70 Phosphine-catalyzed reduction of silylperoxides.

ful; however, the reduction and reuse of the byproduct phosphine oxide is realized at the cost of relatively expensive silanes.[81] The development of phosphine-economical synthetic reactions is still in its infancy. More ingenious protocols for the phosphine oxide issue are highly desirable.

6. Conclusion

As highlighted in this review, stoichiometric phosphine-meditated organic reactions have been gaining more research interest from the chemistry community due to their high efficiency and versatility in organic synthesis which has been continuously witnessed, particularly with respect to phosphine-mediated olefination and annulation reactions. A variety of readily available substrates such as electron-deficient alkenes, alkynes, allenes, and azoesters can frequently be used to construct structurally diverse alkenes, dienes, and carbo- and heterocycles under very mild conditions. In contrast to the emerging phosphine-catalyzed reactions which are presumably effected by the decent nucleophilicity and leaving group ability of tertiary phosphines, the stoichiometric phosphine-mediated reactions may be attributed mechanistically to the characteristic nucleophilicity and oxyphilicity of tertiary phosphines. From the view point of atom economy, concomitant byproduct phosphine oxide is a common issue of stoichiometric phosphine reactions. Fulfilment of inherently stoichiometric chemical transformations with catalytic amounts of phosphorus reagents will be one topic of future investigations in this area. Exploring innovative strategies including *in situ* reduction of phosphine oxide with silanes represents one new direction in the field of organophosphorus synthetic chemistry.

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