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Short communication

Immobilisation of catalytically active proline on H_2N-MIL-101(Al) accompanied with reversal in enantioselectivity

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ABSTRACT

Proline-functionalized H_2N-MIL-101(Al) was synthesized from L- or D-proline-terephthalic acid and used in the catalytic aldol reaction of *p*-nitrobenzaldehyde with acetone to achieve up to 95% conversion and an ee-value of 29% but in a reversal in enantioselectivity compared to the reaction under homogeneous L- or D-proline organocatalytic condition.

1. Introduction

Metal-organic frameworks (MOFs) are a class of highly porous and crystalline hybrid materials consisting of metal atoms or clusters, which are connected by organic linkers [1]. The term MOF was established by Yaghi et al. [2]. Since then this class of materials got tremendous attention [1,3]. Applications envisioned for MOFs include drug delivery [4], separation processes [5], sensing by luminescence [6], hosts for catalytic metal nanoparticles [7] and water adsorption for heat transformation [8]. Further, MOFs offer the opportunity for enantioselective heterogeneous catalysis [9].

It is possible to design MOFs with well-defined characteristics and to build in various functional groups including privileged ligands with catalytically active chiral metal centers so that MOFs act as hosts and thereby resemble enzymes [10].

Incorporation of chiral amino acids is one way to synthesize chiral MOFs [11]. The amino acid L-proline is a thoroughly used organocatalyst for aldol-, Mannich- and Michael-reactions [12]. The incorporation of L-proline in a MOF by using a Boc-proline-functionalized linker was carried out by Telfer et al. [13] and Kaskel et al. [14]. They used an aminobiphenyldicarboxylate ligand in DUT-32, which was modified with Boc-protected proline. However, during the thermal deprotection Kaskel et al. observed that racemization of the stereocenter occurred [14]. The successful Boc-deprotection was reported by Canivet et al. who used post-synthetic modification (PSM) to modify MOFs with proline and short peptide chains [15]. However, the surface area of the obtained L-Pro-modified H_2N-MIL-101(Al) with 15 mol% L-Pro-terephthalate ligands was only 330 m^2/g [15].

To avoid these drawbacks in our approach we used a ligand mixture of 2-(pyrrolidine-2-carboxamido)terephthalic acid (L-Pro-bdcH_2 or D-Pro-bdcH_2) and 2-aminoterephthalic acid (H_2N-bdcH_2) (Fig. 1) to synthesize L-Pro/H_2N-MIL-101(Al) with varying amounts of the mixed ligands. We also employed the Boc-protected building block 2-(1-(*tert*-butoxycarbonyl)pyrrolidine-2-carboxamido)terephthalic acid (Boc-L-Pro-bdcH_2) to obtain L-Pro-MIL-101(Al) by in-situ deprotection caused by the Lewis-acidic aluminum ions [16]. From Boc-L-Pro-bdc only the L-Pro-bdc linker is incorporated in the resulting L-Pro-MIL-101(Al) (Fig. S3 in Supp. Info.).

H_2N-MIL-101(Al) was chosen because of its high pore volume and because it does not catalyze the chosen aldol addition reaction significantly.

2. Experimental

The MIL-101(Al) MOFs were synthesized according to a previously reported procedure [17]. The functionalized ligand L-Pro-bdc was used in 10, 20, and 30 mol%, respectively; D-Pro-bdc was used in 30 mol% (Table 1). The functionalized linker was synthesized in analogy to literature [18]. The actual amount of incorporated ligand in the mixed-ligand MIL products was determined from solution NMR spectra of the

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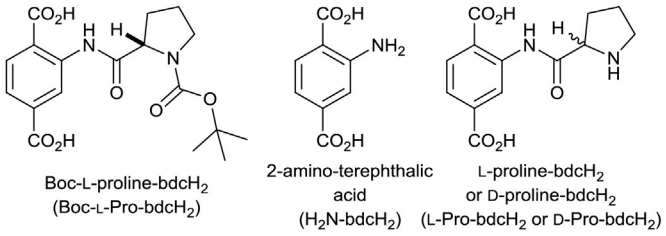


Fig. 1. Linkers used in the synthesis of proline- and amino-modified MIL-101(Al).

product dissolved ("digested") in NaOD/D_2O (see Supp. Info. for details and Table 1).

For catalysis studies, 50 mg (0.33 mmol) 4-nitrobenzaldehyde were dissolved in 2 mL (27 mmol) of acetone. To the reaction mixture 40 μL (2 vol%, 2 mmol) water were added to enhance the reaction rate [19]. When using a larger amount of water a negative influence on the ee value had been reported [20]. After adding the catalyst, the mixture was stirred at 30 °C in a water bath.

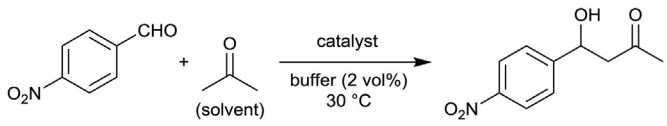
Compound 22-L-Pro/H_2N-MIL-101(Al) containing 22 mol% L-proline-functionalized ligands (Table 1, entry 5) was used for the aldol reaction of 4-nitrobenzaldehyde with acetone to determine the enantioselective induction (Scheme 1). The reaction progress was monitored using chiral HPLC (see Supp. Info.). Product identification was based on comparison of the retention times with the products which were synthesized using L-proline in a homogeneous reaction.

3. Results and discussion

From the L-Pro-bdc or D-Pro-bdc ligand less than the offered amount was incorporated (Table 1). This is in accordance to literature results, where in mixed-ligand MOF synthesis the bulkier ligand was usually deficient in the MOF product [21].

As the in-situ loss of the protecting group from Boc-L-Pro-bdc during synthesis resulted in L-Pro-MIL-101(Al) we also tried to use L-Pro-bdc directly as single ligand in the MIL synthesis but only a non-porous product could be obtained. Employing the aforementioned mixture of L-Pro-$bdcH_2$ (up to 30 mol%) and 2-aminoterephthalic acid, H_2N-$bdcH_2$ proved more successful. An attempt to increase L-Pro-bdc to 40 mol% resulted in a jelly product.

The values of the surface areas of the L- and D-Pro/H_2N-MIL-101(Al) MOFs with different amounts of proline functionalization do not follow the expected decrease with increasing proline content. Compounds L-Pro and D-Pro/H_2N-MIL-101(Al) have the same BET surface areas of around 1900 m^2/g within experimental error, which is about ±50 m^2/g in this area region (Table 2). It was checked and ensured



Scheme 1. Aldol reaction of 4-nitrobenzaldehyde with acetone in the presence of 22-L-Pro/H_2N-MIL-101(Al) as catalyst.

that the nitrogen adsorption isotherms were evaluated in the same pressure region (p/p_0 = 0.05–0.20) for the BET plot from which the BET surface area was derived (See Supp. Info., Fig. S3).

The 22-L-Pro/H_2N-MIL-101(Al)-catalyzed reaction resulted in a conversion of 4-nitrobenzaldehyde of ca. 73% after 1 d (Table 2) and 95% after 4 d (Fig. 2, Table 2) when using 13 mol% catalyst (based on proline moieties). This has to be compared with non-functionalized H_2N-MIL-101(Al) which resulted in a conversion of the aldehyde below 10% after 7 d (Fig. 2). The value of the enantiomeric excess of 29% ee when using 22-L-Pro/H_2N-MIL-101(Al) is in good accordance to the literature [13]. Using L-Pro-MIL-101(Al) containing solely the proline-functionalized ligand (Table 2, entry 5) does not increase the ee. Instead the reaction is slowed down presumable because of inaccessible and congested pores through the bulky proline groups (cf. S_{BET} = 460 m^2/g in Table 1). The heterogeneous nature of the MIL catalyst was proven by filtration after 24 h, with no significant increase in conversion being observable in the filtrate in the absence of the MIL catalyst. The increase in conversion was below 3% over 7 d (Fig. S15 in Supp. Info.).

Noteworthy, L-Pro/H_2N-MIL-101(Al) gave the *S*-configured aldol product in 29% ee (see Table 2, entry 4). This is a remarkable case of reversal in enantioselectivity as the organocatalyst L-proline under homogeneous conditions affords the *R*-configured aldol product in 66% ee [22]. For a better understanding of the catalyst action and enantio-control, the dimethyl ester of the proline-modified terephthalate ligand (Pro-$bdcMe_2$) was also tested in the aldol reaction under homogeneous conditions (Table 2, entries 2 and 7) [23]. Herein, the same *R*-configured product enantiomer was formed, albeit in a lower enantioselectivity (21% ee compared to 66% ee, when L-proline was employed). This observation is in line with the assumption of the electron-deficient amide acting as a hydrogen bond donor to the aldehyde in a similar fashion than the free carboxylic acid in proline.

Recently, Kaskel et al. reported proline-functionalized UiO-67 and -68 as catalysts in the aldol addition reaction between cyclohexanone and 4-nitrobenzaldehyde where they observed a reversal of diastereoselectivity compared to the homogeneous organocatalyst proline but no enantioselectivity was found [24]. This change in selectivity seems to be an effect of the catalytically active proline moiety confinement. Such an effect may be expected if the catalyst strongly interacts with the pore surface and the pore size matches [25]. Kaskel et al.

Table 1
Results of NMR analysis and BET measurements of functionalized MIL-101(Al) products.

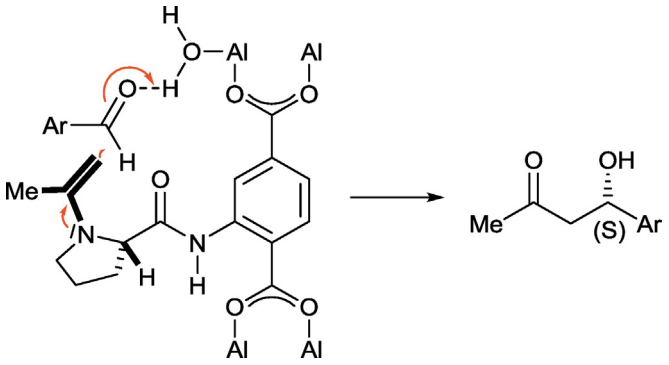
Entry	Ligands used in synthesis [mol%][a]	Product[b]	BET-surface area [m^2/g][c]
1	H_2N-$bdcH_2$	H_2N-MIL-101(Al)	2680[d]
2	Boc-L-Pro-$bdcH_2$	L-Pro-MIL-101(Al)	460
3	10:90 L-Pro-: H_2N-$bdcH_2$	9-L-Pro/H_2N-MIL-101(Al)	2110
4	20:80 L-Pro-: H_2N-$bdcH_2$	17-L-Pro/H_2N-MIL-101(Al)	1940
5	30:70 L-Pro-: H_2N-$bdcH_2$	22-L-Pro/H_2N-MIL-101(Al)	1950
6	30:70 D-Pro-: H_2N-$bdcH_2$	14-D-Pro/H_2N-MIL-101(Al)	1840

[a] Molar ratio used in case of mixed-ligand synthesis.
[b] The number in front of the L- or D-Pro-bdc ligand gives the experimentally determined mol percentage of the proline ligand determined from solution NMR spectra after digestive dissolution in NaOD/D_2O.
[c] For sorption isotherms and pore volumes see Supp. Info.
[d] BET in literature for H_2N-MIL-101(Al) is given as 3099 m^2/g [17].

Table 2
Catalytic aldol reaction results.

Entry	Catalyst[a]	Total conversion after 24 h [%]	yield of addition product after 24 h [%]	ee [%] (major enantiomer)
1	L-proline	>98	>97	66 (R)
2	L-proline-bdcMe$_2$	>95	>94	21 (R)
3	H$_2$N-MIL-101(Al)	<5	<2	–
4	22-L-Pro/H$_2$N-MIL-101(Al)	73	63	29 (S)
5	L-Pro-MIL-101(Al)	12[b]	10	10 (S)
6	D-proline	>98	>97	60 (S)
7	D-proline-bdcMe$_2$	>95	>94	20 (S)
8	14-D-Pro/H$_2$N-MIL-101(Al)	44	31	28 (R)

[a] 15 mol% of catalyst except for 22-L-Pro/H$_2$N-MIL-101(Al) where 13 mol% catalyst was used and 11 mol% of 14-D-Pro/H$_2$N-MIL-101(Al), respectively.
[b] Conversion after 4 d.



Scheme 2. Rational for the stereochemical outcome in the aldol addition reaction of acetone and nitrobenzaldehyde catalyzed by L-Pro/H$_2$N-MIL-101(Al).

suggested mechanistic differences caused by Lewis-acidic MOF clusters, pore wall interactions or additional interactions with neighboring proline functionalities [24]. Earlier, Banerjee et al. used an L-proline-functionalized ligand coordinated to a free metal site in MIL-101(Cr) and found that the expected *R*-enantiomer was formed preferentially [26].

While changes in enantioselectivity are commonly observed using different catalysts or reaction conditions, the formation of the opposite enantiomer in this case may hint at a change in electrophile activation as shown in Scheme 2. By coordination of the aldehyde to the metal cluster via a hydrogen bond to an aqua ligand its *Si*-side is preferentially attacked by the enamine. It appears that coordination of the aldehyde does not occur from the metal center adjacent to the proline substituent due to significant ring strain but from the distant one. The interaction of two neighboring proline groups is less likely due to the mixed-linker approach where only 22% or even 14% are proline-functionalized linkers in L-Pro/H$_2$N-MIL-101(Al) or D-Pro/H$_2$N-MIL-101(Al), respectively.

For testing the MIL-catalyst stability three recycling runs were carried out. For 22-L-Pro/H$_2$N-MIL-101(Al) the conversion was reduced from 95% to ca 70% after the 3rd run (Fig. 3). The ee values remained nearly constant. For 14-D-Pro/H$_2$N-MIL-101(Al) recycling resulted in a greater loss of conversion and the ee value also dropped significantly. Also in related work of MOF-catalyzed aldol reactions recycling led to decrease in conversion [24]. The PXRD showed that the 14-D-Pro/H$_2$N-MIL-101(Al) remained crystalline but for 22-L-Pro/H$_2$N-MIL-101(Al) there are substantial structural changes probably due to degradation in the presence of water (Fig. S18 in Supp. Info.). The parent MOF H$_2$N-MIL-101(Al) is not water-stable [27]. After three runs a loss in porosity in the MIL-101(Al) (Table S5, Supp. Info.) can be explained by this MOF degradation and less by reaction components remaining inside the pores. Digestive dissolution of the MIL-101(Al) after the third run afforded a solution with a distinctive yellow color, possibly from a strong chromophore like the α,β-unsaturated ketone evolving from the aldol product but the ^{1}H NMR spectrum did not show significant impurities (Fig. S19, Supp. Info.).

In previous reports by other groups using the same MIL-101(Al) there have been comparable degrees of functionalization, but with a greater loss of porosity and less conversion [15]. Telfer et al. achieved the same result in the described aldol reaction regarding the ee value and the conversion but they used a cubic Zn IRMOF.

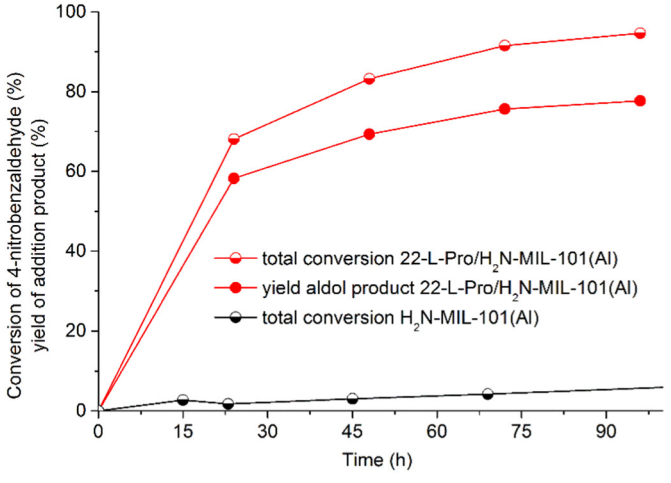


Fig. 2. Time-conversion plot for the aldol reaction with-22-L-Pro/H$_2$N-MIL-101(Al) and H$_2$N-MIL-101(Al) as catalyst. Values for total conversion of 4-nitrobenzaldehyde and yield of aldol addition product are average values from two independent runs. Conditions: 30 °C, 13 mol% 22-L-Pro/H$_2$N-MIL-101(Al), and 15 mol% H$_2$N-MIL-101(Al), respectively. The difference between total conversion and the formation of the aldol product is due to the by-product (E)-4-(4-nitrophenyl)but-3-en-2-one (see Supp. Info.)

4. Conclusions

In summary, we presented the synthesis of chiral proline-functionalized MIL-101(Al) by using a ligand mixture of 2-aminoterephthalic acid and the proline-functionalized derivate. For a heterogeneous catalyst, high yields in a short amount of time were obtained by making use of the incorporated catalytically active proline moieties in an aldol reaction. Though proline as homogenous catalyst offers an even faster conversion our heterogeneous catalyst offers the advantage of easy separation and recycling. A main feature is the observed reversal in

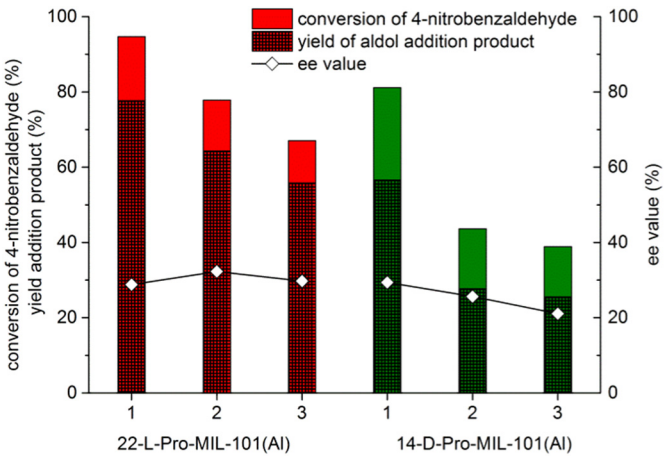


Fig. 3. Conversion in the aldol addition and ee value for three recycling runs. Conditions: 30 °C, 4 d, 13 mol% 22-L-Pro/H$_2$N-MIL-101(Al) or 11 mol% 14-D-Pro/H$_2$N-MIL-101(Al), respectively.

enantioselectivity compared to the aldol reaction when conducted under homogeneous conditions.

Appendix A. Supplementary data

Supplementary data associated with this article (synthesis and characterization details, results from catalysis, including HPLC chromatograms, NMR spectra, PXRDs and sorption isotherms) can be found, in the online version, at http://dx.doi.org/10.1016/j.catcom.2017.02.027.

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