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Superparamagnetic Nanoparticle-Supported (*S*)-Diphenylprolinol Trimethylsilyl Ether as a Recyclable Catalyst for Asymmetric Michael Addition in Water

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Abstract: A new superparamagnetic nanoparticle-supported (*S*)-diphenylprolinol trimethylsilyl ether (Jørgensen–Hayashi catalyst) was synthesized and applied for the asymmetric Michael addition of aldehydes to nitroalkenes in water, which gives products in moderate to good yields (up to 96%), good enantioselectivity (up to 90% *ee*) and diastereoselectivities (up to 99:1). The immobilized catalyst could be easily separated from the reaction by an external magnet and recycled for four times without significant loss of catalytic efficiency.

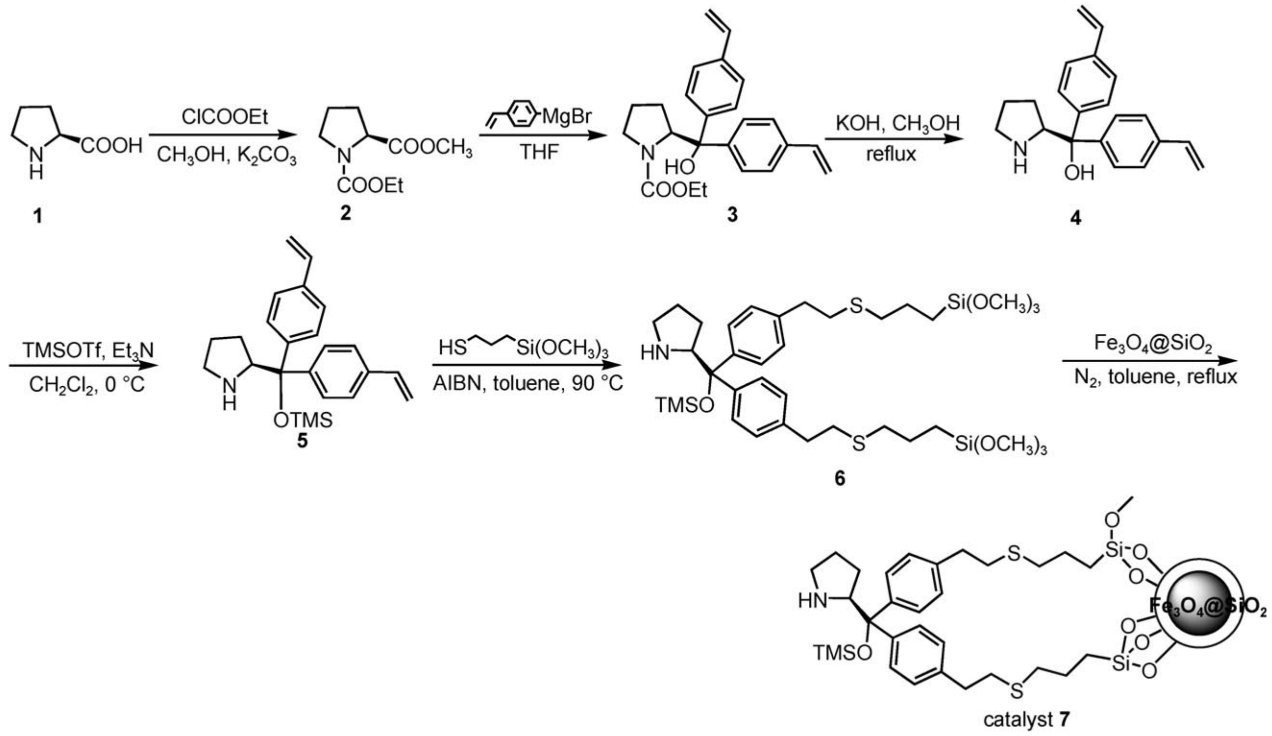
Keywords: asymmetric Michael addition; immobilization; magnetic nanoparticles; organocatalysis

During the past decade, organocatalysis has become one of the most rapidly growing research areas in synthetic organic chemistry.[1] Many asymmetric organocatalysts have been developed and applied in a wide range of organic processes and methodologies, providing efficient and environmentally friendly access to chiral compounds including many drugs and bioactive natural products. In this aspect, one of the most versatile organocatalysts is the Jørgensen–Hayashi catalysts, i.e., α,α-diarylprolinol ethers[2,3], which activate aldehydes *via* an enamine mechanism[4] and α,β-unsaturated carbonyl substrates *via* an iminium ion mechanism.[5] Moreover, the Jørgensen–Hayashi catalysts have been utilized in tandem and multi-component reactions, through which many complicated compounds have been conveniently constructed.[6]

In most cases of organocatalyzed reactions, however, a large amount of the organocatalyst (typically, 10–30 mol%) is needed, which presents a challenge for organic chemists to utilize organocatalysts more efficiently and economically. A solution to this problem could be catalyst immoblization[7] onto some solid supports, such as mesoporous silica or polymers. After the reaction is completed, the working catalyst could be re-collected by filtration or centrifugation and further used for the next run. For example, Mager and Zeitler[8] have very recently developed a highly efficient approach for the immobilization of Jørgensen–Hayashi catalyst onto the MeOPEG polymer. More strikingly, the recyclable MeOPEG-supported catalyst shows comparable reactivity and selectivity as the homogeneous Jørgensen–Hayashi counterpart.

On the other hand, magnetic nanoparticles (MNPs) of Fe_3O_4[9] have emerged recently as a new support[10] for heterogeneous catalyst. The MNPs of Fe_3O_4 are inexpensive, non-toxic, chemically stable and can be simply prepared. Most importantly, the MNP-supported catalyst could be re-collected by using an external magnet conveniently without filtration or centrifugation. Due to the above-mentioned advantages, immobilization of organocatalysts,[11] enzymes,[12] and transition-metal catalysts[13] onto the MNP support has been exploited. To the best of our knowledge, however, there is only one example reported so far for an MNP-supported asymmetric organocatalyst, which was developed by Luo et al. in 2008.[11c] Immobilization of chiral cyclohexanediamine onto the MNPs of Fe_3O_4 coated with SiO_2 was successfully achieved and the immobilized catalyst was further applied in the asymmetric aldol reaction of cyclohexanone in water. The reaction gives the aldol product with up to 98% *ee* and up to 98% yield. Moreover, the MNP-supported asymmetric organocatalyst could be reused for 11 times without significant loss in activity and stereoselectivities.

As described above, the Jørgensen–Hayashi catalysts, i.e., α,α-diarylprolinol ethers are of great impor-



Scheme 1. Preparation of the MNP-supported Jørgensen–Hayashi catalyst **7**.

tance and of general use in organocatalysis. Exploring new approaches for the immobilization of these catalysts may, therefore, offer further possibilities for their applications in asymmetric organocatalysis.[14] Herein, we report on the MNP-supported (*S*)-diphenylprolinol trimethylsilyl ether (catalyst **7**) and its application in asymmetric Michael addition[2c,15] of aldehydes to nitroalkenes in water.

The MNPs of Fe_3O_4 coated with SiO_2 (denoted as $Fe_3O_4@SiO_2$) were prepared according to the literature.[13a,16] As described in Scheme 1, the MNP-supported Jørgensen-Hayashi catalyst **7** was accordingly synthesized and immobilized onto the MNPs of $Fe_3O_4@SiO_2$. To a solution of compound **6** in anhydrous toluene, the MNPs of $Fe_3O_4@SiO_2$ were added and refluxed for 48 h. When the reaction was completed, the MNP-supported catalyst **7** was washed with ethyl acetate and CH_2Cl_2 three times in turn, and dried under vacuum at 55 °C for 24 h. The obtained catalyst was then characterized by transmission electron microscopy (TEM), magnetization measurement, and powder X-ray diffraction (XRD). As shown in Figure 1, the nanometer dimensions of MNPs before and after immobilization were confirmed by TEM analysis. Dynamic light scattering (DLS) analysis indicates that the diameters of MNPs before and after immobilization are 145 ± 20 nm and 190 ± 10 nm, respectively. Magnetization curves measured at ambient temperature showed that the MNP-supported catalyst **7** is superparamagnetic (Figure 2). XRD images indicated that the MNPs of Fe_3O_4 were intact after immobilization (Figure 3). According to the elemental analysis of nitrogen, the loading of catalyst **7** was 0.66 $mmol\,g^{-1}$.

To evaluate the catalytic activity of catalyst **7**, the asymmetric Michael addition of propanal to *trans*-β-nitrostyrene was selected as a model reaction (Table 1). Firstly, the effect of solvent on this reaction was examined and the obtained results are summarized in Table 1. In CH_3CN or toluene (Table 1, entries 1 and 2), only a trace of product was observed. On the contrary, moderate yields could be achieved when CH_2Cl_2, $CHCl_3$ or ethanol was applied as the solvent (Table 1, entries 3–5). More strikingly, we found that the reaction proceeded smoothly in water and gave the desired product in 85% yield (Table 1, entry 6). In all the cases tested, stereoselectivities for the obtained products were, however, at the same level (82% to 91% *ee*; 84:16 to 90:10 *dr*). The effect of co-solvent on the reaction was also examined: CH_2Cl_2:H_2O (v/v = 1:1) gave the desired product in 49% yield, 91% *ee*, and 90:10 *dr* (Table 1, entry 7); while EtOH:H_2O (v/v = 1:1) gave 85% yield, 87% *ee*, and 86:14 *dr* (Table 1, entry 8).[17] Therefore, water was chosen as the solvent for the asymmetric Michael addition of aldehydes to nitroalkenes using catalyst **7** at ambient temperature.

With the optimized conditions at hand, we further examined the substrate scope for the asymmetric Michael addition catalyzed by **7** and the obtained results

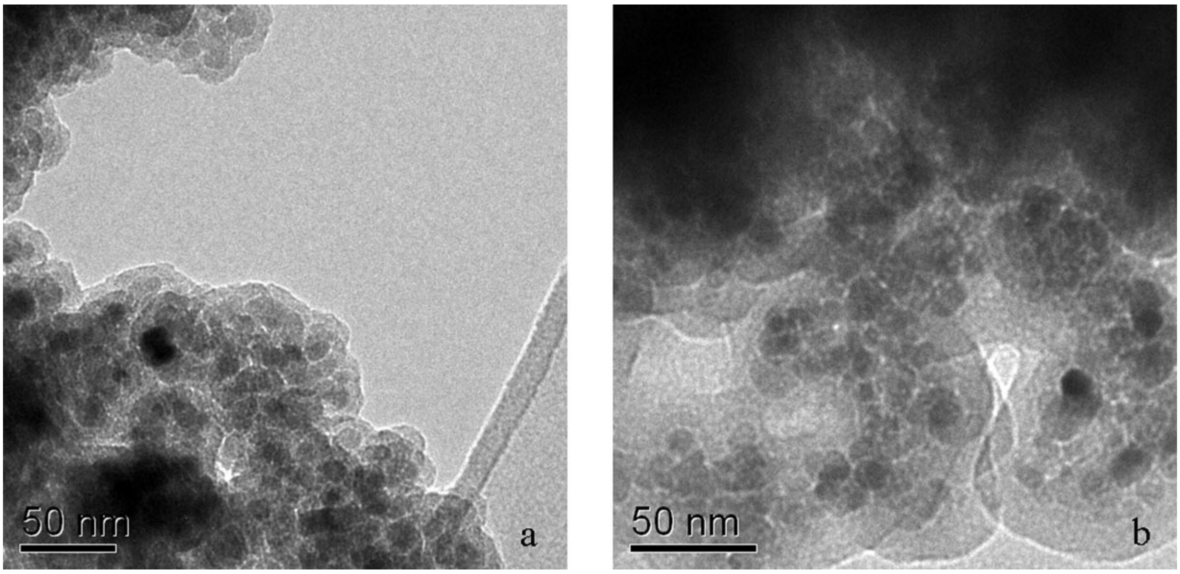


Figure 1. TEM images for MNPs of $Fe_3O_4@SiO_2$ (**a**) and MNP-supported catalyst **7** (**b**).

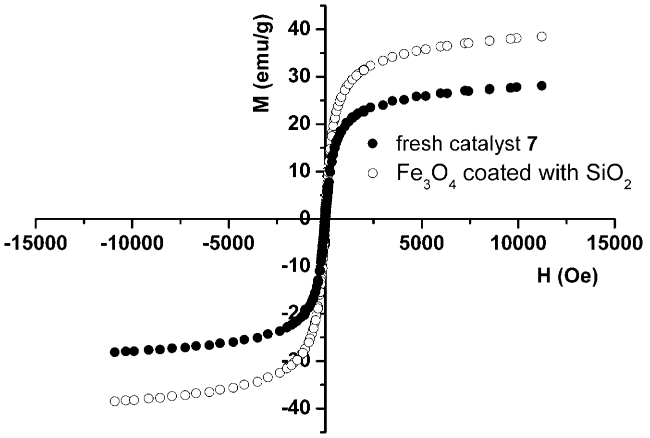


Figure 2. Magnetization curves for MNPs of $Fe_3O_4@SiO_2$ (*open symbols*) and MNP-supported fresh catalyst **7** (*solid symbols*).

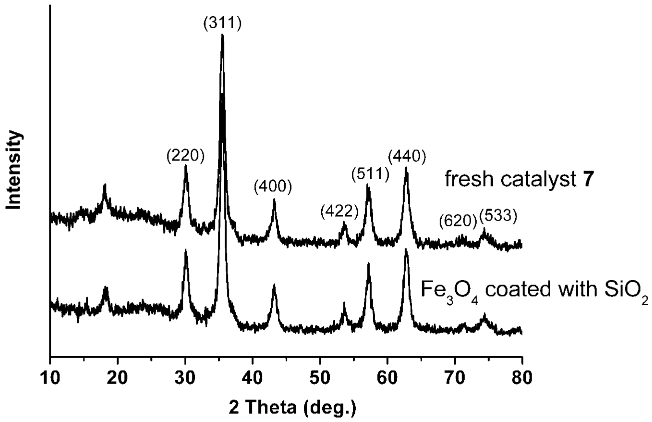
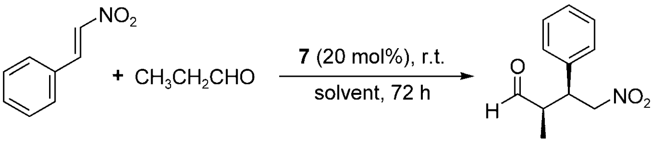


Figure 3. XRD patterns of for MNPs of $Fe_3O_4@SiO_2$ (*bottom*) and MNP-supported catalyst **7** (*top*).

Table 1. Screening of solvents for the asymmetric Michael addition reaction in the presence of catalyst **7**.[a]



Entry	Solvent	Yield [%][b]	*ee* [%][c]	*dr*[d]
1	CH_3CN	trace	n.d.[e]	n.d.
2	$C_6H_5CH_3$	trace	n.d.	n.d.
3	CH_2Cl_2	49	83	84:16
4	$CHCl_3$	49	82	85:15
5	EtOH	44	84	86:14
6	H_2O	85 (80)[f]	84 (90)	84:16
7	CH_2Cl_2:H_2O (1:1)	49[g]	91	90:10
8	EtOH:H_2O (1:1)	85[g]	87	86:14

[a] *Reaction conditions: trans*-β-nitrostyrene (0.2 mmol), propanal (2.0 mmol) and catalyst **7** (0.04 mmol) in solvent (0.5 mL) at ambient temperature for 72 h.

[b] Isolated yields after silica gel column chromatography.

[c] Determined by chiral HPLC (Daicel chiral OD-H column). The absolute configuration of reaction product is determined according to ref.[2c]

[d] Determined by ^1H NMR.

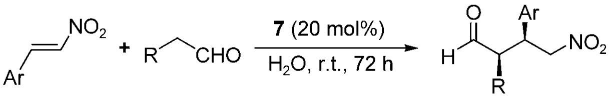
[e] Not determined.

[f] 1.0 equivalent of benzoic acid was added.

[g] Reaction time of 48 h.

are listed in Table 2. When the aromatic ring of the arylnitroalkene was substituted by either electron-withdrawing groups or electron-donating groups (Table 2, entries 2–7), the yield of reaction product was a little lower (53% to 79%) than that without substitution (85%, Table 2, entry 1), but the enantioselectivity and diastereoselectivity remained at the

Table 2. Asymmetric Michael addition of aldehydes to nitroalkenes using heterogeneous catalyst **7**.[a]



Entry	Ar	R	Yield [%][b]	*ee* [%][c]	*dr*[d]
1	Ph	CH_3	85 (80)[e]	84	84:16
2	*o*-$NO_2C_6H_4$	CH_3	64	90	82:18
3	*p*-ClC_6H_4	CH_3	79	80	85:15
4	*o*-ClC_6H_4	CH_3	67	75	76:24
5	*o*-BrC_6H_4	CH_3	70	77	75:25
6	*p*-$CH_3OC_6H_4$	CH_3	53 (32)[e]	83	86:14
7	*m*-$CH_3C_6H_4$	CH_3	64	81	86:14
8	Ph	$CH_2CH_2CH_3$	57	82	92:8
9	Ph	$(CH_2)_7CH{=}CH_2$	54	81	> 99:1
10	1-naphthyl	CH_3	67	84	77:23
11	2-furyl	CH_3	96	76	80:20
12[f]	*p*-$CH_3OC_6H_4$	CH_3	74	85	79:21
13[f]	Ph	$(CH_2)_7CH{=}CH_2$	70	86	> 99:1

[a] *Reaction conditions:* nitroalkene (0.2 mmol), aldehyde (2.0 mmol) and catalyst **7** (0.04 mmol) in H_2O (0.5 mL) at ambient temperature for 72 h.

[b] Isolated yields after silica gel column chromatography.

[c] Determined by chiral HPLC analysis (Daicel chiral columns, see Supporting Information for details). The absolute configuration is determined according to ref.[2c]

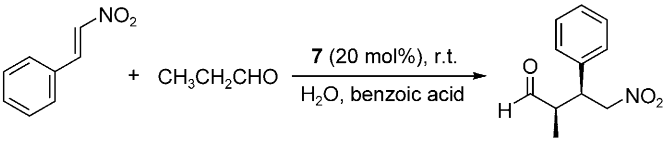
[d] Determined by ^1H NMR.

[e] The yields were given in parentheses when addition of 1.0 equiv of benzoic acid was applied in the reaction.

[f] Reactions carried out in EtOH:H_2O (0.5 mL, v/v = 1:1) at ambient temperature for 48 h.

same level (75% to 90% *ee*; 75:25 to 86:14 *dr*). Prolongation of the chains of the aldehydes caused a decrease of the reaction yields (54% and 57%, respectively, see Table 2, entries 8 and 9), but the *dr* value could be increased to 99:1 (Table 2, entry 9). The nitroalkene with a naphthyl substituent (Table 2, entry 10) gave a slightly lower yield (67%) but good enantioselectivity (84% *ee*). A nitroalkene with a heterocyclic substituent, such as the 2-furyl group, achieved a high yield of 96% but gave only 76% *ee* (Table 2, entry 11).

Table 3. Recycle use of catalyst **7**.[a]



Cycle	Yield [%][b]	*ee* [%][c]	*dr*[d]
1	80	90	84:16
2	83	88	86:14
3	54	85	83:17
4	42	84	80:20

[a] *Reaction conditions: trans*-β-nitrostyrene (0.2 mmol), propanal (2.0 mmol), benzoic acid (0.2 mmol) and catalyst **7** (0.04 mmol) in H_2O (0.5 mL) at ambient temperature for 72 h.

[b] Isolated yields after silica gel column chromatography.

[c] Determined by chiral HPLC (Daicel chiral OD-H column). The absolute configuration of reaction product is determined according to ref.[2c]

[d] Determined by ^1H NMR.

Next we investigated the recyclability of catalyst **7**. The re-collection of superparamagnetic catalyst **7** is very facile with an external magnet. When the reaction is completed, a small magnet was put nearby the reaction flask to concentrate catalyst **7** so that the aqueous solution can easily be decanted. In the similar way, the used catalyst **7** was repeatedly washed by ethyl acetate and further dried under vacuum at 55 °C for 24 h for the next run. During the recycle experiments (Table 3), we found that addition of benzoic acid to the reaction system is crucial for the recycle use of catalyst **7** in the asymmetric Michael addition reaction.[18] When 1.0 equivalent of benzoic acid was added, the recycle reaction proceeded smoothly. The results of recycle experiments with the addition of benzoic acid are summarized in Table 3. The reaction yields remained at the same level in the first two cycles (80% and 83%, respectively), but decreased to 54% in the third cycle and further to 42% in the fourth cycle.[19] On the contrary, no significant loss of stereoselectivities occurred in each cycle (Table 3, cycles 1–4).

In summary, we have immobilized, for the first time, the Jørgensen–Hayashi catalyst of (*S*)-diphenylprolinol trimethylsilyl ether onto the MNPs of

$Fe_3O_4@SiO_2$ and applied the immobilized catalyst in the asymmetric Michael addition of aldehydes to nitroalkenes. Moderate to good yields (up to 96%), good enantioselectivity (up to 90% *ee*) and diastereoselectivities (up to 99:1) were obtained. The NMP-supported catalyst could be reused in the asymmetric Michael addition reaction for four times without significant loss of stereoselectivities.

Experimental Section

General Procedure for the Asymmetric Michael Addition Reaction using Catalyst 7

To a solution of aldehyde (2.0 mmol) in water (0.5 mL) was added nitroalkene (0.2 mmol) and heterogeneous catalyst **7** (60 mg, 0.04 mmol). After the resulting mixture had been stirred at ambient temperature for 72 h, catalyst **7** was concentrated by using an external magnet and the aqueous solution was decanted. Ethyl acetate was then added to wash catalyst **7** for several times and the aqueous solution decanted was extracted with ethyl acetate three times. The organic layers were then combined, dried over anhydrous Na_2SO_4 and further purified by column chromatography on silica to obtain the desired products, with petroleum ether/EtOAc = 4:1 to 10:1 as the eluent.

Recycle Use of Catalyst 7

After being washed with ethyl acetate for several times, the used catalyst **7** was dried under vacuum at 55 °C for 24 h. The recycled catalyst **7** (60 mg, 0.04 mmol) was then added to the solution of propanal (116 mg, 2.0 mmol), *trans*-β-nitrostyrene (30 mg, 0.2 mmol), and benzoic acid (24 mg, 0.2 mmol) in water (0.5 mL). After being stirred for 72 h at ambient temperature, the reaction mixture and the recycled catalyst **7** were treated as described above.

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[17] These results, which are comparable to those using water as the solvent, were, however, obtained after the reaction was carried out for 48 h. Therefore, the co-solvent system of EtOH:H_2O (v/v = 1:1) may accelerate the reaction rate. Further study indicates that, for the substrates with Ar = *p*-CH_3OPh (Table 2, entry 12) or with R = $(CH_2)_7CH{=}CH_2$ (Table 2, entry 13), the reaction yields were increased to 74% and 70%, respectively, when EtOH:H_2O (v/v = 1:1) was applied as the co-solvent.

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[19] According to the elemental analysis on nitrogen, the loading of the Jørgensen–Hayashi catalytic moiety onto catalyst **7** after the 4th cycle is 0.59 mmol$\,g^{-1}$ which is slightly lower than that for the fresh catalyst (0.66 mmol g)$^{-1}$. Therefore, catalyst leaching should not be the main reason for the reactivity loss of the catalyst. Hydrolysis of the labile silyl ether could be crucial for the catalyst deactivation, see. for example: M. C. Varela, S. M. Dixon, K. S. Lam, N. E. Schore, *Tetrahedron* **2008**, *64*, 10087–10090, or ref.[14a]