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O-Phosphination of Aldehydes/Ketones toward Phosphoric Esters: Experimental and Mechanistic Studies

Yanyan Qian, Qiang Dai, Zhiming Li,* Yu Liu,* and Junliang Zhang*

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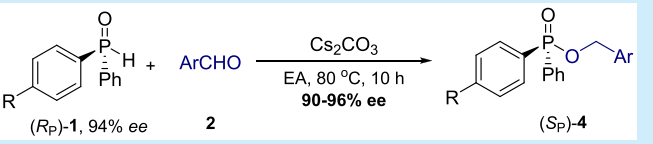
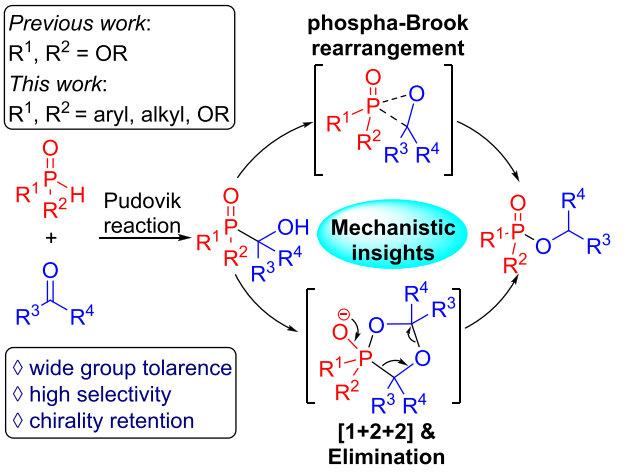
ABSTRACT: Addition of P−H species to carbonyl groups, namely the Pudovik reaction, normally delivers hydroxyl phosphorus compounds, along with phosphate byproducts in some cases. A few controllable systems starting from phosphites were set up to mainly provide the phosphates. Herein, we present a highly selective protocol starting from phosphonate precursors leading to phosphinate derivatives. Enantioenriched phosphinates were successfully achieved from chiral phosphine oxide precursors. Experimental and theoretical investigations were conducted to understand the mechanistic details.



Organophosphorus compounds are frequently presented scaffolds in bioactive molecules,[1] synthetic agents,[2] pharmeceuticals,[3] and materials,[4] among others,[5] stimulating extensive interests in exploring convenient and practical methods for the preparation of these analogues. During the past decades, a number of synthetic tools toward phosphoric esters have been developed.[5,6] Traditional methods for P−O bond construction involve nucleophilic substitution of highly air sensitive and hazardous phosphorus reagents with alcohols or phenols.[7] In recent years, many methods have been developed to synthesize phosphate esters.[8] As a practical method for the preparation of hydroxyl phosphorus compounds from the addition of P−H species to carbonyl motifs, the Pudovik reaction[9] delivers phosphates as minor products in some cases.[10] Recent explorations by several groups including Kaïm's and Chakravarty's established conditions for selective preparation of the phosphate derivatives starting from phosphites bearing two alkoxyl groups.[11] To the best of our knowledge, other types of phosphine oxide precursors have seldom been applied in such a strategy to prepare the corresponding phosphoric esters in high selectivity.[12] In addition, the existing methods often suffer from limitations, such as low functional group tolerance and harsh conditions. Moreover, although phospha-Brook rearrangement is believed to be operative in all reported cases,[6d,11] definitive evidence is still lacking to prove the mechanistic proposal. As part of our ongoing interest in organophosphorus compounds,[13] we disclose herein a mild and efficient protocol toward phosphoric esters, especially phosphinates. The reaction features wide functional group tolerance and mild conditions. Furthermore, chiral phosphinates can be facilely derived from enantioenriched phosphine oxides. DFT calculation was resorted to discriminate the three mechanistic proposals, namely, the Brook rearrangement, antiregioselective addition to the carbonyl group, and [1 + 2 + 2]/elimination pathways, which could not be unambiguously discerned experimentally (Scheme 1).

Scheme 1. Reaction Patterns of Phosphine Oxides and Aldehydes/Ketones



As a starting point, the reaction of diphenylphosphine oxide **1a** and benzaldehyde **2a** in the presence of K_3PO_4 at 80 °C in ethyl acetate (EA) delivered a 49% NMR yield of *O*-phosphination product **4aa** along with 13% NMR yield of the normal Pudovik adduct **3aa** (Table 1, entry 1). Inspired by

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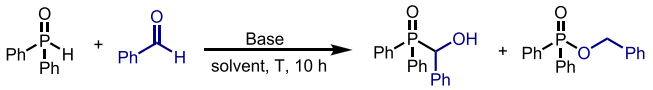
Table 1. Reaction Optimization[a]



1a 2a 3aa 4aa

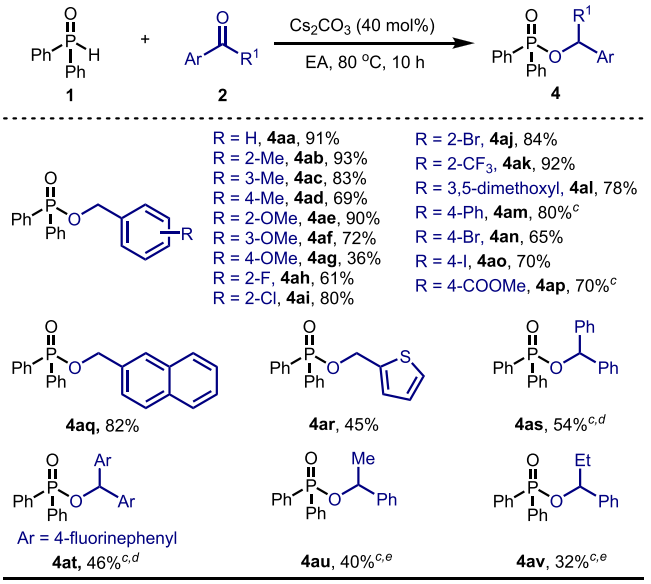
entry	base	solvent	3aa[b] (%)	4aa[b] (%)
1	K_3PO_4	EA	13	49
2	NaO^tBu	EA	trace	35
3	KO^tBu	EA		48
4	LiO^tBu	EA	9	15
5	Cs_2CO_3	EA		93
6	K_2CO_3	EA	24	trace
7	Na_2CO_3	EA	41	
8	Cs_2CO_3	*n*-hexane	33	9
9	Cs_2CO_3	toluene		77
10	Cs_2CO_3	dioxane		64
11	Cs_2CO_3	THF		64
12[c]	Cs_2CO_3	EA	29	27
13[d]	Cs_2CO_3	EA		73
14[e]	Cs_2CO_3	EA		69
15[f]	Cs_2CO_3	EA		72
16[g]	Cs_2CO_3	EA		66

[a]Reaction conditions: diphenylphosphine oxide (0.2 mmol), benzaldehyde (0.3 mmol), base (40 mol %), solvent (2 mL) under N_2 at 80 °C for 10 h. [b]NMR yield with the use of CH_2Br_2 as the internal standard. [c]Reaction temp: rt. [d]Reaction temp: 60 °C. [e]Reaction temp: 100 °C. [f]Reaction time: 8 h. [g]2.0 equiv of benzaldehyde was added.

this delightful result, we conducted careful screening of the reaction factors to improve the reaction outcome.[14] As expected, base exerts a profound influence on the reactivity. Thus, the product **4aa** was obtained in moderate yield with NaO^tBu or KO^tBu, but only in trace amounts with LiO^tBu (Table 1, entries 2−4). Gratifyingly, the yield was dramatically improved to 93% using Cs_2CO_3 as base (Table 1, entry 5). In contrast, trace or no desired *O*-phosphination product was detected in the presence of K_2CO_3 or Na_2CO_3, offering only **3aa** in low yields (Table 1, entries 6 and 7). Although the reaction was suppressed in *n*-hexane, other solvents, such as toluene, dioxane, and tetrahydrofuran could be employed, furnishing **4aa** in good yields (Table 1, entries 8−11). The reaction temperature also played a pivotal role, as inferior results were obtained at lower or higher temperatures (Table 1, entries 12−15). Finally, increasing the loading of benzaldehyde had a deleterious effect, resulting in significant erosion of the yield (Table 1, entry 16).

With the optimal conditions in hand, the generality of our protocol was explored (Table 2). As shown, benzaldehydes decorated with a diverse set of substituents could be well accommodated. Substrates bearing *o*-, *m*-, or *p*-methyl groups all proceeded smoothly under the standard conditions (**4ab**−**4ad**), suggesting the insensitivity of the reaction to steric effect. An electron-donating methoxy substituent was also tolerated (**4ae**−**4ag**, **4al**). Aldehydes containing electron-withdrawing trifluoromethyl and ester groups could be well accommodated, delivering the desired products in good yields (**4ak**, **4ap**). Various halogen-containing products were afforded uneventfully (**4ah**−**4aj**, **4an**−**4ao**), leaving space for further derivatization. Biphenyl and naphthyl aldehydes could also be applied, providing the phosphinates in high yields (**4am**, **4aq**). The generality of the system was further showcased by the

Table 2. Scope of Aldehydes/Ketones[a]

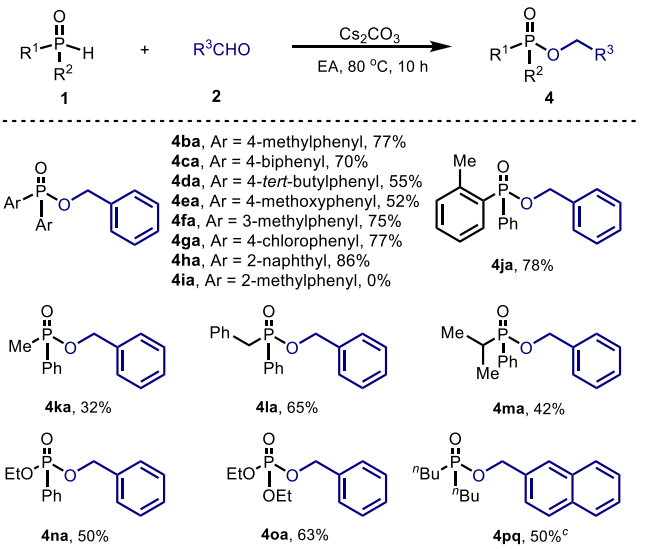


[a]Reaction conditions: $Ph_2P(O)H$ (0.2 mmol), aldehyde (0.3 mmol), Cs_2CO_3 (40 mol %), ethyl acetate (2 mL) under N_2 at 80 °C for 10 h. [b]Isolated yield. [c]100 °C. [d]$Ph_2P(O)H$ (0.4 mmol), ketone (0.6 mmol), Cs_2CO_3 (40 mol %), ethyl acetate (4 mL). [e]$Ph_2P(O)H$ (0.4 mmol), ketone (0.6 mmol), Cs_2CO_3 (40 mol %), ethyl acetate (4 mL), 120 °C, 5 h.

tolerance of the thiophene moiety, as product **4ar** was afforded in moderate yield. Delightfully, ketones are also applicable, albeit affording the products in relatively lower yields, probably due to the lower reactivity and steric hindrance of the substrates (**4as**−**4av**).

As depicted in Table 3, a series of secondary phosphine oxides phosphonates and phosphinate efficiently coupled with benzaldehyde to produce the corresponding *O*-phosphination

Table 3. Scope of SPO Compounds.[a]



[a]Reaction conditions: secondary phosphine oxide (0.2 mmol), aldehyde (0.3 mmol), Cs_2CO_3 (40 mol %), ethyl acetate (2 mL) under N_2 at 80 °C for 10 h. [b]Isolated yield. [c]Tetrahydrofuran (2 mL) was used as solvent.

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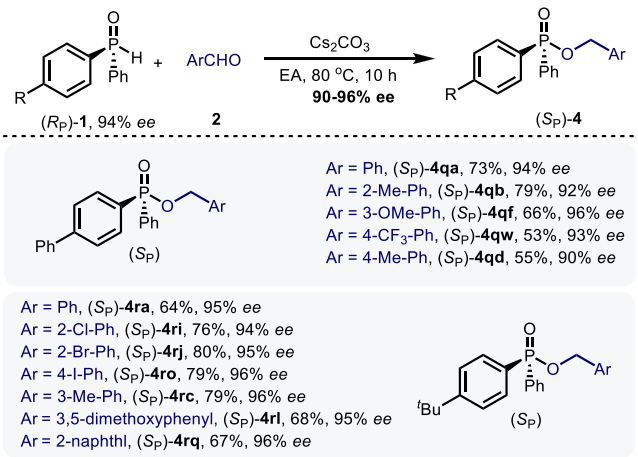
products. All diarylphosphine oxide substrates bearing an alkyl-, methoxy-, chloro-, or phenyl group on the phenyl ring could be tolerated, providing the corresponding phosphinate products **4ba**−**4ga** facilely. Binaphthyl phosphinate **4ha** could also be achieved in 86% yield. However, sterically hindered bis(2-tolyl)phosphine oxide showed no reactivity in the protocol, since no expected product **4ia** was observed. The applicability of the reaction system was further demonstrated with various unsymmetric phosphine oxides. Thus, benzyl phenyl(*o*-tolyl)phosphinate **4ja** was generated in 78% yield. Moreover, phosphine oxides with an alkyl substituent such as a methyl, benzyl, or isopropyl group on the P atom could all be transformed into the corresponding products **4ka**−**4ma**, although the yields were lower. Notably, phosphonates **4na** and phosphate **4oa**[6d] could both be prepared in moderate to good yields, respectively. With THF as solvent, bisalkyl phosphinate **4pq** was also delivered in moderate yield.

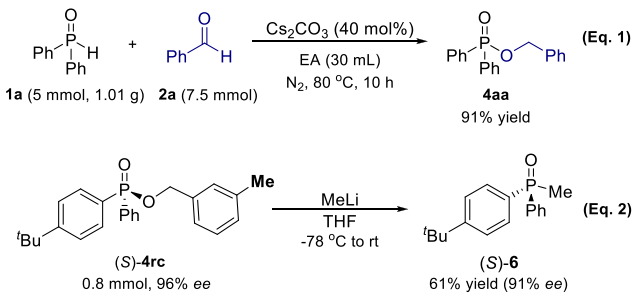
Optically active phosphinate derivatives are important compounds with diverse biological activities and potential applications in asymmetric synthesis.[15] However, methods for their preparation are rather limited.[16] In this regard, we examined the reaction of two different chiral secondary phosphine oxide precursors. As shown in Scheme 2, the

Scheme 2. Synthesis of Chiral Phosphinate Compounds via Chirality Transfer



reaction of (*R*)-(4-(*tert*-butyl)phenyl)(phenyl)phosphine oxide (**1q**) and (*R*)-[1,1′-biphenyl]-4-yl(phenyl)phosphine oxide (**1r**) proceeded smoothly in the current transformation, providing the corresponding products (S_P)-**4** in good yields and high ee values. A handful of aryl aldehydes could all be tolerated, with no or slight erosion on the enantioselectivity.

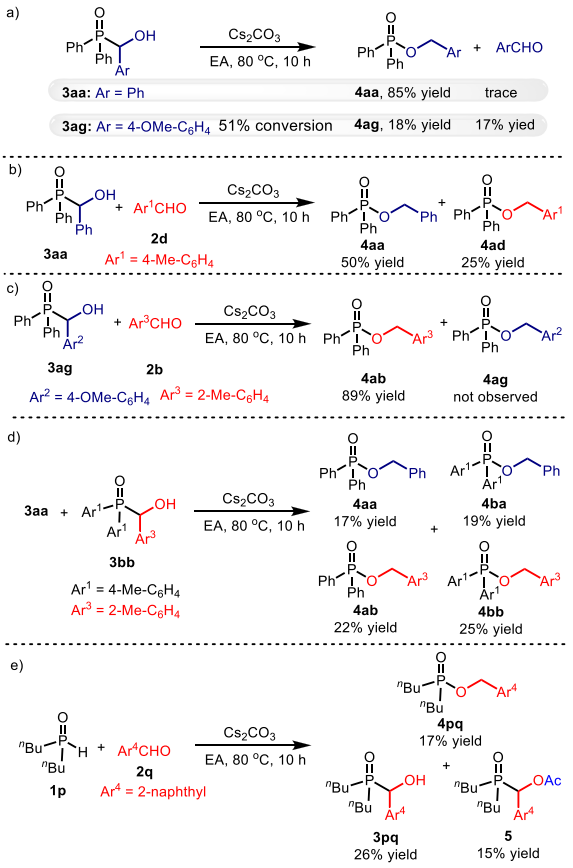
The reaction could be performed on gram-scale, delivering the target compound **4aa** in excellent yield (eq 1). The



synthetic potential of the reaction was further demonstrated by subjecting the obtained enantioenriched phosphinate (*S*)-**4rc** to CH_3Li. S_N2 nucleophilic substitution[17] took place to furnish the chiral phosphine oxide (*S*)-**6** in good yield and high enantioselectivity (eq 2).

Additional experiments were conducted in order to clarify the reaction mechanism. When potential intermediates (hydroxy(phenyl)methyl)diphenylphosphine oxide **3aa** and **3ag** were tested under the standard conditions, phosphinates **4aa** and **4ag** were delivered, respectively. 4-Methoxybenzaldehyde was also observed in the latter case (Scheme 3, a). 4-

Scheme 3. Control Experiments for Mechanistic Study



Methylbenzaldehyde (**2b**) reacted with **3aa** leading to both **4aa** and **4ad** as final products (Scheme 3, b). These results suggest that the nucleophilic addition of phosphine oxide to aldehyde leading to generate **3aa** is reversible. In comparison, the reaction between **3ag** and 2-methylbenzaldehyde (**2d**) only afforded **3ab** as a single product, without the formation of **4ag**, indicating that the electron-donating group on the aldehyde deactivates the reactivity (Scheme 3, c). The crossover experiments by feeding **3aa** and **3bb** into the optimal conditions lead to all of the four possible phosphinate products, further confirming the reversibility of the addition process. (Scheme 3, d). During the reaction between dibutylphosphine oxide and 2-naphthaldehyde under the standard conditions, ethyl acetate involved product **5** was observed along with **3pq** and **4pq** (Scheme 3, e).

Three reaction pathways as shown in Scheme 4 are proposed on the basis of the above experiments. Initially, substrates **1** and **2** underwent a Cs_2CO_3-facilitated nucleophilic addition leading to intermediate **I**. This process turned out to be

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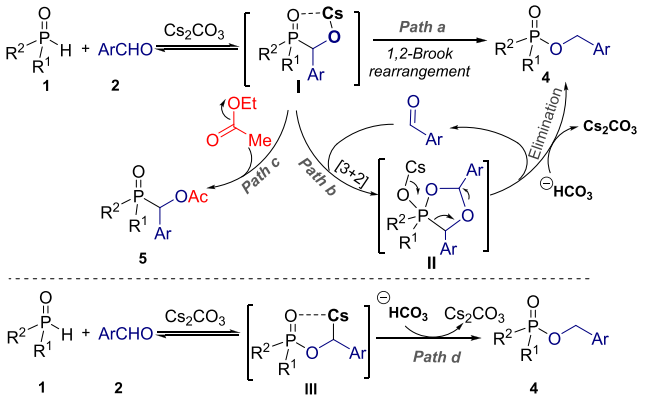
Scheme 4. Proposed Reaction Mechanism



reversible according to the experimental results (Scheme 3). 1,2-Brook rearrangement would deliver the phosphinates as final products (path a).[6d,11] Alternatively, the involvement of another aryl aldehyde molecule through [3 + 2] cycloaddition may result in a five-membered species **II**, which eliminates the aldehyde to afford the final product **4** upon protonation (path b). In the presence of ethyl acetate, intermediate **I** might be captured leading to byproduct **5** (path c). Direct nucleophilic attack of cesium phosphite on the O atom of the carbonyl group to create intermediate **III** cannot be excluded (path d).

To gain further insight into the reaction mechanism and distinguish the three possibilities mentioned above, density functional theory (DFT) calculations were carried out using the Gaussian 09 software package (for details, see the SI).[18,19] The free energy profiles are shown in Figure 1. First, Cs-

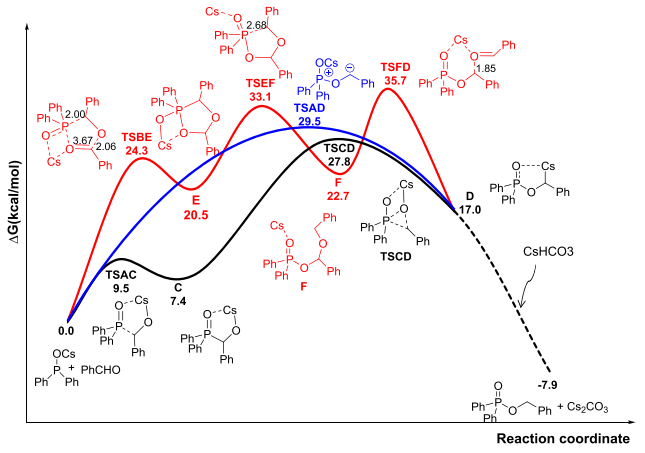


Figure 1. Computed free energy profiles for the reaction process.

mediated [3 + 2] cycloaddition leading to the five-membered species **E** (TS_{BE}) was found to require a barrier of 24.3 kcal/mol. A stepwise cycloaddition path was also located, which is less favored due to a slightly higher barrier (Figure S1). The following elimination process is stepwise according to our computation results, since no concerted elimination transition states can be located despite many attempts. From **E**, elimination occurs to form intermediate **F**. Further elimination of benzaldehyde delivers the final intermeidate **D** with a barrier of 13.0 kcal/mol. Direct nucleophilic attack of cesium phosphite on the O atom of the carbonyl group required a barrier of 29.5 kcal/mol through TS_{AD}. Alternatively, cesium phosphite attacks benzaldehyde nucleophilically leading to intermediate **C** via a low barrier of 9.5 kcal/mol. Subsequently, a concerted phospha-Brook rearrangement through TS_{CD} and protonation gives product **4** with a barrier of 20.4 kcal/mol. Obviously, the lower activation energy of phospha-Brook rearrangement pathway is confirmed to be more favorable.

In summary, we have developed a mild and practical route to prepare phosphoric ester compounds. Aldehydes and ketones were both coupled with secondary phosphine oxides, forming P−O bond in the presence of base. Enantioenriched phosphoric esters could be facilely prepared from chiral phosphine oxide precursors. Three different reaction mechanisms including phospha-Brook rearrangement, direct anti-regioselective addition, and [3 + 2] cycloaddition/elimination were proposed according to the experimental results. The former was proved to take effect by DFT calculations. Further investigations on the reaction system are ongoing in our lab.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01537.

Computational details, experimental procedures, and characterization data (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Zhiming Li − *Department of Chemistry, Fudan University, Shanghai 200438, P.R. China*; Email: zmli@fudan.edu.cn

Yu Liu − *College of Chemistry and Life Science, Jilin Provincial Key Laboratory of Carbon Fiber Development and Application, Changchun University of Technology, Changchun 130012, P.R. China*; orcid.org/0000-0003-1304-9498; Email: yuliu@ccut.edu.cn

Junliang Zhang − *Department of Chemistry, Fudan University, Shanghai 200438, P.R. China; Zhuhai Fudan Innovation Institute, Zhuhai 519000, P.R. China*; orcid.org/0000-0002-4636-2846; Email: junliangzhang@fudan.edu.cn

Authors

Yanyan Qian − *College of Chemistry and Life Science, Jilin Provincial Key Laboratory of Carbon Fiber Development and Application, Changchun University of Technology, Changchun 130012, P.R. China*

Qiang Dai − *Shanghai Key Laboratory of Green Chemistry and Chemical Processes, School of Chemistry and Molecular Engineering, East China Normal University, Shanghai 200062, P.R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01537

Notes

The authors declare no competing financial interest.

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