J|A|C|S COMMUNICATIONS

Published on Web 02/27/2009

Generation of Chiral Phosphonium Dialkyl Phosphite as a Highly Reactive *P*-Nucleophile: Application to Asymmetric Hydrophosphonylation of Aldehydes

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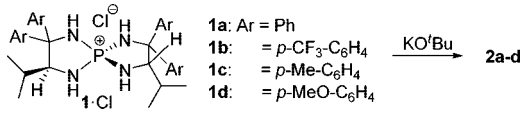
Dialkyl phosphonates (dialkyl phosphites) are versatile chemical reagents for the asymmetric construction of the phosphorus−carbon (P−C) bond to synthesize chiral phosphonic acid derivatives,[1,2] an important class of naturally occurring compounds with regard to biological applications.[3] There is now substantial agreement among chemists that dialkyl phosphonates undergo phosphite−phosphonate tautomerism and exist largely, if not entirely, in the phosphonate form under neutral conditions (eq 1).[4]

(1)

Thus, the chemistry of dialkyl phosphonates as a *P*-nucleophile is rather complicated and influenced by the fact that the phosphite tautomer, which is reactive and believed to be an actual nucleophilic species in the bond-forming step, would only be present in $\sim 10^{-4}$ %.[4a] For instance, this equilibrium would significantly affect the rate of their addition reactions such as the simple hydrophosphonylation of aldehydes,[2,5] which particularly relies on electrophilic activation.[6−10] In fact, previously elaborated chiral Lewis acid catalysts unfortunately required relatively high loading and a long reaction time,[7,8] except for Yamamoto's system wherein fluorinated phosphite was nicely utilized as a reactive nucleophile.[9] On the other hand, the activation of phosphonate using an appropriate base is expected to be advantageous for achieving sufficient reactivity because the equilibrium could shift toward the reactive phosphite form under such conditions. Although this possibility has been proposed and also implicated in the effectiveness of chiral bifunctional catalysts[7,8e] including the titanium−BINOL−cinchonidine complex introduced by You,[10] no experimental insight has yet been gained into the contribution of the phosphite tautomer. Largely associated with this situation, the development of an asymmetric catalysis of a chiral organic base for the hydrophosphonylation of aldehydes remains almost unexplored ever since Wynberg's pioneering efforts using *cinchona* alkaloids.[11] In conjunction with our research program directed at the molecular design and synthetic applications of a chiral tetraaminophosphonium salt **1**·Cl,[12] we envisaged that a spectroscopic evaluation of the behavior



of dialkyl phosphonates under the influence of triaminoiminophosphorane (**2**),[13] prepared in situ from **1**·Cl and KO^{t}Bu,[12] in comparison with a series of strong organic bases would provide an ideal platform for not only the elucidation of the phosphite−phosphonate tautomerism but also a further revelation of the unique property of **1** as an anion-recognizable chiral organic cation. Herein, we describe that the structure of **1** capable of double H-bonding is suitable for stabilizing the phosphite anion and imparting remarkable nucleophilicity to it, thereby allowing a substantial generation of chiral phosphonium dialkyl phosphite as a highly reactive *P*-nucleophile. This phenomenon can be successfully applied to the establishment of highly efficient and enantioselective hydrophosphonylation of aldehydes.

First, we attempted to detect the reactive phosphite form as a metallophosphite by using a low-temperature (−98 °C) ^{31}P NMR technique.[14] When dimethyl phosphonate (**3**, pK_a = 18.4 in DMSO[15]) was mixed with KO^{t}Bu (1 equiv, the pK_a value of ^{t}BuOH is 32.2 in DMSO[16]) in THF, the original signal at 9.5 ppm underwent a significant downfield shift to 150.6 ppm (Figure 1a), which indicated

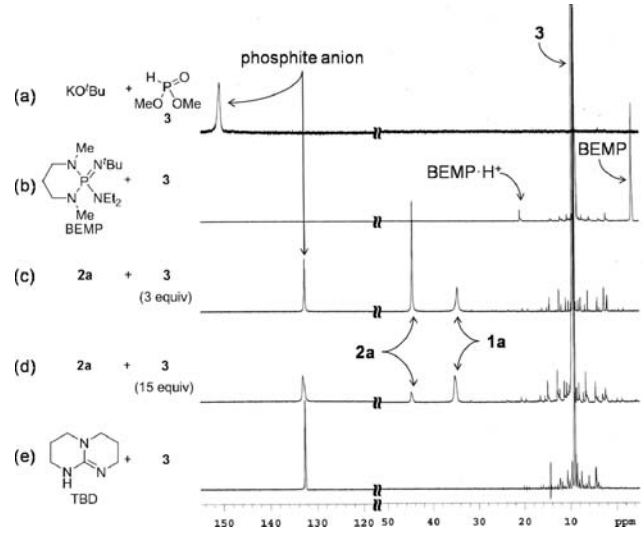


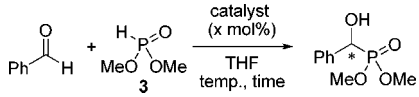
Figure 1. Charts of the ^{31}P NMR analysis at −98 °C.

the clean formation of the corresponding potassium salt $(MeO)_2PO^-K^+$.[17] With this information in hand, we examined the behavior of **3** in the presence of several representative organic bases. The addition of DBU and TMG (pK_a = 16.6, 15.3 in THF, respectively[18,19]) essentially caused no change in the spectrum, probably because of their insufficient basicity. Even the use of BEMP (pK_a = 27.6 in MeCN,[20] –3.17 ppm) allowed the detection of anionic species only by the signal of protonated BEMP at 21.0 ppm (Figure 1b).[21] Interestingly, however, an initial preparation of triaminoiminophosphorane **2a** (44.6 ppm) by treating **1a**·Cl with KO^{t}Bu[12] and subsequently mixing it with **3** resulted in the considerable generation of anionic phosphite at 132.7 ppm, with concomitant formation of the phosphonium counterion **1a** (34.8 ppm) (Figure 1c).[22] Note that the addition of an excess amount of **3** forced this acid−base equilibrium to further shift toward the phosphonium phosphite, as estimated by the decrease in the peak area of **2a** with the increase in that of **1a** (Figure 1d).[22] These observations suggest that the stability of the anion would be important for enhancing its contribution to the equilibrium and could be increased by the double H-bonding ability of a countercation. In fact, treatment of **3** with TBD (pK_a = 19.4 in THF[18,19]) afforded an intensive signal at 132.6 ppm, supporting our interpretation (Figure 1e).

10.1021/ja810043d CCC: $40.75

To elucidate the relationship between the base-dependent generation of the requisite phosphite anion revealed by the NMR study and its reactivity as a *P*-nucleophile, the catalytic activity of each organic base was systematically examined in the hydrophosphonylation of benzaldehyde with **3** (Table 1). DBU and TMG showed similar reactivities,

Table 1. Dependence of Reaction Efficiency on Catalyst Structure[a]



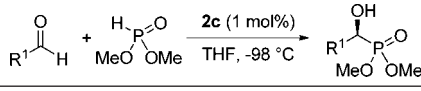
entry	catalyst	*x*	temp (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	DBU	5	−20	2	43 (45)[d]	−
2	TMG	5	−20	2	30 (33)[d]	−
3	BEMP	5	−78	2	97	−
4	TBD	5	−78	2	95	−
5	**2a**	5	−78	1	97	85
6	**2b**	5	−78	4	98	78
7	**2c**	5	−78	0.5	92	92
8	**2d**	5	−78	0.25	99	78
9	**2c**	1	−78	1	99	91
10	**2c**	1	−98	4	97	98

[a] See Supporting Information for details. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Conversion yield was shown in parentheses.

and the P−C bond formation proceeded slowly at −20 °C (entries 1, 2). In contrast, other bases, with which the existence of the phosphite anion was detected, enabled a considerably faster reaction even at −78 °C (entries 3−5). Among these, in situ generated iminophosphorane **2a** turned out to be the most reactive catalyst, and fortunately, the desired α-hydroxy phosphonate was obtained with 85% ee.[23] It should be emphasized that an electronic effect of the aromatic substitutions (Ar) was observed, particularly on its catalytic activity (entries 5−8). While the reaction with **2b** prepared from **1b** possessing electron-withdrawing functionality required 4 h for completion, large acceleration was induced with increasing the electron density of the aryl groups.[24] The most enantioselective catalyst **2c** was then used for further experiments. Catalyst loading can be reduced to 1 mol%, and the prominent reactivity of the phosphonium phosphite made it feasible to perform the reaction at −98 °C, where the reaction product was isolated almost quantitatively with excellent enantioselectivity (entries 9, 10).

Finally, the generality of this **2c**-catalyzed, highly efficient, and enantioselective hydrophosphonylation was investigated. As listed in Table 2, a series of aromatic aldehydes with substituents having

Table 2. Substrate Scope[a]



entry	R^1	time (h)	yield[b] (%)	ee[c] (%)	entry	R^1	time (h)	yield[b] (%)	ee[c] (%)
1	*o*-F−C_6H_4	3	97	98	6	*m*-Br−C_6H_4	6.5	98	98
2	*o*-Me−C_6H_4	4	98	96	7	1-naphthyl	3	96	99
3	*p*-F−C_6H_4	4	97	97	8[d]	2-furyl	2	90	98
4	*p*-MeO−C_6H_4	8	99	94	9	(*E*)-PhCH=CH	13	90	96
5	*p*-Me−C_6H_4	3	91	96	10	$Ph(CH_2)_2$	6	99	91

[a−c] See footnotes in Table 1. [d] The reaction was performed at −78 °C.

different electronic properties were employable (entries 1−7). In the case of 2-furylaldehyde, a smooth reaction and virtually complete stereocontrol were achieved at −78 °C (entry 8). Moreover, the present system tolerated α,β-unsaturated as well as aliphatic aldehydes (entries 9, 10).

In conclusion, the generation of chiral tetraaminophosphonium phosphite has been detected by low-temperature NMR analysis, and its synthetic relevance has been successfully demonstrated by its application to the establishment of highly efficient and enantioselective hydrophosphonylation of aldehydes. A comparison of **2** with representative strong organic bases clearly shows that the molecular structure of the cationic conjugate acid is a key element for substantial generation of phosphite anions with an unprecedented level of nucleophilicity as well as for rigorous stereocontrol. We believe that the present study offers a general yet valuable framework for designing even more superior chiral organic base catalysts.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformation of Carbon Resources" from MEXT and Grants of JSPS for Scientific Research.

Supporting Information Available: Representative experimental procedures and the details of the NMR study. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) The signal corresponding to the anionic species was detectable in DMF at −60 °C. See Supporting Information for details.
(22) The peak area of anionic phosphite corresponds to that of **1a**.
(23) The origin of the higher efficiency of **2** than that of TBD is unclear at present.
(24) For the effect of the aromatic substituents of **2** on its ability of generating a phosphite anion, see the ^{31}P NMR analysis in the Supporting Information.

JA810043D