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E-factor minimized protocols for the polystyryl-BEMP catalyzed conjugate additions of various nucleophiles to α , β -unsaturated carbonyl compounds[†]

Simona Bonollo, Daniela Lanari, Julie M. Longo and Luigi Vaccaro*

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Efficient protocols for the addition of carbon-, sulphur- and nitrogen-nucleophiles to α , β -unsaturated carbonyl compounds catalyzed by PS-BEMP have been reported. The adoption of solvent-free conditions (SoIFC) was crucial for improving the efficiency of all the processes, while by using an organic reaction medium poor results were obtained. Addition reactions were performed by using equimolar amounts of reagents, and the products were isolated by simple filtration with the minimal amount of organic solvent. This approach allowed the E-factor, a measure of the waste of a reaction, to be minimized. Further waste minimization (95.7% compared to batch protocol) has been accomplished by defining a larger scale continuous-flow protocol operating under SoIFC.

Introduction

The Michael addition is one of the more important carbon– carbon bond forming reactions in organic chemistry.¹ The azaand sulfa-Michael additions² are equally important carbonnitrogen and carbon-sulfur bond forming reactions, respectively, which are key steps in the preparation of several intermediates. In general, these reactions must take place in either strongly basic or strongly acidic conditions.

Recently, we have focused our work on the optimization of synthetic procedures, including Michael additions, by employing eco-friendly reaction protocols based on the use of water,³ solvent-free conditions (SoIFC),⁴ and polymer-supported organocatalysts.⁵ With our approach we have achieved efficient waste minimization (E-factor minimization)⁶ by setting singleand multistep cyclic continuous-flow reactors.^{5a-d,f}

The development of polymer-supported material as reagents or organocatalysts has greatly increased in recent years.⁷ These supported catalysts are a more sustainable and chemically efficient alternative to traditional basic catalysts used in Michael additions because they are easily recoverable and recyclable.

The use of SolFC together with polymer-supported organocatalysts has been shown to increase the effectiveness of the catalysts, which are generally but not always,^{7c-e} less efficient than their non-supported counterparts. In the past, this group has shown that polystyrene-supported 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PS-TBD, **1b**) is more effective under SolFC than in typical organic solvents.^{5h,i} Further efforts have been made to reduce the environmental impact of these processes by using an equimolar ratio of reactants to reduce waste. This, in turn, helps to reduce the E-factor of these addition reactions.

In particular, our attention has been focused on 2*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2diazaphosphorine supported on polystyrene (PS-BEMP, 1a) (Fig. 1), a very strong base ($^{MeCN}pK_a$ is 27.63) and a member of the class of Schwesinger's phosphazene bases that have proved to be widely useful, uncharged auxiliary bases.⁸ By using a catalytic amount of PS-BEMP, we have reported the nucleophilic addition of nitroalkanes to α,β -unsaturated carbonyl compounds^{5f} and the addition of carbon nucleophiles^{5e} and phenols^{5c} to epoxides under solvent-free conditions, in batch condition and also by using a cyclic continuous flow reactor.

In this paper, we present the application of our approach to the use of PS-BEMP as catalyst for the Michael and hetero-Michael addition of a variety of nucleophiles to α , β -unsaturated carbonyl compounds.

Results and discussion

Initially, the efficiency of PS-BEMP (1a) was compared to that of PS-TBD (1b), JJ-TBD (1c), and PS-DMAP (1d) (Fig. 1) in the reaction of equimolar amounts of benzylidene acetone (2a) and dimethylmalonate (3a) under SolFC with 5 mol% of catalyst (Table 1).

Laboratory of Green Synthetic Organic Chemistry, CEMIN -

Dipartimento di Chimica, Università di Perugia, Via Elce di Sotto, 8, Perugia, Italia. E-mail: luigi@unipg.it; Fax: +39 075 5855560; Tel: +39 075 5855541

[†] Electronic supplementary information (ESI) available: Characterization data and copies of the ¹H and ¹³C NMR spectra for compounds **6**, **9**, **10**, **15**, **23**, **25**, **27a**, **27b**, **28a**, **28b**, **29**. See DOI: 10.1039/c1gc16088e

	2a + <	O ₂ Me Catalyst (5 mol%) D ₂ Me ³ 0 °C, 24h 3a	
Entry	Catalyst	Solvent (M)	Conversion (%) ^b
1 2 3 4 5 6 7 8	PS-BEMP PS-BEMP PS-TBD JJ-TBD PS-DMAP PS-BEMP PS-BEMP PS-BEMP	 CH ₃ CN (0.5) CH ₂ Cl ₂ (0.5) THF (0.5)	86 100 (97) ^c 2 54 0 10 9 2

Table 1 Optimization of the base-catalyzed Michael addition of
dimethylmalonate (3a) to *trans*-4-phenyl-3-buten-2-one $(2a)^a$

^{*a*} Reaction conditions: **2a** (1.0 mmol), **3a** (1.0 mmol), catalyst (5 mol%), 30 °C. ^{*b*} Determined by GC analyses. ^{*c*} Reaction conducted at 60 °C; isolated yield for **4** reported in parentheses.



Fig. 1 Supported bases used in this study.

After 24 h at 30 °C, the reaction with PS-BEMP was at 86% conversion (Table 1, entry 1), while other supported bases, PS-TBD and PS-DMAP respectively, gave only traces of product 4 (Table 1, entries 3,5). JJ-TBD, a more efficient catalyst than PS-TBD, ^{5a} allowed us to obtain product 4 with a 54% conversion (Table 1, entry 4).

PS-BEMP was then tested in a variety of reaction media and the best isolated yield was obtained under SolFC (Table 1, entries 1-2 vs. entries 6–9). Also, in the presence of dichloromethane, which is reported to be the most appropriate swelling solvent for polystyrene resins, an unsatisfactory result was obtained (Table 1, entry 7).

The applicability of this protocol was then tested in the Michael addition of carbon $(3\mathbf{a}-\mathbf{c})$, sulfur $(13\mathbf{a}-\mathbf{b})$, and nitrogen nucleophiles $(20\mathbf{a}-\mathbf{c})$ with three representative α,β -unsaturated carbonyl compounds $2\mathbf{a}-\mathbf{c}$.

Table 2 shows the results for the reactions of **2a–c** with **3a–c**.

As with the reaction of 2a with 3a, PS-BEMP proved to be an effective catalyst for the Michael additions of the other carbon nucleophiles furnishing products 4-12 in high yields (85–97%). The reactions proceeded with 5 mol% of the catalyst and equimolar amounts of reactants (for exceptions see entries 3,7 and 8). These conditions, together with the use of SolFC, allowed us to define a simple and chemically efficient protocol for minimizing the amount of waste and consequently the E-factor of the processes (for calculation of E-factor see Electronic Supplementary Information[†]).

Waste was further minimized through the work-up procedure consisting of a simple filtration of the reaction mixture using the minimum possible amount of solvent. In the case of the carbon nucleophiles, the E-factor ranged from 5.9 to 12.1. When methylacrylate (2c) was used in the reaction with dimethylmalonate (3a) and ethylnitroacetate (3b) an additional bis-adduct product was formed when the reactants were used in a one to one ratio (37% and 20% respectively).

To suppress this side product, three equivalents of the nucleophile were used, though for the production of 10, 12% of the product was still the bis-adduct.

The two sulfur nucleophiles, benzenethiol (13a) and butanethiol (13b), were very reactive (Table 3). In all cases, the reactions reached 100% conversion at 30 °C in a very short time and the products 14–19 were isolated in yields ranging from 92–97%.

These nucleophiles also required the least amount of catalyst (0.5 mol%), except for the formation of **15** (Table 3, entry 2), in which 2 mol% of PS-BEMP was used. The E-factor for the formation of **14–19** ranged from 5.7–8.8.

The results of the Michael additions of nitrogen nucleophiles, **20a–c** are shown in Table 4. Due to the low nucleophilicity of these heterocycles, temperatures from 60 to 80 °C were generally required, except in the formation of **27a** and **27b** in which the temperature was kept at 30 °C (Table 4, entry 7). These reactions also proceeded much more slowly than the sulfur nucleophiles, with reaction times ranging from 24 to 120 h. The E-factor ranged from 9.5 to 12.7.

Finally, the recovery of the catalyst was also considered. PS-BEMP was able to be reused for five consecutive runs without any decrease of its catalytic efficiency.

In addition, we have also set a continuous-flow procedure for the reaction of 2c with 3c (Scheme 1) to show that by this



Scheme 1 Continuous-flow protocol for the representative reaction of 2c with 3c.

				PS-BEM (5 mol% SolFC	$ \xrightarrow{\text{NU}} R_1 \xrightarrow{\text{NU}} R_2 $		
			2a-c	3а-с О	4-12		
			A		OMe		
				2a			
			NuH MeO ₂ C	CO ₂ Me O ₂ N			
Entry	A	NuH	T/°C	<i>t</i> (h)	Product	Yield (%) ^b	E-factor ^c
1	2a	3a	60	24	MeO ₂ C CO ₂ Me	97	5.9
2	2a	3b	60	120	EtO ₂ C NO ₂	95 ^d	9.0
3 ^e	2a	3c	80	48	O Ph O II I II	90 ^d	6.5
					COMe 6		
4	2b	3a	30	24	Ļ	95	11.0
					CO ₂ Me		
5	2b	3b	30	24	0 	93 ^d	7.5
					CO ₂ Et		
<i>.</i>	21	2	20	24	8 NO ₂	0 Ad	11.2
0	20	30	30	24		94"	11.3
					o COMe		
$\mathcal{T}^{f,g}$	2c	3a	30	72		85	10.1
					MeO 002Me		
8 ^{<i>f</i>,<i>g</i>}	2c	3b	30	3.5		90	9.5
					$\frac{\text{MeO}^{2}}{11} \qquad $		
9	2c	3c	30	3		92	12.1
					COMe 12		

Table 2PS-BEMP catalyzed Michael addition of carbon nucleophiles 3a-c to α,β -unsaturated carbonyl compounds $2a-c^{\alpha}$

^{*a*} Reaction conditions: acceptor (1.0 mmol), donor (1.0 mmol), catalyst (5 mol%). ^{*b*} Isolated yield of the pure products. ^{*c*} For calculation see Electronic Supplementary Information.[†] ^{*d*} Diastereoisomeric mixture. ^{*c*} 20 mol% of catalyst were used. ^{*f*} 3 equiv. of nucleophiles were used. ^{*g*} Column chromatography purification was necessary.

		R1 2a-c	0 R₂ + R₃-SH - 13a-b	PS-BEMP (0.5 mol%) SolFC R1 R2 14-19		
			SH 13a	SH 13b		
Entry	А	R₃SH	<i>t</i> (h)	Product	Yield (%) ^{<i>b</i>}	E-Factor ^c
1	2a	13a	5	SPh O 14	97	5.7
2 ^{<i>d</i>}	2a	13b	1	SBu O 15	95	6.4
3	2b	13a	5	SPh 16	92	7.6
4	2b	13b	3	SBu 17	96	8.0
5	2c	13a	2	MeO 18	96	7.6
6	2c	13b	1	MeO SBu	93	8.8

Table 3 PS-BEMP catalyzed sulfa-Michael addition of thiols 13a-b to α,β-unsaturated carbonyl compounds 2a-c^a

^{*a*} Reaction conditions: acceptor (1.0 mmol), donor (1.0 mmol), catalyst (0.5 mol%), 30 °C. ^{*b*} Isolated yield of the pure products. ^{*c*} For calculation see Electronic Supplementary Information.[†] ^{*d*} 2 mol% of catalyst were used.

approach it is also possible to even further reduce the waste of processes performed under SoIFC. According to our previous reports in this field, the reactor is also a very effective tool to maintain the catalyst integrity (chemical and physical) and perform the process at large scale without further optimization.^{5a-d,f} The schematic representation of the reactor is depicted in Scheme 1 (thermostated box is not showed for clarity).

The equimolar mixture (50 mmol) of 2c and 3c was charged into a glass column functioning as a reservoir. The catalyst PS-BEMP (5 mol%, 2.5 mmol of BEMP) was charged into a glass column and the reaction mixture was continuously pumped through it at 30 °C for 3.0 h (the time necessary for the complete conversion to 12. At this point, the pump was left to run in order to recover the reaction mixture into the reservoir. Then MeOH was added (3 × 2 mL) to wash the catalyst and to isolate product 12 in 95% yield after removal of the solvent under reduced pressure. The same protocol was repeated for five consecutive runs and the efficiency of the catalyst was unchanged. After 3 h the conversion of 2c and 3c to 12 was always complete and the final product was always recovered in very high yields (93-95%).

The E-factor of the process in flow is 0.52 (see Electronic Supplementary Information† for details) with a reduction of 95.7% compared to the 12.1 value obtained in the batch process (Table 2, entry 9).

Conclusions

In conclusion, we have reported an efficient protocol for the Michael addition of carbon-, sulphur- and nitrogennucleophiles to α,β -unsaturated carbonyl compounds employing PS-BEMP as catalyst. Reactions were conducted under SolFC with equimolar amounts of reagents and the products

					PS-BEMP (5 mol%) Nu Q		
				R ₁	2 + NuH SolFC R1 R2		
				2a-c	20a-c 21-29		
	•	Nati	T/°C	(h)	20a 20b 20c	V:-11(0/)b	E Eastar(
Entry	A	NuH	<i>1/3</i> C	<i>t</i> (n)	Product	Yield (%) ⁵	E-Factor
1	2a	20a	60	120	$ \begin{array}{c} \begin{array}{c} \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \end{array} $ } \\ \end{array}	90 ^{<i>d</i>}	9.5
2	2a	20b	80	24		75	11.2
3	2a	20c	60	24		72	12.2
4	2b	20a	80	24	$\begin{array}{c} & & & \\ & & & & \\ & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & &$	92 ^d	12.1
5	2b	20b	80	24		91	10.9
6	2b	20c	60	24		83	12.7
7	2c	20a	30	72	27a (80%) 27b (20%)	94 ^{<i>d</i>}	12.4
8e	2c	20b	60	96	(273 (30%)) $(273 (30%))$	96	11.5
9f	2c	20c	60	72	200 (1170)	99	9.8

Table 4	PS-BEMP catalyzed aza-	-Michael addition o	f N-heterocycles 2	$0a-c$ to α,β -unsatura	ted carbonyl compounds $2\mathbf{a}-\mathbf{c}^a$

^{*a*} Reaction conditions: acceptor (1.0 mmol), donor (1.0 mmol), catalyst (5 mol%). ^{*b*} Isolated yield of the pure products. ^{*c*} For calculation see Electronic Supplementary Information.† ^{*d*} Regioisomeric mixture. ^{*e*} 3 equiv. of acceptor were used. ^{*f*} 2 equiv. of acceptor were used.

were isolated by simple filtration using the minimal amount of organic solvent necessary for the workup. This approach allowed us to reduce dramatically the reaction's waste, thus minimizing the E-factor. We have also defined a continuous-flow protocol for the representative reactions of **2c** with **3c** operating under SolFC on a 50 mmol scale. Under these conditions the same catalyst can be used for at least 5 consecutive runs with no decrease of its efficiency. E-factor has been reduced by 95.7%. This approach has allowed the physical integrity of the catalyst to be conserved and proves that continuous-flow reactors operating under SolFC is a promising tool to reduce waste.

Experimental section

Compounds 4,⁹ 5,¹⁰ 7,⁹ 8,¹⁰ 11,¹¹ 12,¹² 14,¹³ 16,¹⁴ 17,¹⁵ 18,¹⁶ 19,¹⁷ 21a–b,¹⁸ 22,¹⁹ 24a–b,²⁰ 26,²¹ are known compounds, compounds 10, 23, 27a–b, 28a, 29 have been already prepared but spectroscopic data have not been reported, while compounds 6, 9, 15, 25, 28b are new compounds. Characterization data (¹H NMR, ¹³C NMR, GC-EIMS, mp, and elemental analyses) for compounds 6, 9, 10, 15, 23, 25, 27a, 27b, 28a, 28b, 29 are reported in Electronic Supplementary Information (ESI).†

Representative experimental procedure

In a screw capped vial equipped with a magnetic stirrer PS-BEMP (0.048 g, 0.1 mmol, 2.1 mmol g⁻¹), *trans*-4-phenyl-3buten-2-one (**2a**) (0.292 g, 2.0 mmol) and dimethylmalonate (**3a**) (0.229 ml, 2.0 mmol) were consecutively added and the resulting mixture was left under vigorous stirring at 60 °C. After 24 h, methanol was added, the catalyst was recovered by filtration and the organic solvent was evaporated under vacuum to give pure dimethyl-2-(1'-phenyl-3'-oxo-butyl)malonate (**4**) as a colourless oil (0.541 g, 97% yield).

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