P-BEMP: A New Efficient and Commercially Available User-Friendly and Recyclable Heterogeneous Organocatalyst for the Michael Addition of 1,3-Dicarbonyl Compounds

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Abstract: Michael addition of 1,3-dicarbonyls with various Michael acceptors has been found to be catalyzed by commercially available, user-friendly and recyclable N-phenyl-tris(dimethylamino)iminophosphorane immobilized on polystyrene resin (P-BEMP). The reaction does not require anhydrous solvents or inert atmosphere and proceeds smoothly at room temperature leading to the corresponding adducts, which can be conveniently isolated in high yield and with high chemical purity by simple filtration.

Key words: 1,3-dicarbonyls, heterogeneous catalysis, Michael addition, polymer supported iminophosphoranes

The homogeneous base-promoted Michael addition is well-recognized as one of the more important carbon–carbon bond forming reactions leading to functionalized adducts of high synthetic value. Although it can be performed with high level of stereo- and enantioselectivity, utilization of basic medium sometimes suffers from several disadvantages. Reactions are often limited by the occurrence of side transformations such as saponification, autocondensation, Knoevenagel condensation, subsequent evolution of Michael adducts by aldolization, and eventually decomposition of sensitive acceptors such as a,b-unsaturated aldehydes. Moreover, isolation of the products usually results from time-consuming and tedious extractive workup. Although utilization of a catalytic amount of base can be a partial solution in some cases, special attention has been given to the use of Lewis acid catalysts, nonionic bases, either in conventional solvents or in water, and other organocatalytic systems. Alternatively, much effort has been devoted to solvent-free conditions or utilization of inorganic or hybrid heterogeneous catalytic systems. More recently, the immobilization of molecular catalysts has emerged as a new user-friendly alternative combining low cost and toxicity, with the control of the production of toxic waste and by-products which constitutes nowadays a challenging problem from industrial, academic and social point of view. Two recent examples concern the utilization of polystyrene-poly(ethylene glycol) supported quaternary ammonium hydroxides which have been used as efficient catalysts for the Michael addition of cyclic β-keto esters with unsaturated ketones and esters and also the conjugate addition of unmodified aldehydes combining a secondary amine grafted on silica with an ionic liquid.

Although strongly basic iminophosphoranes have emerged as powerful reagents in synthetic organic chemistry, little attention has been given to Michael additions, and more surprisingly to the best of our knowledge, the commercially available polystyrene supported P₁ iminophosphorane P-BEMP (Figure 1) has not been used in such transformation to date.

In this paper we wish to report on the heterogeneous catalytic activity of the commercially available P-BEMP towards Michael addition of acyclic- and cyclic-1,3-dicarbonyl compounds with various acceptors including highly base-sensitive a,b-unsaturated aldehydes, leading to synthetically valuable adducts (Scheme 1).

The transformation proved to be general and although unoptimized, gave reproducible results under standard conditions, which do not require dry solvents or inert atmosphere (Table 1). The desired Michael adducts were obtained in good to excellent yields, and conveniently isolated after a simple filtration to remove the catalyst. Moreover, they were substantially free of impurities as shown by TLC, ¹H, and ¹³C NMR analyses.

As expected, acrolein and methyl vinyl ketone gave very good results (entries 1–6) either with cyclic and acyclic β-keto esters or 1,3-diketones. Moreover, no further evolution of the adducts, either by intramolecular aldolization or Robinson annulation, was detected in the crude reac-
**Table 1**  Michael Reaction of 1,3-Dicarbonyl Catalyzed by P-BEMP

<table>
<thead>
<tr>
<th>Entry</th>
<th>1,3-Dicarbonyl</th>
<th>Acceptor</th>
<th>Conditions$^a$</th>
<th>Adduct</th>
<th>Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td>THF, 24 h</td>
<td><img src="image3.png" alt="Image" /></td>
<td>78$^{26}$</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td>THF, 8 h</td>
<td><img src="image6.png" alt="Image" /></td>
<td>$&gt;$98$^{26}$</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td>THF, 24 h</td>
<td><img src="image9.png" alt="Image" /></td>
<td>87$^{27}$</td>
</tr>
<tr>
<td>4</td>
<td><img src="image10.png" alt="Image" /></td>
<td><img src="image11.png" alt="Image" /></td>
<td>THF, 23 h</td>
<td><img src="image12.png" alt="Image" /></td>
<td>$&gt;$98$^{28}$</td>
</tr>
<tr>
<td>5</td>
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<td><img src="image14.png" alt="Image" /></td>
<td>THF, 4 h</td>
<td><img src="image15.png" alt="Image" /></td>
<td>$&gt;$98$^{29}$</td>
</tr>
<tr>
<td>6</td>
<td><img src="image16.png" alt="Image" /></td>
<td><img src="image17.png" alt="Image" /></td>
<td>THF, 4 h</td>
<td><img src="image18.png" alt="Image" /></td>
<td>$&gt;$98$^{29}$</td>
</tr>
<tr>
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<td><img src="image20.png" alt="Image" /></td>
<td>THF, 72 h$^c$</td>
<td><img src="image21.png" alt="Image" /></td>
<td>77$^d$</td>
</tr>
<tr>
<td>8</td>
<td><img src="image22.png" alt="Image" /></td>
<td><img src="image23.png" alt="Image" /></td>
<td>THF, 3 h</td>
<td><img src="image24.png" alt="Image" /></td>
<td>$&gt;$98</td>
</tr>
<tr>
<td>9</td>
<td><img src="image25.png" alt="Image" /></td>
<td><img src="image26.png" alt="Image" /></td>
<td>THF, 24 h</td>
<td><img src="image27.png" alt="Image" /></td>
<td>46$^{e,f}$</td>
</tr>
<tr>
<td>10</td>
<td><img src="image28.png" alt="Image" /></td>
<td><img src="image29.png" alt="Image" /></td>
<td>MeOH, 12 h</td>
<td><img src="image30.png" alt="Image" /></td>
<td>78</td>
</tr>
<tr>
<td>11</td>
<td><img src="image31.png" alt="Image" /></td>
<td><img src="image32.png" alt="Image" /></td>
<td>THF, 48 h</td>
<td><img src="image33.png" alt="Image" /></td>
<td>42$^{e,f}$</td>
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<tr>
<td>12</td>
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<td><img src="image35.png" alt="Image" /></td>
<td>EtOH, 22 h</td>
<td><img src="image36.png" alt="Image" /></td>
<td>75$^{d,e,f}$</td>
</tr>
</tbody>
</table>

$^a$ All reactions were performed at r.t. with 5 mol% of P-BEMP.

$^b$ Isolated.

$^c$ Using a rotatory stirring, see experimental.

$^d$ Isolated yield after purification on silica gel.

$^e$ 1:1 diastereomeric mixture.

$^f$ Unreacted starting β-keto ester was recovered.
The expected adducts were obtained in high yields (entries 7,8). In these cases, we found no trace of the corresponding Michael adduct in the crude reaction mixture when performed in THF without catalyst even after 72 hours, which clearly established the efficiency of this heterogeneous organocatalytic system.

Also worthy of mention and synthetically important are the good results found with 3-substituted acrolein such as crotonaldehyde (entries 9–12) for which only few successful examples are described. Nevertheless, a protic solvent such as MeOH or EtOH instead of THF is required to get good yields of the corresponding adduct. Moreover, it is interesting to point out that no bis-Michael adduct or Knoevenagel reaction was detected in the crude reaction mixture of a malonyl keto ester and crotonaldehyde (entries 11,12).

As a final point, although we did not make a systematic study, we have clearly shown the reusability character of the catalyst. For example, in the case of acetylbutyrolactone and methyl acrylate (entry 8), we found that it was possible to recycle the catalyst up to three times without significant loss of product yield, although the reaction time increased from 4 to 7 hours and 16 hours. However, after three cycles, the catalyst beads were crunched by mechanical stirring leading to an inactive powder. Alternatively, use of a nondestructive rotatory stirring allowed reuse of the catalyst up to five times without significant loss of activity.

In conclusion, the easily accessible user-friendly polymer supported nonionic phosphazene base P-BEMP proved to be an efficient recyclable heterogeneous organocatalyst for the Michael addition of 1,3-dicarbonyl compounds. Due to the availability of chiral iminophosphoranes amenable to solid support our results could be of interest in the development of a new heterogeneous catalytic enantioselective version of the Michael addition.

All reactions were monitored by TLC on Alugram SIL G/UV 254 silica gel analytical plates with a 250 μm coating. IR spectra were recorded as KBr discs, and NMR spectra were obtained in CDCl₃ at 300 MHz for 1H and at 75.5 MHz for 13C with chemical shifts expressed in ppm using residual CHCl₃ as internal reference. The Michael adducts were purified by FC (flash chromatography) on Merck silica gel 60 (230–240 mesh). Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without further purification. P-BEMP (ca. 2.2 mmol/g) was purchased from Fluka.

**Michael Addition of 1,3-Dicarbonyls to α,β-Unsaturated Compounds; General Procedure**

*Method A; Mechanical Stirring:* In a 15 mL round-bottomed flask equipped with a stirring bar and containing a solution of 1,3-dicarbonyl compound (2 mmol) and Michael acceptor (2.2 mmol) in an appropriate solvent (8 mL) at r.t., was added P-BEMP (5 mol%).

The resultant suspension was stopped and stirred for the indicated time (see Table 1). After completion of the reaction, filtration and concentration usually gave the Michael adducts with a purity estimated by NMR >95%. Analytical samples were obtained by FC using Et₂O–petroleum ether mixture as eluent.

*Method B; Rotatory Stirring:* In a 5 mL syringe filter containing a solution of 1,3-dicarbonyl compound (0.5 mmol) and Michael acceptor (1 mmol) in an appropriate solvent (3 mL) at r.t., was added P-BEMP (5 mol%). The resultant suspension was stopped and stirred in a rotatory stirrer until no starting material remained (TLC). After completion of the reaction, filtration and concentration usually gave the Michael adducts with a purity estimated by NMR >95%.

The analytical and spectral of the new compounds prepared are given below.

**Methyl 2-(3-Oxopropyl)-2-(2-prop-2-ynyl)propanedioate (Table 1, entry 5)**

- Colorless oil; yield: >98%; Rf 0.27 (Et₂O–petroleum ether, 1:1).
- IR (KBr): 3297, 2870, 2722, 2249, 1740 cm⁻¹.
- 1H NMR: δ = 2.00 (t, J = 3.0 Hz, 1 H), 2.29–2.36 (m, 2 H), 2.42–2.49 (m, 2 H), 2.75 (d, J = 3.0 Hz, 2 H), 3.68 (s, 6 H), 9.68 (br s, 1 H).
- 13C NMR: δ = 23.5, 24.8, 38.8, 52.8, 55.8, 71.9, 78.1, 170.1, 200.3.
- MS: m/z (%) = 227 ([M + H⁺]²), 195 (29), 170 (100), 138 (54), 110 (35), 77 (59), 51 (24).

**Methyl 3-(3-Acetyl-2-oxotetrahydrofuran-3-yl)propionitrile (Table 1, entry 7)**

- Colorless oil; yield: 77%; Rf 0.15 (Et₂O–petroleum ether, 1:1).
- IR (KBr): 2928, 2248, 1765, 1712 cm⁻¹.
- 1H NMR: δ = 2.15 (dt, J = 15.0, 9.0 Hz, 1 H), 2.22–2.42 (m, 4 H), 2.33 (s, 3 H), 2.89 (ddd, J = 3.0, 9.0, 15.0 Hz, 1 H), 4.22 (dt, J = 9.0, 10.0 Hz, 1 H), 4.37 (td, J = 9.0, 6.0 Hz, 1 H).
- MS: m/z (%) = 182 ([M + H⁺]²), 154 (100), 138 (45), 103 (92), 84 (43), 43 (52).

**Methyl 3-(3-Acetyl-2-oxotetrahydrofuran-3-yl)propionoate (Table 1, entry 8)**

- Colorless oil; yield: >98%; Rf 0.44 (Et₂O–petroleum ether, 1:1).
- IR (KBr): 2953, 1777, 1734, 1721 cm⁻¹.
- 1H NMR: δ = 2.02 (dt, J = 12.0, 9.0 Hz, 1 H), 2.15–2.29 (m, 3 H), 2.33 (s, 3 H), 2.38–2.46 (m, 1 H), 2.85 (ddd, J = 3.0, 9.0, 12.0 Hz, 1 H), 3.67 (s, 3 H), 4.15 (dt, J = 6.0, 9.0 Hz, 1 H), 4.31 (td, J = 9.0, 6.0 Hz, 1 H).
- 13C NMR: δ = 25.4, 28.9, 29.1, 29.2, 51.7, 60.3, 66.0, 172.1, 174.9, 201.9.
- MS: m/z (%) = 215 ([M + H⁺]²), 213 (100), 172 (32), 140 (100), 112 (27), 99 (23), 43 (31).

**Methyl 1-Oxo-2-(1-methyl-3-oxopropyl)indan-2-carboxylate (1:1 Mixture of Two Diastereomers) (Table 1, entry 10)**

- Colorless oil; yield: 78%; Rf 0.24 (Et₂O–petroleum ether, 1:1).
- IR (KBr): 3050, 2956, 1712 cm⁻¹.

**First Isomer**

- 1H NMR: δ = 0.75 (d, J = 6 Hz, 3 H), 2.16 (dd, J = 3, 9 Hz, 1 H), 2.31 (dd, J = 3, 9 Hz, 1 H), 2.63 (d, J = 15 Hz, 1 H), 2.65 (d, J = 15 Hz, 1 H), 2.83 (m, 1 H), 3.66 (s, 3 H), 7.37 (br t, J = 6 Hz, 1 H), 7.49 (br d, J = 6 Hz, 1 H), 7.62 (br t, J = 6 Hz, 1 H), 7.74 (br d, J = 6 Hz, 1 H), 9.69 (br d, J = 3 Hz, 1 H).

Synthesis 2004, No. 6, 923–927 © Thieme Stuttgart · New York
\textsuperscript{13}C NMR: \(\delta = 15.5, 32.0, 33.0, 46.1, 53.1, 64.6, 124.9, 126.6, 128.2, 135.6, 135.9, 153.6, 170.8, 200.9, 201.7.\\)

**Second Isomer**

\(\text{H NMR: } \delta = 0.93 \text{ (d, } J = 6 \text{ Hz, } 3 \text{ H), 2.16 (dd, } J = 3, 9 \text{ Hz, } 1 \text{ H), 2.83 (d, } J = 15 \text{ Hz, } 1 \text{ H), 2.75 (dd, } J = 6 \text{ Hz, } 3 \text{ H), 2.67 (m, } J = 13.9, 17.6, 28.0, 48.4, 58.4, 61.4, 123.6, 128.5, 128.7, 133.6, 136.3, 168.6, 194.3, 201.1.\\)

\(\text{C NMR: } \delta = 16.4, 32.1, 33.5, 47.5, 53.1, 64.9, 124.9, 126.6, 128.2, 135.6, 135.9, 153.6, 170.8, 201.1, 201.7.\\)


\(\text{Second Isomer: Colorless oil; yield: 75%; } R_f 0.34 \text{ (Et}_2\text{O–petroleum ether, 1:1).}\\

Two Diastereomers (Table 1, entry 12)

\(1^H \text{ NMR: } J = 9 \text{ Hz, } 3 \text{ H), } 1.15 \text{ (t, } J = 6 \text{ Hz, } 3 \text{ H), 2.45 (ddd, } J = 15, 9, 3 \text{ Hz, } 1 \text{ H), 2.72 (dd, } J = 15, 3 \text{ Hz, } 1 \text{ H), 3.05 (m, } 3 \text{ H), 4.12 (q, } J = 6 \text{ Hz, } 2 \text{ H), 4.39 (d, } J = 6 \text{ Hz, } 1 \text{ H), 7.47 (t, } J = 6 \text{ Hz, } 2 \text{ H), 7.58 (d, } J = 6 \text{ Hz, } 1 \text{ H), 7.99 (t, } J = 6 \text{ Hz, } 2 \text{ H), 9.76 (br d, } J = 3 \text{ Hz, } 1 \text{ H).}\\

\(\text{C NMR: } \delta = 13.9, 18.6, 28.4, 48.4, 58.4, 61.4, 128.5, 128.7, 133.6, 136.5, 168.7, 194.3, 201.1.\\

Anal. Calcd for C\(_{15}\)H\(_{16}\)O\(_4\) (260.29): C, 69.22; H, 6.20. Found: C, 135.6, 135.9, 153.6, 170.8, 201.1, 201.7.


(17) (a) Legrand, O. *Synlett* 1999, 752. (b) See also a special issue on strong and hindered bases: *Chem. Files, Fluka* 2003, 3, No. 1.


(20) For an example of synthetic utilization of the corresponding Michael adduct, see: Chareyron, M.; Devin, P.; Fensterbank, L.; Malacria, M. *Synlett* 2000, 83.

(21) For the first example of a supported proline-derived organocatalyst used in the kinetic resolution of racemic alcohols, see: Pelotier, B.; Priem, G.; Campbell, I. B.; Macdonald, S. J. F.; Anson, M. S. *Synlett* 2003, 679.


(23) After the first reaction the color of the catalyst changed from yellow to brown, but this modification remains insensitive towards the catalytic activity.


