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Polystyryl-BEMP as an Efficient Recyclable Catalyst for the Nucleophilic Addition of Nitroalkanes to α,β-Unsaturated Carbonyl Compounds under Solvent-Free Conditions

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Abstract: 2-*tert*-Butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine supported on polystyrene (PS-BEMP) is an efficient catalyst for the addition of nitroalkanes (1–1.5 equiv.) to α,β-unsaturated carbonyl compounds (1.0 equiv.) in the absence of a reaction medium (solvent-free conditions). The corresponding γ-nitro carbonyl compounds have been isolated in excellent yields but the catalyst can be satisfactorily recovered and used for only 3 times due to the magnetic stirring which caused crunching of the catalyst beads thus hampering its complete recovery. To optimize the catalyst's reuse and improve the environmental efficacy of solvent-free conditions, the first solvent-free cyclic continuous-flow reactor has been set up. This reactor has allowed the product to be isolated in an almost quantitative yield by using a very small amount of organic solvent, making the recovery and reuse of the catalyst efficient and reproducible.

Keywords: BEMP; 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP); green chemistry; Michael addition; nitroalkanes; solid catalysts; solvent-free conditions

Nitroalkanes are valuable intermediates with a wide synthetic versatility due to both the electron-withdrawing property of the nitro group and its ability to be transformed to other functionalities.[1] The conjugate addition of nitroalkanes to α,β-unsaturated compounds is a widely studied process for the formation of new carbon-carbon bonds and for the preparation of γ-nitro carbonyl compounds and γ-nitro esters.[1,2]

This transformation has been object of a vast research activity and new protocols have continuously appeared in the literature proposing the use of a catalytic amount of a base or a Lewis acid.[3,4] Much effort has been paid to improve the efficiency of this process by using a 1:1 ratio of reactants and by developing new catalytic systems.[4c–e]

In the production of fine chemicals, an important issue concerns the use of noxious and environmentally costly reaction media and, for this purpose, excellent protocols for the addition of nitroalkanes to α,β-enones have recently proposed the use of water[5] as reaction medium or the drastic and effective elimination of the reaction medium by using solvent-free reaction conditions (SolFC).[4b–d,6]

For many years, we have been investigating the use of unconventional reaction media that could replace harmful organic solvents while maintaining the highest chemical efficiency. In particular, we have been focusing our attention on the use of water[7] or SolFC,[8] proving that, by using these alternatives to organic solvents, significant improvements of both chemical efficiency and sustainability of a process can be obtained.

In our experience, under SolFC, the reactivity is significantly improved allowing faster reactions and highest efficiency of a catalyst.[8] In the last few years we have been studying the use of SolFC to increase the efficiency of polymer-supported organocatalysts which are generally less efficient than their non-supported counterparts. For example, we have proved that, under SolFC, polystyrene-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PS-TBD) is an effective and reusable catalyst for a variety of organic transformations and it is much more efficient than when used in organic solvents such as DCM or MeCN.[8a] Similar-

PS -base	Conversion to **3a** (%)[a]
PS-BEMP	> 99[b]
PS-TBD	36
PS-DMAP	< 1
PS-MP	< 1

[a] Measured by GLC analyses.

[b] Product **3a** was isolated pure in 90% yield.

Scheme 1. Polystyrene-supported organic base-catalyzed Michael addition of nitromethane (**2**) to (*E*)-benzylideneacetone (**1a**) under SolFC.

ly, the β-azidation of α,β-enones by trimethylsilyl azide under SolFC has been catalyzed by a polystyrene-supported azide (Amberlite IRA900N_3).[8g]

The study of the reactivity of nitro compounds in unconventional media is one of our main research interests.[5a–c,7c,8f] As a recent example, we have reported the one-pot multicomponent synthesis of biphenyl-2-carbonitriles starting from aryl aldehydes where the key steps are the preparation of (*E*)-2-aryl-1-cyano-1-nitroethenes *via* a Knoevenagel reaction with nitroacetonitrile, and their Diels–Alder cycloaddition under SolFC.[8f]

As a continuation of our interest in the chemistry of nitro compounds and in the use of solid bases under SolFC, we have investigated the addition of nitroalkanes (**2**, **4**, **6**, and **8**) to α,β-unsaturated ketones (**1a–i**) and esters (**10a–d**) catalyzed by 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine supported on polystyrene (PS-BEMP).

We have previously reported that 20 mol% of PS-TBD promotes the addition of nitroethane (**4**) to (*E*)-benzylideneacetone (**1a**) under SolFC.[8a] PS-TBD was chosen on considering its larger basicity among the commonly used nitrogen-containing organic bases (the pK_a of the conjugate acid of PS-TBD is $>$ 14 in water and 25.39 in MeCN).[9,10]

Considering that the pK_a of a nitroalkane ($AlkNO_2$) in MeCN falls in the range 27–31, a base stronger than PS-TBD would be helpful to increase the efficiency of the addition of $AlkNO_2$ to an α,β-unsaturated ketone or ester, and to reduce the amount of catalyst needed. We focused our attention on PS-BEMP (${}^{MeCN}pK_a$ is 27.63),[10] a member of the class of Schwesinger's phosphazene bases, that have proved to be very strong and widely useful uncharged auxiliary bases.[10]

We have initially compared the efficiency of PS-BEMP (5 mol%) to that of PS-TBD (5 mol%) in the reaction of equimolecular amounts of benzylidene acetone (**1a**) and nitromethane (**2**) under SolFC at 30 °C (Scheme 1). Conversion of **1a** to γ-nitro ketone **3a** was complete after 4 h in the presence of 5 mol% of PS-BEMP while it was only 36% complete when 5 mol% of PS-TBD was used, leaving the remaining material as a mixture of unreacted **1a** and **2** (Scheme 1). To confirm the efficiency of the strongly basic PS-BEMP, we have also tested other solid bases (Figure 1) which were commercially available on the same solid support (polystyrene, 200–400 mesh, 2% DVB) and the results are reported in Scheme 1. Polystyryl-supported 4-dimethylaminopyridine (PS-DMAP) and -methylpiperidine (PS-MP) gave only traces of **3a**.

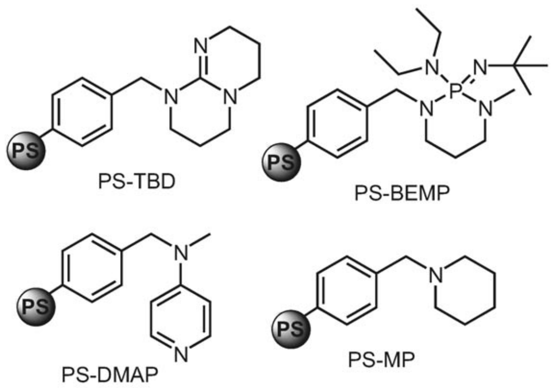
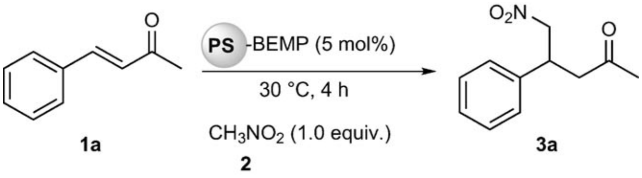


Figure 1. Bases supported on polystyrene used in this study.

A variety of media were also tested (Table 1) and the best isolated yield of γ-nitro ketone **3a** was obtained under SolFC (Table 1, entry 1). Also in the case of DCM, which is reported to be the most appropriate swelling solvent for polystyrene resins, an unsatisfactory result was obtained (Table 1, entry 2).

To verify the efficiency of PS-BEMP in this transformation, we have also performed the reaction of **1a**

Table 1. Michael addition of nitromethane (**2**) to (*E*)-benzylideneacetone (**1a**) catalyzed by PS-BEMP (5 mol%) in different reaction media.



Entry	Reaction Medium	Conversion [%][a]
1	SolFC	> 99[b]
2	DCM	24
3	MeCN	14
4	MeOH	21
5	H_2O	20
6	[Bmim]BF_4	-

[a] Measured by GLC analyses.
[b] Pure product **3a** was isolated in 90% yield.

with **4**, **6**, and **8** as representatives of linear, branched and cyclic nitroalkanes. Also in theses cases PS-BEMP proved to be an efficient catalyst for this transformation (Scheme 2) and the corresponding γ-nitro ketones **5**, **7**, and **9** were isolated in satisfactory yields. In the case of **5**, a *syn*/*anti* 1/1 diasteroisomeric mixture was formed (Scheme 2).

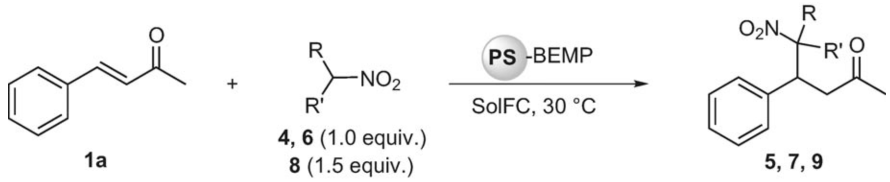
The range of application of PS-BEMP as catalyst was further confirmed by carrying out the reactions of nitromethane (**2**) with a variety of α,β-unsaturated ketones (**1b–i**) under the same conditions as described above and the results are reported in Table 2.

At 30 °C and in the presence of 5 mol% of PS-BEMP, enones **1b–d** reacted according to the electronic properties of their susbtituents. (*E*)-*p*-Chlorobenzylideneacetone (**1c**) reacted faster than benzophenone (**1b**) giving the desired product **3c** after 4 h instead of the 18 h necessary for the conversion of **1b** to **3b** (Table 2, entry 2 *vs.* entry 1). The reaction of **1d** with nitromethane (**2**) was even slower and **3d** was isolated as the pure product in 80% yield after 72 h at 30 °C (Table 2, entry 3).

The heteroaromatic (2*E*)-3-(2′-furyl)-1-phenylprop-2-enone (**1e**) showed a slightly different behaviour and together with the desired product **3e**, an additional bis-adduct product was formed, coming from the nucleophilic attack of **3e** on **1e** (Table 2, entry 4). By using 3.0 equiv. of nitromethane (**2**) formation of the bis-adduct was suppressed and the corresponding γ-nitro ketone **3e** was isolated in 76% yield (Table 2, entry 5).

Alkyl substituted α,β-enones **1f–i** reacted efficiently with nitromethane (**2**) (1.0–1.5 equiv.) in the presence of 5 mol% of PS-BEMP and gave the corresponding γ-nitro ketones in very satisfactory yields (85–95%, Table 3, entries 6–9). In the case of **1h** the addition of nitromethane (**2**) was completely regioselective giving only the product coming from the attack at the C-3 position.

The study on the efficiency of PS-BEMP was then extended to α,β-unsaturated esters **10a–d**. Also in these cases the reactions proceeded satisfactorily and in the presence of 10 mol% of the catalyst, the corresponding γ-nitro esters **11a–d** were isolated in good yields (78–95%). In the case of methyl 3-(2′-furyl)-ac-

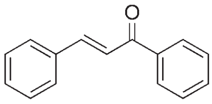
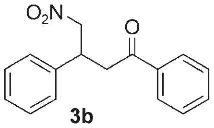
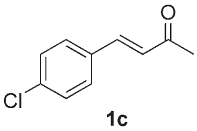
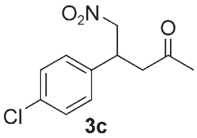
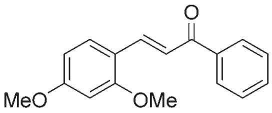
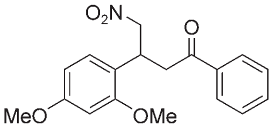
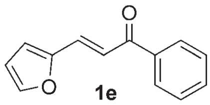
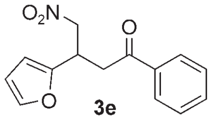
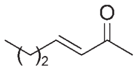
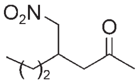
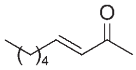
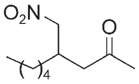
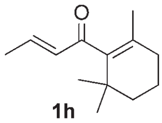
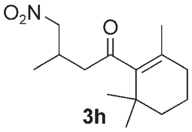
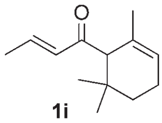
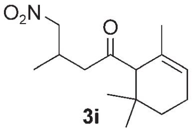


R	R'	PS-BEMP [mol%]	Time [h]	Product	Yield [%][a]
CH_3	H	5	4	**5**	98
4					
CH_3	CH_3	5	20	**7**	98
6					
-$(CH_2)_4$-		10	4	**9**	85
8					

[a] Isolated yield of the pure product.

Scheme 2. PS-BEMP-catalyzed Michael addition of nitroethane (**4**), 2-nitropropane (**6**) and nitrocyclopentane (**8**) to (*E*)-benzylideneacetone (**1a**).

Table 2. PS-BEMP-catalyzed Michael addition of nitromethane (**2**) to α,β-enones **1** under SolFC.

Entry	α,β-Enone **1**	*t* [h]	Product **3**	Yield [%][a]
1	 **1b**	18	 **3b**	88
2	 **1c**	4	 **3c**	85
3	 **1d**	72	 **3d**	80
4	 **1e**	15	 **3e**	30[b]
5		15		76[c]
6	 **1f**	4	 **3f**	95
7	 **1g**	4	 **3g**	94
8	 **1h**	2	 **3h**	85[d]
9	 **1i**	2	 **3i**	88[d]

[a] Isolated yield of the pure product **3**.
[b] 26% of the bis-adduct coming from the attack of **3e** on **1e**.
[c] 3.0 equiv. of **2** were used.
[d] 1.5 equiv. of **2** were used.

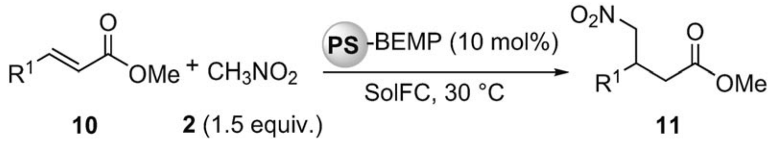
rylate (**10c**) by using 1.0 equiv. of **2** a considerable amount of bis-adduct coming from the attack of **11c** on another molecule of **10c**, was formed (Table 3, entry 3). The yield of **11c** was satisfactory when 3.0 equiv. of **2** were used at 60 °C (Table 3, entry 4).

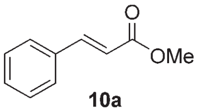
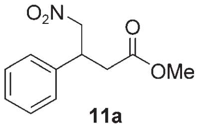
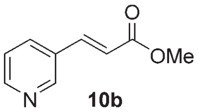
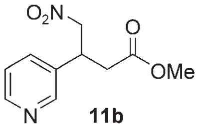
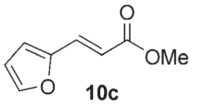
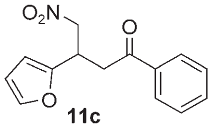
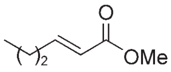
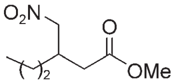
PS-BEMP showed to be generally efficient under SolFC, in the case of variously substituted α,β-enones as well as in the case of sterically demanding Michael donors such as **6** and **8**.

We have then focused our investigation on the recovery and reuse of PS-BEMP.

An important issue when polystyrene-supported catalysts are employed concerns the decrease of their activity after being recovered. Constantieux et al.

Table 3. PS-BEMP-catalyzed Michael addition of **2** to α,β-unsaturated esters **10** under SolFC.



Entry	α,β-Unsaturated ester **10**	*t* [h]	Product **11**	Yield [%][a]
1	 **10a**	18	 **11a**	85
2	 **10b**	15	 **11b**	78
3	 **10c**	24	 **11c**	55[b,c]
4		23		79[c,d]
5	 **10d**	22	 **11d**	95

[a] Isolated yield of the pure product **11**.
[b] 16% of the bis-adduct coming from the attack of **11c** on **10c**.
[c] Reaction performed at 60 °C.
[d] 3.0 equiv. of **2** were used.

have previously reported[11] that PS-BEMP used in THF for the addition of carbonyl compounds to electron-poor alkenes could be recovered and reused but with a significant loss in terms of its catalytic efficiency when a mechanical (magnetic bar) stirring was employed.[11] The authors justified this deactivation with a concomitant crunching of the catalyst beads into an inactive powder.

In our case, we have used PS-BEMP under SolFC by using a magnetic stirring bar (mechanical stirring) and we observed no detectable reduction of its efficiency in terms of reaction time. For example, in the case of **1a** and **4** for 3 consequent runs and after a reaction time of 4 h, product **5** was isolated in 95–96% yield. According to Constantieux et al.,[11] after the third run we have observed an evident change of the PS-BEMP into a very fine powder making impossible its complete recovery. The recovered catalyst was used in a fourth run and after a longer reaction time (16 h) a poor conversion to γ-nitro ketone **5** was observed (Figure 2). Due to its powdery physical state, attempts to regenerate the catalyst efficiency proved to be impossible.

To avoid the crunching of the catalysts caused by mechanical stirring and to optimize its reuse, we have planned to realize a reactor where the reactants under SolFC were continuously flowed through the PS-BEMP, avoiding in this way the use of an additional stirring system.

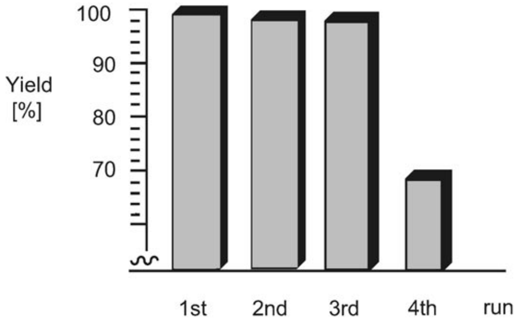


Figure 2. Reuse of PS-BEMP in the Michael addition of nitroethane (**4**) to (*E*)-benzylideneacetone (**1a**).

We have charged the PS-BEMP catalyst in a glass column and let the solvent-less equimolar mixture of reactants **1a** and **4** flow through it (see Figure 3). The reaction mixture coming out the column has been then pumped again to the top of glass column and this cycle continued for the time necessary to complete the conversion of **1a** to **5**. This experiment was run on a 50.0-mmol scale allowing within 4 h the com-

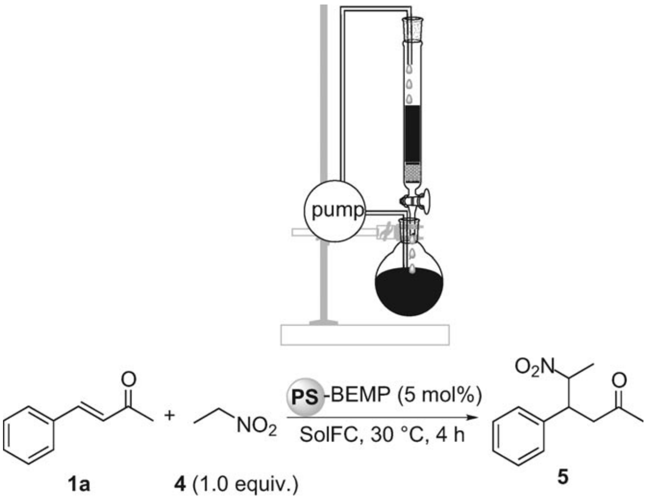


Figure 3. Cyclic continuous-flow reactor using PS-BEMP as catalyst for the Michael addition of nitroethane (**4**) to (*E*)-benzylideneacetone (**1a**).

plete conversion of an equimolar solvent-less solution of **1a** and **4** to γ-nitro ketone **5** and by using 5 mol% of PS-BEMP.

At the end of the reaction process, the product **5** was collected into the flask by leaving the pump to work for 10 min without suctioning the reaction mixture. In this way **5** was isolated in a pure form in 90% yield without using any organic solvent. The yield of **5** can be further improved by cleaning the system with only 10 mL of ethyl acetate (0.2 mL/mmol) (which was cyclically flowed for 5 min at a 1 mL min^{-1} rate), reaching a 98% yield of pure product.

With this procedure the catalyst was left inside the reactor and was successfully reused for other two runs with the subsequent runs achieving identical results. To keep the highest efficiency, at the fourth run reactivation of PS-BEMP was necessary and this can be performed directly by flowing a 0.13 M ethyl acetate solution of BEMP (1.2 equiv.) through the catalyst into the column (for the details see the Experimental Section). After regeneration, the catalyst has been reused for three more runs showing always the same efficiency as in the first run.

In conclusion, we have proved that PS-BEMP (5–10 mol%) is an efficient catalysts under SolFC for promoting the Michael addition of nitroalkanes **2**, **4**, **6** and **8** on α,β-unsaturated ketones **1a–i** and esters **10a–d** allowing the corresponding products γ-nitro compounds **3a–i**, **5**, **7**, **9**, and **11a–d** to be isolated in good yields (76–98%) and generally short times (2–23 h).

The solvent-free conditions, the minimal amount of solvent used for the isolation of the product in an excellent yield, together with the easy recovery and recycling of the catalyst make this protocol very efficient from both the chemical and environmental points of view.

In our opinion, the cyclic continuous-flow reactor represents a very promising tool to keep the efficiency of a solid catalyst and minimize the organic solvent needed for performing reactions and isolation of the products. Further developments are directed to its optimization for application in other organic chemical transformations.

Experimental Section

General Remarks

GS-MS analyses were carried out by means of the EI technique (70 eV). All chemicals were purchased and used without further purifications; PS-BEMP (200–400 mesh, 2% DVB, 2.08 mmol BEMP/g) was purchased by Fluka. Enones **1d**[13] and **1e**[14] were prepared according to the described procedures. Methyl esters **10b–d** were synthesized by refluxing the corresponding acids in MeOH, in the presence of a catalytic amount of sulfuric acid. Nitro derivatives **3a**,[15] **3b**,[16] **3e**,[17] **3h**,[18] **3i**,[19] **5**,[20] **7**,[20] **9**,[20] and **11a**,[21] are known compounds, but essential characterization data (^{1}H NMR, ^{13}C NMR and GC-EI-MS) were reported for clarity, whereas adducts **3c**, **3d**, **3f**, **3g**, and **11b–d** are new products.

Representative Batch Experimental Procedure

In a screw-capped vial equipped with a magnetic stirrer PS-BEMP (0.096 g, 2.08 mmol g^{-1}), (3*E*)-4-phenylbut-3-en-2-one [(*E*)-benzylideneacetone] (**1a**) (0.585 g, 4.0 mmol) and nitromethane (**2**) (0.217 mL, 4.0 mmol) were consecutively added and the resulting mixture was left under vigorous stirring at 30 °C.

After 4 h, ethyl acetate was added, the catalyst was recovered by filtration and the organic solvent was evaporated under vacuum to give, pure 5-nitro-4-phenylpentan-2-one (**3a**) as a white solid; yield: 0.745 g (90%).

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