Heterogeneous Catalysis

Cooperative Catalysis by General Acid and Base Bifunctionalized Mesoporous Silica Nanospheres**

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Enzymes engaged in carbonyl chemistry often employ both general acid and general base catalytic residues in the active sites to activate specific substrates cooperatively.[1] Recently, several synthetic catalytic systems have utilized the double hydrogen-bonding capability of a urea or thiourea functionality as a general acid catalyst to activate carbonyl compounds in homogeneous reactions.[2] However, to our knowledge, the cooperation of general acid and base groups has yet to be demonstrated in any synthetic heterogeneous catalyst. Clearly, an important prerequisite for the construction of

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such a cooperative catalytic system would be the multifunctionalization of a solid support with control of the relative concentrations and proper spatial arrangements between these functional groups. Many monofunctionalized mesoporous silica catalysts have been reported;[3] however, we and others have focused on multifunctionalized mesoporous catalysts.[4]

Herein, we report a new cooperative catalytic system comprising a series of bifunctionalized mesoporous silica nanosphere (MSN) materials with various relative concentrations of a general acid, the ureidopropyl (UDP) group, and a general base, the 3-[2-(2-aminoethylamino)ethylamino]-propyl (AEP) group (Figure 1). Three bifunctional AEP/UDP–MSN catalysts, which are described by their initial molar ratio of the organoalkoxysilane precursors as AEP/UDP = 2/8, 5/5, and 8/2, were synthesized by using our previously reported cocondensation method.[5,6] The synthesis and characterization of the monofunctionalized MSNs with either AEP or UDP functionality were reported previously.[5a] All of the mono- and bifunctionalized MSNs exhibited spherical particle shapes with similar particle sizes (0.6 μm).[5a,6] The actual concentrations of the two functional groups (AEP and UDP) were measured with the previously described solid-state ^{13}C CP MAS and ^{29}Si MAS NMR spectroscopic methods (CP MAS is cross-polarized magic-angle spinning).[5b,6] The total surface concentrations of the organic functional groups (AEP+UDP) in the 2/8, 5/5, and 8/2 AEP/UDP–MSNs were determined to be 1.3, 1.0, and 1.5 mmol g^{-1}, respectively, and the concentration ratios of AEP/UDP were 2.5/7.5, 5.4/4.6, and 6.7/3.3, respectively.[6] The XRD measurements of these materials showed large (100) peaks and broad higher diffraction patterns, which are typical of a disordered pore structure.[5] The observed d_{100} values were 37.8, 41.7, and 38.1 Å for sample 2/8, 5/5, and 8/2 AEP/UDP-MSNs, respectively. The TEM micrographs of these materials also confirmed their disordered pore structure (Figure 2).

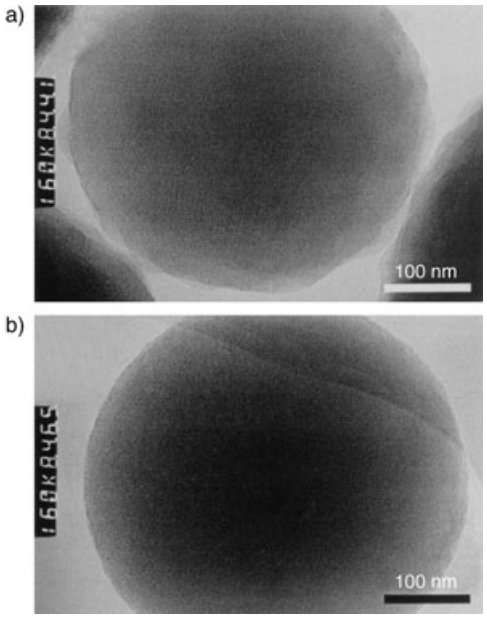


Figure 2. TEM micrographs of a) 2/8 AEP/UDP–MSN and b) 8/2 AEP/UDP–MSN) materials (Philips CM-30 at 300 kV).

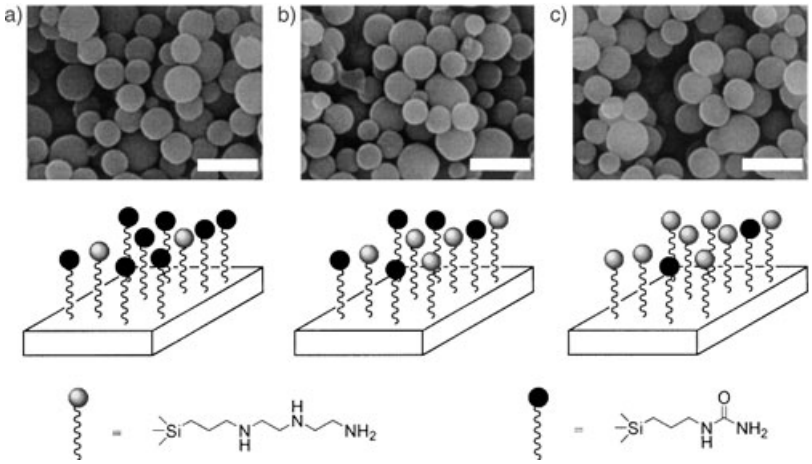
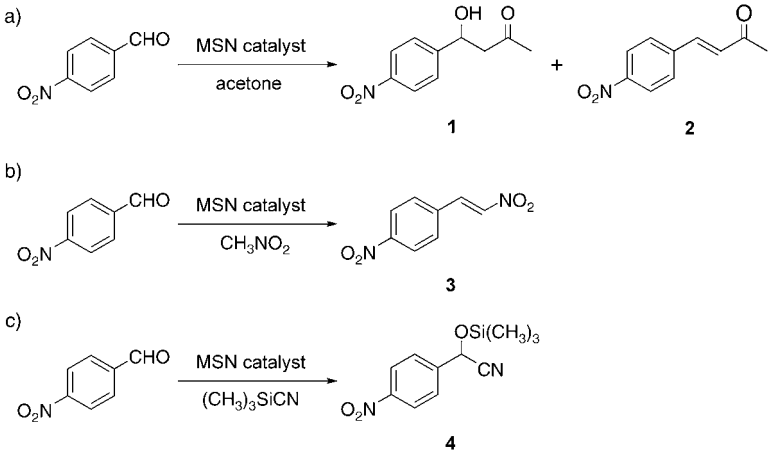


Figure 1. Scanning electron micrographs (SEM, top) and schematic drawings (bottom) of the bifunctional MSNs: a) 2/8 AEP/UDP–MSN, b) 5/5 AEP/UDP–MSN, and c) 8/2 AEP/UDP–MSN. Scale bar: 2.0 μm.

The N_2 surface sorption analyses of these bifunctionalized MSNs revealed typical type-IV BET (Brunauer–Emmett–Teller) isotherms. The measured BET surface areas of 2/8, 5/5, and 8/2 AEP/UDP–MSNs were 938.7, 759.6, and 830.4 $m^2 g^{-1}$, respectively. The corresponding BJH (Barret–Joyber–Halenda) average pore diameters of these MSNs were 27.8, 22.9, and 25.9 Å.

To investigate how UDP and AEP could catalyze cooperatively different reactions involving carbonyl activation, the aforementioned AEP/UDP–MSN materials were employed as catalysts for aldol, Henry, and cyanosilylation reactions. As shown in Scheme 1, a common electrophile, 4-nitro-



Scheme 1. Three model reactions catalyzed by the MSN catalysts: a) aldol reaction, b) Henry reaction, c) cyanosilylation.

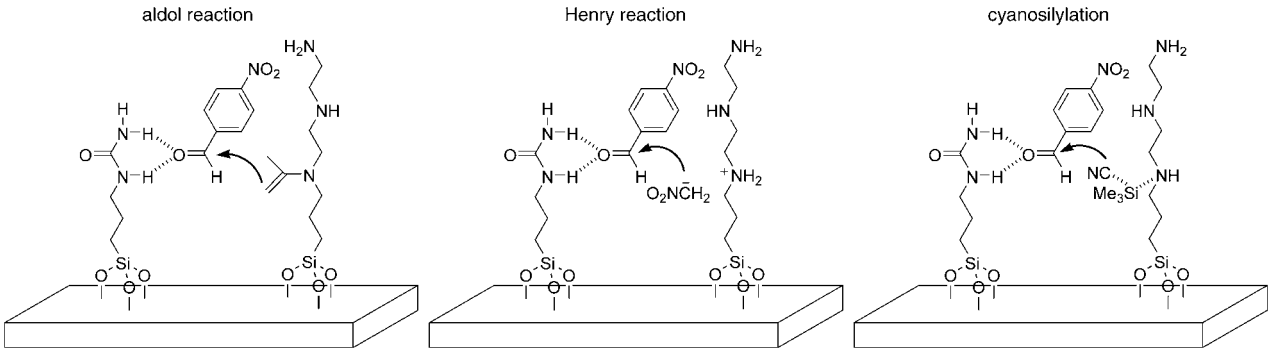
benzaldehyde, and different nucleophiles, acetone, nitromethane, and trimethylsilyl cyanide, were used as reactants. In these reactions, the secondary amines of the AEP group were shown to be responsible for the enamine formation with acetone (aldol reaction),[7] the deprotonation of CH_3NO_2 (Henry reaction),[4] and the generation of a potential nucleophile from $(CH_3)_3SiCN$ through hypervalent silicate formation (cyanosilylation).[8] On the other hand, a general acid group (UDP) could activate the carbonyl group of 4-nitrobenzaldehyde to nucleophilic attack through double hydrogen bonding.[2] Therefore, the presence of both AEP and UDP groups in close proximity could activate cooperatively the electrophile and nucleophile to enhance the reaction rates of the desired catalytic reactions (Scheme 2). Indeed, the observed turnover numbers (TONs) of the catalysts in these reactions (Table 1) are consistent with this hypothesis. In the case of the aldol reaction, the monofunctionalized AEP–MSN catalyzed the conversion of 4-nitrobenzaldehyde (0.5 mmol) into compound **1** (0.091 mmol) and a small amount of the dehydrated product, compound **2** (0.018 mmol), in the presence of acetone (10 mL). In contrast, UDP–MSN did not show any catalytic activity under the same reaction conditions. This result suggested that the presence of the AEP functionality is crucial for the conversion of acetone solvent molecules into the active enamine species.[7] However, a synergistic effect between the AEP and UDP groups was observed in the case of the bifunctionalized AEP/UDP–MSN catalysts.

As shown in Table 1 and Figure 3, the TONs of all three AEP/UDP–MSNs were always higher than those of AEP–MSN. The largest TONs were observed in the case of the 2/8 AEP/UDP–MSN catalyst. For example, in the Henry and cyanosilylation reactions catalyzed by 2/8 AEP/UDP–MSN, the observed high TONs (125.0 and 276.1, respectively) indicate a genuine and superior catalytic performance in comparison with those of other bifunctional AEP/UDP–MSNs. In the aldol reaction, the largest TON (22.6) was also observed with 2/8 AEP/UDP–MSN as the catalyst. Furthermore, the TON (6.4) of a 1:1 mixture of the monofunctionalized AEP–MSN and UDP–MSN was clearly lower than that of the 5/5 AEP/UDP–MSN (11.9). The TONs of the bifunctionalized MSNs decreased significantly as the ratio of the surface concentrations of the AEP and UDP groups increased from 2.5/7.5 to 5.4/4.6 to 6.7/3.3. According to our solid-state NMR spectroscopic data, the total numbers of organic functional groups (AEP+UDP) in these bifunctionalized MSNs were similar; only the relative concentrations between the AEP and UDP groups varied. The recyclability of each of the bifunctional AEP/UDP–MSN catalysts was examined by isolating the catalysts from the reaction mixtures after 20 h by centrifugation. The catalysts were reused three times without purification. The TEM images[6] of the recycled MSN materials showed some surface depositions of amorphous substances, which presumably arose from physisorbed reactants or products. Nonetheless, in all three reactions catalyzed by these recycled bifunctional MSNs, the TONs

Table 1: TONs for the MSN-catalyzed reactions.[a]

Reaction	MSN catalyst	*T* [°C]	Product	TON
aldol	2/8 AEP/UDP	50	**1**, **2**	22.6
	5/5 AEP/UDP	50	**1**, **2**	11.9
	8/2 AEP/UDP	50	**1**, **2**	8.6
	AEP	50	**1**, **2**	5.4
	physical mixture[b]	50	**1**, **2**	6.4
	UDP	50	**1**, **2**	0.0[d]
	pure MSN[c]	50	**1**, **2**	0.0[d]
	2/8 AEP/CP	50	**1**, **2**	12.4
	5/5 AEP/CP	50	**1**, **2**	9.3
Henry	2/8 AEP/UDP	90	**3**	125.0
	5/5 AEP/UDP	90	**3**	91.1
	8/2 AEP/UDP	90	**3**	65.8
	AEP	90	**3**	55.9
	physical mixture[b]	90	**3**	79.2
	UDP	90	**3**	5.8
	pure MSN[c]	90	**3**	0.0[d]
	2/8 AEP/CP	90	**3**	78.0
	5/5 AEP/CP	90	**3**	71.0
cyanosilylation	2/8 AEP/UDP	50	**4**	276.1
	5/5 AEP/UDP	50	**4**	170.5
	8/2 AEP/UDP	50	**4**	109.4
	AEP	50	**4**	111.4
	physical mixture[b]	50	**4**	126.9
	UDP	50	**4**	45.9
	pure MSN[c]	50	**4**	43.0[d]

[a] TON = mmol product per mmol catalyst during 20-h reaction time for aldol and Henry reactions and 24 h for the cyanosilylation reaction with 20 mg of MSN. [b] Physical mixture = AEP–MSN (20 mg)+UDP–MSN (20 mg). [c] Nonfunctionalized MCM-41. [d] Yield [%].



Scheme 2. AEP and UDP groups may activate the electrophile and nucleophile cooperatively to enhance the reaction rates of the desired catalytic reactions.

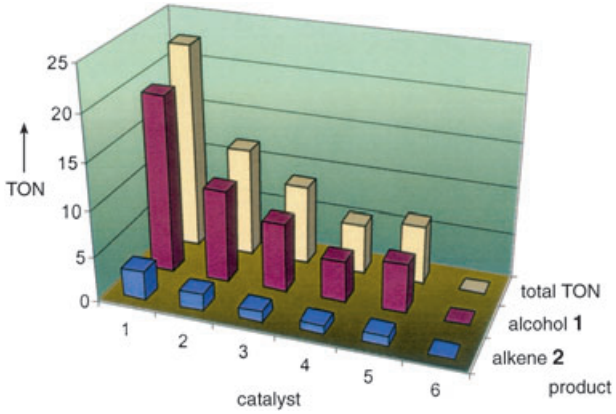


Figure 3. Diagram showing the TONs for the aldol reaction with the catalysts 2/8 AEP/UDP–MSN (1), 5/5 AEP/UDP–MSN (2), 8/2 AEP/UDP–MSN (3), AEP–MSN (4), physical mixture of AEP–MSN and UDP–MSN (5), and UDP–MSN (6).

were no more than 10% lower than those of the freshly prepared catalysts.

To examine whether this activity enhancement was due to the "surface dilution effect" of the AEP group, we investigated the catalytic performance of two bifunctional MSN materials (2/8 and 5/5 AEP/CP–MSN) that have the AEP group and a cyanopropyl (CP) functionality. CP cannot activate the electrophiles through a double hydrogen-bonding interaction. The synthesis and characterization of these two materials were reported previously.[5b] As shown in Table 1, the TONs of the 2/8 and 5/5 AEP/CP–MSNs are 12.4 and 9.3, respectively. Indeed, the TON increased slightly as the AEP/CP ratio decreased. However, the large difference in TONs between the AEP/CP–MSN and the AEP/UDP–MSN catalysts, which have similar surface concentrations of the AEP group, can not be explained by the surface dilution effect. These results strongly indicate that the rate of the aldol reaction is accelerated as the surface concentration of UDP groups increases. Given that the UDP group can only activate the electrophile, the observed rate acceleration in the UDP-abundant MSN catalysts suggested that the activation of the carbonyl group of 4-nitrobenzaldehyde might be the rate-determining step in our cooperative catalysts. Such a "cooperative dual catalysis" effect in a homogeneous system, in which one catalyst activates the nucleophile and the other catalyst is responsible for the activation of the electrophile, was reported recently by Jacobsen and co-workers.[9] In their study, the best molar ratio between the two catalysts was 0.67 and not 1, which indicates that the best ratio between the cooperative catalytic groups greatly depends on the kinetic nature of the reaction of interest. A similar trend in catalytic reactivity was also observed in the Henry and cyanosilylation reactions. A pronounced cooperative effect was manifested by a twofold increase in the TON of 2/8 AEP/UDP–MSN relative to that of 8/2 AEP/UDP–MSN in both reactions (Table 1). As the surface concentration of the primary catalytic group (AEP) in 2/8 AEP/UDP–MSN (AEP = $0.32\ \mathrm{mmol\,g^{-1}}$) is only a third that of 8/2 AEP/UDP–MSN (AEP = $1.00\ \mathrm{mmol\,g^{-1}}$), these unusual catalytic enhancements are strong indications of the existence of cooperation between the general acid (UDP) and base (AEP) groups in our system. The control experiment with the physical mixture of AEP–MSN and UDP–MSN exhibited a slightly higher reaction rate in the cyanosilylation than AEP–MSN alone owing to the increased number of surface silanol groups, which can also moderately catalyze the reaction.

In conclusion, we have demonstrated that a general acid group, UDP, can activate substrates in cooperation with a general base group, AEP, to catalyze various reactions that involve carbonyl activation. By fine-tuning the relative concentrations and proper spatial arrangement of different cooperative functional groups, we envisage that our multifunctionalized MSNs could serve as new selective catalysts for many important reactions.

Experimental Section

The functionalized materials were synthesized by using the previously described cocondensation reaction.[5] Typical procedure (2/8 AEP/UDP–MSN): A mixture of cetyltrimethylammonium bromide (CTAB; 2.0 g, 5.49 mmol), NaOH (2.0 M, aqueous; 7.0 mL, 14.00 mmol), and H_2O (480 g, 26.67 mol) was heated to 80 °C for 30 min. Tetraethoxysilane (TEOS; 9.34 g, 44.8 mmol), 3-[2-(2-aminoethylamino)ethylamino]propyltrimethoxysilane (AEPTMS; 0.305 g, 1.15 mmol), and ureidopropyltrimethoxysilane (UDPTMS; 1.023 g, 4.60 mmol) were added rapidly and sequentially to the resulting solution to yield an opaque reaction mixture. White precipitates were observed after vigorous (550 rpm) stirring of the reaction mixture for about 2 min. After an additional 2 h of heating at 80 °C, the as-synthesized bifunctionalized 2/8 AEP/UDP–MSN material was isolated by hot filtration, washed with copious amounts of water and methanol, and dried under vacuum. The CTAB surfactant molecules were extracted from the mesopores of the MSN by placing the as-synthesized material (1.0 g) in a mixture of methanol (100 mL) and hydrochloric acid (0.6 mL) for 2.5 h at 60 °C. The resulting solid product, which was free of surfactant, was filtered and washed with water and methanol, then dried under vacuum for 3 h at 90 °C. The non-functionalized MSN was prepared according to a reported method.[5a]

Aldol reaction: All chemicals were purchased from Aldrich and used without further purification. Reagent-grade acetone was used without further purification. A mixture of the MSN catalyst (20 mg) and 4-nitrobenzaldehyde (0.076 g, 0.5 mmol) in acetone (10 mL) was heated at 50 °C with constant stirring for 20 h. The reaction mixture was then filtered through a glass frit, and the solids were washed with chloroform and acetone. The solvent was removed from the filtrate by rotary evaporation, and the product was dried under high vacuum. The residue was completely dissolved in $CDCl_3$, and THF ($\approx$10 mmol) was added as an internal standard to the $CDCl_3$ solution. Analysis of the product mixture was performed by measuring ^{1}H NMR spectra on a Bruker DRX400 spectrometer. Distinctive chemical shifts were observed for the hydrogen atoms of the two products. The signals were assigned by comparing the chemical shifts observed in the spectra of the products with literature values.

Henry (nitroaldol) reaction: Reagent-grade nitromethane was used without further purification. A mixture of the MSN catalyst (20 mg) and 4-nitrobenzaldehyde (0.453 g, 3.0 mmol) in nitromethane (10 mL) was heated at 90 °C with constant stirring for 20 h. The reaction mixture was filtered through a glass frit, and the solids were washed with chloroform and acetone. The solvent was removed from the filtrate by rotary evaporation, and the residue was dried under high vacuum then completely dissolved in [D_6]acetone (10 mL). THF ($\approx$10 mmol) was added as an internal standard to the [D_6]acetone solution. The product was analyzed by ^{1}H NMR spectroscopy on a Bruker DRX400 spectrometer. Distinctive chemical shifts were

observed for the vinylic hydrogen atoms of the product. The signals were assigned by comparing the chemical shifts observed for the product with literature values.

Cyanosilylation: A mixture of the MSN catalyst (20 mg), 4-nitrobenzaldehyde (0.453 g, 3.0 mmol), and $(CH_3)_3SiCN$ (0.298 g, 3.0 mmol) in dry toluene (10 mL) was heated at 50 °C with constant stirring for 24 h. The reaction mixture was then filtered through a glass frit, and the solids were washed with chloroform and acetone. The solvent was removed from the filtrate by rotary evaporation, and the residue was dried under high vacuum then completely dissolved in $CDCl_3$. THF ($\approx$ 10 mmol) was added as an internal standard to the $CDCl_3$ solution. The product was analyzed by ^{1}H NMR spectroscopy on a Bruker DRX400 spectrometer. A distinctive chemical shift of 5.6 ppm was observed for the silyl ether product. The signals were assigned by comparing the chemical shifts observed for the products with literature values.

Solid-state NMR spectra were obtained at 100.59 (^{13}C) and 79.47 MHz (^{29}Si) on a Varian/Chemagnetics Infinity spectrometer equipped with a doubly tuned 5-mm MAS probe. Direct polarization (DP) and variable-amplitude CP MAS methods were used under the conditions described in our previously published studies.[4a,5b] These measurements provided quantitative evidence for functionalization of the mesopores with the organic moieties and confirmed the structure of the bifunctionalized materials. For AEP–MSNs, UDP–MSNs, and AEP/UDP–MSNs, the ^{29}Si and ^{13}C NMR spectra were assigned as described for our earlier study (see the Supporting Information).[4a,5a] The methods used for quantitative measurements of the ^{29}Si and ^{13}C signal intensities are detailed below. All NMR spectroscopic results are summarized in the Supporting Information,[6] which contains the relative concentrations of T^n and Q^n groups (silicon groups $(\equiv SiO)_n\mathbf{Si}(OH)_{(4-n-m)}R_m$ are designated as T^n for $m = 1$ and as Q^n for $m = 0$), the molar concentrations of organic functional groups, and the corresponding average molecular formulae.

Relative concentrations of T^n and Q^n silicon groups[10] were obtained from the analysis of ^{29}Si DPMAS spectra. In agreement with our earlier results,[5a] the measurements of the T_1 relaxation in functionalized MSNs yielded T_1 values in the order of 50–65 s for T^n groups and 30–45 s for Q^n groups. Therefore, a delay of 300 s between scans was used during the acquisition of ^{29}Si NMR spectra. The accumulation of 270 scans yielded intensities that were accurate within $\pm$10 %. Although direct polarization is the preferred method for quantitative measurements, relative intensities of ^{13}C signals were measured by using a CP MAS based method. The strategy, developed in our earlier study,[5b] was also successfully used for the AEP/UDP–MSN system in our previous report.[4a] The procedure uses differences in values of $T_{1\rho}^{H}$ and τ_{CH} times between AEP and UDP.[5b] The bifunctionalized samples could be characterized quantitatively without tedious measurements of the ^{13}C build-up curves[4a,5b] by properly measuring and processing the CP MAS spectra with two different contact times (i.e., 0.4 and 1.5 ms) with known physical mixtures of monofunctionalized samples as intensity standards.[4a,5a]

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