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Indium Metal–Organic Frameworks as High-Performance Heterogeneous Catalysts for the Synthesis of Amino Acid Derivatives

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Supporting Information

ABSTRACT: Indium metal–organic frameworks (MOFs) were first used as recyclable heterogeneous Lewis acid catalysts for the synthesis of amino acid derivatives with excellent conversion yields. Moreover, exposed ether groups (Lewis basic sites) on the pore walls of In-MOF **2** could activate trimethylsilyl cyanide, forming hypervalent silicate intermediates, as proven by ^{29}Si NMR.

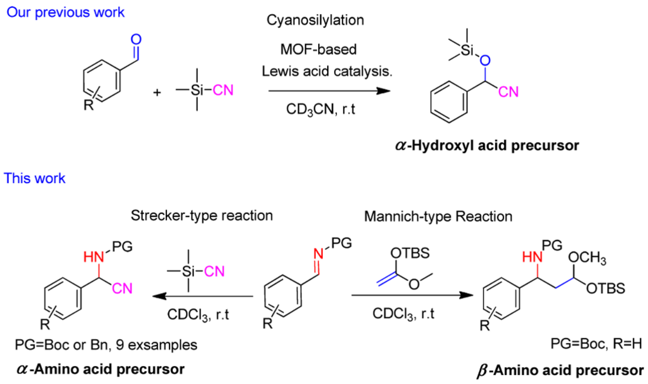
The synthesis of natural and unnatural α-amino acids is of current interest because of their significance in chemistry and biology.[1] The Strecker reaction offers one of the most direct and viable methods for the synthesis of α-aminonitriles, which are versatile building blocks in the synthesis of α-amino acids and theirp derivatives.[2] Over the past few years, this reaction has been successfully catalyzed by various Lewis acid and Lewis base organocatalysts[3] with attendant difficulties in catalyst recovery and recycling and a few heterogeneous catalysts such as metal complexes, metal-salen complexes, and metal oxides.[4] Now the design and synthesis of a Lewis acid–base bifunctional catalyst, especially the recyclable bifunctional activation, is the hot topic of chemistry research.

Metal–organic frameworks (MOFs) have emerged as promising crystalline materials because of their aesthetically pleasing structures and latent applications in gas storage, chemical sensing, catalysis, and controlled release of drugs.[5] In particular, MOFs as heterogeneous catalysts have many good advantages, such as allowing simple filtration and facilitating product separation and catalyst reuse. Moreover, MOFs can be designed as shape-selective, size-selective, or chemo- or enantioselective catalysts. Several groups have shown that MOFs as heterogeneous catalysts can exhibit high activity and selectivity in various reactions.[6] Especially, De Vos and coworkers have reported that UiO-66(NH_2) can be used as a bifunctional acid–base catalyst for cross-aldol condensation.[7] However, to the best of our knowledge, the Strecker reaction catalyzed by MOFs has not been mentioned in the literature so far.

Previously, we have reported an indium(III) heterogeneous catalyst, $In(OH)(H_2O)(1,4\text{-bdc})$ (**1**; 1,4-H_2bdc = 1,4-benzendicarboxylic acid), which exhibits good catalytic activity for cyanosilylation of aromatic aldehydes.[8] Because of the small pore size, its activity took place on the surface. Then we examined the catalytic property of $In(OH)(4,4'\text{-oba})\cdot DMF\cdot 2H_2O$ [**2**; 4,4′-H_2oba = 4,4′-oxybis(benzoic acid)][9] for cyanosilylation. In contrast with In-MOF **1**, In-MOF **2** features large open channels (about 5.7 × 5.8 Å) and has accessibly functional ether groups, imparting basic character to the material. The subsequent experimental results show that the catalytic activity of In-MOF **2** for cyanosilylation of aromatic aldehydes is obviously better than that of catalyst **1** (Figure S1 in the Supporting Information, SI).

The successes of In-MOFs **1** and **2** in cyanosilylation of aromatic aldehydes prompt us to undertake investigations of their catalytic activities in the Strecker reaction between the various aldimines and trimethylsilyl cyanide (TMSCN), determining the actual origin of the catalytic performance of In-MOF **2** and aiming at finding an efficient method to synthesize α-aminonitriles (Scheme 1). It will be shown that here In-MOF **2** exhibits good-to-excellent catalytic performance, and besides the unsaturated indium(III) centers (Lewis acidic sites) present as responsible active sites, the presence of ether oxygen atoms (Lewis basic sites) of organic linkers can also contribute to the Strecker reaction, as proven by solid-state ^{29}Si NMR.

Scheme 1. C–C Bond Formation Reactions Catalyzed by In-MOFs



In-MOFs **1** and **2** were initially evaluated in the Strecker reaction between *N*-Boc-phenylaldimine **3a** and TMSCN at room temperature (Table 1, entries 1–4). It was observed that, in contrast to In-MOF **1**, In-MOF **2** can catalyze the Strecker

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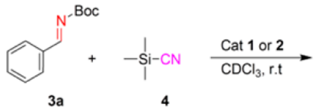
Table 1. Strecker Reaction between *N*-Boc-aldimine 3a and TMSCN Catalyzed by In-MOFs 1 and 2

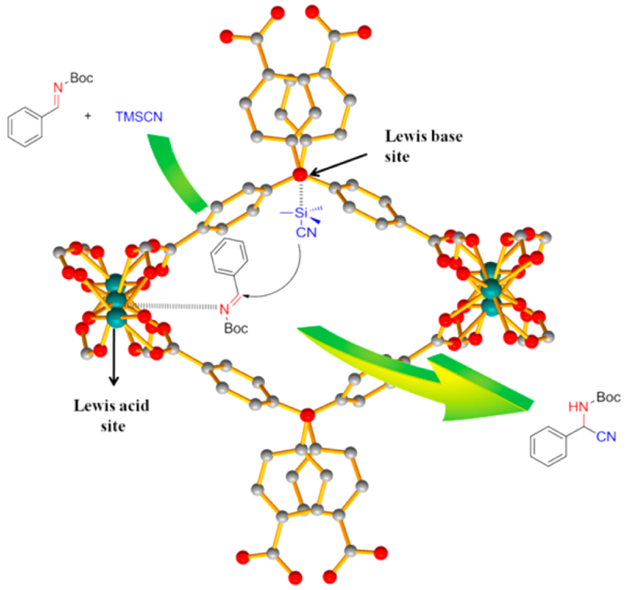


entry^a	catalyst	time (h)	conversion yield (%)^b
1	**1**	24	19.3
2	**1**	96	46.5
3	**2**	24	55.9
4	**2**	96	99.6

[a]Reaction conditions: *N*-Boc-aldimine (0.07 mmol), TMSCN (0.18 mmol), catalyst **1** or **2** (0.035 mmol), and $CDCl_3$ (0.5 mL) at room temperature. [b]% yield calculated by ^1H NMR with aldimines (see the SI).

reaction in fairly high yields. *N*-Boc-aldimine **3a** proceeded smoothly in the presence of 50 mol % In-MOF **2** in deuterochloroform ($CDCl_3$) for 96 h, providing the corresponding α-aminonitrile in 99.6% yield (entry 4), while In-MOF **1** catalyzed **3a** only provided 46.5% yield after 96 h. Even if the catalyst loading of In-MOF **1** was doubly increased, the reaction rate was still slow.

Scheme 2. Proposed Mechanisms for the Strecker Reaction Catalyzed by In-MOF 2



To understand the relationship between the structure and reactivity of In-MOFs **1** and **2** in the Strecker reaction, it is significant to know the structure and nature of their reactive sites. Compared to In-MOF **1**, In-MOF **2** possesses an open-framework structure, which allows the substrates to diffuse through the pores/channels to reach the catalytic indium(III) centers, leading to inherently high surface reactivity per unit area. Thus, In-MOF **2** indeed displayed higher activity compared to In-MOF **1**. Besides this, In-MOF **2** has accessibly functional ether oxygen atoms on the pore walls of the framework, which can impart basic character to the material. The Strecker reactions are known to be driven by base catalysts. So, In-MOF **2** can be viewed as a Lewis acid–base bifunctional catalyst; that is, besides the indium(III) centers (Lewis acid) presented as responsible active sites, the presence of ether groups (Lewis base) of organic linkers can also contribute to the cyanation of imines. As to the mechanism, we speculated that the Strecker reaction proceeds via dual activation of both substrates (electrophiles and nucleophiles) by In-MOF **2**, where the Lewis base moiety (ether group) activates TMSCN and the Lewis acid moiety [indium(III) center] activates the nitrogen atom of aldimines. As illustrated in Scheme 2, TMSCN was activated by the ether oxygen atom of the 4,4′-oba^{2-} ligand and coordinated with it to produce a hypervalent silicate species, resulting in the cyanide group being polarized to acquire more reactivity. Meanwhile, the aldimines are activated by indium(III) centers. The highly reactive cyanide group then attacks the aldimine activated by the indium(III) center, resulting in the formation of an intermediate. The enhancement of the nucleophilicity and reactivity of the cyano group can be proven by solid-state ^{29}Si CP/MAS NMR spectra. As shown in Figure S2 in the SI, compared to the mixture of In-MOF **1** and TMSCN, when TMSCN is added to In-MOF **2**, another strong signal is found at δ −84.9 ppm. The spectral change strongly shows that the environments around the silicon atoms of some TMSCN species are changed when the ether group is present, and these silicon atoms of TMSCN could form pentacoordinate silicate species by coordination to ether oxygen atoms due to the rigidity and steric hindrance of the 4,4′-oba^{2-} ligand. The formation of hypervalent silicates can be found in Kantam's and Feng's reports in which TMSCN could be activated by Lewis basic sites.[4g,10]

We next studied the Strecker reaction with *N*-PG (PG = protected group) phenylaldimines **3** as the model substrates with TMSCN using In-MOF **2** for optimization (Scheme 3). The reaction was performed at room temperature with $CDCl_3$ as the solvent. With low catalyst loading (30 mol % of substrate), *N*-Boc-phenylaldimine could give the product in 98.1% yield after 96 h, while *N*-Bn-phenylaldimine showed high reactivity, affording quantitative yields of the product after 48 h. So, the substrate generality of the Strecker reaction was carried out for several *N*-Bn-phenylaldimine derivatives having different substituents, with TMSCN using In-MOF **2** under the optimized conditions. It was found that various aromatic aldimines afforded good-to-excellent yields (Table S1 in the SI).

Scheme 3. Strecker Reaction between *N*-PG Aldimines 3 and TMSCN Catalyzed by In-MOF 2

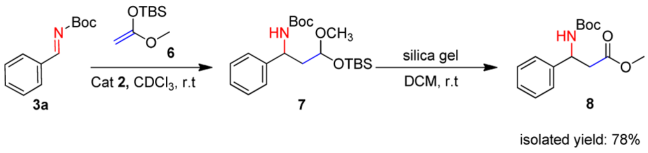
PG = Boc, **5a**, 96h, conversion yield: 98.1%

PG = Bn, **5b**, 48h, conversion yield: 100%

Upon completion of the cyanation of phenylaldimines, In-MOF **2** could be easily recovered by centrifugal separation and reused at least in three cycles without any significant loss of their catalytic activities. Powder X-ray diffraction (PXRD) showed that the framework of In-MOF **2** remained almost unchanged after three reaction cycles (Figure S3 in the SI). Furthermore, as a bifunctional heterogeneous catalyst, In-MOF **2** shows catalytic reactivity comparable with that of nanocrystalline magnesium oxide[4g] under relatively low catalyst loadings.

Encouraged by the high yields observed in the Strecker reactions, we tested the catalytic activity of In-MOF **2** toward a transformation typically requiring Lewis acids. The Mannich-type reaction involves the reaction of an aldimine with a silyl ketene acetal and is one of the efficient methods for the formation of β-amino esters, which are versatile precursors in the synthesis of β-amino acids.[11] As shown in Scheme 4, in the presence of 30 mol % In-MOF **2**, unactivated silyl ketene acetal reacted with *N*-Boc-phenylaldimine at room temperature in $CDCl_3$ to afford the corresponding β-amino esters in 91.0% conversion yield after 90 h. When the reaction time lasted for 168 h, the conversion yield increased up to 96.9%.

Scheme 4. Mannich Reaction between *N*-Boc-phenylaldimine 3a and Silyl Ketene Acetal 6 Catalyzed by In-MOF 2



In addition, as a further demonstration of the utilities of the Strecker and Mannich reactions, the large-scale experiments of *N*-Boc-phenylaldimine were performed, providing the corresponding α-aminonitrile **5a** and β-amino ester **8** in 85% and 78% isolated yields, respectively (see the SI).

It was worth mentioning here that we are the first to use MOFs as recyclable heterogeneous catalysts in the synthesis of amine acid derivatives. The foregoing results demonstrate that the microporous In-MOF **2**, featuring a high concentration of Lewis acidic indium(III) sites on its internal surfaces, can catalyze both the Strecker and Mannich reactions of aromatic aldimines in high yields. Meanwhile, Lewis basic ether groups exposed in its pore walls can effectively activate TMSCN to enhance the nucleophilicity and reactivity of the cyano group. The successful application in the synthesis of amine acid derivatives of this bifunctional heterogeneous catalyst provides us a new idea to rationally design the structure of the catalyst. Further studies will focus on investigating the differences arising upon exchange of indium(III) for other reactive metal centers, such as scandium(III) and lanthanum(III) toward these reactions.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Syntheses of In-MOFs, ^1H, ^{13}C, and ^{29} Si NMR and MS spectra, PXRD patterns, syntheses of aldimines, and catalytic experiment. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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