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Umpolung of a Hydrogen Atom of Water by Using a Hexacoordinated Phosphate and Its Application to Deuteride Reduction Reactions of Carbonyl Compounds

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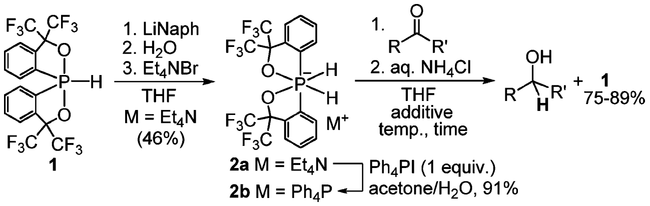
Umpolung,[1] which is a method for reversing polarity, is one of the most useful methods for organic synthesis. Umpolung of an isotope of hydrogen in heavy water (D_2O or T_2O) will provide deuteride ion (D^-) and tritide ion (T^-) donors valuable for isotope labeling,[2] which is popular for the study of biomolecules and reaction mechanisms, because heavy water is cheaper and more easily usable than other isotope-labeled hydride reagents ($LiAlD_4$, etc.). However, umpolung of a hydrogen atom is difficult, because a reaction of a proton source, such as water ($H^{\delta+}-OH$), with the product of the umpolung ($H^{\delta-}-Z$) or the reagents used results in facile conversion to molecular hydrogen. While numerous works have been reported on the development of isotope-labeling methods utilizing D_2O under strongly acidic conditions, at high temperatures, or in the presence of transition metal catalysts, the deuterium does not work as a deuteride ion in those cases.[3] Here, we report on the umpolung of a hydrogen atom of water by using a hexacoordinated dihydrophosphate as a key species.[4] And, we also report the reductive deuteration of carbonyl compounds by using the umpolung of D_2O under mild conditions without the presence of a transition metal. To achieve the umpolung, there are two requirements: first, a proton of water should be exchanged with hydrogens on the phosphorus of the phosphate anyhow, and second, the P−H groups of the phosphate should show hydridic reactivity.

Scheme 1. Synthesis and Reactions of Dihydrophosphates **2a,b**



Hydrophosphorane **1**,[5] which was synthesized from phosphorus trichloride by a one-step reaction, was successively treated with lithium naphthalenide (3 equiv), water (excess), and tetraethylammonium bromide (1.5 equiv) in one pot to give dihydrophosphate **2a** in 46% yield (Scheme 1). Cation exchange of **2a** gave **2b** in 91% yield. Compounds **2a,b** could also be synthesized by a reaction of **1** with $LiAlH_4$ followed by the cation exchange reactions in higher yields (**2a**: 73%, **2b**: 52%). They were characterized by the NMR and IR spectroscopy, MS, and elemental analysis, and the structure of **2b** was determined by the X-ray crystallographic analysis which was the first example for a hexacoordinated dihydrophosphate as far as we know (Figure 1). The anion part of **2b** has an octahedral geometry with C_2 symmetry around the P1 atom, and the hydrogen atoms are located at the trans positions to the oxygen atoms. Compounds **2a,b** can be handled easily in the air due to their higher stabilities than other reported dihydrophosphates.[6]

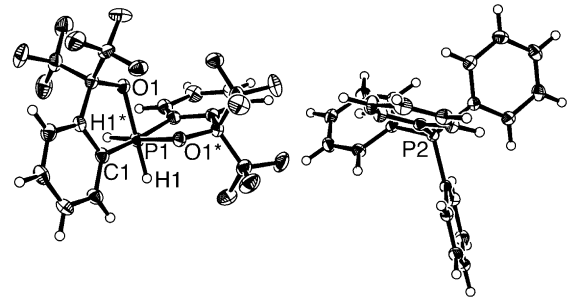
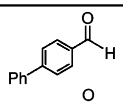
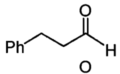
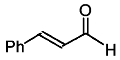
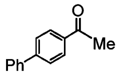


Figure 1. ORTEP drawing of **2b** with thermal ellipsoid plot (50% probability).

Table 1. Hydride Reduction of Carbonyl Compounds with **2a**

entry	substrate	additive (equiv.)	temp.	time/h	yield[a]/%
1		none	reflux	10	85
2		LiCl (1)	r.t.	1	90
3		AcOH (5)	r.t.	1	88
4		LiCl (1)	r.t.	1	72
5		AcOH (30)	r.t.	1	55[b]
6		LiCl (10)	r.t.	20	61

[a] Isolated yield of alcohol.[b] Obtained as a mixture with $Ph(CH_2)_3OH$ (12%). The yields are determined by the ^1H NMR spectroscopy.

To confirm the first requirement for the umpolung, an H−D (hydrogen−deuterium) exchange reaction of **2a** with D_2O was attempted in DMSO-d_6 in anticipation of the protic character of an O−H group in a tautomer of **2a**. Although the hydrogen atoms on the phosphorus atom of **2a** were hardly exchanged for the deuterium atoms in D_2O under both basic and neutral conditions, the H−D exchange proceeded efficiently in the presence of AcOH (1 equiv) to give **2a-*d*$_2$** bearing two P−D bonds (95%D) after 0.5 h. The same reaction in the presence of AcOH (0.03 equiv) in THF also gave **2a-*d*$_2$** (98%D) in 81% isolated yield.

The second requirement for the umpolung is hydridic reactivity of **2a**. Compound **2a** was subjected to hydride reduction reactions of aldehydes and a ketone in anticipation of its particular structure, although a hydrogen atom of a P−H bond rarely behaves as a hydride.[7] The reaction of **2a** with 4-phenylbenzaldehyde (1 equiv) in refluxing THF for 10 h, followed by treatment with aqueous NH_4Cl solution, gave the corresponding alcohol and **1** in good yields

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(Table 1, entry 1). The reduction reaction was dramatically accelerated by the addition of LiCl (1 equiv) or AcOH (5 equiv), which activated the aldehyde, and consequently the reaction was completed after 1 h at ambient temperature (entries 2 and 3). This is remarkable, considering that most hydridic reagents easily decompose to produce hydrogen gas under acidic conditions. This reduction method is also applicable to an aliphatic aldehyde (entry 4). In the reduction of an α,β-unsaturated aldehyde, excess acid was necessary to prevent consumption of the aldehyde by the side reaction with the in situ generated conjugate base of **1** (entry 5). The reduction of a ketone also proceeded in a moderate yield, although more LiCl and a longer reaction time were necessary (entry 6). Hydrophosphorane **1** was recovered in 75−89% yields (Scheme 1) and is reusable as a precursor of **2a**.

Compound **2a-*d*₂**, which had been prepared by the H−D exchange of **2a** with D_2O, naturally reduced 4-phenylbenzaldehyde to give the deuterated alcohol 4-PhC_6H_4CHDOH (83% yield, 95%D) in the presence of LiCl. The reductive deuteration, even in the presence of more than 100 equiv of H_2O under the same conditions, also gave the deuterated alcohol (87% yield, 88%D) showing a deuteride transfer mechanism. This is good evidence for the umpolung of deuterium of D_2O, and it is a clear difference from other reductive deuterations utilizing D_2O such as a reaction of an anionic carbon atom with a deuteron (D^+)[3b,c] and deuteration of alkenes or alkynes with a transition metal catalysis.[3d,e] Furthermore, a one-pot reaction of the H−D exchange and reduction was successful (Figure 2). The H−D exchange from **2a** to **2a-*d*₂** using D_2O and AcOH (1.5 equiv), followed by the addition of 4-PhC_6H_4CHO in THF, also gave the deuterated alcohol (82% yield, 97%D). This is a promising isotope-labeling method because the reaction achieves deuteride reduction under mild conditions by simple procedures, does not need expensive deuteride reagents, and does not use transition metal reagents that need careful handling.

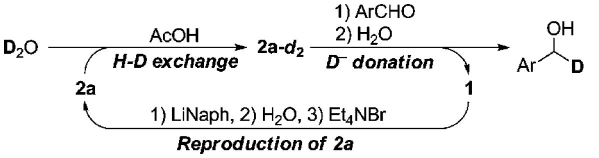
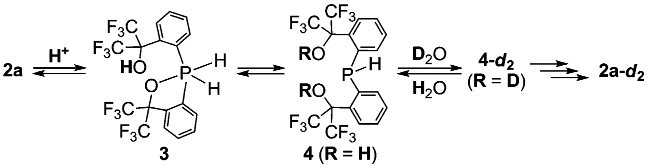


Figure 2. One-pot reductive deuteration with D_2O ($Ar = 4\text{-PhC}_6H_4$).

The exchange of a proton of water for the hydrogen atoms of **2a**, which shows hydridic reactivity, as revealed by the H−D exchange of deuterium of D_2O, is interesting, and a plausible mechanism of the H−D exchange is described as follows: when an acid is added to **2a**, a negatively charged oxygen atom of **2a** is protonated to form dihydrophosphorane **3** that equilibrates with **2a** (Scheme 2). The pentavalent phosphorane **3** also equilibrates with trivalent phosphine **4** by a tautomerization, which is common in such phosphorus compounds.[8] Actually, when a large excess amount of AcOH (300 equiv) was added to **2a** in DMSO-d_6, a doublet signal at δ_P −19.9 (d, $^1J_{PH} = 223$ Hz) in a ^{31}P NMR spectrum (with coupling) was observed, suggesting the formation of **4**. One of the hydrogen atoms on the phosphorus in **2a** migrates to the oxygen in **4** through the tautomerization, and then it should be protic and exchangeable. The three processes, protonation, tautomerization, and H−D exchange, would be reversible, and hence treatment of **2a** with D_2O under an acidic condition would finally give **2a-*d*₂** by repetition of these processes. While the polarity of a hydrogen atom of a transition metal hydride can be controlled by exchanging its ligands,[9] this work is significant in terms of umpolung of a hydrogen atom in one pot only via equilibrium reactions in addition to its achievement without any metal.

Scheme 2. Plausible Mechanism of H−D Exchange Reaction of **2a**



In summary, we have shown the hexacoordinated dihydrophosphate can reduce carbonyl compounds, while the hydrogen atoms are exchangeable for a proton of water via tautomerization. The reactivities enabled the umpolung of a deuterium atom of D_2O. This reductive deuteration with D_2O without any metal is valuable for some favorable points such as mild conditions, ease of handling, and scope of substrates.

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Supporting Information Available: Experimental procedures, spectral data of **1**, **2a**, **2b**, and **2a-*d*₂**, and the details of the X-ray crystallographic analysis of **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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