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Single-Step Synthesis of Secondary Phosphine Oxides

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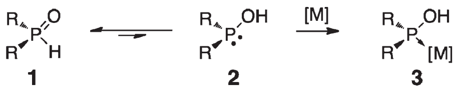
Summary: We report that in the presence of trifluoroacetic acid primary phosphines undergo efficient addition to aldehydes to form the corresponding secondary phosphine oxides in 47−97% yield. This transformation is compatible with aryl and alkyl phosphines, as well as a broad range of aldehydes, including formaldehyde. By using 1,5-dialdehydes as reaction partners, the addition provides a straightforward route to bis(phosphine oxides), which are difficult to prepare by alternative methods. In the presence of boron trifluoride diethyl etherate as reagent, benzophenone was shown to couple to phenylphosphine and cyclohexylphosphine in 92% and 72% yield, respectively. Twenty-three examples are presented.

Secondary phosphine oxides are an important class of reagents that find many applications in synthesis and catalysis.[1] Secondary phosphine oxides exist as a tautomeric mixture of P(V) (**1**) and P(III) (**2**) isomers, with the air-stable P(V) tautomer **1** predominating under ambient conditions (eq 1).[2] In the presence of a metal this equilibrium is driven toward the P(III) tautomer via coordination.[3] The phosphinous acid complexes so formed (**3**) are active catalysts for cross-coupling,[4] hydrogenation,[5] allylic alkylation,[6] and C−H arylation reactions.[7,8] Racemic secondary phosphine oxides are readily resolved using derivatives of tartaric acid.[9] Secondary phosphine oxides may also serve as precursors to other phosphorus-containing reagents. For example, they are easily elaborated to tertiary phosphine oxides,[10] and both secondary and tertiary phosphine oxides can be reduced in high yields to form the cooresponding phosphines.[11,12]



(1)

In the course of our research we required access to complex secondary phosphine oxides. Established methods for their synthesis, such as alkylation of primary phosphine-borane complexes,[13] followed by deprotection and oxidation, or the addition of organometal reagents to dialkyl phosphonates,[14] did not provide the generality we required. In 1962, Epstein and Buckler reported that heating of primary phosphines and aldehydes or ketones in mineral acids formed α-hydroxy tertiary phosphine oxides (**4**; eq 2).[15−17] These reactions were suggested to proceed via the secondary phosphine oxide, but in only two instances could the reaction be stopped at this stage. Namely, the addition of cyclohexylphosphine to cyclohexanone in refluxing concentrated hydrochloric acid formed dicyclohexylphosphine oxide in 52% yield. Under

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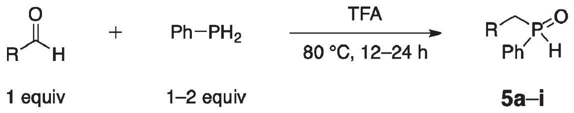
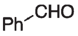
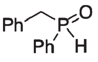
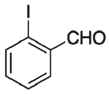
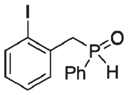
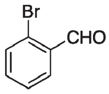
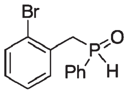
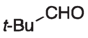
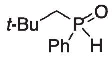
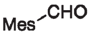
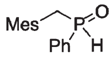
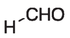
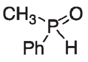
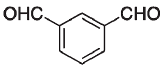
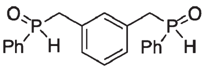
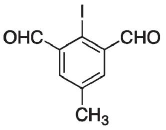
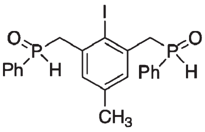
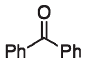
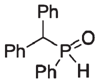
Table 1. Secondary Phosphine Oxides Formed by Addition of Phenylphosphine to Aldehydes and Ketones[a]

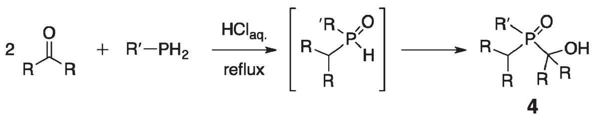


5a–i

entry	carbonyl	product		yield[b]
1			5a	89%
2[c]				88%
3[d]				78%
4			5b	76%
5			5c	63%
6			5d	75%
7			5e	74%
8			5f	71%
9			5g	72%[e,f]
10			5h	67%[f,g]
11			5i	92%[h]

[a] All reactions were conducted in deoxygenated trifluoroacetic acid employing distilled phenylphosphine (prepared by reduction of dichlorophenylphosphine; see Supporting Information), unless otherwise noted. [b] Isolated yield after purification by flash-column chromatography, unless otherwise noted. [c] Reaction conducted using commercial phenylphosphine, without prior distillation. [d] Reaction conducted without prior deoxygenation of trifluoroacetic acid. [e] Isolated as a 1.5:1 mixture of diastereomers. [f] Product was obtained in >95% purity after aqueous workup (see Supporting Information). [g] Isolated as a 1:1 mixture of diastereomers. [h] Reaction performed using $BF_3 \cdot OEt_2$ (1.79 equiv) in toluene (0.3 M) at 80 °C.

similar conditions, the addition of phenylphosphine to acetophenone formed (α-methylbenzyl)phenylphosphine oxide in 45% yield.



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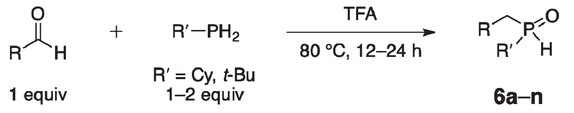
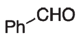
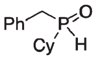
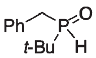
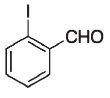
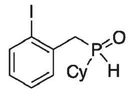
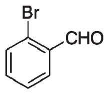
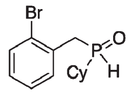
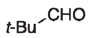
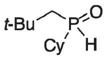
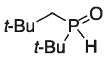
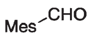
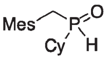
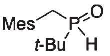
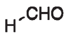
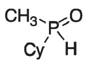
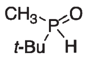
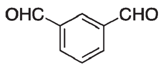
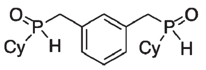
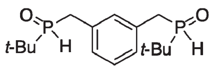
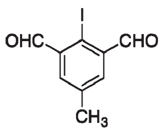
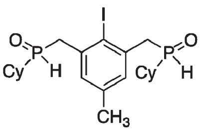
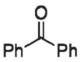
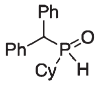
(2)

Table 2. Secondary Phosphine Oxides Formed by Addition of Cyclohexyl- and *tert*-Butylphosphine to Aldehydes and Ketones[a]



6a–n

entry	carbonyl	product		yield[b]
1			6a	88%
2			6b	95%
3			6c	96%
4			6d	94%
5			6e	97%
6			6f	96%
7			6g	89%
8			6h	93%
9			6i	71%
10			6j	61%
11			6k	47%[c,d]
12			6l	48%[c,d]
13			6m	48%[d,e]
14			6n	72%[f]

[a] All reactions were conducted in deoxygenated trifluoroacetic acid. [b] Isolated yield after purification by flash-column chromatography, unless otherwise noted. [c] Isolated as a 1:1 mixture of diastereomers. [d] Product was obtained in >95% purity after aqueous workup (see Supporting Information). [e] Isolated as a 1.1:1 mixture of diastereomers. [f] Reaction performed using $BF_3 \cdot OEt_2$ (1.40 equiv) in toluene (0.3 M) at 80 °C.

We revisited this reaction with the goal of finding conditions that would allow for isolation of the secondary phosphine oxides. A number of Lewis and Brønsted acids were evaluated for their ability to couple alkyl and aryl phosphines with different aldehydes and ketones. As described below, we found that heating a mixture of the aldehyde and phosphine in trifluoroacetic acid as solvent formed the corresponding secondary phosphine oxides in 47−97% yield. When using ketones as the coupling partner, boron trifluoride diethyl etherate in toluene was determined to be superior.

The scope of the aldehydes that underwent efficient reaction with phenylphosphine is shown in Table 1. Benzaldehyde reacted cleanly to afford benzylphenylphosphine oxide (**5a**) in 89% yield (entry 1). Monitoring of this reaction by ^{31}P NMR revealed nearly complete conversion of phenylphosphine within 20 min at 80 °C. However, we have observed a wide distribution of reaction times between aldehyde substrates, and to ensure quantitative conversion each reaction was conducted with heating for 12−24 h. We note two important points regarding the practicality of this reaction. First, although the experiments depicted in Table 1 employed phenylphosphine that was obtained by lithium aluminum hydride reduction of dichlorophenylphosphine, followed by distillation (see Supporting Information),[18] comparable yields were obtained with commercial, unpurified phenylphosphine (88%, entry 2). In addition, although deoxygenation of the trifluoroacetic acid solvent (freeze−pump−thaw) was necessary to obtain the highest yields of product, the reaction still proceeded smoothly without this measure (compare entries 1 and 3).

By analogy to the reactivity of benzaldehyde, *ortho*-iodobenzaldehye and *ortho*-bromobenzaldehyde also reacted in good yield to form the corresponding halogenated phosphine oxide products **5b** and **5c**, respectively (entries 4 and 5). These products (**5b** and **5c**) are envisioned to be useful precursors for the synthesis of transition metal complexes incorporating bidentate *C*,*P*-ligands. Non-enolizable aldehydes such as pivaldehyde (entry 6) and mesityl aldehyde (entry 7) formed the corresponding secondary phosphine oxides **5d** and **5e** in 75% and 74% yield, respectively. The successful addition to paraformaldehyde (71%, entry 8) is important, as it provides direct access to differentially substituted *P*-methylated phosphine oxides, avoiding the generation of methylphosphine.[19] In addition, two novel PCP ligands were easily prepared by this method (entries 9, 10). Heating of isophthalylaldehyde with phenylphosphine formed the bis(phosphine oxide) **5g** in 72% yield. Alternatively, the iodinated PCP ligand precursor **5h** was obtained in 67% yield by addition of phenylphosphine to 1,3-diformyl-2-iodo-5-methylbenzene. The bis(phosphine)oxide products **5g** and **5h** were isolated as mixtures of *meso* and *d*/*l* isomers (dr = 1−1.5:1). Although difficult to purify by flash-column chromatography, **5g** and **5h** could be obtained in >97% purity by extraction of an aqueous solution of the unpurified reaction mixture with nonpolar solvents to remove less polar impurities, followed by dichloromethane extraction to isolate the bis(phosphine oxide) products. Finally, we found that non-enolizable ketones such as benzophenone reacted in high yield when boron trifluoroide diethyl etherate was used to promote the reaction (92%, entry 11).

To investigate the influence of the phosphorus substituent on this transformation, we evaluated the addition of cyclohexyl- and *tert*-butylphosphine to the aldehydes shown in Table 2. In general, we found that the addition of alkylphosphines to aldehydes occurred with efficiencies similar to that of phenylphosphine, affording the secondary phosphine oxide products **6a**−**m** in 47−97% yield. The addition of cyclohexylphosphine to benzophenone in the presence of boron trifluoride diethyl etherate also occurred smoothly to provide the phosphine oxide product **6n** in 72% yield (entry 14).

In summary, we have shown that in the presence of trifluoroacetic acid or boron trifluoride diethyletherate primary phosphines may be coupled with aldehydes and ketones in moderate to excellent yield. This reaction is operationally simple and allows direct access to a variety of secondary phosphine oxides, including products that may serve as CP and PCP ligands. The synthesis of novel organometallic complexes incorporating these ligands is currently under investigation.

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Supporting Information Available: Detailed experimental procedures and spectral data (^{1}H, ^{13}C, and ^{31}P NMR, IR, and HRMS) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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