

# Catalytic Approaches to Stoichiometric Phosphine-Mediated Organic Reactions

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**Abstract:** Organic reactions mediated by stoichiometric phosphines play a key role in modern organic synthesis as testified by the classic Wittig, Mitsunobu, Staudinger and Appel reactions. Mechanistically these reactions are usually driven by the strong oxophilicity of tertiary phosphines. As a result, the formation of phosphine oxide as a concomitant byproduct represents a drawback which impacts heavily on the atom economy and large-scale applicability of these reactions. To tackle the “phosphine-oxide” issue, considerable efforts have been recently engaged in how to convert a stoichiometric phosphine-mediated reaction into a catalytic one, which has stimulated much research interest in organic chemistry community. In this mini-review, recent developments on catalytic approaches to stoichiometric phosphine-mediated reactions primarily including *in situ* reduction and activation strategies are summarized.

**Keywords:** Appel reaction, catalysis, phosphine, reduction, Staudinger reaction, Wittig reaction.

## 1. INTRODUCTION

Tertiary phosphines [1, 2], as one of the most versatile organophosphorus reagents, have attracted enormous interest from organic chemistry community owing to their unique and diverse characteristics such as pronounced nucleophilicity, strong oxophilicity, good coordination ability, decent stabilization for ylides, *etc.* As a result, tertiary phosphines have been widely used in organic synthesis, even on multiton scale in industry [3]. The popular application of phosphines can be simply divided into two categories: the catalytic uses and stoichiometric applications. The catalytic utilities of phosphines include the uses as ligands in transition-metal catalysis [4] playing the role on modulating the reactivity and selectivity of the catalysts, and the uses as catalysts in their own right in the area of Lewis base catalysis [5-10]. On the other hand, the stoichiometric applications of tertiary phosphines in organic synthesis have been developed much earlier, typically including the classic Wittig [11], Mitsunobu [12], Staudinger [13, 14], Appel [15] reactions and others [16]. These stoichiometric reactions are mechanistically reliant on the strong oxophilicity of phosphines; the formation of phosphine oxides with strong P=O bond (ca. 400 kJ/mol) [17] provides the major driving force for these transformations.

The Wittig, Mitsunobu, Staudinger and Appel reactions are highly ranked on the list of useful organic transformations and widely used in industrial processes. However, the concomitant formation of phosphine oxides usually constitutes a frustrating purification issue. Phosphine oxides (usually  $\text{Ph}_3\text{PO}$ ) are polar and organic soluble amorphous

solids whose separation from desired products can be difficult and often resort to chromatography purification, a process that is economically and practically disfavored on a manufacturing scale. In addition, the relatively high molecular weight of phosphine oxides plagues these transformations from the atom-economical point of view [18].

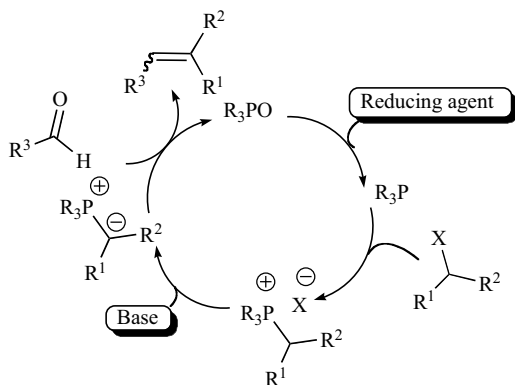
Many creative strategies to the separation of phosphine oxides have been developed such as immobilization [19], extraction [20, 21], and further conversion [22]; however, the fundamental inefficiency of the processes remains. Ideally, the evolution of the stoichiometric phosphorus-consuming reactions into a process that is catalytic in the key phosphorus reagent would greatly enhance the overall efficiency and synthetic utility of the reactions. During the last 5 years, several ingenious approaches have been taken to realize the catalytic manifolds of stoichiometric phosphine-mediated reactions such as Wittig, Appel, Staudinger type reactions. This mini-review aims to summarize recent developments on catalytic approaches to stoichiometric phosphorus-consuming reactions primarily including an *in situ* reduction protocol and an activation strategy.

## 2. CATALYTIC APPROACHES BASED ON IN SITU REDUCTION OF PHOSPHINE OXIDES

Reduction *in situ* of phosphine oxides back to phosphines with appropriate reducing agents represents a promising strategy for the development of catalytic variants of stoichiometric phosphine-mediated reactions. In this manner, phosphines (or phosphine oxides) can be used as the catalysts (or precatalysts) with stoichiometric amount of reducing agents present. Yet, this seemingly simple conception appears to be a challenge owing to the remarkable energy of the P=O bond (ca. 400 kJ/mol). Reduction of phosphine oxides usually requires harsh reducing agents [23, 24] which

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may reduce other reaction components as well, thus raising a selective issue to be resolved. Therefore, identifying a viable combination of a reducing agent and a phosphine (or phosphine oxide) is the key to the success of the catalytic approaches.

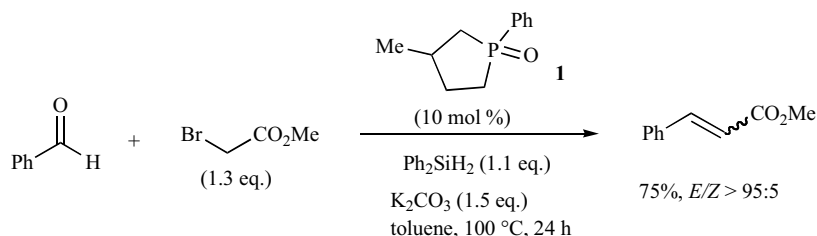


**Scheme 1.** Proposed phosphine-catalyzed Wittig reaction.

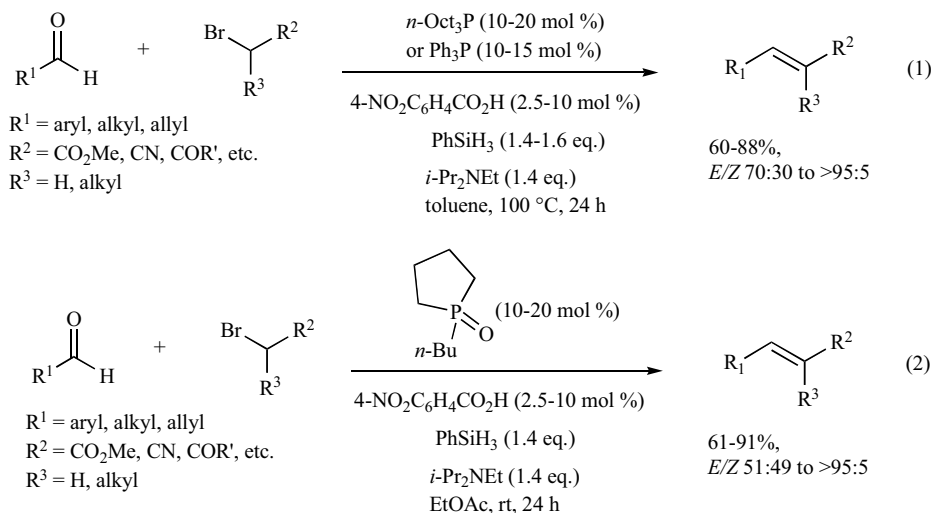
In 2009, O'Brien and co-workers [25-27] reported the first phosphine-catalyzed Wittig reaction adopting the *in situ* reduction strategy. The Wittig reaction, well known for its paramount importance for alkene synthesis, involves the condensation of a carbon-phosphorus ylide and an aldehyde or ketone to generate the alkene and a phosphine oxide. In the development of a phosphine-catalyzed Wittig reaction (Scheme 1), O'Brien devised that the carbon-phosphorus ylide could be generated *in situ* from a phosphine and an alkyl halide with a base. In the presence of an aldehyde coupling partner, intermolecular Wittig reaction would follow to

generate the target alkene and the phosphine oxide. Completion of the catalytic cycle should resort to the chemoselective reduction of phosphine oxide to the phosphine. The author identified that the combination of diphenylsilane ( $\text{Ph}_2\text{SiH}_2$ ) as the reducing agent and the cyclic phosphine oxide **1** as the precatalyst was compatible with the catalytic Wittig reaction. As shown in Scheme 2, treatment of benzaldehyde with methyl bromoacetate and 10 mol % of **1** in the presence of  $\text{Ph}_2\text{SiH}_2$  and  $\text{Na}_2\text{CO}_3$  in toluene at 100 °C produced the desired alkene in 75% yield with an excellent *E/Z*-selectivity (>95:5). With regard to other silanes, trimethoxysilane and phenylsilane were also effective albeit with lowered yields, while triphenylsilane was essentially inefficient. Using  $\text{Ph}_3\text{PO}$  as the precatalyst instead of the cyclic **1** was unsuccessful under the same conditions since the former may be harder to be reduced [28]. A higher temperature was beneficial to achieve a high *E/Z*-selectivity of the reaction probably attributed to a phosphine-mediated post-isomerization event. The catalytic Wittig reaction worked well for a broad range of aldehydes (aryl, heteroaryl,  $\alpha,\beta$ -unsaturated and alkyl) and a series of alkyl halides involving the formation of both stabilized and semi-stabilized ylides, affording the alkene products in generally good yields (61-81%) and high *E/Z*-selectivities (60:40 to >95:5).

To further improve the efficiency and flexibility of the catalytic Wittig reaction, O'Brien [29] very recently expanded the reaction to include readily available acyclic phosphine oxides such as *n*-Oct<sub>3</sub>PO and  $\text{Ph}_3\text{PO}$  as the precatalysts by introducing an acid additive (*e.g.* 4-nitrobenzoic acid). In the reaction,  $\text{PhSiH}_3$  and *i*-Pr<sub>2</sub>NEt were validated as the optimal reducing agent and base, respectively. Good



**Scheme 2.** The first catalytic Wittig reaction.



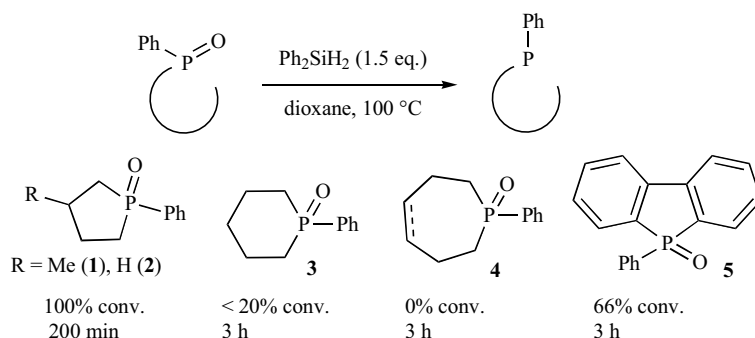
**Scheme 3.** Catalytic Wittig reactions assisted by an acid additive.

yields and *E/Z*-selectivities were achieved with a wide substrate scope at a high temperature (100 °C) (Scheme 3, eq. 1). The acid additive was believed to produce dual effect on the reaction enhancing phosphine oxide reduction rate [30] and at the same time adding in the solubility of the produced phosphonium salt. By this means, the author also realized the catalytic Wittig reaction at room temperature with a cyclic phosphine oxide, obtaining good yields and high kinetic *E/Z*-selectivities (Scheme 3, eq. 2).

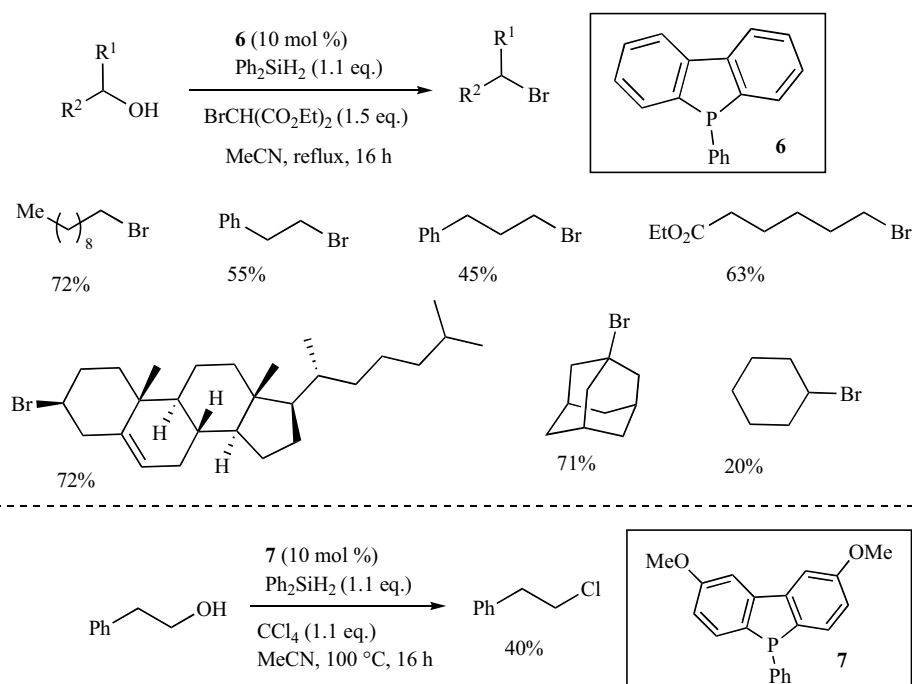
To determine the effect of ring size of phosphine oxides on the reduction rate, van Delft and co-workers [31, 32] recently explored the silane reductions of a range of cyclic phosphine oxides with different ring structures. It was found that phosphines of five-membered rings were preferred candidates for catalytic applications (Scheme 4). With 1.5 eq. of diphenylsilane as the reducing agent, complete reduction of the five-membered phosphine oxides **1** and **2** was achieved over 200 minutes in 1,4-dioxane at 100 °C, while the six-membered **3** only gave less than 20% conversion after 3 hours, and the seven-membered phosphine oxides **4** were inert under the conditions. It was also found that the five-

membered aromatic phosphole oxide **5** was efficient, with a comparable reduction rate to that of **1** and **2**. Additional advantages of aromatic phosphole oxides are the good air-stability of the corresponding phospholes and the potential tunability of electronic properties by introduction of substituents.

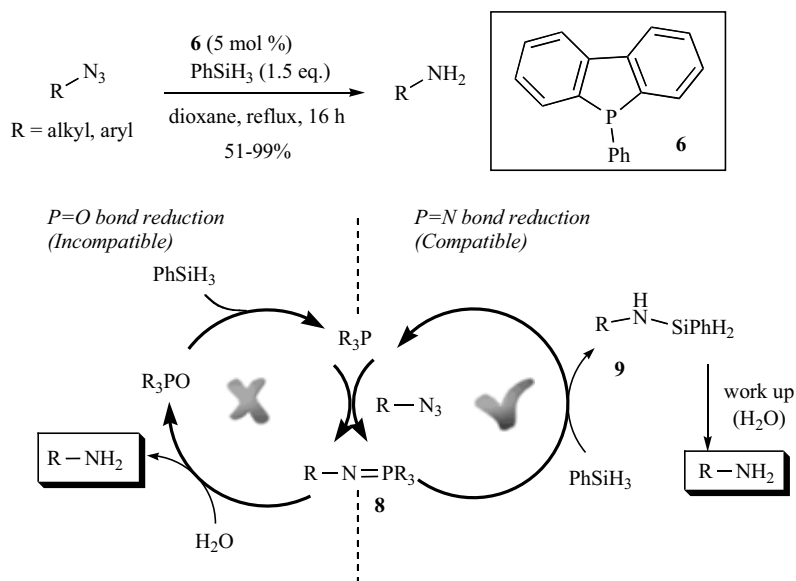
The author further demonstrated that phosphole **6** (reduced form of **5**) and Ph<sub>2</sub>SiH<sub>2</sub> could be successfully applied in the catalytic Appel reaction, a process famous for the mild conditions and stereospecific conversion of alcohols to halides with stoichiometric phosphines. With 10 mol % of **6** and 1.1 eq. of Ph<sub>2</sub>SiH<sub>2</sub>, a series of primary, secondary and tertiary alcohols smoothly underwent the catalytic Appel reaction with diethyl bromomalonate as bromide source, producing the corresponding bromides in moderate to good yields (Scheme 5). Switching the catalyst to more nucleophilic 2,8-dimethoxy-substituted dibenzophosphole **7**, the chlorination of phenylethyl alcohol also occurred in a moderate yield with tetrachloromethane as the halide source (Scheme 5). It is noteworthy that 3-methyl-1-phenylphospholane oxide **1** is incompatible with the catalytic Appel reaction since a com-



**Scheme 4.** Silane reductions of different cyclic phosphine oxides.



**Scheme 5.** Phosphine-catalyzed Appel reactions.



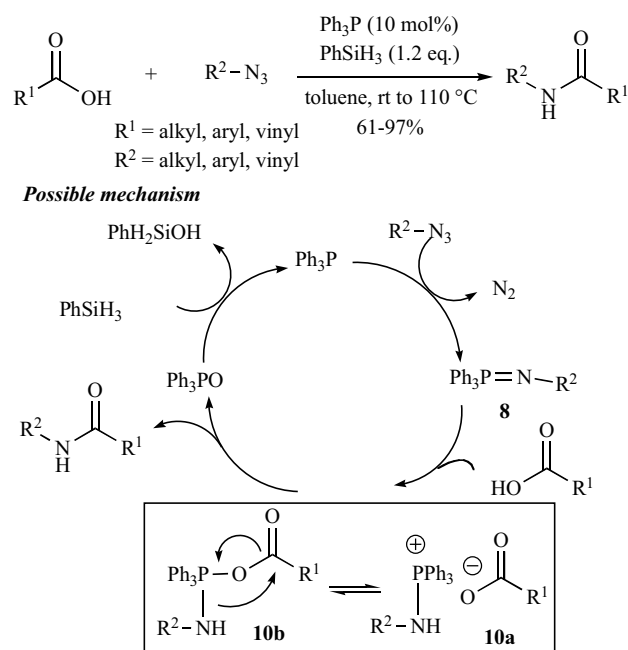
**Scheme 6.** Phosphine-catalyzed Staudinger reduction.

petitive alkylation of the corresponding phosphine with the halogenated product would be dominant thus terminating the catalytic cycle.

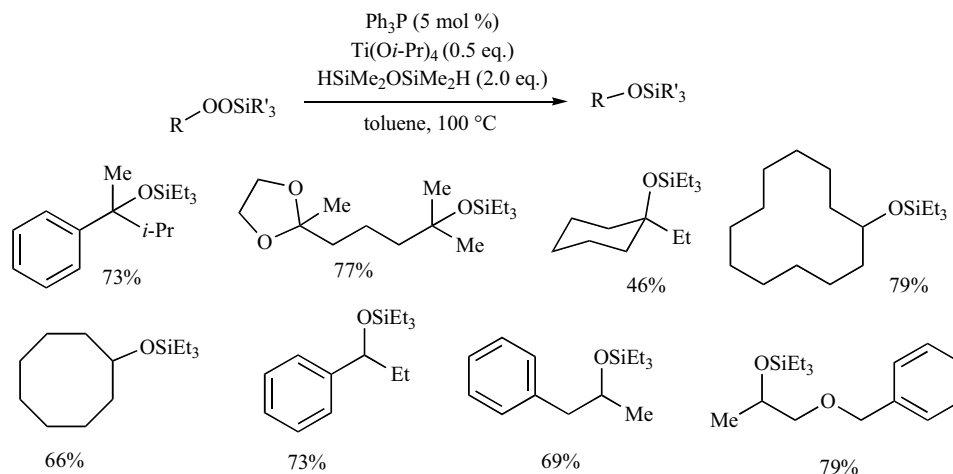
Staudinger reduction [33] represents a practical method for the preparation of amines from azides. The reaction mechanistically involves the formation of an iminophosphorane **8** from an azide with a phosphine and subsequent hydrolysis with water to form the amine product and phosphine oxide (Scheme 6). In the development of the phosphine-catalyzed Staudinger reduction, the strategy of *in situ* reduction of phosphine oxide by silanes is supposed to be incompatible owing to the sensitivity of silanes to the present water (Scheme 6). Van Delft and co-workers [34] recently developed an alternative catalytic strategy involving direct reduction of the iminophosphorane **8** with silanes. The generated aminosilane intermediate **9** could rapidly hydrolyze to the amine products during work-up [35], thus avoiding the use of water in the reduction step (Scheme 6). With only 5 mol % of dibenzophosphole **6** as the catalyst and 1.5 eq. of  $\text{PhSiH}_3$ , a range of alkyl and aryl azides smoothly underwent the catalytic Staudinger reduction to provide the corresponding amines in good to excellent yields with high functional group tolerance. Although  $\text{Ph}_3\text{P}$  also proved effective in the catalytic system, careful exclusion of water and oxygen was required since the formation of triphenylphosphine oxide upon hydrolysis or oxidation would shut off the catalytic cycle. Dibenzophosphole oxide **5** could be formed as well; however, in contrast to triphenylphosphine oxide, it can be easily reduced back to the corresponding phosphine with the silane [28].

Phosphine-promoted Staudinger ligation [36, 37] of carboxylic acid derivatives and azides represents a preeminent 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 [38] developed the first phosphine-catalyzed Staudinger ligation reaction of carboxylic acids and azides applying the *in situ* reduction protocol (Scheme 7). A combination of 0.1 eq. of  $\text{Ph}_3\text{P}$  and 1.2 eq. of  $\text{Ph}_2\text{SiH}_2$  was found to be

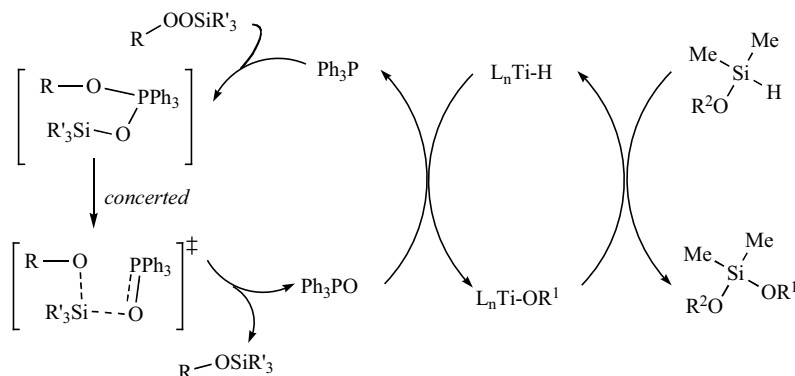
highly efficient to promote the catalytic Staudinger ligation. Mechanistically, the reaction of an azide with  $\text{Ph}_3\text{P}$  initially gives an aza-ylide **8** (iminophosphorane) and  $\text{N}_2$ . Subsequent deprotonation of the carboxylic acid provides phosphonium carboxylate **10a** which is in equilibrium with intermediate **10b**. The partially covalent P-O bond of **10b** activates the carboxylate leading to the amide C-N bond formation with the departure of  $\text{Ph}_3\text{PO}$ . Reduction *in situ* of  $\text{Ph}_3\text{PO}$  with  $\text{Ph}_2\text{SiH}_2$  regenerates  $\text{Ph}_3\text{P}$  to complete the catalytic cycle (Scheme 7). It is interesting to note that, in contrast to those cases mentioned above, cyclic phosphines are inferior to  $\text{Ph}_3\text{P}$  in this catalytic system, probably because their aza-ylides are susceptible to silanes consequently suffering from



**Scheme 7.**  $\text{Ph}_3\text{P}$ -catalyzed Staudinger ligation of azides with carboxylic acids.



**Possible mechanism**



**Scheme 8.** Phosphine-catalyzed reduction of silyperoxides.

a competitive Staudinger reduction [34]. It can be also reasoning that the carboxylic acid also serves as an additive to facilitate the reduction of  $\text{Ph}_3\text{PO}$  with the silane [30].

The catalytic Staudinger ligation worked well for various carboxylic acids and azides producing the corresponding amides in excellent yields. Intramolecular ligation was also feasible providing a formidable method for the synthesis of lactams. Impressively, this catalytic variant is applicable to the assembly of peptides from amino acids without loss of optical purity, which is expected to find wide use in preparing biologically active peptides.

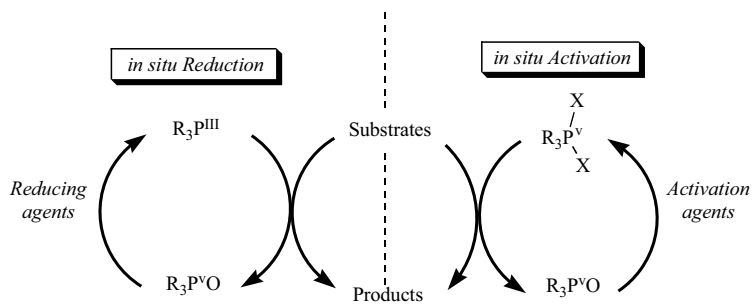
Reduction of peroxides with stoichiometric phosphines provides a useful method for the synthesis of alcohol derivatives. The generation of equivalent of phosphine oxide, however, also complicates the purification of the products. Worpel and co-workers [39] recently developed a  $\text{Ph}_3\text{P}$ -catalyzed reduction of alkyl silyperoxides utilizing the *in situ* reduction protocol (Scheme 8). Titanium hydride, generated *in situ* from  $\text{Ti(O}i\text{-Pr)}_4$  and  $\text{HSiMe}_2\text{OSiMe}_2\text{H}$ , acts as an efficient reducing agent [40–42] to achieve the phosphine turnover. Other reducing reagents (e.g.  $\text{LiAlH}_4$  and  $\text{Cl}_3\text{SiH}$ ) were incompatible with the catalytic system. Silyl groups were found to be essential to the reaction, since other masking groups such as benzyl and ketal all failed to achieve the catalytic reduction. Various silyperoxides were subjected to the reaction to provide the corresponding silylated alcohols in

good yields. Mechanistic investigations including isotopic labeling and crossover experiments suggested that the oxygen atom adjacent to the silicon atom is removed and the silyl group is transferred in a concerted step to form the silylated alcohols (Scheme 8).

As evidently shown in the above examples, the strategy of *in situ* reduction of phosphine oxides with silanes has been successfully applied in catalytic development of several important phosphorus-consuming reactions. The replacement of stoichiometric phosphines with silanes offers convenient purification of the products and great environmental improvements [43]. However, the phosphine structure, silane identity, substrate functionality as well as reaction conditions have to be carefully fine-tuned to fulfill the catalytic transformations. Optimization of the catalytic processes as well as application of the strategy in other phosphorus-consuming transformations may be the aim for further investigations.

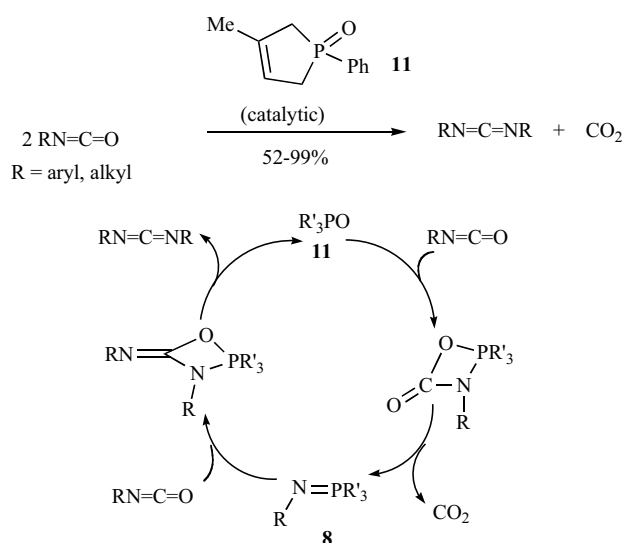
### 3. CATALYTIC APPROACHES BASED ON IN SITU ACTIVATION OF PHOSPHINE OXIDES

The other catalytic approach to phosphorus-consuming reactions involves *in situ* activation of phosphine oxides with oxygen transfer agents to generate reactive  $\text{P(V)}$  intermediates responsible for the reactions, thereby making the reactions catalytic in phosphine oxide. Different from the *in situ* reduction protocol, the activation strategy operates solely at



**Scheme 9.** Two catalytic strategies for phosphorus-consuming reactions.

the P(V) oxidation state throughout the catalytic cycle (Scheme 9).



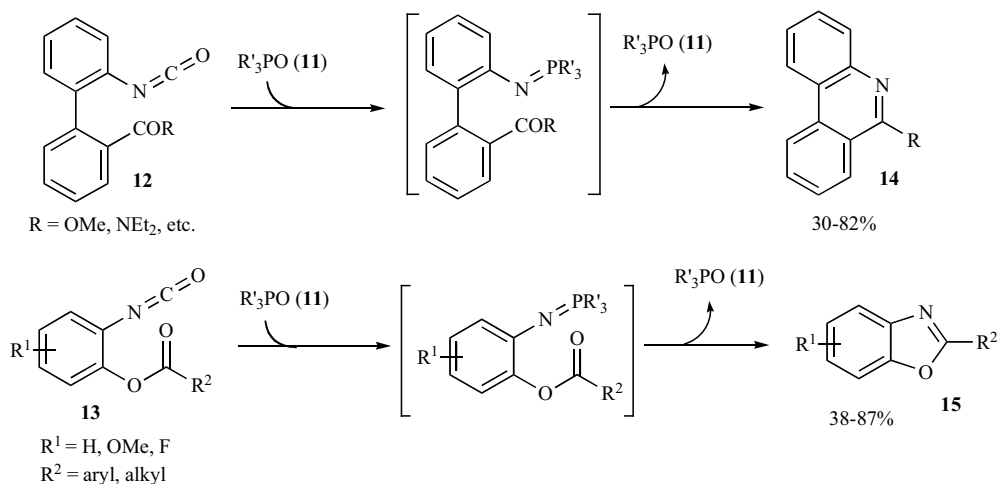
**Scheme 10.** Self-condensation of isocyanate via phosphine oxide-catalyzed aza-Wittig reaction.

As early as 1962 Campbell and Monagle [44, 45] pioneered the *in situ* activation strategy in the self-condensation reaction of isocyanates to form carbodiimides under the catalysis of phosphine oxide **11** (Scheme 10). This reaction constitutes the first phosphine oxide-catalyzed aza-Wittig reaction. The catalytic mechanism involves the initial activa-

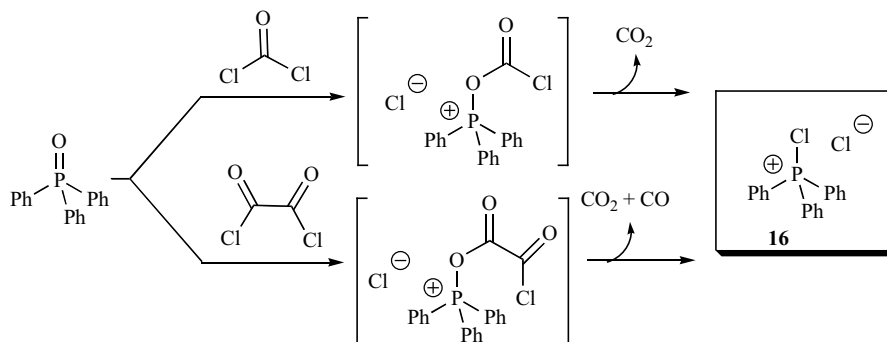
tion of the phosphine oxide with an isocyanate to generate an iminophosphorane intermediate **8** and CO<sub>2</sub>. Subsequent aza-Wittig reaction with a second molecule of isocyanate produces the carbodiimide product and regenerates the phosphine oxide (Scheme 10) [46]. Elimination of CO<sub>2</sub> was believed to be the driving force for the activation of the phosphine oxide in the catalytic reaction.

In 2008, Marsden and co-workers [47] realized the intramolecular variant of the above reaction for the preparation of heterocycles (Scheme 11). With isocyanates **12** or **13** as the substrates, the iminophosphoranes generated from the phosphine oxide **11** and the isocyanate groups were trapped by the pendant carbonyls via the intramolecular aza-Wittig reaction, providing a novel process to prepare privileged phenanthridine **14** and benzoxazole **15** motifs. In some cases the formation of carbodiimide (by the intermolecular condensation process) was competing with the desired cyclization; however, a lower catalyst loading (3 mol %) eliminated the side reaction and gave high yields of the products. *In situ* IR monitoring of the reactions confirmed the involvement of the phosphine oxide in the catalytic cycle and revealed that the formation of iminophosphoranes was the rate-determining step of the reaction.

Chlorophosphonium salts (R<sub>3</sub>PCl<sub>2</sub>) are a class of highly reactive and versatile intermediates in organic synthesis widely used as chlorination reagents. The salts are traditionally prepared from phosphines and Cl<sub>2</sub> and usually convert to phosphine oxides as the final state in many reactions, *e.g.* the Appel reaction [15]. Interestingly, it was documented that

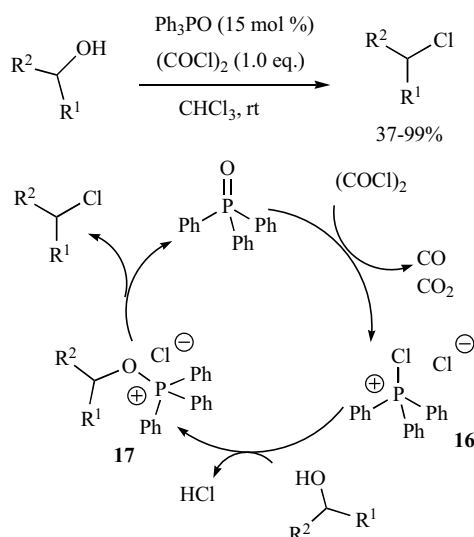


**Scheme 11.** Phosphine oxide-catalyzed intramolecular aza-Wittig reaction.



**Scheme 12.** Formation of chlorophosphonium salt **16** from Ph<sub>3</sub>PO and phosgene or oxalyl chloride.

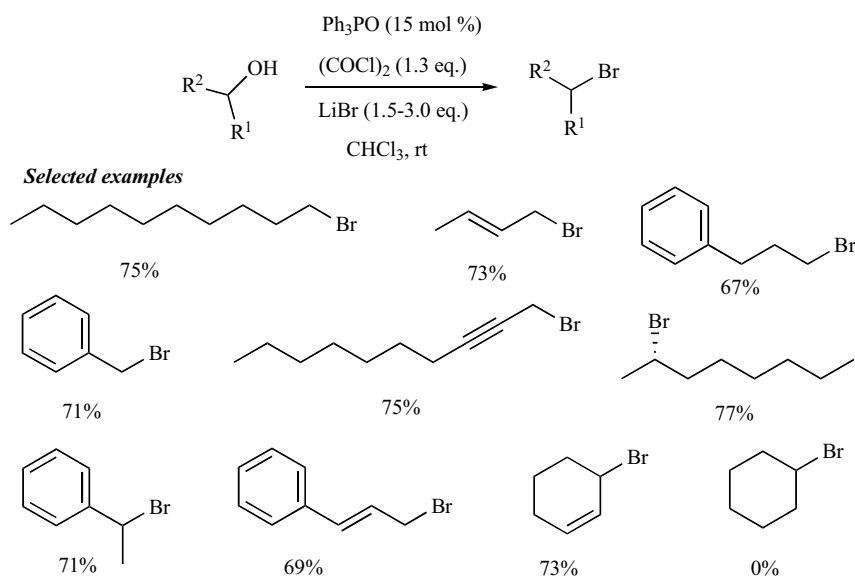
the salt could be generated from phosphine oxide with phosgene or oxalyl chloride under mild conditions, with the concomitant loss of CO<sub>2</sub> (and CO) (Scheme 12) [3,48-51]. To this end, it offers a great possibility to develop catalytic variants of reactions involving chlorophosphonium salts as intermediates.



**Scheme 13.** Ph<sub>3</sub>PO-catalyzed Appel chlorination reaction.

Denton and co-workers [52, 53] pioneered the catalytic strategy in the development of a Ph<sub>3</sub>PO-catalyzed Appel chlorination of alcohols. Mechanistically, the chlorophosphonium salt **16** generated from the phosphine oxide and oxalyl chloride chlorinates the alcohols and regenerates the phosphine oxide to re-enter the catalytic cycle (Scheme 13). A simultaneous addition of both oxalyl chloride (0.85 eq.) and alcohols (1.0 eq.) to a solution of Ph<sub>3</sub>PO (0.15 eq.) and oxalyl chloride (0.15 eq.) over 7 hours at room temperature was established as the optimal conditions for chemoselective chlorination. Unwanted background reactions between oxalyl chloride and alcohols could be efficiently suppressed. Various acyclic primary and secondary alcohols smoothly underwent the catalytic chlorination giving the corresponding chlorides in moderate to excellent yields.

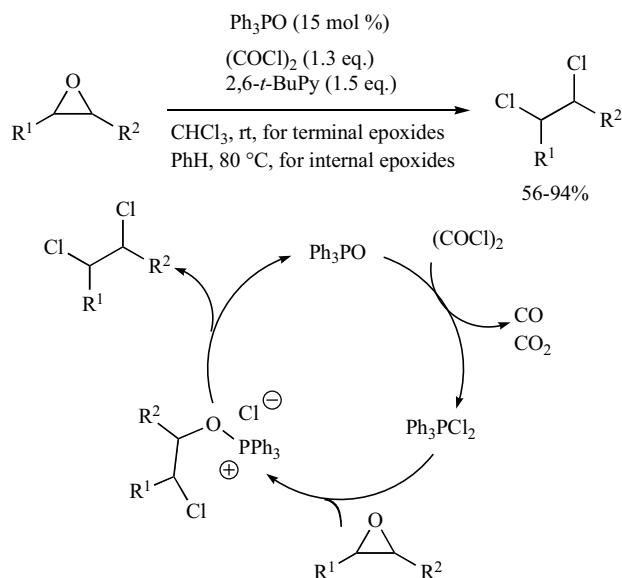
Attempt of the analogous catalytic bromination using oxalyl bromide was also feasible albeit with a modest yield [52, 53]. Another efficient bromination strategy was achieved by the introduction of a bromide ion to the Ph<sub>3</sub>PO/(COCl)<sub>2</sub> system. The bromide ion is proposed to intercept the pivotal alkoxyphosphonium chloride intermediate **17** that is originally responsible for the chlorination, directing the reaction to an alternative bromide substitution. In the presence of 1.5-3.0 eq. of lithium bromide (LiBr) and 1.3 eq. of oxalyl chloride, the Ph<sub>3</sub>PO-catalyzed brominations chemoselectively



**Scheme 14.** Ph<sub>3</sub>PO-catalyzed Appel bromination reaction.

occurred with a similar substrate scope to that of the chlorination reactions (Scheme 14).

Denton [54] subsequently extended the phosphine oxide catalysis to 1,2-dichlorination of epoxides. In a similar manner, oxalyl chloride is used as a stoichiometric reagent to generate the chlorophosphonium salt responsible for the dichlorination (Scheme 15). In the presence of 15 mol % of  $\text{Ph}_3\text{PO}$  and 1.3 eq. of oxalyl chloride with a base additive (2,6-di-*tert*-butylpyridine), a range of terminal epoxides underwent the catalytic dichlorination at room temperature providing vicinal dichlorides in moderate to excellent yields. Less reactive internal epoxides were also effective at a higher temperature (80 °C, benzene), affording the corresponding products in useful yields with single diastereoselectivity, in which *cis*-epoxides gave *syn*-dichlorides and *trans*-epoxides produced *anti*-products.



**Scheme 15.**  $\text{Ph}_3\text{PO}$ -catalyzed dichlorination of epoxides.

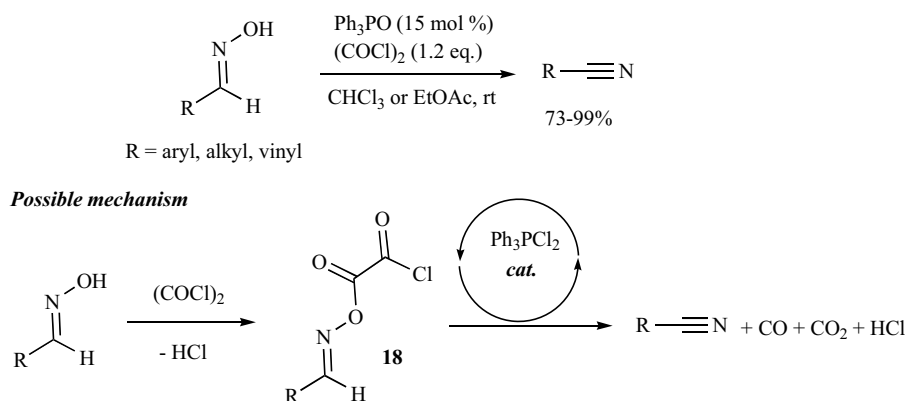
In a related work, Denton and co-workers [55] reported a catalytic dehydration of aldoximes for preparation of nitriles, a method that is traditionally promoted by stoichiometric halophosphonium salts [56, 57]. By using 1.2 eq. of oxalyl chloride in combination with 5 mol % of  $\text{Ph}_3\text{PO}$ , both aromatic and aliphatic aldoximes converted to the corresponding nitriles in good to excellent yields (Scheme 16). Me-

chanic investigations revealed, however, oxalyl chloride played the role on activation of oximes by forming chlorooxalate intermediates **18** rather than serve as the oxygen transfer agent to achieve phosphine oxide turnover. The resulting chlorooxalates then collapse to form the nitrile products probably under the catalysis of the chlorophosphonium salt generated *in situ* from  $\text{Ph}_3\text{PO}$  and  $(\text{COCl})_2$  (Scheme 16).

As illustrated in the above examples, the *in situ* activation strategy featuring conversion of phosphine oxide into a reactive P(V) intermediate has proven viable in the development of catalytic variants of stoichiometric phosphine-mediated reactions. Isocyanates and oxalyl chloride have been validated as efficient activation agents to fulfill this purpose; however, the search for other activation modes is desirable.

#### 4. CONCLUSION

Stoichiometric phosphine-mediated reactions such as Wittig, Mitsunobu, Staudinger and Appel reactions have enormous potential in organic synthesis. However, these transformations suffer from a common drawback of the generation of stoichiometric phosphine oxide, which heavily lowers the atom economy and hampers purification of the product. This mini-review summarizes recent progress on the development of catalytic approaches to stoichiometric phosphine-mediated reactions. The established approaches are varied within two major categories. One is based on the *in situ* reduction of phosphine oxides to phosphines with reducing agents *e.g.* silanes to achieve phosphine turnover. Catalytic Wittig, Appel, Staudinger type reactions and others have been achieved in this context. The other approach involves the activation of phosphine oxides with oxygen transfer agents to generate active P(V) intermediates to realize phosphorus cycling, which is successfully applied in catalytic aza-Wittig, Appel reactions, *etc.* Further studies should expand the application scope of these protocols (*e.g.* for the Mitsunobu reaction) as well as devising newer strategies for catalytic phosphorus recycling. With a view on its great potential on industrial applications, we can anticipate that the development of phosphine catalysis for stoichiometric phosphorus-consuming reactions will remain as an active research area in synthetic organic chemistry in the years to come.



**Scheme 16.**  $\text{Ph}_3\text{PO}$ -catalyzed dehydration of aldoximes for preparation of nitriles.



## CONFLICT OF INTEREST

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Dr. Silong Xu and Prof. Yuhai Tang contribute equally to the design, analysis, and writing for this mini-review.

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