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## Improving the Selectivity toward Three-Component Biginelli versus Hantzsch Reactions by Controlling the Catalyst Hydrophobic/Hydrophilic Surface Balance

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The catalytic activities and selectivities of two kinds of mesoporous solid acids SBA-15-PrSO<sub>3</sub>H **1**, SBA-15-Ph-PrSO<sub>3</sub>H **2**, and a periodic mesoporous organosilica (PMO) based solid acid Et-PMO-Me-PrSO<sub>3</sub>H **3** that comprise different physicochemical surface properties were compared in an environmentally benign one-pot, three-component Biginelli reaction of aldehydes,  $\beta$ -ketoesters and urea or thiourea under solvent-free conditions. Among these mesoporous solid acid catalysts, **3**, which has a hydrophobic/hydrophobic balance in the nanospaces (mesochannels) in which the active sites are located, is found to be a significantly more selective catalytic system in the Biginelli reaction; it produces the corresponding 3,4-dihydropyrimidin-2-one\thione (DHPM) **5** derivatives in good to excellent yields and excellent selectivities. Notably, in the case of conducting the three-component coupling reaction of benzaldehyde, metylacetoacetate and urea in the presence of **1** result in the generation of a mixture of Hantzsch dihydropyridine **4** ( $\approx$  37%) and Biginelli dihydropyrimidinone **5** ( $\approx$  49%), whereas the same reaction with **2** (catalyst loading of 1 mol% as well) furnishes the corresponding aldolic product methyl-2-benzylidene-3-oxobutanoate **6** as the major product ( $\approx$  80%) with concomitant formation of small amounts of **5** (< 10%) under essentially the same reaction conditions that are employed with catalyst **3**. Water adsorption–desorption analysis of the catalysts is employed to possibly relate the observed selectivity to the difference in physicochemical properties of the materials.

#### Introduction

Ordered mesoporous silica (OMS) materials have gained increasing interest because of their high surface area, narrow pore size distribution, adjustable mesopore diameter, and highly tunable physicochemical properties by varying the nature and extent of the surface functionalization.<sup>[1]</sup> In catalytic applications, these characteristics render OMS materials as a versatile platform in preparing novel sophisticated materials, which display enhanced catalytic performance; these include the activity and/or the selectivity. Therefore, a critical stage in designing a high-performance catalytic system based on OMS materials is directly concerned with a better understanding of the surface physicochemical properties and their relationship with the reaction partners, as well as with the reaction profile.

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For example, it is well documented that if all reacting partners (starting materials) are lipophilic, the product formation is more favorable in the case of employing the catalyst that has more surface hydrophobicity in close proximity to the active sites.<sup>[2,3]</sup>

A more interesting case is the reaction profiles that involve both hydrophobic and hydrophilic reaction partners; these should first diffuse onto the catalyst surface (the system pores in the case of an OMS-based catalyst) and then react at the available active sites. In these circumstances, it is often necessary to have an optimum hydrophobic/hydrophilic characteristic inside the system pores to equally accommodate both the hydrophilic and hydrophobic substrates, thus improving the reaction rate.<sup>[2,3]</sup> In contrast, because of the inorganic nature and thus inherent hydrophilic character of the mesoporous silica network, if there are one or more polar constituents, the activity of the silica-based catalysts would tend to decrease through extended physical adsorption of these polar molecules onto the catalyst surface. Therefore, the control of the hydrophobic/hydrophilic balance in the solid catalysts might indeed influence their catalytic performance and durability as well. Based on our experience in design and application of novel nanostructured catalysts in recent years,<sup>[3,4]</sup> we discovered that the concomitant control of hydrophobic and acidic properties in the interior of mesochannels of sulfonic acidfunctionalized OMS can remarkably facilitate diffusion of the reactants and products for a number of selected acid-catalyzed reactions, thus improving the overall catalyst efficiency and/or sometimes the selectivity.<sup>[3]</sup> These results stimulated our interest in finding whether hydrophobic channels would be able to influence the catalytic performance of OMS-based sulfonic acid catalysts in the Biginelli reaction. We have chosen the Biginelli reaction because it consists of triple condensation of both hydrophilic (urea or one of its derivative) and hydrophobic (an aldehyde and 1,3-dicarbonyl) starting materi-

als and produces two equivalents of water (Scheme 1).

Since the initial Biginelli reports in 1891,<sup>[5]</sup> a plethora of protocols and/or catalytic systems have been developed for this important synthetic transformation. Along this line, many Brønsted and Lewis acids have been used to promote the Biginelli reaction.<sup>[6,7]</sup> In spite of these advances; most of these protocols require a high loading of expensive and nonrecoverable



Scheme 1. Representation of the Biginelli reaction.

catalysts and require prolonged reaction times in many instances. In addition, the selectivity of the three-component Biginelli reaction toward dihydropyrimidinones (DHPMs) is not always satisfactory owing to the significant formation of unwanted dihydropyridine (DHP) derivatives through the competitive Hantzsch reaction, which often imposes further separation steps and strongly limits the scope of this process, a feature not often highlighted in the literature by the researchers. The loss of the reaction selectivity may be unambiguously caused by the insitu decomposition of urea (or urea derivatives) by the byproduct water to give ammonia, which can subsequently react with the other reaction partners (aldehyde and 1,3-dicarbonyl), thus furnishing the corresponding Hantzsch adduct. Therefore, it is expected that in the case of using a catalytic system that has a suitable hydrophobic/hydrophilic balance, the byproduct water in this process can in principle be driven out from the catalyst surface (active sites) as soon as it is produced, thereby preventing its subsequent reaction with urea to ammonia at the active sites, and suppressing the Hantzsch



Figure 1. Solid sulfonic acid catalysts based on OMS and PMO.

properties of mesoporous-based sulfonic acid could also influence the selectivity of the Biginelli reaction. Thus, we first prepared three different solid sulfonic acid-based catalysts on either OMS (SBA-15) or periodic mesoporous organosilica (PMO), which followed the reported protocols with slight modifications (Figure 1).<sup>[9]</sup>

#### **Results and Discussion**

The structural parameters of all materials were determined by employing N<sub>2</sub> adsorption–desorption analysis at T=77 K. All samples show N<sub>2</sub> adsorption isotherms of type IV, which indicates the formation of mesopores. The nitrogen isotherm patterns of mesoporous solid acid 1 and 2 exhibit a sharp H1 hysteresis loop, which is the characteristic pattern for mesoporous materials with a narrow pore size determination (PSD) (Figure S2 and S7, Supporting Information).<sup>[3a,b]</sup> Conversely, ethanebridged PMO-based sulfonic acid 3 displays an indistinct H2 hysteresis loop, which points to the fact that the structure consists of mesopores with a relatively broad PSD (Figure S16, Supporting Information).<sup>[3e]</sup> The amount adsorbed at the relative pressure 0.99 was used to estimate the total pore volume.<sup>[10]</sup> The specific surface area and average PSD were calculated by using the Brunauer-Emmett-Teller (BET) and Barrett-Joyner-Halenda (BJH) methods, respectively (Table 1). The thermogravimetric analysis and differential thermal analysis (TGA/DTA) were concomitantly employed with elemental (sulfur) analysis in all cases to estimate the loading of functionalized groups in the materials. Moreover, the precise sulfonic acid function in the catalyst 1-3 (acid capacity) was measured by using pH analysis of an ion-exchange sample with saturated aqueous NaCl solution (Table 1).<sup>[11]</sup>

To get additional insight into the structural feature of the materials, they were studied by means of transmission electron microscopy (TEM).

As can be clearly seen all materials show a well-defined 2Dhexagonal mesoporous structure, a feature which is in good

reaction. In recent years, several groups,<sup>[2,8]</sup> including ours,<sup>[3]</sup> have discovered that the catalytic performance of OMS-based catalysts and thus their selectivity in some organic reactions markedly depends on the nature and the extent of surface functionalization of these materials. Along the line of these achievements, we were interested to determine whether the physicochemical

Table 1. Characterization of functionalized PMOs.						
Entry	Solid acid	$S_{BET}^{[a]}$ [m <sup>2</sup> g <sup>-1</sup> ]	$V_{p}^{[b]}$ [cm <sup>3</sup> g <sup>-1</sup> ]	Pore size <sup>[c]</sup> [nm]	Sulfur content <sup>[d]</sup> [mmol $g^{-1}$ ]	Acid capacity <sup>[e]</sup> [ mmolH <sup>+</sup> g <sup>-1</sup> ]
1	Et-PMO-Me-PrSH	213	0.24	3.5	-	-
2	3	318	0.27	3.4	0.8	0.50
3	3 (recycled)	83	0.10	5.2	-	0.40
4	2	356	0.58	5.4	-	1.61
5	1	430	0.67	6.2	-	1.77
[a] BET surface area. [b] Total pore volume. [c] BJH pore size. [d] Sulfur content measured by elemental analysis. [e] Determined by titration after ion-exchange (mmolH $^+$ g $^{-1}$ ) (see the Supporting Information).						

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agreement with the ordered mesoporous structure estimated by  $N_2$ -sorption analyses of the materials (Figure 2).

After the initial characterization of the materials 1–3, their catalytic performance (both selectivity and activity) was then compared in the three-component reaction of methylacetoace-tate (1 mmol), benzaldehyde (1 mmol), urea (1.2 mmol) under solvent-free conditions at T=90 °C in the presence of 1 mol% of the catalyst within 1.5 h (Scheme 2). Although, the use of



**Figure 2.** TEM images of the catalyst: a) **1** (scale bar 100 nm), b) **2** (scale bar 20 nm), c) **3** (scale bar 100 nm). For further images see the Supporting Information.

solid sulfonic acids based on either OMS or PMO are welldocumented in several important functional group transformations,<sup>[2,12,13]</sup> to our knowledge there is no precedent example of the effect of surface physicochemical properties of these materials in the selectivity control of multicomponent reactions such as the Biginelli reaction. Our preliminary investigations revealed that the physicochemical properties of the employed

sulfonic acid catalyst indeed have a significant and somewhat interesting impact on both the efficiency and the selectivity of the titled reaction under the described reaction conditions. Although the performance of the three-component coupling reaction of benzaldehyde, metylacetoacetate and urea in the presence of SBA-15-PrSO<sub>3</sub>H 1 (1 mol%) results in the generation of a mixture of Hantzsch dihydropyridine 4 ( $\approx$  37%) and Biginelli dihydropyrimidinone 5 ( $\approx$ 49%), the same reaction with 1 (1 mol% as well) furnishes the corresponding aldolic product methyl-2-benzylidene-3-oxobutanoate 6 as the major product ( $\approx$  80%) with concomitant formation of a trace amount of 5 (<10%). Most interestingly, if the PMO-based sulfonic acid 3 (Et-PMO-Me-PrSO<sub>3</sub>H) is used as the catalyst rather than 1 and 2 under otherwise the same reaction conditions, a substantial changeover of the product selectivity toward the formation of DHPM 5 in excellent yields of 91% occurs (Scheme 2). To the best of our knowledge there are no reports of such a changeover in the product selectivity in a similar three-component reaction by changing the surface physicochemical properties of the employed solid catalysts.

If this observed variation in the product selectivity can be amenable to matching the physicochemical properties in the nanospaces of the mesoporous support, in which the acidic sites are located, with the hydrophobic/hydrophilic nature of the reaction constituents (reactant and products) it would be a remarkable advance in the field. For this reason, we were interested to get more insight into this issue. To do this, we proceeded to measure the water adsorption–desorption isotherm of the catalysts **1–3** in the gas phase at T=25 °C (Figure 3).

**1** exhibits a large water adsorption at  $P/P_0$  that ranges from 0.6–0.8, which indicates that the nanospaces of this material have a significant hydrophilic nature. Conversely, the organo-functionalized SBA-15-Ph-PrSO<sub>3</sub>H **2** shows almost no water uptake under the same conditions, which demonstrates that the nanospaces of **1** become extremely hydrophobic upon



Scheme 2. Three-component reaction of methylacetoacetate (1 mmol), benzaldehyde (1 mmol), and urea (1.2 mmol) in the presence of solid acid catalysts 1–3 at 90  $^{\circ}$ C within 1.5 h under solvent-free conditions.

Water adsorption / desorption isotherm



Figure 3. Water adsorption–desorption isotherms of solid acid catalysts 1 ( $\blacksquare$ ), 2 ( $\bullet$ ), and 3 ( $\blacktriangle$ ).

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functionalization with the phenyl group. In contrast, the amount of water uptake in the case of **3** is much lower than for **1**, whereas this value is much higher than the value measured for **2**. These observation can be attributed to the fact that whereas the nanospaces in material **3** have considerable hydrophobic character, they are still hydrophilic enough compared to those of material **2**, a feature which seems to be crucial for allowing both the hydrophobic and hydrophilic starting materials to readily diffuse into the nanospaces of the catalyst, where the acidic sites are located.

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At this stage, a critical question is this: how do the physicochemical properties of the nanospaces in mesoporous solid acids 1-3 influence the observed product selectivities demonstrated in Scheme 2? On the basis of the fact that the threecomponent Biginelli reaction consists of both hydrophilic (urea or thiourea) and hydrophobic (aldehyde and  $\beta$ -ketoester) starting materials, facile diffusion of these physically divergent reactants into the system pore of the catalyst is an important catalytic implication that should be resolved. It thus appears that faster adsorption of, for example, more hydrophobic starting materials onto the catalyst surface would certainly prohibit the penetration of reactants that have a higher hydrophilic nature and vice versa, thus, strongly suppressing the Biginelli reaction. It is thereby reasonable that an optimum hydrophobic/hydrophilic balance in the nanospaces of the catalyst is necessary for favorable penetration of all reactants into the system pores to achieve high catalytic activity and, in particular, the product selectivity. Based on this explanation, the high hydrophobic character of sulfonic acid catalyst 2 may indeed provide a means of faster diffusion of benzaldehyde as well as ethylacetoacetate (but not urea) to the active sites provided by open mesopores, thus shifting the reaction selectivity toward the formation of aldolic adduct 6 as the major product in the absence of urea derivatives (Scheme 2). This model may also explain the significant selectivity changeover of the process toward the formation of dihydropyrimidinone 5 if PMO-based sulfonic acid 3 is employed rather than mesoporous solid acids 1 and 2. This observation most likely originates from a hydrophobic/hydrophilic balance in the system pores (mesochannels) of 3, which inevitably renders its mesoporous environment favorable to interact with both hydrophobic and hydrophilic starting materials, thus increasing their concentration in near proximity to sulfonic acid moieties, which causes efficient and selective formation of dihydropyrimidinone 5. Based on this model, the concomitant formation of 4 and 5 in the case of employing 1 might be also ascribed to the pronounced hydrophilic nature of system pores in 1, which arise from a relatively high concentration of silanol groups; these can strongly interact with both urea and the byproduct water and facilitate the unwanted hydrolysis of urea (or thiourea) to produce ammonia to a greater extent, thereby gradually shifting the process selectivity toward the production of Hantzsch dihydropyridine upon subsequent condensation with bezaldehyde and ethylacetoacetate (Scheme 2). From these unprecedented observations, it is particularly conspicuous that the hydrophobic/hydrophilic balance in the mesoporous environments of the employed catalyst has a decisive role in achieving the high selectivity toward the formation of dihydropyrimidinone in the three-component Biginelli reaction. By obtaining the appropriate catalytic system (catalyst **3**), we were next interested in investigating the scope of this catalytic system in the Biginelli reaction of various aldehydes,  $\beta$ -ketoesters, and urea as well as thiourea. To do this we thus managed to find the optimum reaction conditions for this process. The impact of catalyst loading, and reaction temperature on the Biginelli reaction of benzaldehyde (1 mmol), methylacetoacetate (1 mmol) and urea (1.2 mmol) as model substrates are summarized in Table 2.

<b>Table 2.</b> Effects of reaction temperature and the loading of the Et-PMO-Me-PrSO $_3$ H solid acid on the Biginelli reaction with urea.					
Entry	Mol [%]	<i>Т</i> [°С]	t [h[min]]	Yield <sup>[a]</sup> [%]	
1	1	50	8	56	
2	1	70	7[30]	86	
3	1	80	2[30]	91	
4	0.5	80	4	93	
5	0.3	80	5	91	
6	1.5	90	1	95	
7	1	90	1[20]	93	
8	0.5	90	1[45]	92	
9	0.3	90	2[15]	92	
10	-	80	9	59	
11	-	90	4	63	
[a] Yields refer to the isolated pure products. ( $R = H, X = O$ ).					

In the presence of catalyst 3 (1 mol%), we stirred the aforementioned components at  $T = 50 \,^{\circ}$ C for 8 h; this afforded the corresponding dihydropyrimidin-2-one in only 56% isolated yield (Table 2, entry 1). As expected, it is found that by increasing the reaction temperature the yield of the desired dihydropyrimidin-2-one is remarkably increased at a constant catalyst loading of 1 mol% (Table 2, entries 2-3 and 7). At the same time, a decrease in the amount of catalyst does not show any significant impact on the product yields at T = 90 °C (Table 2, entries 7-9). We also examined the reaction in catalyst-free conditions. This gives the expected product in a moderate yield at T = 80 °C after prolonging the reaction time (Table 2, entries 10-11). Taken together, among the examined reaction conditions, this three-component reaction can be most efficiently catalyzed by 0.3 mol% of **3** at T = 90 °C for 135 min under solvent-free conditions (Table 2, entry 9). Our next objective was to apply the present procedure for the synthesis of thiopyrimidin-2-ones by employing thiourea as one of the reaction partners instead of urea because thiopyrimidin-2-ones are important pharmacophores with regard to biological activity.

An initial assessment demonstrated that the aforementioned optimized conditions were not successful for the three-component Biginelli condensation reaction in the presence of thiourea. Therefore, the reaction was performed at a higher temperature and concentration of catalyst (T = 110 °C, 0.7 mol%) to ensure that excellent yields were also achieved for various thiopyrimidin-2-one derivatives (Table 3).

<b>Table 3.</b> Effects of reaction temperature and loading of catalyst <b>3</b> on theBiginelli reaction with thiourea.					
Entry	Mol [%]	<i>Т</i> [°С]	<i>t</i> [h]	Yield <sup>[a]</sup> [%]	
1	0.3	90	5	53	
2	0.3	100	5	59	
3	0.3	110	7	74	
4	0.5	110	7	83	
5	0.7	110	7	91	
6	-	110	7	43	
[a] Yields refer to the isolated pure products.(R=H, X=S).					

With the optimized reaction conditions in hand, to study the generality of the procedure, the scope of the Biginelli-like scaffolds reaction was investigated with various aldehydes,  $\beta$ -ketoester and urea or thiourea, and a library of substituted DHPMs was obtained in good to excellent yields in appropriate time under solvent-free conditions (Table 4). Both electron-withdrawing as well as electron-donating substituents on the aldehyde aryl ring are tolerated and react with methyl acetoacetate and urea under the optimized conditions. *Meta*- and *para*-fluoro and *meta*-bromobenzaldehydes successfully produce the desired products in similarly excellent yields (Table 4,

Table 4. Yields of various substituted DHPM derivatives on Et-PMO-Me-PrSO_3H.					
Entry	Aldehyde	R group	X substituent	t [h[min]]	Yield <sup>[a,b]</sup> [%]
1	benzaldehyde	Me	0	2[15]	92
2	benzaldehyde	Me	S	7	91
3	3-fluorobenzaldehyde	Me	0	2	93
4	3-fluorobenzaldehyde	Me	S	5[55]	92
5	4-fluorobenzaldehyde	Me	0	2[5]	91
6	4-fluorobenzaldehyde	Me	S	6[10]	89
7	3-bromobenzaldehyde	Me	0	2[10]	93
8	3-bromobenzaldehyde	Me	S	6[50]	89
9	3-methylbenzaldehyde	Me	0	2[25]	90
10	3-methylbenzaldehyde	Me	S	7	88
11	3,5-dimethylbenzaldehyde	Me	0	2[20]	89
12	3,5-dimethylbenzaldehyde	Me	S	6[55]	90
13	4-isopropylbenzaldehyde	Me	0	2[35]	90
14	4-isopropylbenzaldehyde	Me	S	7[15]	91
15	4-methoxybenzaldehyde	Me	0	2[40]	88
16	4-methoxybenzaldehyde	Me	S	7[10]	89
17	naphthaldehyde	Me	0	1[50]	92
18	naphthaldehyde	Me	S	5[30]	91
19	3-phenylpropionaldehyde	Me	0	3[40]	89
20	3-phenylpropionaldehyde	Me	S	8[35]	87
21	2-furfuraldehyde	Me	0	1[45]	83
22	2-furfuraldehyde	Me	S	5[35]	79
23	benzaldehyde	Et	0	2[25]	90
24	benzaldehyde	Et	S	7[45]	89

[a] Aldehyde (1 mmol), methyl acetoacetate (1 mmol), urea or thiourea (1.2 mmol) and catalyst **3** (0.3 mol%) at T=90 °C. [b] Reaction was performed at T=110 °C by using 0.7 mol% of catalyst **3**. Yields refer to the isolated pure products based on the aldehydes. Structures of the products were confirmed by <sup>1</sup>H and <sup>13</sup>C NMR and IR spectral data. The melting points of the products were also compared with authentic samples that were prepared according to the known procedures (see the Supporting Information).

entries 3-8), which indicates that the position of the electronwithdrawing substituent has no significant effect on the yields of DHPM adducts. A similar behavior is observed with electronreleasing groups. Meta-methyl (Table 4, entries 9-10), 3,5-dimethyl (Table 4, entries 11-12), para-isopropyl (Table 4, entries 13-14), and para-methoxy (Table 4, entries 15-16) benzaldehydes produce the expected DHPMs in good quantities. Also, the bulky aromatic naphthyl group gives the desired product in good yields (Table 4, entries 17-18). Furthermore, under similar reaction conditions, 3-phenylpropionaldehyde as a model for an aliphatic and enolizable aldehyde gives the corresponding DHPMs in high yield but longer reaction times are required to obtain high yields of the corresponding condensation products (Table 4, entries 19-20). Notably, the methodology is also successfully employed for heterocyclic aldehydes such as furfural (Table 4, entries 21-22), which gives the respected DHPM adducts in good yields. It is also found that the use of ethyl acetoacetate instead of methyl acetoacetate in the three-component reaction gives the corresponding products in excellent yields (Table 4, entries 23-24). These results are quite comparable to recent interesting reports by Bhaumik and coworkers<sup>[6k]</sup> and Alvim et al.,<sup>[6l]</sup> in which they employ a novel functionalized Fe<sub>3</sub>O<sub>4</sub>@mesoporous SBA-15 and several types of ionic liquid-based systems, respectively, as the catalysts in the Biginelli reaction with urea to synthesize DHPMs with more or less close turnover numbers (TONs) and selectivities.

#### Reusability of the Et-PMO-Me-PrSO<sub>3</sub>H (3) catalyst

The recovery of catalyst **3** in the Biginelli reaction of benzaldehyde (1 mmol) with methylacetoacetate (1 mmol) and urea (1.2 mmol) with 0.3 mol% catalyst loading of the catalyst under solvent-free conditions at T=90 °C was also tested. The catalyst is easily recovered from the reaction mixture by filtration, then washed with acetonitrile, water and ethanol and finally dried at T=110 °C for 2 h before another reaction is performed. During the recycling experiment with fresh reactants under the same reaction conditions, no considerable change in the activity of the catalyst for at least 8 consecutive runs is observed, which clearly demonstrates the stability of the catalyst for these conditions in the Biginelli reaction (Figure 4).

We also performed N<sub>2</sub>-sorption analysis and acid-base titration of catalyst **3** after the tenth reaction cycle to determine if any structural changes and leaching of the sulfonic acid sites had occurred in the catalyst or not. Both N<sub>2</sub>-sorption diagrams (see S20, the Supporting Information) and the TEM image (Figure 5) of the recovered catalyst show little (almost ignorable) changes in the morphology of the catalyst after recovery.

Although, the catalyst does not show significant structural changes, to show the overall stability of catalyst **3**, the acidic capacity was measured by titration of ion-exchanged catalysts after the tenth reaction cycles. Our studies reveal that the sulfonic acid loading in catalyst **3** is slightly reduced from 0.5 to 0.40 mmolH<sup>+</sup>g<sup>-1</sup> ( $\approx$ 80% survival), which is still quite interesting. Notably, for the reactions in which water participates as a byproduct, only a few solid acids show acceptable performance and stability.<sup>[2a,14]</sup>

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**Figure 4.** Recyclability of catalyst **3** in the Biginelli reaction of benzaldehyde, methylacetoacetate, and urea at T=90 °C under solvent-free conditions. Yield ( $\Box$ ) and Time ( $\blacksquare$ )



Figure 5. TEM images of catalyst 3 (scale bar 100 nm) after the tenth reaction cycle.

#### Conclusions

In summary, the preparation and characterization of two kinds of mesoporous solid acids SBA-15-PrSO<sub>3</sub>H 1, SBA-15-Ph-PrSO<sub>3</sub>H 2, and a periodic mesoporous organosilica (PMO) based solid acid Et-PMO-Me-PrSO<sub>3</sub>H 3 are described. The catalytic performance (both activity and selectivity) of these catalytic systems is compared in the three-component Biginelli condensation reaction of aldehydes,  $\beta$ -ketoesters, and urea as well as thiourea. Amongst them, catalyst 3 is found to be significantly more selective in the Biginelli reaction, which affords the corresponding DHPM derivatives in good to excellent yields and excellent selectivities without the formation of any detectable dihydropyridine (DHP, Hantzch adduct) and/or aldolic products. This remarkable and unprecedented selectivity improvement of the Et-PMO-Me-PrSO<sub>3</sub>H catalyst in the Biginelli reaction versus the Hantzsch reaction and/or aldolic products most likely owes to the hydrophobic/hydrophilic balance in the nanospaces (mesochannels) of the material in which the active sulfonic acid groups are located. It is assumed that this hydrophobic/hydrophilic balance in the system pores (mesochannels) of 3, renders its mesoporous environment favorable for interaction with both hydrophobic (aldehyde and  $\beta$ -ketoester molecules) and hydrophilic (urea or thiourea) starting materials, thus increasing their concentration in near proximity to sulfonic acid moieties and causing efficient and selective formation of dihydropyrimidinone 5. In the same way, the concomitant formation of 4 and 5 in the case of employing 1 might be also ascribed to the pronounced hydrophilic nature of system pores in 1, which arise from a relatively high concentration of silanol groups; these can strongly interact with both urea and the byproduct water and facilitate the unwanted hydrolysis of urea (or thiourea) to produce ammonia to a greater extent, thereby gradually shifting the process selectivity toward the production of Hantzsch dihydropyridine upon subsequent condensation with bezaldehyde and ethylacetoacetate. To the best of our knowledge, there are no precedent reports of such a changeover in the product selectivity in a similar three-component reaction by changing the surface physicochemical properties of the employed solid catalysts. Work is underway to expand the application of this approach in other important chemical transformations. It is believed that this finding will stimulate the creation of new areas in designing novel solid acid catalysts that have an appropriate surface hydrophobic/hydrophilic balance to control the selectivity of a typical transformation in a designated pathway.

#### **Experimental Section**

#### Preparation of SBA-15-PrSH

The synthesis of SBA-15-PrSH was achieved by using the procedure described by Stucky and co-workers.<sup>[9c]</sup> This procedure involved a synthetic strategy based on the co-condensation of tetraethoxysilane (TEOS) and 3-mercaptopropyltrimethoxysilane (MPTMS) in the presence of Pluronic P123 ( $EO_{20}PO_{70}EO_{20}$ ) as the structure-directing agent. In a typical preparation procedure, Pluronic P123 (4.0 g, Aldrich, average Mw  $^{1}\!/_{\!_{4}}$  5800) was dissolved in HCl solution (125 g, 1.9 M) with stirring at room temperature. The solution was heated to T=40°C before TEOS (6.83 g) was added. After 3 h prehydrolysis of TEOS, the thiol precursor MPTMS (1.6 g) was added. The resultant solution was stirred for 20 h at  $T = 40 \degree$ C, after which the mixture was aged at  $T = 100 \degree$ C for 24 h under static conditions. The solid was recovered by filtration and air dried at room temperature overnight. The template was removed from the as-synthesized material by washing with ethanol by using a Soxhlet apparatus for 24 h.

#### Preparation of SBA-15-Ph-PrSH

PhSi(OEt)<sub>3</sub> (PTES, 4 mmol) was added to a suspension of SBA-15-PrSH (3 g) in dry toluene. The resulting mixture was first stirred at room temperature for 1 h and then heated under reflux for a further 24 h. The solid materials were filtered off and successively washed with toluene, EtOH, and Et<sub>2</sub>O, and dried overnight at T= 120 °C to afford the corresponding SBA-15-Ph-Pr-SH.

#### Preparation of SBA-15-PrSO<sub>3</sub>H (1) and SBA-15-Ph-PrSO<sub>3</sub>H (2)

The conversion of the thiol groups of the catalysts to sulfonic acid moieties was accomplished by using hydrogen peroxide. Typically, the solid materials (0.3 g) were suspended in aqueous  $H_2O_2$  (10 g,

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30 wt%). These suspensions were stirred at room temperature in an argon atmosphere for 24 h. After the oxidation treatment, the resulting solutions were filtered and washed separately with water and ethanol. Finally the wet materials were suspended in  $H_2SO_4$  (1 M) solution for 2 h, washed several times with water and ethanol, and dried at T=60 °C under vacuum overnight to give the corresponding 1 and 2 catalysts.

#### Preparation of Et-PMO-Me-PrSO<sub>3</sub>H (3)

Organosulfonic acid-functionalized periodic mesoporous organosilicas 3 was synthesized as we described before.<sup>[3e]</sup> In a typical preparation procedure, Pluronic P123 (0.66 g) was dissolved in HCl (70 mL, 2м) solution with stirring at room temperature. After addition and agitation of 1,2-bis(triethoxysilyl)-ethane (BTEE) (2.77 g) for 3 h at T=35 °C as a backbone for PMO, the thiol precursor 3mercaptopropylmethyldimethoxysilane (MPMDS) (0.478 g) was added and stirred for approximately 24 h at T = 35 °C. White precipitates were obtained after aging the mixture at T=85 °C for 24 h under static conditions. The solid was recovered by filtration, washing (by deionized water) and dried at room temperature for 24 h. The residual block copolymer was removed from the as-synthesized material by washing with ethanol by using a Soxhelet apparatus for 24 h. Conversion of the thiol groups on the catalyst to sulfonic acid moieties was accomplished by hydrogen peroxide. Typically, the solid hydrophobic material (0.2 g) was suspended in aqueous  $H_2O_2$  (8 g, 30 wt%). The suspension was stirred at room temperature in an argon atmosphere for 24 h. After the oxidation treatment, the resulting solution was filtered and washed separately with deionized water and ethanol. Finally the wet material was suspended in H<sub>2</sub>SO<sub>4</sub> (0.1 M) solution for 2 h, and then washed several times with deionized water until a neutral pH was reached. This was then dried at  $T = 60 \degree C$  under vacuum overnight to give the corresponding Et-PMO-Me-PrSO<sub>3</sub>H (3).

# Acidity of Et-PMO-Me-PrSO<sub>3</sub>H (3), SBA-15-Ph-PrSO<sub>3</sub>H (2) and SBA-15-PrSO<sub>3</sub>H (1)

The concentration of sulfonic acid groups was quantitatively estimated by ion-exchange pH analysis. The catalysts (50 mg) were added to an aqueous solution of NaCl (1 M, 25 mL), and the resulting mixture was stirred for 3 days, after which reverse titration by NaOH (0.05 M) was conducted on the above obtained solutions. The acid concentrations of **1**, **2**, and **3** were determined to be 1.77, 1.61, and 0.50 mmolg<sup>-1</sup>, respectively.

#### General procedure for the one-pot preparation of 3,4-dihydropyrimidinones

A mixture of aldehyde (1 mmol), methylacetoacetate (1 mmol), urea (1.2 mmol) and catalyst (6 mg, 0.3 mol%) were stirred at T = 90 °C for an appropriate time in solvent-free conditions (Table 2). The progress and completion of the reaction was monitored by TLC. After the completion of the reaction, the mixture was diluted with acetonitrile (or dichloromethane if necessary) and finally, the reaction mixture was separated from the catalyst by filtration and washing with warm ethanol. The crude products were recrystallized in ethanol or subjected to silica gel column chromatography to further purify them if necessary.

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