Recent advances in stoichiometric phosphine-mediated organic synthetic reactions

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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. 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 phosphate-mediated organic reac-

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

Nucleophilic phosphine organocatalysis has recently emerged as a powerful tool for the construction of carbon–carbon and carbon–heteroatom bonds. Synthetically important phosphine-catalyzed reactions include the Morita–Baylis–Hillman reaction, the Rauhut–Currier reaction, isomerization of alkynes, and allene-based annulation reactions. 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 tetrahedral 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 oxophilicity 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 chemistry community. This review aims to summarize the

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 reported the PPh₃-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 with exclusive E-selectivity (Scheme 2, eqn 1). McClure 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.

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 between electron-deficient olefins and aldehydes under similar conditions (Scheme 3, path b). The divergent olefination may mechanistically arise...
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 PBu3 and Ti(O’Pr)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 PBu3, 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

Ye16 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-workers17 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...
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-workers19 disclosed a novel olefination reaction between γ-substituted allenoates 19 and aldehydes under the mediation of phosphines such as PPh3 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 (R1 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 23. When the substituent R1 in 23 is a conjugative phenyl or methoxycarbonyl, the more stable resonance form 23b (R1 = Ph, CO2Me) 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 R1 = 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] annihilation 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...
utility of the dienes 20 was also exemplified in the Diels–Alder reaction with \( \text{N}-\text{methylmaleimide} \) to afford \( \text{endo} \)-selective cyclohexenes 28 (Scheme 13, eqn 2).

The phosphine-mediated olefination reactions of \( \alpha \)-substituted allenoates with aldehydes was recently developed by He and co-workers. Under the mediation of stoichiometric \( \text{PBu}_3 \) or \( \text{PPh}_2\text{Me} \), \( \alpha \)-substituted allenoates 29, e.g. \( \alpha\)-(ethoxycarbonyl)methyl, \( \alpha \)-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 chemoselectivities and stereocontrol (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 \( ^{31}\text{P} \) 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 13** PTA-mediated olefination of alkyanoates 27 and aldehydes.

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

**Scheme 15** \( \text{PBu}_3 \)-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 \( \alpha \)-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 \( \alpha \)-methyl group of the allenoate was directly involved in the \( \text{C}_L \text{C} \) bond formation. It constitutes a unique example of a vinylogous Wittig reaction. This reaction was previously observed independently by He and Kwon with triarylphosphines used as the mediator. Further studies by He disclosed that the vinylogous Wittig reaction mediated by strongly nucleophilic \( \text{PBu}_3 \) 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 deuteration-labeling, intermediate entrapment, and NMR monitoring, a novel mechanism was proposed to rationalize the vinylogous Wittig reaction (Scheme 15). Initially, the nucleophilic attack of \( \text{PBu}_3 \) 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 \( \text{PBu}_3 \)-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.

Electron-deficient alkynes may be effective substrates in the stoichiometric phosphine-mediated olefination reactions. Ramazani reported that, in the presence of stoichiometric \( \text{PPh}_3 \) and alcohol, acetylenedicarbonylates 41 and ninhydrin 42 readily delivered highly functionalized alkenes 43 in good yields (Scheme 16). Presumably, the reaction proceeds through...
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). 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 oxophilicity 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.

2.3 Reactions based on other substrates

In 2004, Hou and co-workers reported a PBu3-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 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 H2O or TsNH2 to give the diene product has been ruled out.

A facile PBu3-mediated olefination between gramines 54 and aldehydes was developed by Magomedov and co-workers 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, PBu3 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
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 carbon- 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-workers34 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 Bu4NI 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).

By a similar strategy, Lin and co-workers35 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 PBu3 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

![Mechanism](image-url)
reaction. Initially, Michael addition of the phosphine to the enone generates a zwitterionic 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 expanded this synthetic methodology by employing more readily available terminal olefins (Scheme 24). Under the mediation of stoichiometric PBu3, 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). Benzaldehydes 72 with a functionality of ester, thioester or amide group readily underwent an annulation with acid chlorides under the mediation of PBu3 and NEt3 to produce benzo furans, benzothiophenes and indoles, respectively. Subsequently, the authors also reported that the aromatic enones 75 undertook a similar annulation under the same conditions to deliver benzo furans, benzothiophenes and indoles, respectively. 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 annihilations of electron-deficient alkenes are also applied in the construction of carbocycles. In 2006, Schaus and co-workers 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 31P 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
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-workers42 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-workers43 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).

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 PPh3 (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 phosphone to DMAD and

![Scheme 27 Phosphine-mediated benzannulation reaction.](image)

![Scheme 28 A plausible mechanism for formation of 84.](image)

![Scheme 29 Phosphine-mediated annulations for three-membered rings.](image)

![Scheme 30 Proposed mechanism for the phosphine-mediated cyclopropanation.](image)

![Scheme 31 Phosphine-mediated synthesis of dihydrofurans.](image)
subsequent deprotonation of \( \alpha \)-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 \( \alpha \)-amino esters, salicylaldehydes, etc. have the same reactivity with DMAD and PPh\(_3\), delivering various cyclic products (Scheme 32).\(^4^6\)

Under similar conditions, 1,3-dicarbonyl compounds with an acidic \( \alpha \)-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).\(^4^7\)

Hekmatshoar\(^4^8\) reported that pentan-2,3,4-trione 3-oxime 95 could also serve as a dual-functional partner in the PPh\(_3\)-mediated annihilation reaction with DMAD, giving an annihilation 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 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\(^4^9\) 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 annihilation 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 annihilation 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).\(^5^0\) 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\(^5^1\) recently reported a rare annulation of acetylenedicarboxylates with \(N\)-phenyl-\(C\)-chromonyl
nitrones 103 in the presence of PPh₃, 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 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(2)-position of the enynoates producing the zwitterionic intermediates 107, which subsequently react with aldehydes to form γ-lactones.

A highly efficient and convergent synthesis of substituted furans 109 was developed by Krische and co-workers from γ-acyloxy butynoates 108 (Scheme 39). 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 PPh₃ 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 PPh₃ 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-
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 annihilation reactions. An interesting cyclopropanation reaction between α-substituted allenoates, aldehydes and PPh₃ was recently reported by He and co-workers, delivering functionalized vinyl cyclopropanes 114 (Scheme 41). 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 ³¹P NMR monitoring experiments have provided supportive evidence for the above putative mechanism.

Recently, Shi and co-workers disclosed a rare phosphine-mediated annihilation reaction to give thiophenes. Thus, under the mediation of stoichiometric PPh₂Me₂, 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 PPh₂Me was converted into PPh₂CH₂CO₂R by possible migration of an ester group from the allenoate (Scheme 42).

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

Scheme 42 PPh₂Me-mediated formation of thiophenes from allenoates and isothiocyanates.

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. Traditionally, the Huisgen zwitterion is known as a key intermediate in the important Mitsunobu reaction. In fact, Huisgen zwitterions are very often involved in many annihilation reactions to construct heterocycles. Early reports about the annulations of Huisgen zwitterions can be traced back to 1960s when Cookson first reported its cyclization with dimethyl acetylenedicarboxylate (DMAD) to form pyrazoles 120, and Huisgen 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). The simple alkyl ketones and aldehydes failed to give the annulation products, but afforded acyclic hydrazine derivatives. In the same year, Nair 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-
duced 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 further developed an interesting annulation of Huisgen zwitterions with \( \alpha,\beta \)-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 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). Using its precursor 139 instead of the imine, the annulation reaction also took place with three equivalents of diethyl azodicarboxylate and PPh\(_3\) used. Presumably, the precursor 139 was converted \textit{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 allenates can readily form reactive zwitterionic intermediates upon nucleophilic attack of phosphines. However, results from Nair group showed that, in the presence of azodicarboxylates, phosphines like PPh\(_3\) preferentially formed Huisgen zwitterions instead. Thus, upon the treatment of PPh\(_3\), \( \alpha \)-substituted allenates 29 and DIAD afforded pyrazolines 140 in good yields (Scheme 51).

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

**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.

**Scheme 49** The annulation of Huisgen zwitterions with imines.
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 Srinivasan64 reported that diazoimides 144 readily cyclized in the presence of phosphines 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 PPh3 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/hydrazone derivatives

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

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R1
\[ \text{NO}_2 \]
N
\[ \text{PR}_3 \]
\[ \text{Me} \]
R1 = H, Me;
R2 = aryl, alkyl
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Scheme 54 Phosphine-mediated cyclizations of 2-nitroanilides 147.

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have displayed rich and diverse annulation reactivity with multi-functional carbonyl compounds such as \(\alpha\)-ketoesters, \(\alpha\)-diketones, 1,2-benzoquinones, and chalcones \textit{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\textsuperscript{58} disclosed that Huisgen zwitterions reacted with alkyl aldehydes and ketones to afford acyclic hydrazines\textsuperscript{151} and vinyl hydrazones\textsuperscript{152}, respectively (Scheme 55).

In contrast to alkyl aldehydes, Nair\textsuperscript{66} demonstrated that aromatic aldehydes and Huisgen zwitterions produced acyl carbamates\textsuperscript{153}. It is conceivable that an oxadiazoline intermediate\textsuperscript{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 \textit{et al.}\textsuperscript{67} reported that dual-functional salicylaldehyde exhibited a distinct reactivity with Huisgen zwitterion\textsuperscript{119c}, producing Boc-protected hydrazone\textsuperscript{155} (Scheme 57).

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

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

### 4.2 Synthesis of enamides

An efficient phosphine-mediated reductive acylation of oximes\textsuperscript{162} with acetic anhydride to give enamides\textsuperscript{163} was developed by Singh and co-workers (Scheme 60).\textsuperscript{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\textsuperscript{71} demonstrated that activated carbonyl groups in \(\alpha\)-keto esters, benzils, 1,2-cyclohexanedi, and \(\alpha\)-ketophosphonates could be reduced.

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

**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.

**Scheme 59** Temperature-dependent syntheses of hydrazones\textsuperscript{160} and azines\textsuperscript{161}.
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).\textsuperscript{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\textsubscript{1} in a deuterium-labeling experiment with deuterated trimethylphosphine-d\textsubscript{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).\textsuperscript{73} Under the mediation of stoichiometric phosphine PBu\textsubscript{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\textsubscript{2}, as is well known in the Staudinger reaction.\textsuperscript{4} However, a recent work by Raines et al.\textsuperscript{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 possess\textsuperscript{167} a proximate N-hydroxysuccinimyl ester group, a wide range of azides could be converted into the corresponding diazo compounds in high yields. This phosphate-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
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 reported the discovery of a viable combination of diphenylsilane (Ph₂SiH₂) as the reducing agent and a cyclic phosphine oxide 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 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 (Ph₂SiH₂) reduced the phosphine oxide 171 selectively in the presence of aldehydes and other reagents. It is noteworthy that OLPPh₃ was less efficient in the catalytic Wittig reaction than cyclic phosphine oxide 171. Very recently, O’Brien demonstrated that a catalytic amount of acid additive e.g. 4-nitrobenzoic acid could promote the efficiency of acyclic phosphine oxides such as OLPBu₃ and OLPPh₃ 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.

In 2011, van Delft and co-workers systematically explored silane reductions of a range of cyclic phosphine oxides and found that phosphines of five-membered rings are preferred...
candidates for catalytic applications. A combination of dibenzophosphole 174 and Ph₂SiH₂ 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 PhSiH₃ (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 N₂; 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 PPh₃ (0.1 equiv.) and Ph₂SiH₂ (1.2 equiv.) could efficiently provide the chemoselective 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 PPh₃-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-
ful; however, the reduction and reuse of the byproduct phosphine oxide is realized at the cost of relatively expensive silanes. 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-mediated 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 carbocyclic and heterocycles under very mild conditions. In contrast to the emerging phosphine-catalyzed reactions which are presumably affected 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. Fulfillment 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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