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Phase Selectively Soluble Dendritic Derivative of 4-(Dimethylamino)-pyridine: An Easily Recyclable Catalyst for Baylis-Hillman Reactions

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Abstract: A new thermomorphic catalytic system for the Baylis-Hillman coupling of aromatic aldehydes with α, β-unsaturated ketone has been described, in which the alkyl-functionalized dendritic catalyst preferred to dissolve in non-polar organic layer in the thermomorphic biphasic system, leading to easy separation of the catalyst from the polar products by changing the temperature of the system at end of the reaction.

Keywords: Baylis-Hillman reaction, dendrimer, thermomorphic biphasic catalysis, immobilization.

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 generation of functional groups[1,2]. Furthermore, compared to the Heck, Suzuki and other palladium catalyzed C-C bond forming reaction[3], the Baylis-Hillman reaction can be promoted by using organic bases in the complete absence of any metal[4].

However, almost all the Baylis-Hillman reactions reported so far use homogeneous catalyst, and it makes isolation of the products very difficult and impedes the reusing of catalyst. Very recently, Avelino Corma and coworkers[5] developed a heterogeneous catalyst system by using a polystyrene-bound 4-(N-benzyl-N-methylamino) pyridine as reusable catalyst. Herein, we report a new thermomorphic catalytic system[6] for the Baylis-Hillman reaction. Our strategy employed the dendritic catalyst together with a binary solvent system (DMF-cyclohexane, 1:1, v/v), which could become homogeneous when heated up to 60℃ and then could be readily separated by cooling the system to 25℃(**Scheme 1**). In contrast to the heterogeneous catalyst system reported by Avelino Corma and coworkers[5], our thermomorphic catalytic system provided the following two key advantages: (a) Thecatalyzed Baylis-Hillman reaction could be carried out in a homogeneous manner; (b) The structure of the dendritic catalyst could be characterized by using common spectral techniques, such as NMR, TOF mass spectroscopy.

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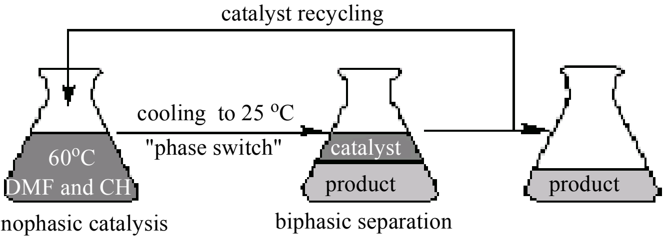
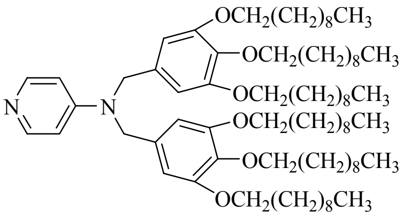
Scheme 1 Illustration of the thermomorphic catalytic system



Scheme 2 N, N-di(3`,4`,5`-tri(*n*-decan-1-yloxy)benzyl)-4-aminopyridine (DAP)



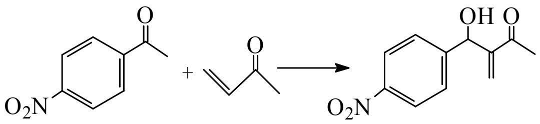
To test the efficacy of our new thermomorphic system for Baylis-Hillman reaction and for the separation of the catalyst, we chose a dendritic derivative of 4-(dimethylamino) pyridine (**Scheme 2**) as catalyst for this study, which was conveniently prepared according to our reported procedure[7].

Then the solvent compositions for the thermomorphic biphasic system are explored. Since the DMF has been found to be the best solvent for most Baylis-Hillman reactions, the binary system DMF-cyclohexane (CH) was studied. Fortunately, it was found that a binary solvent system consisting of DMF and CH (1:1, v/v) is monophasic at 60℃, while turn to be biphasic by cooling to 25℃. Importantly, about 97.5% of the catalyst could be extracted to the non-polar CH phase in the binary solvent system.

In order to determine the activity of the 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[8] (**Scheme 3**). Firstly, we studied the reaction in the binary system (DMF and CH, 1:1, v/v) to find out the best reaction conditions and the results were summarized in **Table 1**. As seen from it, the highest yield was achieved when the molar ratio of aldehyde: MVK: DAP being 1:3:1 and reaction time being 48 h (**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 25℃ at the end of the reaction. In the four runs reaction, the catalyst decreased activity with reaction yields from 92.3% to 47.6% (**Table 1**, entries 8 and 10-12). 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**)[5]. In order to regain the initial activity, the deactivated catalyst was treated with 2mol/L NaOH at 60℃ for 2 h and subsequent applied to the reaction in the same condition, giving 92.1% yield (**Table 1**, entry 13). **Scheme 4** shows a reasonable proposal to rationalize the reactivation of the catalyst upon base treatment.

To demonstrate the applicability of DAP as a homogeneous catalyst for the Baylis-Hillman reaction, other aldehydes were tested as reactants and the results are shown in **Table 2**. Aldehydes with chloro- and bromo-substituent and benzaldehyde gave moderate to high reaction yield. However, aldehyde with electron-donating substituents provided much low reaction yield.

Scheme 3



Scheme 4 The deactivation and reactivation of DAP

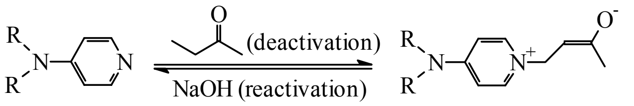


Table 1 Results for the Baylis-Hillman reaction of 4-nitrobenzaldehyde(1.0 mmol) with MVK[a]

Entry	Aldehyde: MVK: DAP (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
10	1:3:1 (1 reuse)	48	78.5
11	1:3:1 (2 reuse)	48	55.4
12	1:3:1 (3 reuse)	48	47.6
13	1:3:1 (reactivated)	48	92.1

[a] All reactions were carried out at 60℃ using DAP as catalyst in 2mL DMF and 2mL CH (1:1, v/v)

Table 2 Results for the Baylis-Hillman reaction of aromatic aldehydes with MVK[a]

Substrate	Time/days	Isolated yield (%)	Isolated yield (reactivated)(%)
p-Nitrobenzaldehyde	2	92.3	92.1
p-Bromobenzaldehyde	2	87.7	89.3
p-Chlorobenzaldehyde	2	85.4	81.2
Benzaldehyde	3	57.8	53.4
Anisaldehyde	5	35.3	38.1

[a] aldehydes : MVK : DAP (1:3:1 molar ratio) in the thermomorphic catalytic system (4 mL) at 60℃.

In summary, we have described a new thermomorphic catalytic system by using dendritic derivative of 4-(dimethylamino)pyridine as catalyst for the Baylis-Hillman reaction. The recyclability and applicability of this catalytic system has been demonstrated in the binary solvent system (DMF-cyclohexane, 1:1, v/v). Further applications of this catalytic system in the Baylis-Hillman reaction with a broader range of substrates are being underwent in our laboratory.

Acknowledgment

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