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## **PS-BEMP** as a Basic Catalyst for the Phospha-Michael Addition to Electron-poor Alkenes

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PS-BEMP was used as a heterogeneous catalyst for the phospha-Michael addition of phosphorus nucleophiles to a variety of electron-poor alkenes. The addition reactions were generally performed with equimolar amounts of reagents in solvent free conditions. The protocol proved to be very efficient for the addition to aromatic, non-aromatic and cyclic ketones, giving in all cases good yields (78-85%). The protocol was also extended with good results to  $\alpha$ , $\beta$ -unsaturated esters and nitriles. This demonstrates that PS-BEMP is a good catalyst for the phospha-Michael addition to electron-poor alkenes.

#### Introduction

Organophosphorus compounds are particularly important for their applications in agriculture, where they are mainly used as herbicides.1 insecticides and In organic chemistry organophosphorus compounds are widely used as intermediates is synthesis and as ligands in transition metal catalysed reactions.<sup>2</sup> For these reasons, the development of new efficient protocols for the formation of carbon-phosphorus bond is of significant interest. A particularly attractive strategy is represented by the conjugate addition of a phosphorus nucleophile to an electron-deficient species, namely the phospha-Michael addition.<sup>3</sup> The interest for such a process is also justified by its high atom economy which classifies it as a potentially valuable tool for achieving a sustainable access to target molecules containing P-C carbon bonds. The typical substrates for phospha-Michael additions are  $\alpha,\beta$ -unsaturated esters,<sup>4</sup> malonates,<sup>4a,5</sup> nitroalkenes<sup>6</sup> and ketones.<sup>4a,7</sup> This reaction has been promoted by Lewis acids,<sup>4c,5d-e,6b,7a-c,</sup> transition metals,<sup>8</sup> microwaves<sup>9,4a</sup> and bases.<sup>10,5a-c,6a,7e-f,7h</sup>

Regarding the phospha-Michael addition to  $\alpha$ , $\beta$ -unsaturated ketones, this process remains challenging in terms of substrate scope and product selectivity. In fact, a strong limit for the efficiency of this reaction is represented by the need for a large amount of a strong base to sufficiently activate the poor P-nucleophiles.

For this class of substrates a base is generally required<sup>7e-f,7h</sup> but, to the best of our knowledge, there is no report on the use of a heterogeneous base in such a process.<sup>11</sup> Heterogeneous catalysis is of obvious interest in chemistry and industry because it offers many advantages such as simplicity in handling, more environmentally safe disposal and easier work-up compared to the related homogeneous processes.<sup>12</sup>

In recent years our research group has focused on the use of heterogeneous bases, particularly phosphazene bases, as catalysts.<sup>13</sup> In fact, 2-tert-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine supported on

polystyrene (PS-BEMP) has been extensively used for several base-catalyzed reactions such as the conjugative addition of C-S- and N- nucleophiles,<sup>14</sup> the hydrophosphonylation of aldehydes<sup>15</sup> and the phenolysis of epoxides.<sup>16</sup>

Based on our previous experiences, in this contribution we report the use of PS-BEMP to promote the phospha-Michael addition to a variety of  $\alpha,\beta$ -unsaturated ketones 1 under solvent free conditions (SoIFC). Moreover, preliminary results about the applicability of this procedure to  $\alpha,\beta$ -unsaturated esters 10 and nitriles 11 are also reported.

#### **Results and discussion**

Initially, we compared the efficiency of different types of heterogeneous bases as catalysts for a representative reaction, namely the addition of diethyl phosphite (2) to (E)-4-phenylbut-3-en-2-one (1a) (see Table 1 for results and Scheme 1 for the structures of the bases used in this study).



Scheme 1 Supported bases used in the present study.

All the reactions were performed under SolFC since, as experienced in other cases by our research group,  $^{\rm 14-16}$  the

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addition of a solvent completely hampered the reactivity, resulting in the complete recovery of reactants. The combination of a heterogeneous catalyst and SolFC are therefore crucial for such kind of transformation to reach the needed reactivity. Indeed, immobilized catalysts are generally affected by a moderate reactivity compared to their homogeneous counterpart, and this drawback can often be overcome by performing the reaction without solvent.<sup>14-16</sup>

For the solid bases used in this study, the polymeric support used was a 200-400 mesh polystyrene in all the cases copolymerized with 2% of divinylbenzene (cross-linker), except in the case of JJ-TBD where a (1,4-bis(vinylphenoxy)-butaneis used as cross-linker).

First we tested few polystyrene immobilized bases, such as 4-(dimethylamino)pyridine (PS-DMAP), dimethylamine (PS-DMA) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PS-TBD) (Scheme 1). Performing the reactions at 30 °C with 5 mol% of catalyst for 24 hours resulted in no conversion for all the three bases (Table 1, entry 2-4) with complete recovery of reactants 1a and 2.

We also tested the influence of the support by performing the reaction with 1,5,7-triazabicyclo[4.4.0]dec-5-ene immobilized on JandaJel (JJ) resin.<sup>17</sup> This considerably improved the reactivity,<sup>13c</sup> resulting in a 78% conversion, but with the exclusive formation of product **3'a** coming from the nucleophilic attack at the carbonyl (Table 1, entry 5). Using polystyrene supported 1,8-diazabicyclo[5.4.0]undec-7-ene (PS-DBU), a 77% conversion was observed but still with the exclusive formation of the 1,2-addition product **3'a** (Table 1, entry 6). Very similar results were obtained using PS-BEMP (Table 1, entry 7).

**Table 1** Catalyst screening and reaction conditions optimization for the phospha-Michael reaction between (E)-4-phenylbut-3-en-2-one (**1a**) and diethyl phosphite (**2**).

$\bigcirc$	0	O + EtO-P-C H	EtO. DEt Cat. SolFC	O POEt +	Eto POEt
1a		2		3a	3'a
Entry <sup>a</sup>	T (°C)	t (h)	Cat. (mol%)	Conversion $(\%)^b$	1,4:1,2 $(3a:3'a)^b$
1	30	24	-	0	/
2	30	24	PS-DMAP (5)	0	/
3	30	24	PS-DMA (5)	0	/
4	30	24	PS-TBD (5)	0	/
5	30	24	$JJ-TBD^{c}(5)$	78	0:>99
6	30	24	$PS-DBU^{d}(5)$	77	0:>99
7	30	24	$PS-BEMP^{e}(5)$	76	0:>99
8	30	48	$PS-BEMP^{e}(5)$	76	20:80
9	60	24	$PS-BEMP^e$ (10)	80	60:40
10	60	24	$PS-BEMP^{e}(20)$	100	>99:0
$11^{f}$	60	24	$PS-BEMP^{e}$ (10)	83	70:30
12	80	24	$PS-BEMP^e$ (10)	87	>99:0

<sup>*a*</sup> 1 eq. of **2** was used. <sup>*b*</sup> Conversion of **1a** to **3** determined by GLC analyses, the remaining material was unreacted **1** and **2** mixture. GC-MS as well as NMR analyses, were used in the assignments of the peaks to the proper products. <sup>*c*</sup> Loading: 0.85 mmol/g. <sup>*d*</sup> Loading: 0.91 mmol/g. <sup>*e*</sup> Loading: 2.13 mmol/g. <sup>*f*</sup> 1.2 eq. of **2** were used.

The results with these last three resins (JJ-TBD, PS-DBU and PS-BEMP) were almost identical and we decided for practical reasons to continue the optimization using PS-BEMP. In fact, JJ-TBD and PS-DBU feature low loadings of the supported bases (0.85 mmol/g and 0.91 mmol/g, respectively), which results in the need of performing the reaction using a relatively large mass of resin, with consequent problems for the stirring in SolFC. The higher loading of PS-BEMP (2.13 mmol/g), on the other hand, allows the use of a smaller mass of solid catalyst with positive effects on the manageability of the reaction.

In an attempt to increase the conversion, we ran the reaction with PS-BEMP for longer time (48 h, Table 1, entry 8). While the conversion remained unchanged, we observed the formation of 20% of the desired product **3a**. This can be explained with the higher thermodynamic stability of product **3a** compared to **3'a**, with the formation of the latter being faster (kinetic product).<sup>7j</sup> Therefore, we decided to increase the temperature to 60 °C and the catalyst loading to 10 mol%, obtaining 80% conversion and a 60:40 mixture of **3a**:**3'a** after 24 h (Table 1, entry 9). Increasing the catalyst loading to 20 mol% lead to complete conversion with full selectivity towards the Michael product **3a** (Table 1, entry 10). Attempts to reduce the catalyst loading to 10 mol% while increasing either the amount of phosphite **2** or the temperature did not lead to satisfactory results (Table 1, entries 11 and 12).

**Table 2** Screening of different phosphorus nucleophiles using 1a

 as electrophile and PS-BEMP as catalyst.

$\bigcirc$	O + R-P-R H	PS-BEMP (20 mol%) SolFC	F		R HR P OH
1a	<b>4-6</b> 1 equiv.	4,7 R = OM 5,8 R = OP 6,9 R = Ph	e n	7a-9a	7'a-9'a
Entry	Nucleophile	T (°C)	t (h)	Conv. $(\%)^a$	1,4:1,2 <sup><i>a</i></sup>
1	4	60	24	70	>99:0
2	4	80	24	100	>99:0
3	5	60	24	37	70:30
4	5	60	72	45	70:30
5	5	100	24	45	70:30
6	5	130	48	55	>99:0
7	6	80	72	45	>99:0

<sup>*a*</sup> Conversion of **1a** to **3** determined by GLC analyses, the remaining material was unreacted **1** and **2** mixture.

Having identified the best reaction conditions, we explored the possibility of extending the protocol to other phosphorus nucleophiles, using  $\alpha,\beta$ -unsaturated ketone **1a** as the electrophile (Table 2). Dimethyl phosphite (**4**) showed good reactivity. Indeed, in the optimized reaction conditions (1 eq. of nucleophile, 20 mol% of PS-BEMP at 60 °C), we observed the selective formation of product **7a** with a 70% conversion (Table 2, entry 1). Increasing the temperature to 80 °C allowed to obtain full conversion while retaining complete selectivity

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(Table 2, entry 2). Diphenyl phosphite (5) showed lower reactivity, with a 37% conversion in the optimized reaction conditions. Moreover, the product was obtained as a mixture with a 70:30 ratio between the 1,4- and 1,2-addition products (Table 2, entry 3). Increasing the reaction time (Table 2, entry 4) or the temperature (Table 2, entry 5) did not lead to significant improvements. Prolonged reaction time at 130 °C (Table 2, entry 6) only led to 55% conversion, but with complete selectivity towards product **8a**. Diphenyl phosphine oxide (6) gave unsatisfactory results, with a 45% conversion of **1a** to **9a** after 72 h at 80 °C (Table 2, entry 7).

Next, we explored the scope of the reaction using nucleophiles **2** and **4** and a variety of  $\alpha$ ,  $\beta$ -unsaturated ketones (1a-g, Table 3). Very satisfactory results were obtained in the reaction of 2with aromatic substrates such as 1a (Table 3, entry 1), and several types of chalcones, such as (E)-chalcone (1b), (E)-3-(4chlorophenyl)-1-phenylprop-2-en-1-one (1c) and (E)-3-(4methoxyphenyl)-1-phenylprop-2-en-1-one (1d), with yields always ranging between 78 and 82%, regardless of the substituents present on the substrates (Table 3, entries 2-4). The representative reaction of 1a with 2 was also performed on a larger scale giving almost identical results with the smaller scale (Table 3, footnote b). Good results were also obtained non-aromatic compounds with such as (E)-1-(2,6,6trimethylcyclohex-1-en-1-yl)but-2-en-1-one (1e) and its isomer (E)-1-(2,6,6-trimethylcyclohex-2-en-1-yl)but-2-en-1-one (1f), obtaining 80% and 82% yields, respectively (Table 2, entries 5 and 6). Similar results were obtained using 4 as nucleophile, obtaining yield between 82% and 85% (Table 3, entries 7-11). It is worth noting that in our reaction conditions products 3f and 7f were obtained without noticeable formation of the related isomerization products 3e and 7e. Finally, also a cyclic enone such as cyclohex-2-enone (1g) in the reaction with phosphite 4 furnished the corresponding product in 80% yield (Table 3, entry 12). All the compounds 3a-f and 7a-g have been fully characterized and copies of the <sup>1</sup>H, <sup>13</sup>C and <sup>31</sup>P NMR spectra are reported as supplementary materials.

These results confirmed that PS-BEMP can be considered as an efficient heterogeneous catalyst for the phospha-Michael addition to different kinds of  $\alpha$ , $\beta$ -unsaturated ketones.

<b>Table 3</b> Substrate scope of the phospha-Michael addition between phosphorus nucleophiles <b>2</b> and <b>4</b> and $\alpha$ , $\beta$ -unsaturated ketones <b>1a-g</b> .				
R	$R^{1} + R^{2} - P^{-} - R^{2}$	PS-BEMP (20 mol%) SoIFC	R <sup>2</sup>	$P^{0}$ $R^{2}$ $R^{2}$ $R^{2}$ $R^{1}$
1a-g	<b>2</b> , R <sup>2</sup> = OEt <b>4</b> , R <sup>2</sup> = OMe		3a	-f or <b>7a-g</b>
Entry	Product	T (°C)	t (h)	Yield $(\%)^a$
1	EtO, OEt PO 3a	60	24	$80^b$

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<sup>*a*</sup> Isolated yields of the pure product; reactions performed using equimolar amounts of reactants. <sup>*b*</sup> Reaction performed on a 5 mmol scale gave 79% yield.

Next, we tested whether this methodology is also applicable to other electron-poor alkenes, such as  $\alpha,\beta$ -unsaturated esters and nitriles (Table 4), using ethyl (2) and methyl phosphite (4) as phosphorus nucleophiles. Methyl acrylate **10a** showed good

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reactivity, affording the expected 1,4-addition products with methyl (4) and ethyl phosphite (2) in 85% and 79% yield, respectively (Table 4, entries 1 and 2). Methyl crotonate (10b) gave less satisfactory results, affording the addition products in 34% and 52% yield when reacting with phosphite 4 and 2, respectively (Table 4, entries 3 and 4).  $\alpha$ , $\beta$ -Unsaturated nitriles such as acrylonitrile (11a) and cinnamonitrile (11b) gave excellent results with both nucleophilic phosphites, with yields ranging from 76% to 90% (Table 4, entries 5-8).

**Table 4** Substrate scope of the phospha-Michael addition between phosphorus nucleophiles **2** and **4** and  $\alpha$ , $\beta$ -unsaturated esters (**10**) or nitriles (**11**).

R	, R <sup>1</sup> +	$egin{array}{c} 0 \\ R^2 - P - R^2 \\ H \\ H \end{array}$	PS-BEMP (20 mol%) SolFC 80 °C, 24h	*	$R^{2} \bigvee_{P}^{O} R^{2}$ $R^{2} \bigvee_{R}^{R^{1}}$
<b>10</b> , R <sup>1</sup> = CO <sub>2</sub> Me <b>11</b> , R <sup>1</sup> = CN		<b>2</b> , R <sup>2</sup> = OEt <b>4</b> , R <sup>2</sup> = OMe			<b>12</b> , $R^1 = CO_2Me$ <b>13</b> , $R^1 = CN$
Entry	Substrate	R	$\mathbb{R}^1$	$\mathbb{R}^2$	Yield $(\%)^a$
1	10a	Н	CO <sub>2</sub> Me	MeO	85 ( <b>12a</b> )
2	10a	Н	$CO_2Me$	EtO	79 ( <b>12b</b> )
3	10b	Me	$CO_2Me$	MeO	34 ( <b>12c</b> )
4	10b	Me	$CO_2Me$	EtO	52 ( <b>12d</b> )
5	11a	Н	CN	MeO	90 ( <b>13a</b> )
6	11a	Н	CN	EtO	89 ( <b>13b</b> )
7	11b	Ph	CN	MeO	76 ( <b>13c</b> )
8	11b	Ph	CN	EtO	86 ( <b>13d</b> )

<sup>*a*</sup> Isolated yields of the pure product; reactions performed using 2 equivalents of electrophile relative to the phosphite.

These preliminary results show that PS-BEMP can also efficiently catalyze the conjugate addition of phosphites to other Michael acceptors other than  $\alpha$ , $\beta$ -unsaturated ketones, such as  $\alpha$ , $\beta$ -unsaturated esters and nitriles.

We should point out, as a possible limitation of our methodology, that all our attempts to date to reuse the recovered catalyst in consecutive reaction runs failed.

#### Conclusions

In conclusion, we reported a simple protocol for the synthesis of different types of diethyl and dimethyl phosphonates under solvent free conditions. Generally equimolar amounts of reactants were used, with 10-20 mol% of PS-BEMP as a heterogeneous basic catalyst. To the best of our knowledge this is the first report on the use of a supported base for catalysing the phospha-Michael reaction on  $\alpha$ , $\beta$ -unsaturated ketones. We obtained in all cases good yields (78-85%) using two phosphorus nucleophiles such as diethyl phosphite (**2**) and dimethyl phosphite (**4**) and a wide array of aromatic and non-aromatic  $\alpha$ , $\beta$ -unsaturated ketones as electrophiles. Moreover, we demonstrated that the methodology is also applicable to other electron-poor alkenes, such as  $\alpha$ , $\beta$ -unsaturated esters and nitriles.

#### Experimental

Compounds 3a,<sup>7j</sup> 3b-d,<sup>7b</sup> 7a,<sup>18</sup> 7b,<sup>7d</sup> 7e,<sup>7h</sup> 7g,<sup>7i</sup> 12a,<sup>19</sup> 12b,<sup>4b</sup> 12c,<sup>20</sup> 12d,<sup>20</sup> 13a,<sup>21</sup> and 13b<sup>7j</sup> are known, while compounds 3e-f, 7d, 7f, 13c and 13d are new. Characterization data and copies of the <sup>1</sup>H, <sup>13</sup>C and <sup>31</sup>P NMR spectra for all compounds 3a-f, 7a-g, 12a-d and 13a-d are presented in the ESI.

# Typical experimental procedure for phospha-Michael addition to $\alpha$ , $\beta$ -unsaturated ketones.

In a screw capped vial equipped with a magnetic stirrer PS-BEMP (43 mg, 0.1 mmol, 2.13 mmol/g), (E)-4-phenylbut-3-en-2-one (1a) (75 mg, 0.5 mmol), and diethyl phosphite (2) (70 mg, 0.065 mL, 0.5 mmol) were consecutively added and the resulting mixture was left under stirring at 60 °C. After 24 hours EtOAc (1 mL) was added and the catalyst was filtered off and the solvent was removed under vacuum. The obtained oil was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 95/5). **3a** was obtained as an oil (114 mg, 80% yield).

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#### Notes and references

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<sup>†</sup> Electronic Supplementary Information (ESI) available: Characterization data and copies of the <sup>1</sup>H, <sup>13</sup>C and <sup>31</sup>P NMR spectra for compounds **3a-f**, **7a-g**, **12a-d** and **13a-d** are reported in ESI. See DOI: 10.1039/b000000x/

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