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1,3,5-Triaza-7-phosphaadamantane (PTA): A Practical and Versatile Nucleophilic Phosphine Organocatalyst

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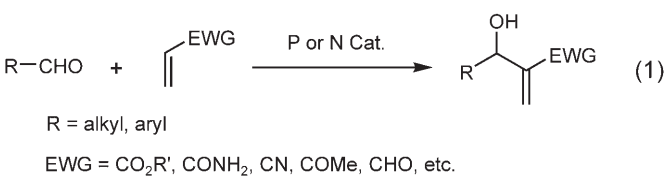
Abstract: In this paper, the air-stable and readily available 1,3,5-triaza-7-phosphaadmantane (PTA) is reported as a practical and versatile nucleophilic phosphine organocatalyst. Under the mediation of 15–30 mol% of PTA, various electrophiles like aldehydes and imines readily undergo the Morita–Baylis–Hillman reactions with a variety of activated olefins, giving the corresponding adducts in high yields. In the phosphine-catalyzed [3+2] cycloaddition reaction of 4-substituted 2,3-butadienoates with *N*-tosylimines, PTA is also proven to be a comparable catalyst as tributylphosphine (PBu_3). By systematic comparison with other structurally similar N,P catalysts, it is concluded that the superiority of PTA in the above nucleophilic catalysis is attributable to its comparable nucleophilicity with that of trialkylphosphines. The feasibility to use PTA as an alternative catalyst in place of the air-sensitive trialkylphosphines is also discussed.

Keywords: [3+2] cycloaddition reaction; Morita–Baylis–Hillman reaction; nucleophilic catalysis; tertiary phosphines; 1,3,5-triaza-7-phosphaadamantane

Introduction

From the viewpoints of green chemistry, reduction of the generation of polluting chemicals and of the use of dangerous chemicals in the chemical process are among the essential steps which must be taken to maintain the sustainability of the global environment.[1] Any optimization on or replacement for a current chemical manufacturing process, and innovation of new processes are fundamentally based on the availability of new and efficient synthetic reactions. Nowadays, many atom-economical reactions with enormous synthetic potentials have attracted much research effort, especially from organic chemists.[2] One of these important reactions is the Morita–Baylis–Hillman (MBH) reaction, which couples aldehydes with activated olefins in an atom-economical fashion, giving densely functionalized allyl alcohol derivatives [Eq. (1)].[3] In general, this reaction needs to be promoted by a nucleophilic tertiary amine or phosphine. Since its discovery, it has been associated with a number of problems, most notably, its sluggish reaction rate and high substrate-dependence of the yield. In the last two decades, although significant progress has been made on its efficiency and selectivity,[4] the majority of the issues remain. As evidenced by the increasing number of publications on this reaction, it is still a hot spot in the field of organic chemistry. Most of the research efforts have been directed towards the following three aspects: exploring new catalysts to improve its efficiency and selectivity, expanding its scope, and increasing its utility in organic synthesis.[5]



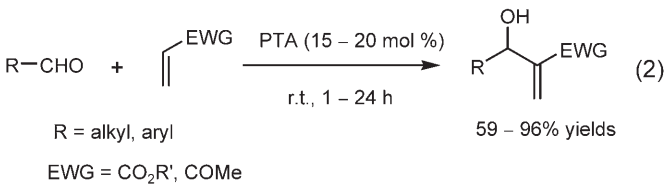
Both tertiary amines and tertiary phosphines are the most often used catalysts in the MBH reaction, even from early beginning. Compared to their amine analogues, tertiary phosphines have better nucleophilicity and weaker basicity; hence they often outperform their amine counterparts in nucleophilic catalysis, as well as in MBH reactions. Currently, both amine and phosphine catalysts are equally important for the MBH reaction with respect to scope, efficiency and selectivity.[5]

Recently, nucleophilic catalysis by tertiary phosphines has emerged as a powerful tool in synthetic organic chemistry as numerous phosphine-catalyzed new reactions have been reported.[6] Since the nucleo-

philicity of trialkylphosphines is the strongest among their amine analogues and triarylphosphines, trialkylphosphines are very often employed alone or in combination with other co-catalysts for enhanced activity, especially in cases where greater nucleophilicity is required.[5i–k,r,7] However, unlike tertiary amines or triarylphosphines, pure trialkylphosphines are highly air-sensitive and in some cases pyrophoric. Extra cautions and manipulations must be therefore taken in their use. A few of precedent attempts were reported to address this air-sensitivity issue. Fu and co-workers[8] 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 including the MBH reaction, although it carries some obvious drawbacks such as involving extra manipulations. In another report,[9] several ferrocenyldialkylphosphines, possessing simultaneously stability to air oxidation and high nucleophilicity, were disclosed as effective catalysts for the MBH reaction between aldehydes and acrylates.

As part of our continuous effort devoted to phosphine-catalyzed carbon-carbon bond forming reactions, we have been engaged in the development of an air-stable and highly nucleophilic alternative for commonly used but extremely air-sensitive trialkylphosphine catalyst such as PBu_3. A readily available cage-like trialkylphosphine, 1,3,5-triaza-7-phosphaadamantane (PTA), is reported and its overall reactivity including nucleophilicity is comparable to those of other pure trialkylphosphines except that it is air-stable.[10] Its air-stability is even much higher than that of triphenylphosphine with respect to the kinetic constants of oxidation.[11] This kind of unique property of PTA prompted us to explore its potential utility as a trialkylphosphine nucleophilic catalyst, although it has been long used as a water-soluble ligand in coordination chemistry.[10]

In our preliminary communication,[12] we reported PTA is highly efficient for the MBH reaction of both aromatic and aliphatic aldehydes with activated alkenes ethyl (butyl) acrylates and methyl vinyl ketone [Eq. (2)]. Herein, we further report the details of the



PTA-catalyzed MBH reaction with a broad range of activated olefins. Also, to demonstrate the feasibility of PTA as an alternative nucleophilic catalyst for air-sensitive trialkylphosphines, we disclose the PTA-catalyzed [3+2] cycloaddition reaction of 4-substituted butadienoates with *N*-tosylimines in this paper.

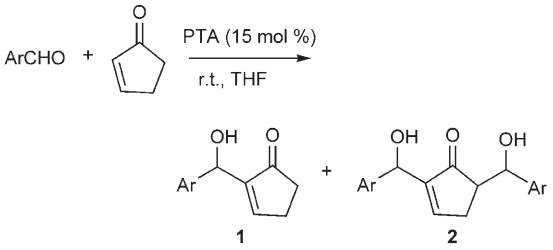
Results and Discussion

PTA-Catalyzed MBH Reactions with a Variety of Activated Olefins

With 2-Cyclopenten-1-one

Cyclic α,β-unsaturated ketones like cyclopentenone and cyclohexenone are often employed as substrates in the MBH reaction. In this work, 2-cyclopenten-1-one was chosen for the PTA-catalyzed MBH reaction as a cyclic activated olefin. 2-Cyclohexen-1-one was not used due to its toxicity. It is found that, under very mild conditions, PTA (15 mol%) can effectively mediate the MBH reaction of aromatic aldehydes with 2-cyclopenten-1-one, giving the normal adducts in good to excellent yields (Table 1). In the cases of more reactive aldehydes with a strong electron-withdrawing group on the aromatic ring, such as nitro-substituted aldehydes, a small amount (less than 5%) of by-product **2** was isolated along with the major MBH product **1** (Table 1, entries 2–4). Obviously, **2** resulted from the side aldol reaction of MBH product **1** with the substrate aldehyde. A similar observation was re-

Table 1. PTA-catalyzed MBH reaction of aromatic aldehydes with 2-cyclopenten-1-one.



Entry	Ar	Reaction Time [h]	Product[a]	Yield[b] [%]
1	C_6H_5	24	**1a**	47
2	2-$NO_2C_6H_4$	20	**1b**	80
3	3-$NO_2C_6H_4$	20	**1c**	87
4	4-$NO_2C_6H_4$	6	**1d**	97
5	3-FC_6H_4	24	**1e**	60
6	2,4-$Cl_2C_6H_3$	24	**1f**	53
7	2-F-4-ClC_6H_3	24	**1g**	54
8	2-furyl	24	**1h**	63

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

ported by Shi in the PBu_3-catalyzed MBH reaction of aromatic aldehydes with 2-cyclopenten-1-one.[13]

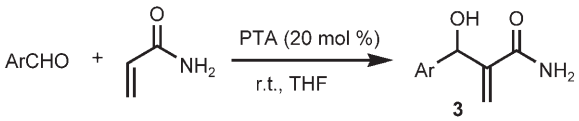
With Acrylamide

Acrylamide is less reactive in the MBH reaction, presumably due to the electron delocalization of the lone pair of electrons on the nitrogen atom of acrylamide decreasing the electron-withdrawing capability of the carbonyl group. As a consequence, few examples of the use of acrylamide as an activated olefin in an efficient MBH reaction were reported,[14] although its MBH adduct is also versatile in organic synthesis. Up to date, the most effective catalyst reported is 1,4-diazabicyclo[2.2.2]octane (DABCO) as a sole example. Under the promotion of 50 mol%–100 mol% of DABCO, a few of aromatic aldehydes gave the normal MBH adducts with acrylamide in fair to excellent yields.[14] This situation intrigued us to expand the scope of the PTA-promoted MBH reaction to acrylamide. Our results show that PTA is also remarkably effective for acrylamide, although only in the MBH reaction with aromatic aldehydes, and in some cases suffering from longer reaction times and lower yields (Table 2). Based on our data and those in reports,[14] it should be concluded that PTA is comparable to DABCO in the MBH reaction with acrylamide in terms of the scope, reaction time, and catalyst loading.

With Acrolein

Acrolein is less often used as a substrate in the MBH reaction, assumingly because of its susceptibility to self-polymerization, which is even more severe in the presence of a basic amine. Only a few of examples were reported with the yields of the adducts generally being low to fair.[15] Employing the highly reactive electrophile polyfluoroaldehyde[15a] or high pressure[15b] are among the effective means of diminishing the self-polymerization to enhance the yield of the normal adduct. Most of the reported catalysts in the MBH reaction with acrolein are tertiary amines including DABCO as the best. Our attempt reveals that PTA is pretty effective in the mediation of this reaction. Under mild conditions, several reactive aromatic aldehydes could readily give the normal MBH adducts with acrolein in fair to good yields (Table 3). However, less reactive aldehydes like benzaldehydes with electron-donating substituents could not afford the normal adducts in appreciable yields. Prolonged reaction time did not help since side reactions like polymerization of acrolein became severe. Despite the limited scope, PTA is still among the best catalysts for the MBH reaction with acrolein.

Table 2. PTA-catalyzed MBH reaction of aromatic aldehydes with acrylamide.

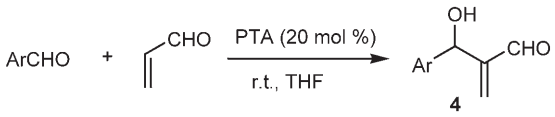


3

Entry	Ar	Reaction Time [h]	Product[a]	Yield[b] [%]
1	2-$NO_2C_6H_4$	3	**3a**	82
2	3-$NO_2C_6H_4$	3	**3b**	55
3	4-$NO_2C_6H_4$	4	**3c**	91
4	3-FC_6H_4	24	**3d**	21
5	2,4-$Cl_2C_6H_3$	24	**3e**	44
6	2-F-4-ClC_6H_3	24	**3f**	30

[a] Identified by ^1H, ^{13}C NMR, and satisfactory microanalysis obtained for new compounds **3d**, **3e** and **3f**.
[b] Isolated yield based on the substrate aldehyde.

Table 3. PTA-catalyzed MBH reaction of aromatic aldehydes with acrolein.



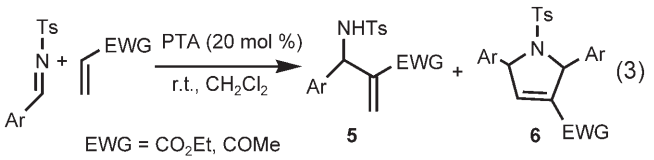
4

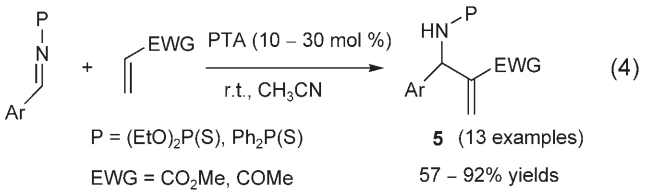
Entry	Ar	Reaction Time [h]	Product[a]	Yield[b] [%]
1	2-$NO_2C_6H_4$	4	**4a**	87
2	3-$NO_2C_6H_4$	4	**4b**	92
3	4-$NO_2C_6H_4$	4	**4c**	83
4	3-FC_6H_4	96	**4d**	56

[a] Identified by ^1H, ^{13}C NMR.
[b] Isolated yield based on the substrate aldehyde.

PTA-Catalyzed Aza-MBH Reactions of Imines

The aza-MBH reaction is another version of the MBH reaction with imines being employed as the electrophilic substrate instead of aldehydes, affording allylamine derivatives as the MBH adduct. Due to its enormous synthetic potential, it has also received extensive studies in recent years.[5d,l–q,s,16] Both tertiary amines and tertiary phosphines are effective catalysts for aza-MBH reactions. In this work, we found that PTA is also an efficient catalyst for aza-MBH reactions of both *N*-tosyl- and *N*-thiophosphinoylimines





with activated alkenes [Eq. (3)and Eq. (4)]. Since phosphine-promoted aza-MBH reactions have been extensively studied for reactive *N*-tosylimines, herein only a few representative *N*-tosylimines and activated olefins were chosen to illustrate PTA's effectiveness.

In the reaction of *N*-tosylimine with methyl vinyl ketone (MVK), an abnormal product, substituted dihydropyrole **6**, forms competitively along with the normal aza-MBH adduct **5** in fair to good combined yield (Table 4). In Shi's report,[16b] a similar reaction, catalyzed by the weak nucleophilic Ph_3P, exclusively gives the normal aza-MBH product **5**; in contrast, the use of the strong nucleophilic Bu_3P leads to the formation of **6** as one of major products. As concluded by Shi, this chemoselectivity is attributed to the difference of the phosphines in nucleophilicity. These results also corroborate that the catalytic behaviour of PTA is similar to that of trialkylphosphine like Bu_3P. In the case of ethyl acrylate, the aza-MBH reaction exclusively gives the normal adducts **5** in moderate yields (Table 4).

Table 4. Representative examples of PTA-catalyzed aza-MBH reaction of N-tosylimine.

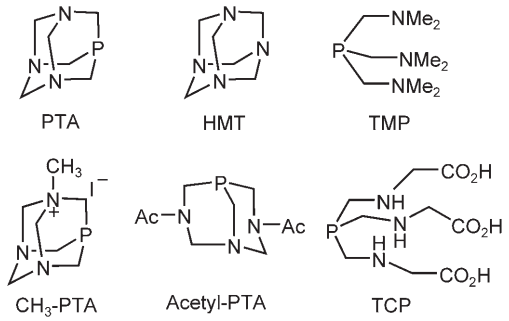
Entry	Ar	EWG	Reaction Time [h]	Yield of **5**[a] [%]	Yield of **6**[a] [%]
1	C_6H_5	COMe	24	**5a**, 42	**6a**, 19
2	4-$CH_3C_6H_4$	COMe	24	**5b**, 25	**6b**, 27
3	4-FC_6H_4	COMe	24	**5c**, 33	**6c**, 49
4	C_6H_5	CO_2Et	48	**5d**, 36	0
5	4-$CH_3C_6H_4$	CO_2Et	48	**5e**, 29	0
6	4-FC_6H_4	CO_2Et	48	**5f**, 20	0

[a] Isolated yield based on substrate imine.

The aza-MBH reaction of *N*-diphenylphosphinylimines has been developed to take advantage of the ease of the P–N bond cleavage under acidic hydrolysis,[16a,d] since the activating group tosyl is difficult to be removed from the corresponding aza-MBH products under mild conditions. To extend this successful strategy to other phosphorus-activating groups, we explored the aza-MBH reactions of *N*-thiophosphoryl- or *N*-thiophosphinylimines with activated olefins such as methyl acrylate and MVK. Under the mediation of PTA (10 mol%–30 mol%), these reactions proceed smoothly, giving the corresponding *N*-thiophosphinoyl adducts in good to excellent yields [Eq. (4)]. Removal of the phosphorus groups from the aza-MBH products has been achieved *via* mild acidic alcoholysis, affording the corresponding deprotected allylamines with hydrolysis sensitive groups like esters remaining intact. These results will be disclosed in detail in due course.

Comparison with Other N,P Catalysts in the MBH Reaction

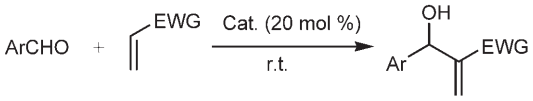
In order to gain some insights into PTA nucleophilic catalysis, as well as its unique physical property, we surveyed five N,P compounds (Scheme 1) with a certain similarity in structure to PTA in the MBH reaction. In our previous communication,[12] on the basis of the difference in catalytic activity between PTA and its nitrogen analogue hexamethylenetetramine (HMT), we concluded that PTA acts as a trialkylphosphine catalyst, and its superiority over its nitrogen counterpart in the MBH reaction is attributed to its better nucleophilicity. In this paper, we provide further evidence in support of this conclusion. For a series of aromatic aldehydes and activated olefins like ethyl acrylate and MVK, PTA is obviously more efficient than HMT in the MBH reaction (Table 5).



Scheme 1. Selected N,P catalysts with structural similarity.

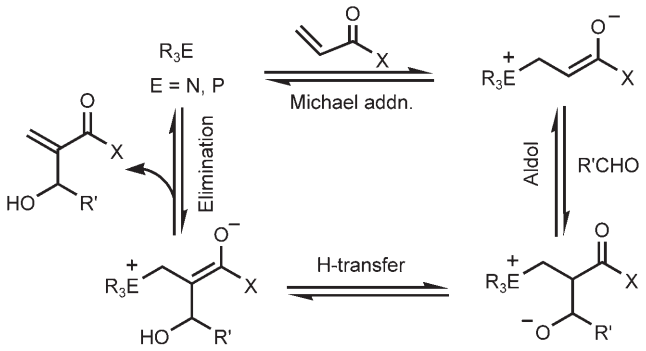
In the nucleophilic catalysis, the catalytic activity is often consistent with nucleophilicity strength of the

Table 5. Comparison of activity between PTA and HMT in the MBH reaction.[a]

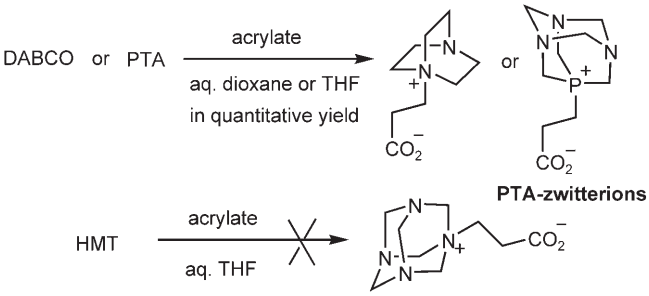


Entry	Ar	EWG	Catalyst	Time [h]	Yield[b] [%]
1	2-$NO_2C_6H_4$	CO_2Et	PTA	5	56
			HMT	24	20
2	3-$NO_2C_6H_4$	CO_2Et	PTA	5	64
			HMT	24	24
3	4-$NO_2C_6H_4$	CO_2Et	PTA	5	72
			HMT	24	28
4	2,4-$Cl_2C_6H_3$	CO_2Et	PTA	5	48
			HMT	24	10
5	2-F-4-ClC_6H_3	CO_2Et	PTA	5	40
			HMT	24	8
6	2-$NO_2C_6H_4$	COMe	PTA	0.5	73
			HMT	0.5	27
7	3-$NO_2C_6H_4$	COMe	PTA	0.5	91
			HMT	0.5	54
8	4-$NO_2C_6H_4$	COMe	PTA	0.5	98
			HMT	0.5	63
9	2,4-$Cl_2C_6H_3$	COMe	PTA	5	90
			HMT	5	40
10	2-F-4-ClC_6H_3	COMe	PTA	3	96
			HMT	3	61

[a] Reaction conditions: aldehyde (1.0 mmol); for ethyl acrylate (2 mL), reaction run solvent-free; for MVK (3.0 mmol), reaction run in THF (2 mL).
[b] Isolated yield of the corresponding MBH adduct.



Scheme 2. Generally accepted mechanism for the MBH reaction.



Scheme 3. Formation of zwitterions with acrylate in aqueous media.

catalyst.[9,17] Nucleophilicity is one of the important factors affecting nucleophilic catalysis. Evaluation or comparison on nucleophilicity is generally based on the reactivity of a nucleophile in certain nucleophilic reactions such as nucleophilic substitution reactions.[18] In light of generally accepted mechanism for the MBH reaction, the Michael addition of nucleophilic catalyst to activated olefins, generating reactive enolate intermediates, is the only step that involves the nucleophilic attack of the catalyst in the whole catalytic cycle (Scheme 2).[19] Accordingly, nucleophilicity of the catalyst in the MBH reaction could be evaluated by its reactivity in the Michael addition with activated olefin. Previously, Hu et al.[20] reported that incubation of methyl acrylate (3 mmol) with DABCO (100 mol%) readily gave the corresponding zwitterions at room temperature in 1,4-dioxane-water (1:1, v/v), which resulted from the Michael addition of DABCO to acrylate followed by hydrolysis of the ester group (Scheme 3); in our study, incubation of PTA (2 mmol) with ethyl acrylate (6 mmol) for 6 h in 5 mL of THF-H_2O (4:1, v/v) led to a 100% conversion of PTA into its corresponding zwitterions (PTA-zwitterions);[12] however, in sharp contrast, no detectable amount of such zwitterions was found by ^{1}H NMR from the reaction with HMT under similar conditions (Scheme 3). These results clearly reflect the difference in nucleophilicity among PTA, DABCO and HMT, that is to say, the first two catalysts are comparably nucleophilic, and the latter much less nucleophilic. This order of the nucleophilicity for these three catalysts matches well the order of their catalytic efficiency in the MBH reaction. Based on the reported data[20,21] and ours, the catalytic activities for PTA and DABCO are generally on the same level, which is much higher than that of HMT. Thus, it should be concluded that the nucleophilicity of a catalyst is vital to its efficiency in the nucleophilic catalysis, as well as in the MBH reaction.

Although there has been a commonly accepted mechanism in place for the MBH reaction (Scheme 2), much research interest has still been directed toward its re-evaluation and refinement.[19,22] Up to date, most of the evidence to support the catalytic cycle is from kinetic studies including isotopic effects. There is only a single experimental finding pro-

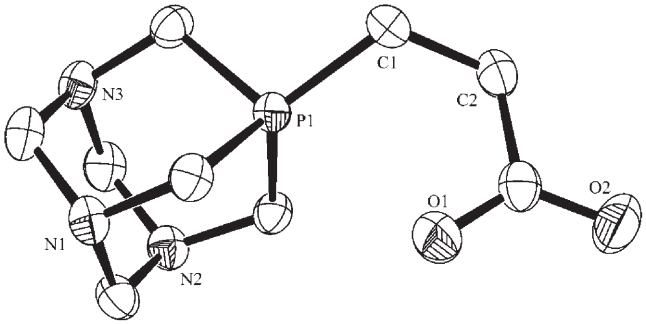


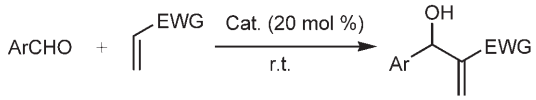
Figure 1. X-ray crystal structure of PTA-zwitterions.

vided by X-ray crystallography of a trapped intermediate from the DABCO-catalyzed MBH reaction of salicylaldehyde with methyl acrylate.[23] In this study, the reaction of PTA with ethyl acrylate in aqueous THF gave crystalline PTA-zwitterions, which was recrystallized from a mixture of THF-methanol to afford some single crystals suitable for X-ray crystallography (Figure 1).[24] The crystal structure of PTA-zwitterions does not only provide unambiguous evidence for the nucleophilic attack of PTA taking place at the phosphorus atom, it also verifies the Michael addition step in the catalytic cycle.

In Scheme 1 are listed several N,P catalysts, which are structurally in proximity to PTA. Among them, *N*-methylated PTA iodide[25a] (CH_3-PTA) and 3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane[25c] (acetyl-PTA) are both air-stable derivatives of PTA. The acyclic compounds tris(*N*,*N*-dimethylaminomethyl)phosphine[26] (TMP) and tris(carboxymethylaminomethyl)phosphine[27] (TCP) both incorporate a phosphorus atom by the same linkages of P–C–*N*–C as PTA. TCP is reportedly air-stable. In contrast, TMP could be considered the closest acyclic phosphine to PTA with regard to electron-effect, but it is extremely air-sensitive (***caution:*** spontaneous ignition!). Certainly, the air stability of trialkylphosphine is closely related to its specific structure. For the purpose of comparison with PTA, these four phosphines, together with PPh_3 and HMT, were surveyed for their catalytic activity in the MBH reaction with active aromatic aldehydes (Table 6 and Table 7).

As shown in Table 6, the weakly nucleophilic catalysts PPh_3 and HMT are both moderately effective in the selected reactions, but clearly less efficient than PTA (entries 1–3, 7–9, 13–15, 19–21). CH_3-PTA and acetyl-PTA were reported to be poorer nucleophiles than the parent PTA, although they could still be used as phosphine ligands in the transition metal complexes.[10] Consequently, both of the compounds are almost ineffective in the MBH reaction. Likewise, TCP does not show any catalytic activity in this study (Table 6).

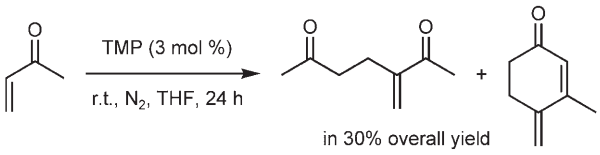
Table 6. Comparuison of activity for selected air-stable N,P catalysts in the MBH reaction.[a]



Entry	Ar	EWG	Catalyst	Time [h]	Yield[b] [%]
1	4-$NO_2C_6H_4$	CO_2Et	PTA	5	72
2	4-$NO_2C_6H_4$	CO_2Et	PPh_3	6	44
3	4-$NO_2C_6H_4$	CO_2Et	HMT	24	28
4	4-$NO_2C_6H_4$	CO_2Et	CH_3-PTA	72	NR
5	4-$NO_2C_6H_4$	CO_2Et	acetyl-PTA	72	trace
6	4-$NO_2C_6H_4$	CO_2Et	TCP	72	NR
7	4-$NO_2C_6H_4$	COMe	PTA	0.5	98
8	4-$NO_2C_6H_4$	COMe	PPh_3	5	55
9	4-$NO_2C_6H_4$	COMe	HMT	0.5	63
10	4-$NO_2C_6H_4$	COMe	CH_3-PTA	72	NR
11	4-$NO_2C_6H_4$	COMe	acetyl-PTA	72	55
12	4-$NO_2C_6H_4$	COMe	TCP	72	NR
13	2-pyridyl	CO_2Et	PTA	12	63
14	2-pyridyl	CO_2Et	PPh_3	24	trace
15	2-pyridyl	CO_2Et	HMT	24	5
16	2-pyridyl	CO_2Et	CH_3-PTA	24	NR
17	2-pyridyl	CO_2Et	acetyl-PTA	24	NR
18	2-pyridyl	CO_2Et	TCP	24	NR
19	2-pyridyl	COMe	PTA	15	73
20	2-pyridyl	COMe	PPh_3	15	70
21	2-pyridyl	COMe	HMT	15	6
22	2-pyridyl	COMe	CH_3-PTA	48	NR
23	2-pyridyl	COMe	acetyl-PTA	48	NR
24	2-pyridyl	COMe	TCP	48	NR

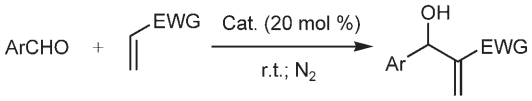
[a] Reaction conditions: aldehyde (1.0 mmol); for ethyl acrylate (2 mL), reaction run solvent-free; for MVK (3.0 mmol), reaction run in THF (2 mL).
[b] Isolated yield of the corresponding MBH adduct.

The air-sensitive phosphine TMP shows similar activity to PTA in the MBH reaction. Under the promotion of 20 mol% of TMP, various aromatic aldehydes readily give normal MBH adducts with the activated olefins ethyl acrylate and acrylonitrile in fair to good yields (Table 7). However, the TMP-mediated reaction of aromatic aldehyde with MVK is pretty complicated. No expected MBH product could be isolated from the reaction mixture in an appreciable amount, except that a dimer of MVK and its intramolecular aldol condensation product were obtained in about 30% overall yield [Eq. (5)]. In a similar fashion, ethyl



(5)

Table 7. $P(CH_2NMe_2)_3$-catalyzed MBH reaction of aromatic aldehydes.



Entry	Ar	EWG	Time [h]	Yield[a] [%]
1	2-$NO_2C_6H_4$	CO_2Et	12	84
2	3-$NO_2C_6H_4$	CO_2Et	4	60
3	4-$NO_2C_6H_4$	CO_2Et	12	80
4	2,4-$Cl_2C_6H_3$	CO_2Et	36	66
5	2-FC_6H_4	CO_2Et	12	65
6	3-FC_6H_4	CO_2Et	12	70
7	4-FC_6H_4	CO_2Et	12	61
8	C_6H_5	CO_2Et	24	50
9	4-$CH_3C_6H_4$	CO_2Et	24	36
10	2-pyridyl	CO_2Et	24	24
11	2-furyl	CO_2Et	24	36
12	2-$NO_2C_6H_4$	CN	12	29
13	3-$NO_2C_6H_4$	CN	12	20
14	4-$NO_2C_6H_4$	CN	12	15
15	2-pyridyl	CN	24	38

[a] Isolated yield based on aldehyde.

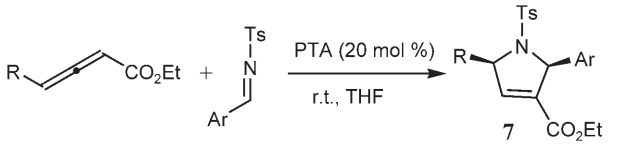
acrylate could undergo the same coupling under the mediation of TMP (2 mol%).

PTA-Catalyzed [3 + 2] Cycloaddition Reaction of 4-Substituted 2,3-Butadienoates with Imines

The nucleophilic phosphine-catalyzed [3+2] cycloaddition reactions of 2,3-butadienoates or 2-alkynoates with the dipolarophiles such as acrylates, acrylonitrile, and *N*-tosylimines, provide a powerful tool for the preparation of cyclopentene derivatives and pyrrolines.[6,17,28] For a reactive dipolar precursor like ethyl butadienoate, the weakly nucleophilic catalyst Ph_3P works well in some [3+2] cycloaddition reactions with various activated olefins.[6a] But in such cycloaddition reactions of less reactive substituted 2,3-butadienoates or 2-alkynoates, as well as in intramolecular cycloaddition reactions, a more nucleophilic catalyst, most likely PBu_3, is most often used.[6b,17,28] In principle, tertiary amines like triethylamine, DABCO, and DMAP are ineffective in the catalysis of the cycloadditions.[6]

As illustrated in the MBH reaction, the high efficiency of PTA as a nucleophilic catalyst intrigued us to explore its use in the above [3+2] cycloaddition reactions as an alternative for air-sensitive trialkylphosphine catalysts like PBu_3. Thus, the less reactive ethyl 4-substituted 2,3-butadienoates and aromatic *N*-tosylimines were selected as the substrates for the [3+2] cycloaddition reaction requiring a highly nucleophilic catalyst. Our results show that under the mediation of 20 mol% of PTA, all three 4-substituted 2,3-butadienoates (R = Me, Ph, *t*-Bu) readily undergo [3+2] cycloaddition reactions with a series of aromatic *N*-tosylimines. The normal cycloaddition products with the *cis* configuration, as verified by their ^1H and ^{13}C NMR spectra together with corroboration of the reported data,[17,28d] were exclusively obtained in good to excellent yields (Table 8). With regards to reaction time, selectivity and yield, PTA's efficiency in this catalysis is definitely comparable with that of PBu_3 as shown in the previous report by Kwon.[17] Thus, PTA should be a preferred catalyst in this type of cycloaddition reaction regarding its superior air stability over other trialkylphosphines.

Table 8. PTA-catalyzed [3+2] cycloaddition reaction of 4-substituted 2,3-butadienoates with imines.



Entry	R	Ar	Reaction Time [h]	Product[a]	Yield[b] [%]
1	Me	C_6H_5	25	**7a**	73
2	Me	4-$CH_3C_6H_4$	6	**7b**	96
3	Me	4-ClC_6H_4	1	**7c**	89
4	Me	2-ClC_6H_4	5	**7d**	90
5	Me	4-FC_6H_4	4	**7e**	90
6	Me	4-$CH_3OC_6H_4$	22	**7f**	84
7	Me	2-furyl	21	**7g**	75
8	Me	3-pyridyl	2	**7h**	86
9	Ph	4-FC_6H_4	4	**7i**	97
10	Ph	4-ClC_6H_4	2	**7j**	99
11	Ph	2-ClC_6H_4	2	**7k**	95
12	Ph	4-$CH_3OC_6H_4$	20	**7l**	65
13	*t*-Bu	4-ClC_6H_4	13	**7m**	89
14	*t*-Bu	2-ClC_6H_4	15	**7n**	57
15	*t*-Bu	4-FC_6H_4	6	**7o**	94
16	*t*-Bu	4-$CH_3OC_6H_4$	3	**7p**	99
17	*t*-Bu	2-furyl	4	**7q**	99
18	*t*-Bu	3-pyridyl	2	**7r**	70

[a] Identified by ^1H, ^{13}C NMR, and satisfactory microanalysis obtained for new compounds **7d**, 7**j**, 7**m**, 7**q** and 7**r**.
[b] Isolated yield based on the substrate imine.

Conclusions

In this work, we have demonstrated that the air-stable and readily available PTA is a practical and versatile nucleophilic phosphine catalyst for both MBH reac-

tion with a broad scope and [3+2] cycloaddition reaction of less reactive substituted allenoates. Its high efficiency in the catalysis is certainly attributable to its superior nucleophilicity originating from the phosphorus atom. As evidenced by the facts that the overall reactivity, including nucleophilicity, of PTA are comparable to those of pure but air-sensitive trialkylphosphines, and also, as proven in this study, that PTA is almost equally effective as the trialkylphosphine catalyst PBu_3 in the [3+2] cycloaddition reaction, it is safe to say that PTA could be used as a preferable alternative for air-sensitive trialkylphosphine in nucleophilic catalysis, which requires a strong nucleophilic catalyst. Since trialkylphosphines have received increasing interest in nucleophilic catalysis due to the enhanced activity over their triarylphosphine or trialkylamine counterparts, we anticipate that PTA will gain more popularity as a practical and versatile nucleophilic phosphine organocatalyst in the future.

Experimental Section

General Remarks

Unless otherwise noted, all catalytic reactions were carried out in the ambient atmosphere. Commercially available chemicals were used as received. PTA was prepared from tetrahydroxymethylphosphonium sulfate according to a previous procedure.[29] Other phosphorus catalysts were prepared as reported in the literature. 4-Substituted 2,3-butadienoates[30] and *N*-tosyl- and *N*-thiophosphinoylimines[31] were also prepared as described in the literature.

Nuclear magnetic resonance spectra (^1H, ^{13}C, and ^{31}P) were recorded on Bruker 300 MHz and Variant 400 MHz NMR spectrometers using TMS as internal standard (^1H, ^{13}C) and 85% phosphoric acid as external standard (^{31}P), with $CDCl_3$ as solvent, unless otherwise mentioned. Elemental analyses were performed on a Yanaco CHN Corder MT-3 automatic analyzer. ESI mass spectra were recorded with a ThermoFinnigan LCQ Advantage LC-MS. X-Ray crystal diffraction data were collected on a Nonius Kappa CCD diffractometer with Mo Kα radiation ($\lambda = 0.7107$ Å) at room temperature.

PTA-Catalyzed MBH Reaction of Aromatic Aldehydes with 2-Cyclopenten-1-one; General Procedure

A mixture of aromatic aldehyde (1.0 mmol), 2-cyclopenten-1-one (1.5 mmol), and PTA (0.15 mmol) in THF-H_2O (2 mL, 4:1, v/v) was stirred at room temperature for the time listed in Table 1. Then the volatile components were removed on a rotary evaporator, and the residue was mixed with dichloromethane (20 mL), 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**.

1e: viscous oil; ^1H NMR ($CDCl_3$): δ = 7.30–6.80 (m, 5H), 5.43 (s, 1H), 3.85 (br s, 1H), 2.50 (m, 2H), 2.33 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 209.3, 162.9 (d, J = 244.4 Hz), 159.7, 147.4, 144.2 (d, J = 7.0 Hz), 129.9 (d, J = 8.0 Hz), 121.9 (d, J = 3.3 Hz), 114.6 (d, J = 21.1 Hz), 113.2 (d, J = 22.0 Hz), 68.8, 35.1, 26.7; anal. calcd. for $C_{12}H_{11}FO_2$: C 69.89, H 5.38; found: C 69.70, H 5.45.

1f: viscous oil; ^1H NMR ($CDCl_3$): δ = 7.50 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 2.1 Hz, 1H), 7.21 (dd, J = 8.4, 2.1 Hz, 1H), 7.06 (m, 1H), 5.78 (s, 1H), 4.10 (br s, 1H), 2.51 (m, 2H), 2.38 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 209.6, 160.2, 145.3, 137.4, 133.8, 132.5, 129.0, 128.8, 127.4, 65.8, 35.1, 26.6; anal. calcd. for $C_{12}H_{10}Cl_2O_2$: C 56.06, H 3.92; found: C 55.89, H 4.05.

1g: viscous oil; ^1H NMR ($CDCl_3$): δ = 7.34–7.18 (m, 3H), 7.12 (dd, J = 9.9, 2.1 Hz, 1H), 5.67 (s, 1H), 4.15 (br s, 1H), 2.52 (m, 2H), 2.36 (m, 2H); ^{13}C NMR ($CDCl_3$): δ = 209.3, 159.8, 159.2 (d, J = 249.8 Hz), 145.6, 129.2 (d, J = 4.4 Hz), 127.8 (d, J = 13.5 Hz), 127.5 (d, J = 3.8 Hz), 121.6 (d, J = 9.7 Hz), 118.8 (d, J = 24.5 Hz), 63.4, 35.0, 26.6; anal. calcd. for $C_{12}H_{10}ClFO_2$: C 59.89, H 4.19; found: C 59.77, H 4.34.

PTA-Catalyzed MBH Reaction of Aromatic Aldehydes with Acrylamide; General Procedure

A mixture of aromatic aldehyde (1.0 mmol), acrylamide (3.0 mmol), and PTA (0.2 mmol) in anhydrous THF (2 mL) was stirred at room temperature for the time listed in Table 2. Then the reaction mixture was concentrated on a rotary evaporator, and the residue was taken up in ethyl acetate (25 mL) and washed with saturated brine (10 mL). The aqueous layer was extracted with dichloromethane (2× 10 mL). The extractings were combined with ethyl acetate layer, 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 3 : 1 as eluant) to afford pure product **3**.

3d: off-white solid, mp 117–119 °C; ^1H NMR (DMSO-d_6): δ = 8.87 (m, 1H), 7.45–7.20 (m, 4H), 6.52 (br s, 1H), 6.35–6.16 (m, 3H), 5.65 (m, 1H); ^{13}C NMR (DMSO-d_6): δ = 163.7, 162.2 (d, J = 223.3 Hz), 145.0, 131.5, 130.0 (d, J = 7.0 Hz), 126.1, 122.0, 114.2 (d, J = 16.0 Hz), 112.5 (d, J = 16.0 Hz), 72.2; anal. calcd. for $C_{10}H_{10}FNO_2$: C 61.53, H 5.16, N 7.16; found: C 61.35, H 5.24, N 7.01.

3e: ^1H NMR (DMSO-d_6): δ = 8.80 (m, 1H), 7.75–7.49 (m, 3H), 6.62 (br s, 1H), 6.49 (m, 1H), 6.18 (m, 2H), 5.64 (m, 1H); ^{13}C NMR (DMSO-d_6): δ = 163.7, 138.3, 133.0, 132.4, 131.3, 129.1, 128.5, 127.1, 126.2, 70.0; anal. calcd. for $C_{10}H_9Cl_2NO_2$: C 48.81, H 3.69, N 5.69; found: C 48.64, H 3.81, N 5.45.

3f: ^1H NMR (DMSO-d_6): δ = 8.88 (m, 1H), 7.60–7.46 (m, 3H), 6.59 (br s, 1H), 6.49 (m, 1H), 6.30–6.13 (m, 2H), 5.65 (m, 1H); ^{13}C NMR (DMSO-d_6): δ = 163.5, 161.9 (d, J = 241.6 Hz), 157.8, 131.3, 129.3, 127.2, 126.3, 121.1 (d, J = 9.7 Hz), 118.5 (d, J = 18.2 Hz), 67.6; anal. calcd. for $C_{10}H_9ClFNO_2$: C 52.30, H 3.95, N 6.10; found: C 52.12, H 4.05, N 5.97.

PTA-Catalyzed MBH Reaction of Aromatic Aldehydes with Acrolein; General Procedure

A mixture of aromatic aldehyde (1.0 mmol), acrolein (2.0 mmol), and PTA (0.2 mmol) in THF (2 mL) was stirred at room temperature for the time given in Table 3. Then the reaction mixture 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 **4**.

PTA-Catalyzed Aza-MBH Reaction of *N*-Tosylimines with Methyl Vinyl Ketone or Ethyl Acrylate; General Procedure

To a mixture of *N*-tosylimine (1.0 mmol) and PTA (0.2 mmol) in CH_2Cl_2 (2 mL, redistilled after refluxing with CaH_2) was added methyl vinyl ketone or ethyl acrylate (3.0 mmol) in one portion. The resulting mixture was stirred at room temperature for the time given in Table 4. Then the reaction mixture 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 products **5** and **6**.

$(Me_2NCH_2)_3P$-Catalyzed MBH Reaction of Aromatic Aldehydes with Acrylate or acrylonitrile; General Procedure

Under the nitrogen atmosphere, to a solution of aldehyde (1.0 mmol) in 2.0 mL of ethyl acrylate or acrylonitrile was added $(Me_2NCH_2)_3P$ (0.2 mmol), and the resulting mixture was stirred at room temperature for the specified time (Table 7). Then the volatile components were removed on a rotary evaporator, and the residue was taken up in ethyl acetate (25 mL), washed with saturated brine 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 6:1 as eluant) to afford pure MBH product.

PTA-Catalyzed [3 + 2] Cycloaddition Reaction of 4-Substituted 2,3-Butadienoates with Imines; General Procedure

To a mixture of *N*-tosylimine (1.0 mmol) and PTA (0.2 mmol) in THF (2 mL) was added 4-substituted 2,3-butadienoate (1.2 mmol). The resulting mixture was stirred at room temperature till the imine was completely consumed (monitored by TLC). Then the solvent was removed on a rotary evaporator, and the crude product was subjected to separation by silica gel column chromatography (petroleum ether - ethyl acetate, gradient elution), giving the corresponding cycloaddition product **7**.

7d: colorless crystalline solid; mp 118–122 °C; ^{1}H NMR ($CDCl_3$): δ = 7.74 (d, *J* = 8.4 Hz, 2H), 7.32–7.10 (m, 6H), 6.64 (br s, 1H), 6.15 (br s, 1H), 4.74 (m, 1H), 3.95 (m, 2H), 2.39 (s, 3H), 1.68 (d, *J* = 6.6 Hz, 3H), 1.04 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 161.6, 143.6, 141.0, 138.0, 134.5, 134.1, 133.7, 129.6, 129.3, 129.1, 128.7, 127.8, 126.9, 65.4, 62.9, 60.8, 22.7, 21.4, 13.7; anal. calcd. for $C_{21}H_{22}ClNO_4S$: C 60.06, H 5.28, N 3.34; found: C 60.26, H 5.25, N 3.35.

7j: colorless crystalline solid; mp 104–106 °C; ^{1}H NMR ($CDCl_3$): δ = 7.48–7.01 (m, 13H), 6.70 (br s, 1H), 6.29 (br s, 1H), 5.74 (m, 1H), 3.90 (m, 2H), 2.27 (s, 3H), 0.96 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR ($CDCl_3$): δ = 161.6, 143.6, 139.5, 138.6, 137.5, 134.3, 134.0, 129.4, 129.3, 128.9, 128.6, 128.1, 127.7, 127.3, 126.8, 69.7, 65.1, 60.9, 21.4, 13.6; ESI-MS: *m/z* = 482 and 484 (approximate ratio of isotopic peak intensities is 2:1), calcd. for $C_{26}H_{25}ClNO_4S$ $[M + 1]^+$: 482 and 484.

7m: colorless crystalline solid; mp 122–124 °C; ^{1}H NMR ($CDCl_3$): δ = 7.70 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.25 (m, 4H), 6.73 (d, *J* = 2.8 Hz, 1H), 5.81 (s, 1H), 4.33 (d, *J* = 2.8 Hz, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 2.38 (s, 3H), 1.13 (t, *J* = 7.2 Hz, 3H), 0.79 (s, 9H); ^{13}C NMR ($CDCl_3$): δ = 162.4, 144.0, 141.6, 138.3, 133.8, 133.7, 133.4, 129.6, 129.5, 128.1, 127.9, 77.8, 67.8, 60.9, 35.8, 27.8, 21.4, 13.9; anal. calcd. for $C_{24}H_{28}ClNO_4S$: C 62.39, H 6.11, N 3.03; found: C 62.21, H 6.29, N 2.94.

7q: colorless crystalline solid; mp 89–90 °C; ^{1}H NMR ($CDCl_3$): δ = 7.67 (d, *J* = 8.4 Hz, 2H), 7.25 (m, 3H), 6.73 (m, 1H), 6.26 (dd, *J* = 3.2, 1.6 Hz, 1H), 6.19 (d, *J* = 3.2 Hz, 1H), 5.81 (s, 1H), 4.44 (m, 1H), 4.04 (m, 2H), 2.36 (s, 3H), 1.11 (t, *J* = 7.2 Hz, 3H), 0.88 (s, 9H); ^{13}C NMR ($CDCl_3$): δ = 161.8, 152.0, 143.8, 141.6, 140.7, 134.5, 131.9, 129.5, 127.8, 110.4, 108.7, 77.0, 63.2, 60.6, 36.2, 27.3, 21.4, 13.8; anal. calcd. for $C_{22}H_{27}NO_5S$: C 63.29, H 6.52, N 3.35; found: C 63.15, H 6.47, N 3.36.

7r: colorless crystalline solid; mp 103–104 °C; ^{1}H NMR ($CDCl_3$): δ = 8.48 (m, 2H), 7.93 (m, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.25 (m, 3H), 6.75 (br s, 1H), 5.83 (s, 1H), 4.34 (m, 1H), 4.08 (q, *J* = 7.2 Hz, 2H), 2.38 (s, 3H), 1.12 (t, *J* = 7.2 Hz, 3H), 0.78 (s, 9H); ^{13}C NMR ($CDCl_3$): δ = 162.1, 148.8, 144.2, 142.0, 136.2, 135.6, 133.5, 133.0, 129.7, 127.9, 123.1, 77.9, 66.6, 61.0, 35.9, 27.8, 21.4, 13.9; anal. calcd. for $C_{23}H_{28}N_2O_4S$: C 64.46, H 6.58, N 6.54; found: C 64.37, H 6.38, N 6.35.

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[24] Selected crystal data for PTA-zwitterions (CCDC 634822): $C_9H_{20}N_3O_4P$ (including 2 molecules of water), $M = 265.25$, monoclinic, space group $P2_1/n$, $a = 10.025(2)$, $b = 10.187(2)$, $c = 12.842(2)$ Å, $\beta = 112.001(3)°$, $F(000) = 568$, $Z = 4$, $\rho_{cald} = 1.449\ g\,cm^{-3}$, $U = 1216.0(4)$ Å^3, $T = 294(2)$ K, λ(Mo-Kα) = 0.7107 Å, 6688 reflections collected in the range of $2.22 \leq \theta \leq 26.35°$, $R_{int} = 0.0295$. The structure was solved by different methods and refinement, based on F^2, was by full-matrix least-squares to $R1 = 0.0526$, $wR2 = 0.1056$. The supplementary crystallographic data for this compound can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data request/cif0.

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