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Catalytic direct 1,4-conjugate addition of aldehydes to vinylketones on secondary-amines immobilised in FSM-16 silica

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Direct 1,4-conjugate addition of naked aldehydes to vinylketones is catalysed effectively by *N*-methyl-3-aminopropylated FSM-16 mesoporous silica, which can be regarded as a novel heterogeneous catalysis for a practical C–C bond formation reaction.

Substituted 5-ketoaldehydes **3** have been important synthons especially for substituted cyclohex-2-en-1-one derivatives which have been versatile starting materials for synthesis of natural products such as terpenoids. Because of the difficulty in controlling high reactivity of formyl groups, the synthesis of 5-ketoaldehydes **3** has been accomplished *via* several-pot reaction *via* 1,4-addition of masked aldehydes such as enamines or silylenol ethers in the presence of Lewis acid.[1] However, it was recently found by Hagiwara *et al.* that diethylamine catalyses the direct 1,4-conjugate addition of naked aldehydes to vinylketones, though a large amount of catalyst was used.[2] In order to improve the catalytic performance of this novel reaction, we have attempted heterogenization of the catalyst to provide a recyclable and efficient solid catalyst.

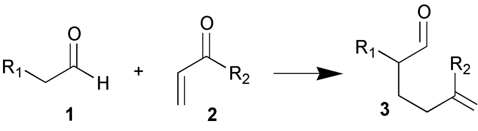
From environmental and economical points of view, the use of heterogeneous catalysts offers several advantages in organic synthesis, *e.g.* simplification of reaction procedures, easy separation of products, repeated use, and so on.[3–12] Mesoporous silicas such as FSM-16[13] and MCM-41,[14] having high surface areas of > 1000 m^2 g^{-1} and large pore sizes, can be unique inorganic supports for introducing reactive species for the catalysis involving bulky substances.[5–12] For example, novel heterogeneous basic catalysts, in which amines are covalently anchored to mesoporous silicas, were reported as noble catalysts.[5–10] However, in most of the studies, this new class of solid catalysts was employed for 'ordinary' reactions such as Knoevenagel,[6,8,9] aldol[9] and nitroaldol[10] condensations, which can also be catalysed by classical oxidic solid bases[4] such as alkali ion-exchanged zeolites, alkaline earth oxides and hydrotalcite. Here, we report that direct 1,4-conjugate addition of naked aldehydes **1** to vinylketones **2**, which cannot be catalysed by ordinary oxidic solid bases, is catalysed efficiently by *N*-methyl-3-aminopropylated FSM-16 mesoporous silica (NMAP-FSM). The truly catalytic behaviour of this material as well as the recycling characteristics are presented to exemplify the effectiveness of this catalytic system.

Pure silica FSM-16 was prepared from kanemite by using $C_{16}H_{33}NMe_3Cl$ according to a method previously described.[13] Amorphous silica (Cab-O-Sil, 200 m^2 g^{-1}) was also used for a comparison. Surface functionalization with amino groups was carried out according to the method described in the literature.[7,15] The catalysts were prepared with a fairly high atom-efficiency: elemental analysis on solid materials (Table 1) revealed that more than 80% of amino-silanes introduced were anchored on the supports. Since XRD patterns of NMAP-FSM were essentially the same as that of FSM-16, the long-range ordered structure of the support was confirmed to be preserved. ^{13}C-MAS NMR spectra of NMAP-FSM showed the presence of *N*-methyl-3-aminopropyl groups (53.0, 34.0, 20.5 and 10.5 ppm). The surface area, pore volume, and pore diameters of the catalysts were as expected for mesoporous materials (Table 1). These values were reduced after amino group introduction, which should be due to the presence of amino groups in the

Table 1 Physical characteristics of immobilised NMAP catalysts

Catalyst	Loading[a]/ mmol g^{-1}	S$_{BET}$[b]/ m^2 g^{-1}	V_p[c]/ cm^3 g^{-1}	APD[d]/ nm
1	0.74	572	0.89	2.74
2	0.48	720	0.96	2.77
3	0.18	788	1.01	2.54
4	0	881	1.23	2.81
5 (AP)[e]	0.75	777	1.05	2.67
6 (DMAP)[f]	0.52	783	1.01	2.54
7 (SiO$_2$)[g]	0.76	164	—	—

[a] Estimated from nitrogen content. [b] BET surface area obtained from the N$_2$ adsorption isotherm. Before the experiment, the sample was dried at 150 °C for 1 h. [c] Pore volume obtained from the BJH equation. [d] Average pore diameter obtained from the BJH equation. [e] Aminopropylated FSM-16. [f] *N*,*N*-Dimethylaminopropylated FSM-16. [g] NMAP immobilised on amorphous silica.



Scheme 1

Table 2 Conjugate addition of decanal to MVK[a]

Entry	Catalyst ([N]/mol%)[b]	*t*/h	**3** Yield (%)	TON[c]
1	**1** (0.8)	3	57	75
2	**2** (0.5)	24	33	72
3	**3** (0.5)	24	41	81
4	**4** (0)[d]	24	0	—
5	**5** (5.0)	6	24	4.9
6	**6** (5.0)	24	2	0.5
7	**7** (1.0)	6	44	50
8	**1** (10)	1	70	7.0
9	1st reuse (10)[e]	1	72	7.2
10	2nd reuse (10)[e]	1	64	6.4
11	3rd reuse (10)[e]	1	63	6.3
12	Et$_2$NH (2.0)[f]	20	29	14
13	PrNHMe (2.0)[g]	20	21	11
14	MgO[dhi]	24	0	—
15	Hydrotalcite[dhj]	24	0	—

[a] Reactions were conducted with decanal (1 mmol), MVK (1.5 mmol) in toluene (5 mL) at reflux temperature under N$_2$. [b] Amount of the catalyst tested. [c] Amount of product per mole of amino groups. [d] The catalyst loading was 0.1 g. [e] Reuse of NMAP-FSM. [f] Diethylamine. [g] *N*-Methyl-3-propylamine. [h] Prior to the reaction, catalysts were evacuated at 500 °C for 1 h. [i] MgO (JRC-MGO-1) was supplied from the Catalysis Society of Japan. [j] Mg–Al hydrotalcite ($Mg_6Al_2(OH)_{16}CO_3{\cdot}4H_2O$) was supplied from Kyowa Chemcl Industry Co., Ltd.

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channels of FSM-16. These results indicate that amino groups were anchored to the channels of FSM-16 silica.

Table 2 shows the results of the 1,4-conjugate addition of decanal (**1**, R_1=C_8H_{17}) to methylvinylketone (MVK) (**2**, R_2=CH_3).[16] The 1,4-adduct, 5-ketoaldehyde **3**, is selectively produced on NMAP-FSM catalysts (entries 1, 2, 3 and 8), although the reactions do not occur with conventional solid bases such as MgO and hydrotalcite (entries 14 and 15). No measurable by-products were observed by GC and HPLC analyses. The present reaction system required no additional regent other than solvent and produced no side-products (Scheme 1).

The amine-free FSM-16 silica is completely inert (entry 4), and hence, anchored amino groups are the catalytic species of NMAP-FSM. The activity depends strongly on the type of amines supported. The order of the activity is secondary > primary > tertiary (entries 1, 5 and 6), suggesting the intervention of the enamine pathway.[2] For secondary-amine supported catalysts, the equivalence of the amine sites was probed by changing the loading of the active site (NMAP group) per unit catalyst mass (entries 1, 2 and 3). The TON values of NMAP-FSM are almost independent of the NMAP loading, which suggests that each immobilised secondary-amine can act as the active site with similar reactivity. The catalysts based on hexagonal mesoporous silica show higher activity than that on amorphous silica, TON being 1.5 times higher by comparing catalysts with similar loading (entries 1 and 7). It is noteworthy that the TON value of the NMAP-FSM is much higher than those of the homogenous amine catalysts, *N*-methyl-3-propylamine or diethylamine (entries 12 and 13). We believe, at present, that the higher TON of NMAP-FSM catalyst than its homogenous counterpart as well as NMAP supported on amorphous silica is due to the increase in the reactant concentration inside the channels of FSM-16 mesoporous silica.

Elemental analysis showed that nitrogen content of the NMAP-FSM catalyst did not decrease after the reaction,[17] confirming that leaching of amino groups during the reaction was negligible. The reaction did not proceed further when the solid catalyst was removed before completion of the reaction, proving heterogeneous catalytic activity of NMAP-FSM and no contribution from homogenous catalysis. The catalyst can be easily separated from the reaction mixture by simple filtration and is recycled. Although the simply filtered catalyst showed a decrease in activity (yield = 43%), the activity of the recovered catalyst (entries 9, 10 and 11) was comparable to that observed for the first run (entry 8) when the filtered catalyst was simply dispersed in a dilute aqueous solution of K_2CO_3 (2 mM) for 5 min, followed by washing with distilled water and subsequent drying at 373 K.[18] By this treatment, the catalyst was reusable for all the three cycles in the repeated runs without a marked loss of activity.

The general applicability of the present 5-ketoaldehyde synthesis has been demonstrated by expanding the reaction to different aldehydes and vinylketones (Table 3). In all cases, the 5-ketoaldehyde **3** is obtained as a sole product in high yields. The best yield (93%) is obtained in the reaction of *n*-hexanal with ethylvinylketone (EVK) on NMAP-FSM catalyst (entry 5). It is worthy of note that the reaction proceeds even with a small amount of the catalyst (0.1 mol%), and a TON of 400 was obtained (entry 6), which indicates a high stability of the immobilised catalyst.

In conclusion, we have developed a highly convenient 1,4-addition of naked aldehydes to vinylketones catalysed by the secondary-amine immobilised FSM-16 mesoporous silica. The present system can be regarded as a novel heterogeneous catalysis for a practical and environmentally friendly C–C formation reaction in view of the following advantages: (1) easy separation of the catalyst by simple filtration, (2) reusability without loss of activity, (3) one-pot reaction without additives, side-products, and by-products.

Table 3 Conjugate addition of aldehydes to vinylketones with the catalyst **1**[a]

Entry	Aldehydes	Vinylketones	**3** Yield (%)	TON
1	*n*-Octanal	MVK	59	59
2	*n*-Hexanal	MVK	87	87
3	*n*-Butanal	MVK	88	88
4	$Ph(CH_2)_2CHO$[b]	MVK	37	37
5	*n*-Hexanal	EVK	93	93
6	*n*-Hexanal[c]	EVK	40	400

[a] Reaction were conducted with aldehydes (1 mmol), vinylketones (1.5 mmol) in toluene (5 mL) at reflux temperature under N_2 with 1 mol% of the catalyst. [b] Acetonitrile was used as solvent. [c] Amount of the catalyst tested was 0.1 mol%.

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15 Typically, 2.0 g of the FSM-16 sample was evacuated at 150 °C and then toluene (20 mL) containing *N*-methyl-3-aminopropyl(triethoxy)silane was introduced. The mixture was heated at reflux for 3 h and the solid was filtered off, washed with toluene and acetone and dried at 100 °C overnight.

16 Before the reaction, the catalyst was dried in air at 150 °C for 1 h. The reaction was carried out by stirring the reaction mixture containing aldehydes (1 mmol) and vinylketones (1.5 mmol) in dry toluene (5 mL) at reflux temperature under nitrogen atmosphere. Progress of the reactions was monitored by GC analyses of aliquots using *o*-xylene as internal standard.

17 Nitrogen contents per gram of the support before and after the reaction were 0.80 mmol g^{-1} and 0.83 mmol g^{-1}, respectively.

18 This observation may be explained as follows. The organic acids, present as impurities in aldehydes or produced during the reaction, neutralised the amine catalysts. The organic acids were removed by treatment with dilute aqueous K_2CO_3 solution.