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Merging metal–organic framework catalysis with organocatalysis: A thiourea functionalized heterogeneous catalyst at the nanoscale†

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Yi Luan, Nannan Zheng, Yue Qi, Jia Tang and Ge Wang*

A new thiourea-containing metal–organic framework (MOF) catalyst was synthesized. It overcomes recycling, self-aggregation and solvation issues that exist in homogeneous thiourea catalysts. Nanomorphology was introduced to increase the dispersion of the solid catalyst in solvent. Acetalization and Morita–Baylis–Hillman reactions were catalyzed using the new thiourea MOF catalyst.

Metal–organic frameworks (MOFs) are crystalline materials with extended structures which can be utilized in many fields, such as gas sorption, sensing, drug delivery and catalysis.[1] In recent years, MOFs were studied as novel heterogeneous catalysts because of their porous and tunable nature.[2] However, established MOF structures have relatively little catalytic reactivity due to the limited selections of metals and organic ligands.[3] In order to further extend the catalytic activity through structure modification, a post-synthetic modification (PSM) strategy can be introduced to provide access to porous materials with new or enhanced properties for specialized applications, such as catalysis.[4] PSM is generally achieved using a pre-installed moiety on the precursor ligand that can be coupled with a reactive species in a heterogeneous fashion.[5] IRMOF-3 (isoreticular metal–organic framework-3) is a porous MOF decorated with primary amine groups, which can be further modified through a PSM approach.[6] Cohen pioneered the modification of the IRMOF-3 structure moiety,[7] and several IRMOF-3 have been post-synthetically modified through different organic transformations.[8] While tremendous amounts of MOF materials have been utilized as catalysts, nanosized MOFs received much less attention.[9] Although IRMOF-3 at the nanoscale has been synthesized, its use in catalysis has not been studied yet.[10] The nanomorphology of MOFs strongly influences or even improves chemical properties of these metal–organic materials. Effective surface areas for catalytic performance can be enhanced by the nanomorphology of MOFs in comparison to their macroscopic counterparts.[11] Furthermore, nanoscale metal–organic materials show well-defined and uniform sizes and morphologies, which improve dispersion in aqueous media or other solvents.

Organocatalysis is used to describe reactions promoted by a small molecule organic catalyst, which offers great advantages in availability, cost and toxicity relative to homogeneous metal-catalyzed reactions.[12] Thiourea catalysts, which operate *via* double hydrogen-bonding interactions with the substrates, are a milestone achievement of modern organocatalysis.[13] A variety of organic transformations have been promoted by thiourea catalysts in a racemic or asymmetric fashion such as Diels–Alder reaction, Michael addition and protection of alcohols.[14] However, several issues need to be overcome in order to make thiourea catalysts more practical. First, homogeneous thiourea catalysts are difficult to recycle. Another issue is that thiourea catalysts are known to deactivate through self-quenching, which is a self-assembly behavior due to catalyst–catalyst interaction, such as dimerization or oligomerization (Fig. 1).[15] Immobilization of the thiourea functionality would be ideal to prevent both recycling and self-quenching issues.

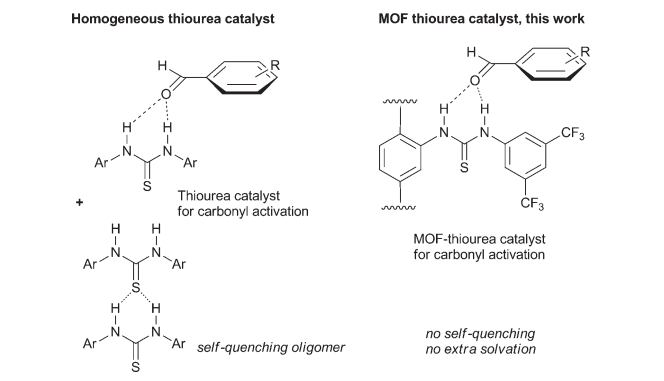

Fig. 1 Thiourea catalyst and the MOF–thiourea catalyst.

School of Materials Science and Engineering, University of Science and Technology Beijing, 30 Xueyuan Road, Beijing 100083, PR China.
E-mail: gewang@mater.ustb.edu.cn; Fax: +86 10 62327878; Tel: +86 10 62333765

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At the same time, solvation issues of thiourea catalysts can also be suppressed.[16] To immobilize the thiourea functionality, various supports such as mesoporous silica,[17] polymer[18] and MOF[19] have recently been reported.

Merging organocatalysis and MOF heterogeneous catalysis offers great opportunities to take advantage from both catalytic processes (Fig. 1). Reactions with excellent catalytic performance under extremely mild conditions, easy separation between the catalyst and substrates and the prevention of self-quenching can all be achieved using one MOF catalyst. Recently, post-synthetic modification reactions have been employed to introduce organocatalytic functional groups into MOFs, which mimic known Brønsted acid catalysts for catalytic transfomations.[20] Important organocatalytic molecules, namely proline,[21] 1,1′-bi-2-naphthol[22] and urea,[23] have been incorporated into MOF structures as catalysts. Urea and thiourea containing MOFs[24] and other hydrogen-bonded MOFs[25] have been synthesized through different approaches but rarely employed as catalysts. Despite much progress in this area, the generation of a thiourea structure motif as part of the MOF catalyst has attracted much less attention. Herein, we report a nanoscale MOF–thiourea catalyst that mimics known organocatalysts – small organic molecules that accelerate chemical reactions. This approach presents the first thiourea hydrogen-bonding catalyst synthesized *via* post-synthetic modification at the nanoscale. Our idea is to take some of the concepts from a hydrogen-bonding catalyst and merge them with the field of metal–organic frameworks, and boost the catalytic reactivity by taking advantage of the MOF nanomorphology.

The synthesis of the IRMOF-3–thiourea catalyst started from the literature known IRMOF-3. Reacting pre-synthesized IRMOF-3 with 3,5-bis(trifluoromethyl)phenyl isothiocyanate under basic conditions provided the desired IRMOF-3–thiourea catalyst (Scheme 1). Scheme 1 illustrates the orientation of the supported 3,5-bis(trifluoromethyl)phenylthiourea after DFT energy minimization. The thiourea group occupies a large portion of the pore structure, allowing the entry and exit of substrate molecules due to its flexibility. The loading of a thiourea moiety can be controlled by reaction conditions and then analyzed using nuclear magnetic resonance (NMR) spectroscopy (Fig. 2). NMR studies provided the different loading ratios of catalysts **C6**, **C7** and **C8**, which correspond to 4%, 17% and 26% thiourea incorporation, respectively. Furthermore, solvent incorporation, which is a common problem in thiourea synthesis and storage, was not observed in our IRMOF-3–thiourea catalyst according to the NMR spectrum. The successful synthesis of the IRMOF-3–thiourea catalyst was also confirmed by electrospray ionization mass spectrometry (ESI-MS) and FTIR. ESI-MS results showed the expected molecular ion peak for the modified component in the IRMOF-3–thiourea molecule. The FTIR study further confirms the observed C═S stretching bands of IRMOF-3–thiourea, which represent the thiourea network at 1132.5 and 1179.0 cm^{-1}.

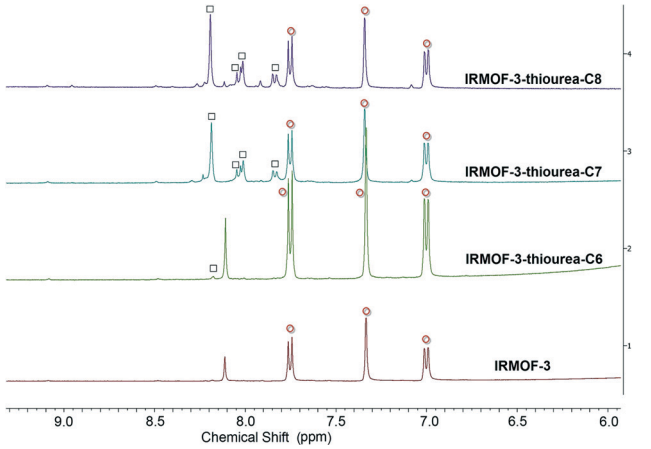
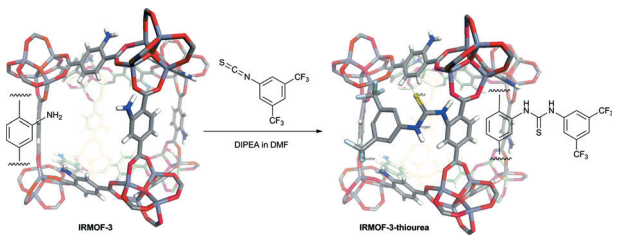


Fig. 2 ^{1}H NMR spectra of digested IRMOF-3. Resonances in the spectra for unmodified IRMOF-3 (bottom) and modified IRMOF-3: IRMOF-3–thiourea-**C6**, 4% modified; IRMOF-3–thiourea-**C7**, 17% modified; and IRMOF-3–thiourea-**C8**, 26% modified. All are based on IRMOF-3. Squares and circles represent signals of modified and 2-aminoterephthalic acid, respectively.

The synthesis of nanoscale IRMOF-3 was achieved using modified literature procedures. Cubic crystals of IRMOF-3 with good monodispersity and crystallinity were successfully produced in very high yield (Fig. 3a). Crystal sizes of about 200–300 nm diameters were observed in the present synthesis at room temperature. The loading of the thiourea functionality did not affect the nanomorphology of IRMOF-3 (Fig. 3b). Our successful synthesis of IRMOF-3 was proved by powder X-ray diffraction (PXRD) studies (Fig. S2†). The PXRD pattern of nano IRMOF-3 was similar to that of regular IRMOF-3. This indicates the high similarity of both crystalline structures. XRD patterns showed that the thiourea modified IRMOF-3 material possessed the same reflections as unmodified IRMOF-3.



Scheme 1 Post-synthetic modification of IRMOF-3 with 3,5-bis(trifluoromethyl)phenyl isothiocyanate.

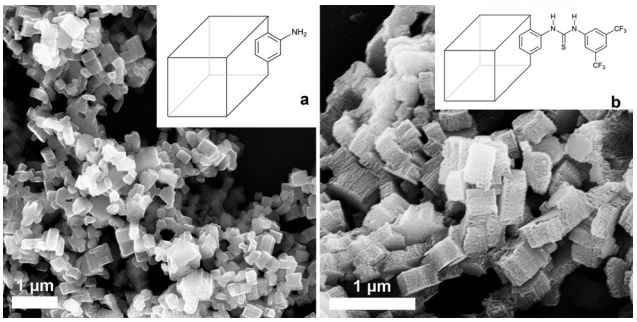


Fig. 3 SEM images of nanoscale IRMOF-3 (a) and IRMOF-3–thiourea (b).

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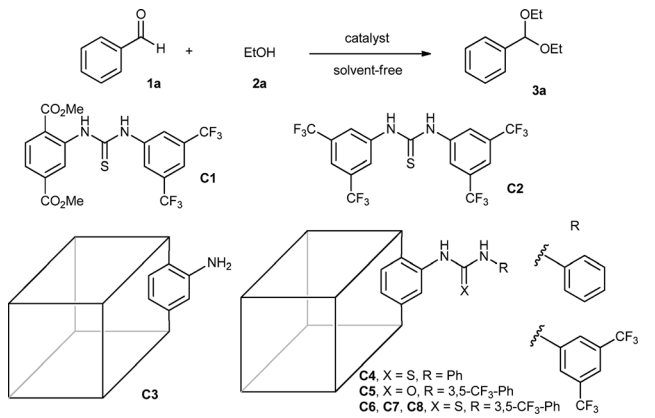
The thiourea-containing IRMOF-3 was examined by thermal gravimetric analysis (TGA) to confirm the thermal and structural stability of the heterogeneous thiourea catalyst. The nano MOF catalyst showed good thermal stability similar to IRMOF-3. A weight loss at ~344 °C and decomposition temperature around 386 °C were observed according to the TG analysis, which agree with the literature data.[26]

We initiated our investigation by evaluating the acetalization reaction of benzaldehyde (**1a**) at room temperature. Strong Brønsted acids are known to promote the acetalization of benzaldehyde (Table 1, entry 2). An organocatalyst offers a great advantage in promoting the same reactivity under much milder conditions. Homogeneous thiourea catalysts for acetalization have been reported.[27] Schreiner's catalyst was able to induce the formation of benzaldehyde acetal (**3a**) (Table 1, entry 4). A similar thiourea catalyst with two carboxylate groups was also evaluated, which gives a good yield of acetal (Table 1, entry 3). Acetal formation can be promoted by certain MOF structures, such as $Cu_3(BTC)_2$ (BTC = 1,3,5-benzenetricarboxylate),[28] FeBTC[29] and In(III) MOFs[30] under various conditions. However, IRMOF-3 shows almost no reactivity at room temperature for 12 h (Table 1, entry 5). It can be concluded that the thiourea moiety is responsible for acetalization reactivity. The phenyl substituted IRMOF-3–thiourea catalyst (**C4**) at the nanoscale showed very low reactivity (Table 1, entry 6). 3,5-Bis(trifluoromethyl)-phenylthiourea (**C7**) showed much improved reactivity compared to its urea counterpart (**C5**) (Table 1, entries 7 and 8). At 17% loading, nanosized IRMOF-3–thiourea **C7** showed better performance than its bulk partner, which suggested a higher utilization rate of the MOF surface and pore (Table 1, entries 8 and 9). A higher thiourea loading (26%) on the IRMOF-3–thiourea catalyst **C8** gave a comparable yield, with the turnover numbers (TON) up to 490 (Table 1, entry 10).

The aforementioned conditions were successfully applied to a range of acetalization and Morita–Baylis–Hillman reactions (Table 2). Halogenated aromatic rings, such as F and Br, were tolerated (Table 2, entries 1–2). Ethene diol **2b** can also act as an alcohol nucleophile (Table 2, entry 3). 9-Anthraldehyde (**1e**) gave almost no desired product based on the crude NMR analysis, which demonstrates reagent size selectivity for such a heterogeneous MOF thiourea catalyst (Table 2, entry 4). This

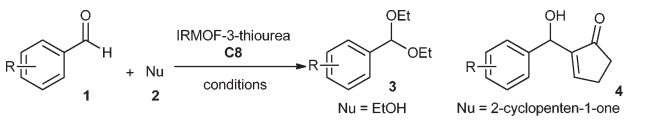
Table 1 Acetalization promoted by various catalysts[a]

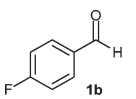
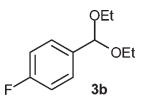
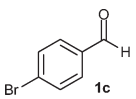
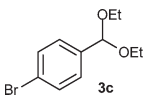
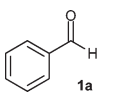
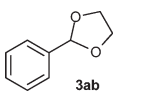
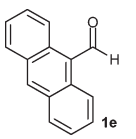
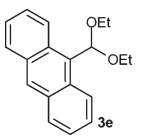
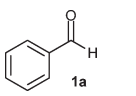
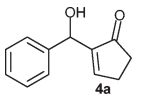
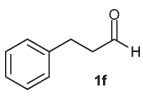
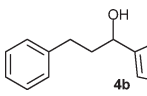


Entry	Catalyst[b]	Loading	Yield[c]	TON
1	—	—	0%	0
2	*p*TsOH	10 mol%	99%	10
3	Thiourea (**C1**)	1 mol%	81%	81
4	Thiourea (**C2**)	1 mol%	89%	89
5	IRMOF-3 (**C3**)	10 mol%	6%	0.6
6	IRMOF-3–thiourea (**C4**)	0.2 mol%	15%	75
7	IRMOF-3–urea (**C5**)	0.2 mol%	64%	320
8	IRMOF-3–thiourea (**C7**)	0.2 mol%	96%	480
9	Bulk **C7**	0.2 mol%	82%	410
10	IRMOF-3–thiourea (**C8**)	0.2 mol%	98%	490

[a] Reaction conditions: benzaldehyde (1.0 mmol), dry ethanol (4.0 mmol) and 0.2 mol% (based on thiourea) organocatalyst at room temperature for 12 h. [b] MOF catalysts are used in nanoscale unless otherwise noted. [c] Determined by GC-MS.

Table 2 IRMOF-3–thiourea catalyzed acetalization and Morita–Baylis–Hillman reactions[a]



Entry	Substrate	Nu	Product	Yield
1		EtOH		92%
2		EtOH		91%
3				96%
4		EtOH		<5%
5[b]				73%
6[b]				81%

[a] Reaction conditions. For acetalization (entries 1–4): the same conditions as in Table 1. [b] For Morita–Baylis–Hillman reaction (entries 5 and 6): benzaldehyde (0.1 mmol), 2-cyclopenten-1-one (2.0 mmol), 1,4-diazabicyclo[2.2.2]octane (0.5 mmol). IRMOF-3–thiourea catalyst (**C8**) (2 mol%) were stirred at 4 °C for 24 h. The product was purified by column chromatography on silica gel and the yield was based on the isolated product.

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observation indicates that acetalization occurs mostly inside the MOF porous tunnel, since substrates that are bigger than the size of the pore will have limited access to catalytic sites inside the MOF tunnel. To further extend the utility of our new IRMOF-3–thiourea catalyst, Morita–Baylis–Hillman reactions of benzaldehyde (**1a**) and 2*H*-cinnamaldehyde (**1f**) were evaluated with 2-cyclohexen-1-one (**5**) as the nucleophile and 1,4-diazabicyclo[2.2.2]octane as the base. An enhanced yield was obtained with only 2 mol% catalyst loading, which is significantly lower than the loading in the previous report (Table 2, entries 5 and 6).[31] A controlled experiment showed that there was no reactivity in the absence of the catalyst.

The stability of IRMOF-3–thiourea was tested by performing repeated reaction cycles under the same reaction conditions. IRMOF-3 is known to be sensitive to weak acid and base, and the loss of framework integrity has been observed in certain cases.[32] However, IRMOF-3–thiourea served as an efficient and stable hydrogen-bonding catalyst under mild organocatalytic conditions. The strong covalent bond between the thiourea moiety and the amino group on IRMOF-3 ensures the stability of the catalytic functional groups, which maintains over 95% yield after five cycles. The supernatant liquid of the ethanol suspension showed no reactivity towards the acetalization of the benzaldehyde substrate, which indicates no leakage of the IRMOF-3–thiourea catalyst. The X-ray powder diffraction patterns and FTIR spectra of the IRMOF-3–thiourea catalyst after five times reuse were also indistinguishable from those of the fresh catalyst (Fig. S2†).

Our current mechanistic proposal for the MOF–thiourea catalyzed acetalization of aldehydes begins with the coordination of the catalyst with the carbonyl group to form **TS2** (Fig. 4). Binding and activation are the driving forces for the coordination, as well as the secondary π–π interaction between the two aromatic groups in **TS2**. The second step is the nucleophilic attack of two alcohols through an ion-pair intermediate, which leads to benzaldehyde acetal and water binding (**TS3**). The dehydration of water through ligand exchange regenerates the catalyst. Morita–Baylis–Hillman reaction undergoes a similar reaction mechanism except that 2-cyclopenten-1-one (**5**) acts as a nucleophile in the presence of a base promoter. Multiple experiments were run under various catalyst loadings, and the rates were extracted from the slopes of the curves using ReactIR. These rates were averaged and plotted as depicted in Fig. 4. From this graph, it is clear that there is a linear relationship between the amount of the catalyst in the acetalization reaction and its rate. This indicated first order reaction kinetics with respect to the catalyst.

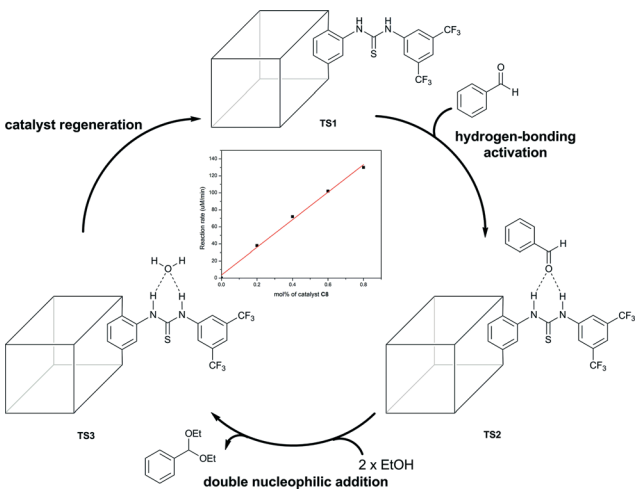

Fig. 4 Proposed acetalization reaction mechanism and determination of first-order reaction kinetics of the catalyst.

Conclusions

In conclusion, a simple and rapid one-step approach to achieve thiourea functionalized IRMOF-3 *via* post-synthetic modification was developed. The structure and nanomorphology of IRMOF-3–thiourea were retained after post-synthetic modification. The new nanoscale IRMOF-3–thiourea showed high activity and selectivity in acetalization and Morita–Baylis–Hillman reactions. The catalyst did not suffer from a leaching problem during catalysis and could be recycled several times without loss of activity or selectivity. This heterogeneous thiourea incorporation strategy overcomes self-aggregation and solvation issues that existed in a homogeneous thiourea catalyst. Future studies including the incorporation of a chiral thiourea moiety are underway.

Acknowledgements

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