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Magnetic Nanoparticle-Supported Morita–Baylis–Hillman Catalysts

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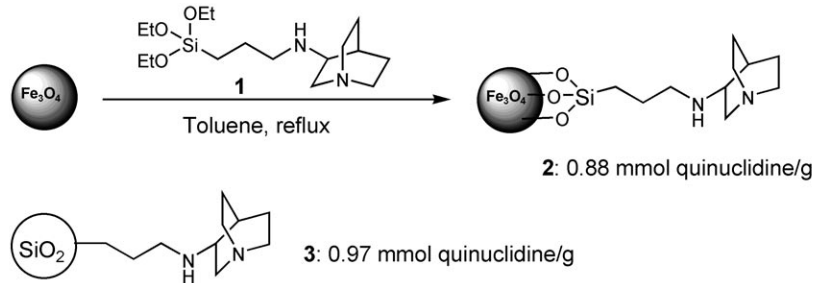
Abstract: A magnetic nanoparticle-supported quinuclidine was prepared and evaluated as a recoverable Morita–Baylis–Hillman catalyst. The supported catalyst **2** demonstrated comparable activity with that of DABCO and could be simply recycled with the assistance of an external magnet. The thus recycled catalyst could be reused for 7 times without significant loss of activity.

Keywords: magnetic nanoparticles; Morita–Baylis–Hillman reaction; organocatalysts; support

The Morita–Baylis–Hillman (MBH) reaction is one of the most popular C–C bond-forming strategies in modern organic synthesis due to its advantages in regard to atom economy, non-metal catalysis, mild conditions, and the promising utility of its multifunctional products.[1] As a classical organocatalytic process, the MBH reaction is typically known for its high loading of catalysts and sluggish reaction rates. Hence, significant efforts have been made in order to overcome these limitations. Remarkable advances along this line in the past decade have led to the discovery of new catalysts with superior activity, the development of novel chemical and physical strategies for rate accelerations as well as the development of reusable Baylis–Hillman catalysts.[2] Recently, several research groups have reported supported Lewis bases as reusable Baylis–Hillman catalysts. Shi and Corma independently investigated the use of commercially available poly-DMAP as the recyclable Baylis–Hillman catalyst.[3] Furthermore, Shi and co-workers examined the activity and reusability of PEG and polystyrene-bound phosphines in Baylis–Hillman reactions.[4] Fan and co-workers reported dendritic DMAP, which exhibited promising biphasic character in Baylis–Hillman catalysis.[5] These supported catalysts normally demonstrated reduced activities compared to their non-supported counterparts and in some cases an additional activating step was required in order for the immobilized catalyst to be reused.[4] As a result, their applications have been mainly limited to active Baylis–Hillman substrates such as methyl vinyl ketone (MVK) and acrylonitrile. Thus, despite these advances, a supported MBH catalyst that fully addresses the critical issues on activity and catalyst recyclability has yet to be reported. In a more recent study, Shi and Toy developed bifunctional polymeric MBH catalysts by anchoring a hydrogen bonding donor (e.g., phenol group) onto the backbone of polymeric Lewis bases.[6] The obtained bifunctional catalysts showed superior activity to their non-hydroxylated derivatives. Although the catalytic activity still fell below that of their homogeneous non-supported counterparts in most cases, the bifunctional strategy provides a potential solution to the design of recoverable MBH catalysts.

We have long been interested in developing efficient MBH catalytic systems.[7] Previously, we reported that ionic liquid-supported quinuclidine was a highly efficient and reusable MBH catalyst.[7f] It was further demonstrated that the use of hydroxylated ionic liquids as supports led to further improvements in activity due to the synergistic effect of the hydroxy group.[7g] In these cases, the ionic liquid-type catalysts were recycled *via* ether precipitation. To further address the issue of recyclability and reusability, we present herein the use of magnetic nanoparticles as MBH catalyst supports. Owing to their good stability, high surface area and easy synthesis, magnetic nanoparticles (MNP) have recently been applied as hetero-



Scheme 1. Synthesis of the magnetic nanoparticle-supported quinuclidine **2**.

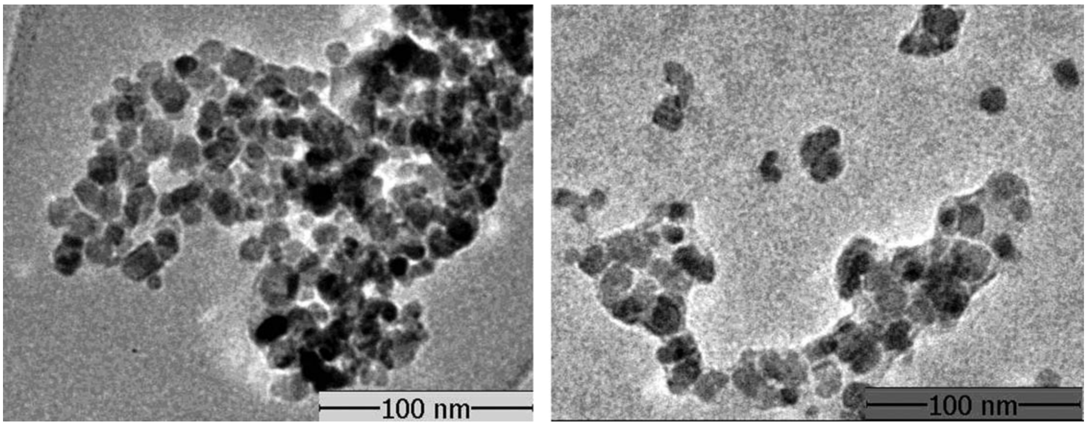


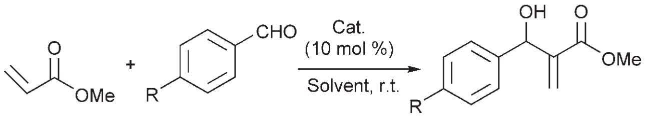
Figure 1. TEM images of catalyst **2**: (*left*) before reaction and (*right*) after reusing it 7 times.

geneous catalytic supports.[8] An attractive feature of MNP-supported catalysts is that they can be easily separated with the aid of an external magnet, thus facilitating easy catalyst recycling without using extra organic solvents and additional filtration steps. Furthermore, high activity is usually achieved in the nanometer-sized supported catalyst due to the high accessible surface area. We therefore envisaged that the use of MNPs as a support would properly address the efficiency issues in organocatalysis by providing readily recyclable and reusable catalysts with reasonably high activity. Indeed, parallel to this work, two other groups reported MNP-supported phase-transfer catalysts and DMAP catalysts, respectively, showing good activity and reusability.[9] These publications prompted us to report our exploration of MNP-supported MBH catalysts.

MNP-supported quinuclidine **2** was synthesized according to the procedure shown in Scheme 1. Polyvinylpyrrolidone (PVP, average MW: 40,000)-protected magnetic nanoparticles of 8–12 nm were prepared following the published co-precipitation procedure.[10] The obtained MNPs were sonicated for one hour before being treated with excess triethoxysilane **1** in anhydrous toluene under refluxing. This one-step procedure gave MNP-supported quinuclidine **2** with a loading of 0.88 mmol$\,g^{-1}$ which was consistent in several different batches. Transmission electron microscopy (TEM) confirmed the nanometer dimensions of catalyst **2** (Figure 1, a). However, powder X-ray diffraction (XRD) indicated that the final MNP catalyst was partially oxidized from magnetite to maghemite (γ-Fe_2O_3). The final MNP-supported quinuclidine **2** is well dispersed in polar solvents such as methanol, ethanol, THF and dichloromethane and can be easily separated by a small magnet. This property meets well with the criteria for the use of MNPs as catalyst supports and the magnetic catalyst **2** was therefore used as is. Using a similar strategy, silica surface-bound quinuclidine **3** was also prepared for the purpose of comparison.

The MNP-supported quinuclidine **2** was next tested in the model reaction of methyl acrylate and *p*-nitrobenzaldehyde. As shown in Table 1, the reaction occurred smoothly in the presence of 10 mol% of **2**, affording the desired product with high yields. The use of protic solvent such as methanol was shown to significantly accelerate the reaction and the reaction time could be shortened from 12 h to 2 h in the presence of methanol compared with that in aprotic solvents (Table 1, entry 6 *vs.* entries 1–4). This observation is in line with the well-proved accelerating effect of hydroxy group-containing additives[11] and is also consistent with our previous observation.[7g] Interestingly, conducting the reaction under neat conditions (with 2.0 equivs. of methyl acrylate) led to an equally

Table 1. MBH reactions of methyl acrylate catalyzed by MNP-quinuclidine.[a]

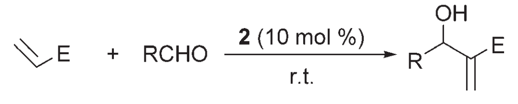


Entry	R	Cat.	Solvent	Time [h]	Yield [%][b]
1	NO_2	**2**	CH_3CN	12	87
2	NO_2	**2**	CH_2Cl_2	12	92
3	NO_2	**2**	$CHCl_3$	12	92
4	NO_2	**2**	THF	12	90
5	NO_2	**2**	EtOH	12	95
6	NO_2	**2**	MeOH	2	88
7	NO_2	**2**	H_2O	12	<5
8	NO_2	**2**	neat	2	87
9	NO_2	**MNP**	MeOH	24	No reaction
10	Cl	**2** (20 mol%)	MeOH	24	86
11	Cl	**3** (20 mol%)	MeOH	48	71
12	Cl	DABCO (20 mol%)	MeOH	24	88

[a] Carried out on a 0.5-mmol scale in the presence of 0.1 equiv. of the catalyst (except those specified) at room temperature. Molar ratio of aldehyde:methyl acrylate = 1:2. Solvent: 4.0 equivs.

[b] Isolated yields of pure product.

Table 2. Substrate scope of MNP-supported quinuclidine **2**.[a]



Entry	E	R	Conditions	Time [h]	Yield [%][b]
1	CO_2Me	4-$NO_2C_6H_4$	A	2	88
2	CO_2Me	2-$NO_2C_6H_4$	A	6	92
3	CO_2Me	3-$NO_2C_6H_4$	A	5	95
4	CO_2Me	2-Pyridinyl	A	2	94
5	CO_2Me	2-Furyl	A	3	90
6	CO_2Me	i-C_4H_9	B	36	80
7	CO_2Me	4-ClC_6H_4	B	24	86 (84)[c]
8	CO_2Me	Ph	B	24	83 (86)[c]
9	CO_2Me	4-MeC_6H_4	B	24	62 (56)[c]
10	CO_2Et	4-ClC_6H_4	B	24	88 (81)[c]
11	CN	4-$NO_2C_6H_4$	B	5	88
12	CN	2-Pyridinyl	B	5	99
13	CN	4-ClC_6H_4	B	16	92
14	CN	Ph	B	24	95
15	CN	4-MeC_6H_4	B	24	80

[a] Carried out on a 0.5-mmol scale in the presence of 0.1 equiv. of the catalyst (except those specified) at room temperature. Molar ratio of aldehyde:methyl acrylate = 1:2. Entries 9–15: 0.2 equivs. of catalyst were used.

[b] Isolated yields of pure product.

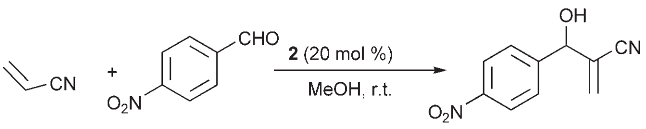
[c] Numbers in the parentheses refer to the data obtained under neat conditions with 2.0 equivs. of acrylate. Conditions A: in the presence of 4.0 equivs. of methanol; Conditions B: neat.

fast reaction (Table 1, entry 8 *vs.* 7). The concentration effect and the free hydroxy groups on the MNP surface may both contribute to the rate enhancement in this case. MNP-supported quinuclidine **2** was then compared with the classical MBH catalyst DABCO using a less active aldehyde, showing comparable catalytic activity with DABCO (Table 1, entry 10 *vs.* 12). Furthermore, catalyst **2** also demonstrated significantly higher activity than the silica-bound quinuclidine **3**, suggesting the importance of a nanosized support (Table 1, entry 10 *vs.* 11). In a control reaction, the magnetic nanoparticle itself was shown to be inert for catalysis (Table 1, entry 9).

The substrate scope of catalyst **2** was then examined. The catalyst could be well-applied to a range of Michael donors and a wide array of aldehydes (Table 2). It should be noted that the reactions work equally well with or without the addition of methanol (Conditions A and B, respectively), providing one of the most effective heterogeneous MBH catalysts.

Product separation and recycling of the MNP-supported quinuclidine **2** were indeed quite easy and simple (for pictures, see Supporting Information). After the reaction, diethyl ether was added to dilute the reaction mixture and the organic layer was simply decanted, assisted by a nearby magnet, to afford the desired products. The MNP catalyst was quickly concentrated to the side wall of the reaction vial once a magnet is placed nearby. The separated catalyst was then washed with ether and dried under vacuum to remove residual solvent. The catalyst could be reused and recycled for 7 times with essentially no loss of activity (Table 3). TEM shows that the MNP catalyst

Table 3. Recycle of catalyst **2**.[a]



Cycle	1	2	3	4	5	6	7
Time [h]	5	5	5	5	5	5	7
Yield [%][b]	88	87	88	88	85	79	80

[a] The reaction was carried out on a 0.5 mmol scale.

[b] Isolated yields.

still maintained the nanostructure after repeated reuse, proving its robustness (Figure 1, b).

In summary, we have prepared the first MNP-supported quinuclidine as a robust and efficient heterogeneous Baylis–Hillman catalyst. The catalyst is easily synthesized and can catalyze the MBH reactions with comparable activity as the traditional catalyst, DABCO. Product separation and catalyst recycling are easier and simpler with the assistance of an external magnet. The catalyst can be recycled and reused for 7 times with little loss of activity. Further applications of the current method to the immobilization of asymmetric organocatalysts will be reported in due course.

Experimental Section

General Procedure

To the solution of catalyst **2** (29 mg, 0.025 mmol) in CH_3OH (41 μL, 4.0 equivs.) were added aldehyde (0.25 mmol) and activated alkene (0.5 mmol). The resulting solution was stirred at ambient temperature and monitored by TLC. After the indicated reaction time, diethyl ether (2 mL × 3) was added, and a small magnet was then applied to separate the organic layer and to recycle the catalyst. The extracts were concentrated to afford the essentially pure products. The crude product could also be purified by flash chromatography on silica gel to afford the desired product. The recycled catalyst was dried under vacuum, and reused directly for the next run. The reactions using the recycled catalyst were conducted in a similar manner. All the Baylis–Hillman products are known compounds (see Supporting Information for further details).[7]

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