Organocatalyzed Reduction of Tertiary Phosphine Oxides

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Abstract: A novel selective catalytic reduction method of tertiary phosphine oxides to the corresponding phosphines has been developed. Notably, the reaction proceeds smoothly with low catalyst loadings of 1–5 mol% even at low temperature (70 °C). Under the optimized conditions various phosphine oxides could be selectively reduced and the desired phosphines were usually obtained in excellent yields above 90%. Furthermore, we have developed a one-pot reaction sequence for the preparation of valuable phosphine-borane adducts. Simple addition of BH₃·THF subsequent to the reduction step gave the desired adducts in yields up to 99%.

Keywords: organocatalysis; phosphine·boranes; phosphines; reduction; silanes

Phosphines and their derivatives are of significant relevance in life science and the chemical industry. Especially trivalent phosphines are an essential class of compounds in organometallic catalysis and numerous fundamental organic transformations. They represent a ubiquitous family of ligands to control the chemo-, regio- as well as stereoselectivity of most transition metal-catalyzed reactions even on the industrial scale.^[1] Furthermore, phosphines are utilized in important classic transformations, such as the Wittig,^[2] Appel^[3] or Mitsunobu reactions,^[4] ultimately vielding the corresponding oxides as undesirable byproducts. Most recently, several methods have emerged addressing this issue by in situ regeneration of the phosphorus reagent leading to novel phosphorus-catalyzed reactions to bypass the phosphine oxide waste.^[5] Even though the reduction of phosphine oxides is the simplest and one of the major methods for the synthesis of phosphines, the selective reduction of the strong P=O bond or its conversion into the corresponding phosphine boranes is still a challenging task.^[6] Although many catalytic procedures for the reduction of carbonyl groups have been established over the past decades only little work is known on the catalytic reduction of the thermodynamically highly stable P=O bond.^[6,7]

In 1994 Lawrence et al. developed the first catalytic P=O reduction based on titanium alkoxides utilizing silanes as stoichiometric reductants.^[8] In fact, this was the only catalytic method for the selective reduction of phosphine oxides for almost two decades. Only recently diarylphosphoric acid,^[9] copper^[10] and indium^[11] salts as well as iron^[12] complex-catalyzed processes have been reported. However, these methods usually require high catalyst loadings, harsh reaction conditions and/or long reaction times. Based on our interest on redox P(III)/P(V)=O catalysis our aim was to develop a metal-free catalytic process operating at reaction temperatures <100 °C and low catalyst loading which might be suitable in such redox coupled processes.^[13] In this context we considered Brønsted acids to be promising candidates to realize this task.^[9,13g,14]

Thus, we initially screened various organic acids as potential metal-free catalysts for the reduction of triphenylphosphine oxide (1a, Table 1). Under the chosen reaction conditions no conversion was observed in the absence of a catalyst (entry 1). Benzoic acid (3a) as well as derivative 3b gave the desired reduction product **2a** in low yields of only 4% and 8%, respectively (entries 2 and 3). In contrast diphenylphosphoric acid (3c) gave 2a in moderate yield of 64% (entry 4). Remarkably, in the presence of trifluoromethanesulfonic acid (3d) as the catalyst 2a was obtained in quantitative yield already after 1 h at 100°C (entry 5). Even at 70°C the desired phosphine 2a was obtained in 62% yield after 1 h (entry 6). Extension of the reaction time to 24 h allowed us to reduce the catalyst loading to 1 mol% still giving an excellent 89% yield of 2a (entry 7). Furthermore, we evaluated various silanes as alternative reductants. Under the optimized reaction conditions conversion of triphenylphosphine oxide (1a) was achieved within

Entry

10

11

12

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4

Table 1. Reduction of triphenylphosphine oxide (1a) in the presence of various Brønsted acids **3** as catalysts and reaction optimization.^[a]



| | 3a | | 3b | | 3C | 3d | |
|-------|------|------|---------------------|--------|---------------|-------------|---------------------------------|
| Entry | Cat. | mol% | Silane | Equiv. | Temp. [°C] | Time [h] | 2a [%] ^[b] |
| 1 | _ | _ | PhSiH ₃ | 4.0 | 100 | 1 | 0 |
| 2 | 3a | 15 | PhSiH ₃ | 4.0 | 100 | 1 | 4 |
| 3 | 3b | 15 | PhSiH ₃ | 4.0 | 100 | 1 | 8 |
| 4 | 3c | 15 | PhSiH ₃ | 4.0 | 100 | 1 | 64 ^[c] |
| 5 | 3d | 15 | PhSiH ₃ | 4.0 | 100 | 1 | >99 |
| 6 | 3d | 15 | PhSiH ₃ | 4.0 | 70 | 1 | 62 |
| 7 | 3d | 1 | PhSiH ₃ | 4.0 | 70 | 24 | 89 |
| 8 | 3d | 1 | HexSiH ₃ | 3.0 | 70 | 24 | 95 |

^[a] *Reaction conditions:* **1a** (1.0 equiv.), cat. (1–15 mol%), silane (3.0–4.0 equiv.), toluene, 70–100 °C, 1–24 h.

^[b] Yield determined by ³¹P NMR.

^[c] Yield determined by GC methods using *n*-hexadecane as internal standard.

24 h at 70 °C and triphenylphosphine (2a) was obtained in 95% yield (entry 8).

With CF_3SO_3H as a highly active reduction catalyst under mild reaction conditions in hand, we evaluated the substrate scope. Since organophosphines **2** are often prone to oxidation we envisioned to isolate them as the corresponding stable borane adducts **4**. Such adducts have attracted increasing attention as versatile building blocks, hydrogen storage materials and ligands as well as stable phosphine precursors.^[15] We envisioned a one-pot, two-step reaction process for the synthesis of **4** (Scheme 1).

Thus, triphenylphosphine oxide (1a) was reduced to 2a and directly converted to 4a by subsequent addition of BH₃·THF to the reaction mixture (Table 2, entry 1). The reduction of diaryl derivatives 1b and 1c in the presence of 1 mol% catalyst gave the desired phosphine oxides 2b and 2c only in moderate to good yields, respectively (entries 2 and 4). However, if the catalyst amount is increased to 5 mol% the desired



Scheme 1. Catalytic reduction of phosphine oxides 1 to the corresponding phosphines 2 and subsequent conversion with BH_3 ·THF into stable complexes 4.

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| | | Cat. | [%] ^[b] | [%] ^[c] |
|---|-----------------------------|-----------------------|-------------------------------|--------------------|
| O II Ph₃P | 1 a | 1 | 95 | 86 |
| | 1b | 1 | 71 | - 02 |
| | 1c | 5 1 | ≥99 31 | 93 - |
| Ph ₂ P ⁻ `OMe O | 1d | 5 1 | 99 69 | 95 - |
| Ph ₂ P O | 10 | 5 ^[d] 1 | 77 >00 | 59 |
| | п | 5 ^[d] | 91 ^[e] | _ |
| Me | | | | |
| Ph-P | 1f | 5 | 77 (≥99) ^[f] | _ |
| Ph-P | 1g | 5 | ≥99 | 85 |
| O II Me ₂ P—Ph | 1h | 5 | 94 | 84 |
| O Ⅱ Me₂P—Ph | 1i | 5 | ≥ 99 | 99 |
| Ph ₂ P | 1j | 5 | 92 | 92 |
| | D ₂ Me 1k | 5 | ≥99 | 96 |
| | 11 | 5 | ≥99 | 94 |
| | 1m | 5 | 96 | 90 |
| OMe | 1n | 5 | ≥99 | ≥99 |
| | 10 | 5 | ≥99 | 95 |
| Ph ₂ P PPh ₂ | 1p | 10 ^[g] | \geq 99 (96) ^[e] | _ |
| O II II Ph ₂ P PPh ₂ | 1q | 10 ^[h] | _ | _ |
| Ph ₂ P Ph ₂ P II O | 2 1r | 10 ^[h] | 72 | 65 |

Table 2. Scope for the acid-catalyzed reduction of phosphine

oxides 1 under mild conditions and one-pot conversion into

mol% 2

stable borane adducts 4.^[a]

Substrate

Table 2. (Continued)



 [a] Reaction conditions: (i) phosphine oxide 1 (1 equiv.), CF₃SO₃H (5 mol%), HexSiH₃ (3.0 equiv.), toluene, 70°C, 24 h; (ii) BH₃·THF (2 equiv., 1 M in THF), 23°C, 2 h.

- ^[b] Yield determined by ³¹P NMR.
- ^[c] Isolated yields for the one-pot procedure.
- ^[d] 100°C, 6 h.
- ^[e] Isolated yield.
- ^[f] 48 h.
- ^[g] CF_3SO_3H (10 mol%), HexSiH₃ (6.0 equiv.), dioxane.
- ^[h] CF₃SO₃H (10 mol%), HexSiH₃ (6.0 equiv.), toluene.
- ^[i] 90% ee.
- ^[j] **4s** was obtained as a racemate.

phosphines **2b** and **2c** were obtained in excellent yields of up to $\geq 99\%$ which could be directly converted to the corresponding borane adducts **4b** and **4c** (entries 3 and 5). Unsaturated phosphine oxides **1d** and **1e** could also be selectively reduced in good to excellent yields (entries 6–9). Notably, **1e** has been utilized for example, by Marsden et al., as a catalyst for aza-Wittig reactions. It is also the precursor for a Wittig reaction catalyst.^[5a,16] We reported that 2-phenylisophosphindoline 2-oxide (**1f**) is an efficient pre-catalyst for the Wittig reaction.^[13d] The reduction of **1f** gave the desired phosphine **2f** in 77% yield after 24 and in $\geq 99\%$ after 48 h.

However, the one-pot conversion of 1e and 1f to their BH₃ adducts was not possible. The conversion to the respective adducts was not complete and partial decomposition back to the phosphine occurred upon chromatography of 4e. In contrast oxides 1g-1i could be easily reduced and the corresponding products 2g-**2i** obtained in yields >90% which could in turn be directly transformed into the stable products 4g-4i (entries 11-13). We then turned our attention to the reduction of aryl derivatives **1j–1o** (entries 14–19). Usually the corresponding phosphines 2 could be obtained in excellent yields up to 99% and converted to the corresponding borane adducts 4j-4o which were isolated in 90-99% yield. Notably, the ester functionality in 1k remained untouched (entry 15). Furthermore, the products 4l and 4n could be obtained as colorless crystals suitable for X-ray crystallographic analysis (Figure 1).^[17]

Having demonstrated the successful reduction of various monophosphine oxides, we finally applied our methodology to the preparation of bisphosphine 2p. In the presence of 10 mol% CF₃SO₃H as the catalyst, oxide 1p could be converted to 2p in an excellent



Figure 1. ORTEP diagrams of the products **41** (*left*) and **4n** (*right*), ellipsoids drawn at 30% probability^[17] (see the Supporting Information for crystallographic data).

yield (entry 20). Notably, oxidized dppe [1,2-bis(diphenylphosphino)ethane] 1q could not be reduced under our conditions (entry 21). In contrast the dppp [1,3-bis(diphenylphosphino)propane] derivative -1r could be reduced to the bisphosphine 2r and further converted the borane adduct 4r which was obtained in 65% yield (entry 22). Finally the P-chiral phosphine oxide S-1s was converted under our standard reaction conditions. Full conversion to the respective phosphine 2s was achieved which was further reacted to the borane adduct 4s. Unfortunately the reaction does not proceed stereospecifically and 4a was isolated in 75% yield as racemate (entry 23). In a first attempt to extend the scope of our protocol to the conversion of secondary phosphine oxides we studied the reduction of diphenylphosphine oxide under our standard reaction conditions. Diphenylphosphine was obtained in 62% yield. Subsequent conversion to the borane adduct gave a 1:1 mixture of the desired borane adduct and diphenylphosphine oxide. This might be explained by partial reoxidation that occurred during the work-up.

Conclusions

In conclusion, we have report a general method for the efficient reduction of phosphine oxides under very mild conditions (70 °C) utilizing readily available trifluoromethanesulfonic acid as an organocatalyst and hexylsilane as the reducing agent. The scope of the reaction has been evaluated and 18 phosphine oxides were reduced under the optimized conditions to the corresponding phosphines in up to 99% yield. Importantly, excellent chemoselectivity was observed even in the presence of other reducible groups such as olefins and esters. Thus, this methodology might be applicable in catalytic processes based on the P(III)/ P(V)=O redox couple such as catalytic Wittig and Appel reactions. Moreover, we have demonstrated the direct access to the respective borane adducts in a one-pot, two-step reaction sequence by simply adding BH_3 . THF subsequent to the reduction. These stable adducts were isolated in excellent yields up to 99%.

Experimental Section

General Procedure for the Reduction of Phosphine Oxides 1 and Subsequent Conversion to the Corresponding Phosphine-Boranes 4

In a vial flushed with argon the phosphine oxide **1** (0.36 mmol) was added to a solution of CF_3SO_3H (1–5 mol%) in toluene (1.2 mL). The reaction mixture was stirred for 5 min at 23 °C. Subsequently, HexSiH₃ was added, the vial was flushed with argon, sealed and the reaction mixture was stirred for 24 h at 70 °C to afford **2**. The vial was cooled to 23 °C, BH₃·THF (2.0 equiv., 1M in THF) was added and the reaction mixture was stirring for further 2 h under argon at 23 °C. The crude product was purified by column chromatography on silica gel (SiO₂) with petroleum ether (PE, 40–60 °C)/diethyl ether (Et₂O) as eluents. After removal of all volatiles under vacuum the desired product **4** was obtained.

Synthesis of Triphenylphosphine-Borane (4a)^[18]

According to the general procedure, CF₃SO₃H (2.7 mg, 0.018 mmol), triphenylphosphine oxide (1a, 100 mg, 0.359 mmol) and HexSiH₃ (128 mg, 1.10 mmol) in toluene (1.2 mL) were converted. After work-up 4a was obtained as colorless crystals; yield: 85.5 mg (0.310 mmol, 86%). $R_{\rm f}$ (SiO₂, CH:EtOAc=2:1); 0.68; ¹H NMR (300 MHz, CDCl₃, 22°C): $\delta = 0.61 - 1.85$ (m, 3H), 7.39–7.67 (m, 15H); ¹³C{¹H} NMR (75 MHz, CDCl₃, 23 °C): $\delta = 128.91$ (d, ³ $J_{CP} =$ 10.2 Hz, 3×2 CH), 129.30 (d, ${}^{1}J_{CP} = 58.0$ Hz, 3 C), 131.39 (d, ${}^{4}J_{CP} = 2.4 \text{ Hz}, 3 \text{ CH}), 133.33 \text{ (d, } {}^{2}J_{CP} = 9.7 \text{ Hz}, 3 \times 2 \text{ CH});$ ³¹P NMR (121 MHz, CDCl₃, 22 °C): $\delta = 21.11$ (m); ¹¹B NMR (96 MHz, CDCl₃, 22 °C): $\delta = -37.82$ (dq); MS (EI, 70 eV): m/z (%)=263 (19) $[M^+-BH_3+H]$, 262 (100) $[M^+-BH_3]$, 261 (19), 184 (16), 183 (81), 152 (12), 108 (25), 107 (16); HR-MS (ESI): m/z = 299.1136, calcd. for C₁₈H₁₈BPNa [M^+ + Na]: 299.1135.

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