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Preparation of Bifunctional Mesoporous Silica Nanoparticles by Orthogonal Click Reactions and Their Application in Cooperative Catalysis

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Abstract: The synthesis of bifunctional mesoporous silica nanoparticles is described. Two chemically orthogonal functionalities are incorporated into mesoporous silica by co-condensation of tetraethoxysilane with two orthogonally functionalized triethoxyalkylsilanes. Post-functionalization is achieved by orthogonal surface chemistry. A thiol–ene reaction, Cu-catalyzed 1,3-dipolar alkyne/azide cycloaddition, and a radical nitroxide exchange reaction are used as orthogonal processes to install two functionalities at the surface that differ in reactivity. Preparation of mesoporous silica nanoparticles bearing acidic and basic sites by this approach is discussed. Particles are analyzed by solid state NMR spectroscopy, elemental analysis, infrared-spectroscopy, and scanning electron microscopy. As a first application, these particles are successfully used as cooperative catalysts in the Henry reaction.

Keywords: acid–base catalysis • click chemistry • cooperative catalysis • MCM-41 • mesoporous silica

Introduction

Mesoporous materials with size-tuneable mesopores have been widely used in the past few years in various fields of research.[1] For example, multifunctional systems based on mesoporous materials have attracted a great deal of interest. Due to the high surface area and the well-ordered structure, mesoporous silica has been regarded as an ideal solid support for the preparation of heterogeneous catalysts. In this regard the Mobil composition of matter No. 41 (MCM-41) material has been intensively studied.[2] Cooperative catalysis on a solid support requires the control of the relative spatial arrangement and the relative concentration of at least two chemically different functionalities at the surface. This is reminiscent of enzymes used as catalysts in biological systems. Catalysts bearing two different active functionalities that are able to individually activate each of the two reaction partners in a cooperative manner are known.[3] Stimulated by nature, acid and base functionalities have been mostly used as active entities in such systems. To suppress direct proton transfer from the acid to the base if stronger acids and bases are used, the two functionalities have to be separated in space. However, the distance of the two active moieties has to be carefully adjusted in such a way that they can act synergistically as cooperative catalysts. The acid and base functionalities have been introduced to the surface either through a stepwise post-grafting strategy[4] or by a co-condensation strategy.[3,5] Few cases are known in which chemical modification of MCM type materials was carried out through click chemistry.[6] To the best of our knowledge, there is no example of the chemical modification of mesoporous silica through orthogonal double click reactions.

Herein, we report a conceptually new approach for the synthesis of bifunctional mesoporous silica nanoparticles (MSNs). Co-condensation of two chemically orthogonal triethoxyalkylsilanes **A** and **B** with tetraethyl orthosilicate (TEOS) should lead to an MSN of type **D** bearing the two functionalities A and B at the surface (Scheme 1). These functionalities should be selectively addressable by orthogonal surface chemistry providing bifunctional MSNs **C**1-**C***n* (strategy 2). In contrast, the alternative co-condensation strategy using trialkoxyalkylsilanes already containing catalytically active moieties leads to a single type of catalyst **C**1 (strategy 1). Hence, our new approach should allow for the synthesis of a series of catalysts **C**1–**C***n* starting with a single type of MSN **D** by late stage functionalization. It is important to note that not every functional group F^A, F^B at the terminus of the triethoxyalkylsilanes **A**, **B** is compatible with the co-condensation process (strategy 1). Therefore, by

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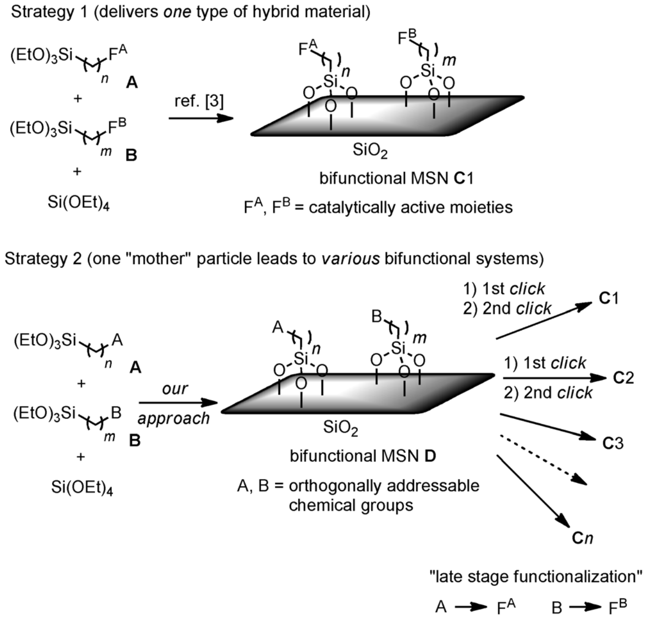
Supporting information for this article (including the experimental procedure for the preparation of alkoxyamine **1** and **10** and the preparation of alkoxyamine and nitroxide conjugates **2**–**9** and **11**, XPS spectra and all detailed data of the surface characterization) is available on the WWW under http://dx.doi.org/10.1002/chem.201200499.

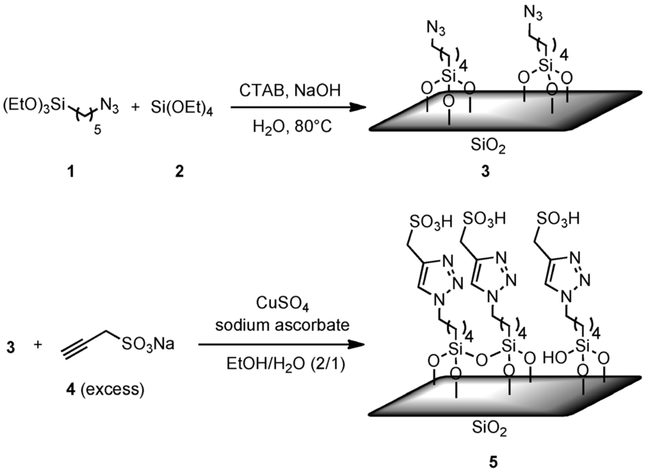


Scheme 1. Conceptually different approaches for the preparation of bifunctional MSNs.

applying the late stage functionalization approach we should gain flexibility in the synthesis of bifunctional MSNs.

Results and Discussion

Preparation and analysis of bifunctional mesoporous silica particles: The terminal functionalities A and B in the triethoxyalkylsilanes **A** and **B** (see Scheme 1) had to be carefully chosen. These groups needed to be orthogonally addressable by two different click reactions and they should not interfere with the co-condensation reaction. Moreover, reactions applied should be modular, wide in scope and high yielding.[7a] A key factor for a process to be categorized as a click reaction is its successful conduction if equimolar amounts of the two coupling partners are used.[7b] However, for the convenience of the reader we would like to call our transformations click reactions even though an excess of one reactant is used. Based on the above requirements, we decided to use azides and olefins as chemically orthogonal termini of the triethoxyalkylsilanes for our initial studies. The synthesis of the azide-terminated triethoxyalkylsilane **1** is shown in the Supporting Information. To test the compatibility of the azide group with the co-condensation process, we first treated **1** and the commercially available tetraethoxysilane (TEOS) **2** in a 8:1 ratio with cetyltrimethylammonium bromide (CTAB) as surfactant to afford the azido-functionalized porous silica **3** (Scheme 2). The ratio of 8:1 turned out to be ideal; a higher concentration of **1** with respect to TEOS led to an amorphous solid and the targeted powder was not obtained. For further chemical functionalization we chose the copper-catalyzed alkyne/azide click-cycloaddition (CuAAC)[7a] and successfully reacted MSN **3** with prop-2-yne sulfonic acid **4** to provide the acid-functionalized particles **5**.



Scheme 2. Synthesis of the monofunctionalized sulfonic acid particles **5**.

The monofunctionalized particles were carefully analyzed by solid-state NMR and IR spectroscopy before (**3**) and after (**5**) the cycloaddition (Figure 1). The ^{13}C CP/MAS NMR spectra of the co-condensed particles **3** prove the successful synthesis and are in good agreement with the corresponding spectra of the educt **1**. No residual ethoxy signals ($\delta = 59$ and 18 ppm) can be observed, indicating that the condensation of the network is quantitative. The marked resonances correspond to residual solvent molecules that are incorporated in the mesopores of the silica matrix ($\delta =$ 50 ppm for methanol as well as $\delta = 14$ and 66 ppm for diethyl ether). The ^{13}C resonance in **3** at 51 ppm can be attributed to the azide-bound carbon; this signal vanishes after the click reaction, which is in excellent agreement with the IR data. The two new distinct signals that appear at $\delta = 47$ and 53 ppm can be attributed to the methylene groups that are bound to the triazole ring and the sulfonic acid moiety, respectively. This is further verified by the ^{1}H MAS NMR spectrum, in which the methylene resonance associated with the CH_2N_3 fragment at $\delta = 3.1$ ppm vanishes upon reaction. For particle **5**, the spectrum not only shows the expected broad resonance of the acid protons at $\delta = 16$ ppm, but also a broad ^{1}H resonance at $\delta = 8.2$ ppm, clearly indicating that the aromatic ring system has been formed. This shift is very close to that expected for 1,2,3-triazole. In the IR spectrum a characteristic peak at 1650 cm^{-1} can be attributed to the triazole ring. The ^{13}C CP/MAS NMR spectra do not show any resonance for aromatic carbons. However, it has been reported and discussed by several authors, that the resonance of spin $^1/_2$ nuclei directly bonded to a quadrupolar nucleus (in this case ^{14}N) may be broadened even beyond detection, because the heteronuclear ^{13}C–^{14}N magnetic dipole–dipole coupling may not be averaged out by magic angle spinning if the quadrupolar interaction is strong.[8–10]

The ^{1}H MAS NMR spectrum of **5** exhibits a significant broadening due to an interaction with the paramagnetic copper that was used as a catalyst in the 1,3-dipolar cycload-

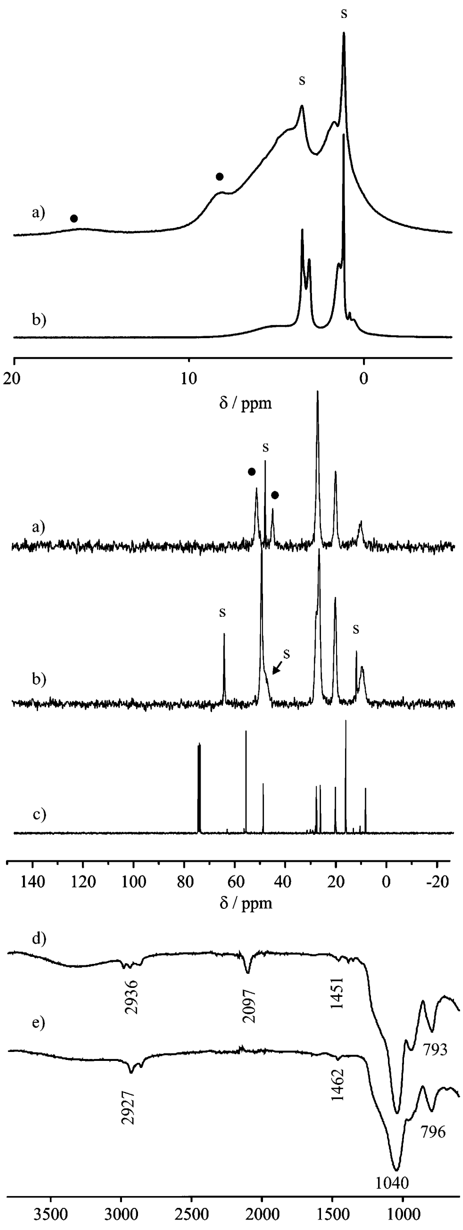
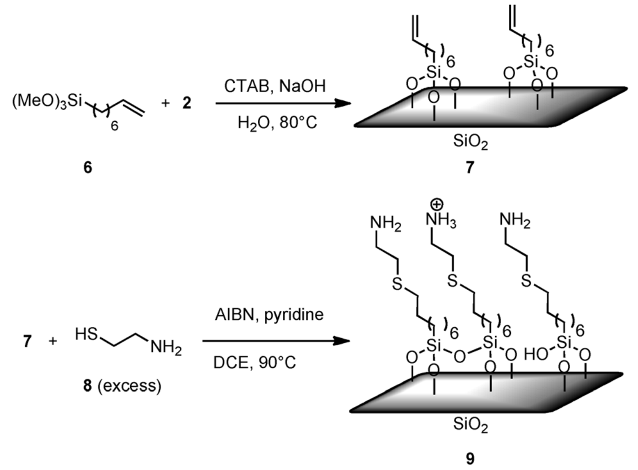


Figure 1. ^{1}H MAS NMR (top) and ^{13}C CP/MAS NMR (center) spectra of a) the acid-functionalized monofunctional particles **5**, and b) the azide-functionalized particles **3**, c) ^{13}C NMR spectrum of azide **1** in $CDCl_3$ solution; d) IR spectrum of the monofunctional particles before CuAAC reaction; e) IR spectrum of the monofunctional particles after CuAAC reaction. s = solvent.

dition. This broadening could also contribute to the failure of observing the triazole-carbon resonances in ^{13}C CP/MAS experiments. Considering these circumstances, the ^{1}H and ^{13}C CP/MAS spectra lend strong support to the successful formation of the triazole ring.

The sulfonic acid loading was estimated by elemental analysis and that value was confirmed by titration of the monofunctionalized particles (see the Supporting Information). By using these methods, the concentration of the acid was determined to be approximately 0.75 mmol g^{-1}.

After these studies we also tested the ability of a terminal olefin to undergo thiol–ene reactions at the surface (Scheme 3). To this end 7-octenyltrimethoxysilane **6** was co-condensed with TEOS (**2**) under identical conditions to afford the monofunctionalized particles **7**. Subsequent thiol–ene reaction with 2-aminoethanethiol provided the amine-functionalized particles **9**.



Scheme 3. Synthesis of the monofunctionalized amine particles **9**.

The NMR spectra of **7** and **9** provide evidence of the successful synthesis (Figure 2). The ^{13}C CP/MAS NMR spectrum of **7** is in perfect agreement with the ^{13}C spectrum measured for **6**. The olefinic resonances of **7** are observed at $\delta = 138$ and 114 ppm, whereas the signals at $\delta = 33$ (α-CH_2), 29 (β-, γ- and δ-CH_2), 22 (ε-CH_2), and 12 ppm (ζ-CH_2) can be attributed to the aliphatic chain. After the thioether formation, three new signals appear at $\delta = 41$, 36, and 31 ppm, which are in excellent agreement with the shifts expected for the three new methylene groups formed in the thioether functionality. In the ^{1}H MAS NMR spectrum a distinct new signal can be found for **9** at $\delta = 7.9$ ppm that could arise from terminal ammonium groups indicating partial protonation of the amine. The signals of the other newly formed methylene groups overlap with the residual signals from the precursor in the 2–4 ppm range. For **7** the ^{1}H resonance at $\delta = 2.1$ ppm has a higher intensity than in **9**. This is most likely due to a contribution of silanol groups. Both the ^{13}C and ^{1}H spectra confirm the successful functionalization at the surface. However, the spectra also indicate that neither the condensation nor the functionalization reactions are quantitative. The ^{13}C resonance at $\delta = 51$ ppm can be attributed to residual methoxy groups, showing an incomplete condensation of **6** with the TEOS. On the other hand, the resonances of the olefinic ^{1}H and ^{13}C are still visible after the thiol–ene reaction, indicating that only a portion of the substrate molecules reacted. This is not unexpected, because parts of the substrate are incorporated in the matrix interior during the condensation process. These molecules would be inaccessible in the second reaction step.

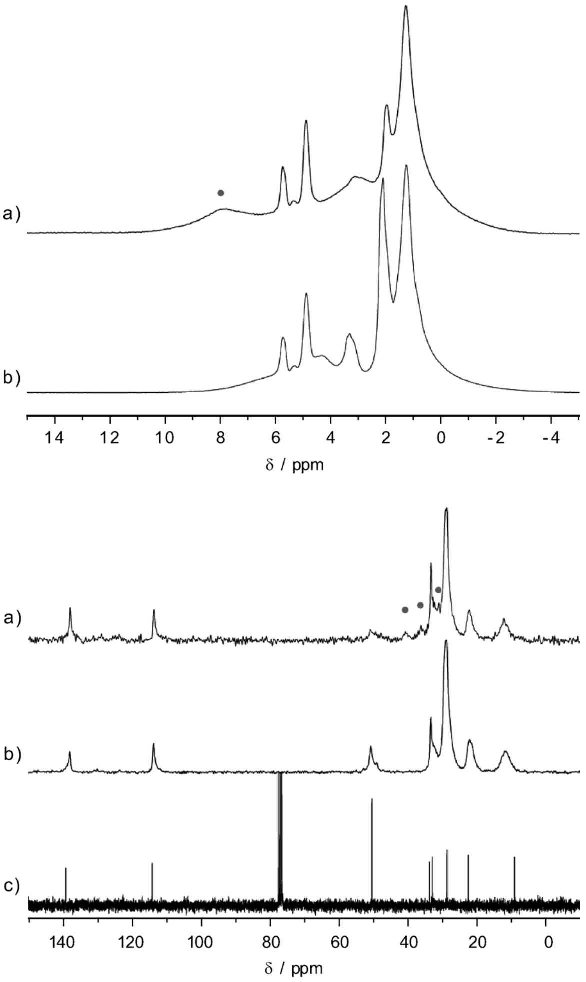
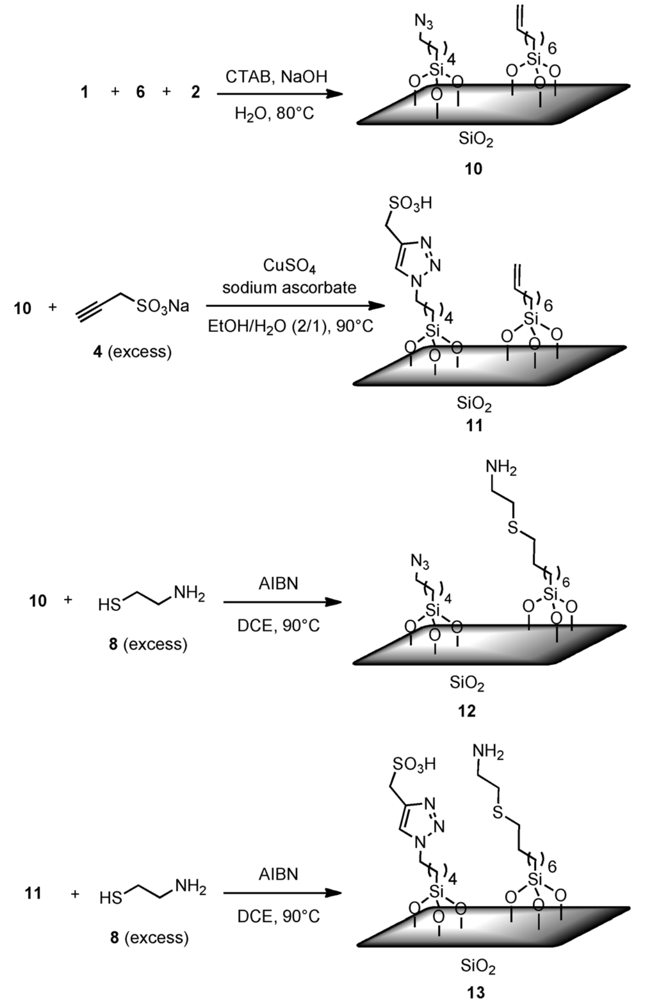


Figure 2. ^{1}H MAS NMR (top) and ^{13}C CP/MAS NMR (bottom) spectra of a) the amine-functionalized monofunctional particles **9** and b) the alkene-functionalized particles **7**, c) ^{13}C NMR spectrum of olefine **6** in $CDCl_3$ solution.

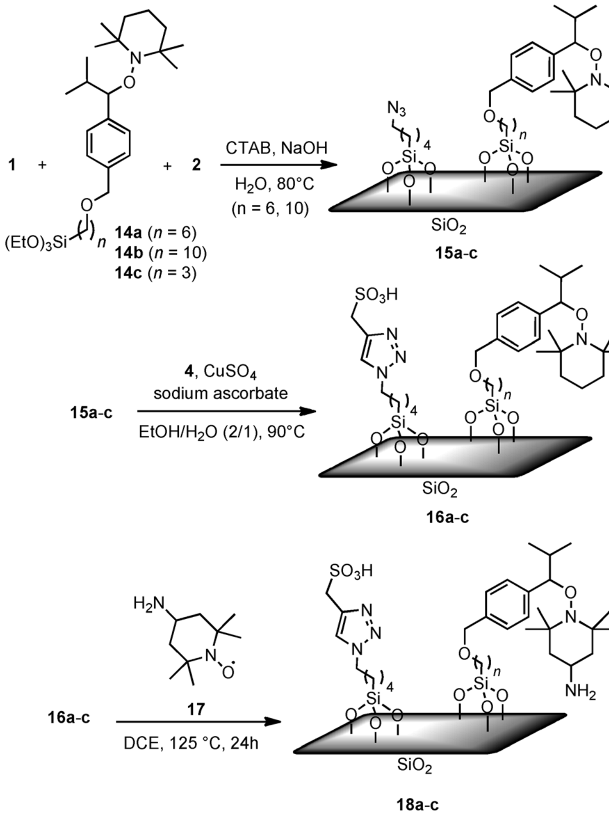
Following these encouraging experiments we prepared bifunctionalized MSN **10** by co-condensation of azide **1**, the commercially available trimethoxyalkylsilane **6** bearing a terminal olefin, and TEOS **2** in a 8:1:1 ratio (TEOS:**1**:**6**, Scheme 4). We introduced the sulfonic acid at the surface through a CuAAC of the surface azide groups in **10** with **4** to provide the acid-functionalized material **11**. The success of the cycloaddition was verified by IR spectroscopy (spectrum is given in the Supporting Information). We have previously shown that the surface thiol click reaction[11] tolerates the azide functionality.[12] Based on that experience, MSN **10** was successfully modified through the thiol-ene reaction. To this end, particles **10** suspended in dichloroethane (DCE) were treated with thiol **8** in the presence of α,α′-azobisisobutyronitrile (AIBN) to give the corresponding azido/amino MSN **12**. By analogy, acid/base bifunctional MSN **13** was prepared through the thiol–ene click reaction. Importantly, neither the triazole nor the sulfonic acid moiety interfered with the thiol–ene process.



Scheme 4. Preparation of bifunctional silica particles **13**.

SEM analysis of the particles **10**, **11**, and **13** revealed that the structure of the particles did not change during the two sequential surface reactions (see the Supporting Information). To gain even more flexibility in the design of bifunctional MSNs, we decided to test a third reaction that should be orthogonal to both the CuAAC and the thiol–ene reaction. We have previously shown[13] that the radical nitroxide exchange reaction is a highly efficient thermal process for chemical surface modification. In the nitroxide exchange reaction an alkoxyamine is covalently bound to the surface of a particle. Heating of the particle in the presence of a soluble nitroxide leads to thermal nitroxide exchange to provide the corresponding surface-bound product alkoxyamine. The radical nitroxide exchange process is orthogonal to most other typical surface reactions.

We first co-condensed alkoxyamine **14**, azide **1** and TEOS under optimized conditions to give the bifunctional particles **15** (Scheme 5). The synthesis of alkoxyamines **14a–c** is discussed in the Supporting Information. We found that the alkoxyamine residues in **14a–c** did not interfere with the co-condensation process. Analysis of particles **15** is provided in the Supporting Information. Compounds **15a–c** were then



Scheme 5. Co-condensation of alkoxyamine **14a–c** and azide **1** and further chemical modification.

subjected to CuAAC with sulfonic acid **4** to obtain particles **16a–c**. Acid/base-functionalized organic/inorganic hybrids **18a–c** were eventually obtained by thermal nitroxide exchange reaction using nitroxide **17**. To this end, the particles were suspended in DCE and heated for 24 h in the presence of an excess of the nitroxide **17** to give particles **18a–c**. The success of the exchange reaction was verified by analyzing the particles by analogy to the other bifunctional MSNs using NMR spectroscopy as discussed above (see the Supporting Information).

We also conducted nitrogen adsorption-desorption experiments on several MSNs. A typical sorption isotherm and the pore size distribution derived from it using the BJH method[14] are shown in Figure 3 for five representative samples. The data reveal a wide distribution of pore sizes in the range of 1.9 to 4.4 nm. The surface areas of these materials vary from 20 to 725 m^2g^{-1}. Surface areas for particles with a higher degree of functionalization are generally found to be lower indicating that pores get partially blocked through the chemical modification.

Importantly, by simply changing the nitroxide component in the exchange reaction, we had fast access to a series of bifunctional silica particles **19–22** starting with a single "mother" particle type **15a**, convincingly documenting the potential of our new strategy for the synthesis of a series of bifunctional MSNs by late stage functionalization (Figure 4).

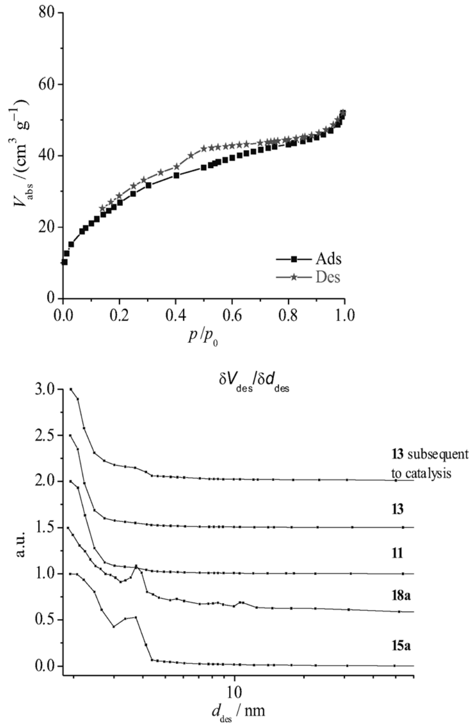


Figure 3. Typical nitrogen adsorption–desorption isotherm (top) and exemplary BJH plots of materials **11**, **13**, **15a**, and **18a** (bottom).

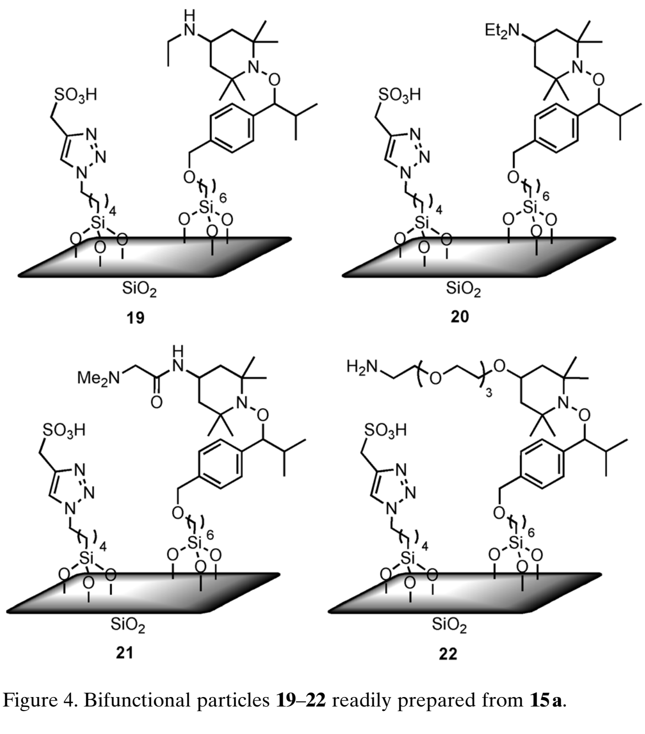


Figure 4. Bifunctional particles **19–22** readily prepared from **15a**.

The synthesis of the corresponding functionalized nitroxides is discussed in the Supporting Information and the success of the nitroxide exchange reaction has been proved by solid state NMR spectroscopy. Whereas for **18a**, **20**, and **21** no large changes are expected in the ^{13}C CP/MAS NMR spectra before and after nitroxide exchange; the introduction of the pegylated amine in **22** should lead to clearly visible methylene groups of the tetraethylene oxide moiety. Indeed, similar spectra were obtained for **18a**, **20**, and **21**; however, the methylene moieties next to the O atoms in **22** were unambiguously identified at about $\delta = 71$ ppm (Figure 5).

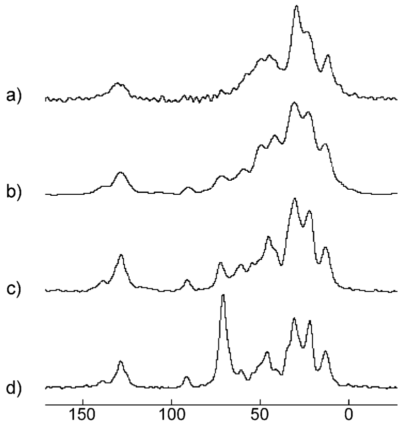


Figure 5. ^{13}C CP/MAS NMR spectra of different amine-functionalized MSNs a) **18a**, b) **20**, c) **21**, and d) **22**.

For particle **22** containing the short PEG-linker, ^{29}Si solid state NMR spectra were also recorded (Figure 6). Three different signals appeared in the ^{29}Si NMR spectra as expected. They belong to the Q^4-groups [$Si(OSi)_4$] at about $\delta = -110$ ppm, the Q^3-groups [$Si(OSi)_3OH$] at about $\delta = -101$ ppm, and the T^3-groups [$Si(OSi)_3R$] at $\delta = -65$ ppm bearing one organic group directly attached to silicon.[15]

Three additional bifunctional MSNs **23**–**25** were successfully prepared by using orthogonal surface chemistry are shown in Figure 7. Preparation of these hybrid materials is described in the Supporting Information.

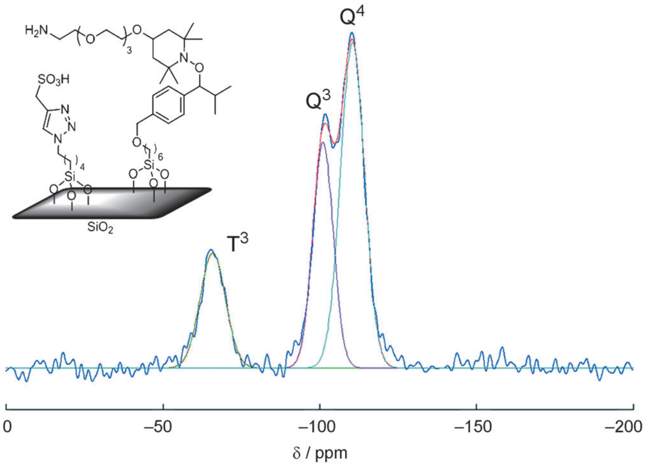


Figure 6. ^{29}Si solid-state NMR spectrum of MSM **22** showing the expected three signals for the Q^4 group at $\delta = -110$ ppm, Q^3 group at $\delta = -101$ ppm, and T^3 group at $\delta = -65$ ppm.

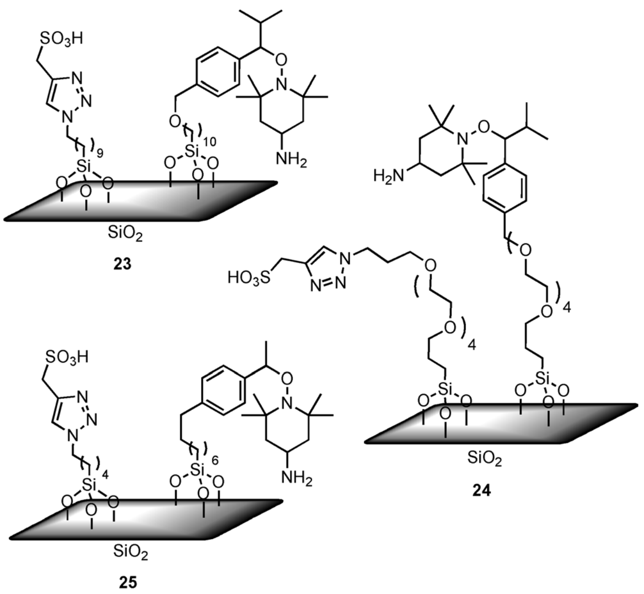
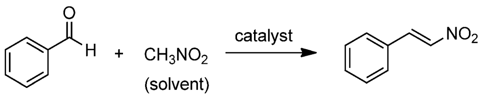


Figure 7. Additional MSNs **23**–**25** prepared by using orthogonal surface chemistry.

Application of the bifunctional mesoporous silica particles in catalysis: To test the catalytic activity of our new hybrid materials we chose the Henry reaction[16] between nitromethane and benzaldehyde to give *trans*-β-nitrostyrene (Scheme 6). This reaction is known to be accelerated by acid/base bifunctional catalysis.[17] The base deprotonates the nitromethane and the Brønsted acid is responsible for activation of the aldehyde component by hydrogen bonding. Reactions were performed by heating nitromethane and benzaldehyde in the presence of a MSN catalyst. Monitoring of conversion was conducted by GC analysis and the results are summarized in Table 1.



Scheme 6. Investigation using the Henry reaction.

Monofunctional MSN **11** bearing only sulfonic acids as functional groups was not active as a catalyst (Table 1, entry 1). No conversion was noted after 20 h. The same result was obtained with MSN **5** also containing exclusively sulfonic acids. In contrast, monofunctional particles **12** bearing primary amines only led to a moderate yield (42 %) of the targeted product (Table 1, entry 2). However, 1,3-dinitro-2-phenylpropane, resulting from nitromethane addition to *trans*-β-nitrostyrene, was formed as a major product in this reaction (47 %). In contrast, the monofunctionalized particles **9** bearing only amino functionalities but lacking the azidylalkyl groups led to the formation of the desired product (36 %) and 1,3-dinitro-2-phenylstyrene was not observed (Table 1, entry 3). The follow up chemistry (addition of a ni-

Table 1. Reaction of benzaldehyde with nitromethane using different MSN catalysts.

Entry	MSN	T [°C]	t [h]	Catalyst loading [mol %]	Yield [%][a]
1	**11**	90	20	3.8	0
2	**12**	90	20	2.4	42[b]
3	**9**	90	20	2.3	36
4	**9**(TMS)	90	20	2.3	27
5	**13**	90	20	3.8	99
6	**11**+**12**	90	24	3.8+2.4	47[c]
7	**13**	20	20	3.8	0
8	**13**	40	20	3.8	0
9	**13**	60	20	3.8	68
10	**13**	80	20	3.8	92
11	**18b**	90	9	2.1	99
12	**18a**	90	12	2.2	>99[d]
13	**18c**	90	12	2–4[e]	0
14	**23**	90	24	1.6	0
15	**25**	90	17	2.1	94
16	**24**	90	24	1.6	0
17	**22**	90	24	2.1	0
18	**19**	90	24	2.3	0
19	**20**	90	24	–[e]	0
20	**21**	90	24	1.7	0

[a] Yield of isolated product. [b] 47 % 1,3-dinitro-2-phenylpropane was isolated. [c] 42 % 1,3-dinitro-2-phenylpropane was isolated. [d] Yield determined by GC. [e] Not exactly determined. However, particles were prepared by analogy and hence a similar loading has to be expected (2–4 mol %).

tromethane to the product) might be caused by polarity effects exerted by the azidylalkyl substituent in **9**. Alternatively, the azide functionality might directly influence the reaction. To investigate the effect of the free silanol groups in such silica particles, we treated **9** with trimethylsilylchloride (TMSCl) to afford **9** (TMS), which showed comparable activity in the catalysis (Table 1, entry 4), documenting that the silanol groups have only minor contribution. To our delight, by using the bifunctional MSN **13** bearing both the sulfonic acid and amine functionalities, the formation of 1,3-dinitro-2-phenylpropane was fully suppressed and *trans*-β-nitrostyrene was isolated in quantitative yield (Table 1, entry 5). A combination of the monofunctional particles **11** (sulfonic acids only) and **12** (amines only) in a 1:1 stoichiometry, which might lead to a cooperatively active system since direct acid/base quench should not occur to a large extent between two particles,[18] afforded a 47 % yield of *trans*-β-nitrostyrene along with 42 % of the double addition product (Table 1, entry 6). This result was very similar to that obtained with monoaminofunctionalized MSN **12**, showing that particles **11** bearing the sulfonic acid moieties did likely not contribute to the reaction. With the most active particles **13** we repeated the Henry reaction at lower temperature. Below 40 °C we did not observe any conversion after 20 h (Table 1, entries 7 and 8). At 60 °C the reaction proceeded slowly (Table 1, entry 9), thus 90 °C was the optimal temperature for that reaction (Table 1, compare entry 10 with 5).

The alkoxyamine acid/base bifunctional catalyst **18b** was highly active and reaction went to completion in 9 h at slightly lower catalyst loading (2.1 mol %, Table 1, entry 11). Knowing that such an alkoxyamine based catalyst showed high activity, we then studied the reactivity of congeners that differ in constitution of their carbon backbones. The distance of the acid or base functionality to the inorganic silica host material was varied. With MSN **18a** bearing a shorter linker, a similar activity was achieved and the test reaction was completed after 12 h (Table 1, entry 12). However, further shortening of the linker length in such MSNs (see **18c**) led to a complete loss of the catalyst activity (Table 1, entry 13). Placing both the sulfonic acid and the amino functionalities farther away from the inorganic particle surface, as in **23**, also led to an inactive catalyst system (Table 1, entry 14). These experiments clearly showed that careful adjustment of the linker length is highly important for catalyst design. The presence of an oxygen atom in the linker revealed a small effect on the activity. Particle **25** containing an all-carbon backbone and the same linker chain-length as system **18a** led to a slightly lower yield (Table 1, compare entry 12 with 15). Particle **24** containing larger PEG-linkers were also inactive (Table 1, entry 16). Along this line, MSN **22** did not show any activity (Table 1, entry 17). Since all systems bearing larger linkers turned out to be inactive, we believe that in these materials the acid and base moieties can approach each other due to the sufficient long linker-length resulting in acid/base quench, which leads to inactive catalysts. After having studied the effect of linker composition and length on the catalyst activity, we next varied the nature of the base but maintained the optimal linker-length and surprisingly we found that secondary and tertiary amines were not active under the tested conditions (Table 1, entries 18–20).

Finally, to study the influence of the concentration of the functional groups at the particle surface, we prepared bifunctional MSNs of type **18b** with lower acid/base content. Particles of type **15b** were prepared by co-condensation of equal amounts of alkoxyamine **14b** and azide **1** with TEOS at different ratios. The resulting particles **15b** were then postmodified through orthogonal click reactions to provide MSNs of type **18b**, as discussed above. We found that particles **18b** with lower acid/base content were still active in the Henry reaction (Table 2, compare entry 1 with entries 2 and 3). However, further lowering of the acid/base TEOS ratio led to particles that showed slightly lower activity (Table 2, entry 4).

Table 2. Variation of acid/base content of the bead in particles of type **18b**.

Entry	Ratio[a] [TEOS/**12b**/**1**]	t [h]	Catalyst loading [mol %]	Yield [%]
1	8:1:1	9	2.1	99[b]
2	14:1:1	12	2.6	99[c]
3	20:1:1	12	0.9	99[c]
4	30:1:1	16	–[d]	89[c]

[a] Ratio used for the formation of the particles **15b**. [b] Conditions: catalyst (30 mg), benzaldehyde (100 μL), $MeNO_2$ (1 mL) (data from Table 1, entry 9). [c] Conditions: catalyst (50 mg), benzaldehyde (100 μL), $MeNO_2$ (1 mL). [d] Catalyst loading not determined.

Conclusion

We have introduced a conceptually new approach for preparation of bifunctional acid/base mesoporous silica nanoparticles. Triethoxyalkylsilanes bearing azides, alkenes, or alkoxyamines at their termini could be co-condensed with TEOS to provide mesoporous silica particles containing orthogonally addressable functionalities. Catalytically active acid and base moieties were readily introduced by late stage orthogonal click chemistry. The Cu-catalyzed azide/alkyne cycloaddition, the radical thiol–ene reaction, and the radical nitroxide exchange reaction turned out to be very efficient for late stage particle functionalization. Our approach allowed for the preparation of a series of catalysts of the same type in a short time. This process was very useful for identifying active catalysts.

Particles were successfully analyzed by IR spectroscopy, elemental analysis, SEM, and solid state ^{1}H and ^{13}C CP/MAS NMR spectroscopy. The results of the present study also highlight the utility of ^{1}H and ^{13}C solid state NMR techniques for the structural analysis of chemically modified surfaces of this kind. The orthogonally functionalized materials were catalytically active in the acid/base-catalyzed Henry reaction of nitromethane with benzaldehyde to give *trans*-β-nitrostyrene. Importantly, it was shown that the linker length between the inorganic host material and the two catalytically active organic functionalities has to be carefully adjusted. If the linker was too long, inactive hybrid materials resulted, likely due to acid/base quenching at the particle surface. Particles containing only the amino functionality showed lower activities and provided 1,3-dinitro-2-phenylpropane as a follow up product as a major component. Particles bearing exclusively sulfonic acid moieties at the surface were inactive. These results clearly revealed that the success of that particular Henry reaction was based on cooperative acid/base catalysis.

Since the applied orthogonal click reactions are very robust processes, other functionalities than organic acids and bases can be introduced at the surface of such prefunctionalized silica particles. For example, various ligands for transition metals should be readily covalently bound to the particle surface through this strategy. This will allow for the preparation of bifunctional catalysts in which one functionality might be an organocatalyst and the other functionality could be a transition-metal-based catalyst acting in concert. Moreover, cooperative catalysis at the surface with two different metals should be possible using this concept; studies along this line are underway.

Experimental Section

General method for preparation azide/alkene-functionalized SiO_2 particles: According to a procedure published by Huh et al.,[5a] cetyltrimethylammonium bromide (CTAB, 2.00 g, 5.49 mmol) and NaOH (7 mL, 2 M, 14 mmol) in H_2O (480 mL) were stirred for 30 min at 80 °C. Tetraethoxysilane **2** (TEOS) (9.94 mL, 44.8 mmol), (5-azidopentyl)triethoxysilane **1** (1.23 g, 4.48 mmol), and 7-octenyltrimethoxysilane **6** (1.12 mL, 1.04 g, 4.48 mmol) were added all at once and the reaction was stirred at 500 rpm for additional 2 h at 80 °C. A white precipitate formed that was filtered off and washed with copious amounts of water and MeOH. To remove CTAB, the particles were suspended in MeOH (≈100 mL per 1 g) and HCl (conc., 300 μL per 1 g) was added and the suspension was heated for another hour at 60 °C. Filtration and drying of the particles in high vacuum afforded the mesoporous silica nanoparticles **10** (MSNs) as white solid (≈3 g).

Typical alkyne/azide click reaction protocol: Azide/alkene-functionalized MSNs **10** (500 mg, ≈0.8 mmol g^{-1}, ≈0.4 mmol) were treated with $CuSO_4$ (40 mg, 0.25 mmol), sodium ascorbate (60 mg, 0.30 mmol), and sodium pro-2-yne sulfonic acid **4** (250 mg, 1.76 mmol) overnight at 90 °C in EtOH/H_2O (2:1, 10 mL). Filtration of the particles and washing with H_2O (50 mL), HCl (2 M, 25 mL), MeOH (50 mL), CH_2Cl_2 (50 mL), and Et_2O (20 mL) afforded the acid-functionalized MSNs **11** (≈500 mg) as white solid.

Typical thiol–ene click reaction protocol: The acid-functionalized MSNs **11** (200 mg, ≈0.16 mmol) were treated with AIBN (30 mg, 0.18 mmol), cysteamine hydrochloride **8** (100 mg, 0.88 mmol), and pyridine (100 μL, 1.24 mmol) in DCE (3 mL) at 90 °C overnight. The MSNs were filtered and washed with H_2O, MeOH, CH_2Cl_2, and Et_2O (30 mL each) and were dried at 500 mbar and 40 °C to afford the bifunctional MSNs **13**.

Typical method for the preparation of azide/alkoxyamine-functionalized SiO_2 particles: According to a procedure described by Huh et al.,[5a] cetyltrimethylammonium bromide (CTAB, 1.50 g, 4.12 mmol) and NaOH (5.25 mL, 2 M, 10.5 mmol) in H_2O (360 mL) were stirred for 30 min at 80 °C. Subsequently tetraethyl orthosilicate **2** (TEOS) (6.64 mL, 30.0 mmol, 8.0 equiv), the corresponding azide **1** (3.75 mmol, 1.0 equiv), and the corresponding alkoxyamine **14 a–c** (3.75 mmol, 1.0 equiv) were added all at once and the reaction was stirred for additional 2 h at 80 °C. The white precipitate formed was filtered off and washed with copious amounts of water and MeOH. To remove CTAB, the particles were suspended in MeOH (≈100 mL per 1 g) and HCl (conc., 300 μL per 1 g) was added and the suspension was heated for another hour at 60 °C. Filtration and drying of the particles in high vacuum afforded the mesoporous silica nanoparticles **15 a–c** (MSNs) as white solid (≈2.5 g).

Typical alkyne/azide click reaction protocol: Azide/alkene-functionalized MSNs **15 a–c** (500 mg, ≈0.8 mmol g^{-1}, ≈0.4 mmol) were reacted with $CuSO_4$ (40 mg, 0.25 mmol), sodium ascorbate (60 mg, 0.30 mmol), and sodium pro-2-yne sulfonic acid **4** (250 mg, 1.76 mmol) overnight at 90 °C in EtOH/H_2O (2:1, 10 mL). Filtration and washing with H_2O (50 mL), HCl (2 M, 25 mL), MeOH (50 mL), CH_2Cl_2 (50 mL), as well as Et_2O (20 mL) afforded the acid-functionalized MSNs **17 a–c** (≈500 mg) as white solid.

Typical nitroxide exchange reaction protocol: The acid-functionalized particles (200 mg, ≈0.8 mmol g^{-1}, ≈0.16 mmol) were suspended in DCE (5 mL) and 4-amino-TEMPO **17** (100 mg, 0.584 mmol) was added. The reaction mixture was heated for 24 h at 125 °C. The nanoparticles were filtered and washed with H_2O, MeOH, CH_2Cl_2, and Et_2O (30 mL each) and were dried at 500 mbar and 40 °C to afford the bifunctional MSNs **18 a–c**.

General procedure for the Henry reaction: The bifunctional MSNs (30 or 50 mg) were suspended in $MeNO_2$ (1 mL) and benzaldehyde (100 μL, 0.984 mmol) was added dropwise. The reaction was stirred at 90 °C. The conversion was controlled by GC and the reaction was quenched by filtration if no further conversion could be detected.

NMR spectroscopy: The solid-state NMR measurements were carried out on Bruker spectrometers equipped with 2.5 and 4 mm single and double resonance NMR probes. The resonance frequencies were 500 MHz for ^{1}H at 11.7 T, 75.433 MHz for ^{13}C at 7.04 T and 99.325 MHz for ^{29}Si at 11.7 T. Chemical shifts are reported relative to TMS, using adamantane ($\delta = 1.78$ ppm), adamantane ($\delta = 38.56$ ppm for the methylene resonance) and tetrakis(trimethylsilyl)silane (TTMSS) ($\delta = -9.8$ ppm, main peak), respectively, as secondary references. ^{1}H MAS-NMR spectra were recorded using rotor synchronized Hahn spin echo experiments with evolution times of 3–6 rotor periods at a spinning frequency of 30 kHz. The 90° pulse length was 3.9 μs. FIDs (256–512) were accumulated using a recycle delay of 5 s. The ^{13}C{^{1}H} CP/MAS and ^{29}Si{^{1}H} CP/

MAS spectra were measured using typical ^{1}H 90° pulse lengths of 3.8–4.0 μs, a spinning frequency of 5–6 kHz, recycle delays of 1–5 s, and contact times of 100–5000 μs, respectively. Depending on the sample and the experiment 5760–160400 scans were accumulated. ^{1}H decoupling during the acquisition was achieved by applying the TPPM-15 decoupling scheme.

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