DOI: 10.1002/adsc.200505403

The First Air-Stable and Efficient Nucleophilic Trialkylphosphine Organocatalyst for the Baylis–Hillman Reaction

Zhengrong He,[a,b] Xiaofang Tang,[a] Yaoming Chen,[b] Zhengjie He[a,*]

[a] Department of Chemistry, Nankai University, Tianjin 300071, People's Republic of China
Fax: (+86)-22-2350-2458, e-mail: zhengjiehe@nankai.edu.cn
[b] Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, People's Republic of China

Received: October 13, 2005; Accepted: January 12, 2006

Abstract: 1,3,5,-Triaza-7-phosphaadamantane (PTA) is first reported to be a convenient and efficient nucleophilic trialkylphosphine organocatalyst for the Baylis–Hillman reaction. Thus, under the mediation of 15–20 mol % of PTA and practical conditions, both aromatic and aliphatic aldehydes react with the activated alkenes like acrylates and methyl vinyl ketone to afford the corresponding adducts in fair to excellent yields.

Keywords: activated alkenes; aldehydes; Baylis–Hillman reaction; nucleophilic organocatalyst; trialkylphosphine

Organocatalysis is an increasingly hot research topic in the field of organic chemistry.[1,2] As the efficiency and selectivity of many organocatalytic reactions have been continuously improved, organocatalytic reactions are becoming powerful tools in modern organic synthesis. In contrast to the transition metal catalysts in which the metal centers generally behave as good Lewis acids, organocatalysts tend to act as heteroatom-centered Lewis bases. These heteroatoms are most likely N, P, and S, which have non-bonded lone pairs of electrons that often play an important role in organocatalysis.

Both tertiary amines and tertiary phosphines are popular in nucleophilic catalysis.[3] Due to their cheaper prices, better stability, and lower toxicity, tertiary amines prevail over phosphines in organocatalysis. Only in last decade or so have phosphines as nucleophilic organocatalysts attracted much attention, and remarkable achievements have been made in this area.[3b, c,4] Compared to their nitrogen analogues, tertiary phosphines have better nucleophilicity and weaker basicity, which are most likely attributed to the greater polarizability and lower electron density of the phosphorus atom. These unique characteristics may render phosphines some advantages over amines as evidenced in some nucleophilic organocatalytic reactions[3b, c] such as the Rauhut–Currier reaction. The nucleophilicity of trialkylphosphines is the strongest among their amine analogues and triarylphosphines. However, due to their extreme air-sensitivity, the potential utility of trialkylphosphines as nucleophilic organocatalysts with enhanced reactivity has been limited. Contrarily, less reactive triarylphosphines, e.g., PPh_3, with relatively higher air stability have been most often used. This situation may be claimed as a factor responsible for the lag in the development of nucleophilic phosphine catalysts. Most recently, the superiority of trialkylphosphines as nucleophilic catalysts over their amine or triarylphosphine counterparts has attracted increasing interest.[3b,4] However, how to resolve the issue of the air sensitivity of trialkylphosphines is still a challenge for organic chemists in the field of organocatalysis. Pioneering work has been done by Fu and coworkers,[5] who suggested converting trialkylphosphines into their air-stable conjugate acids such as tetrafluoroborate, and then releasing them *in situ* by treatment with an appropriate base. This simple and practical method has been proven effective in a diverse set of reactions although it carries some obvious drawbacks such as involving extra manipulations, not being atom economic, and still requiring inert atmosphere protection in the final step. Up to date, there are no reports concerning the use of air-stable trialkylphosphines as a nucleophilic catalyst.

A cage-like phosphine, 1,3,5-triaza-7-phosphaadamantane (PTA), was first reported in 1974 by Daigle and co-workers.[6] It can be easily prepared in high yield from a commercially available material, tetrahydroxymethylphosphonium chloride or sulfate.[7] After its discovery, related research activity had been quiet until recently when it attracted renewed interest due to its properties of water solubility and strong coordinating ability with a wide range of transition metals.[8] In most of the recent reports, PTA has been used as a unique water-soluble phosphine ligand. To the best of our knowledge, there have been no reports concerning its utility as a phosphine organocatalyst before. In addition to its coordinating ability, the overall reactivity, including nucleo-

philicity, of PTA is comparable to other pure trialkylphosphines except that PTA is air stable. Its air stability is even much higher than triphenylphosphine with respect to the kinetic constants of oxidation.[9] This kind of unique property of PTA prompted us to explore its potential utility as an air-stable trialkylphosphine alternative organocatalyst. Herein, we report that PTA is a convenient and efficient phosphine catalyst for the Baylis–Hillman reaction of both aromatic and aliphatic aldehydes with activated alkenes.

The Baylis–Hillman reaction, also known as the Morita–Baylis–Hillman reaction, is an attractive method for forming carbon-carbon bonds and yields highly functionalized products. It can be broadly defined as a coupling reaction between an alkene activated by an electron-withdrawing group and an aldehyde under the mediation of a nucleophilic catalyst, usually a tertiary amine such as 1,4-diazabicyclo[2.2.2]octane (DABCO) and a tertiary phosphine. Since its discovery, it has been associated with a number of problems, most notably, its sluggish reaction rate, especially for the substrate acrylate. In the last decade, much research effort has been directed toward its efficiency and selectivity, and significant advances have been made.[10]

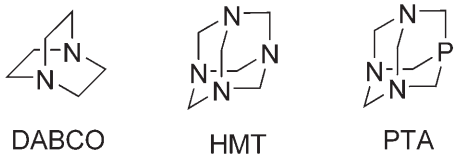
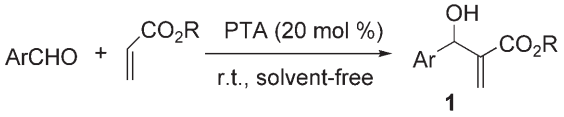


Figure 1. Catalysts in the Baylis–Hillman reaction.

A set of aromatic and aliphatic aldehydes was selected to react with two kinds of activated alkenes, acrylate and methyl vinyl ketone (MVK). Preliminary results show that in the presence of PTA (15–20 mol %), the Baylis–Hillman reactions readily proceed giving the normal adducts in fair to excellent yields and within acceptable reaction times (Tables 1 and 2). In the case of acrylate, only aromatic aldehydes can substantially give the expected products in a relatively short reaction time, as shown in Table 1. The availability of previous experimental data on similar Baylis–Hillman reactions catalyzed by tertiary amines allows us to make a rough comparison of PTA's catalytic efficiency with those of amine catalysts. Based on the results reported by Hu and coworkers,[11] PTA shows a comparable catalytic activity to the most often used tertiary amine catalyst DABCO with respects to catalyst loading, reaction time and yield of product (Table 1, entries 1–3, 6–8). In 2004, Vasconcellos et al.[12] reported that hexamethylenetetramine (HMT) could be used as an alternative catalyst in the Baylis–Hillman reaction of aromatic aldehydes. Regarding its structural similarity to PTA, HMT should be a perfect catalyst candidate for the purpose of comparison, which structurally differentiates itself with PTA only by the displacement of one nitrogen atom with phosphorus (Figure 1). On the basis of the reported results for HMT and those for PTA (Table 1, entries 3, 6, 8), it may be concluded that PTA is overall much superior over HMT in the Baylis–Hillman reaction of aromatic aldehydes with acrylate. For the precise comparison, two reactions of 4-nitrobenzaldehyde with ethyl acrylate were run under otherwise identical conditions, except for the catalysts, and results confirm the superiority of PTA over HMT, again.[13] This superiority does not only indicate that PTA is a better catalyst than HMT in the Baylis–Hillman reaction of aromatic aldehydes, but also implies that the phosphorus makes a vital contribution to the catalysis, and PTA acts as an efficient nucleophilic phosphine catalyst.

Under very friendly conditions (room temperature and ambient atmosphere), the Baylis–Hillman reaction of both aromatic and aliphatic aldehydes with MVK

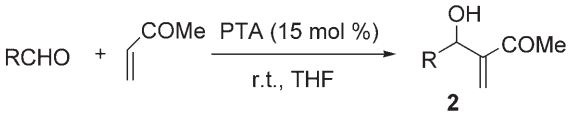
Table 1. The PTA-catalyzed Baylis–Hillman reaction of aromatic aldehydes with ethyl (*n*-butyl) acrylates.



Entry	Ar	R	Reaction time [h]	Product[a]	Yield[b] [%]
1	2-$NO_2C_6H_4$	Et	9	**1a**	84
2	3-$NO_2C_6H_4$	Et	7	**1b**	72
3	4-$NO_2C_6H_4$	Et	5	**1c**	91
4	2,4-$Cl_2C_6H_3$	Et	15	**1d**	80
5	2-F-4-ClC_6H_3	Et	7	**1e**	60
6	2-pyridyl	Et	7	**1f**	59
7	2-$NO_2C_6H_4$	n-Bu	19	**1g**	93
8	4-$NO_2C_6H_4$	n-Bu	15	**1h**	79

[a] Identified by ^1H and ^{13}C NMR, and satisfactory microanalysis obtained for new compounds **1d** and **1e**.
[b] Isolated yield based on the aldehyde.

Table 2. The PTA-catalyzed Baylis–Hillman reaction of aldehydes with methyl vinyl ketone.



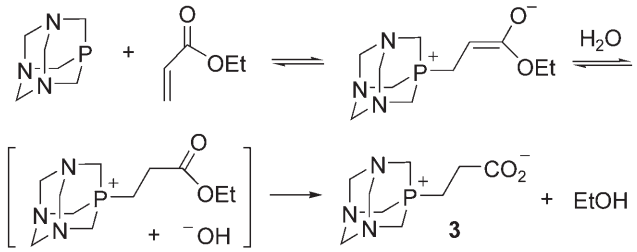
Entry	R	Reaction time [h]	Product[a]	Yield[b] [%]
1	2-$NO_2C_6H_4$	4	**2a**	91
2	3-$NO_2C_6H_4$	2.5	**2b**	95
3	4-$NO_2C_6H_4$	1	**2c**	82
4	3-FC_6H_4	20	**2d**	57
5	2,4-$Cl_2C_6H_3$	4	**2e**	86
6	2-Cl-4-FC_6H_3	3.5	**2f**	96
7	2-pyridyl	6	**2g**	63
8	C_6H_5	9	**2h**	80
9	H	24	**2i**	66
10	C_2H_5	5	**2j**	93

[a] Identified by ^1H and ^{13}C NMR, and satisfactory microanalysis obtained for new compound **2f**.
[b] Isolated yield based on the aldehyde.

readily proceeds under the mediation of a catalytic amount of PTA (15 mol %). Most of reactions can be complete in a couple of hours to give the normal adducts in 57–96% yields (Table 2).

In the course of this study, we observed that the reaction of 4-nitrobenzaldehyde with ethyl acrylate in THF-H_2O (4:1, v/v) under the mediation of PTA (20 mol %) completely subsided within 6 h after an initially rapid conversion (TLC monitored). ^{31}P NMR analysis of the reaction mixture showed that the catalyst PTA ($\delta_P = -98.3$ ppm in D_2O) had disappeared and a new species ($\delta_P = -37.6$ ppm in D_2O) had emerged. Subsequent investigation disclosed that this species is the zwitterion **3** resulting from the Michael addition of PTA with ethyl acrylate followed by protonation and hydrolysis of the intermediate ester (Scheme 1). Species **3** can be readily prepared by the reaction of PTA with ethyl acrylate in aqueous THF. The Baylis–Hillman reaction with acrylate takes place smoothly under anhydrous condition, even in a protic solvent like alcohol, although the results listed in Table 1 were all obtained from solvent-free reactions. The formation of **3** unanimously confirms the occurrence of the Michael addition between the phosphorus and acrylate. It also provides solid evidence for the Michael addition step in the catalytic cycle, and proves that PTA acts as a tertiary trialkylphosphine, not a tertiary amine, in the catalysis. An analogous zwitterion from the reaction of DABCO with methyl acrylate in aqueous 1,4-dioxane was isolated and characterized by Hu.[11]

In conclusion, we have demonstrated that 1,3,5-triaza-7-phosphaadamantane, as the first air-stable, nucleophilic trialkylphosphine organocatalyst, is efficient for the Baylis–Hillman reaction of both aromatic and aliphatic aldehydes with activated alkenes including ethyl acrylate and methyl vinyl ketone. On the basis of the reported data for tertiary amine-catalyzed Baylis–Hillman reactions and of the formation of the zwitterionic adduct **3**, we concluded that the phosphorus in PTA plays a critical role in the catalysis. As trialkylphosphines are emerging as important nucleophilic catalysts in an array of new organic reactions as a result of their unique nucleophilicity, we anticipate that PTA will be widely used as a convenient alternative organocatalyst for air-sensitive trialkylphosphines. PTA-promoted nucleophilic reactions of aldehydes with electron-deficient alkynes and allenes are currently under investigation in our laboratory.



Scheme 1. Formation of the zwitterions **3** of PTA.

Experimental Section

Commercially available chemicals were used as received. PTA was prepared from tetrahydroxymethylphosphonium sulfate according to a previously reported procedure.[7] Nuclear magnetic resonances (^1H, ^{13}C, and ^{31}P) were recorded on a Bruker 300 MHz NMR spectrometer using TMS as internal standard (^1H, ^{13}C) and 85% phosphoric acid as external standard (^{31}P), unless otherwise mentioned. Elemental analyses were performed on a Yanaco CHN Corder MT-3 automatic analyzer.

PTA-Catalyzed Baylis–Hillman Reaction of Aromatic Aldehydes with Ethyl (*n*-Butyl) Acrylates; General Procedure

A mixture of aromatic aldehyde (1.0 mmol) and PTA (0.2 mmol) in 1.0 mL of ethyl acrylate or butyl acrylate (in excess) was stirred at room temperature for the time specified in Table 1. Then the volatile components were removed on a rotary evaporator, and the residue was mixed with 20 mL of dichloromethane, washed twice with water (2 × 5 mL), and dried over anhydrous sodium sulfate. After filtration and evaporation of solvent, the crude product was purified by column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution) to afford pure product **1**.

1d: viscous oil; ^{1}H NMR ($CDCl_3$): δ = 7.50 (d, J = 8.1 Hz, 1H), 7.37 (d, J = 0.5 Hz, 1H), 7.28 (dd, J = 8.1, 0.5 Hz, 1H), 6.34 (s, 1H), 5.91 (br s, 1H), 5.57 (s, 1H), 4.22 (q, J = 7.2 Hz, 2H), 3.41 (br s, 1H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 166.3, 140.7, 137.2, 134.0, 133.4, 129.2, 129.1, 127.2, 126.6, 68.7, 61.1, 14.0; anal. calcd. for $C_{12}H_{12}Cl_2O_3$: C 52.39, H 4.40; found: C 52.28, H 4.41.

1e: viscous oil; ^{1}H NMR ($CDCl_3$): δ = 7.21 (m, 2H), 7.10 (dd, J = 9.6, 1.2 Hz, 1H), 6.24 (s, 1H), 5.68 (d, J = 5.4 Hz, 1H), 5.56 (s, 1H), 4.07 (q, J = 7.2 Hz, 2H), 3.52 (d, J = 5.4 Hz, 1H), 1.15 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 166.1, 140.5, 137.0, 133.8, 133.3, 128.9, 128.8, 127.0, 126.4, 68.5, 60.9, 13.7; anal. calcd. for $C_{12}H_{12}ClFO_3$: C 55.72, H 4.68; found: C 55.36, H 4.65.

PTA-Catalyzed Baylis–Hillman Reaction of Aldehydes with Methyl Vinyl Ketone; General Procedure

A mixture of aldehyde (1.0 mmol), methyl vinyl ketone (3.0 mmol), and PTA (0.15 mmol) in 2.0 mL of THF was stirred at room temperature for time specified in Table 2. Then the reaction mixture was concentrated on a rotary evaporator, and the crude product was subjected to similar work-up and purification by silica gel column chromatography as described in the general procedure for compounds **1** to give pure product **2**.

2f: viscous oil; ^{1}H NMR ($CDCl_3$): δ = 7.33 (m, 2H), 7.20 (dd, J = 9.9, 1.8 Hz, 1H), 6.19 (s, 1H), 5.88 (br s, 1H), 5.80 (d, J = 5.7 Hz, 1H), 3.52 (d, J = 5.4 Hz, 1H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$): δ = 200.2, 161.7 (d, J = 83.2 Hz), 157.8, 148.2, 129.4, 127.5, 127.3 (d, J = 27.0 Hz), 121.6, 118.8 (d, J = 27.0 Hz), 66.6, 26.2; anal. calcd. for $C_{11}H_{10}ClFO_2$: C 57.78, H 4.41; Found: C 57.62, H 4.56.

Formation of the Zwitterionic Adduct 3 of PTA with Ethyl Acrylate

PTA (0.32 g, 2.0 mmol) was added in one portion into a solution of ethyl acrylate (0.60 g, 6.0 mmol) in 5 mL of a THF-H_2O (4:1, v/v) mixture. The resulting mixture was stirred at room temperature for 6 h. Then the solvent was removed under reduced pressure and the crude product was dissolved in 5 mL of distilled water. The aqueous solution was extracted twice with ether (2 × 5 mL) and the ethereal layer was discarded. The aqueous layer was evaporated to dryness under vacuum to give a pale yellow crystalline solid **3**; yield: 0.53 g (100%); mp 238 °C (dec.); ^{1}H NMR (D_2O): δ = 4.45–4.28 (m, 12H), 2.39 (dt, J = 17.1, 6.3 Hz, 2H), 2.15 (m, 2H); ^{13}C NMR (D_2O, DMSO as internal reference): δ = 179.1 (s), 71.4 (d, J = 6.8 Hz), 39.4 (s), 28.9 (s), 18.5 (d, J = 27.8 Hz); ^{31}P NMR (D_2O): δ = −37.6; anal. calcd. For $C_9H_{16}N_3O_2P \cdot 2\,H_2O$: C 40.75, H 7.60, N 15.84; found: C 40.69, H 7.96, N 15.97.

Acknowledgements

This work was supported by National Natural Science Foundation of China (Grant No. 20421202) and Research Starting Fund from Nankai University. We also thank Professor Chuchi Tang of Nankai University for the generous gifting of some chemical reagents.

References and Notes

[1] For reviews, see: a) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138–5175; b) M. Benaglia, A. Puglisi, F. Cozzi, *Chem. Rew.* **2003**, *103*, 3401–3430.

[2] For most recent reports, see: a) G. D. Joly, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, *126*, 4102–4103; b) Z. Tang, Z. Yang, X. Chen, L. Cun, A. Mi, Y. Jiang, L. Gong, *J. Am. Chem. Soc.* **2005**, *127*, 9285–9289; c) A. Lattanzi, *Org. Lett.* **2005**, *7*, 2579–2582; d) H. Li, J. Song, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2005**, *127*, 8948–8949; e) Y. Du, J. Feng, X. Lu, *Org. Lett.* **2005**, *7*, 1987–1989; f) D. E. Fuerst, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 8964–8965.

[3] For reviews, see: a) S. France, D. J. Guerin, S. J. Miller, T. Lectka, *Chem. Rev.* **2003**, *103*, 2985–3012; b) J. L. Methot, W. R. Roush, *Adv. Synth. Catal.* **2004**, *346*, 1035–1050; c) X. Lu, C. Zhang, Z. Xu, *Acc. Chem. Res.* **2001**, *34*, 535–544.

[4] a) S. A. Frank, D. J. Mergott, W. R. Roush, *J. Am. Chem. Soc.* **2002**, *124*, 2404–2405; b) J. Wang, S. Ng, M. J. Krische, *J. Am. Chem. Soc.* **2003**, *125*, 3682–3683; c) X. Zhu, C. E. Henry, J. Wang, T. Dudding, O. Kwon, *Org. Lett.* **2005**, *7*, 1387–1390; d) X. Zhu, A. Schaffner, R. C. Li, O. Kwon, *Org. Lett.* **2005**, *7*, 2977–2980.

[5] M. R. Netherton, G. C. Fu, *Org. Lett.* **2001**, *3*, 4295–4298.

[6] D. J. Daigle, A. B. Jr. Pepperman, S. L. Vail, *J. Heterocycl. Chem.* **1974**, *11*, 407–408.

[7] D. J. Daigle, *Inorg. Synth.* **1998**, *32*, 40.

[8] A. D. Philips, L. Gonsalvi, A. Romerosa, F. Vizza, M. Peruzzini, *Coordination Chem. Rev.* **2004**, *248*, 955–993.

[9] M. M. Abu-Omar, J. H. Espenson, *J. Am. Chem. Soc.* **1995**, *117*, 272–280.

[10] For reviews, see: a) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811–892; b) J. Cai, Z. Zhou, C. Tang, *Huaxue Yanjiu* **2001**, *12*, 54–64; for the most recent reports, see: c) M. Shi, L. Chen, C. Li, *J. Am. Chem. Soc.* **2005**, *127*, 3790–3800; d) M. Shi, C. Li, *Tetrahedron: Asymmetry* **2005**, *16*, 1385–1391; e) X. Mi, S. Luo, J. Cheng, *J. Org. Chem.* **2005**, *70*, 2338–2341; f) Y. Hayashi, T. Tamura, M. Shoji, *Adv. Synth. Catal.* **2004**, *346*, 1106–1110; g) N. T. McDougal, W. L. Trevellini, S. A. Rodgen, L. T. Kliman, S. E. Schaus, *Adv. Synth.*

Catal. **2004**, *346*, 1231–1240; h) S. Luo, P. G. Wang, J. Cheng, *J. Org. Chem.* **2004**, *69*, 555–558; i) D. J. Maher, S. J. Connon, *Tetrahedron Lett.* **2004**, *45*, 1301–1305.
[11] C. Yu, B. Liu, L. Hu, *J. Org. Chem.* **2001**, *66*, 5413–5418.
[12] R. De Souza, B. A. Meireles, L. Aguiar, M. Vasconcellos, *Synthesis* **2004**, 1595–1600.
[13] Reactions were run as follows: at room temperature, a mixture of 4-nitrobenzaldehyde (1.0 mmol) and the catalyst (0.2 mmol) in ethyl acrylate (2.0 mL) was stirred for 6 h. After removal of volatile components on a rotary evaporator, the residue was subjected to silica gel column chromatography (petroleum ether-ethyl acetate, 6:1, v/v) to afford the product. The average yields for HMT and PTA were 8% and 86%, respectively, for 3 runs.

