Phase selectively soluble dendritic derivative of 4-(*N*,*N*-dimethylamino)pyridine: an easily recyclable catalyst for Baylis–Hillman reactions

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Abstract

The Baylis–Hillman reaction of various aryl aldehydes with methyl vinyl ketone and acrylonitrile in the thermomorphic binary system (DMF/cyclohexane, 1/1, v/v) has been investigated. The phase selectively soluble alkyl-modified dendritic DMAP catalyst could be easily recycled via phase separation which was induced by cooling the temperature from 60 °C to room temperature. The corresponding Baylis–Hillman adducts were obtained in good yields and the recycled and reactivated dendritic catalyst almost gave the same results.
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1. Introduction

The problems associated with the recovery of catalysts after product formation pose a serious drawback for large-scale applications of homogeneous catalysis and are the main reason why heterogeneous catalysis has a share of more than 80% in industrial processes.

Consequently, numerous approaches that deal with the problem of catalyst recovery, such as thermal or chemical recovery, immobilization of catalysts on solid, liquid or aqueous supports, membrane processes or multiphase systems (phase-transfer catalysis, thermoregulated phase-transfer catalysis, liquid–liquid biphasic catalysis) have been studied [1–4].

Among the reactions in which C–C bonds are formed, the Baylis–Hillman coupling of aldehydes with α,β-unsaturated carbonylic compounds is currently attracting much interest due to the atom economy, the mild conditions and the generality of functional groups [5,6]. Furthermore, compared to the Heck, Suzuki and other palladium catalyzed C–C bond forming reaction [7], the Baylis–Hillman reaction can be promoted by using organic bases in the complete absence of any metal [8,9].

However, almost all the Baylis–Hillman reactions reported so far use homogeneous catalyst, and it makes product isolation very difficult and impedes the reusing of the catalyst. In addition, this reaction could be accomplished in a perfect atom-economic way if a recyclable Lewis base was employed as the promoter. Recently, Corma et al. [10] developed a heterogeneous catalyst system by using an insoluble Merrifield type resin-supported 4-(*N*-benzyl-*N*-methyl amino)pyridine as reusable catalyst for the Baylis–Hillman coupling of aromatic aldehydes and α,β-unsaturated ketones. Shi and coworker [11] reported the use of soluble polymer-supported Lewis bases such as PEG4600-(PPh$_2$)$_2$ and linear poly(DMAP) in the Baylis–Hillman reactions of *N*-tosylimines with α,β-unsaturated ketones.

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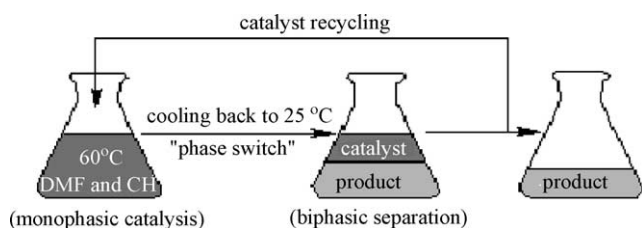
Scheme 1. Illustration of the switched biphasic catalysis.

Herein, we report a novel thermomorphic catalytic system [12] for the Baylis–Hillman reaction of α,β-unsaturated ketones and aromatic aldehydes. Our strategy employed the dendritic Lewis base as the catalyst together with a binary solvent system (DMF–cyclohexane, 1:1, v/v) which could become homogeneous when heated up to 60 °C and then could be readily separated by cooling the system to room temperature (Scheme 1). Our thermomorphic catalytic system thus provided the following key advantages: (a) unlike the heterogeneous system reported by Corma et al. [10], this thermomorphic biphasic system provided complete miscibility of the two phase under the reaction temperature; (b) the structure of dendrimer catalyst is well-defined and could be analyzed by using common spectral techniques, such as NMR and mass spectroscopy; (c) as compared to soluble polymer supported catalytic Baylis–Hillman reaction reported by Shi and coworker [11], this strategy avoided the use of large amounts of diethyl ether for catalyst precipitation. Therefore, this system has the potential to combine the advantages of homogenous and heterogeneous catalysis.

2. Results and discussion

To test the efficacy of our new thermomorphic system for Baylis–Hillman reaction and for the separation of the catalyst, we chose a dendritic derivative of 4-(N,N-dimethylamino)pyridine (DMAP) (Scheme 2) as catalyst for this study, which was conveniently prepared according to our reported procedure [13].

With the dendritic DMAP on hand, we then explored the solvent compositions in order to meet the requirements of the thermomorphic biphasic system and the catalyst recycling. Since the DMF has been found to be best for most Baylis–Hillman reactions, the binary system DMF–cyclohexane (CH) was firstly studied. It was found
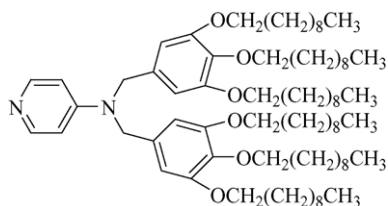
Scheme 2. Structure of N,N-di(3′,4′,5′-tri(n-decan-1-yloxy) benzyl)-4-aminopyridine (dendritic DMAP).
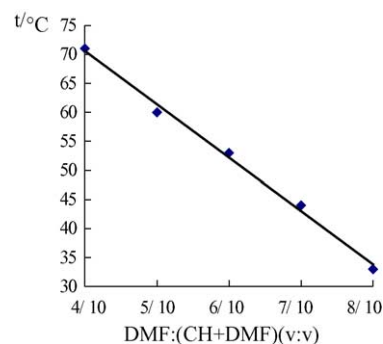

Scheme 3. Effect of solvent composition on the miscible temperature. Each biphasic solvent mixture was gradually heated (1 °C/min) with stirring to form a homogeneous solution at the temperature plotted above.

that the miscibility of the mixture containing all two of these solvents depended on the proportions of solvents used and the temperature of the system. As shown in Scheme 3, the miscible temperature decreased with increase ratio of DMF. For example, when the ratio of DMF and CH is 1:1(v/v), the binary system become monophasic at 60 °C. Under the same temperature, the dendritic DMAP was found to be well soluble in this solvent mixture. Importantly, after this system was cooled to room temperature, 97.5% of the dendritic catalyst could be extracted to the non-polar CH phase. We thus chose the solvent mixture of DMF and CH (1:1, v/v) as the solvent system for this study.

In order to determine the activity of this dendritic catalyst in the biphasic thermomorphic system, we chose the coupling of 4-nitrobenzaldehyde with methyl vinyl ketone (MVK) as the model reaction, which is a paradigmatic example of the Baylis–Hillman reaction [10,14]. In all cases only the normal Baylis–Hillman product was found [14a,15].

Firstly, we studied the reaction in the binary system (DMF/CH, 1:1, v/v) to find out the best reaction conditions and the results were summarized in Table 1. As seen from the

Table 1
Baylis–Hillman Reactions of 4-nitrobenzaldehyde (1.0 equiv.) with MVK in the presence of dendritic DMAP[a]
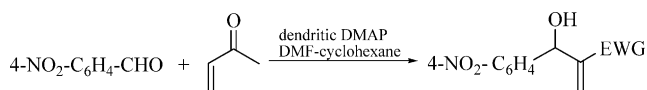
Entry	Aldehyde:MVK:dendritic DMAP (molar ratio)	Time (h)	Isolated yield (%)
1	1:1:1	24	33.6
2	1:1.5:1	24	40.4
3	1:2:1	24	49.1
4	1:3:1	24	64.7
5	1:4:1	24	63.9
6	1:3:0.2	24	30.7
7	1:3:1	36	81.2
8	1:3:1	48	92.3
9	1:3:1	60	92.0

[a] Reactions were carried out in 4 ml binary solvent (DMF:CH, 1:1, v/v) at 60 °C.

Table 2
Recyclability of the dendritic catalyst without and with reactivation[a]

| Entry	Isolated yield (%)				
	First run	Second run	Third run	Fourth run	Fifth run
1[b]	78.5	55.4	47.6	–	–
2[c]	92.1	91.0	92.6	92.1	91.2

[a] Reactions were carried out on a 1.0 mmol scale, in 4 ml binary solvent (DMF:CH, 1:1, v/v) using a ratio of 1:3:1 (4-nitrobenzaldehyde/MVK/dendritic DMAP at 60 °C).
[b] The catalyst was directly used in the nest run without reactivation.
[c] The catalyst was reactivated before the next run.

table, the highest yield was achieved when the molar ratio of aldehyde:MVK:dendritic DMAP being 1:3:1, and reacting time 48 h was used as the conditions (Table 1, entry 8).

The recyclability of the dendritic catalyst was then evaluated under the optimized conditions. It was found that the catalyst could be easily recovered via phase separation by cooling the reaction mixtures to room temperature at the end of the reaction. After having performed one reaction under the conditions indicated in Table 1, entry 8, the catalyst was recovered from the CH layer by cooling back to 25 °C and directly reused for a consecutive run under the same conditions (Table 2, entry 1). In the four runs reaction, the catalyst showed decrease in activity with reaction yields from 92.3% to 47.6% (Table 1, entry 8; Table 2, entry 1). The deactivation of the catalyst was probably due to the covalent attachment of MVK or any α,β-unsaturated ketone to the pyridine nitrogen of the catalyst (Scheme 4) [10,16]. In order to regain the initial activity, the deactivated catalyst was treated with
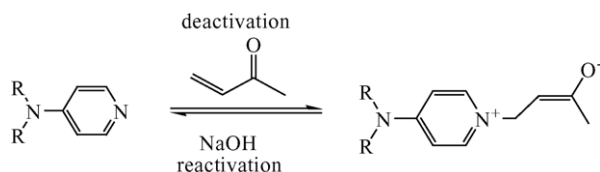
Scheme 4. The deactivation and reactivation of dendritic DMAP.

Table 4
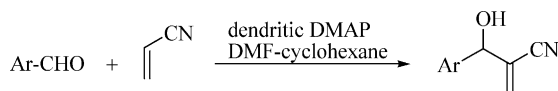The Baylis–Hillman reactions of aryl aldehydes with acrylonitrile in the presence of dendritic DMAP[a]

Entry	Ar	Time (days)	Product	Yield[b] (%)	Yield[b,c] (%)
1	4-O$_2$NC$_6$H$_4$	2	**1b**	94.6	95.0
2	2-O$_2$NC$_6$H$_4$	2	**2b**	93.0	93.7
3	4-CNC$_6$H$_4$	2	**3b**	90.0	91.2
4	4-BrC$_6$H$_4$	2	**4b**	90.0	88.9
5	4-ClC$_6$H$_4$	2	**5b**	87.1	88.9
6	C$_6$H$_5$	3	**6b**	66.8	67.8
7	4-CH$_3$OC$_6$H$_4$	5	**7b**	50.2	51.6
8	2-CH$_3$OC$_6$H$_4$	5	**8b**	48.2	49.5

[a] Reactions were conducted on 1.0 mmol scale using 1:3:1 molar ratio of aldehydes:MVK:dendritic DMAP, in 4 ml binary solvent (DMF:CH, 1:1, v/v).
[b] Isolated yield.
[c] The recycled and reactivated dendritic DMAP was used.

2 M NaOH at 60 °C for 2 h and subsequent was applied to the reaction under otherwise the same conditions, giving equivalent yield (Table 2, entry 2). Scheme 4 shows a reasonable proposal to rationalize the reactivation of the catalyst upon base treatment.

To demonstrate the applicability of dendritic DMAP as a homogeneous catalyst for the Baylis–Hillman reaction, various other aldehydes were tested as reactants reacting with MVK and the results are shown in Table 3. It was found that the aryl aldehydes having strongly electron-withdrawing groups on the benzene rings such as nitrobenzaldehydes and nitrilbenzaldehydes reacting with MVK gave the corresponding Baylis–Hillman adducts with high yields (entries 1–3). On the contrary, other aryl aldehydes, in particular with electron-donating substituents provided low to good reaction yields (entries 6–8). We also examined the Baylis–Hillman reaction of aryl aldehydes with acrylonitrile in the binary

Table 3
The Baylis–Hillman reactions of aryl aldehydes with MVK in the presence of dendritic DMAP[a]
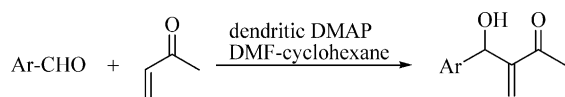
Entry	Ar	Time/days	Product	Yield (%)[b]	Yield (%)[b,c]
1	4-O$_2$NC$_6$H$_4$	2	**1a**	92.3	92.1
2	2-O$_2$NC$_6$H$_4$	2	**2a**	92.0	92.4
3	4-CNC$_6$H$_4$	2	**3a**	89.7	90.1
4	4-BrC$_6$H$_4$	2	**4a**	87.7	89.3
5	4-ClC$_6$H$_4$	2	**5a**	85.4	81.2
6	C$_6$H$_5$	3	**6a**	47.8	53.4
7	4-CH$_3$OC$_6$H$_4$	5	**7a**	35.3	38.1
8	2-CH$_3$OC$_6$H$_4$	5	**8a**	27.7	27.6

[a] Reactions were conducted on 1.0 mmol scale using 1:3:1 molar ratio of aldehydes:MVK:dendritic DMAP, in 4 ml binary solvent (DMF:CH, 1:1, v/v).
[b] Isolated yield.
[c] The recycled and reactivated dendritic DMAP was used.

thermomorphic system. Very similar results were obtained (Table 4). It was noted that the recycled and reactivated dendritic DMAP almost gave the same reaction yields.

3. Conclusions

In summary, we have described a new thermomorphic catalytic system by using dendritic derivative of 4-(*N,N*-dimethylamino) pyridine as catalyst for the Baylis–Hillman reactions of aryl aldehydes with MVK and acrylonitrile. The recyclability and applicability of this catalytic system has been well demonstrated in the binary solvent system (DMF–cyclohexane, 1:1, v/v).

4. Experimental

4.1. General remarks

All glassware was oven dried and cooled in a desiccator (silica gel desiccant) prior to use. Aryl aldehydes and acrylonitrile were distilled and stored under a nitrogen atmosphere before used. Other commercially supplied reagents were used as supplied without further purification. Organic solvents were dried by standard methods when necessary.

^{1}H NMR spectra were recorded on a BRUKER 400 spectrometer for solution in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. Chemical shifts are reported downfield in parts per million (ppm) and *J*-values are in Hz.

4.2. General procedure for the Baylis–Hillman reaction of aryl aldehydes with MVK and acrylonitrile

To a 10 ml bottom flask charged with **1** (1.0 mmol) and dendritic DMAP (1.21 g, 1.0 mmol) in 4 ml binary solvent (DMF:CH, 1:1, v/v) was added methyl vinyl ketone (MVK) (249 μl, 3.0 mmol) or acrylonitrile (197 μl, 3.0 mmol) under nitrogen atmosphere and the reaction mixture was stirred 48 h at 60 °C. At the end of the reaction, after the reaction mixture was cooled back to 25 °C, the reaction mixture turned to be biphasic. The catalyst was recovered from the CH layer and was directly used in the next run (Table 2, entry 1) or reused after reactivated for a consecutive run under the same conditions (Table 2, entry2; Tables 3 and 4). The product was remained in the DMF layer, the solvent was removed under reduced pressure and the residue was further purified by flash chromatography and characterized by ^{1}H NMR.

4.3. Characterization of the Baylis–Hillman reaction adducts

Compounds **1a**, **2a**, **4a**, **5a**, **6a**, **1b** and **6b** have been successfully characterized in the literature [15,17].

Compound **3a** ^{1}H NMR ($CDCl_3$, 400 MHZ, TMS): δ 2.35 (3H, s, Me), 3.00 (1H, br., s, OH) 5.63 (1H, s, CH), 6.01 (1H, s, olefinic), 6.24 (1H, s, olefinic), 7.49 (2H, d, *J* = 8.4 Hz, Ar), 7.62 (2H, d, *J* = 8.0 Hz, Ar).

Compound **7a** ^{1}H NMR ($CDCl_3$, 400 MHZ, TMS): δ 2.00 (1H, br., s, OH), 2.13 (3H, s, Me), 3.87 (3H, s, OCH_3), 5.80 (1H, s, CH), 5.83 (1H, s, olefinic), 6.02 (1H, s, olefinic), 6.87 (2H, d, *J* = 8.3 Hz, Ar), 7.27 (2H, d, *J* = 8.4 Hz, Ar).

Compound **8a** ^{1}H NMR ($CDCl_3$, 400 MHZ, TMS): δ 2.36 (3H, s, Me), 3.35 (1H, br., s, OH), 3.82 (3H, s, MeO), 5.86 (1H, s, olefinic), 5.93 (1H, s, olefinic), 6.15 (1H, s, CH), 6.87 (1H, d, *J* = 8.4 Hz, Ar), 6.96 (1H, dd, *J* = 7.6, 7.6 Hz, Ar), 7.26 (1H, dd, *J* = 7.2, 7.2 Hz, Ar), 7.35 (1H, d, *J* = 7.6 Hz, Ar).

Compound **2b** ^{1}H NMR ($CDCl_3$, 400 MHZ, TMS): δ 3.45 (1H, br., s, OH), 6.02 (1H, s, CH), 6.12 (1H, s, olefinic), 6.14 (1H, s, olefinic), 7.55 (1H, t, *J* = 15.6 Hz, Ar), 7.74 (1H, t, *J* = 15.2 Hz, Ar), 7.87 (1H, d, *J* = 7.6 Hz, Ar), 8.04 (1H, d, *J* = 8.0 Hz, Ar).

Compound **3b** ^{1}H NMR ($CDCl_3$, 400 MHZ, TMS): δ 2.00 (1H, br., s, OH), 5.40 (1H, s, CH), 6.09 (1H, d, *J* = 0.8 Hz, olefinic), 6.17 (1H, d, *J* = 1.2 Hz, olefinic), 7.55 (2H, d, *J* = 8.0 Hz, Ar), 7.70 (2H, d, *J* = 8.4 Hz, Ar).

Compound **4b** ^{1}H NMR ($CDCl_3$, 400 MHZ, TMS): δ 2.18 (1H, br., s, OH), 5.27 (1H, s, CH), 6.04 (1H, d, *J* = 0.76 Hz, olefinic), 6.11 (1H, d, *J* = 1.2 Hz, olefinic), 7.27 (2H, d, *J* = 8.4 Hz, Ar), 7.54 (2H, d, *J* = 4.0 Hz, Ar).

Compound **5b** ^{1}H NMR ($CDCl_3$, 400 MHZ, TMS): δ 2.38 (1H, br., s, OH), 5.27 (1H, s, CH), 6.03 (1H, s, olefinic), 6.09 (1H, s, olefinic), 7.32 (2H, d, *J* = 8.53 Hz, Ar), 7.37 (2H, d, *J* = 8.53 Hz, Ar).

Compound **7b** ^{1}H NMR ($CDCl_3$, 400 MHZ, TMS): δ 2.18 (1H, br., s, OH), 3.82 (3H, s, MeO), 5.26 (1H, s, CH), 6.03 (1H, d, *J* = 1.0 Hz, olefinic), 6.11 (1H, d, *J* = 1.4 Hz, olefinic), 6.93 (2H, d, *J* = 8.0 Hz, Ar), 7.31 (2H, d, *J* = 7.8 Hz, Ar).

Compound **8b** ^{1}H NMR ($CDCl_3$, 400 MHZ, TMS): δ 2.22 (1H, br., s, OH), 3.86 (3H, s, MeO), 5.50 (H, s, CH), 6.00 (H, s, olefinic), 6.01 (H, s, olefinic), 6.92 (1H, d, *J* = 8.4 Hz, Ar), 7.00 (1H, dd, *J* = 8.0, 8.0 Hz, Ar), 7.33 (2H, m, Ar).

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