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Highly efficient and convenient access to phosphinates *via* $CHCl_3$-assisted direct phosphorylation between $R_2P(O)H$ and ROH by phosphonium salt catalysis

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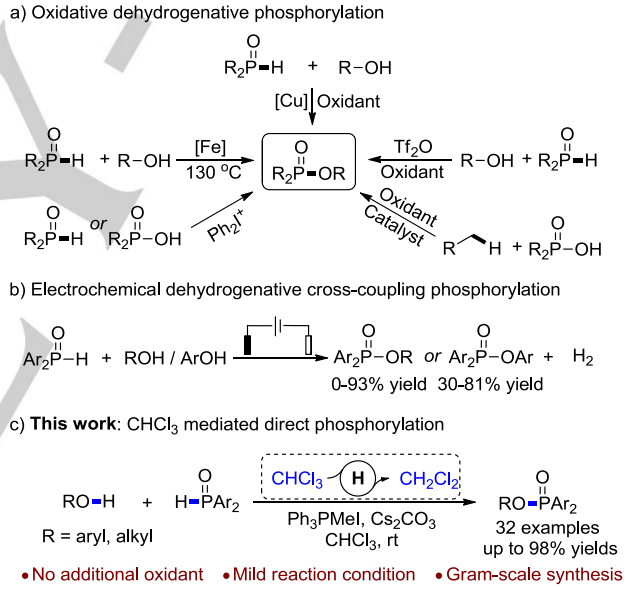
Abstract: A mild, efficient, convenient and scalable method to synthesize phosphinates via direct phosphorylation between $R_2P(O)H$ and ROH was developed. All aromatic substrates completed this transformation with excellent yields (up to 98%), and preliminary mechanistic studies suggest that a carbene-involving process from $CHCl_3$ to CH_2Cl_2 facilitates the phosphorylation.

Compounds containing P–O bonds, such as phosphinates (R_2POR), serve as important classes of ligands, catalysts, and synthetic intermediates in modern organic chemistry. As they are also widely present in pharmaceuticals and other valuable organic materials.[1] Accordingly, much attention has been dedicated to P–O bond formation for the construction of phosphinate compounds. Over the past decades, several typical routes reported relied on the addition of alcohols to sensitive phosphinic chlorides ($R_2P(O)Cl$),[2] or on the esterification of phosphinic acids ($R_2P(O)OH$),[3] including via the CCl_4-mediated Atherton-Todd process.[4] In view of the need for more environmentally-friendly and atom-economical organic reactions, developing greener syntheses of phosphinate derivatives remains a highly desirable, albeit challenging task.[5]

Over the past years, the transition metal or other reagent promoted oxidative phosphorylation reactions (Scheme 1a) have been extensively studied for constructing phosphinate compounds *via* a P–O bond formation process.[6] In 2014, Yang disclosed a copper-catalyzed phosphorylation reaction by employing excess DDQ as oxidant.[7] Later, Han reported the iron-catalyzed direct phosphorylation under oxidant-free conditions with high reaction temperature.[8] Meanwhile, the metal-free systems including Tf_2O/H_2O_2 and Ph_2I^+ could also promote this transformation, yielding corresponding phosphinate products.[9,3b] Moreover, the C–H activation/phosphorylation[10] and other related strategies[11] were disclosed as efficient ways as well. Of note, among all reported approaches so far, either metal catalyst or oxidant was essential for the reactivity. Very recently, the research groups of Zhen, Han and Tang reported the electrochemical dehydrogenative phosphorylation under mild conditions to afford phosphinates in moderate to good yields (Scheme 1b), respectively.[12] Generally, these established approaches are impressive and capable for producing desired phosphorylation products, yet accompanying with unsatisfactory yields. Additionally, synthesis of fully aromatic phosphinates [$Ar_2P(O)OAr$] still remains a formidable challenge.[13] Herein, we disclosed a mild, efficient and convenient protocol to prepare diaryl-phosphinates *via* direct phosphorylation between $R_2P(O)H$ and ROH under ambient condition in the absence of oxidants. Moreover, it was found that a carbene-involving process from $CHCl_3$ to CH_2Cl_2 facilitates the phosphorylation (Scheme 1c).



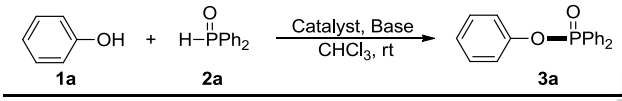
Scheme 1. Synthetic ways to phosphinate compounds.

Initially, the model reaction was performed under the following reaction condition: phenol **1a** (0.1 mmol), diphenyl phosphine oxide **2a** (0.1 mmol), Cs_2CO_3 (0.2 mmol), PPh_3MeI (0.01 mmol) in 1 mL $CHCl_3$. Under this condition, 90% isolated yield was obtained with a reaction time of either 12 hours or 1 hour (Table 1, entries 1 and 2). However, it was found that chloroform and strong base are crucial for this transformation, by comparison, weak bases and other solvents could not give the desired phosphorylation product **3a,** respecitively (see SI for details). As a consequence, further screening was only performed in chlorforom, and some strong bases were employed afterward (Table 1, entries 3 and 4). Pleasingly, the isolated yield of desired product was further improved to 97% while 1.2 equivalent of diphenylphosphine oxide **2a** was utilized (Table 1, entry 5). Meanwhile, we found that 2.0 equivalents of Cs_2CO_3 gave the best result (Table 1, entries 5–8). While PPh_3MeI was absent in the reaction system, the yield was sharply decreased to 40% (Table 1, entry 9). Subsequently,

catalyst usage was surveyed and 10 mol% PPh_3MeI turned out to provide corresponding product **3a** in high yield (Table 1, entries 10–11). Of note, trace amount of water could inhibit the formation of P–O bond (Table 1, entries 12 and 13). Finally, the catalytic system maintained its catalytic ability in the scaled-up reaction (Table 1, entry 14).

With the optimal reaction condition in hand (Table 1, entry 14), we subsequently surveyed the scopes of different alcohols (R–OH). In general, various mono-substituted phenols bearing electron-neutral, electron-donating, or electron-withdrawing groups on the phenyl ring were employed to furnish the corresponding products (**3a**–**l**) in high yields (90–98%). Additionally, when either 1-naphthol or 2-naphthol substrates were used, the desired phosphinate products were also obtained with high yields (**3m** and **3n**). Comparing with 2, 6-dimethyl phenol (**3o**) and 2, 6-diisopropyl phenol (**3p**), the latter showed slightly lower reactivity towards this transformation. Even more, the reaction would be terminated while bulky *tert*-butyl groups substituted at 2,6-positions of the phenyl ring (**3q**). The 3-amino substituted 2-naphthol was also suitable substrate for affording corresponding phosphinate product with slightly lower yield (**3r**). Encouraged by these promising results, a series of alkyl alcohols were used as substrates to conduct the phosphorylations. Despite these alcohols presented much

Table 1. Screening of reaction conditions on phosphorylation of ROH.[a]

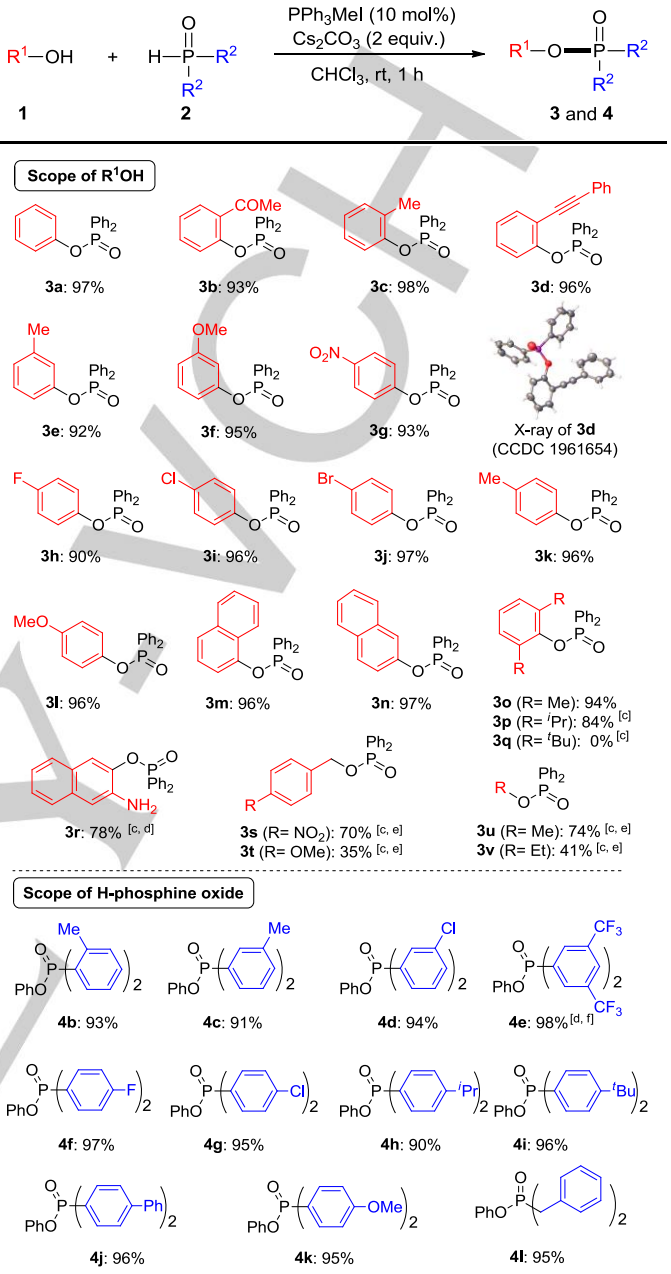


1a 2a 3a

Entry	Base(x equiv.)	t(h)	Yield(%)[b]	Catalyst (y mol%)
1[c]	Cs_2CO_3 (2)	12	90	PPh_3MeI (10)
2[c]	Cs_2CO_3 (2)	1	90	PPh_3MeI (10)
3[c]	KOH (2)	1	77	PPh_3MeI (10)
4[c]	DBU (2)	1	57	PPh_3MeI (10)
5	Cs_2CO_3 (2)	1	97	PPh_3MeI (10)
6	Cs_2CO_3 (1.5)	12	87	PPh_3MeI (10)
7	Cs_2CO_3 (1)	12	49	PPh_3MeI (10)
8	Cs_2CO_3 (0.5)	12	22	PPh_3MeI (10)
9	Cs_2CO_3 (2)	1	40	--
10	Cs_2CO_3 (2)	1	80	PPh_3MeI (5)
11	Cs_2CO_3 (2)	1	97	PPh_3MeI (20)
12[d]	Cs_2CO_3 (2)	1	68	PPh_3MeI (10)
13[e]	Cs_2CO_3 (2)	1	Trace	PPh_3MeI (10)
14[f]	Cs_2CO_3 (2)	1	97	PPh_3MeI (10)

[a] Reaction condition: phenol **1a** (0.1 mmol), diphenyl phosphine oxide **2a** (0.12 mmol), base and catalyst in $CHCl_3$ (1 mL) at room temperature. [b] Isolated yield. [c] 1.0 equivalent of diphenyl phosphine oxide **2a** was used. [d] 1 μL H_2O (0.55 equiv.) was added. [e] 2 μL H_2O (1.1 equiv.) was added. [f] Reaction condition: phenol **1a** (0.4 mmol), diphenyl phosphine oxide **2a** (0.48 mmol), Cs_2CO_3 (0.8 mmol) and PPh_3MeI (0.04 mmol) in $CHCl_3$ (2 mL) at room temperature for 1 hour.

Table 2. Substrate Scope.[a, b]

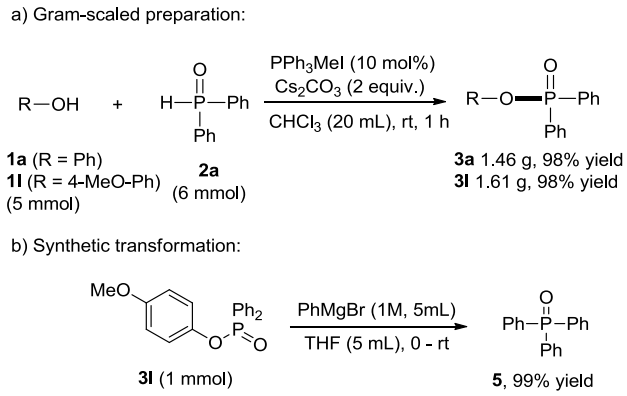


[a] Reaction condition: R^1OH **1** (0.4 mmol), phosphine oxide **2** (0.48 mmol), Cs_2CO_3 (0.8 mmol) and PPh_3MeI (0.04 mmol) in $CHCl_3$ (2 mL) at room temperature for 1 hour. [b] Isolated yield. [c] 24 hours. [d] 3.0 equivalents of Cs_2CO_3 were used. [e] 2.0 equivalents of phosphine oxides were used. [f] 3.0 equivalents of phosphine oxides were used.

higher stability of H–O bond, the phosphorylation reaction could proceed smoothly in the presence of excessive Cs_2CO_3 and diphenyl phosphine oxide and thus gave corresponding products in moderate yields (**3s**–**v**). Moreover, product **3d** was further characterized by X-ray diffraction of single crystal (CCDC 1961654).[14]

Subsequently, we further explored the substrate scope of phosphine oxides under the optimal reaction conditions. A wide range of aromatic phosphine oxides with substituents on the *ortho*-, *meta*-, or *para*-position of the phenyl ring proceeded very well to furnish the desired products (**3a** and **4b**–**k**) in high yields

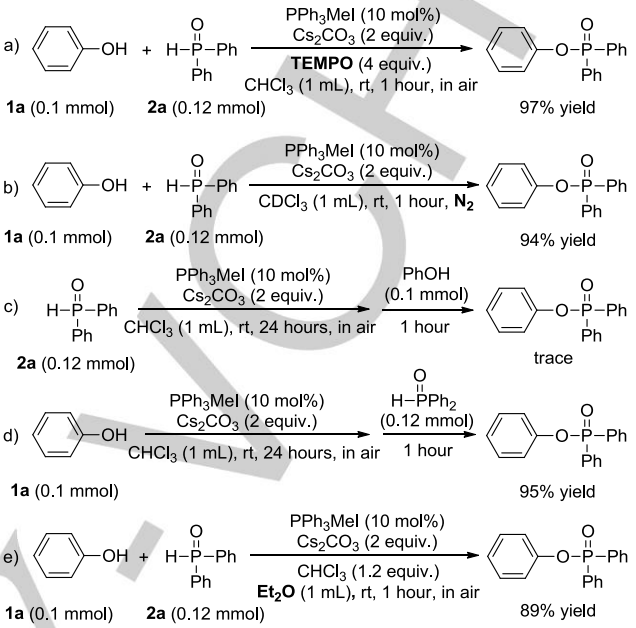
(90–98%). Notably, 3.0 equivalents of bis(3,5-bis(trifluoromethyl) phenyl)phosphine oxide (**2e**) were required to complete the corresponding transformation and to afford the product with excellent yield (98%), mainly because such phosphine oxide substrate bearing two trifluoromethyl substituents is highly reactive and can thus be easily converted to undefined by-product. Moreover, the dialkyl phosphine oxide (**2l**) was also suitable substrate for the construction of the corresponding product **4l** in high yield.



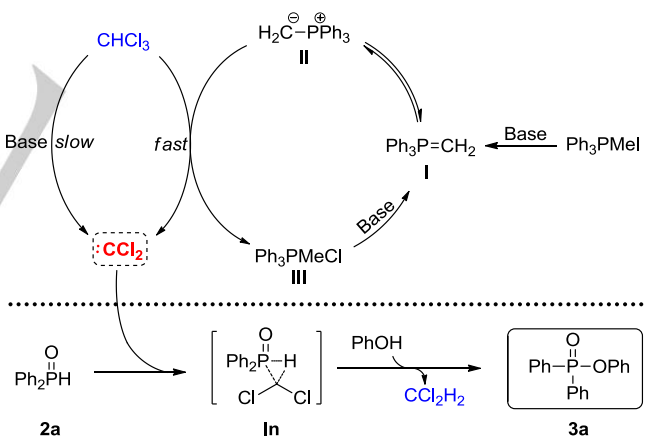
Scheme 2. Gram-scaled preparation and synthetic transformation.

Furthermore, gram-scaled synthetic reactions were performed and the corresponding phosphinate products **3a** and **3l** were prepared in high yields under above optimal conditions (Scheme 2a), which indicated that such process was scalable and practical for its further utilities in organic synthesis. The phosphinate product **3l** could be readily converted into triphenylphosphine oxide **5** in high yield (Scheme 2b).

Motivated by these results, we carried out further experiments for better understanding the reaction mechanism. The control experiments were firstly conducted and the results were presented in Scheme 3. When 4.0 equivalents of **TEMPO** were added into the model reaction mixture, the reactivity maintained (Scheme 3a). Additionally, when the reaction was performed under N_2 atmosphere, the same result was observed as that under ambient condition (Scheme 3b). These preliminary results indicated that the reaction does not follow either single electron radical or O_2-mediated oxidation mechanism. It was worth noting that the adding sequence of substrates dramatically influenced the reactivity of phosphorylation (Scheme 3c and 3d). All these results suggested that the reaction was initiated by the activation of diphenylphosphine oxide **2a**, which was supported by the *in situ* ^{1}H, ^{13}C, ^{31}P NMR results of the reaction mixture (see the SI for details). Meanwhile, a triplet signal at 5.27 ppm on ^{1}H NMR spectrum of the reaction mixture in $CDCl_3$ was observed (see the SI for details), which implied the formation of $CDHCl_2$ under the $CDCl_3$ solvent condition. Fortunately, GC-MS successfully detected all the species including CH_2Cl_2, $CDHCl_2$ and CD_2Cl_2 (m/z 84, 85 and 86, respectively, see the SI for details). Therefore, dichlorocarbene intermediate, which might be generated from base-treated $CHCl_3$, may be the key reactive species. As expected, a control experiment was conducted in the solvent of ether by using 1.2 equivalents of $CHCl_3$ as additive, the desired product can be also isolated in high yield (Scheme 3e). Interestingly, the *in-situ* ^{31}P NMR of reation mixture suggested that a plausible three-centred cyclic intermediate (**In**) with having a new signal located at *ca.* 15 ppm was generated *via* a carbene insertion to activate $HP(O)Ph_2$ (Figure S6 in SI).[15] Furthermore, the carbene insertion was also supported by the result from H/D exchange reaction in $CDCl_3$ at the same time.



Scheme 3. Control experiments.



Scheme 4. Proposed reaction mechanism.

Based on above results, the reaction mechanism was proposed in Scheme 4. In the presence of excessive Cs_2CO_3, phosphorus ylide (**I**) is formed from PPh_3MeI through a base-triggered elimination of HI (*in situ* ^{1}H, ^{13}C and ^{31}P NMR).[16] Subsquently, this ylide trapps the HCl from $CHCl_3$ to furnish dichlorocarbene as the key reagent for the formation of intermediate **In**.[17] It is noteworthy that, under basic condition, $CHCl_3$ could also complete this process in very slow rate without addition of any other reagent. Finally, the formed three-centred cyclic intermediate (**In**) is attacked by PhOH **1a** to generate CH_2Cl_2 and final product **3a**.

In conclusion, we have developed the first chloroform-assisted direct phosphorylation reaction between $R_2P(O)H$ and

ROH under phosphonium salt catalysis condition. This reaction provided an efficient, scalable and convenient way to synthesize phosphinate derivatives in a highly reactive manner. Furthermore, no oxidant additives were needed for this phosphorylation reaction owing to the new acitivation mode of a carbene-involving process. Further investigation on its detailed mechanism and applications are in progress.

Acknowledgements

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Keywords: phosphorylation • phosphinate • phosphonium salt catalysis • dichlorocarbene

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[14] Deposition Number CCDC 1961654 (**3d**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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[16] When the *in situ* generated CH_2=PPh_3 (PPh_3MeI and ^tBuOK in ether) was added into the mixture of phenol **1a** and diphenyl phosphine oxide **2a** in $CHCl_3$, the reaction proceeded smoothly and thus provided the desired product **3a** with 63% yield.

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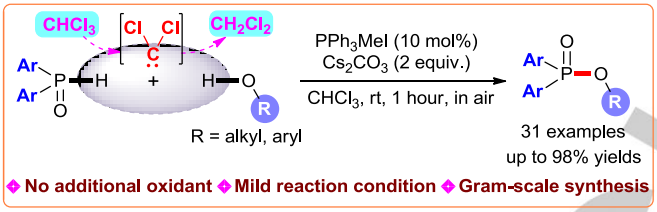
Phosphorylation



A mild, efficient, convenient and scalable method to synthesize phosphinates via direct phosphorylation between $R_2P(O)H$ and ROH was developed. Preliminary mechanistic studies suggest that a carbene-involving process from $CHCl_3$ to CH_2Cl_2 facilitates the phosphorylation.