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Cover Page

MIL-101 supported highly active single-site metal catalysts for tricomponent coupling

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Graphical abstract



Highlights

- A highly active Cu(II)-functionalized MOF catalyzes the A³ (alkyne-aldehyde-amine) coupling reaction.
- The heterogeneous catalyst exhibits a record high TOF of 6.8×10^5 h⁻¹ and is recyclable.
- The catalyst also exhibit high activity for the construction of indole rings through cascade A³ coupling and intramolecular cyclization reactions.
- The high activity arises from the single-site dispersion and the unhindered open environment of the metal ion.

Abstract:

Metal-organic frameworks with regular pore structures provide powerful platforms for the design of single-site metal catalysts for chemical transformation. In this paper, we develop a facile, stable and recyclable MOF-supported Cu(II) catalyst, MIL-101-SO₃Cu. It shows extremely high activity for the A^3 coupling of alkynes, aldehydes and amines. The turnover frequency can reach 6.8×10^5 h⁻¹ under neat conditions, which is the highest so far reported for the reaction. The high activity is because the specific structure of the MIL-101-SO₃ support enables a single-site dispersion and an unhindered open environment for the metal ion. MIL-101-SO₃Cu also exhibits high activity for the one-pot cascade reactions combining A^3 coupling and 5-*endo-dig* cyclization.

Keywords: metal-organic frameworks; single-site catalysis; copper(II) catalysis; heterogeneous catalysis; A³ coupling

1. Introduction

The multicomponent reaction of an alkyne, an aldehyde and an amine, known as A³ coupling, has attracted much interest because it provides an efficient, convenient and atom-economic access to propargylamines, which are crucial components of many natural products and versatile intermediates for biologically active and pharmacological compounds [1-4]. The reaction is catalyzed by various metal compounds, including those with Au [5, 6], Ag [7, 8], and Cu [9-11], which are generally good at alkyne C-H activation. Because heterogeneous catalysis can have the advantages such as simple separation, easy recyclability of catalysts and good adaptability to continuous-flow processes, particular efforts have been devoted to the development of supported A³ catalysts on inorganic (oxides, zeolites, silicas, graphenes), organic, or hybrid solids [8, 12-17]. However, the catalysts are still far from satisfactory. A major challenge is to enhance the catalytic activity so as to reduce the catalyst dosage and the reaction time/temperature. From this viewpoint, isolated single-site metal catalysts are highly intriguing. In addition, it is desirable to avoid tedious synthetic steps, eco-unfriendly solvents/additives and air sensitivity during the preparation and the use of the catalysts.

Metal-organic frameworks (MOFs), which feature diverse and tailorable crystalline structures, porosity and functionalities, have emerged as versatile platforms to engineer solid catalysts [18, 19]. MOFs can behave as catalysts themselves with the organic or inorganic components containing the active sites. More remarkably, MOFs have great potential as catalyst supports, with the desired active sites being installed onto the organic/inorganic units or encapsulated within the pore space by diverse postsynthetic approaches. In particular, the regular pore structure can afford isolated single catalytic sites in favor of high catalytic activity [20-23].

MOF-based catalysts for A^3 coupling have been reported recently, including a few Cu-MOFs utilizing the intrinsic metal sites and a few Zn-MOF supported Cu(I), Ag(0), Au(0/III) and Pd(0) catalysts [2, 7, 24-26]. The study still remains in its infancy. We are focused on MIL-101-SO₃ supported metal catalysts for the following reasons. The facile preparation, the high porosity and the excellent stability of the MIL-101-type MOF are advantageous to postsynthesis and catalysis [27]; the anionic sulfonate groups provide facile

handles to immobilize open metal cations through charge-assisted coordination [28-30]; the MOFs with varying metal ions provides nice systems for studying the metal dependence of catalytic performance. We recently reported that MIL-101-SO₃Ag is a recyclable and very active catalyst for A^3 coupling, the turnover frequency (TOF) reaching up to 6.6×10^3 h⁻¹ [30]. Considering the requirement of sustainable chemistry for earth-abundant metal catalysts, we initialized and present here a study on MIL-101-SO₃Cu. To our satisfaction, the Cu(II) catalyst shows even higher activity, with a record high TOF of 6.8×10^5 h⁻¹ for A^3 coupling. We attribute the high activity to single-site dispersion and unhindered open environments enabled by the MIL-101-SO₃ support. We also extend the study to tandem A^3 coupling and cyclization reactions.

2. Experimental

2.1 Synthesis of MIL-101-SO₃Cu

MIL-101-SO₃H was prepared according to a procedure described elsewhere [30]. Different Cu(II) salts and solvents were tried for the synthesis of MIL-101-SO₃Cu (Table S1). For typical preparation, a given amount of Cu(II) salt was dissolved in a solvent, and MIL-101-SO₃H (200 mg, 0.209 mol) was added. The mixture was stirred under room temperature for 12 h. The solid was collected by filtration, washed with water for five times and with CH₃CN twice, and dried at 110 °C for 4 h.

2.2 Typical procedure for A³ coupling reactions

A mixture of phenylacetylene (0.55 ml, 5.0 mmol) and piperidine (0.50 ml, 5.0 mmol) was added under stirring to a 25 ml flask containing dried MIL-101-SO₃Cu (6.0 mg, containing 2.6 μ mol Cu) and paraformaldehyde (195 mg, 6.5 mmol). After stirred at 80 °C for a given time, the slurry was centrifuged, and the supernatant was diluted with CDCl₃ and subjected to ¹H NMR analysis. The recycling tests were performed on a larger scale under the typical conditions, with the starting amount of all reagents increased to 10 times the aforementioned amount. After each run, the solid obtained by centrifugation was washed with dichloromethane (20 ml × 3) and dried overnight for the next run.

2.3 Typical procedure for the cascade reactions

Paraformaldehyde (40 mg, 1.3 mmol), piperidine (100 μ l, 1.0 mmol) and ethyl acetate (1 ml) was added under stirring to a 25 ml flask containing dried MIL-101-SO₃Cu (24 mg, containing 10 μ mol Cu). After the temperature was raised to 60 °C, N-tosyl-2-ethynylaniline (270 mg, 1.0 mmol) was added and the mixture was stirred for 0.5 h. The slurry was centrifuged, and the yield was obtained from ¹H NMR of the supernatant dissolved in CDCl₃.

2.4 Characterization

X-ray powder diffraction patterns of the samples were measured using a Rigaku Ultima IV X-ray Diffractometer with Cu K_a radiation ($\lambda = 1.5418$ Å) at a scanning rate of 10° /min, with accelerating voltage and current of 35 kV and 25 mA, respectively. Nitrogen adsorption and desorption isotherm measurements were performed on a Micromeritics ASAP2020 analyzer at 77K. Scan electron microscopy (SEM) and elemental distribution map study was carried out with a S-4800 HITACHI scanning electron microscope. Transmission electron microscopy (TEM) images were recorded with a JEOL JEM-2100 microscope. FT-IR spectra were recorded in the range $500 - 4000 \text{ cm}^{-1}$ using KBr pellets on a Nicolet NEXUS 670 spectrophotometer. The metal amount was detected by inductively coupled plasma atomic emission spectroscopy (ICP-AES) using an IRIS Intrepid II XSP spectrometer. Proton nuclear magnetic resonance spectra (¹H NMR) were obtained on a Bruker Ascend 400 (400 MHz) hydrogen temperature-programmed reduction spectrometer. The (H_2-TPR) and temperature-programmed desorption of ammonia (NH₃-TPD) were performed on a Micromeritics autochem 2920 instrument. For the purpose, 0.050 g sample was put into a U-shaped quartz tube and treated in argon (20 mL/min) at 150 °C for 30 min. The TPR and TPD curves were obtained at the 10 °C / min rate.

3. Results and discussion

3.1 Catalyst preparation and characterization

MIL-101-SO₃Cu was synthesized by a facile two-step protocol (Scheme 1): hydrothermal synthesis of MIL-101-SO₃H from 2-sulfoterephthalic acid and CrO₃ [30, 31], followed by simple room-temperature cation exchange in an aqueous solution containing excessive

 $Cu(ClO_4)_2$ (3.5 equivalents relative to the sulfonate group). The solid was filtered and thoroughly washed with water until no Cu(II) was detected by DDTC (sodium diethyldithiocarbamate).



Scheme 1. Synthesis of the single-site catalyst MIL-101-SO₃Cu

Powder X-ray diffraction (PXRD, Fig. 1a) confirms that the framework remains intact after Cu(II) complexation. According to ICP-AES analysis, the loading amount of Cu(II) is about 14 mol% with respect to the sulfonic groups in the MOF. The loading amount was only slightly increased to 18 mol% when the quantity of Cu(ClO₄)₂ used in the preparation was increased by 10 times. Subsequent characterization and catalytic study were performed using the material with 14 mol% Cu(II) loading. To see if the anion of the Cu(II) source has influence on Cu(II) loading, different Cu(II) salts (CuCl₂, Cu(BF₄)₂ and Cu(ClO₄)₂) have been used to react with MIL-101-SO₃H. ICP-AES analysis suggested that the loading amount of Cu(II) is always around 14 mol%, with no appreciable dependence on the anion in the Cu(II) source. The FTIR spectra of the products are essentially identical (Fig. 1b), with no indications of absorption bands characteristic of BF₄⁻ or ClO₄⁻. The results show that Cu(II) is not charge compensated (and coordinated) by the exogenous anions but by sulfonate from the framework. The IR absorptions at 1230, 1180, and 1080 cm⁻¹ arising from the O=S=O and S-O stretching vibrations show no significant change after H⁺-Cu²⁺ cation exchange.



Fig. 1. PXRD profiles (a) and FTIR spectra (b) of MIL-101-SO₃H and MIL-101-SO₃Cu from different Cu(II) sources

SEM and TEM images were taken for MIL-101-SO₃H and MIL-101-SO₃Cu (Figs. S1 and S2). The materials show no significant change in morphology before and after metalation, and no metal nanoparticles were found in the TEM images of MIL-101-SO₃Cu. Element mapping (Fig. S3) suggest that Cr and Cu are uniformly distributed in MIL-101-SO₃Cu, and the Cu:Cr atomic ratio (0.11) according to energy dispersive spectroscopy (EDS) is in good agreement with the ICP analysis. X-ray photoelectron spectroscopy (XPS) with MIL-101-SO₃Cu (Fig. 2a) revealed Cu $2p_{3/2}$ and $2p_{1/2}$ peaks at 934.5 and 954.7 eV, respectively, together with the shake-up satellite signals, confirming the Cu(II) state [32]. The H₂-TPR profile of MIL-101-SO₃H begins to rise slightly above 350°C and shows a strong peak at 505 °C (Fig. S4). This should be due to decomposition of the organic component of the MOF in the reductive atmosphere rather than reduction of the Cr(III) center. The H₂-TPR profile of MIL-101-SO₃Cu shows a weak shoulder peak at 330 °C and a strong peak at 485 °C. Because the shoulder peak is absent before metallation, it can be safely attributed to the reduction of

Cu(II). Meanwhile, the main peak is shifted by about 20 °C to lower temperature, which could indicate that the framework decomposition is promoted by copper. The NH₃-TPD profiles are shown in Figure S5. For MIL-101-SO₃H, the broad desorption peak around 80-200 °C can be due to the open Cr(III) sites of the framework [33], and the peak at about 340 °C can be assigned to the strong acidic sulfonic sites [34]. For MIL-101-SO₃Cu, the two framework-originated peaks remain with some shifts toward lower temperatures. An additional broad signal was observed around 230 °C, which we tentatively ascribe to the Cu(II) sites.



Fig. 2. (a) Cu 2p XPS spectra of MIL-101-SO₃Cu before and after catalytic use (The peaks marked with * are the shake-up satellites) (b) Nitrogen adsorption (solid) and desorption (open) isotherms of

MIL-101-SO₃H and MIL-101-SO₃Cu

According to nitrogen adsorption isotherm at 77 K (Fig. 2b), the Brunauer–Emmett–Teller (BET) specific surface area of MIL-101-SO₃Cu is 1590 m²/g, which is somewhat lower than that of MIL-101-SO₃H (1761 m²/g) and higher than that of MIL-101-SO₃Ag (1497 m²/g, with 21 mol% Ag(I) loading) [30]. The results indicate that the MOF remains highly porous after Cu modification.

3.2 Catalytic A³ coupling over MIL-101-SO₃Cu

To evaluate the catalytic performance, the A^3 coupling reaction of phenylacetylene, paraformaldehyde and piperidine was performed over MIL-101-SO₃Cu (14 mol% Cu loading) at a low dosage of 0.05 mol% (the amount of Cu(II) relative to phenylacetylene) without any protecting atmosphere. Solvent survey at 80 °C (entries 1-3, Table 1) suggested that DMF and toluene are better than 1,4-dioxane and afford moderate yields in 15 min. To our satisfaction, the solvent-free reaction (entry 4) gave the best results, the yield reaching 99% (isolated yield, 98%) in 15 min, with a TOF up to $7.9 \times 10^3 h^{-1} (1.0 \times 10^4 h^{-1} in 5 min)$. Hence the neat condition was chosen for further investigation. The reaction rate is strongly dependent on temperature. At room temperature (25°C), no propargylamine product was detected even after much prolonged time. The reaction at 40 °C yielded the product nearly quantitatively in 6 h, and further increasing the reaction gave a yield of 94% in only 5 min (entry 5), the TOF being as high as $2.2 \times 10^4 h^{-1}$.

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Entry	Catalyst	T (°C)	Time (min)	Yield (%) ^b	TOF (h ⁻¹)
1 ^c	MIL-101-SO ₃ Cu	80	15	18	1.4×10^{3}
2^d	MIL-101-SO ₃ Cu	80	15	72	5.8×10^{3}
3 ^e	MIL-101-SO ₃ Cu	80	15	59	4.7×10^{3}
4	MIL-101-SO ₃ Cu	80	5/15	43/99 (98 ^f)	$1.0 \times 10^4 / 7.9 \times 10^3$
5	MIL-101-SO ₃ Cu	100	5	94	2.2×10^{4}
6	MIL-101-SO ₃ Cu	60	60	84	1.7×10^{3}
7	MIL-101-SO ₃ Cu	40	60/360	19/99	380/330
8	MIL-101-SO ₃ Cu	25	24h	trace	-
9 ^g	MIL-101-SO ₃ Cu	100	5	57	6.8×10 ⁵
10	-	100	120	12	-
11	MIL-101-SO ₃ H	100	120	10	-

Table 1. Catalytic data for A³ coupling of phenylacetylene, paraformaldehyde and piperidine^a

^a Reaction conditions: phenylacetylene, 5.0 mmol; paraformaldehyde, 6.5 mmol; piperidine, 5.0 mmol, catalysis, 0.05 mol% (or specified otherwise); solvent-free or specified otherwise. ^b Calculated via ¹H NMR. ^c Solvent: 2 ml 1,4-dioxane. ^d Solvent: 2 ml toluene. ^e Solvent: 2 ml DMF. ^f Isolated yield. ^g Catalyst amount: 0.001 mol%.

Encouraged by the high catalytic activity, the dosage of MIL-101-SO₃Cu was further decreased (entry 9). With an extremely low dosage of 0.001 mol%, the reaction at 100 °C can give a moderate yield of 57% within 5 min, the TOF being as high as 6.8×10^5 h⁻¹. To determine the active site, control experiments were performed without any catalyst or with the MIL-101-SO₃H precursor as potential catalyst. Both reactions gave very low yields (~10%, entries 10 and 11) even in much prolonged time. The results clearly confirm that the Cu(II) site is responsible for the high catalytic activity of MIL-101-SO₃Cu.

To our delight, MIL-101-SO₃Cu has the highest activity ever reported for the A³ coupling of phenylacetylene, paraformaldehyde and piperidine. The optimized catalytic data of previous heterogeneous catalysts for the reaction are collected in Table 2. Diverse conditions have been used for different catalysts. Because the catalytic activity generally increases with temperature, the data for MIL-101-SO₃Cu at different temperatures are included in the table for reasonable comparison. As can be seen, a variety of catalysts, including a few MOF-based ones, have been used at 40 - 120 °C with dosages of 0.3-10 mol%, the TOFs ranging from 0.3 to 103 h⁻¹ at the yield levels of 80-99% in 0.5-24 h (entries 1-10). By contrast, a much lower dosage of MIL-101-SO₃Cu can catalyze the reaction with much higher efficiency. With the 0.05 mol% dosage and at the yield levels of 94-99%, the TOFs over MIL-101-SO₃Cu vary from 330 h⁻¹ at 40 °C to 22000 h⁻¹ at 100 °C (entries 11-13). A still lower dosage of 0.001 mol% afforded the extremely high TOF of 680000 h⁻¹ (entry 14). The TOF value is four times higher than the previous record high value (~150000 h⁻¹), which was reported recently for Ag@IRMOF-3 (Ag nanoparticles encapsulated within IRMOF-3) at 120 °C under microwave-assisted heating conditions (entry 15) [7]. It should be noted that microwave irradiation makes vital contribution to the high activity of Ag@IRMOF-3. When used at 120 °C without microwave, Ag@IRMOF-3 showed a TOF of 1400 h⁻¹ (entry 16) [7], which is much lower than the values for MIL-101-SO₃Cu at 100 and even 80 °C.

Entry	Catalyst	Dose (mol%)	T (°C)	t (h)	Yield (%)	$TOF(h^{-1})$	Ref.
1	Cu(2-pymo) ₂	1	40	21	99	4.7	[35]
2	Ag-NHC	2	40	6	91	7.6	[36]
3	Hg ₂ Cl ₂	5	70	4	89	4.4	[37]
4	GO-Fe ₃ O ₄	0.3	90	16	90	18.8	[38]
5	Au@SH-CNC	4.4	80	24	99	0.94	[39]
6	Ag@SBA-15	5	100	0.5	95	38.0	[40]
7	Cu@PS-ala	0.6	100	6	93	25.8	[41]
8	InCl ₃	10	120	20	80	0.40	[42]
9	Au@MOF-199	1.8	120	0.5	93	103	[5]
10	MIL-101-SO ₃ Cu	0.05	40	6	99	330	This work
11	MIL-101-SO ₃ Cu	0.05	80	0.25	99	7.9×10 ³	This work
12	MIL-101-SO ₃ Cu	0.05	100	0.083	94	2.2×10 ⁴	This work
13	MIL-101-SO ₃ Cu	0.001	100	0.083	57	6.8×10 ⁵	This work
14	Ag@IRMOF-3	0.09	120 (MW) ^b	0.017	80	1.5×10 ^{5, a}	[7]
15	Ag@IRMOF-3	0.09	120	1	44	1.4×10 ^{3, a}	[7]
16	MIL-101-SO ₃ Ag	0.06	100	0.083	33	6.6×10 ³	[30]
17	MIL-101-SO ₃ Ag	0.05	80	0.25	40	3.2×10 ³	[30]

Table 2. Comparison of different A³-reaction catalyst

^a Calculated based on the exposed Ag surface atoms. ^b MW = microwave

The superior catalytic activity of MIL-101-SO₃Cu could be because the MIL-101-SO₃ support enables full exposure and complete site-isolation of the metal ions. Generally, the key to A³ catalysis is the terminal C-H activation of alkyne, which involves an intermediate π complex with η^2 side-on coordination of C=C to a metal site [2]. For a metal ion chelated by multidentate ligands or a nodal metal site in MOFs, there could be steric hindrance for the side-on coordination, even if the metal site is coordinatively unsaturated. For metal nanoparticles, the utilization of metal atoms is limited because they are not single-site isolated.

By contrast, the SO₃M groups in MIL-101-SO₃M are well isolated from each other and stick out from organic linkers towards the pore space, so each metal ion has a very open environment (probably with easily leaving water ligands) and can be efficiently accessed by substrates without significant steric hindrance. The advantages of MIL-101-SO₃ as metal-ion support are also illustrated by MIL-101-SO₃Ag. Although not conscious of the advantages in our previous report [30], we showed that MIL-101-SO₃Ag shows a high TOF of 6600 h⁻¹ at 100 °C for the A³ coupling reaction (entry 16, Table 2). A new control experiment with MIL-101-SO₃Ag revealed a TOF of 3200 h⁻¹ at 80 °C (entry 17, Table 2). The TOFs over MIL-101-SO₃Ag are lower than that of MIL-101-SO₃Cu but significantly higher than those over other catalysts, including Ag@IRMOF-3 under microwave-free conditions. The different activities of MIL-101-SO₃Cu and MIL-101-SO₃Ag can be due to the different nature of the metal centers.



Fig. 3. Recycle tests of MIL-101-SO₃Cu

It is highly desirable that a heterogeneous catalyst can be easily recycled. Recycle tests with MIL-101-SO₃Cu showed that it can be used for at least five consecutive runs after simple centrifugal separation and washing, without significant deterioration in activity (Fig. 3). The slight decrease in yield could be due to the mass loss of the catalyst during work-up and separation. ICP-AES analysis with the used catalyst indicated no appreciable leaching of Cu(II) (within the experimental error) during the catalytic reaction. This should be because

the Cu(II) ion is charge compensated by the framework and the reaction system does not contain anionic coordinative species that compete with sulfonate for Cu(II) ions.

The similarity of the PXRD profiles after used for 1-4 turns suggests that the MIL-101 framework is essentially retained after the catalytic reactions (Fig. 4). The IR spectrum also shows no significant changes except that the used catalyst displays weak IR absorptions at 2862, 2949 and 3210 cm⁻¹ (Fig. 5). These bands also appear if the fresh catalyst is treated with only piperidine, so they are attributable to v(C-H) and v(N-H) of the piperidine molecules adsorbed in the MOF. The piperidine molecules cannot be completely removed by washing, which could be due to the coordination interactions of piperidine with Cu(II) or the acid-base reaction of piperidine has no significant impact on the catalytic performance. XPS revealed the Cu $2p_{3/2}$ and $2p_{1/2}$ peaks shift slightly to lower energies after catalytic use, which could be ascribed to coordination of piperidine. The retention of the shake-up satellites indicates that Cu remains in the paramagnetic +II state [32], and there are no indications for reduction of Cu(II) to Cu(I) or Cu(0). Furthermore, no Cu(0) particles were found in the TEM images of MIL-101-SO₃Cu after the catalytic reaction (Fig. S2 (b)).



Fig. 4. PXRD profiles of MIL-101-SO₃Cu for recycling runs of the catalytic reaction



Fig. 5. FTIR spectra of MIL-101-SO₃Cu before and after catalytic use and after treatment with piperidine

The application scope of the catalyst was examined for different substrates. As shown in Scheme 2, aromatic terminal alkynes with either electron-donating or electron-withdrawing substituents react rapidly with paraformaldehyde and piperidine to reach complete conversion within 15 min (1-4). 4-Ethynylpyridine, a heterocyclic alkyne, could also achieve 95% conversion in 30 min (5). With bulky substituents such as t-butyl and hexyl at the benzene ring, the reactions become somewhat slower, but excellent yields can still be achieved in 30 min (6 and 7). This can be because of the effects of the pore size on diffusion or formation of the species (including intermediates and transition states) involved in the reactions. Aliphatic terminal alkynes can also give good yield if the reaction time is prolonged (8). Because the mechanism of A³ coupling involves deprotonation of the terminal C-H group, the lower reactivity of aliphatic alkynes can be due to their weaker acidity relative to aromatic ones, as indicated by pK_a values (for example, $pK_a = 27.4$ for propyne, while $pK_a = 22.6$ for phenylacetylene [43]). The catalyst is also applicable to different secondary amines, which serve as bases to help deprotonation of alkynes. Morpholine ($pK_a = 8.49$ for the corresponding ammonium cation) and diethylamine ($pK_a = 10.80$) are less basic than piperidine $(pK_a = 11.12)$ [43] and hence less reactive for the A³ coupling with phenylacetylene and paraformaldehyde (9 and 10). Nevertheless, prolonged reactions (2-7 h) could lead to good yields. The reaction rate also declined if paraformaldehyde was replaced

by other aliphatic aldehydes, but modest to good yields can still be achieved by prolonged reactions (**11-13**, Scheme 2).



Scheme 2. Catalytic data for A³ coupling of various substrates. The yields were calculated via ¹H NMR. For **4** and **5**, 2 ml toluene was used to dissolve the solid alkyne. Compounds **14b** and **15b** are the by-products appearing with the corresponding A³-coupling products (**14a** and **15a**, respectively).

When benzaldehyde was used, a conversion of 98% was reached after 4 h, and the yield of the propargylamine product (14a) is 85%, with chalcone (14b) as byproduct (13%). A prolonged reaction led to the conversion from 14a to 14b. The coupling reaction with

p-fluorobenzaldehyde also afforded an excellent conversion (**15a**), with a smaller amount of the enone byproduct (**15b**). *p*-Methylbenzaldehyde shows a lower conversion to propargylamine (**16**), with no enone byproduct in 4 h, which however can be formed after prolonged time. The formation of enones from aromatic aldehydes, alkynes and amines has recently been recognized as a Cu- or Ag-catalyzed secondary reaction following the formation of propargylamines [30, 44]. No enone byproduct was not observed in the reactions using aliphatic aldehydes. The different reactivity of aromatic aldehydes compared with aliphatic ones is because the benzylic-type tertiary C-H group in the propargylamine products (for example, **14a**) derived from aromatic aldehydes has high acidity in favor of propargyl-to-allenyl isomerization [30, 44].

3.3 Cascade A³ coupling and cyclization over MIL-101-SO₃Cu

Propargylamines are versatile precursors to N-containing heterocycles. An example is the indole motif, which is distributed in a wide variety of natural products and pharmaceuticals [45]. There have been intriguing protocols that using one-pot tandem A^3 coupling and cyclization reactions to synthesize indole derivatives [46, 47]. To expand the utility of MIL-101-SO₃Cu, the one-pot reactions combining A^3 coupling and 5-*endo-dig* cyclization were performed using N-protected ethynylaniline, paraformaldehyde and piperidine. As shown in Table 3 (entry 1), the one-pot catalytic reaction at 60 °C under solvent-free conditions led to complete conversion of Ts-protected-2-ethynylaniline (I) in 0.5 h. However, product analysis indicated that the yield of the target product (IV) was only 34%. No propargylamine intermediate was detected, and the remaining product was confirmed by NMR to be an N-protected indole (V). The undesired product obviously arises from intramolecular cycloaddition of I, which competes with and dominates over the cascade A^3 -cyclization reaction under the conditions used.

C NH-Ts	+ (CH ₂ O) _n + F	IN catalyst						
I	П	ш	Ts IV	Ts V				
Entry	Reactant	Solvent (ml) ^b	T (⁰ C)	t (h)	Yield (%)		Yield (%)	
					IV	v		
1	I+II+ III	-	60	0.5	34	65		
2°	I+III	EA (0.4)	60	2.5	0	35		
3	Ι	EA(0.4)	60	2.5	0	0		
4	I+III	EA (0.4)	60	0.5	0	73		
5	I+II+ III	CHCl ₃ (0.4)	60	0.5	26	39		
6	I+II+ III	DMF (0.4)	60	0.5	22	77		
7	I+II+ III	MeOH (0.4)	60	0.5	55	44		
8	I+II+ III	acetone (0.4)	60	0.5	85	14		
9	I+II+ III	EA (0.4)	60	0.5	92	7		
10	I+II+ III	EA (1.0)	60	0.5	97	2		
11	I+II+ III	EA (2.0)	60	0.5	97	2		
12	I+II+ III	EA (1.0)	80	0.5	86	13		

Table 3. Optimization study for tandem A³ coupling and cyclization reactions over MIL-101-SO₃Cu^a

^a Reactants: **I** (1.0 mmol), **II** (1.3 mmol), **III** (1.0 mmol); catalyst: 24 mg. Yields were calculated via ¹H NMR of the crude reaction mixture. ^b EA = ethyl acetate, DMF = N,N'-dimethylformide. ^c Without the solid catalyst.

The intramolecular cycloaddition is known to be catalyzed by some metal catalysts [48, 49] but has not been recognized in previous studies of A³ coupling. Control tests indicated that **I** alone cannot undergo the intramolecular reaction, and the reaction proceeds slowly in the presence of piperidine (entry 2, Table 3). MIL-101-SO₃Cu alone cannot catalyze the reaction (entry 3) but can significantly accelerate the reaction in the presence of amine (entry 4). These

results justify the formation of **V** under the A^3 coupling conditions. Considering that the high concentration of piperidine under solvent-free conditions could favor **V** more than **IV**, we have performed optimization experiments using different types and amount of solvents to maximize the yield of **IV**. As can be seen from Table 3, CHCl₃ is not a good solvent for both reactions (entry 5), DMF is in favor of the intramolecular cycloaddition (entry 6), and MeOH gives comparable selectivities for the two products (entry 7). Acetone affords a good selectivity for **IV**, while an excellent selectivity is achieved in ethyl acetate (entries 8 and 9). The selectivity can be further improved if using more ethyl acetate (entries 9-11). The reaction at the higher temperature gives a lower selectivity for **IV** (entry 12). Under the optimized conditions (entries 10 and 11, Table 3), the yield and selectivity of **IV** can reach 97 % in 30 min. The TOF is about 200 h⁻¹, which is much higher than those (less than 70 h⁻¹) for the same cascade reaction over different Au and Cu catalysts [35, 47]. The high catalytic efficiency of MIL-101-SO₃Cu for the cascade reaction could also arise from the structural features outlined above.

4. Conclusions

In summary, we have developed an efficient MOF-supported Cu catalyst for A^3 coupling, which features facile preparative and catalytic procedures (solvent-free and air-resistant), good recyclability, and most importantly, extremely high activity, with the highest TOF $(6.8 \times 10^5 \text{ h}^{-1})$ so far reported for the reaction. The high activity can be related to the single-site metal dispersion and unhindered open metal environments enabled by the structure of the supporting MOF. The catalyst is also very efficient for the preparation of indole derivatives through tandem A^3 coupling and cyclization reactions. This work not only indicates MIL-101-SO₃Cu to be a promising catalyst for applications, but also demonstrates MIL-101 as a simple and nice platform for the development of highly active earth-abundant metal catalysts that are desired for sustainable chemical synthesis.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/xxxx.

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