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The Aza-Morita–Baylis–Hillman Reaction of *N*-Thiophosphoryl Imines Catalyzed by 1,3,5-Triaza-7-phosphaadamantane (PTA) — Convenient Synthesis of α-Methylene-β-Amino Ketone or Acid Derivatives

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In the presence of an effective air-stable nucleophilic trialkylphosphane orgaocatalyst, 1,3,5-triaza-7-phosphaadamantane, *N*-diethoxythiophosphorylimines **1** and *N*-diphenylthiophosphinoylimines **2** exhibited good reactivity in the methyl vinyl ketone or methyl acrylate based aza-Morita–Baylis–Hillman reaction. The corresponding products were obtained in fair-to-excellent chemical yields. Moreover, the chiral-imine-induced diastereoselective aza-MBH reaction was also realized with 90 % *de*. This reaction provides a convenient method for the synthesis of synthetically valuable α-methylene-β-amino ketone or acid derivatives.

Introduction

The Morita–Baylis–Hillman reaction (MBH) is an effective carbon–carbon bond forming reaction that gives densely multifunctional adducts under mild conditions.[1] Because of its enormous potential in organic synthesis, it has received much research interest.[2] As we know, most recent efforts on this reaction have been directed towards the following two aspects: the asymmetric MBH reaction catalyzed by chiral catalysts[3] and the aza-MBH reaction.[4,5] For the former, recent research has been focused on the search of efficient chiral catalysts to accelerate the reaction rates and promote efficiency (yields) and selectivity (*ee* values), and for the latter, major efforts have been focused on the scope of the reaction and search for practical catalysts[4] including chiral catalysts for the asymmetric version of the aza-MBH reaction.[5] In 1984, Perlmutter reported the first example of an aza-MBH reaction from *N*-tosyl imines and ethyl acrylate catalyzed by DABCO.[4a] However, this report did not attract much attention until the last decade of the 20th century; the situation was turned around and lots of new reports emerged.[4d–4p] For examples, Yamamoto first explored the aza-MBH reaction of *N*-methoxycarbonyl protected imines;[4b] Bertendshaw established a three-component version of the aza-MBH reaction from an activated olefin, an aldehyde, and an *N*-protected amine;[4c] Adolfsson used a Lewis base or a Lewis acid as a cocatalyst to the aza-MBH reaction;[4g,4h] and Shi made a significant contribution to this reaction by expanding the scope of substrates to include activated olefins[4f,4l,4n,4p] and by employing tertiary phosphanes[4i,4j,4m] as catalysts and *N*-diphenylphosphinoylimines[4i] as alternative imine substrates.

In the reported aza-MBH reactions, the tosyl and acyl groups are most often used as protecting groups for the imine moiety, probably because the protected imines have better reactivities. In contrast, *N*-phosphinoyl imine was rarely used owing to its troublesome preparation, poor stability, and low reactivity; however, the phosphinoyl group could be easily deprotected by acidic hydrolysis from the aza-MBH reaction adduct. Up to date, there is only one report concerning the aza-MBH reaction of *N*-phosphinoyl imines.[4i] The reported catalysts for aza-MBH reactions mainly include the conventional MBH reaction catalysts such as DABCO, triphenylphosphane, and DMAP.

Recently, we found that an easily prepared and air-stable trialkylphosphane 1,3,5-triaza-7-phosphaadamantane (PTA) was an efficient organocatalyst for the MBH reaction of a variety of substrates, including aromatic and aliphatic aldehydes, activated olefins acrylates, and methyl vinyl ketone (MVK).[6] Because PTA has comparable nucleophilicity to pure trialkylphosphane and because it is air-stable, it should be an alternative catalyst for important nucleophilic organocatalysis; for example it may serve as a catalyst in the aza-MBH reaction. Herein, we report the PTA-catalyzed aza-MBH reaction of *N*-thiophosphoryl or *N*-thiophosphinoyl imines. *N*-thiophosphoryl imines are chosen

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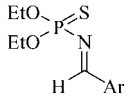
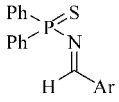
because of their ease of preparation and better stability relative to *N*-diphenylphosphinoyl imines. Also, by introducing different substituents at the phosphorus center could easily modulate its electronic properties. Therefore, this attempt provides a convenient and practical synthetic method for versatile α-methylene-β-amino ketone or acid derivatives.[4a,5a,5o,7]

Results and Discussion

N-Diethoxythiophosphorylimines **1** and *N*-diphenylthiophosphinoylimines **2** were synthesized in excellent yields through the thermal condensation of acetals and the corresponding thiophosphoramides.[8] With these imines in hand, their reactivity as electrophiles in the aza-MBH reaction was investigated.



1



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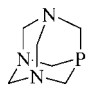


PTA

Firstly, rough comparison of the catalytic activity of PTA with the hitherto known catalysts, such as DABCO and Ph_3P, was performed by using the reaction of imine **1a** and MVK as a model (Table 1). The preliminary results shown in Table 1 revealed that PTA is to some extent a suitable catalyst in the present aza-MBH reaction. In addition, as we expected, these *N*-thiophosphoryl imines display good stability. No decomposition towards the carbonyl compound was observed under the reaction conditions.

Table 1. Different catalysts used in the aza-MBH reaction of imines **1a** and **2a** with MVK.[a]

Catalyst	Imine **1a**		Imine **2a**	
	Time [h]	Yield [%] [b]	Time [h]	Yield [%][b]
PTA	96	84	48	82
DABCO	96	78	68	59
Ph_3P	96	82	48	78

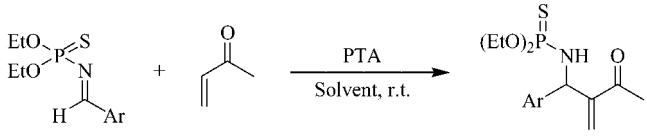
[a] All reactions were carried out in acetonitrile in the presence of 10 mol-% of catalyst with a 1:3 molar ratio of imine to activated MVK. [b] Isolated yield.

On the basis of these results, the aza-MBH reaction of *N*-thiophosphoryl imines **1** and **2** was thoroughly investigated by employing PTA as the nucleophilic catalyst. The aza-MBH reaction between *N*-thiophosphoryl imines **1** and MVK in the presence of PTA at room temperature led to promising results (Table 2).

The reaction of imine **1a** and MVK was chosen as a model. As shown in Table 2, the evaluation of the solvents revealed that the reaction performed best in acetonitrile with a catalyst loading of 10 mol-% (Table 2, Entry 1). Adjustment of the catalyst loading to 5 mol-% made the reaction very sluggish, as only 25% conversion of imine **1a** was achieved after stirring for 120 h (Table 2, Entry 6). An increase in the catalyst loading to 30 mol-% resulted in a dramatic rate acceleration with a slight increase in yield (Table 2, Entry 7). Under the optimal conditions (10 mol-% catalyst loading, acetonitrile), this reaction was then extended to *N*-thiophosphoryl imines **1b**–**g**. It was found that the reaction displayed a high substrate generality. The aza-MBH products were obtained in good yield no matter what kind of imine was used. In addition, the electronic nature of the imine had an obvious influence on the reaction. Relative to the imines containing electron-withdrawing groups (**1d**–**f**; Table 2, Entries 10–12), those imines bearing an electron-donating group on the benzene ring (**1b**–**c**; Table 2, Entries 8, 9) or derived from electron-enriched 2-furylaldehyde (**1g**; Table 2, Entry 13) exhibited much lower electrophilic activities in terms of yield and reaction time.

Similarly, solvent evaluation proved that acetonitrile was also the preferred solvent for the PTA-catalyzed aza-MBH

Table 2. The PTA-catalyzed aza-MBH reaction of imine **1** and MVK.

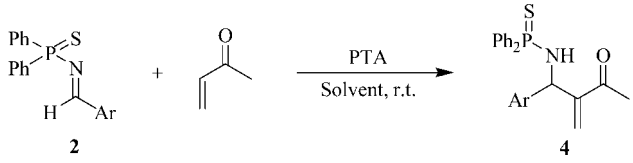


1 **3**

Entry	**1** or **3**	Ar	Solvent	PTA [mol-%]	Time [h]	Yield [%][a]
1	**a**	Ph	MeCN	10	96	84
2	**a**	Ph	CH_2Cl_2	10	96	63
3	**a**	Ph	$CHCl_3$	10	96	61
4	**a**	Ph	THF	10	96	77
5	**a**	Ph	MePh	10	96	76
6	**a**	Ph	MeCN	5	120	57(25)[b]
7	**a**	Ph	MeCN	30	5	86
8	**b**	4-MeC_6H_4	MeCN	10	108	67
9	**c**	3-$MeOC_6H_4$	MeCN	10	96	81
10	**d**	4-ClC_6H_4	MeCN	10	84	84
11	**e**	4-BrC_6H_4	MeCN	10	60	92
12	**f**	4-$O_2NC_6H_4$	MeCN	10	84	86
13	**g**	2-Furyl	MeCN	10	96	79

[a] Isolated yield. [b] Data in parentheses is the conversion of the imine substrate.

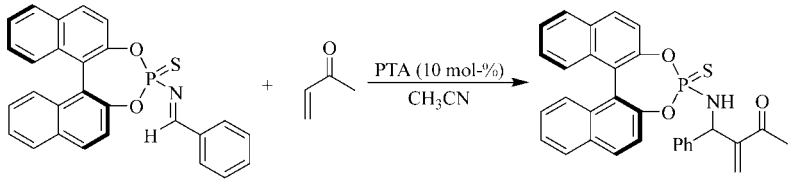
Table 3. The PTA-catalyzed aza-MBH reaction between imine **2** and MVK.



2 **4**

Entry	**2** or **4**	Ar	PTA [mol-%]	Time [h][a]	Yield [%][a,b]
1	**a**	Ph	10	60	82
2	**a**	Ph	5	120	73
3	**a**	Ph	20	36	85
4	**a**	Ph	30	4	88
5	**b**	4-MeC_6H_4	10	72(5)	52(89)
6	**c**	2-$MeOC_6H_4$	10	72(5)	56(87)
7	**d**	2-ClC_6H_4	10	60(4)	78(90)
8	**e**	3-$F_3CC_6H_4$	10	72(4)	85(94)
9	**f**	4-BrC_6H_4	10	72(4)	88(93)
10	**g**	3-FC_6H_4	10	60(6)	92(92)
11	**h**	4-$O_2NC_6H_4$	10	48(2)	57(97)
12	**i**	PhCH=CH	10	60(48)	33(88)

[a] Data in the parentheses were obtained for 30 mol-% catalyst loading. [b] Isolated yield.

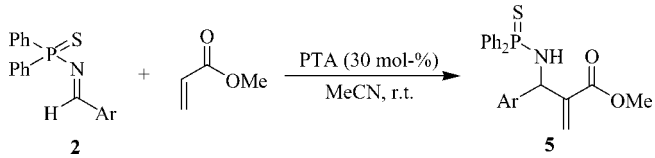


6 **7** 64 %, 95:5 *dr*

reaction between *N*-diphenylthiophosphinoylimines **2** and MVK. Unlike the reaction of imine **1**, the catalyst loading had a significant influence both on the reaction rate and the chemical yield. Generally, obvious rate accelerations and yield improvements were observed with increasing amounts of catalyst loadings. However, in most cases, satisfactory results were also obtained in the presence of 10 mol-% of catalyst at the expense of prolonged reaction times. In all cases, the MBH reactions proceeded readily to give the normal adducts in fair-to-excellent yields within acceptable reaction times in the presence of 10–30 mol-% PTA. The nature of the imine substrate was found to be an essential factor to the reaction in the presence of 10 mol-% of catalyst. For example, satisfactory results were obtained for those imines with an electron-withdrawing group on the benzene ring (Table 3, Entries 7–10; 78–92%). The nitro-substituted imine is an exception. The reaction was quite complicated because of its high reactivity (Table 3, Entry 11; 57%). Only moderate yields were obtained for less reactive imines derived from aromatic aldehydes bearing an electron-donating group (Table 3, Entries 5 and 6; 52 and 56%, respectively). The reaction was very sluggish for the imine derived from aliphatic cinnamic aldehyde (Table 3, Entry 12; 33%). Nevertheless, the reaction ran smoothly in the presence of 30 mol-% catalyst (Table 3, Entry 12; 88%, data in parentheses).

To demonstrate the versatility of these *N*-thiophosphoryl imines, their aza-MBH reactions with the less reactive activated alkene methyl acrylate (MA) was also carried out under identical conditions. The coupling of *N*-diphenylphosphinoylimines **2** with MA afforded satisfactory results. The corresponding adducts **5** were obtained in moderate yields with a PTA loading of 30 mol-% (Table 4). Under the same conditions, no reaction was observed for imines **1**. This can probably be ascribed to the difference in the electrophilicities of the two types of electrophiles in this reaction.

Table 4. The PTA-catalyzed aza-MBH reaction between imine **2** and MA.



2 **5**

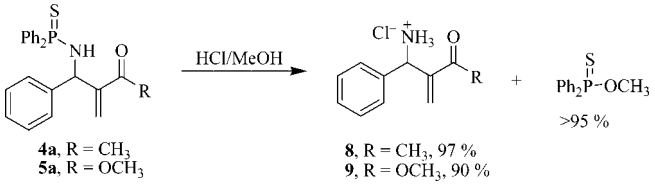
Entry	Adduct **5**	Ar	Time [h]	Yield [%][a]
1	**a**	Ph	72	66
2	**c**	2-ClC_6H_4	84	57
3	**c**	3-FC_6H_4	72	60
4	**d**	3-$F_3CC_6H_4$	60	63
5	**e**	4-BrC_6H_4	60	72

[a] Isolated yield.

Moreover, under the otherwise same conditions, the diastereoselective aza-MBH reaction of chiral thiophosphoryl-imine **6** derived from (*S*)-1,1′-binaphthyl-2,2′-diol and

MVK was realized with 90% *de* (determined by ^{31}P and ^{1}H NMR spectroscopic analysis, see Supporting Information).

Finally, to exemplify that the above-mentioned methodology is a convenient and practical method for the synthesis of synthetically valuable α-methylene-β-amino ketone or acid derivatives, adducts **4a** and **5a** were readily converted to α-methylene-β-amino ketone hydrochloride **8** and acid ester hydrochloride **9**, respectively, in excellent yields upon acidic methanolysis with 3.75 M HCl/MeOH at room temperature within several hours. In addition, the byproduct *O*-methyl diphenylphosphinothioate can be conveniently transformed into diphenylphosphinothioic chloride through basic hydrolysis and chlorination in excellent yield according to the literature,[9,10] and it can be reused in the preparation of the starting diphenylphosphinothioic amide.



4a, R = CH_3
5a, R = OCH_3

8, R = CH_3, 97 %
9, R = OCH_3, 90 %

Conclusions

We developed a novel *N*-thiophosphoryl imine based aza-MBH reaction. The corresponding aza-MBH adducts were obtained in fair-to-excellent yields in the presence of an efficient air-stable nucleophilic trialkylphosphane orgaocatalyst – PTA. On the basis of these results, the chiral-imine-induced diastereoselective aza-MBH reaction was realized with good diastereoselectivity (90% *de*). Because the *N*-thiophosphoryl moiety can be readily deprotected through acidic methanolysis in excellent yields, this protocol provides a convenient method for the synthesis of synthetically valuable α-methylene-β-amino ketone or acid derivatives.

Supporting Information (see footnote on the first page of this article)**:** Experimental details and characteristic data of aza-MBH adducts **3a**–**h**, **4a**–**g**, and **5** and the corresponding α-methylene-β-amino ketone hydrochloride **8** and acid ester hydrochloride **9**.

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