Hypophosphorous Acid

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Introduction

Hypophosphorous acid (H₃PO₂) is a colorless low-melting compound (m.p. 26.5 °C), which is a commercially available inorganic acid, and is usually supplied as a 50% aqueous solution.¹ H₃PO₂ is a powerful reducing agent, and its aqueous solution can be used under moderate conditions in contrast to some other strong reducing agents, which are normally applied in the absence of water (e.g., LiAlH₄, DIBAL). Furthermore, it is also an important hydrogen donor.

Beside the good reducing ability, e.g. in the reduction of diazonium salts,² halide compounds,³ benzylic alcohols,⁴ etc., H₃PO₂ has been extensively used in a variety of functional group transformations.

Table 1 Use of Hypophosphorous Acid

(A) Reduction of diazonium salts
Kornblum and co-workers pioneered the reduction of aromatic diazonium salts with H₃PO₂.⁵ The deamination of aromatic primary amines usually undergoes diazotization followed by hydrogenation of diazonium salts. H₃PO₂ has proved to be an excellent reducing agent for this transformation. It could also be applied to heterocyclic primary amines for the reduction of diazonium salts with good results.⁶

(B) Reduction of nitroarenes and aryl ketones
Wu's group declaimed a novel iodide-catalyzed reduction method using H₃PO₂ to reduce both diaryl ketones and nitroarenes chemoselectively of an intermediate of Lonafarnib, a potential anticancer agent, in the presence of chloro and bromo substituents.⁷ The reduction proceeded under mild conditions and excellent yields were obtained with the halogens unaffected.

(C) Cross-coupling of benzylic alcohols with H₃PO₂
The cross-coupling of benzylic alcohols with H₃PO₂ catalyzed by palladium formed benzylic H-phosphinates, while the C–P bond formed efficiently without any prior activation. Coudray et al. tested a broad range of benzylic alcohols and got the desired products in moderate to good yields.⁸ Reaction with the chiral (R)-1-(2-naphthyl)ethanol provided the corresponding H-phosphinic acid in 89% yield and with 77% ee.
(D) Addition of \( \text{H}_3\text{PO}_2 \) to alkenes
Altamirano et al. reported a novel approach to \( \text{H} \)-phosphinic acids via a Pd-catalyzed tandem C–P bond addition–oxidation.\(^9\) Under an air atmosphere, 1-octene was heated with \( \text{H}_3\text{PO}_2 \) in the presence of \( \text{Pd}_{2}\text{dba}_3 \) and xantphos to form \( \text{H} \)-phosphinic acid 2, which was then converted into phosphonic acid 3 smoothly by heating in air.

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\begin{align*}
\text{Hex} & \overset{\text{Pd}_{2}\text{dba}_3 (2 \text{ mol%). xantphos}}{\text{DMF, 110 °C, 12 h, air}} \rightarrow \text{Oct}
\end{align*}
\]

\( \text{77\% yield} \)

(E) Diastereoselective addition to terephthalic Schiff bases
Lewkowski et al. reported the addition of \( \text{H}_3\text{PO}_2 \) to symmetrical terephthalic \( \text{N} \)-aliphatic and \( \text{N} \)-aromatic Schiff bases, which formed the 1,4-phenylene-bis-aminomethane-bis-phosphonous acids.\(^10\) NMR studies demonstrated that the reaction led to the exclusive formation of only one diastereomeric form.

(F) Selective semihydrogenation of terminal alkynes
Semihydrogenation of terminal alkynes is one of the most straightforward methods for the synthesis of terminal alkenes, which are important building blocks in organic synthesis. Cao’s group reported a novel selective semihydrogenation of terminal alkynes, catalyzed by copper in the presence of \( \text{H}_3\text{PO}_2 \) as hydrogen donor.\(^11\) The reaction took place with high selectivity so that over-reduction products of ethylbenzene were not detected. The employment of fully deuterated hypophosphorous acid (\( \text{D}_3\text{PO}_2 \)) showed the distribution of deuterium incorporation in the alkenes.

(G) Catalyst-free synthesis of diaryl selenides
The conventional methods for C–Se bond formation usually require harsh transition-metal-catalyzed conditions. Balaguez et al. recently described a simple and catalyst-free method to synthesize diaryl selenides.\(^12\) The new method obtained diaryl selenides in moderate to good yields via a direct nucleophilic aromatic substitution reaction of arenediazonium tetrafluoroborate salts and arylselenols in the presence of \( \text{H}_3\text{PO}_2 \).

References