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Induced Chirality in a Metal–Organic Framework by Postsynthetic Modification for Highly Selective Asymmetric Aldol Reactions

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A straightforward synthetic route to chiral metal–organic frameworks is proposed that relies on an acid–base interaction between an acid linker and a chiral primary amino acid derived diamine organocatalyst. High *ee* values for the aldol condensation of linear ketones and aromatic aldehydes are reported with this heterogeneous catalyst. Three consecutive catalyst reuse experiments demonstrated that the majority of the activity was preserved, as was the enantioselectivity.

Although organocatalysis with amino acids and their derivatives has proven very successful towards highly enantioselective condensation reactions, there is an urgent need to immobilize these elegant and bioinspired chiral catalysis for easy reuse. Many immobilization protocols that employ different organic and inorganic support materials have been discussed in the literature, and most of them follow a covalent anchoring strategy, sometimes with the prospect of using them in a flow setup.[1] Metal–organic frameworks (MOFs)[2] are among the most promising supporting materials: distinct from traditional inorganic materials, MOFs can be synthesized from a large variety of building blocks. In spite of the large degree of unpredictability in synthesis,[3] thousands of MOF structures have been reported to date.[4] Different strategies have been employed to prepare homochiral MOFs, including chiral-template and direct synthesis methods, either starting with enantiopure ligands or through self-resolution from achiral or racemic molecules.[5] The current methods for the synthesis of homochiral MOFs have shown limited flexibility: on the one hand, if the organocatalyst is used as a linker for MOF synthesis, catalysts with limited stability are formed owing to linker dimensions that are usually large. On the other hand, the templated approach is limited by the stability of the organocatalyst.[6]

In this work, we present a straightforward postfunctionalization based on the noncovalent immobilization of a phenylalanine-derived chiral ligand on a sulfated achiral MOF derivative through acid–base pair interaction. The presence of the organocatalyst in the MOF structure was confirmed with N_2 sorption measurements, FTIR spectroscopy, and thermal gravimetrical analyses. The morphology and framework of the solid chiral catalyst was characterized by SEM and X-ray diffraction, respectively. Very high enantioselectivities were obtained in the direct asymmetric aldol reactions of various linear ketones with aromatic aldehydes. The presented postsynthetic modification strategy is very practical, straightforward, and flexible towards the synthesis of a variety of chiral MOF structures with very high stability.

Postsynthetic modification[7] of a preassembled achiral MOF offers the advantage that a single, stable parental framework can be converted into an active chiral MOF by carefully selecting the suitable catalytic chiral units. In 2009, Banerjee et al. reported the synthesis of a chiral MOF by the attachment of L-proline-derived chiral ligands to the open metal coordination sites of MIL-101(Cr).[8] These homochiral MOFs were successfully used in direct asymmetric aldol reactions. However, despite reasonable activities in aldol reactions of ketones and aromatic aldehydes, the enantioselectivity of the resulting framework was low relative to that of other systems.[9] Previously, we reported the use of primary amino acid derived diamines with long alkyl tails as organocatalysts for direct *syn*-selective aldol reactions.[10] Such chiral amines have been demonstrated to be well suited for simple noncovalent immobilization on sulfonated solid supports such as Nafion through electrostatic interaction.[9e] In this approach, the acid acts as the anchor for the amine, but its acid strength also plays a crucial role in modulating the activity and stereoselectivity of the supported catalyst.

Building on the successful immobilization experiments with the use of sulfonate-functionalized solid acids, herein we present the first postmodification of a unique sulfated MIL-101(Cr), denoted S-MIL-101(Cr), with chiral diamine organocatalysts through acid–base interaction (Figure 1). As described recently, treatment of preassembled MIL-101(Cr) with a stoichiometric mixture of triflic anhydride and sulfuric acid results in an acidic framework with Brønsted sulfoxy acid groups attached to 20% of the aromatic terephthalate linkers.[11] This novel

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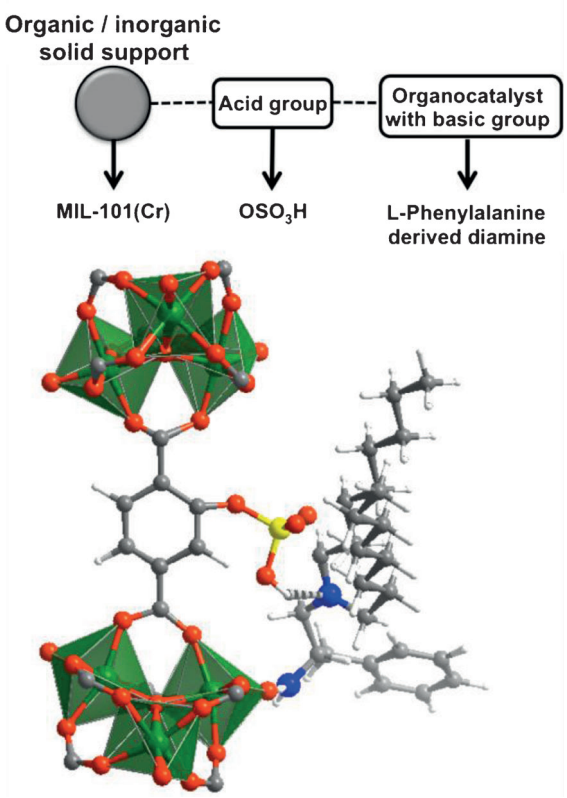


Figure 1. Schematic representation of the postsynthetic modification of a sulfated MIL-101(Cr) with a chiral primary amino acid derived diamine by acid–base interaction.

S-MIL-101(Cr) has been employed as an acid catalyst in the esterification of *n*-butanol with acetic acid.[11,12] By subsequent noncovalent immobilization of a chiral diamine ligand [i.e., 2-(*S*)-amino-3-phenylpropanoic acid dioctylamine] on the sulfoxy acid groups of S-MIL-101(Cr), a MOF bearing chiral catalytic functionalities was created.

The presented postmodification strategy is straightforward and versatile towards the synthesis of a variety of chiral MOF structures. Although this communication particularly demonstrates its use in catalyzing direct asymmetric aldol reactions of ketones and aldehydes with very high enantiomeric excess (*ee*) values, the range of potential catalytic applications is much broader. Synthesis of the diamine/S-MIL-101(Cr) is simply performed by dropwise addition of the diamine solution to a suspension of S-MIL-101(Cr) in, for example, diethyl ether or another polar volatile solvent of choice, followed by evaporation of the solvent (for details see the Supporting Information). Characterization of the diamine/S-MIL-101(Cr) was accomplished by using a range of standard techniques including N_2 physisorption, XRD, thermogravimetric analysis (TGA), FTIR spectroscopy, and SEM. The XRD pattern of the diamine/S-MIL-101(Cr) material is similar to that of the MOF without the diamine (see Figure 2a), which indicates that the parental framework structure after immobilization of the diamine ligand is retained. The intensity of the diffraction peaks at approximately $2\theta < 4$ is considerably lower if the amine is adsorbed: the rela-

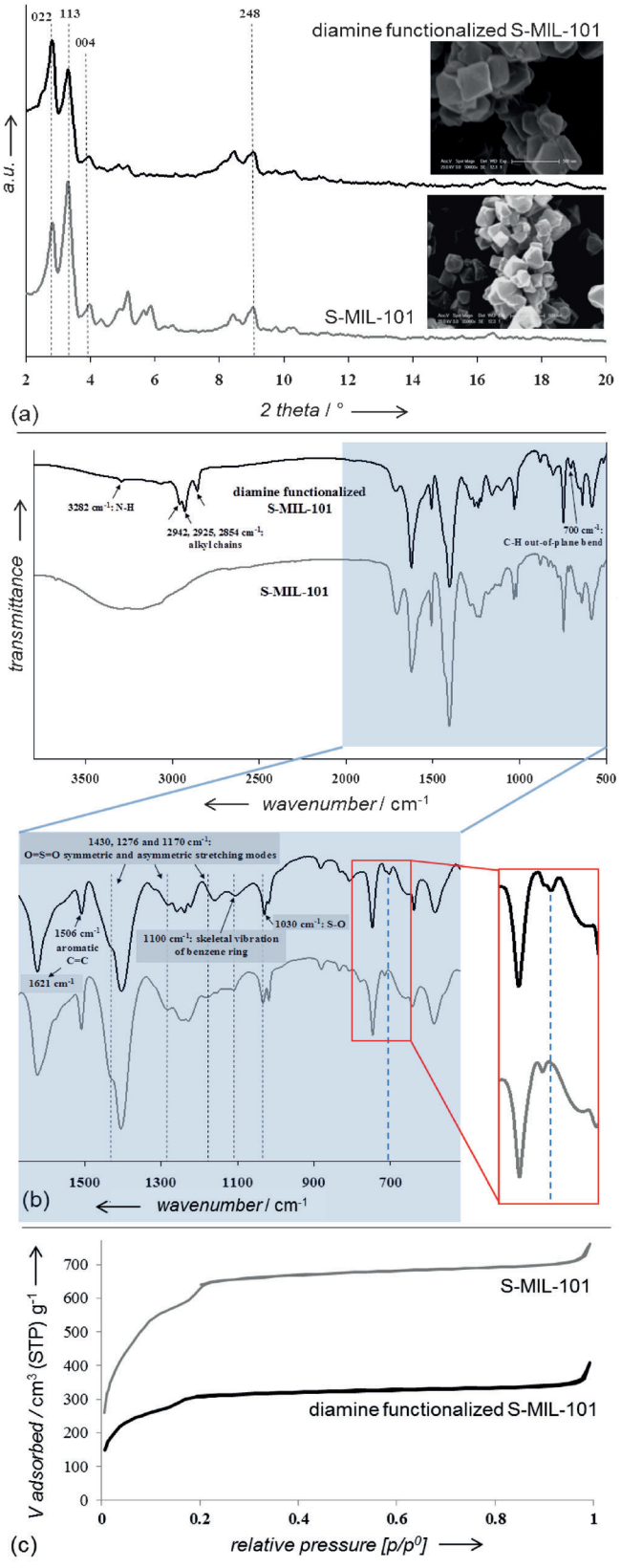


Figure 2. Physicochemical characterization of the chiral diamine modified S-MIL-101(Cr) versus S-MIL-101(Cr): a) X-ray diffractogram with SEM images given in the inset, b) FTIR spectra with zoom-in regions, and c) N_2 physisorption.

tive intensity of reflections [022], [113], and [222] is also clearly affected. We attribute this intensity change to the successful encapsulation of the amine unit in both the middle and the large cavities, which is in line with results presented earlier by Férey et al. after impregnation of heteropoly acids in MIL-101(Cr)[13] and by Canioni et al. after encapsulation of other HPAs in MIL-100(Fe).[14]

Similar crystal morphologies measured by SEM before and after treatment with the diamine ligand confirm the stability of the crystals and the absence of additional phases resulting from nonabsorbed diamine (Figure 2a, see also Figure S3 in the Supporting Information). The IR spectrum of the diamine/S-MIL-101(Cr) shows additional bands at 2942, 2925, and 2854 cm^{-1}, which represent the alkyl chains of the diamine, and at 3282 cm^{-1}, which corresponds to one of the N–H stretching bands (compare Figure 2b with Figure S4c).

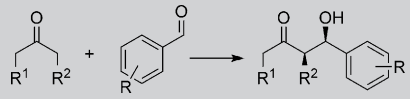
In the fingerprint region, a small band appears at 700 cm^{-1} that represents one of the C–H out-of-plane bending modes of the diamine benzyl group. The bands at 1621 and 1506 cm^{-1} in Figure 2b corresponding to the C=C modes of the aromatic rings in S-MIL-101(Cr) are maintained after functionalization with the diamine. Further, the bands at 1276 and 1170 cm^{-1} along with the characteristic shoulder at 1430 cm^{-1}, which are attributed to O=S=O symmetric and asymmetric stretching modes, can still be observed after postmodification, as can the band at 1100 cm^{-1} corresponding to the interplane skeletal vibration of the sulfoxy acid substituted benzene ring.[11] The S–O stretching band at 1030 cm^{-1} is slightly changed, which is indicative of the interaction of the sulfonic acid hydrogen atom with the tertiary amine nitrogen atom of the chiral ligand.

As could be expected, diamine/S-MIL-101(Cr) contains a larger carbon fraction than the parent MOF, as determined by TGA analysis and in agreement with the amount of added binding complex (see Figure S5 and calculations). TGA analysis also suggests the presence of diamine in the pores of S-MIL-101(Cr), as without the diamine more water was released from the pores relative to that released by diamine-functionalized S-MIL-101(Cr). The N_2 physisorption data in Figure 2c clearly show a reduced micropore volume owing to diamine grafting. Together with the IR spectroscopy data, these results indicate the successful attachment of the chiral diamine ligand in the porous MOF structure.

The catalytic performance of the diamine immobilized on S-MIL-101(Cr) was evaluated in asymmetric aldol reactions of various linear ketones and aromatic aldehydes. First, the supported diamine was applied in the model reaction with 2-butanone and the reaction conditions were optimized. As shown in Table 1, fairly high activity and very high enantioselectivity for the *syn* product were obtained in the model reaction with 15 mol% diamine/S-MIL-101(Cr) under neat conditions (Table 1, entries 1 and 2). Neither increasing the aldehyde concentration (Table 1, entry 3) nor raising the temperature (Table 1, entry 4) had a beneficial influence on either the activity or the stereoselectivity of the diamine/S-MIL-101(Cr) catalyst. Next, the model reaction was catalyzed by the diamine in the presence of the original, non-sulfated MIL-101(Cr) framework as the acid support (Table 1, entry 5). Despite high stereoselectivity, the activity of the organocatalyst was significantly reduced compared to the reaction with the sulfated MOF, which yielded only 18% of the aldol product after a reaction time of 20 h. Note that the latter experiment was similar to aldol reactions performed with the homochiral postmodified MIL-101(Cr) as described by Banerjee et al., though with a primary amino acid derivative instead of a proline-based ligand as the chiral unit.[8] Interestingly, the activity of the diamine catalyst is clearly higher with the sulfated MOF than with the previously investigated commercial sulfonated silica-polymer Nafion SAC-13 as support (Table 1, entry 6),[9e] with 53 versus 38% yield after a reaction time of 20 h, than with the sulfonated carbon and homemade resins,[9e] though the reason is not yet clear.

Ultimately, the scope of the diamine/S-MIL-101(Cr) catalyst was extended to other substrates (Table 1, entries 7–15). With 2-butanone, 3-pentanone, and hydroxyacetone as ketone donors, good activities and fair to outstanding stereoselectivities were achieved. For instance, in the reaction of hydroxyacetone and 4-trifluoromethylbenzaldehyde a very high yield and enantiomeric excess of 95% for the *syn* product were observed (Table 1, entry 15). With acetone and 2-pentanone (Table 1, entries 11 and 12), the catalytic performance of diamine/S-MIL-101(Cr) was somewhat limited, inherent to the homogeneous

Table 1. Aldol reactions of linear ketones and aromatic aldehydes catalyzed by diamine/S-MIL-101(Cr).[a]



Entry	R^1, R^2, R^3	Solid acid	Time [h]	Yield[b] [%]	*dr*[b] *syn/anti*	*ee*[c] [%]
1	H, CH_3, 4-CF_3	S-MIL-101	20	53	5:2	96
2	H, CH_3, 4-CF_3	S-MIL-101	44	83	2:1	93
3[d]	H, CH_3, 4-CF_3	S-MIL-101	20	52	2:1	93
4[e]	H, CH_3, 4-CF_3	S-MIL-101	20	89	3:2	89
5	H, CH_3, 4-CF_3	MIL-101	20	18	7:2	96
6[f]	H, CH_3, 4-CF_3	Nafion SAC-13	20	38	5:2	98
7	H, CH_3, 2-NO_2	S-MIL-101	20	91	5:2	90
8	H, CH_3, 4-NO_2	S-MIL-101	20	95	4:1	78
9	H, CH_3, 2-Cl	S-MIL-101	20	87	3:1	97
10	CH_3, CH_3, 4-CF_3	S-MIL-101	90	49	3:1	94
11	H, H, 4-CF_3	S-MIL-101	20	82	–	62
12[g]	H, CH_2CH_3, 4-CF_3	S-MIL-101	40	78	2:1	61
13	H, OH, 2-NO_2	S-MIL-101	40	73	11:1	95
14	H, OH, 4-NO_2	S-MIL-101	40	70	4:1	87
15	H, OH, 4-CF_3	S-MIL-101	20	97	5:1	95
16[h]	H, OH, 4-CF_3	S-MIL-101	24	94	5:1	93
17[h]	H, OH, 4-CF_3	S-MIL-101	26	93	5:1	94
18[h]	H, OH, 4-CF_3	S-MIL-101	30	90	5:1	92

[a] All reactions were performed under neat conditions in ketone with aldehyde (0.125 M), diamine (15 mol%), and solid acid (15 mol%) at room temperature, unless indicated otherwise. [b] Determined by GC (chiral stationary phase) or ^{1}H NMR spectroscopy. [c] The *ee* of the major *syn* isomer, as determined by GC or HPLC on a chiral stationary phase. [d] With 0.25 M aldehyde. [e] Reaction at 45 °C. [f] See Ref. [10]. [g] Regioisomeric ratio branched/linear = 2:5. [h] Entries 16–18: three consecutive reuses of the catalyst used in entry 15.

complex, but this was also observed with previous heterogeneous catalysts such as Nafion as a solid acid.[9e,10]

To exclude significant leaching of the chiral ligand during catalytic reactions, the ^{1}H NMR spectra of the filtered reaction solutions and the diamine catalyst were compared region by region. In Figure S6, the regions from 3.2 to 2.0 ppm of the ^{1}H NMR spectra of the diamine and the reactions mixtures with different ketones are displayed. The absence of characteristic signals of the diamine in the ^{1}H NMR spectra of the filtrate solutions suggests that catalysis occurs mainly in a heterogeneous manner.

As catalyst reuse is a vital requirement for every heterogeneous catalyst, the chiral MOF (of Table 1, entry 15) was washed after reaction and reused in three consecutive reactions under identical conditions (i.e., Table 1, entries 16–18). A slight deactivation was witnessed, as longer reaction times were needed to achieve yields $>90\%$. However, the majority of the activity was preserved, as was the enantioselectivity.

In summary, we presented a new strategy for the synthesis of MOFs bearing chiral functionalities by postsynthetic modification of an achiral parental MOF. Within this approach, an L-phenylalanine-derived diamine was immobilized on a sulfated MIL-101(Cr) framework through acid–base pair electrostatic interaction. The resulting chiral MOF exhibited good activity and excellent enantioselectivities in direct asymmetric aldol reactions of linear ketones and aromatic aldehydes. We believe that this synthesis method is an elegant and practical method to obtain MOFs with chiral properties, as synthetic efforts for the parent MOF are limited. The modular and combinatorial nature of the immobilization technique enables the fine-tuning of both the chiral ligand and the supporting MOF. In addition, the combination of this chirality induction with the intrinsic catalytic properties of some MOF materials paves the way to the design of multifunctional catalytic MOFs with potential application in one-pot multistep synthetic processes.

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