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Heterogeneous Baylis–Hillman using a polystyrene-bound 4-(*N*-benzyl-*N*-methylamino)pyridine as reusable catalyst†

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An insoluble Merrifield type resin having 4-aminopyridine units is a suitable and reusable heterogeneous catalyst for the Baylis–Hillman coupling of aromatic aldehydes and α,β-unsaturated ketones.

Among the reactions in which C–C bonds are formed, the Baylis–Hillman coupling of aromatic or aliphatic aldehydes with α,β-unsaturated carbonylic compounds is currently attracting much interest due to the mild conditions, the compatibility with many functional groups and the absence of transition metal catalyst and residues.[1,2] For instance, compared to the Heck, Suzuki and other palladium catalysed C–C bond forming reactions,[3] the Baylis–Hillman can be promoted using organic bases in the complete absence of any metal.[4,5]

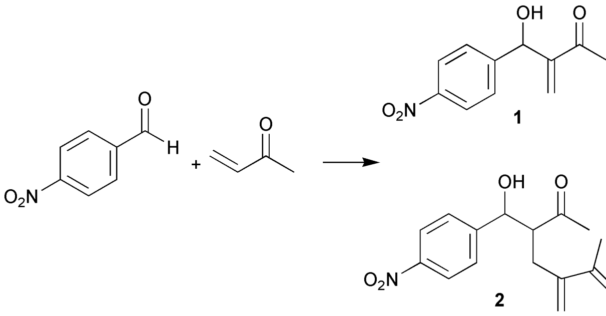
However, all the Baylis–Hillman reactions reported so far use homogeneous catalysis, therefore making difficult the product isolation and impeding the reuse of the catalyst. It is worth commenting that the normal conditions for the Baylis–Hillman reaction use stoichiometric or overstoichiometric amounts of an organic amine as a base and, therefore, it would be highly convenient to recover and reuse the catalyst.

Herein, we report a truly heterogeneous Baylis–Hillman reaction promoted by 4-(*N*-benzyl-*N*-methylamino)pyridine bound to an insoluble polystyrene scaffold (PAP). We will show that the catalyst can be reused and eventually reactivated upon deactivation.

A general strategy to transform a homogeneous into a heterogeneous process consists of anchoring a successful soluble catalyst onto an insoluble support. Polymers have been widely used as insoluble scaffolds for anchoring catalytically active species.[6]

Thus, in view of the fact that nitrogenated nucleophiles are the most common catalysts for the homogeneous Baylis–Hillman reaction,[4,7] we proceeded to study the activity of a polymer in which pyridine units (3 mmol g^{-1}) are covalently attached to a Merrifield type resin through an *N*-benzylamino group (see ESI†). The structure of the polymer is indicated in Fig. 1.

As a test reaction to determine the activity of this polymer we selected the coupling of 4-nitrobenzaldehyde with methyl vinyl ketone, which is a paradigmatic example of the Baylis–Hillman reaction.[8]‡ In all cases the major product was the corresponding β-hydroxyketone accompanied by minor amounts of the Michael adduct [eqn. (1)]. The latter compound **2** is a secondary product derived from **1**[8] and only appears at high conversions when the stoichiometric ratio between 4-nitrobenzaldehyde and methyl vinyl ketone is 1 to 3, but it is undetectable using a 1 to 1.5 molar ratio. Fig. 2a shows a representative time conversion plot for this reaction. Firstly, we studied the reaction in the presence of PAP in several solvents. Table 1 summarizes the results obtained. As can be seen there, while the reaction does not work well in protic solvents, high conversions are obtained in DMF or dichloromethane. This trend is similar to that observed in homogeneous Baylis–Hillman reactions.[8]



(1)

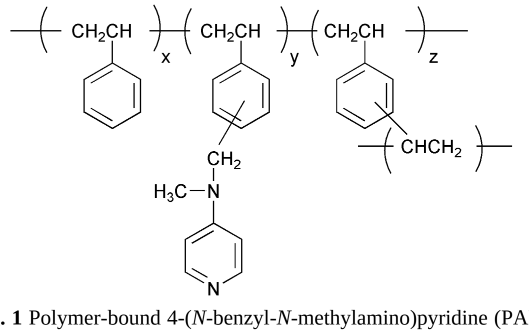


Fig. 1 Polymer-bound 4-(*N*-benzyl-*N*-methylamino)pyridine (PAP).

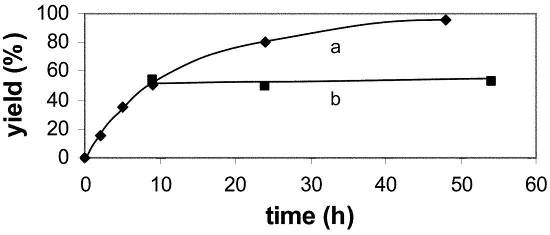


Fig. 2 Time conversion plot for the room temperature Baylis–Hillman reaction of 4-nitrobenzaldehyde (1 equiv.) and methyl vinyl ketone (3 equiv.) in DMF (5 mL) in the presence of solid catalyst (1 equiv.) (a) and after filtering the solid at 50% conversion (b).

Table 1 Results for the Baylis–Hillman reaction of 4-nitrobenzaldehyde (0.5 mmol) and methyl vinyl ketone at 20 °C using PAP as catalyst in different solvents (5 mL). For the molar ratios see Table

Entry	Aldehyde : methyl vinyl ketone : catalyst molar ratio	Solvent	Time/h	Product yield (%)
1	1 : 3 : 1	DMF	18	70
2	1 : 3 : 1	CH_2Cl_2	18	22
3	1 : 3 : 1	CH_3CN	18	25
4	1 : 3 : 1	MeOH	18	6
5	1 : 3 : 1	H_2O	18	4
6	1 : 3 : 0.2	DMF	72	89
7	1 : 3 : 3	DMF	24	90
8	1 : 1.5 : 1	DMF	24	75
9	1 : 1.5 : 1	DMF	48	93
10	1 : 1.5 : 1 (1 reuse)	DMF	24	67
11	1 : 1.5 : 1 (2 reuse)	DMF	24	59
12	1 : 1.5 : 1 (3 reuse)	DMF	24	51
13	1 : 1.5 : 1 (reactivated)	DMF	24	85

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† Electronic supplementary information (ESI) available: procedure for the synthesis of PAP. See http://www.rsc.org/suppdata/cc/b3/b309117a/

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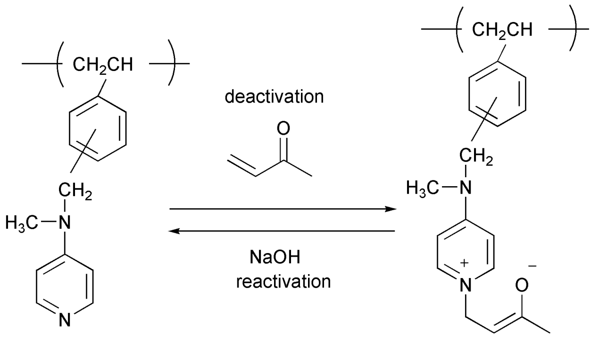
To demonstrate that the Baylis–Hillman coupling catalysed by the pyridine polymer is really a heterogeneous process, an experiment was carried out in DMF in which the catalyst was filtered at 50% conversion and the resulting clear solution surveyed for additional conversion in the absence of the solid. Fig. 2b shows that no further increase in the conversion level occurs after filtration of the catalyst, thus indicating that the solution does not contain any catalytically active species that could have been leached from the solid to the solution.

Besides the solvent and the reactant ratio, another parameter that was also studied was the substrate to catalyst molar ratio, which varied from 0.33 to 5 mol of 4-nitrobenzaldehyde to mol of pyridine units in PAP. As expected, the initial rate decreases upon increase of this ratio, but conversions higher than 90% were also achieved at long times for high ratios (5 mol/mol). This indicates the slow deactivation of PAP and this subject is related to the recycling of the catalyst.

Thus, one aspect of relevance in heterogeneous catalysis is the recycle of the catalyst and its reactivation upon extensive reuse. After having performed one reaction under the conditions indicated in Table 1, the catalyst was recovered by filtration, washed with an aliquot of fresh DMF and CH_2Cl_2, dried in the open air and reused for a consecutive run under the reaction conditions. As expected, the activity of the used catalyst decreased gradually upon successive reuses (Table 1, entries 10–12), the product yield in the fourth run being slightly above 50%. We speculated that the main cause of deactivation could be the covalent attachment of methyl vinyl ketone or any α,β-unsaturated ketone to the pyridine nitrogen of the polymer [eqn. (2)]. Fig. 3 shows an expansion of the aromatic region of the IR spectrum of the catalyst before and after extensive deactivation. This Figure shows that reuse of the catalyst causes the appearance of several bands from 1750 to 1650 cm^{-1} attributable to the presence of several types of carbonyl groups in the deactivated polymer. In order to regain the initial activity, the deactivated catalyst was submitted to treatment with acid or base. While no activity recovery occurs upon contacting the polymer with acid, a reactivation higher than 95% of the initial activity was accomplished by stirring a suspension of the polymer in 2 M NaOH at 60 °C for 1 h. In accordance, the IR of the original PAP was restored. Eqn. (2) shows a reasonable proposal to rationalize the reactivation of the catalyst upon base treatment.



(2)

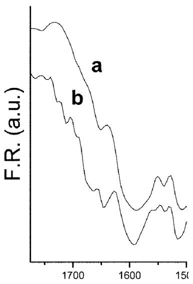
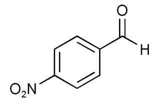
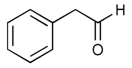
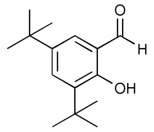
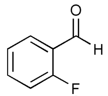
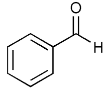
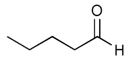


Fig. 3 Part of the IR spectrum of fresh PAP (a) and after its fourth reuse (b).

Table 2 Results for the room temperature Baylis–Hillman reaction of aldehydes : methyl vinyl ketone : PAP (1 : 1.5 : 1 molar ratio) in DMF (5 mL)

Substrate	Time/days	Product yield (%)
	1	81
	3	82[a]
	10	63
	3	41
	10	25
	6	26

[a] Corresponding to the normal Baylis–Hillman product (10%) plus the subsequent Michael addition product (72%).

To demonstrate the applicability of PAP as a heterogeneous catalyst for the Baylis–Hillman coupling, other aldehydes were tested as reactants. Table 2 shows the results achieved in DMF. High chemical yields were also obtained for other aromatic aldehydes and the polymeric catalyst was recovered and reused.

In summary, herein we have demonstrated that an insoluble polymer having aminopyridine groups covalently bonded is a recoverable and reusable heterogeneous catalyst for the Baylis–Hillman coupling of aromatic aldehydes and α,β-unsaturated ketones.

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Notes and references

‡ Reaction procedure: 4-nitrobenzaldehyde (75.6 mg, 0.5 mmol), methyl vinyl ketone (from 1 to 3 equiv.) and polymer (for ratios see Tables, 6 mmol N/g) were placed in a vessel. Then, DMF (5 mL) was added and the suspension was magnetically stirred. The course of the reaction was monitored by taking periodically aliquots from the solution and analyzing them by GC. When no further conversion was observed, the suspension was filtered under vacuum and the solid was washed with DMF (30 mL) and CH_2Cl_2 (30 mL) and dried in the open air. All the products were characterised by GC-MS, ^1H and ^{13}C NMR.

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