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Yolk–Shell–Structured Mesoporous Silica: A Bifunctional Catalyst for Nitroaldol–Michael One-Pot Cascade Reaction

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An important interest in heterogeneous asymmetric catalysis expects to obtain an enantioselective cascade reaction through a controllable active site-isolated heterogeneous catalyst. Herein, we utilize a yolk-shell-structured mesoporous silica and assemble an active site-isolated bifunctional heterogeneous catalyst, where chiral cinchonine-based squaramide molecules are anchored within silicate channel as an outer shell while amine-functionalities are entrapped onto silicate yolk as inner core. Structural analyses and characterizations of the heterogenesous catalyst reveal its well-defined single-site chiral active species within its silicate network. Electron microscopies confirm its yolk-shell-structured mesoporous material. As presented in this study, as a bifunctional heterogeneous catalyst, it enables an efficiently nitroaldol–Michael cascade reaction to convert three-component coupling of nitromethane, aldehyde and acetylacetone into various chiral diones with high yields and up to 99% enantioselectivities in one-pot process. As expected, this active site-isolated catalyst not only enhances the catalytic selectivity of first-step nitroaldol condensation but also keeps the enantioselectivity of second-step Michael addition. Moreover, heterogeneous catalyst can be also recovered easily and recycled repeatedly, making it an interesting feature in a three-component organic transformation.

1. Introduction

Development of mesoporous silicas as supports for construction of silica-supported catalysts and their application in enantioselective reactions have obtained great achievements in heterogeneous asymmetric catalysis, where benefits from confinement effect and synergistic effect of mesoporous silicas have led to lots of highly efficient heterogeneous catalysts.[1] Especially, site-isolated strategy used in mesoporous silicate materials have opened new opportunity for construction of bifunctional heterogeneous catalysts.[2] This strategy not only complements nicely the drawbacks of homogeneous catalysis through overcoming intrinsic incompatibility of two types of active species in one-pot reaction, but also finds a new tandem reaction that is unfeasible in a homogeneous condition. Recently, some significiant cascade reactions catalyzed by active site-isolated heterogeneous catalysts had appeared in the literatures.[2f-2h] Yolk-shell-structured silicas, as a kind of special mesoporous materials,[3] possess inherent superiority in design of active site-isolated heterogenous catalysts because their yolk and shell can anchor separately different active species. This feature make these yolk-shell-structured mesoporous silicas attracting in construction of various novel active site-isolated bifunctional heterogenous catalysts,[3a] however, application them in some unexplored tandem reactions is still unmit challenge in heterogeneous asymmetric catalysis.

Nitroaldol condensation and Michael addition, as two classical carbon-carbon bond formation reactions, have been studied both theoretically and practically. In particular, nitroaldol condensation of nitromethane and aromatic aldehyde, and enantioselective Michael addition of β-dicarbonyl compounds to nitrostyrene are well-documented in the literature, respectively.[4] Despite of great interest in nitroaldol–Michael one-pot reaction for construction of complicated organic molecules because of atom economy and minimum workup, direct one-pot nitroaldol–Michael reactions are still rare,[5] especially for nitroaldol–Michael one-pot cascade reaction for construction of optically pure products. Recently, chiral cinchonine-based squaramides have exhibit excellent enantioselectivity in asymmetric Michael addition of 1,3-dicarbonyl compounds to nitroalkenes.[6] These findings offer a practical approach to explore their application in one-pot nitroaldol–Michael cascade reaction. Therefore, utilizing the advantage of yolk-shell-structured mesoporous silica, facile construction of an active site-isolated heterogenous catalyst and realization of a nitroaldol–Michael one-pot cascade reaction are highly desirable.

As an effort to develop silica-supported heterogeneous catalysts,[7] recently, we found that chiral cinchonine-based squaramides supported on ionic liquid could retain the enantioselectivity performance of homogeneous catalytic system in asymmetric Michael addition of acetylacetone to nitrostyrene while nickel-amine-functionalized periodic mesoporous organosilica promoted the catalytic performance of asymmetric Michael addition.[7a-7c] Based on these findings, together with the benefit of yolk-shell-structured mesoporous silicas, we herein assemble conveniently amine-functionality onto silicate yolk as inner core and chiral cinchonine-based squaramide within silicate

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channel as an outer shell, constructing a yolk-shell-structured active site-isolated bifunctional heterogeneous catalyst through a simple thiol-ene click reaction. As expected, this bifunctional heterogeneous catalyst enables an efficiently nitroaldol–Michael cascade reaction to convert three-component coupling of nitromethane, aldehyde and acetylacetone into various chiral diones with high yields and up to 99% enantioselectivity in one-pot process. Moreover, heterogeneous catalyst can be also recovered easily and recycled repeatedly four times without obvious loss of its catalytic activity.

2. Experimental

2.1. Characterization

Fourier transform infrared (FT-IR) spectra were collected on a Nicolet Magna 550 spectrometer using KBr method. Scanning electron microscopy (SEM) images were obtained using a JEOL JSM-6380LV microscope operating at 20 kV. Transmission electron microscopy (TEM) images were performed on a JEOL JEM2010 electron microscope at an acceleration voltage of 220 kV. Nitrogen adsorption isotherms were measured at 77 K with a Quantachrome Nova 4000 analyzer. The samples were measured after being outgassed at 423 K overnight. Pore size distributions were calculated by using the BJH model. The specific surface areas (*S*BET) of samples were determined from the linear parts of BET plots (p/p_0 = 0.05-1.00). Thermal gravimetric analysis (TGA) was performed with a Perkin-Elmer Pyris Diamond TG analyzer under air atmosphere with a heating ramp of 5 K/min. Solid state NMR experiments were explored on a Bruker AVANCE spectrometer at a magnetic field strength of 9.4 T with ^{1}H frequency of 400.1 MHz, ^{13}C frequency of 100.5 MHz and ^{29}Si frequency of 79.4 MHz with 4 mm rotor at two spinning frequency of 5.5 kHz and 8.0 kHz, TPPM decoupling is applied in the during acquisition period. ^{1}H cross polarization in all solid state NMR experiments was employed using a contact time of 2 ms and the pulse lengths of 4μs.

2.2. Preparation of the heterogeneous Catalyst 3.

In a typical synthesis, (*The first step for the synthesis of silinate yolk)* 0.10 g (0.27 mmol) of cetyltrimethylammonium bromide (CTAB) was completely dissolved in 45.0 mL of aqueous sodium hydroxide (0.35 mL, 2.0 N). The mixture was stirred at room temperature for 0.5 h. Subsequently, 0.20 g (0.90 mmol) of 3-(triethoxysilyl)propan-1-amine, and 0.43 g of (2.07 mmol) of tetraethoxysilane (TEOS) was added at room temperature under vigorous stirring. Finally, 0.40 mL of ethyl acetate was added and the mixture was stirred at 80 °C for 2 h. (*The second step for the coating above yolk)* After cooling the above mixture down to 38 °C, an aqueous solution (80 mL of water, 50 mL of ethanol, 0.30 g (0.82 mmol) of CTAB and 1.0 mL (25 wt%) of $NH_3{\cdot}H_2O$) was added and the mixture was stirred 38 °C for 0.5 h. Subsequently, 0.5 mL, 0.47 g (2.26 mmol) of TEOS was added and the mixture was stirred at 38 °C for another 2 h. After that, an aqueous solution (3 mL of water containing 0.040 g (0.044 mmol) of FC-4 ($[C_3F_7O(CF(CF_3)CF_2O)_2CF(CF_3)CONH(CH_2)_3N^+(C_2H_5)_2CH_3]I^-$), 0.080 g (0.22 mmol) of CTAB and 0.20 mL (25 wt%) of $NH_3{\cdot}H_2O$) was added and the mixture was stirred at 38 °C for 0.5 h. Then, 0.25 g of 1,2-bis(triethoxysilyl)ethane (0.70 mmol) in 2 mL of ethanol and 0.15 g (0.60 mmol) of 3-mercaptopropyltrimethoxylsilane (2 min later) were added subsequently under vigorous stirring for 1.5 h. Finally, the temperature was raised to 80 °C and the mixture was stirred at 80 °C for another 5 h. After cooling the above mixture down to room temperature, the solid was collected by filtration. (*The third step for the selective etching*) To remove the surfactant and form yolk-shell structured mesoporous nanoparticles, the collected solids (1.0 g) were dispersed in 120 mL of solution (80 mg (1.0 mmol) of ammonium nitrate in 120 mL (95%) of ethanol), and the mixture was stirred at 60 °C for 12 h. After cooling the above mixture down to room temperature, the solid was filtered and washed with excess water and ethanol, and dried at ambient temperature under vacuum overnight to afford SH@NH2@NMPs (1) as a white powder (0.65 g) [IR (KBr) cm^{-1}: 3442.7 (s), 2928.2 (w), 1633.0 (m), 1391.6 (w), 1064.6 (s), 784.6 (m), 457.4 (m). ^{13}C CP MAS NMR (161.9 MHz): 57.9 (*C*H$_2$ of −O*C*H$_2$CH$_3$), 42.8 (*C* of −SiCH$_2$*C*H$_2$N), 31.3−17.2 (*C* of −S*C*H$_2$, −SiCH$_2$*C*H$_2$CH$_2$N and −OCH$_2$*C*H$_3$), 5.7 (*C* of −Si*C*H$_2$ group) ppm. ^{29}Si MAS NMR (79.4 MHz): T^2 (δ = −57.9 ppm), T^3 (δ = −65.9 ppm), Q^2 (δ = −91.9 ppm), Q^3 (δ = −101.8 ppm), Q^4 (δ = −110.8 ppm)]. (*The fourth step for the thiol-ene click reaction*). a dry 50 mL round-bottom flask was charged with SH@NH2@NMPs (1) (0.50 g), squaramide (2) (75.0 mg, 0.12 mmol), and 2.0 mol% of 2,2-dimethoxy-1,2-diphenylethanone photoinitiator, backfilled with argon, and irradiated for 24 h with a 15 W blacklight (λ_{max} = 365 nm). The mixture was filtered through filter paper and then rinsed with excess CH_2Cl_2. After Soxhlet extraction for 24 h in CH_2Cl_2 to remove homogeneous and unreacted starting materials, the solid was dried at ambient temperature under vacuum overnight to afford Squaramide@NH_2@MNPs (**3**) (0.53 g) as a light-yellow powder. IR (KBr) cm^{-1}: 3433.6 (s), 2939.4 (w), 1623.9 (m), 1531.5 (w), 1475.1 (w), 1391.6 (w), 1287.8 (w), 1064.4 (s), 784.6 (m), 701.1 (m), 457.4 (m). ^{13}C CP MAS NMR (161.9 MHz): 184.7−181.1 (*C* of C=O groups), 161.9-168.9 (*C* of −CO*C*H=*C*HCO group), 152.3-115.9 (*C* of Ar, Ph and CF_3), 58.6 (*C*H$_2$ of −O*C*H$_2$CH$_3$), 49.8−34.9 (*C* of carbon connected to N atom in alkyl part), 31.3−16.9 (*C* of −S*C*H$_2$, −SiCH$_2$*C*H$_2$CH$_2$N, *C* of cyclic alkyl groups in cycling group without connected to N atom and −OCH$_2$*C*H$_3$), 5.8 (*C* of −Si*C*H$_2$ group) ppm. ^{29}Si MAS NMR (79.4 MHz): T^2 (δ = −57.1 ppm), T^3 (δ = −66.3 ppm), Q^2 (δ = −91.8 ppm), Q^3 (δ = −102.2 ppm), Q^4 (δ = −110.3 ppm).

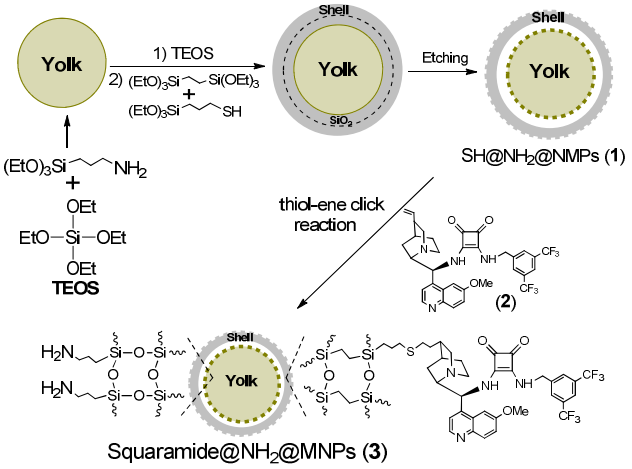
2.3. General procedure for the one-pot enantioselective nitroaldol–Michael coupling of aldehydes, nitromethane and acetylacetone.

A typical procedure was as follows: catalyst **3** (25.0 mg, 5.0 μmol of squaramide based on the TG analysis) and aldehydes (0.50 mmol) in 1.0 mL of nitromethane were added in a 10 mL round−bottom flask. The mixture was allowed to react at 90 °C for 3-6 h. During that time, the reaction was monitored constantly by TLC to determine the completion of reaction, After cooling down to room temperature, acetylacetone (2.0 mmol) in 1.0 mL of CH_2Cl_2 was added and the mixture was allowed to further react at room temperature for 12–24 h. Then the heterogeneous catalyst was separated by centrifugation (10,000 rpm) for the recycling experiment. The aqueous solution was extracted by Et_2O (3 × 3.0 mL). The combined Et_2O was washed with brine

twice and dehydrated with Na_2SO_4. After the evaporation of Et_2O, the residue was purified by silica gel flash column chromatography to afford the desired product. The conversion was calculated by the internal standard method and the ee value could be determined by chiral HPLC analysis with a UV-Vis detector using a Daicel OD-H, AS-H, or AD-H chiralcel column (Φ 0.46 × 25 cm).

3. Results and discussion

3.1. Synthesis and structural characterization of the heterogeneous catalyst



Scheme 1. Preparation of the heterogeneous catalysts **3**.

Yolk-shell-structured chiral cinchonine-based squaramide-functionalized mesoporous silica, abbreviated as Squaramide@NH_2@MNPs (**3**), was synthesized through a dual silica-coated strategy. As shown in Scheme 1, a silicate yolk was formed by co-condensation of tetraethoxysilane (TEOS) and 2-(triethoxysilyl)propylamine, and the continuous grown of TEOS followed by further co-condensation of 1,2-bis(triethoxysilyl)ethane and 3-(triethoxysilyl)propanethiol led to a core-shell-structured mesoporous silica. This core-shell-structured mesoporous silica was then etched selectively, affording a yolk-shell-structured SH@NH_2@MNPs (**1**) as a white powder.[3a] Finally, a direction thiol-ene click reaction[8] of **1** and chiral squaramide (**2**)[6a] afforded the rude catalyst **3**, which was subjected to Soxhlet extraction to give its pure form as a light-yellow powder (see SI in Experimental Section, and in Figures S1-S2). The thermal gravimetric (TG) analysis revealed that the loadings of chiral squaramide in catalyst **3** was 128.90 mg (0.20 mmol) per gram catalyst (see SI in Figure S2).

Incorporation of chiral cinchonine-based squaramide-functionality within the yolk-shell-structured mesoporous silicate network of **3** could be confirmed by solid-state ^{13}C cross-polarization (CP)/magic angle spinning (MAS) NMR spectroscopy. As shown in Figure 1, catalyst **3** produced the strong carbon signals of –Si<u>C</u>H$_2$<u>C</u>H$_2$Si– groups around 6 ppm for the ethylene-bridged moiety, suggesting its ethylene-bridged network of organosilicate shell. Peaks around ~5, ~16 and ~31 or ~49 ppm in the spectrum of **3** were corresponded to carbon atoms of of propyl groups in propylamine or propanethiol moieties, which were similar to those of its parent material **1** that were marked in the spectrum of **3**.[3a] It was worth mentioning that catalyst **3** produced the characteristic carbon signals of squaramide groups between ~161 and ~185 ppm for the carbon atoms of –<u>C</u>O<u>C</u>H=<u>C</u>H<u>C</u>O– moieties in four-ring squaramide molecule. In addition, the strong signals for those carbon atoms of aromatic ring could be observed clearly in the spectrum of **3**. All these peaks are absent in the spectrum of **1**, suggesting that chiral cinchonine-based squaramide molecules were anchored successfully onto **1** through the thiol-ene click reaction. Chemical shifts of **3** were similar to those of its homogeneous counterpart,[8a] demonstrating that they had the same well-defined single-site active species.

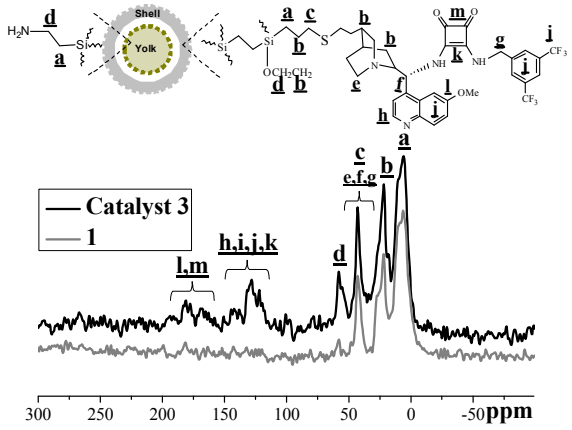


Figure 1. The solid-state ^{13}C CP MAS NMR spectra of of **1** and catalyst **3**.

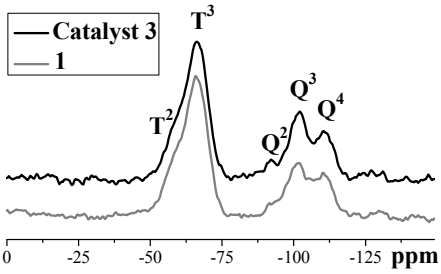


Figure 2. The solid-state ^{29}Si MAS NMR spectra of of **1** and catalyst **3**.

In addition, its organosilicate network and composition of catalyst **3** could be confirmed by the solid-state ^{29}Si MAS NMR spectroscopy. As shown in Figure 2, both **1** and **3** produced two groups of typical signals (Q- and T-series) distributed broadly from -40 to -150 ppm as marked in its spectrum, where Q signals are attributed to inorganosilica while T signals are corresponded to organosilica. As compared with those typical isomer shift

values in the literature,[9] the strong T^3 signal of T-series at −66.3 ppm in the spectrum of **3** suggested the organosilicate R–Si(OSi)$_3$ species (R = alkyl-linked chiral squaramide and amine groups) as its main part of organosilica while the strongest Q^3 signal of Q-series at −102.2 ppm demonstrated its main inorganosilicate networks of [(OH)Si(OSi)$_3$].

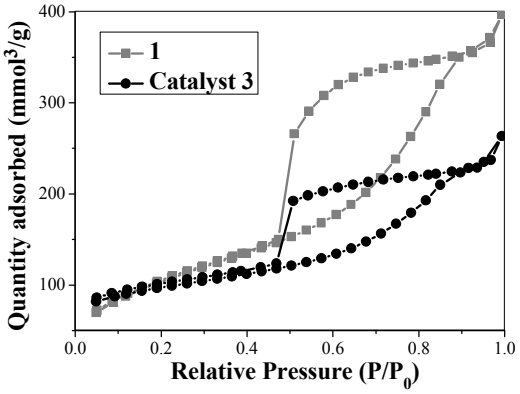


Figure 3. The nitrogen adsorption-desorption isotherms of **1** and catalyst **3**.

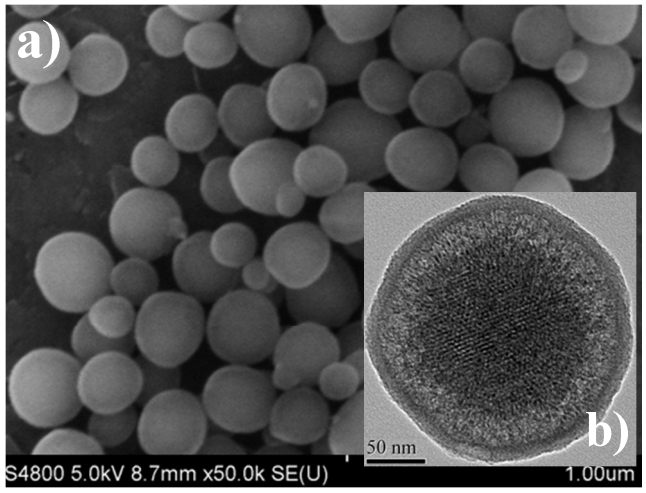


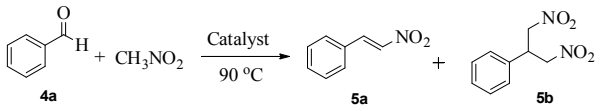
Figure 4. (a) The SEM images of catalyst **3**, (b) The TEM images of catalyst **3**.

The ordered mesostructure and morphology of **3** were further investigated by nitrogen adsorption–desorption measurements, scanning electron microscopy (SEM), and transmission electron microscopy (TEM). As shown in Figure 3, the nitrogen adsorption–desorption isotherm of **3** demonstrated its mesoporous structure due to its typical type IV isotherm with an H_1 hysteresis loop and a visible step at P/P_0 = 0.40–0.90, where its pore size distribution reveals that catalyst **3** has uniform mesopores of about 2.2 nm (see SI in Figure S3). Figure 4 presented the yolk-shell-structured morphology of catalyst **3**, where SEM image disclosed its monodisperse nanospheres (Figure 4a) while TEM image confirmed its yolk-shell nanostructure (Figure 4b, also see enlarge TEM images in Figure S4 of SI).

3.2. Catalytic performance of the heterogeneous catalyst

Based on the obtained site-isolated bifunctional heterogeneous catalyst, two single-step reactions, nitroaldol condensation of nitromethane and benzaldehyde to nitrostyrene, and enantioselective Michael addition of acetylacetone to nitrostyrene, was investigated separately. In the first-step nitroaldol condensation, in order to gain better insight into the catalytic nature of amine-functionality, several affecting factors coming from squaramide-functionality and surface silanols of materials in catalyst **3** were evaluated, determining the optimal nitroaldol condensation of nitromethane and benzaldehyde to nitrostyrene.

Table 1. Nitroaldol condensation of nitromethane and benzaldehyde.[a]



4a 5a 5b

Entry	Catalyst	Amount of catalyst (mol%)	Time	Conv. of 4a (%)[b]	Yield of 5a (Sel.[c]) (%)
1	**2**	1.0	12	18	17 (99)
2	**3**	1.0	3	78	76 (97)
3	**3**	3.0	3	86	85 (99)
4	**3**	5.0	3	>99	99 (99)
5	Capped **3**	5.0	3	48	45 (94)
6	Propylamine	5.0	3	98	79 (80)

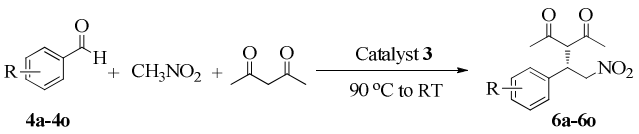
[a] Reaction conditions: catalyst and benzaldehyde (1.0 mmol) in 1.0 mL of nitromethane was reacted at 90°C for 3-12 h. [b] Conversions were determined by ^{1}H-NMR. [c] (Yield/Conversion) ×100.

As shown in Table 1, firstly, we investigated the basic role of squaramide-functionality in the first-step nitroaldol condensation through the use of homogeneous chiral squaramide (**2**) as a parallel base. It was found that the single-step nitroaldol condensation catalyzed by **2** only gave very poor conversion of **4a** in an obviously prolonged reaction time, suggesting squaramide-functionality within **3** did only slightly affect the nitroaldol condensation (Table 1, entry 1). This result eliminated the interference coming from squaramide-functionality within **3**.

Then, we investigated the affecting factor of the loading amount of amine-functionality in order to elucidate the role of amine-functionality onto the silicate yolk. In this case, three different loading amount of amine-functionality the silicate yolk was tested in single-step nitroaldol condensation (Table 1, entries 2-4). The results showed that the nitroaldol condensation depended heavily on the loading amount of amine-functionality in catalyst **3**, where 5% loading amount of amine-functionality could reach the reaction completion within 3.0 h. As expected, the single-step nitroaldol condensation catalyzed by **3** should be of first order because the initial reaction rate was proportional to the loading amount of amine-functionality (Table 1, entry 2-4), indicating the nitro Mannich pathway[10] rather than nitroaldol

pathway [11] (nitro Mannich and nitroaldol pathways are two typically chemical mechanisms for nitroaldol condensation of nitromethane and aromatic aldehyde). An evidence to support the nitro Mannich pathway came from a FT-IR spectrum investigation (see SI in Figure S1). It was found that the characteristic vibrations of C=N bond at 1643 cm^{-1} for reactive imine intermediate could be observed clearly when the supported propylamine in **1** was treated with benzaldehyde. This finding confirm its nitro Mannich pathway in the nitroaldol condensation of nitromethane and benzaldehyde.[2d, 12]

Table 2. One-pot cascade nitroaldol–Michael coupling of nitromethane, aldehydes and acetylacetone.[a]



4a-4o **6a-6o**

Entry	R	6	Conv. of 4 (%) [b]	Yield of 6 (%)	Ee (%)[b]
1	H	**6a**	99	93	99
2	H	**6a**	99	77	97[c]
3	4-F	**6b**	99	95	99
4	4-Cl	**6c**	99	96	99
5	3-Cl	**6d**	99	96	99
6	2-Cl	**6e**	99	94	99
7	4-Br	**6f**	99	95	99
8	3-Br	**6g**	99	95	95
9	4-CF_3	**6h**	99	96	99
10	3-CF_3	**6i**	99	97	97
11	3-NO_2	**6j**	99	95	99
12	4-Me	**6k**	99	93	97
13	3-Me	**6l**	99	94	99
14	4-OMe	**6m**	99	93	99
15	3-OMe	**6n**	99	95	98
16	2-OMe	**6o**	99	91	97

[a] Reaction conditions: catalyst **3** (25.0 mg, 5.0 μmol of squaramide based on the TG analysis) aldehydes (0.50 mmol) in 1.0 mL of nitromethane was reacted at 90°C for 3-6 h. After that, acetylacetone (2.0 mmol) in 1.0 mL CH_2Cl_2 was added and the mixture was stirred in room temperature for 12-24 h. [b] Conversions were determined by ^{1}H-NMR and *ee* values were determined chiral HPLC analysis (see SI in Figure S5, S7). [c] Data were obtained using the mixed propylamine plus **2** as dual catalysts.

Thirdly, in order to elucidate the benefit of surface silanols for the designed silica-supported heterogeneous catalyst **3**, we also proved the cooperative role of surface silanols in the promotion of the single-step nitroaldol condensation reported by Katz, Asefa and Davis groups.[13] In this case, we utilized a parallel comparison of nitroaldol condensation catalyzed by **3** and **3** capped with -$Si(CH_3)_3$ groups (The **3** capped with-$Si(CH_3)_3$ groups was obtained by silanization of **3** and hexamethyldisilazane), demonstrating their differences in the catalytic performance. It was found that the former had obviously higher yield and selectivity than that attained with the latter (Table 1, entry 4 versus entry 5), elucidating that surface silanols in catalyst **3** could promote synergistically nitroaldol condensation. This observation is strongly similar to that reported in literature,[5a, 2d] disclosing the superiority of the designed catalyst **3**.

It was worth mentioning that the single-step nitroaldol condensation of nitromethane and benzaldehyde catalyzed by **3** had obviously higher selectivity than that attained with its parent propylamine (Table 1, entry 6 versus entry 4). Notably, relatively high yield in the **3**-catalyzed nitroaldol condensation benefited from its higher selectivity, which should be ascribed as its nitro Mannich pathway and suitable cavum to restrain the formation of byproducts. Furthermore, when catalyst **3** was applied to the single-step enantioselective Michael addition, we find that enantioselective Michael addition of acetylacetone to nitrostyrene could afford the same *ee* value as its homogeneous counterpart **2** although the reaction time was prolonged to 12 hour due to slow diffusible nature of substrates in heterogeneous catalysis.[8c] More importantly, when two single-step reactions was combinated into one-pot nitroaldol–Michael cascade reaction, it was found that this cascade reaction catalyzed by **3** could still afford target chiral products of (*S*)-3-(2-nitro-1-phenylethyl)pentane-2,4-dione with 93% yield and 99% *ee* value, where *ee* value was comparable to its single-step enantioselective Michael addition catalyzed by its homogeneous counterpart (**2**).[8c] It was notable that nitroaldol–Michael one-pot cascade reaction catalyzed **3** was better than that catalyzed by its homogeneous counterparts (the mixed propylamine plus **2** as dual catalysts) (Table 2, entry 2), further confirming the superiority of the designed catalyst **3**.

Table 2 summarized the general applicability of catalyst **3** in nitroaldol–Michael one-pot cascade reactions with a series of substituted aromatic aldehydes as substrates. As expected, one-pot cascade reactions catalyzed **3** could convert smoothly various three-component substrates to the responding chiral diones with high yields and high enatioselectivities. It was found that the structures and electronic properties of the substituents on the aromatic ring at R group did not affect significantly their enantioselectivities, that were, various electron-withdrawing and -donating R groups regardless of at 2- or 3- or 4-position on the aromatic ring were equally efficient (Entries 3–16).

Beyond the aim for construction of a site-isolated bifunctional heterogeneous catalyst **3** for the enantioselective cascade nitroaldol–Michael one-pot reaction, another important consideration in the design of heterogeneous catalyst is the ease of separation by simple centrifugation and the ability to retain its catalytic activity and enantioselectivity after multiple recycles. It was found that the heterogeneous catalyst **3** could be easily recovered by simple centrifugation. It was found that, in four

consecutive reactions, the recycled catalyst **3** could still give 86% yield and 96% *ee* in the nitroaldol–Michael one-pot cascade reaction of nitromethane, aldehyde and acetylacetone (see SI Figure S6).

Conclusions

In conclusions, by utilizing yolk-shell-structured mesoporous silica, we assemble conveniently a yolk-shell-structured, active site-isolated bifunctional heterogeneous catalyst. As presented in this study, this catalyst undergoes a nitro-Mannich pathway in nitroaldol condensation of nitromethane and aromatic aldehyde, realizing an efficient nitroaldol–Michael cascade reaction through three-component coupling of aldehydes, nitromethane and acetylacetone to afford various chiral diones with high yield and up to 99% enantioselectivity in one-pot manner. Furthermore, catalyst can be also recovered, and the recycled catalyst could still afford a highly catalytic performance in four consecutive reactions in nitroaldol–Michael coupling of nitromethane, benzaldehyde and acetylacetone.

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Graphical Abstract :

Yolk–Shell–Structured Mesoporous Silica: A Bifunctional Catalyst for Nitroaldol–Michael One-Pot Cascade Reaction

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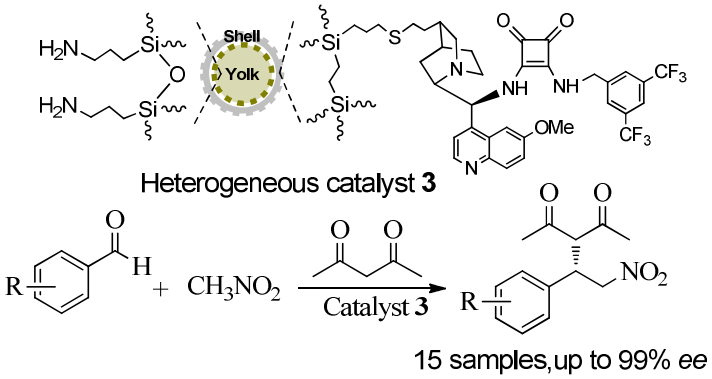

A site-isolated yolk-shell-structured mesoporous silica for nitroaldol–Michael one-pot enantio–relay reaction of aldehydes, nitromethane and acetylacetone to convert chiral diones are developed.