

Hypophosphorous Acid

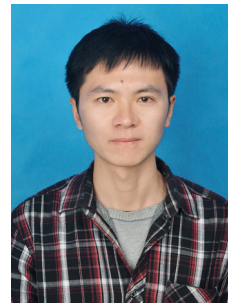
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Published online: 03.12.2014

DOI: 10.1055/s-0034-1379775; Art ID: st-2014-v0501-v

Kai Gao was born in 1987 and raised in Huanggang City, Hubei Province, China. He received his degree in chemistry from Hubei University of Science and Technology in 2012. Currently, he is carrying out research under the supervision of Prof. Bo Yang and Dr. Xiali Liao at the Kunming University of Science and Technology. His research focuses on the synthesis of novel phosphoramidate ligands and small molecules with important bioactivities.



Introduction

Hypophosphorous acid (H_3PO_2) 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 H_3PO_2 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

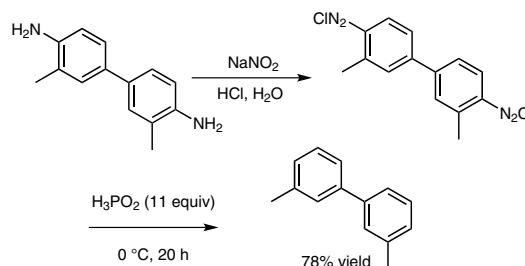
normally applied in the absence of water (e.g., LiAlH_4 , DIBAL). Furthermore, it is also an important hydrogen donor.

Beside the good reducing ability, e.g. in the reduction of diazonium salts,² halide compounds,³ benzylic alcohols,⁴ etc., H_3PO_2 has been extensively used in a variety of functional group transformations.

Table 1 Use of Hypophosphorous Acid

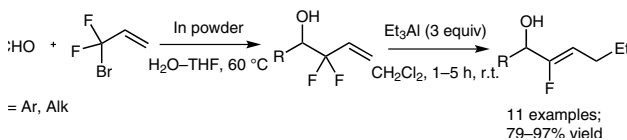
(A) Reduction of diazonium salts

Kornblum and co-workers pioneered the reduction of aromatic diazonium salts with H_3PO_2 .⁵ The deamination of aromatic primary amines usually undergoes diazotization followed by hydrogenation of diazonium salts. H_3PO_2 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



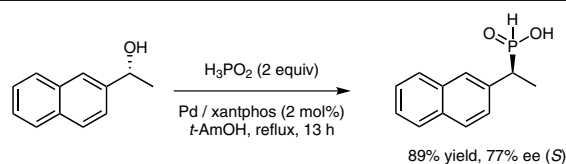
(B) Reduction of nitroarenes and aryl ketones

Wu's group declaimed a novel iodide-catalyzed reduction method using H_3PO_2 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.



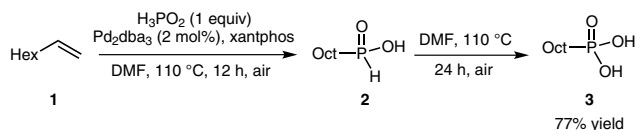
(C) Cross-coupling of benzylic alcohols with H_3PO_2

The cross-coupling of benzylic alcohols with H_3PO_2 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.



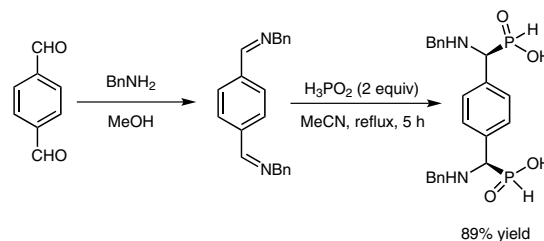
(D) Addition of H_3PO_2 to alkenes

Altamirano et al. reported a novel approach to *H*-phosphinic acids via a Pd-catalyzed tandem C–P bond addition–oxidation.⁹ Under an air atmosphere, 1-octene was heated with H_3PO_2 in the presence of Pd_2dba_3 and xantphos to form *H*-phosphinic acid **2**, which was then converted into phosphonic acid **3** smoothly by heating in air.



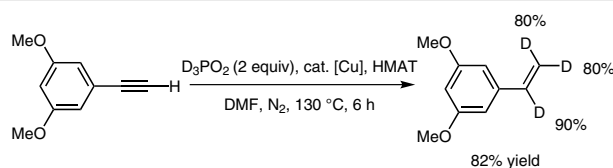
(E) Diastereoselective addition to terephthalic Schiff bases

Lewkowski et al. reported the addition of H_3PO_2 to symmetrical terephthalic *N*-aliphatic and *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.



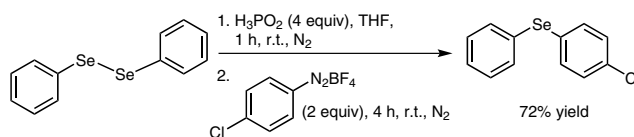
(F) Selective semihydrogenation of terminal alkynes

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 H_3PO_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 (D_3PO_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 arylselenenols in the presence of H_3PO_2 .



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