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Water mediated synthesis of dialkylphosphine oxides from white phosphorus and *N*-(acyloxy) phthalimides†

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The multicomponent synthesis of dialkylphosphine oxides from P_4 without a chlorination step is reported. With the use of *N*-(acyloxy)phthalimides (NHPI esters) as the alkylation reagents, H_2O as the oxygen source, tris(2,2′-bipyridine)ruthenium dichloride as a photocatalyst, 2,6-lutidine as a base, and *N*,*N*-dimethylacetamide as a solvent, the reactions are performed under green light irradiation, yielding the desired products in moderate to good yields. Notably, this catalytic system is also capable of synthesizing α-hydroxy phosphine oxides from P_4 in one-pot. This two step-economic approach, which directly utilizes P_4 as the P-atom source, avoids the traditional chlorination stage and oxidation processes.

Introduction

Organophosphorus compounds (OPCs) containing C–P bonds are ubiquitous in both industrial and academic fields, such as materials science, pharmaceutical chemistry, catalysis, and coordination chemistry.[1] In general, the preparation of OPCs predominately relies on white phosphorus (P_4) as the source of P atoms.[2] However, the conversion of P_4 to OPCs involves (oxy) chlorination process and uses corrosive chlorine gas (Cl_2) and intermediates such as PCl_3/PCl_5/$POCl_3$. Another approach toward OPCs is the hydrophosphinylation of alkenes with toxic and explosive PH_3.[3] To circumvent the use of PCl_3 and PH_3, significant progress has been made in forming of heteroatom–P bonds, such as S–P bonds[4] or O–P bonds[5] from P_4 (Scheme 1).

Dialkyl phosphine oxides [$R_2P(O)H$] containing reactive P(O)–H bonds are versatile building blocks for synthesizing trialkyl phosphine oxides such as α-hydroxy phosphine oxides. The direct transformation of P_4 into tertiary phosphines (PR_3) and their oxides containing the same three alkyl/ary groups was investigated by the Cummins, Wolf, and Zhang groups and others.[6] Due to the complex P–P bond breaking patterns, it is still challenging to construct $R_2P(O)H$ containing both C–P and P(O)–H bonds directly from P_4 with good selectivity. In 2022, our group made a breakthrough and published the paper entitled "Decarboxylative Selective Phosphorylation of Aliphatic Acids: A Transition-Metal- and Photocatalyst-Free Avenue to Dialkyl and Trialkyl Phosphine Oxides from White Phosphorus".[7a] Since then, we have reported the selective construction of $R_2P(O)H$ from P_4 with alkyl bromides and iodides.[7b,c] All these experiments required excess alkylation reagents. Furthermore, strict anhydrous operation and subsequent oxidation workup were needed (Scheme 1B).

One-pot multicomponent reactions enable the efficient and atom-economical synthesis of OPCs directly from P_4. Significant progress has been made in multicomponent reactions for the synthesis of P–heteroatom bonds (Scheme 1A).[8] In 2020, the first general synthesis of mixed phosphorotrithioates involving P_4, disulfides, KOH, and alkyl halides was presented.[8a] In 2022, we described a four-component functionalization of P_4 with disulfides, amines and KOH to synthesize phosphoramidodithioates.[8b] In 2023, we published a one-pot direct synthesis of tetrathiophosphates from P_4, NaSH, disulfides and alkyl halides with sodium alkyltetrathiophosphates as the key intermediates.[8c] In 2024, we presented the first copper-catalyzed three-component reaction for generating phosphorothioates from P_4, disulfides, and alcohols in a single reaction step.[8d]

To construct C–P bonds, many novel phosphorus transfer reagents have been developed in recent years.[9] From the perspective of step-economy, it is highly appealing to directly convert P_4 into OPCs in one-pot process without the use of phosphorus transfer reagents. Compared to the research of P–heteroatom bonds formation, few multicomponent reactions

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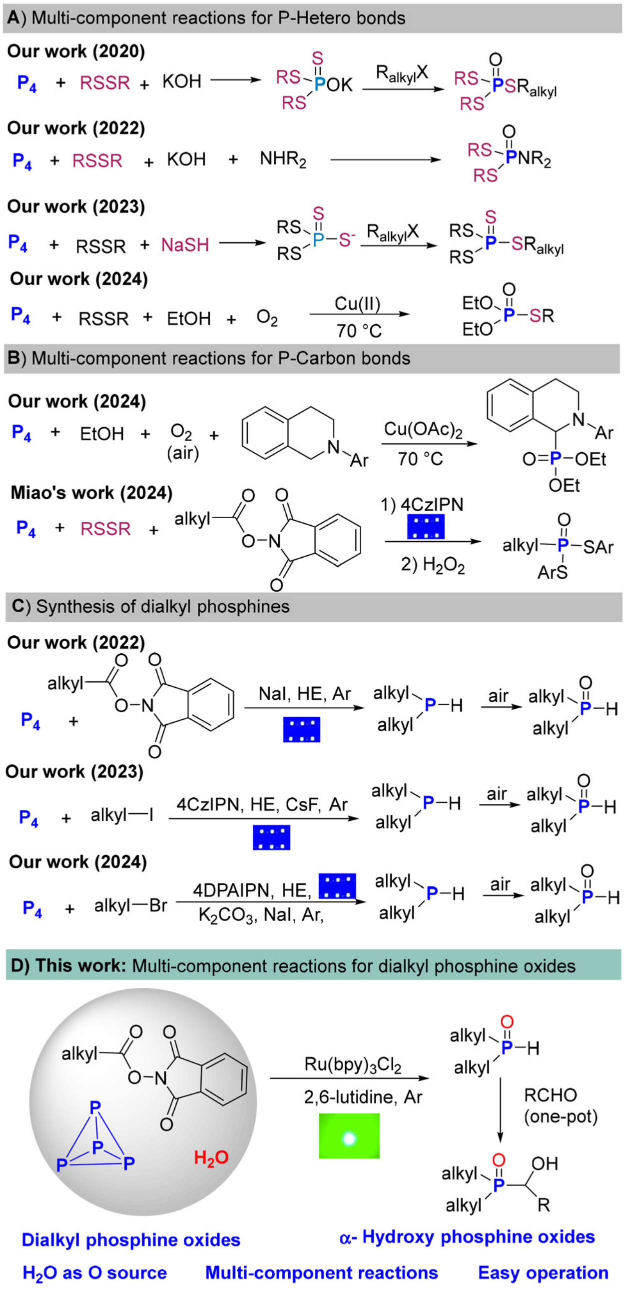


Scheme 1 Multi-component reactions with P_4.

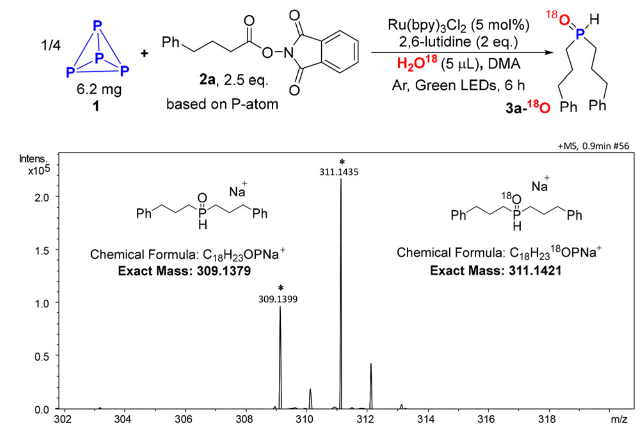
for the construction of C–P bonds have been explored (Scheme 1C). In 2024, the first multicomponent oxidative α-phosphonylation of amines with P_4 and alcohols was developed.[10a] In the same year, Miao *et al.* reported a visible light-induced three-component reaction integrating P_4, disufides, and *N*-(acyloxy)phthalimides (NHPI esters) to produce alky-substituted phosphonodithioates.[10b]

As a continuum of our efforts in P_4 chemistry, we envisioned that with the use of H_2O as the oxygen source, and *N*-(acyloxy)phthalimides as the carbon source, $R_2P(O)H$ could be directly synthesized from P_4 under an argon atmosphere without additional oxidation processes (Scheme 1D).

Results and discussion

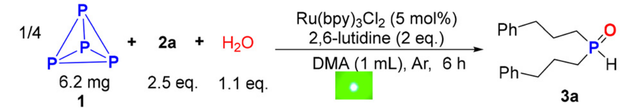
To verify our conjecture, we commenced our project by employing $H_2{}^{18}O$, and 4-phenylbutanic acid NHPI ester (**2a**) as model substrates to direct functionalization of P_4 (**1**). When a solution of P_4 (6.20 mg), $H_2{}^{18}O$ (5 µL), **2a** (0.5 mmol, 2.5 equivalents per P-atom), 2,6-lutidine in *N*,*N*-dimethylacetamide (DMA) was irradiated by green LEDs at room temperature for 6 h in the presence of $Ru(bpy)_3Cl_2$ under argon atmosphere, **3a-^{18}O** was obtained as the main product (Scheme 2).

Inspired by this result, we began optimizing the conditions for the synthesis of $R_2P(O)H$ **3a** using H_2O as the oxygen source. After extensive screening of bases, solvents, and catalysts, the desired product **3a** was obtained in 90% yield (entry 1 in Table 1). No $R_2P(O)H$ and R_2PH were obtained in the



Scheme 2 Water-^{18}O as the *O*-resource.

Table 1 Synthesis of $(PhCH_2CH_2CH_2)_2P(O)H$ (**3a**)[a]



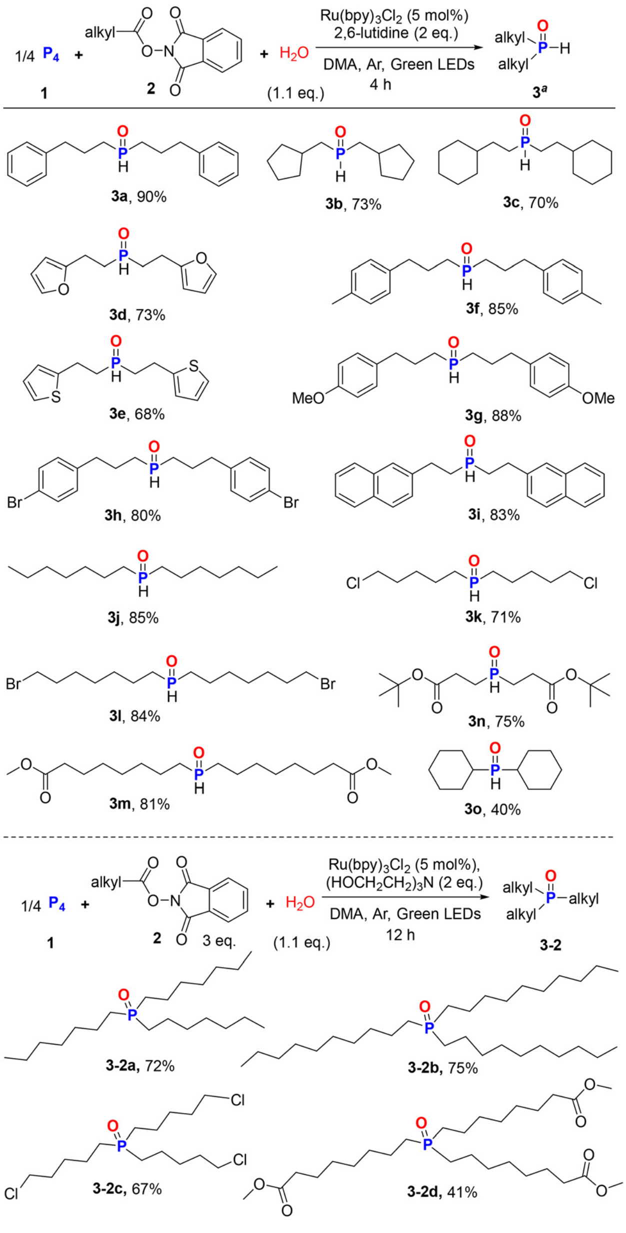
Entry	Deviation from standard conditions	Yield (%)
1[b]	Standard conditions	94 (90)
2	Without H_2O	Trace
3	H_2O (0.5 eq.)	13
4	DIPEA, DABCO instead of 2,6-lutidine	60–70
5	NMP instead of DMA	89
6	DMF, DMSO, MeCN instead of DMA	32–49
7	Other organo-PC	0–70
8	Air instead of Ar	0
9	No light or PC	0

[a] Reaction conditions: P_4 (6.20 mg, 0.20 mmol of P atom, a 0.74 M solution of P_4 in toluene, 0.27 mL), **2a** (2.5 equivalents per P-atom), $Ru(bpy)_3Cl_2$ (0.01 mmol, 5 mol%), H_2O (1.1 eq., 4 µL), 2,6-lutidine (0.40 mmol, 2 eq.) in DMA (1 mL) irradiated by green LEDs (2 × 3 W, 565–575 nm) at room temperature for 6 h under argon atmosphere. Yield of **3a** was determined by the $^{31}P\{^1H\}$ NMR analysis of the crude reaction mixture using $(C_6H_5O)_3P(O)$ as an internal standard. [b] Isolated yield in parenthesis. PC = photocatalyst.

absence of H_2O (entry 2). Increasing the amount of H_2O to 0.5 equivalents gave **3a** but in only 13% yield (entry 3). Using $H_2{}^{18}O$ and H_2O as the *O*-resouces verifed that water was the key starting material in this transformation. Other bases, such as DIPEA and DABCO, resulted in lower yield of **3a** (entry 4). DMA and NMP were found to be good solvents for this reaction (entry 5), while other polar solvents, such as DMF, DMSO, and MeCN, led to much lower yields (entry 6). When transition-metal-free photocatalysts were tested, most performed poorly (entry 7), although Na_2-eosin Y gave the product in 70% yield. No C–P bond formation was observed when the reaction was conducted under air conditions (entry 8). The reaction was inhibited in the absence of either photocatalyst or light (entry 9).

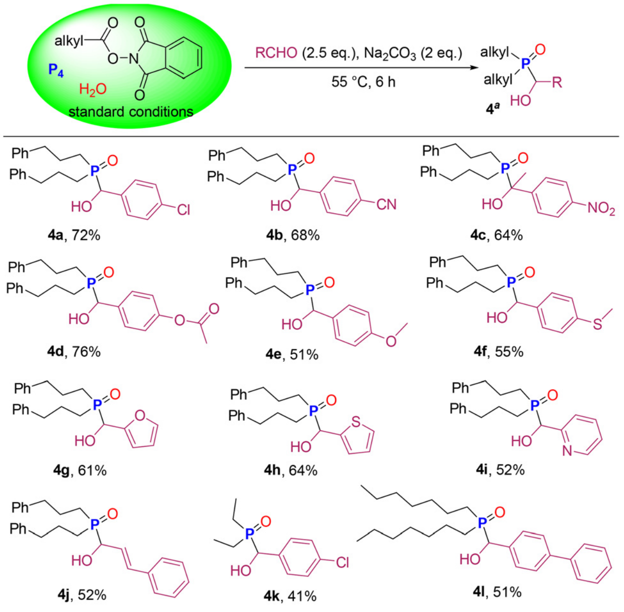
After optimizing the reaction conditions for the synthesis of **3a**, we explored the scope of carboxylic acids for the synthesis of structurally diverse $R_2P(O)H$ **3** (Scheme 3). Under photoirradiation conditions, various alkyl acid NHPI esters can participate in this process, providing the desired products in good yields. 2-Cyclopentylacetic acid and 3-cyclohexylpropanoic acid NHPI esters gave products **3b** and **3c** in 73% and 70% yields, respectively. Linear acid NHPI esters with heterocyclic rings such as O-heterocycle (**3d**), S-heterocycle (**3e**) underwent phosphonylation without difficulty. Aryl-substituted linear acid NHPI esters with electron donating groups (methyl, methoxy, naphthalene) or electron withdrawing group (bromo) on the benzene ring gave **3f**–**3i** in 80–88% yields. Simple primary saturated fatty acid ester gave **3j** in 85% yield. Furthermore, a range of synthetically useful functional groups, such as $C(sp^3)$–Cl, $C(sp^3)$–Br, and ester (**3m** and **3n**), were also compatible with the mild conditions, providing respective dialkyl phosphine oxides in 71–85% yields. Due to steric hindrance, cyclohexanecarboxylic acid ester produced dicyclohexylphosphine oxide in a low yield (**3o**, 40%). When linear secondary or tertiary carbon radical precursors were employed, no C–P bonds were formed. In these failed experiments, white phosphorus remained completely ($\delta = -529$ ppm). It is speculated that the sharp decrease in the yield of secondary and tertiary carbon free radical reactions may be due to the stability and steric hindrance effect of their free radicals.

We then speculated about whether this water mediated multicomponent strategy could be used to produce valuable trialkyl phosphine oxides (Scheme 3). With $Ru(bpy)_3Cl_2$ as the best catalyst and trolamine as the best base, the reaction was performed for 12 h to afford the desired product **3-2a** in 72% yield. A series of chain primary fatty acid ester selected as substrates provided the corresponding trialkyl phosphine oxides **3-2b**–**3-2d** in satisfactory yields.



Scheme 3 Scope of alkyl acid *N*-hydroxyphthalimide esters for the synthesis of dialkyl/trialkyl phosphine oxides.

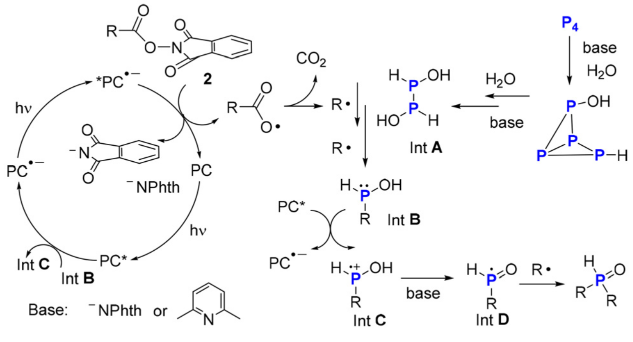
Dialkyl phosphine oxides are often used as starting materials for the preparation of various organophosphorus compounds. Encouraged by the findings described above, we continued to explore the one-pot synthesis of α-hydroxy phosphine oxides from P_4, avoiding the purification process of $R_2P(O)H$ and the use of dangerous Cl_2 and PCl_3. Pleasingly, we added aldehydes and Na_2CO_3 to the crude product **3a** solution to produce α-hydroxy phosphine oxides in good yields (Scheme 4). Benzaldehyde with electron withdrawing group (–Cl, –CN, and $-NO_2$) and electron donating groups ($-OCOCH_3$, $-OCH_3$, and $-SCH_3$) provided the corresponding products in yields of 51–76% (**4a**–**4f**). When aromatic heterocyclic formaldehydes such as furan-2-carbaldehyde, thiophene-2-carbaldehyde and pyridine-2-carbaldehyde were employed as substrates, products **4g**–**4i** were obtained in the range of 52–64%. Cinnamaldehyde, with a double bond, afforded the product **4j** in 52% yield. This method was found to be compatible with primary saturated fatty acid esters. Decarboxylative phosphorylation of propionic acid NHPI ester followed by nucleophilic addition reaction of aldehyde gave product **4k** in 41% yield. Long-chain *n*-octoic acid NHPI ester



Scheme 4 One-pot synthesis of α-hydroxy phosphine oxides from P_4.

successfully participated in this one-pot synthesis of α-hydroxy phosphine oxide **4l**.

Furthermore, *in situ* NMR studies on the reaction of NHPI ester **2a** and P_4 were conducted and the corresponding $^{31}P\{^1H\}$ NMR spectra were shown in Fig. 1–3 (see ESI†). When the reaction mixture was irradiated by white light-emitting diodes (LEDs) for 30 min, the signal of the product **3a** and byproduct (RP(O)(OH)H) appeared. No RPH_2 or R_2PH was detected. Based on these results and previous studies,[7] a tentative mechanism for the photoinduced functionalization of P_4 was proposed (Scheme 5). Initially, water breaks the P–P bond of P_4 in a manner like super-basic systems (OH^- in DMSO) to yield intermediate **A**.[11] Subsequently, the alkyl radical breaks the P–P bond of intermediate **A** to give an unstable intermediate **B**, which then reacts with excited PC* and base to form the phosphinoyl radical **D**. Radical **D** can directly combine with another $R^•$ yields $R_2P(O)H$ as the main product of the reaction.



Scheme 5 Proposed reaction mechanism.

Conclusions

In conclusion, we developed the first water mediated multicomponent synthesis of dialkylphosphine oxides and α-hydroxy phosphine oxides from P_4 without a chlorination step. With the use of *N*-(acyloxy)phthalimides as the alkylation reagents, H_2O as the oxygen source, the reactions are performed under green light irradiation. The desired dialkylphosphine oxides [$R_2P(O)H$] can be directly synthesized from P_4 under argon atmosphere without additional oxidation processes in moderate to good yields. Advantageously, the catalytic system can also synthesize α-hydroxy phosphine oxides from P_4. These step-economic approaches use P_4 as the P-atom source, avoiding the traditional chlorination stage and oxidation processes.

Experimental

Synthesis of dialkyl phosphine oxides from white phosphorus

A Schlenk tube containing $Ru(bpy)_3Cl_2$ (6.4 mg, 0.01 mmol, 5 mol%) and *N*-(acyloxy)phthalimides (0.50 mmol, 2.5 eq.) was evacuated and purged with argon three times. P_4 (6.20 mg, 0.20 mmol of P atom, a 0.74 M solution of P_4 in toluene, 0.27 mL), H_2O (1.1 eq., 4 μL), 2,6-lutidine (0.40 mmol, 2 eq.) and DMA (1 mL) were sequentially added to the system at room temperature. Then the reaction mixture was stirred at room temperature under the irradiation of 6 W green LEDs (565–575 nm) for 6 h. Afterwards, the reaction mixture was quenched with the addition of saturated brine (0.5 mL), and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and then removed in a vacuum. The residue was purified by flash chromatography using DCM/MeOH (from 40 : 1 to 20 : 1, v/v) as the eluent to afford the desired dialkyl phosphine oxides **3a–3o**.

One-pot synthesis of α-hydroxy phosphine oxides from white phosphorus

After the above-mentioned reaction mixture was stirred at room temperature under the irradiation of 6 W green LEDs (565–575 nm) for 6 h without any work-up, aldehyde (0.50 mmol, 2.5 eq.) and Na_2CO_3 (42.40 mg, 0.4 mmol, 2.0 eq.) were added in air. The reaction mixture was stirred for 22 hours at 55 °C for 6 hours. After completion, saturated brine (0.5 mL) was added; the mixture was diluted by EtOAc (10.0 mL). The mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and then removed in a vacuum. The residue was purified by flash chromatography using DCM/MeOH (from 40 : 1 to 10 : 1, v/v) as the eluent to afford the desired α-hydroxy phosphine oxides **4a–4l**.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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