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COMMUNICATION

A novel mesoporous silica-grafted organocatalyst for the Michael addition reaction, synthesized *via* the click method†

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An efficient and recyclable mesoporous silica-grafted bifunctional acid–base organocatalyst for the Michael addition of ketones to β-nitrostyrenes has been synthesized by click chemistry, affording the products with excellent diastereoselectivity. A remarkable enhancement in the reaction rates could be observed with respect to the corresponding monofunctional organocatalyst.

Introduction

The utilization of organic compounds as catalysts, an area termed 'organocatalysis',[1] has become an area of tremendous importance, and a significant amount of research has been carried out in this direction in the last few years.[2] Unlike conventional metal-based catalysts, organocatalysts offer a number of advantages, such as little or no activation, ease of functionalization, absence of the possibility of metal leaching, reduced toxicity and simple reaction conditions. Therefore, designing novel metal-free organocatalysts for organic reactions is a key aspect of achieving the aim of sustainable chemical synthesis.

Immobilization of homogeneous catalysts is another important goal, which helps in minimizing the environmental hazards caused by homogeneous catalysts.[3] Among various methods such as ion exchange, physical adsorption, dipolar attraction and covalent attachment of the species containing the active sites to solid supports, the latter has been established as the most efficient, since it prevents leaching, as well as enabling better catalyst recycling.[4] However, this approach often requires multi-step reaction procedures, excess reagents and extreme conditions, which causes decomposition of the catalyst or ligand, either due to the properties of the inorganic support or the harsh reaction conditions used for immobilization. Ordered mesoporous materials[5–8] synthesized in the presence of supramolecular assemblies of surfactant molecules have been utilized extensively as supports for immobilizing catalytically active centers, due to their exceptionally high surface area and tunable pore width, which favors easy diffusion of the substrate

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† **Experimental details:** *General*: All commercially available substrates and solvents were used as received. The melting points were determined in open-capillaries on a Buchi apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer FT-IR X 1760 instrument. Elemental analyses were carried out using ASTM D-3828 (Kjeldhal method). X-ray diffraction patterns were obtained by a Bruker AXS D8 Advanced SWAX diffractometer using Cu Kα ($\lambda = 0.15406$ nm) radiation. Nitrogen adsorption–desorption isotherms were obtained using a Bel Japan Inc. Belsorp-HP at 77 K. A JEOL JEM 6700F field emission scanning electron microscope was used for the determination of morphology of the particles. FT IR spectra of these samples were recorded using a Nicolet MAGNA-FT IR 750 Spectrometer Series II. GC analyses were performed on Varian CP 3800 Gas Chromatograph for the identification of the reaction products. *Preparation of azide-functionalized SBA-15 (SBA-N_3)*:[10a] 3-Chloroproyl-functionalized mesoporous silica (1 g) was added to the saturated solution of sodium azide (50 mL) in dry DMF. The resulting mixture was stirred at 90 °C for 3 h. The material was filtered off and soxhlet-extracted in ethanol for 24 h. The obtained material was dried at 60 °C for 12 h. Elemental analysis (%):N, 2.18; C, 1.92; H, 1.21 Loading: 0.52 mmol N_3 g^{-1} as determined by the value of nitrogen content and TGA analysis. *Immobilization of the three ponytailed compound **2** to the silica support by click reaction*: Stirring of the mixture containing SBA-N_3 **3** (2 g. 0.52 mmol g^{-1}), three ponytailed compound **2** (0.15 g, 0.5 mmol), CuI (5 mol%), triethylamine (0.25 ml, excess 5 mmol) in dry DMF (15 ml) under nitrogen for 24 h at room temperature to yield silica immobilized three ponytailed material **4**. The prepared material **4** was thoroughly washed with DMF, dichloromethane and dried under vacuum. To check the Cu-coordination with triazole moieties, we performed Cu-analysis by ICP-AES – no copper was observed, indicating the absence of copper and thus precluding its role in the catalytic reaction. Elemental analysis of compound **4** gave N (1.85%); C (5.2%); H (1.12%). Heating of **3** with 4-aminopyridine in a 1 : 1 molar ratio in DMF for 5–6 h gave a quantitative yield of silica-immobilized pyridinium salts **1**. Elemental analysis (%): N, 1.69, C, 3.75, Cu, 0. Loading: 0.11 mmol g^{-1} as determined by the value of nitrogen content in elemental analysis. *General experimental procedure for Michael addition*: To a mixture of nitroalkenes (0.5 mmol) and catalyst **1** (0.05 mmol, 10 mol%) was added ketone (2.5 mmol), and the resulting suspension was vigorously stirred at 40–50 °C. The progress of the reaction was monitored by TLC (silica gel). After completion, the catalyst was separated by filtration, washed with CH_2Cl_2, dried and used as such for subsequent runs. The combined organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by flash column chromatography. The isolated yields of the products are mentioned in Table 1. The diastereoselectivity (*syn*/*anti* ratio) of the products was determined by GC analysis.

and product molecules during the reaction. Thus, organic catalytically active centers can be grafted onto functionalized mesoporous surfaces through covalent bonding, potentially opening up applications of these organic–inorganic hybrid materials in catalytic reactions.

[3+2] Azide–alkyne cycloaddition,[9] termed the 'click' reaction due to its simplicity, fidelity, high conversion, absence of side products and mild reaction conditions, has proven to be an efficient approach for the assembly of functionalized organic molecules. Recent work has described many applications of this approach in the field of bioactive molecules/supported reagents and catalysts,[10] but there are relatively few reports from the field of organocatalysis.[11]

The Michael addition of ketone nucleophiles to β-nitroolefins represents an important transformation, since the resulting γ-nitro ketones are valuable synthons in the synthesis of highly useful building blocks in organic synthesis.[12] Organocatalytic approaches, in particular immobilization of organocatalysts, are gaining ever-increasing interest due to the continuously growing demand for green chemical synthesis. In this context, Tuchman-Shukrona[13] reported a bifunctional organocatalyst, possessing both acidic (H-bond donating) and basic (nucleophilic) moieties for Michael addition. Alza *et al.*[14] reported a highly selective polystyrene-supported organocatalyst for Michael additions. However, this method involves a multistep catalyst synthesis, longer reaction times and the use of additives. Zhao *et al.*[15] describes the use of silica-supported pyrrolidine-triazoles prepared by click chemistry for the Michael addition of ketones to nitroolefins. However, the time-consuming multistep synthetic procedure and the long reaction times (72 h) certainly provide scope for developing an efficient organocatalyst for this reaction.

In this paper we wish to report a novel silica-supported bifunctional acid–base organocatalyst **1** (Fig. 1), synthesised using click chemistry, which efficiently catalyzes the Michael addition of ketones to aryl-substituted nitroolefins. Excellent yields and high diastereoselectivities of nitroalkanes are obtained, under mild solventless reaction conditions.

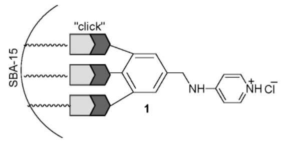
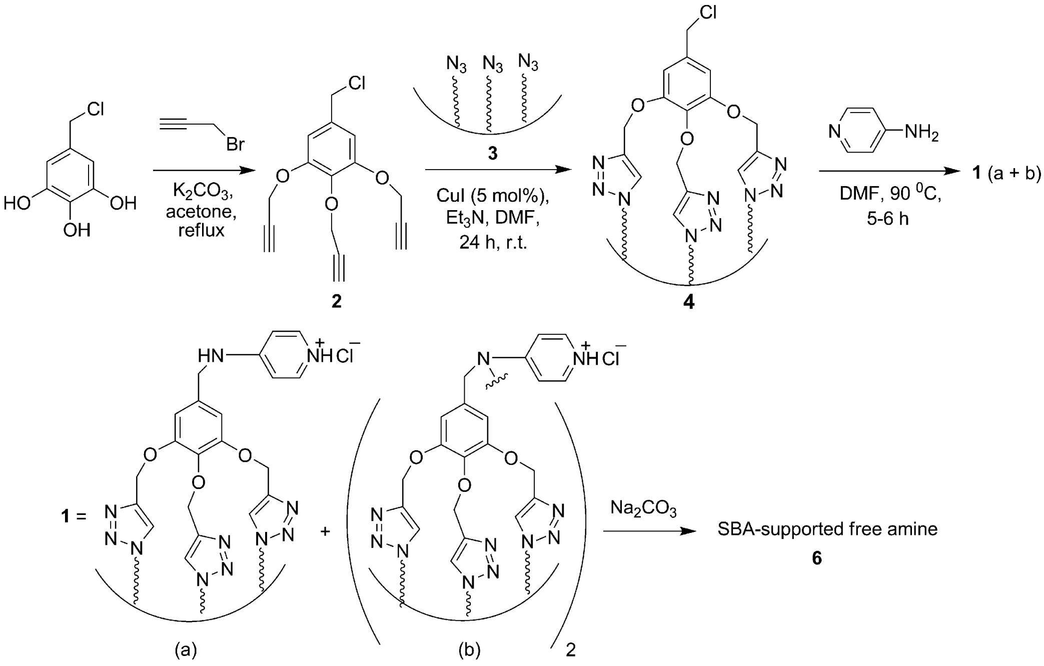


Fig. 1 Mesoporous silica-supported organocatalysts **1**.

Results and discussion

Catalyst preparation and characterization

The synthetic pathway for the preparation of silica-supported organocatalyst **1** is shown in Scheme 1. 3-Azidopropyl-functionalized mesoporous silica **3** (4 mol%), prepared following the literature procedure,[10a] was used as the support. The other coupling partner **2** was readily prepared by the reaction of 3,4,5-trihydroxybenzyl chloridewith propargyl bromide under basic conditions. Subsequently, the Cu(I)-catalyzed [3+2] cycloaddition of azido-functionalized mesoporous silica support **3** with **2** ('click' conditions) resulted in the formation of silica-supported organocatalyst **4**. The loading of catalyst **4** was found to be 0.15 mmol g^{-1}, as determined by the nitrogen content (1.85%) in the elemental analysis. Subsequently, the reaction of **4** with 4-aminopyridine in a 1 : 1 molar ratio readily gave mesoporous silica-supported organocatalyst **1**. The possibility of the synthesis of dimeric species during this step (Scheme 1) could not be ruled out completely. Therefore, the heterogeneous material synthesized for use in catalytic reactions may be a mixture of monomeric and dimeric formst.



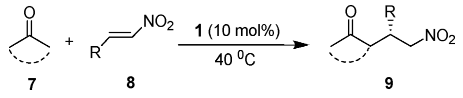
Scheme 1 Synthesis of organocatalyst **1**.

The powder X-ray diffraction pattern for mesoporous silica-supported organocatalyst **1** is shown in Fig. S1†. This reveals that the organocatalyst has a highly ordered 2D-hexagonal mesophase, with three strong reflections corresponding to the (100), (110) and (200) planes.[7] The unit cell parameter (a_0) for this functionalized organocatalyst was *ca.* 11.1 nm. All the samples retained their mesostructures after the immobilization of the organocatalyst at the mesopore surface by the three functionalization reactions shown in Scheme 1. The N_2 adsorption–desorption isotherms of **1** are shown in Fig. S2†. These isotherms, classified as type IV, are characteristic of materials with large mesopores.[8] A sharp increase in N_2 uptake for adsorption is observed at $P/P_0 = 0.6–0.76$, together with a large hysteresis, characteristic of a SBA-15 type material.[8j] The pore size distribution of these samples was estimated by employing the NLDFT method (inset of Fig. S2), suggesting a peak pore width of *ca.* 4.35 nm. A considerably smaller pore width of **1** relative to the SBA-15 host suggested functionalization on the internal pore surface. The BET surface area of immobilized catalyst was 336 $m^2\ g^{-1}$, and the pore volume was 0.5 $cm^3\ g^{-1}$.

The FE SEM image of **1** is shown in Fig. S3†. This figure indicates that the material is mainly composed of bar-like particles 1–1.5 nm long. Some fine particles of diameter 0.1 nm can also be seen. The small particle size of our immobilized catalyst could be helpful for easy diffusion of reagents during the catalytic reactions. The covalent bonding in **1** was evident from the FTIR spectroscopic result, wherein a remarkable reduction in the intensity of the frequency of the azido band (*ca.* 2100 cm^{-1}) was observed (Fig. S4†). The presence of Si–OH stretching at *ca.* 956 cm^{-1} in this FTIR spectrum due to the surface silanol groups of the mesoporous support further supports the immobilization of organocatalyst **1**. The loading of the organocatalysts was found to be 0.11 mmol g^{-1}, as calculated by the nitrogen content (1.69%) obtained by elemental analysis (considering the predominant formation of **1a**).[16]

Catalytic activity for Michael addition

The catalytic efficiency of the organocatalyst **1** was examined for the Michael addition of ketones **7** to β-nitrostyrenes **8** under solvent-free conditions (Scheme 2).



Scheme 2 Michael addition reaction.

Initially, organocatalyst **1** (10 mol%, 0.05 mmol) was added to a mixture of cyclohexanone (2.5 mmol) and β-nitrostyrene (0.5 mmol), and the resulting mixture stirred vigorously at 40 °C under solventless conditions. The reaction was found to proceed efficiently, and afforded an excellent yield (98%) of the Michael adduct, with high diastereoselectivity towards the *syn*-adduct (*syn*/*anti* ratio 97 : 3). It is interesting to note that adding a solvent (acetonitrile, toluene, dichloromethane, water) had an adverse effect, giving a poor yield of product (Table 1, entries 1–4). When mesoporous silica support **3** was used, no reaction between cyclohexanone and β-nitrostyrene occurred, whereas the catalytic activity of the silica-supported monofunctional organocatalyst **4** was found to be poorer than catalyst **1** under similar reaction conditions (Table 1, entries 6 and 7). Similarly, the use of the homogeneous catalyst 4-aminopyridine afforded a very poor yield of the desired product (Table 1, entry 8). An immobilized organocatalyst **5** prepared by the reaction of 4-aminopyridine with 3-chloropropyl SBA-15 was also found to be a poor catalyst for this reaction (Table 1, entry 9).

Table 1 Michael addition reactions under different reaction conditions[a]

Entry	Solvent	Catalyst	*T* (°C)	Yield (%)[b]	dr (*syn*/*anti*)[c]
1	CH_3CN	**1**	40	86	82 : 12
2	$CHCl_3$	**1**	40	Trace	—
3	Toluene	**1**	40	20	96 : 4
4	H_2O	**1**	40	65	95 : 5
5	—	**1**	40	98	97 : 3
6	—	**3**	40	—	—
7	—	**4**	40	82	95 : 5
8	—	4-Aminopyridine	40	30	96 : 4
9	—	**5**	40	75	94 : 6
10	—	**6**	40	92	95 : 5
11	—	**1**	25	68	97 : 3

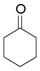
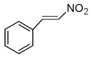
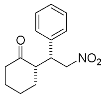
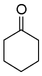
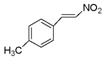
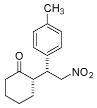
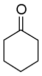
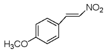
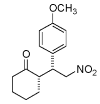
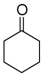
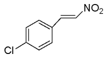
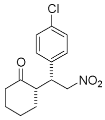
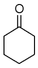
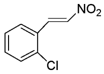
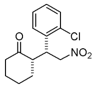
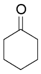
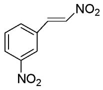
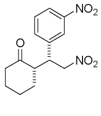
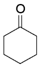
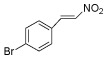
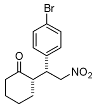
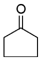
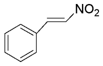
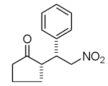
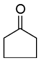
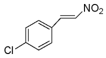
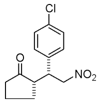
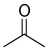
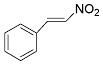
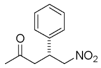
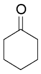
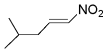
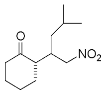
[a] Reaction conditions: cyclohexanone (2.5 mmol), β-nitrostyrene (0.5 mmol), catalyst (10 mol%), 24 h. [b] Isolated yields. [c] Calculated by ^1H NMR.

We also synthesized the SBA-supported free amine **6** by treating **1** with a solution of Na_2CO_3, and studied its catalytic activity. The prepared material showed slightly lower catalytic activity than **1** under similar reaction conditions (Table 1, entry 10). These findings established the superiority of the catalyst **1**, which benefits from the triazole rings being present on its surface due to the click reaction. The reaction was mainly dependent on the base used, the yield of the product increasing with the amount of the base, as presented in Table 1 (entries 5, 7, 8 and 10). Moreover, no reaction occurred between cyclohexanone and β-nitrostyrene in the absence of any base. As shown in Table 1 (entries 5 and 10) the effect of the protonated species (catalyst **1** *vs.* **6**) was found to be minor, and provided comparable yields of product (98 *vs.* 92%, respectively). Also, the reaction was found to be slow at room temperature, 40 °C being optimum for this reaction (Table 1, entry 11).

To establish the generality of the protocol, we carried out the Michael addition reaction of a variety of ketones **7** and β-nitroalkenes **8** in the presence of catalyst **1** (10 mol%) at room temperature under similar conditions. The results of these experiments are presented in Table 2. Aromatic β-nitroalkenes, substituted with either electron-donating or electron-withdrawing groups, reacted efficiently with cyclic ketones, and provided good product yields with high diastereoselectivities (*syn*/*anti* > 85 : 1). In contrast, the reaction of aliphatic nitroalkenes (Table 2, entry 11) was found to be very slow, yielding only trace amounts of the product along with unidentified by-products. Among the cyclic ketones used, cyclohexanone was found to be more reactive than cyclopentanone. However, aliphatic ketones such as acetone (Table 1, entry 10) gave comparable results to cyclohexanone under the reaction conditions used.

In order to establish the recyclability of the catalyst **1**, the reaction of cyclohexanone and β-nitrostyrene were studied

Table 2 Michael addition using catalyst **1**[a]

Entry	Ketone **7**	Nitroalkene **8**	Product **9**	Time (h)	Yield (%)[b]	dr (*syn*/*anti*)[c]
1				24	98	97 : 3
2				20	99	98 : 2
3				20	98	99 : 1
4				24	88	96 : 4
5				24	84	98 : 2
6				30	92	92 : 8
7				30	97	99 : 1
8				20	72	87 : 13
9				24	65	88 : 12
10				18	94	—
11				60	Trace	—

[a] Reaction conditions: nitroalkene (0.5 mmol), ketone (2.5 mmol), catalyst (10 mol%, 0.05 mmol) at 40 °C. [b] Isolated yield. [c] Determined by GC. [d] Using acetonitrile (5 ml) as solvent. [e] Using **4** as the catalyst.

under similar reaction conditions. After completion of the reaction, the catalyst was separated by filtration, washed with dichloromethane, dried at room temperature and reused in five additional experiments. In all cases, silica-supported organocatalyst **1** exhibited consistent catalytic activity and provided similar product yields with high diastereoselectivity, establishing the recycling and reusability of the catalyst without further activation or adding further catalyst (Table 3). Furthermore, to check the leaching of the organic group from the support, the supported catalyst **1** was added to dichloromethane and stirred at room temperature for 24 h. The catalyst was then separated by filtration, and the filtrate treated with cyclohexanone and β-nitrostyrene for 2 days at room temperature. No reaction occurred, establishing that no leaching had taken place during the course of the reaction, and therefore the reaction was truly heterogeneous in nature.

Table 3 Recycling studies of silica-supported catalyst **1** in the Michael reaction of cyclohexanone with β-nitrostyrene

Run	Yield (%)	dr (*syn*/*anti*)
1	98	97 : 3
2	98	97 : 3
3	98	96 : 4
4	96	97 : 3
5	97	95 : 5
6	97	97 : 3

Conclusions

In summary, we have developed a novel mesoporous silica-grafted bifunctional acid–base organocatalyst **1** using an azide–alkyne click reaction. This organocatalyst showed excellent catalytic activity for the Michael reaction of ketones to nitroolefins, affording high yields with excellent diastereoselectivities. Organocatalyst **1** was found not only to be superior to the corresponding monofunctional organocatalyst, but also enhanced the reaction rates significantly as a result of the triazole moieties being present. The ease of catalyst synthesis, efficient recycling, and mild reaction conditions are other key advantages of this methodology.

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