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Short communication

L-proline functionalized pillar-layered MOF as a heterogeneous catalyst for aldol addition reaction

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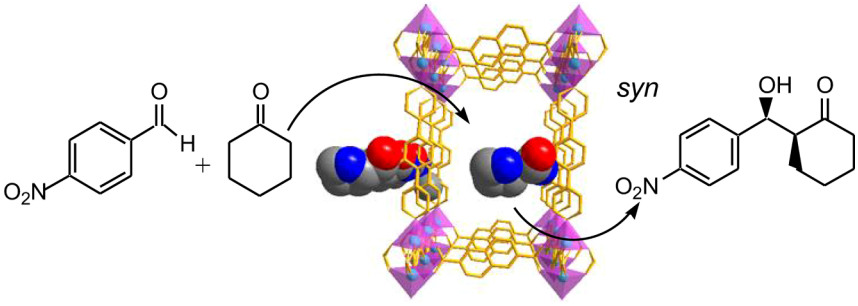
GRAPHICAL ABSTRACT

A pillar-layered chiral MOF catalyst, [Zn_2(2,6-ndc)$_2$(bpb-NHPro)], was synthesized by the self-assembly of Zn(II) with proline-functioned ligand (bpb-NHPro) and 2,6-naphthalenedicarboxylic acid (H_2ndc), and showed excellent yield up to 98% in aldol addition, preferring *syn*-adduct with excellent diastereomeric excess up to 98:2 (syn:anti).



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ABSTRACT

A pillar-layered proline-functionalized MOF, [Zn_2(2,6-ndc)$_2$(bpb-NHPro)] (**I**), was synthesized through a solvothermal reaction of $Zn(NO_3)_2$ with 1-L-Pyrrolidine-2-carboxamide-2, 5-bis(4-pyridyl)benzene (bpb-NHPro) and 2,6-naphthalenedicarboxylic acid (H_2ndc) in N,N-diethyl formamide (DEF). The aldol addition between cyclopentanone and 4-nitrobenzaldehyde was selected as a model reaction for the estimation of the catalytic performance of **I**, which showed reversed diastereoselectivity, preferring *syn*-adduct, in contrast to homogeneous catalysis with excellent yield up to 98% and diastereomeric excess up to 98:2 (syn:anti).

Metal-organic frameworks (MOFs), which are the materials featuring high porosity, large surface area and considerable capacity to accommodate guest molecules, have caught much attention due to their attractive applications in different fields such as sensing, gas storage, separation, and catalyst [1–4]. MOFs provide an attractive platforms as heterogeneous catalysts because of the well-defined pore geometry, active-site uniformity and structural variability.

L-Proline and its derivatives, the most privileged asymmetric organocatalysts, have been used for catalyzing some important C—C coupling reactions, such as asymmetric Mannich, Michael and aldol reaction [5]. As a homogeneous catalyst, L-Proline exhibits high catalytic activity and selectivity but is difficult to recover and reuse. In order to overcome the disadvantages, supported proline and proline-derivatives as recyclable homogeneous (*e.g.* PEG or Ionic liquid-supported) and heterogeneous (*e.g.* polystyrene or silica-supported) catalysts have been studied [6]. The asymmetric aldol reactions, catalyzed by proline functionalized MOFs as heterogeneous catalysts, have attracted much interests, since the modular structure of MOFs allows

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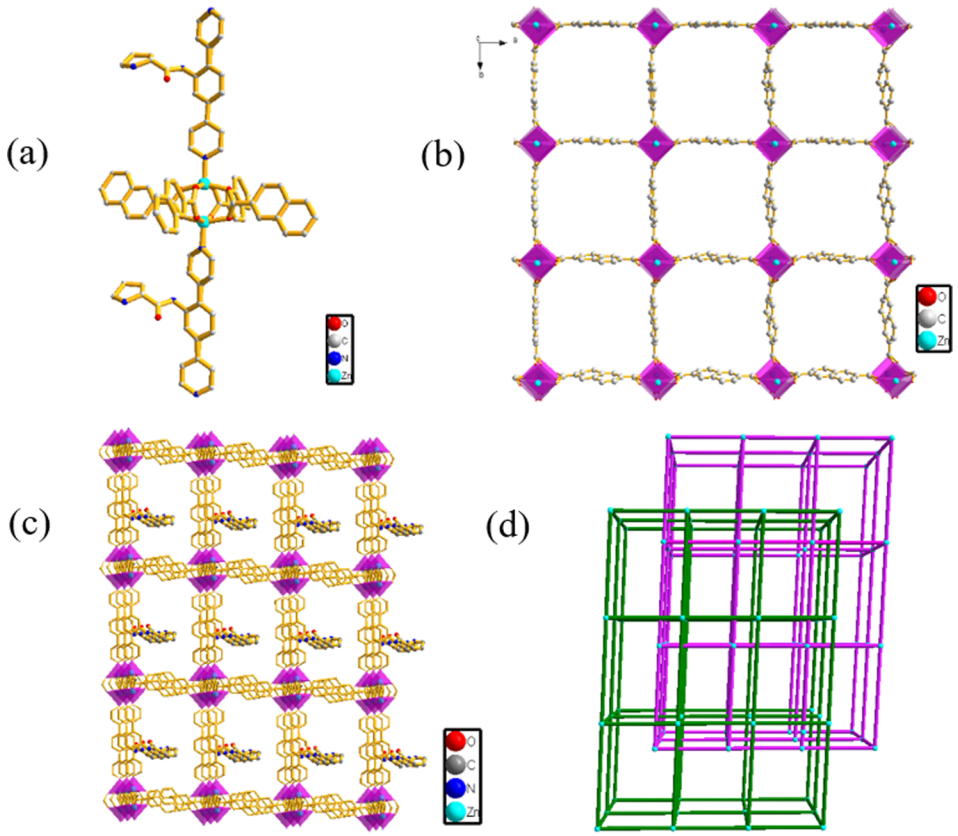


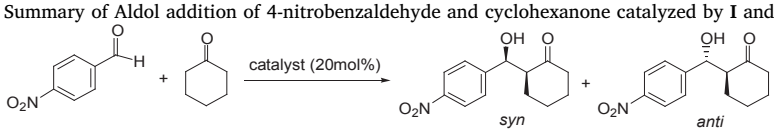
Fig. 1. (a) Coordination environment of [Zn2(2,6-ndc)2(bpb-NHPro)]. The hydrogen atoms are omitted for clarity; (b) Flat structure formed by SBUs and 2,6-ndc; (c) View of 3D framework of a single net; (d) Schematic representation of 2-fold interpenetrating 3D framework.

well-defined functionalization by linker design and postsynthetic modification. However, only a few reports on proline functionalized MOFs used as heterogeneous catalysts for asymmetric aldol reaction have been given to date [7–17].

Generally, three approaches anchoring L-proline onto MOF are applied to create the chiral heterogeneous catalysts. One possible approach to obtain proline-functionalized MOF is post-synthetic modification of MOF through amide reaction between amino group on the linkers and carboxyl group of L-proline [7–9], or coordination to the open metal sites of the cluster in MOF by exchanging the coordinated H_2O molecule with pyridine-containing proline-derivatives [10]. The approach of simultaneous synthesis is also adopted to prepare the proline-functionalized MOF by solvothermal reaction of metal centre together with carboxylate and L-proline or its derivatives [11,12]. A widely used approach is pre-synthetic modification, by direct grafting proline onto organic polycarboxylate backbone via amide bond before the formation of framework [13–17]. For example, Telfer et a reported a proline functionalized IRMOF by using a Boc-protected proline derived biphenyl-4,4′-dicarboxylate, deprotection of the proline can be triggered by heating to generate IRMOF-Pro [13]. However, racemization may occur when deprotection of the thermolabile Boc-group at a high temperature over 100 °C. IRMOF-Pro was applied in aldol reaction between cyclopentanone and 4-nitrobenzaldehyde showing ee-values of 3% and 14% for *syn* and *anti* isomers respectively, and diastereomeric excess of 25:75 (*syn*:*anti*). Later, several proline-containing multicomponent frameworks, MUF-77, were designed and synthesized by Telfer group using three-component carboxylate linkers [14]. The asymmetric aldol transformation of 4-nitrobenzaldehyde and acetone/cyclopentanone, catalyzed by MUF-77, was utilized to explore the correlations between pore environment around the site of catalysis and the catalytic activity, and the results showed that the preferred enantiomer of both diastereomers could be reversed by switching the location of the catalytic group in the MOF. Kaskel et al reported a highly porous chiral Zn-MOF (DUT-32-NHProBoc), which prepared by solvothermal reaction of Zn(II) with Boc-protected proline-functionalized biphenyl-4,4′-dicarboxylate and tritopic carboxylate coligand, and then catalytic activity of deprotected DUT-32-NHPro was examined in aldol addition between 4-nitrobenzaldehyde and cyclohexanone. Unfortunately, the catalytic results showed no specific stereoselectivity between *syn* and *anti* adducts, which attributed to the racemization during the deprotection process of DUT-32NHProBoc [15]. Furthermore, the same group also reported proline functionalized Zr-MOFs (UiO-67 and UiO-68) by pre-synthetic modification of biphenyl-4, 4′-dicarboxylate and triphenyl-4, 4′-dicarboxylate [16]. Both MOFs showed opposite diastereoselectivity in aldol addition, preferring *syn*-aldol adduct formation for reaction of cyclohexanone with 4-nitrobenzaldehyde, in contrast to homogeneous catalysis preferring the *anti*-aldol adduct, but the aldol adducts were nearly racemic. Our group [17] recently reported a proline functionlized MOF (PCN-261-NHPro), which was constructed by directly using deprotected proline tritopic carboxylate, avoiding the possible racemization in thermal deprotection of MOF-NHProBoc as reported in literatures [13–16]. Like UiO-67/68, PCN-261-NHPro also showed reversed diastereoselectivity in aldol reaction compared to L-proline as a homogeneous catalyst, but performed very low enantioselectivity.

The reported proline functionalized MOFs are built on the framework of MIL, UiO, INFORM, MUF and PCN, in which there exist different types of pores like tetrahedral and octahedral pores, and show a moderate to good diastereoselectivity as well as yiled, but an unsatisfactory enantioselectivity in heterogeneous asymmetric aldol addition. However, the construction of pillar-layered MOFs with cubic pores by incorporation of proline moieties remains an unexplored and may offer great potential. In this work, we demonstrate the assembly of an L-proline functionalized pillar-layered MOF and its application in

Table 1
Summary of Aldol addition of 4-nitrobenzaldehyde and cyclohexanone catalyzed by **I** and comparison with other Proline-functionalized MOF.



No.	Catalyst	Solvent	Yield[a] (%)	ee[b] (%) syn anti	Dr[b] (syn:anti)
1	bpb-NHPro	DCM	64	19 62	14:86
2	**I**	DCM	25	1 25	51:49
3	**I**	EtOH	65	1 5	61:39
4	**I**	DMF	72	0 10	98:2
5	**I**	DMSO	98	2 4	63:37
6	**I**	Cyclohexanone	23	4 5	68:32
Ref. [11]	Uio-66-LP-120	Methanol	95[c]	0 4	82:18
Ref. [13]	IRMOF-Pro	Cyclohexanone	n.d.	3 14	25:75
Ref. [14]	DUT-32-NHPro	DCM	n.d.	0 0	50:50
Ref. [15]	UiO-68-NHPro	EtOH	97	0 0	88:12
Ref. [16]	PCN-261-NHPro	Cyclohexanone	51	1.6 3.5	60:40

Reactions conditions: 40 °C, 5 days, 0.25 mmol of 4-nitrobenzaldehyde, 2.5 mmol of cyclohexanones, 2.5 mL of solvent, 0.05 mmol (20 mol %) catalyst (related to the proline amount in the MOF).
[a] Yield of the isolated adducts.
[b] Determined by HPLC.
[c] Conversion.

asymmetric aldol addition involving cyclohexanone and 4-nitrobenzaldehyde.

Proline-functionalized linker of bpb-NHPro (1-L-Pyrrolidine-2-carboxamide-2, 5-bis(4-pyridyl)benzene) was synthesized from 2, 5-dibromoaniline and 4-pyridylbenzeneboronic acid (Scheme S1–S2). The chiral catalyst **I** was prepared through a solvothermal reaction of Zn $(NO_3)_2$ with bpb-NHPro and H_2ndc (2,6-naphthalenedicarboxylic acid) in N,N-diethyl formamide (DEF), heating up to 100 °C for 24 h, produced yellow, cubic crystals, formulated as $[Zn_2(2,6\text{-ndc})_2(\text{bpb-NHPro})]$. Deprotected bpb-NHPro was directly used to construct the pillar-layered MOF, avoiding the undesirable racemization in thermal deprotection of MOF-NHProBoc. The detailed synthesis of bpb-NHPro and **I** were given in SM.

The structure of **I** was confirmed by the analysis of single-crystal XRD. Crystallographic data are listed in Table S1. Selective bond length and angle are listed in Table S2. In the structure, Zn(II) is five-coordinated and forms a $[Zn_2(COO)_4]$ cluster, a paddle-wheel-type secondary building unit (SBU; Fig. 1a). These SBUs are linked by 2, 6-ndc^{2-} in the ab plane and create a 2D grid-like arrangement (Fig. 1b). The square-shaped 2D grids are pillared by bpb-NHPro along the c axis to form a 3D framework with *α*-Polonium net topology (Fig. 1c) [18]. The space that a single net provides along the c direction is adequate for accommodating a second net, resulting in a two-fold interpenetration (Fig. 1d). Despite 2-fold entanglement, channels of molecular dimensions can be seen along a or c axis, which are occupied by solvent molecules. PLATON calculations indicate that the pore volume of **I** is 2992.0 Å^3, corresponding to a void of around 47.4% per unit cell (6311.4 Å^3 in total) [19].

Solvent molecules are extremely disordered, processed by the SQUEEZE method [20]. Unfortunately, due to the rotational disorder as well as low occupancy of each position, the L-proline moieties except nitrogen atom could not be given the fixed position from the diffraction data. ^{1}H NMR studies of **I** after digestion in D_2SO_4 and DMSO-d_6 indicated the existence of proline moieties at the linker portion (Fig. S3). The observation confirmed that the chiral groups were successfully incorporated into the MOF. Reasonably, the prolinyl group was modeled to the each bpb-NHPro in the structure by using Materials Studio 5.0 [21]. As shown in Fig. 1c, the prolinyl groups are in representative positions oriented toward the interior of cubic pores defined by bpb-NHPro and 2,6-ndc.

I was further characterized by microanalysis, IR spectroscopy (Fig. S4), XRD and TG. Powder XRD of as synthesized **I** indicated the phrase purity of its bulky sample, where the diffraction pattern matched the pattern of predicted from the single-crystal structure. The results of PXRD pattern confirmed that solvent-free **I**, which was gained by exchanging with dichloromethane (DCM), retained the original skeleton (Fig. S5). Thermogravimetric analyses (TGA) of as-synthesized **I** showed that a mass loss of 19.6% was observed around 100–280 °C corresponding to the removal of solvent molecules from the pores. Further loss, due to framework decomposition, started at 480 °C. TGA showed that MOF **I** exhibited high thermal stability (Fig. S6).

The nitrogen adsorption was performed on a sample of activated **I** to determine its permanent porosity (Fig. S7). The BET and Langmuir surface areas, estimated by N_2 adsorption isotherm, were 350.0 and 710.7 m^2 g^{-1}, respectively. The moderate N_2 uptake may attribute both to the two-fold interpenetration and to the high concentration of proline groups in the pores. The N_2 sorption isotherm for **I** showed a behavior of microporous materials.

Due to the deprotection of the proline group during the synthesis of bpb-NHPro, the activated **I** was directly applied to catalyze the asymmetric aldol addition of 4-nitrobenzaldehyde to cyclohexanone. As expected, four stereoisomers of 2-[1′-hydroxy-(4-nitrophenyl)methyl] cyclohexanone including two pairs of enantiomers via *syn* and *anti* addition were obtained after the reaction, which can be identified HPLC measurement (Fig. S8 and S9) [22]. Ligand bpb-NHPro was also employed as homogenous catalyst for comparison, providing the general catalytic activity of the prolinamide side group coupled to the phenyl ring backbone. Consistent with the result in aldol addition catalyzed by proline, the preferred *anti*-adduct was observed in this homogeneous reaction with a diastereomeric ratio (dr) of 14:86 (syn:anti) (Table 1, entriy 1).

Several solvents were tested in catalytic screening (Table S3), because solvent had been found to have an important effect on the adsorption behavior of substrates on MOFs [23]. The lowest conversion was observed for the reaction in pure cyclohexanone giving a yield of about 23% (Table 1, entry 6). The best performance was achieved using DMSO as solvent with a yield up to 98% (Table 1, entry 5). Obviously, DMSO enables the best substrate/product transport. As indicated in Table 1, enantioselectivity study showed that ee value was not satisfactory in catalytic reaction using **I**. Approximately 25% ee value of *anti*-adduct was detected if DCM was used as the solvent (Table 1, entry 2), which was the best ee value for anti-isomer compared with other

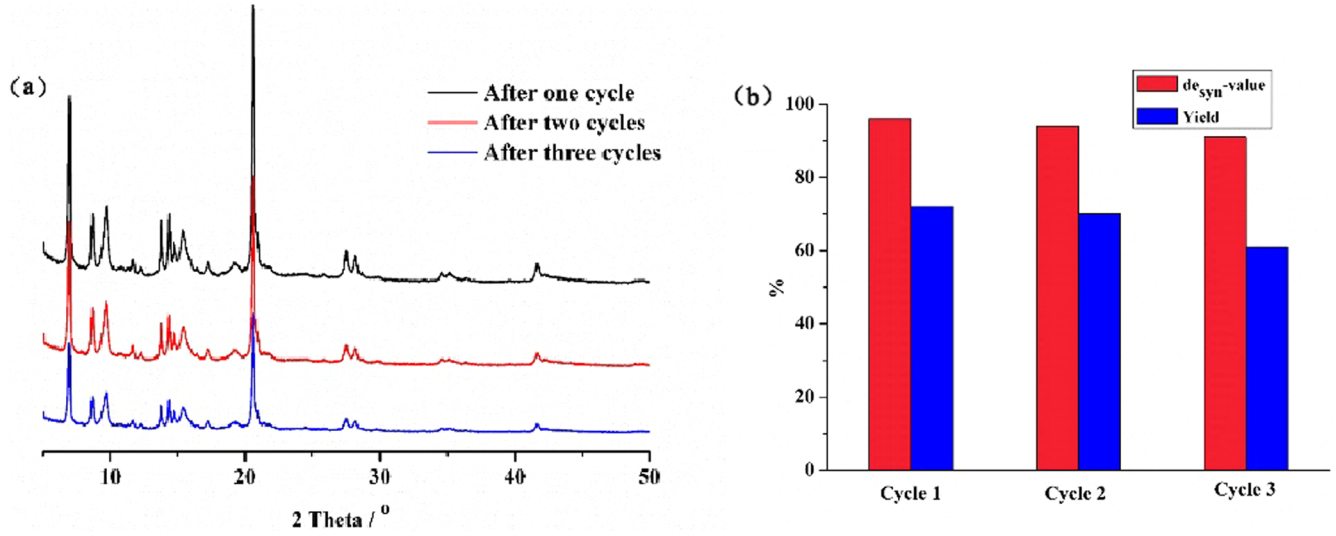


Fig. 2. (a) PXRD patterns of **I** following one, two and three catalytic cycles; (b) Yield and de*syn* value development for three cycles of asymmetric aldol addition in DMF at 40 °C for 5 days.

catalytic systems in Table 1. The highest ee values for *syn*-isomer in these catalytic systems was only 4%. The aldol reaction catalyzed by DUT-32-NHPro [14] and UiO-68-NHPro [15] did not even show any enantioselectivity.

In general, the stereoselectivity of this proline catalyzed homogeneous aldol reaction is based on the hydrogen bonded cyclic transition state between the aldehyde and enamine species [24,25]. Typically, *anti*-adduct formation by aldol addition of 4-nitrobenzaldehyde and cyclohexanone catalyzed by L-proline or proline-derivatives is favored. Also other proline-functionalized MOFs, like CMIL-1 [10], IRMOF-Pro [13], showed *anti*-selectivity in this reaction. Interestingly, the *syn*-adduct formation was preferred in this heterogeneous reaction by **I**, which was opposite to the homogeneous reaction catalysed by L-proline. The proline-functionalized MOFs, Uio-66 to 68 and PCN-261-NHPro, also exhibited *syn*-preferred formation [11,16,17]. The highest stereoselectivity was achieved in DMF with excellent dr-values up to 98:2 (syn:anti) and the de_{syn}-value (diastereomeric excess comparing to *anti*-adduct) of 96% (Table 1, entry 4). Both the high concentration of proline groups in relatively small pores and the interpenetration framework might be a possible explanation for the preferred *syn*-adduct formation by affecting the cyclic intermediate state.

To test the recyclability of the catalyst **I**, three cycles of aldol reaction in DMF were performed. **I** was separated by centrifugation from the reaction mixture after 5 days, washed with CH_2Cl_2, dried under vacuum overnight, and reused in the next reaction run. The second and third cycles were completed under the same condition as the first cycle. From the PXRD measurements of the recovered catalyst, **I** retained its structural framework even after three cycling reaction process (Fig. 2a). As shown in Fig. 2b, reactions catalyzed by **I** show a slight decrease in de_{syn} (diastereomeric excel based on *syn*-amount) after three cycles. Furthermore, the yield gradually decreases.

In conclusion, a proline-incorporated dipyridylbenzene ligand was prepared and utilized to construct a chiral pillar-layered metal–organic framework, $[Zn_2(2,6\text{-ndc})_2(bpb\text{-NHPro})]$, which was used to catalyze the asymmetric aldol addition between 4-nitrobenzaldehyde and cyclohexanone. By using the Boc-deprotected ligand, the chiral proline-functionalized MOF could be directly applied to catalyze the aldol addition, avoiding the racemization usually happened during the thermal deprotection of Boc-protected MOF in the reported literatures. $[Zn_2(2,6\text{-ndc})_2(bpb\text{-NHPro})]$ showed excellent yield up to 98% in DMF and the opposite diastereomeric selectivity, preferring *syn*-adduct with diastereomeric ratio up to 98:2(syn:anti), in comparision to homocatalytic reactions performed by bpb-NHPro, but the unsatisfied ee values for both *syn* and *anti*-adducts. How to improve yield and stereoselectivity in asymmetric aldol reactions catalyzed by proline-functionalized MOFs as the heterogeneous catalysts still requires further research. The open and noninterpenetrated pillar-layered MOFs are being explored in our group.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.inoche.2020.108052.

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