Metal organic frameworks as solid catalysts for the synthesis of nitrogen-containing heterocycles

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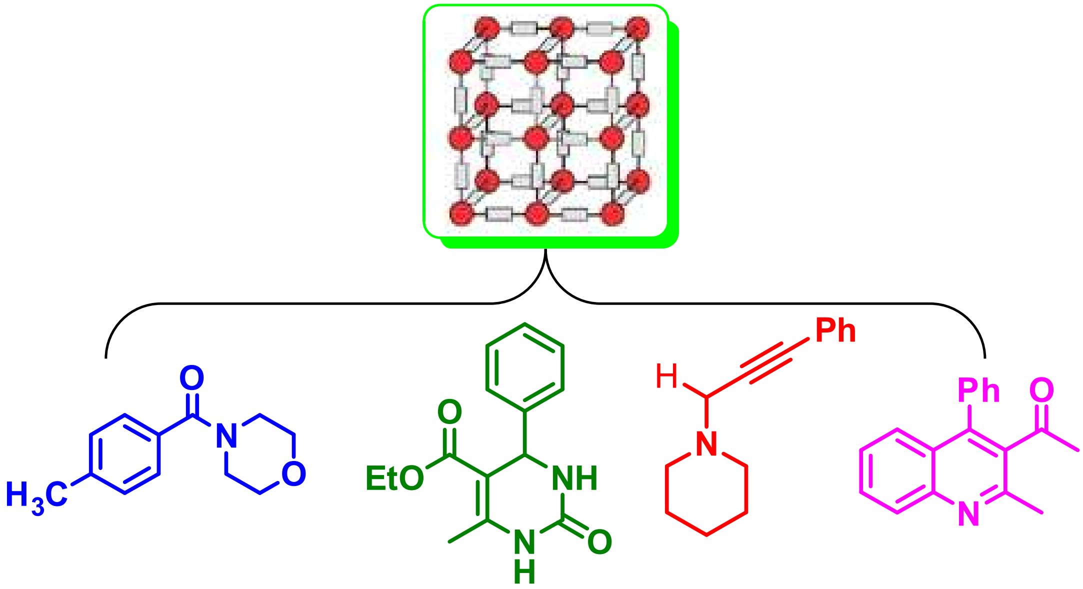

This Critical Review summarizes the recent developments in the use of metal-organic frameworks as catalysts for the synthesis of nitrogen-containing heterocycles.

Metal organic frameworks as solid catalysts for the synthesis of nitrogen-containing heterocycles

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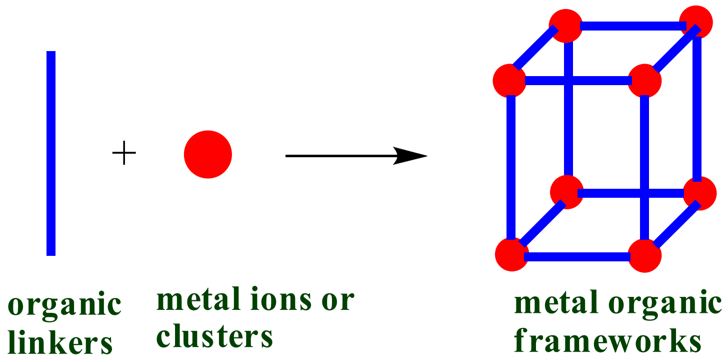
Abstract

Metal organic frameworks (MOFs) are finding increasing application as solid catalysts for liquid phase reactions leading in the synthesis of fine chemicals. In the present review we have focused on those reports describing the use of MOFs as catalysts for the synthesis of N-containing heterocycles that is a class of organic compounds with high added value due to their therapeutic use as drugs and their remarkable biological activities. After an introduction describing relevant structural features of MOFs and the nature of their active sites, this manuscript is organized according to the type of N-containing heterocycle synthesized employing MOFs as catalysts including pyrimidines, N-substituted piperidines, quinolines, indoles, N-substituted imidazoles, triazoles and heterocyclic amides. Special attention has been paid to the structural stability of MOFs under the reaction conditions, to the occurrence of metal leaching and reusability. The final section of this review provides some concluding remarks and future prospects for the field, with the emphasis in showing the superiority of MOFs with respect to other solid catalysts for this type of liquid phase organic reactions and pointing out that the final goal in this research would be the use of these materials as catalysts in real industrial synthesis. The literature appeared up to mid 2013 is covered.

1. Introduction

Metal-organic frameworks (MOFs) are nanoporous crystalline materials whose structure is constituted by a tridimensional array of metal ions or metal clusters connected by rigid bi- or multipodal organic linkers (Scheme 1).[1-5] Porosity, crystallinity and relatively strong metal-ligand coordination bonds are the characteristic properties of MOFs. One of the most interesting features of MOFs is that frequently their structure can be deduced from the directionality of organic linkers and the coordination geometry of metal building blocks.[5] In this way, MOFs can be engineered in a large extent and can be synthesized by design with the desired structure and dimension of the voids. MOFs are among the solids exhibiting the largest internal pore volume, largest surface area and lowest framework density and these features have been exploited for the use of these solids as gas adsorbents or for gas and liquid separation.[6-10]



Scheme 1. Illustration of the building blocks and structure of metal organic frameworks

The synthesis of MOFs is a very active area of research and MOFs have been reported virtually with all the transition metals.[11, 12] In some cases, the metal ions or clusters have exchangeable coordination positions not involved in the structure of MOF that after the synthesis are generally occupied by solvent molecules or water. In these cases in where the metal nodes have coordinatively unsaturated positions not compromised with the structure, these metal ions can act as Lewis acid sites by binding with substrates or reagents. Also defects in the crystal structure can leave coordinatively unsaturated sites in MOFs whose ideal lattice should have all the coordinative positions around the metal nodes occupied by the ligands in the construction of the solid framework. These coordinatively unsaturated positions can be responsible for the activity of MOFs as catalysts.[13, 14] In addition, the organic ligands can have substituents that can exhibit catalytic activity and/or the empty spaces can host some noble metal, metal oxide or guests with activity to promote organic reactions.[15] The combination of large surface area, large pore dimensions, adequate framework stability and the presence of active sites either in the framework or hosted in the voids, make MOFs very promising as heterogeneous catalysts for liquid phase reactions.

In this context, the use of MOFs as solid catalysts to promote organic reactions is a topic under much current investigation trying to take advantage of the potential of these materials and a series of reviews have appeared describing the general activity of MOFs as catalysts or focused on several particular aspects such as application of commercial MOFs as catalysts, comparison of the catalytic activity of MOFs with other porous solids or their activity to promote oxidation reactions.[16-23]

In the present manuscript we will focus particularly on the use of MOFs as solid catalysts for the synthesis of nitrogen-containing heterocycles. Generally heterocycles are obtained by condensation of the corresponding precursors or by functionalization of the heterocyclic ring and both types of processes are carried out in the liquid phase at moderate temperatures in the presence of Brønsted or Lewis acids. MOFs are solid catalysts specially suited for these conditions, since they may exhibit acidity at the coordinatively unsaturated metal ions as well as sufficient lattice robustness for liquid phase reactions.[24] In addition, the large pore size of MOFs compared to zeolites or other microporous materials also favors intracrystalline diffusion that can be the limiting factor for liquid phase reactions compared to those in the gas phase. Zeolites are crystalline microporous aluminosilicates whose structure is robust at high temperatures. Zeolites are paradigmatic solid catalysts employed in very large industrial processes like oil refining and petrochemistry [25]. However, while zeolites are the ideal porous solids for many gas phase processes, their limited pore size and restricted diffusion, makes zeolites much less efficient for liquid phase reactions and for the production of fine chemicals. In this regard, MOFs can be considered as complementary with zeolites, since their properties makes them suitable for different reaction conditions [24].

Heterocycles are organic compounds that can have large added value and, for this reason, optimization of their synthesis can be important and this optimization should be largely based on the development of more efficient and selective catalysts. While most of the classical heterocycle synthesis routes are based on the use of homogeneous acids or bases, there is a continuous effort in heterogeneous catalysis in replacing liquid acids and bases by solids that can be recovered and recycled at the end of the reaction. Table 1 summarizes some of the advantages and disadvantages of homogeneous with respect to heterogeneous catalysts for the synthesis of organic compounds.

Table 1. Differences between homogeneous and heterogeneous catalysts.

Property	Homogeneous catalysts	Heterogeneous catalysts
Metal impurity in products	high possibility	can be low
Selectivity	high	high

Stability	possibility of deactivation is high	low to medium
Catalyst mass	frequently stoichiometric amount due to strong interaction with products	less than stoichiometric and most of the time catalytic
Solvent	mostly requires an organic solvent	not always needed
Isolation of products	workup required to separate the catalyst.	simple filtration or immobilization
Recovery of catalyst	cannot be recovered	can be recovered and recycled
Cost	can be low	higher cost that needs to be compensated with higher productivity

Thus, there is a real opportunity in applying MOFs as solid catalysts for the liquid-phase synthesis of heterocycles, as examples of a class of fine chemicals that can afford the use of MOFs as catalysts. In the present review, we will focus on describing those reports that used MOFs as solid catalyst for the synthesis of N-containing heterocycles. The purpose of this review is to illustrate that MOFs can be highly active catalysts for the preparation of this type of fine chemicals and, when possible, we will provide adequate comparison with the activity of other solids to show that MOFs can be the type of catalysts of choice. Besides comparison of the activity of MOFs to other solids, special emphasis will be made commenting whether or not evidence supporting the diffusion of reagents and substrates inside MOFs pores is provided. When using porous solids, the activity of the material can be due to the external surface or to the combination of the external and internal sites. The last situation is the preferred one since the efficiency of the material should be much lower if only the external surface of the crystallite is intervening in the catalysis. Intracrystalline diffusion requires the use of substrates, reagents and products whose molecular dimensions are smaller than the size of the pores of the material and, therefore, a judicious selection of catalyst with appropriate structure should be made. Also we will comment on the need of MOF preactivation to generate the coordinatively unsaturated sites around the metal ions and the selection of the experimental conditions, including temperature, solvents and reagents. It should be commented that MOFs can be dissolved in some media under certain circumstances and that aliphatic amines frequently used in the synthesis of nitrogen-containing heterocycles can damage totally or partially the crystal structure of these solids. Thus, there could be incompatibility of using MOFs for certain processes.

Best Practices in MOF catalysis.

As a general remark in this area, MOF stability, maintenance of its crystal structure and porosity under the reaction conditions has to be continuously carefully surveyed and firmly proved, particularly when using polar solvents and corrosive reagents [26]. Comparison of XRD patterns of the material before and after extensive use as catalyst should report on the preservation or not of the crystal structure, Also, porosity measurements of the used catalyst after careful evacuation of solvents and adsorbed products should provide surface area values and pore volumes close to the fresh material.

Related with the issue of catalyst stability is the possibility of occurrence of leaching of the active site, generally metals, from MOF to the solution. The possibility of leaching has to be always considered and evidence of its absence provided. When using a solid as catalyst, it is in principle assumed that process is heterogeneous with mass transfer from the liquid to the solid. However, the possibility that the active sites migrates under the reaction conditions from the solid to the solution, acting there in homogeneous phase has to be contemplated, particularly since frequently MOF stability is not high. Leaching tests should include at least, the so-called hot filtration test in which the reaction is initiated under the regular reaction conditions and, then, the solid filtered while the mixture is hot at the reaction temperature.

The main problem of this simple test is that unavoidable temperature decrease during filtering can produce in some cases, such as for palladium nanoparticles, reprecipitation of the leached species, the *boomerang* effect. For this reason, for negative hot filtration tests, other methodologies like selective poisoning of soluble species or the *three-phase* tests in which the reagents or substrates are anchored on a solid support have also been performed. Besides hot filtration tests, chemical analyses of the metals in the solid and the liquid phases have to show that there is no loss of metal in the composition of MOF.

Leaching is always an undesired process in heterogeneous catalysis since it always reflect the instability of the catalyst and at long term should lead to irreversible deactivation. In addition, particularly for the synthesis of drugs, the presence of metals in the product in certain percentages could be highly detrimental for the quality and uses of the products, requiring costly purifications.

In some cases, leaching can be minimized or avoided by judicious selection of solvent and conditions. As a general rule of thumb considering the composition of MOFs and the nature of the interactions, polar solvents should be avoided as reaction media and, in principle, apolar solvent should be preferred to reduce the possibility of structural damage. Also the temperature should be kept as low as possible. In addition, there are some reagents, such as aliphatic amines or thiols [27], that can compete with the linker for the interaction with the metal nodes of MOFs and can lead to deterioration of the structure.

Stability of MOF as catalyst has to be also proved in batch reactions by reuse of the material for consecutive runs and observation that the activity is maintained. This requires not only determining the conversion and yields at final reaction times, but also measurement of the initial reaction rate of the fresh and used material showing that this kinetic parameter remains constant. These reusability tests should be completed with a study of when deactivation occurs and the main causes for it [28].

Another general point of concern in MOF catalysis that is common to any heterogeneous catalysis with microporous solids is to provide evidence in support that the reaction is taking place inside the pores. Two general methodologies, either observation of an influence of the substrate molecular size on the reaction rate or the reduction of the particle size can be employed to address this point. For substrates having the same functional groups and inherent intrinsic reactivity, an increase in the molecular size should lead to a decrease in the diffusion coefficient of the large molecule inside the pore voids of the MOF and this should be reflected with a slowdown of the reaction rate. Alternatively, evaluation of the catalytic activity of a series of MOFs with the same composition, but with smaller average particle size should lead to the same (when the reaction takes place inside the pores) or higher (when the reaction takes place partially or completely on the external surface) reaction rates, as consequence of the increase in the proportion of the external surface area as the particle size of the crystallite is reduced [29].

Organization and scope of the review

This manuscript covers the literature appeared up to mid 2013 reporting the use of MOFs as solid catalyst for the synthesis of N-containing heterocycles and has been organized according to the class of compound. Table 2 compiles all the references that will be discussed in the main body of this article, indicating the MOF that has been used as catalyst, the heterocycle that has been prepared and the corresponding reference. Due to its importance, a column indicates whether or not the materials have been surveyed for stability and recyclability. The final section summarizes the main conclusions and provides our view on future developments in the field and the ultimate goals that would be application of MOFs as industrial catalysts in the synthesis of heterocycles of commercial value.

Table 2. List of MOFs used in the synthesis of heterocyclic compounds.

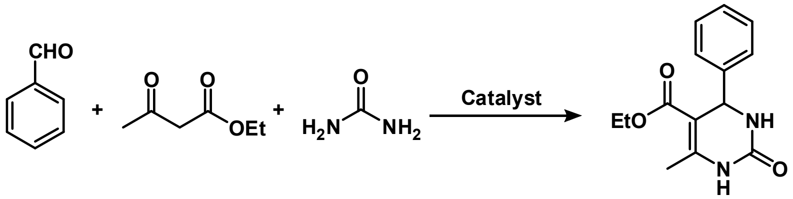
MOF formula	Reaction/Heterocycle	Stability evidence	Ref.
Zn(4,4'-bpe)$_2$(H$_2$O)$_4$.(*m*-BDS)	Biginelli reaction/ dihydropyrimidinone	-	[30]
Zn(4,4'-bpe)$_2$(H$_2$O)$_4$.(*m*-BDS)	2-amino-6-(arylthio)pyridine-3,5-dicarbonitriles	-	[31]
Cu$_3$(BTC)$_2$	Aldol-condensation/ pyrimidine-chalcones	XRD	[32]
Pd/[Zn(Himdc)(bipy)$_{0.5}$].DMF	A^3 coupling/ piperidyl propargylamines	TEM	[33]
Cu(2-pymo)$_2$	A^3 coupling/ piperidyl propargylamines	XRD, hot filtration	[34]
IRMOF-3-GI-Cu^{I}	A^3 coupling/ piperidyl	XRD, hot filtration	[35]

	propargylamines		
Au/IRMOF-3	A^3 coupling/ piperidyl propargylamines	TEM, TPR	36
$Cu_3(BTC)_2$	Friedlander reaction/ 3-acetyl-2-methyl-4-phenylquinoline	XRD	37
$Cu_3(BTC)_2$	Friedlander reaction/ 9-chloroacridine	XRD, filtration	38
MIL-101-SI-Pd	Quinoline	-	39
IRMOF-3-SI-Au	N-tosyl protected indole	XRD, ICP-AES, TPR	40
Pd/MIL-101	2-phenylindole	TEM	41
Pd/MIL-101	N-methyl-2-phenylindole	XRD,ICP-AES, TEM	42
$[Cu(ima)_2]_n$	N-phenylimidazole	XRD, ICP-AES	43
$Cu(2\text{-}pymo)_2$	triazole derivative	XRD, ICP-AES	44
$Cu_3(BTC)_2$-PdL1	triazolo[5,1-a]isoindoles	XRD	45
Pd/MOF-5	morpholino(p-tolyl)methanone	Hot filtration	46
Pd/ZIF-8	Amidocarbonylation of bromo- and iodoarenes	-	47
MIL-101(Cr)/PTA	N-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)-acetamide	XRD	48

Abbreviations: 4,4'-bpe: 1,2-bis(4-pyridyl)ethylene; m-BDS = 1,3-benzenedisulfonic acid; BTC: 1,3,5-benzenetricarboxylate; bipy: 4,4'-bipyridine; DMF: N,N-dimethylformamide; Himdc: 4,5-imidazoledicarboxylate; 2-pymo: 2-hydroxypyrimidinolate; IRMOF-3: Zn(2-atp) where 2-atp stands for 2-aminoterephthalic acid; GI: glyoxalimine; SI:salicylaldehydeimine; ima: imidazole; L1: 4-aminopyridine; PTA: phosphotungstic acid.

2. Pyrimidine and pyridine based heterocycles

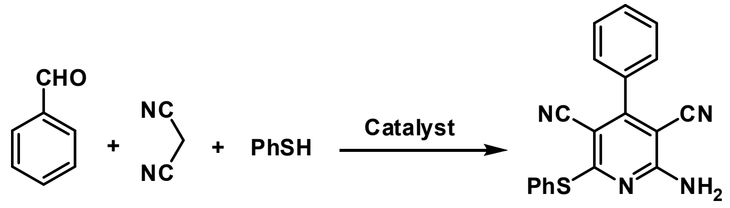
The Biginelli reaction[30] consists in the three-component condensation of an aldehyde, acetoacetate and urea (Scheme 2). This condensation is one of the most convenient ways to synthesize dihydropyrimidinones which have important pharmacological activities.[49] Two isostructural MOFs have been synthesized using Zn^{2+} and Cd^{2+} as metal ions and 4,4'-bpe and m-BDS as ligands leading to the formation of $M(4,4'\text{-bpe})_2(H_2O)_4.(m\text{-BDS})$ (M = Zn^{2+} and Cd^{2+}) and their activity tested in Biginelli reaction by taking benzaldehyde, acetoacetate, and urea as substrates (Scheme 2).[50] High yield (92 %) of the desired product was observed using both MOFs (2.5 mol %) under solvent free conditions at 80 °C in 2 h, whereas Cd based catalyst resulted in only 66 % of the product yield in ethanol in 8 h.[50] When Zn-MOF loading was decreased from 2.5 to 0.5 mol %, the reaction time increased from 2 to 6 h resulting still 86 % yield of the product.[50] Both catalysts were reused five times with no significant changes in the yield indicating the robustness of the crystal structure of these catalysts.[50] However, it would have been convenient to perform leaching experiments to exclude the possible contribution to the catalytic activity of leached metal ions. Also, powder XRD pattern of the fresh and used catalyst would have given some information about the catalyst poisoning by observing changes in the peak intensities. A series of dihydropyrimidinone derivatives with electron donating and withdrawing groups on the aromatic aldehyde have been synthesized with high yields in short reaction times.[50] Although the present catalytic system exhibited high yield under neat conditions, the possibility of diffusion limitations to reactants and products and details of the reaction mechanism are yet to be disclosed.



Scheme 2. Synthesis of dihydropyrimidinone derivative using Cd or Zn MOFs as catalysts. Reaction conditions: benzaldehyde (1 mmol), acetoacetate (1 mmol) and urea (1 mmol), catalyst (0.025 mmol, 2.5 mol %), neat mixture without solvent, 80 °C.

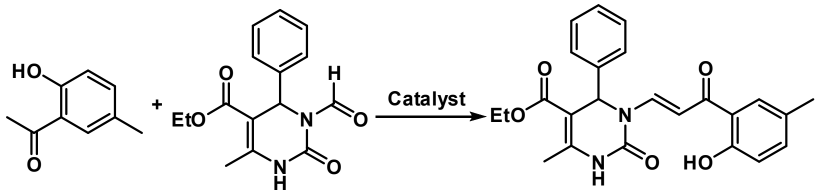
Later, the same group has extended the catalytic activity of these Zn and Cd containing MOFs to the synthesis of 2-amino-6-(arylthio)pyridine-3,5-dicarbonitriles under solvent free conditions using benzaldehyde, malononitrile, and thiophenol (Scheme 3).[31] The use of Zn and Cd MOFs as catalysts resulted in 86 and 87 % of product yield, respectively, in 30 min. On the other hand, these MOFs have shown also high activity in toluene, but required 10 h of reaction time.[31] These longer reaction times probably indicate the competing interaction of solvent molecules with the coordinatively unsaturated sites available in MOFs. It should be commented that this effect of toluene decreasing significantly the reaction rate has been previously observed and could derive from the excellent packing of toluene molecules inside the MOF cavities.[51, 52] The presence of both electron-donating and electron-withdrawing substituents on benzaldehyde does not seem, in contrast, to play a role since both types of benzaldehydes resulted in the desired products in excellent yields. In addition, good to high yields were obtained for thiophene-2-carbaldehyde and n-hexanal indicating the wide scope of these catalysts.[31] Similarly, the substituents on thiophenol showed almost no effect on the reaction, resulting pyridine derivatives in good to excellent yields with both catalysts.

Both catalysts were reused for five times without much change in their activity,[31] but, however, leaching studies and comparison of the powder XRD of fresh and used catalyst are lacking. Although Cd-based MOF showed high activity towards the synthesis of pyridine derivatives, the use of Cd as metal ion may be a drawback due to its toxic nature. On the other hand, the nature of active sites responsible for catalyzing this reaction also needs more clarification. The interest in providing comparison of the catalytic activity of these MOFs with other conventional solid catalysts under the same conditions is large, in order to delineate the possible advantages of MOFs over other solid catalysts, but information on this issue is still missing.



Scheme 3. Synthesis of pyridine derivative catalyzed by Cd or Zn MOFs. Reaction conditions: benzaldehyde (0.2 mmol), malononitrile (0.3 mmol), thiophenol (0.1 mmol), catalyst (0.0020 mmol, 2.0 mol %), 100 ^oC.

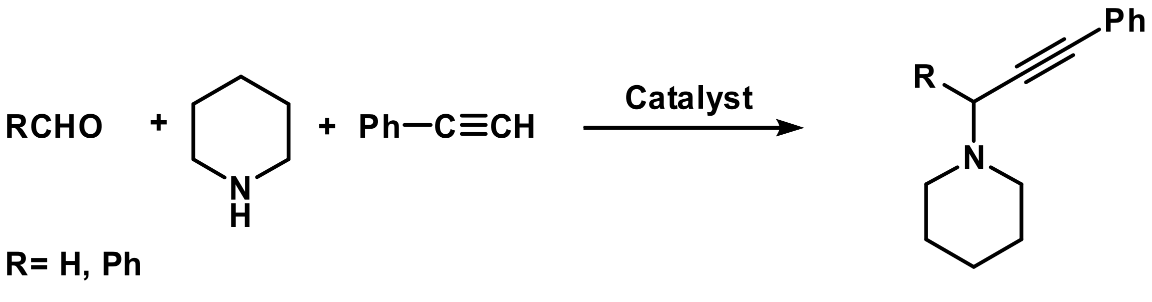
Chalcones are versatile key precursors for the synthesis of many heterocyclic compounds that can exhibit biological or therapeutic activity.[53, 54] On the other hand, pyrimidines exhibit diverse pharmacological properties as effective bactericides, fungicides, viricides and insecticides.[55-64] Pyrimidines and annulated pyrimidine derivatives are also known to display anticancer, antimalarial, antileshmanial and antifilarial activity.[65] In this aspect, $Cu_3(BTC)_2$ has been reported as a general catalyst for the synthesis of pyrimidine-chalcone conjugates through an aldol condensation under mild reaction conditions in toluene adding a few drops of concentrated sulfuric acid (Scheme 4).[32] The catalyst loading was tested and it was found that 11 mol % is required to give the maximum yield (87%) for 1 mmol of substrate. Control experiments clearly indicate that sulfuric acid alone does not catalyze this reaction and when mixing $Cu_3(BTC)_2$ and sulfuric acid, the reaction stops if the solid MOF is removed from the reaction mixture. To explain this synergism, it has been proposed that the Lewis acid activity in $Cu_3(BTC)_2$ is activated or regenerated by the addition of sulfuric acid.[32] No noticeable structural variations were observed in the powder XRD patterns of the fresh and reused $Cu_3(BTC)_2$ catalyst.[32] It is worth reminding that the structural stability of MOFs has always to be conclusively proved and that typically MOFs are dissolved and damaged by strong acid media. In addition, $Cu_3(BTC)_2$ is not a particularly stable MOF and it is known that $Cu_3(BTC)_2$ collapses under not so harsh conditions. Thus, a full study of the how the addition of concentrated sulfuric acid affects the crystal structure of $Cu_3(BTC)_2$ and the condition range in which $Cu_3(BTC)_2$ is stable should be determined prior to any application using strong Brønsted acids as co-catalysts. Another issue to be discussed is if the intraparticle diffusion of reactants inside the pores of $Cu_3(BTC)_2$ to give the products takes place or if only the external surface of $Cu_3(BTC)_2$ participates in the catalysis.



Scheme 4. Synthesis of pyrimidine-chalcone conjugates catalyzed by $Cu_3(BTC)_2$ as catalyst and H_2SO_4 as co-catalyst. Reaction conditions: substituted acetophenone (1 mmol), N-formylpyrimidinone (1.1 mmol), toluene (4 mL), $Cu_3(BTC)_2$ (0.075 g), 40 °C, 1 to 2 drops of conc. H_2SO_4 10-12 h.

3. Heterocyclic Propargylamines

Propargylamines are key intermediates for the preparation of many nitrogen-containing biologically active compounds, such as β-lactams and oxotremorine analogues, as well as common motifs in natural products and therapeutics drugs.[66, 67] The interest of the preparation of propargylamines lies on the versatility of these substituted heterocycles as intermediates in organic synthesis as well as the importance of this structural motif in natural products and therapeutic drug molecules.[68, 69] Preparation of heterocyclic propargylamines can be carried out by catalytic coupling of aldehyde, an amine and a terminal alkyne that undergoes C-H activation where water is considered to be one of the byproducts. This reaction is often called as A^3 coupling and can be applied to the synthesis of propargylamines in general,[70] although piperidine is one of the preferred reagents.



Scheme 5. Synthesis of heterocyclic propargylamine derivatives catalyzed by MOFs.

In this way, Pd NPs were supported on desolvated $\{[Zn(Himdc)(bipy)_{0.5}].DMF\}$ to give [Pd/Zn-MOF] and its activity tested for A^3 coupling with piperidine.[33] The powder XRD pattern of Pd/Zn-MOF showed some changes compared to Zn-MOF. XPS analysis indicated that Pd is present in the metallic state.[33] The high-resolution transmission electron microscope (HRTEM) image revealed fine dispersion of Pd NPs over the Zn-MOF matrix in the narrow size range of 1–2 nm.[33] The loading of Pd was found to be 1.54 wt % as determined by inductively coupled plasma–optical emission spectrometry (ICP-OES) analysis. The reaction between benzaldehyde, piperidine and phenylacetylene resulted in 72 % conversion with 58 % selectivity of propargylamine using Pd/Zn-MOF as catalyst at 90 ^{o}C in toluene (Scheme 5).[33] This reaction also needs 0.5 equivalents of cesium carbonate as cocatalyst. The role of the base is not clear and further studies are necessary to clarify this point. In contrast, the observed selectivity towards propargylamine is low (58 %), indicating the formation of other products.[33] The nature of these byproducts and the factors responsible for their formation remain unclear.

A similar trend in terms of conversion and selectivity were observed when replacing benzaldehyde by substituted benzaldehydes with significant changes in the yield, but again results in moderate selectivity.[33] This may be explained from the operation of shape selectivity and the influence of the electronic nature of the substituents. Pd/Zn-MOF was reused for four cycles with slight decrease in the conversion.[33] In addition, the particle size of Pd NPs remains almost unchanged even after four catalytic cycles as evidenced from TEM images. Leaching experiments are, however, lacking and the possibility of Pd depletion from the solid together with the partial pore blockage may be responsible for the lower activity observed after four catalytic tests. It should be commented that, although it is a common practice in the field to determine reusability by given data at final reaction times, observation of a constant conversion at a certain reaction time does not necessarily imply that the solid catalyst is not partially deactivated, since the temporal evolution of conversion and product yield and their corresponding initial reaction rates are the key parameters to affirm catalyst stability.

Similarly, [Cu(2-pymo)$_2$] (1 mol % Cu) devoid of noble metal NPs has been reported as heterogeneous catalyst for the reaction between piperidine, paraformaldehyde, and phenylacetylene (Scheme 5) at 40 ^{o}C resulting in 99 % yield of the corresponding propargylamine.[34] No significant loss of crystallinity and activity were observed for Cu(2-pymo)$_2$ after five runs. Also, leaching experiments showed the absence of Cu in the solution. The activity of [Cu(2-pymo)$_2$] is also comparable to that of other heterogeneous copper-containing catalysts reported in literature, such as copper-exchanged USY zeolite, that afforded 90% yield of propargylamine after 15 h.[71] The yield of propargylamine obtained after 4 h of reaction in the case of phenylacetylene was 60 %, while in the case of 1-ethynylnaphthalene was only 8 % and a longer time is required to attain full conversion. These differences in product yield cannot be rationalized as due the intrinsic reactivity of the two substrates that behave similarly in solution and were attributed to the slower diffusion of bulkier naphthylpropargylamine through the pores of MOF. It is reasonable to assume that for reactions taking place inside the internal voids of MOF the yield of the corresponding propargylamine would depend, among other factors, on the size of aldehyde, alkyne and amine. However, the decrease in the reactivity of substrates should also be taken into account and, thus, propargylamine is hardly formed when paraformaldehyde was replaced by benzaldehyde.[34] A^3 couplings using formaldehyde are generally less demanding from the catalytic point of view than with benzaldehyde. In this case, this failure should be attributed to the sluggish formation of the iminium species by addition of piperidine to benzaldehyde, since this uncatalyzed reaction should require higher temperature than for formaldehyde or its precursor para-formaldehyde. Thus, for benzaldehyde, piperidine and phenylacetylene, full conversion was achieved when the catalyst loading was 10 mol % Cu and the reaction temperature was increased from 40 to 100 ^{o}C. This relatively low temperature and small increase of catalyst ratio should not lead to this high yield of propargylamine if substrates or product could not diffuse through the pore system.

A MOF-supported Cu(I) catalyst containing N,O-chelating ligands [IRMOF-3-GI-Cu^{I}] was prepared by postsynthetic modification of IRMOF-3 and used as heterogeneous catalyst for A^{3} coupling.[35] Preparation of IRMOF-3-GI-Cu^{I} was carried out in a stepwise manner, the first process being the preparation of IRMOF-3-GI by reacting at room temperature glyoxal with freshly synthesized IRMOF-3.[35] The functionalized IRMOF-3-GI was then treated with CuI to generate the corresponding Cu(I)-containing catalyst material, IRMOF-3-GI-Cu^{I}. The powder XRD patterns of both IRMOF-3 and modified IRMOF-3-GI showed identical peaks, confirming that the original MOF framework structure is maintained after functionalization. ICP analysis of IRMOF-3-GI-Cu^{I} indicated that coordination with CuI leads to a Cu weight loading of 1.05 wt.% in the Cu MOF, corresponding to a degree of functionalization of 4.7 % of the total NH_2 groups present in IRMOF-3.[35] Piperidine was again selected to determine the catalytic activity of this material and the reaction conditions were optimized for paraformaldehyde, phenylacetylene, and piperidine (Scheme 5).[35] A yield of 91 % with TON of 282 was achieved in chloroform at 40 ^{o}C using IRMOF-3-GI-Cu^{I} as catalysts. To provide a quantitative assessment of the activity of IRMOF-3-GI-Cu^I, the performance of physical mixture of IRMOF-3 and CuI was checked as catalyst under the same conditions, whereby a lower yield (21 %) was obtained.[35] The superiority of IRMOF-3-GI-Cu^I as catalyst illustrates the advantages of distributing the sites on a high surface area and large pore volume, derived from the maintenance of the IRMOF crystal lattice. The lower activity observed by the physical mixture can be simply ascribed to the agglomeration of the active sites and loss of porosity as CuI adsorbs on IRMOF-3. It should be commented that although the comparison of CuI/IRMOF-3 mixture with IRMOF-3-GI-Cu^I is pertinent, the nature of the active sites are not coincident and it may be that the catalytic data reflect mainly on the higher activity of the Cu^I Schiff base attached to the IRMOF-3 framework.

Data on the scope of IRMOF-3-GI-Cu^I as catalyst indicate that secondary aliphatic amines render high yields of the desired products.[35] Although, aliphatic aldehydes including cyclic and acyclic display good reactivity affording high yields of the corresponding propargylamine, the reactivity of paraformaldehyde was higher than that of butyraldehyde, isopentaldehyde or cyclohexanecarbaldehyde. The latter aldehydes required longer reaction times than paraformaldehyde to achieve high yields, a fact that was attributed to the operation of shape selectivity.[35] It is clear, however, that the higher intrinsic reactivity of formaldehyde should have been taken into account in this comparison.

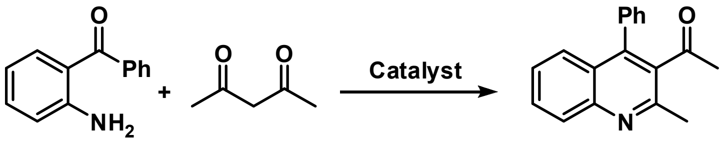
The heterogeneity of the catalytic process using IRMOF-3-GI-Cu^I was supported by performing a hot filtration test.[35] ICP analysis revealed the presence of 0.5 ppm of Cu in the filtrate. Stability of the IRMOF-3-GI-Cu^I as catalyst was addressed by reusing the material in four consecutive cycles, observing a slight decrease in the yield although it was still higher than 82 % at the fourth run.[35] Furthermore, powder XRD showed no structural variation between the parent and the four times used catalyst. It has to be commented that measurements of the initial reaction rates are also necessary to prove that the catalytic activity is maintained upon recycling.[35]

Au functionalized IRMOF-3 was synthesized either by post covalent modification or by one pot synthesis.[36] Post synthetic covalent modification resulted in 4.6 % of Au with a fraction of cationic gold (Au^{3+}/Au^0 = 0.2), while one pot synthesis led to the formation of materials with either 3.2 or 0.6 % of Au. Powder XRD of the Au functionalized IRMOF-3 by post covalent modification exhibited some changes in the crystal lattice compared to parent IRMOF-3, due to the deviation, shrinkage or even the collapse of pores during the modification process.[36] In contrast, the samples prepared by one pot synthesis, either 0.6 %Au/IRMOF-3 and 3.2 %Au/ IRMOF-3, are characterized by a higher crystallinity.[36] Au NPs were close to spherical shapes with average diameters of 3.3, 1.7, and 2.5 nm for 4.6 % Au/IRMOF-3, 0.6 % Au/IRMOF-3 and 3.2%Au/IRMOF-3, respectively. The catalytic activity of these Au catalysts was tested in dioxane at 120 °C for the three-component coupling of benzaldehyde, phenylacetylene and piperidine leading to N-substituted piperidines (Scheme 5).[36] It was shown that the 4.6 % Au/IRMOF-3 catalyst prepared by post covalent modification exhibited higher catalytic activity than that of 3.2 % or 0.6 % Au/IRMOF-3 prepared by one pot method, although the former exhibits much lower crystallinity than the latter two catalysts at 120 °C. This increased activity of the former catalyst was attributed to the contribution of a fraction of cationic gold. Considering the total Au content, the reaction rates at the maximum conversions were calculated to be 120.5, 9.2, and 3.6 mmol $g_{Au}{}^{-1}$ h^{-1} for 4.6 % Au/IRMOF-3, 0.6 % Au/IRMOF-3, and 3.2 % Au/IRMOF-3, respectively,[36] showing that the reaction rate of 4.6%Au/IRMOF-3 is one order of magnitude higher than those of 0.6% Au /IRMOF-3 and 3.2%Au/IRMOF-3. Reusability tests showed that the activity of 4.6%Au/IRMOF-3 decreases from a benzaldehyde conversion of 77 to 66 from the 1st to 4th run, indicating the gradual deactivation of catalyst. This activity decay of 4.6 % Au/IRMOF-3 upon use appears to be correlated to the agglomeration of Au NPs, whose average size increases to 13.8 nm, with maximum sizes up to 34.5 nm. Although the location of these large are not discussed, it is unlikely that they can be included within the MOF void and it is more reasonable to assume that relocation of Au NPs from the interior to the external surface of the crystallites has taken place. Furthermore, the deactivation of 4.6%Au/IRMOF-3 could also be partly due to the reduction of Au^{3+}, as demonstrated by the TPR analysis, and to a slight leaching of gold (ca. 5%) over the recycled 4.6%Au/IRMOF-3. Notably, aliphatic aldehydes such as cyclohexanecarboxaldehyde and n-octanaldehyde exhibited higher activities than aromatic aldehydes with the 4.6%Au/IRMOF-3, 0.6%Au/IRMOF-3, and 3.2%Au/IRMOF-3.[36] Among the various amines tested, heterocyclic piperidine, pyrrolidine, and morpholine gave 77, 91.2 and 54.6 % conversions of benzaldehyde respectively, whereas diethylamine afforded 26.6 % conversion.[36] This reactivity order was probably due to the iminium ions generated from alicyclic amines and benzaldehyde which are more stable than the one generated from dialkyl amine and benzaldehyde.

4. Quinoline based heterocycles

Quinolines have been found to exhibit important antifungal and antibacterial activity[72] that depends largely on the substituents present on the aromatic heterocycle.[73] For this reason, there is a continuous interest in developing general catalytic synthetic methods for the synthesis of this important class of N-containing compounds.

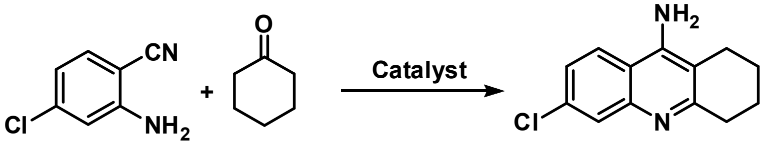
One of the general routes for the synthesis of quinolines is the so-called Friedländer reaction consisting in the condensation of 2-aminophenones with carbonylic compounds having unsubstituted α-methylene groups.[72] $Cu_3(BTC)_2$ has been reported to be an efficient catalyst for the Friedländer synthesis of quinoline derivatives under solvent-free conditions at 80 °C.[37] The reaction between 2-aminobenzophenone and acetylacetone in the presence of 8.3 mol % $Cu_3(BTC)_2$ resulted in 80 % of 3-acetyl-2-methyl-4-phenylquinoline in 1 h and the reaction was complete in 2 h (Scheme 6).[37] One key point in heterogeneous catalysis by MOFs is to compare the activity of these materials with respect to other solid catalysts. In this regard, it was found that under the same experimental conditions, H-BEA (a large pore zeolite) and Al-SBA-15 (a mesoporous aluminosilicate) yielded, 38 and 36 %, respectively, after 1 h.[37] The high activity of $Cu_3(BTC)_2$ compares, thus, favorably with that of acid zeolites or mesoporous aluminosilicates. Control experiments have proved that the reaction was catalyzed by the Lewis acid sites present in $Cu_3(BTC)_2$ and the contribution from the Brønsted acid sites were negligible. Certainly, this type of comparative studies is very useful to rank the activity and stability of MOFs with respect to solid acids and porous materials in particular.[24] The catalyst was recovered after the reaction without any significant structural change.



Scheme 6. Synthesis of quinoline derivative catalyzed by $Cu_3(BTC)_2$. Reaction conditions: acetylacetone (5 mmol), 2-aminobenzophenone (1 mmol), activated $Cu_3(BTC)_2$ (0.083 mmol), 80 °C.

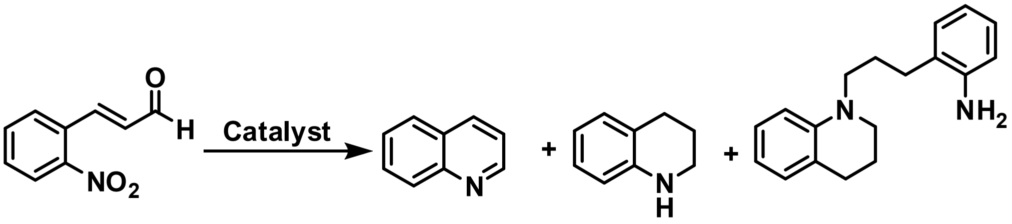
Recently, the same group has extended their work on elucidating the Lewis acid nature by adsorption experiments with pyridine and CO as probe molecules.[74] Pyridine as a probe can distinguish between Brønsted or Lewis acid sites leading to the formation of pyridinium ions or Lewis acid adducts that can be differentiated and quantified by monitoring in IR the intensity of the vibration bands at about 1550 and 1450 cm^{-1} characteristic of each of these species.[75] Similarly, CO exhibits distinctive vibration bands in the region between 2200 and 1900 cm^{-1} that also reports on the interaction with the Brønsted/Lewis acid sites.[76] These studies provide information about the nature of the active sites and serve to design more active and selective materials for these condensation reactions. The influence of the temperature and catalyst loading on the activity of $Cu_3(BTC)_2$ were also reported for the above mentioned Friedländer reaction.[74] The better performance of $Cu_3(BTC)_2$ compared to H-BEA and Al-SBA-15 could be attributed to the lowering of energy barriers, especially for the annulation reaction step and to a favorable geometry of the reaction precursor formed by adsorption of reactants on two adjacent Cu^{2+} sites in $Cu_3(BTC)_2$.[74] The effect of the adjacent (dual) active sites in $Cu_3(BTC)_2$ in the Friedlander reaction was recently confirmed by a detailed theoretical study and is relevant to understand how a high density of Lewis acid sites in the same reaction cavity can cooperate to the activity by providing simultaneous activation of more than one site on the same reaction intermediate.[77] This presumable multiple activation resulting from the presence of coordinatively unsaturated Cu^{2+} ions in $Cu_3(BTC)_2$ separated by 0.81 nm can explain the higher activity of this MOF when compared with H-BEA or Cu-BEA.[74]

Notably, $Cu_3(BTC)_2$ has been successfully used as catalyst (8.3 mol%) for the synthesis of 9-chloroacridine in 58% yield from 2-amino-4-chlorobenzonitrile and cyclohexanone (Scheme 7) which is widely used as building block for the synthesis of acetylcholine esterase inhibitors.[38] This example is particularly important considering that MOF catalysis should aim to at the synthesis of highly valuable chemicals targeting for a commercial process. It should be, however, commented that $Cu_3(BTC)_2$ is not among the most stable MOFs and also the mol percent of catalyst used is relatively large. For this reason, it is still desirable to explore the activity of other more robust MOFs that could be employed in higher substrate/catalyst ratios.



Scheme 7. Synthesis of 9-chloroacridine catalyzed by $Cu_3(BTC)_2$.

MOFs offer the possibility to design multifunctional catalysts,[16] by combining the activity of various sites that can be located at the metallic cluster units, at the organic linker or in the cavities and this multifunctional catalyst can be applied to the synthesis of heterocycles in which several steps are necessary for the formation of the final compound. For instance, MIL-101(Cr) contains coordinatively unsaturated Cr^{3+} sites that can act as Lewis acid centers and can simultaneously incorporate Pd or Pt, either as isolated metal complexes or in the form of encapsulated metal NPs, as hydrogenation/oxidation centers. In this way, MIL-101(Cr) containing a noble metal can be a bifunctional catalysts with activity for the one-pot synthesis of quinoline starting from 2-nitrocinnamaldehyde.[39] The Pd and Pt loading in the example reported were 0.35 and 0.34 wt %, respectively, as determined by ICP analysis. The average particle size of Pd and Pt NPs were 3 and 4 nm, respectively, as evidenced from TEM analysis. The Pd and Pt loading in the MIL-101(Cr) functionalized metal complex was 0.37 wt %. Pd/MIL-101(Cr) resulted in 99 % conversion with the maximum selectivity towards the formation of tetrahydroquinoline of 73% and also 13 % of dimeric product (Scheme 8).[39] In contrast, Pt/MIL-101(Cr) yielded exclusively 97 % of tetrahydroquinoline.[39] The catalytic activity of these MOF catalysts is comparable to those of Pd/Al_2O_3 and Pt/Al_2O_3 in terms of conversion and selectivity towards tetrahydroquinoline. On the other hand, Pt and Pd NPs supported on active carbon exhibited much higher activity than MOF based catalysts leading to the highest selectivity of tetrahydroquinoline. This activity of solid catalysts containing metal NPs contrasts with that of the corresponding complexes, that exhibit the desirable selectivity towards the aromatic quinoline.[39] Thus, Pd complex supported on MIL-101(Cr), MIL-101(Cr)-SI-Pd, gave 99 % yield of quinoline in 10 h, what is a remarkable result in terms of selectivity for a tandem process.[39] Moreover, increasing the time to 120 h reduces the yield of quinoline to 30 %, but increases the yield of tetrahydroquinoline to 70 %. In this way a certain control on the process can be achieved by stopping the reaction once the primary product is formed or allowing the transformation of the primary into the secondary tetrahydroquinoline product.



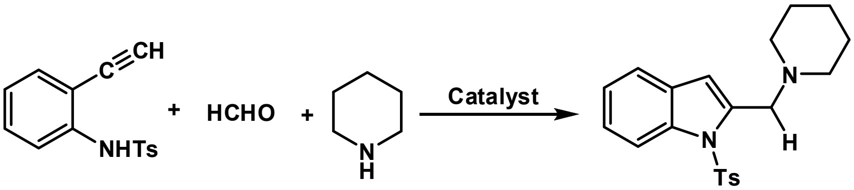
Scheme 8. Synthesis of quinoline through one-pot tandem reaction using Pd/MIL-101 or MIL-101-SI-Pd. Reaction conditions: 2-nitrocinnamaldehyde (0.1 mmol), toluene (1 mL), 100 °C. $pH_2 = 0.5$ MPa, 5 mg MOF (metal/2-nitrocynnamaldehyde molar ratio ≈ 1:760).

5. Indole and its derivatives

The indole nucleus is one of the most ubiquitous heterocycle in nature and in synthetic compounds with biological activities,[78] and, thus, the development of new, efficient, and sustainable syntheses is of high interest.

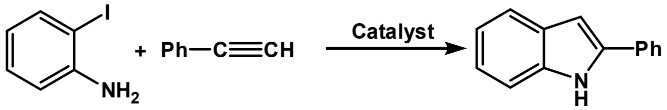
In this context, post-synthetic modification of IRMOF-3 by treating with salicylaldehyde resulted in the formation of IRMOF-3-SI. This modified host material was further allowed to react with $NaAuCl_4$ to give the corresponding Au complex covalently attached to the framework of IRMOF-3 as IRMOF-3-SI-Au.[40] Elemental analysis indicated that the maximum percentage of $–NH_2$ functionalization by salicylaldehyde from the total $–NH_2$ amount without losing framework integrity was about 3%, while the percentage of Au Schiff complexes was 2 %. Structural stability was monitored during the post-synthetic modification by powder XRD. The N_2 adsorption-desorption measurements showed a decrease in BET surface area from 750 to 400 m^2/g after reaction of the IRMOF-3 with salicyladehyde, while Au(III) complexation did not produce significant further reduction (380 m^2/g). Overall, this sequence starting from as-synthesized IRMOF-3 illustrates the possibility that post-synthetic modification offers to introduce active sites in porous MOFs.

The catalytic activity of IRMOF-3-SI-Au was tested in the domino coupling-cyclization of ethynylaniline, piperidine and paraformaldehyde leading to the formation of indole derivatives (Scheme 9).[40] Also, the catalytic activity of this MOF was compared with Au/ZrO_2, Au(III) Schiff base complex and $AuCl_3$. From the initial reaction rate and the estimated number of sites, the TOF was found to be 52, 12, 40, and 3 h^{-1} for IRMOF-3-SI-Au, Au/ZrO_2, Au(III) Schiff base complex, and $AuCl_3$, respectively. Comparing with the homogeneous Au(III) Schiff base complex, IRMOF-3-SI-Au gave a similar, but higher, initial TOF value (52 vs. 40 h^{-1}) and, in addition, is more stable. In fact, IRMOF-3-SI-Au catalyst can be successfully reused for four cycles without any loss in its activity. Nitrogen adsorption isotherms showed no change in the surface area, ICP-AES was not able to detect leaching of Au and TPR studies confirmed the presence of Au^{III} in the used material indicating that no reduction was occurred. However, powder XRD revealed an apparent crystallinity loss of the framework. It remains to be established if this decrease in the intensity of the XRD peaks really reflects a deterioration of the framework structure or if it is due to other causes, such as an increase in the disorder of the structure accompanied by the presence of spurious organic matter, while the porous lattice remains mostly unchanged. On the other hand, the much higher TOF of IRMOF-3-SI-Au compared to that of Au/ZrO_2 is not unexpected since it has been found that in the latter catalyst the fraction of Au^{III} with respect to total gold is only 0.25. However, when the TOF value is calculated considering only the fraction of the cationic gold in Au/ZrO_2, which are presumed to be the active sites of this tandem reaction, then, a TOF of 48 h^{-1}, that is not too different from the value measured for the MOF, is estimated. According to this rationalization of the kinetic information, the main feature of IRMOF-3-SI-Au as solid catalyst is that, in this solid, all the Au atoms would be accessible and in the form of the Au^{III} active species. Single-site solid catalysts with accessible sites, as it is apparently the case of IRMOF-3-SI-Au, are the target in heterogeneous catalyst**.** This catalytic system allowed synthesizing a variety of N-tosyl protected indole compounds in high yields (80-95 %).



Scheme 9. One-pot synthesis of indole derivatives using IRMOF-3-SI-Au. Reaction conditions: ethynylaniline (0.2 mmol), paraformaldehyde (0.4 mmol), piperidine (0.24 mmol), IRMOF-3-SI-Au (14 mg, 0.001 mmol Au), 1,4-dioxane (1.0 mL), 40 °C.

One-pot synthesis of 2-arylindole from 2-iodoaniline and phenylacetylene (Scheme 10) using Pd/MIL-101 as catalyst in aqueous media has been reported.[41] The catalytic activity of Pd/MIL-101 was compared with Pd/MCM-41. Pd/MIL-101 and Pd/MCM-41 were prepared with very similar palladium loading in 2.9 and 2.8 wt % with a mean particle size of 2.6 and 3.9 nm, respectively. In principle, the tridirectional geometry of the pores in of MIL-101 is more suited for the formation of independent, highly dispersed, immobilized palladium NPs of particle size commensurate with the cavity dimensions in the range from 1 to 3 nm. In contrast, the unidirectional geometry of the straight channels in mesoporous MCM-41 silica should allow mobility of the particles in the axis along the channels with no immobilization of the NPs in one direction. This freedom should allow the growth of the NPs and, more importantly, their migration outside the mesopores. Migration of Pd NPs outside the pore channels of MCM-41 would result in their agglomeration on the outer MCM-41 surface forming bigger particles. This will affect to the durability and recyclability of the Pd-containing solid as catalyst, but may not have influence on the activity of the fresh materials. However, experimentally, it was observed that that the initial reaction rate using Pd/MIL-101 was two times that over Pd/MCM-41 and that the time required for complete 2-iodoaniline conversion in Pd/MIL-101 was in half that time needed for Pd/MCM-41. This higher activity of Pd/MIL-101 has been mainly attributed to the larger number of Pd active sites in Pd/MIL-101 relative to Pd/MCM-41, even though the two solids contain the same Pd loading. This is, however, in contradiction of similar Pd distribution in both solids at initial reaction time. It has also been proposed that enhanced surface hydrophobicity owing to the organic linkers BDC and the existence of Lewis acidity on MIL-101 at the exchangeable metal coordination sites (Cr^{3+}) could play a role in the catalytic activity of Pd/MIL-101. Both factors, hydrophobicity and adsorption, would favor the reactivity of 2-iodoaniline, and thus, would contribute positively to the activity of Pd/MIL-101 with respect to other porous materials with lower affinity for the substrate. Considering the flexibility in design and synthesis of MOFs, it would be of interest to explore further the potential of hydrophobicity and co-operative sites to develop catalysts with enhanced activity, particularly in this case where co-catalysts such as Cu(I) and base are necessary to render the indol derivative. Further, commercial 3% Pd/C also showed lower reactivity than Pd/MIL-101 and this higher activity was ascribed to the higher dispersion of Pd active sites resulting from the immobilization and confinement of small nanometric Pd NPs on the cages of MIL-101. No oxidation of Pd NPs was observed during the course of reaction and the leaching test showed the presence of negligible 0.9 ppb concentration of Pd in the reaction mixture, these two facts illustrating the advantages of MIL-101 as porous matrix to host Pd NPs.



Scheme 10. One-pot synthesis of 2-phenylindole using Pd/MIL-101. Reaction conditions: 2-iodoaniline (1.0 mmol), phenylacetylene (1.2 mmol), PPh_3 (0.02 mmol), CuI (0.05 mmol), K_2CO_3 (1.5 mmol), H_2O (10mL), Pd/MIL-101 (1.0 mol % Pd), 90 ^oC, 15 h.

Besides the activity of fresh materials, catalyst stability was another issue to be addressed. Pd/MIL-101 could be reused ten times for the reaction between 2-iodoaniline and phenylacetylene without much loss in the catalytic activity, while Pd/MCM-41 showed a decrease in the yield of 2-phenylindole after the 6th run. As evidenced from TEM images, this decrease in the catalytic activity of Pd/MCM-41 was explained as mainly due to the collapse of the pore structure of the MCM-41 support and agglomeration of Pd NPs during the reaction. Apparently, the crystal structure of the MIL-101 matrix is more robust in the reaction conditions than mesoporous MCM-41 silica and Pd NPs remain confined in the cages of MIL-101, being the catalyst durable during the reaction. In summary it appears that the higher catalytic recyclability of Pd/MIL-101 derives from the structural robustness of MIL-101 framework compared to MCM-41, impeding agglomeration of Pd NPs under the reaction conditions. It should be commented, however, that Pd NPs agglomeration is a process that not necessarily implies the collapse of the MCM-41 mesopores and that large particles blocking the pore opening would lead to apparent low surface area values without necessarily implying structure collapse.

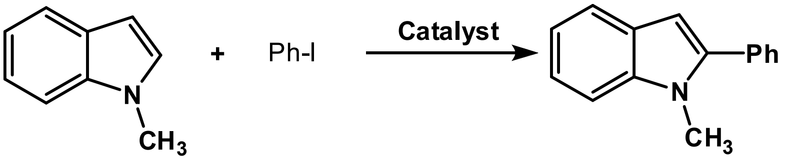
One problem of the cyclocondensation of 2-iodoaniline and phenylacetylene is that the reaction protocol requires triphenylphosphine, copper iodide and potassium carbonate as base to achieve high yields of the 2-arylindole. These co-catalysts are afterwards impossible to separate from the MOF, making contamination of Pd/MIL-101 unavoidable under these conditions. Alternative procedures avoiding the use of these co-catalysts would be convenient to increase even further the productivity of Pd/MIL-101. It can be envision for instance that the Cu(I) could be co-incorporated in the MOF and that a phosphine-free process could be feasible. Overall, the results of the two-component coupling of 2-iodoaniline and phenylacetylene exemplify again the superiority of Pd/MIL-101 over other conventional Pd catalysts, both in terms of activity and durability. It is desirable, however, to develop improved reaction procedures that do not lead to contamination of the solid catalyst, allowing its recyclability. Further work should be carried out to provide evidence to understand the origin of this higher activity of Pd incorporated in MIL-101 and to exploit this understanding to other related reactions. Additionally, the use of more robust MOFs or MOFs with optimal pore size/acidity could enhance the activity of Pd NPs even more.

Arylation of indole at C_2 position is one of the most important reactions for the synthesis of functional indoles with interesting biological activity.[79] It has been found [42] that Pd/MIL-101 can promote the reaction of *N*-methylindole with phenyl iodide (Scheme 11). The Pd/MIL-101 sample employed for this coupling contained Pd NPs (0.5 wt%, 2.6 ± 0.5 nm average diameter) highly dispersed into the pores of MIL-101. It was found, however, unavoidable to form some NPs outside the pores due to the electrostatic interaction between MIL-101 and the palladium ion used as precursor of Pd NPs. It can be anticipated that the presence of Pd NPs located on the external surface will play a negative role on the catalytic performance of the material and, therefore, its percentage should be minimized to increase TON values, product selectivity and catalyst recyclability.

Out of the various reaction conditions screened to achieve high yield of the desired product, the best ones were those in which cesium acetate was used as base and dimethylformamide or dimethylacetamide as solvents at 120 ^{o}C. The target 2-phenyl substituted indole resulted in 85 % yield and without observation of C_3 arylation. The reaction did not occur in the presence of MIL-101 or in the presence of Pd/MIL-101 without cesium acetate. Increasing the amount of the catalyst in the range from 0.5 to 5 mol % Pd led to a steady decrease (78 to 45%) of the yield of the desired product accompanied by a concomitant increase up to 32 % in the yield of the biphenyl byproduct arising from the homocoupling of iodobenzene. This shift in product selectivity probably indicates a variation of the nature of the active Pd site and would deserve further study to be fully understood. A commercial Pd/C catalyst (5 wt % Pd) resulted in traces of the C_2-arylation product and 22 % of the biphenyl byproduct. This comparison of the activity of Pd/MIL-101 with that of other related or common Pd catalysts for the indole coupling with iodobenzene provides another remarkable example of the superior performance that Pd NPs can exhibit when encapsulated inside stable MOFs having adequate properties. The catalytic activity of embedded Pd NPs should depend on the composition, structure and properties of MOF as host. In this context, a low activity was observed for Pd NPs embedded on MIL-53(Al)–NH_2 giving rise to 25 % conversion. The higher activity of Pd/MIL-101 compared to MIL-53(Al)–NH_2 may be explained as arising from the larger surface area and accessible mesoporous cages of MIL-101, which would be responsible for the high dispersion of the palladium active sites, while at the same time allows an easy diffusion of the reactants into the pores reaching the active sites. Other alternative explanations such as that the enhanced surface Lewis acidity of MIL-101 due to the presence of a coordinatively unsaturated position for each Cr^{3+} ion not present in MIL-53(Al) may favor the adsorption of reagents, thus, increasing the activity of this solid, cannot be excluded.

Although the reaction was carried out in DMF in the presence of base, conditions that always favor Pd leaching, the concentration of Pd on the liquid phase at the end of the reaction employing Pd/MIL-101 as catalyst was measured to be 0.4 ppm from ICP-AES analysis. After using the catalyst five times, the crystallinity and particle size were retained as evidenced by XRD and TEM, suggesting catalyst stability.

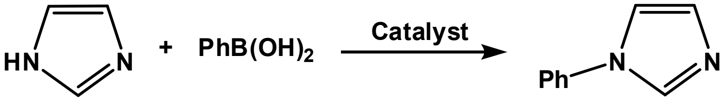
Activation of bromobenzene and chlorobenzene is well-known to be more difficult than activation of iodobenzene, a fact that has been rationalized as due to the higher bond energy of the C–Br and C–Cl bonds with respect to C–I. Thus, not surprisingly, the reaction of bromobenzene or chlorobenzene with N-methylindole required harsh conditions and extended reaction time to take place. Even at 150 ^{o}C for 48 h, low yields were obtained for the reaction of bromobenzene (31%) and chlorobenzene (21%) with N-methylindole. Sterically hindered *o*-substituted aryl halides or substituted in any position with electron donating groups are also less reactive substrates for C-C coupling. In the present case, 2-iodoanisole reacts with N-methylindol in a limited extent, affording the corresponding C_2-arylation product in moderate yield (49 %). These unsatisfactory yields for bromo and chloroarenes as well as for the ortho isomers clearly indicate that there is still a need for new generations of more active heterogeneous Pd catalysts, following the lead of highly active Pd complexes developed in homogeneous catalysis to overcome low substrate reactivity.



Scheme 11. C_2 arylation of N-methylindole using Pd/MIL-101 as catalyst. Reaction conditions: N-methylindole (1 mmol), iodobenzene (1.2 mmol), CsOAc (2 mmol), Pd/MIL-101 (0.1 mol % Pd), DMF (3 mL), 120 °C, 24 h, under air.

6. Derivatization of imidazoles

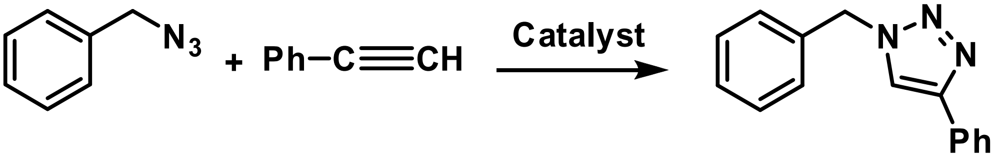
$[Cu(ima)_2]_n$ has been tested as catalyst for the *N*-arylation of imidazoles using phenylboronic acid (Scheme 12) in methanol at room temperature.[43] Under the optimized reaction conditions, $[Cu(ima)_2]_n$ promotes *N*-arylation in 86 % yield, while homogeneous catalysts showed lower yields. The catalyst was recovered quantitatively from the reaction mixture and reused four times with consistent activity. Leaching experiments showed 0.05 ppm of Cu in the filtrate as evidenced from ICP-AES. Hot filtration test showed no further increase in the conversion after removing the solid catalyst from the reaction mixture. Powder XRD of the fresh and five times used catalyst showed very similar diffraction pattern suggesting the structural stability of the Cu MOF catalyst. The reaction is catalyzed by coordinatively unsaturated sites around Cu^{2+} ions, available in the structure of $[Cu(ima)_2]_n$. Considering the wide interest in imidazoles and imidazolium ionic liquids, it would be important to expand the scope of this catalyst to the synthesis of *N*-aryl imidazoles of commercial interest.



Scheme 12. N-arylation of imidazole catalyzed by $[Cu(ima)_2]_n$. Reaction conditions: phenylboronic acid (1.0 mmol), imidazole (1.2 mmol), methanol (3 mL), and catalyst (5 mol %), under air.

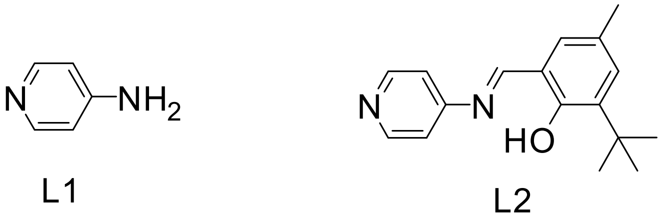
7. Triazole derivatives

Various copper-containing MOF namely, $Cu(2\text{-}pymo)_2$, $Cu(im)_2$, $Cu_3(BTC)_2$ and Cu(BDC) [im: imidazolate; BDC: 1,4-benzenedicarboxylate] have been tested as catalysts for the 1,3-dipolar cycloaddition ("*click*" reaction) between benzyl azide and phenylacetylene.[44] $Cu(2\text{-}pymo)_2$ exhibited high activity resulting in complete conversion of the benzyl azide in ethanol at 70 ^{o}C in 4 h, leading to the formation of 1,4-substituted triazole as the only product (Scheme 13). This catalyst was used for six consecutive cycles without any change in its activity and powder XRD of fresh and used $Cu(2\text{-}pymo)_2$ showed no significant changes in the crystallinity. Further, ICP-AES revealed that the copper content in the liquid phase after the reaction was below the detection limit. $Cu(im)_2$, on the other hand, resulted in 99 % yield of 1,4-substituted triazole in 1 h. In contrast, $Cu_3(BTC)_2$ and Cu(BDC) exhibited 37 and 42 % yield respectively in 8 h. The differences in activity cannot be explained based on pore dimensions, since all the MOFs tested have channel dimensions larger than the substrates and products and hence diffusion limitations are not expected to play a role. The catalytic activity of the series of Cu MOFs evaluated seems to point out that those MOFs comprising copper(II) sites surrounded by four diaza heterocyclic nitrogen atoms (CuN_4) are more active catalysts than those having copper centers surrounded by four carboxylate oxygen atoms (CuO_4). The reaction exhibits an induction period that depends on each particular MOF catalyst. The lower activity of $Cu_3(BTC)_2$ and Cu(BDC) was due to the strong coordination of the copper active sites with water molecules, thus, making the interaction of substrates with active sites less facile. It was found that this induction period can be avoided by pretreating the solids before the catalytic test. Activation of the MOF catalyst before use by evacuating the solid under vacuum at temperatures about 150 °C is always an advisable pretreatment to ensure the reproducibility of the results and high initial activity. The higher catalytic activity of $Cu(im)_2$ compared to $Cu(2\text{-pymo})_2$ could be related to the fact that in the latter material, copper ions are in square planar coordination, while in the former, copper ions are displaced out of the plane, in a highly distorted tetrahedral coordination. Thus, the deformation energy necessary to allow the interaction between the copper site with the substrate is probably lower in the case of $Cu(im)_2$. Overall, this study has clearly demonstrated how the structure and metal ion coordination in a MOF can influence its catalytic activity altering the reaction rate and the final yield.



Scheme 13. Synthesis of triazole derivative catalyzed by $Cu(2\text{-pymo})_2$. Reaction conditions: benzyl azide (1 mmol) and phenylacetylene (1.2 mmol), ethanol (6 ml), catalyst (0.1 mol% Cu), 70 °C, N_2 atmospheric pressure.

Dark-violet dehydrated $Cu_3(BTC)_2$ was treated with two different types of 4-substituted pyridines (L1 and L2, Scheme 14) in dry toluene at reflux temperature followed by washing with dichloromethane, resulting in 4-substituted pyridine attached to $Cu_3(BTC)_2$.[45] The powder XRD pattern of the resultant material is similar to that of $Cu_3(BTC)_2$ in d-spacing and line shape, indicating that chemical functionalization can be achieved without a loss of structural integrity, but with some slight variations of the Bragg intensities. The presence of these ligands was also confirmed by FT-IR spectroscopy. Elemental analysis showed that the pyridine content is between one and two molecules per trimer of copper octahedra for the L1-$Cu_3(BTC)_2$ and L2-$Cu_3(BTC)_2$ solids, respectively. Subsequent reaction of L1-$Cu_3(BTC)_2$ and L2-$Cu_3(BTC)_2$ solids with $PdCl_2(PhCN)_2$ led to the formation of bimetallic MOFs namely $Cu_3(BTC)_2$-PdL1 and $Cu_3(BTC)_2$-PdL2, respectively. The IR spectra showed the expected changes in the stretching vibrations due to the coordination of the palladium. Furthermore, no apparent loss of crystallinity in X-ray diffraction patterns was observed and without appearance of supplementary Bragg peaks after the metal complex formation. The relative intensities of the XRD peaks of $Cu_3(BTC)_2$ change, however, confirming the formation of the complex into the pores. The analytical results by ICP-MS gave 2.67 and 0.68 wt % of Pd metal loading for ($Cu_3(BTC)_2$-PdL1) and ($Cu_3(BTC)_2$-PdL2), respectively, in agreement with the successful formation of the Pd complex.[45]

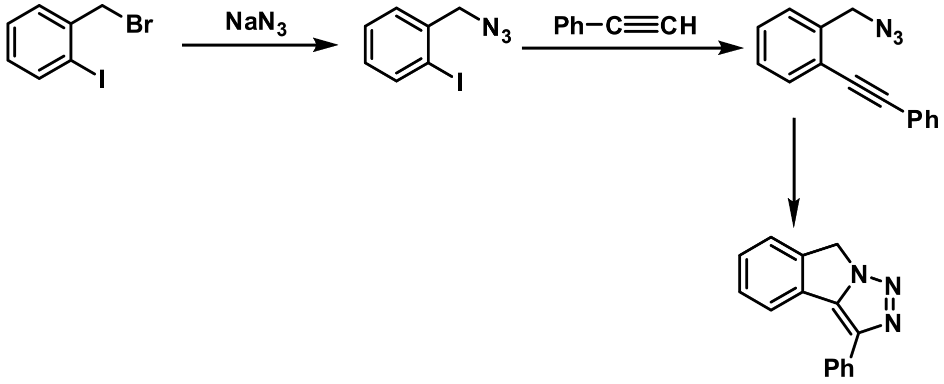


Scheme 14. Structures of 4-substituted pyridines

MOF catalysts containing simultaneously Cu and Pd sites in the same framework could have remarkable activity as bifunctional heterogeneous catalyst, since there are many reactions in which the catalytic activity of Pd requires the promotional effect of

Cu(I).[80-85] Also for tandem reactions, the activity of Pd for one elementary process could be coupled with that of Cu for other individual transformation. For instance, the Sonogashira C-C coupling promoted by Pd could be combined with an intramolecular cycloaddition “click” reaction catalyzed by Cu(I). This tandem process could lead to obtain triazolo[5,1-a]isoindoles in an one-pot tandem sequence from an aryl halide, sodium azide and a terminal acetylene (Scheme 15). This concept has been elegantly proved by using $Cu_3(BTC)_2$-PdL1 as catalyst in the preparation of a series of triazolo[5,1-a]isoindoles with 99 % yield and 99 % selectivity in most of the cases.[45] The process is, however, not general and some substrates react with lower selectivity.[45] Thus, when phenylacetylene and its derivatives were used as substrates, higher yield with selectivity better than 99 % are achieved, but replacing phenylacetylene by aliphatic acetylene resulted in 25 % conversion with 89 % selectivity.[45]

The recycling experiments revealed that the decay in the activity upon catalyst reuse depends on how demanding is the reaction due to the high or low reactivity of the starting materials, but powder XRD showed the destruction of structural integrity after first reuse.[45] The collapse of MOF crystal structure can be responsible for the occurrence of leaching with observation of the presence of some Pd in the liquid phase after the reaction. Also adsorption of organic products or intermediates on the active metal sites present in the catalyst must contribute to the decay in the activity acting as poisons. In this regard, characterization of fresh and used catalyst by gas adsorption studies will give an idea about the extent of pore blocking by possible poisons and strength of their adsorption.



Scheme 15. Cascade synthesis of triazole derivatives using $Cu_3(BTC)_2$-PdL1 as catalyst. Reaction conditions: 2-iodobenzyl bromide (0.034 mmol), sodium azide (0.035 mmol) MOF-L-Cu[Pd] catalyst (0.007 mmol Pd), K_2CO_3 (0.072 mmol) in water (0.2 mL), phenylacetylene (0.067 mmol), DMF (1.5 mL), argon atmosphere, 60 °C.

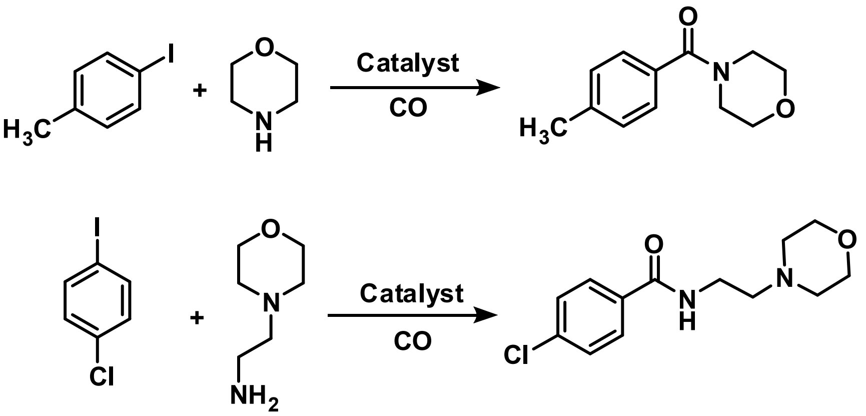
8. Synthesis of heterocyclic amides

Aminocarbonylation is an elegant and single-step catalytic method for the synthesis of heterocyclic amides directly from inexpensive and easily available feedstocks such as carbon monoxide and aryl halides in the presence of suitable heterocyclic amines.[86] Amides are one of the most valuable intermediates for synthesis as well as final products for chemical and pharmaceutical industry.[87]

A Pd/MOF-5 catalyst has been tested for the aminocarbonylation of aryl iodides at atmospheric pressure of CO.[46] SEM images of MOF-5 and Pd/MOF-5 samples indicate no significant change in surface morphology after Pd incorporation.[46] Based on this SEM study, it was concluded that Pd NPs were well dispersed on the surface of MOF-5, without obvious aggregation of Pd NPs at low levels of palladium loading (0.25 and 1.0 wt %) in Pd/MOF-5. Aggregation of Pd NPs was, in contrast, observed for palladium loadings in Pd/MOF-5 higher than 1 wt %.[46] HRTEM images showed that Pd NPs on the MOF-5 matrix have particle size ranging between 3 and 12 nm.

The reaction was screened to optimize different parameters such as catalyst support, temperature, nature of base, reaction time and amount of catalyst.[46] Quantitative isolated yield of morpholino(p-tolyl)methanone was achieved by using 15 mg of 0.5 wt % Pd/MOF-5 catalyst at 120 °C at atmospheric pressure of CO (Scheme 16). Sterically demanding ortho substituted substrates such as *o*-iodotoluene required higher catalyst loadings and prolonged reaction time to obtain 72% yield. This catalytic amino carbonylation process is also applicable to aromatic primary amines, although they showed lower reactivity and required higher catalyst loading of 1 wt% and an extended reaction time.[46] The high performance of Pd/MOF-5 allowed the use of solid catalyst for the synthesis of moclobemide (Scheme 16), an antidepressant drug, achieving 94% yield under the standard conditions.[46] Furthermore, the process was successfully scaled up to 1 mmol of 4-chloroiodobenzene achieving 94% yield.

The 0.5 wt% Pd-MOF-5 catalyst was used up to four recycles at 2 atm of CO without any appreciable change in the yield of morpholino(*p*-tolyl)methanone at 120 °C.[46] Pd leaching was negligible (< 2 ppm in each recycle) and no aminocarbonylation activity was observed using the supernatant liquid after removal of the solid catalyst.[46] It should, however, commented that due to the poor stability of MOF-5 even at ambient conditions, the selection of this MOF is probably not the most adequate and further studies using more stable MOFs, including detailed information about the recyclability will be welcome. In this sense, powder XRD of the used catalyst should have been presented, since it could provide some information about structural integrity of MOF-5 after catalysis.

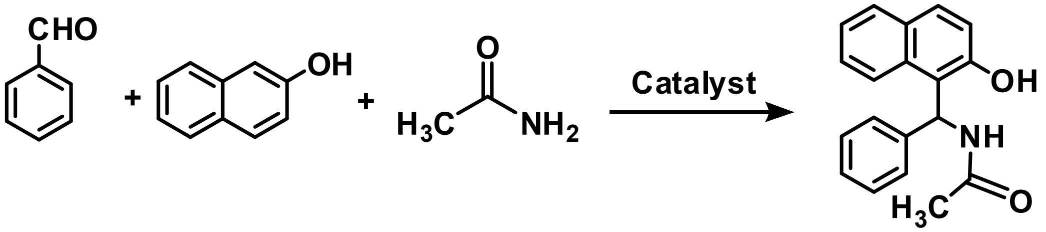


Scheme 16. Synthesis of heterocyclic amides catalyzed by Pd/MOF-5. Reaction conditions: 4-iodotoluene (0.25 mmol), morpholine (0.3 mmol), Pd/MOF-5 (1 wt %), CO (1 atm), K_2CO_3 (3 eq.), 120 °C, 4 h, toluene; 4-iodochlorobenzene (1 mmol), morpholine derivative (1.5 eq.), Pd/MOF-5 (0.5 wt %), CO (2 atm), K_2CO_3 (1.2 eq.), 120 °C, 24 h, toluene.

Recently, the same group has reported the catalytic activity of Pd NPs supported on ZIF-8 (Pd/ZIF-8) as an efficient heterogeneous catalyst for the aminocarbonylation of bromoarenes in the presence of phosphines and iodoarenes under phosphine-free conditions.[47] The catalyst can be readily prepared and is air-stable. The palladium loading can be as low as 1 wt % and Pd particle size was between 4 to 9 nm. The catalyst was recycled four times with negligible change in catalytic activity. A TON of 2540 was readily achieved for a batch reaction. The catalyst was found to be active for the synthesis of cyclic and primary amides as well as an alkoxycarbonylation reaction to form an ester.

Recently, hybrid materials of MIL-101(Cr) and PTA were synthesized in aqueous media in the absence of hydrofluoric acid.[48] The powder XRD pattern of the MIL-101(Cr)/PTA composites indicated the presence of ordered PTA assemblies located in both the large cages and small pores of MIL-101(Cr). The catalytic performance of the

MIL-101(Cr)/PTA (9.2 wt% PTA) composites was studied for the Baeyer condensation[88-90] of benzaldehyde and 2-naphthol resulting in the formation of dibenzoxanthene in 96% yield at 90 °C using 300 W microwave heating for 2 min.[48] This catalyst was also used to synthesize N-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)acetamide starting from benzaldehyde, 2-naphthol and acetamide (Scheme 17).[48]



Scheme 17. Synthesis of N-((2-hydroxynaphthalen-1-yl)(phenyl)methyl)-acetamide using MIL101/PTA as catalyst. Reaction conditions: 2-naphthol (1.2 mmol), benzaldehyde (1.2 mmol), acetamide (1.7 mmol), MIL101/PTA, 130 °C, 5 min.

9. Conclusions and future prospects

The above sections have shown that MOFs can be considered in general as recoverable and reusable solid catalysts for the preparation of N-containing heterocycles, avoiding the use of conventional Brønsted or Lewis acids such as HCl, H_2SO_4, $AlCl_3$ and $ZnCl_2$ among others homogeneous acids employed in classical synthesis. More work is still necessary to expand the MOFs to the synthesis of other types of heterocycles. Also this area will benefit from the development of new robust MOFs that can stand harsher reaction conditions without undergoing structural collapse and could exhibit enhanced activity. The synthesis of MOF will soon develop to the point that it would be possible to control the composition and crystallinity of the materials at will. In this way, MOFs with high purity in the composition or with a target combination of various metals or mixed ligands will be available. Also, the materials will be on demand either highly crystalline structure or with appropriate lattice defects. These advances in MOF synthesis reflect the flexibility in the design of these porous solids and will make available for catalytic applications a wide range of novel, defined multi-site catalysts appropriate for multi-step synthesis as those needed in heterocycle synthesis.

When using MOFs as catalysts, it is of special relevance to compare their activity with that of other related solid catalysts such as organic polymers, metal oxides, zeolites or mesoporous materials. The point is to delineate the advantages that MOFs can present over other possible catalysts as consequence of their large surface area and pore volume and the high metal content of these materials. In these studies, stability and productivity of MOFs should be carefully assessed, showing the recyclability of the solid and the absence of leaching or structural damage.

Complementary to experimental work on the synthesis of new MOFs and the use of these materials as catalysts, theoretical work is necessary determining the geometry of site-substrate adduct, the rate determining step in the mechanism, the reaction intermediates, predicting the bottle-neck of some processes and leading to the design of more efficient MOF catalysts.

As commented above, MOFs offer a large range of possibilities to develop multifunctional catalysts that should be very appropriate for multistep synthesis that are very common in heterocycle synthesis. Besides the scarce examples commented on the synthesis of quinolines, this field of catalysts for tandem processes remains almost unexplored, but could lead to a new generation of advanced catalysts for process intensification.

Finally, one major achievement in this area is to prove that the activity, selectivity and durability of MOFs can be high enough to develop a competitive commercial synthesis of heterocycles based on these materials as solid catalysts. Some of them, as those indicated in the graphical abstract, are produced in multi-ton scale using non-recusable catalysts. Considering the large number of examples that have been already reported on the use of MOFs for the synthesis of N-containing heterocycles, we may not be far from this target that will overcome most of the strongest criticisms against MOFs due to the relative low stability of some of them.

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Biography of Amarajothi Dhakshinamoorthy

Amarajothi Dhakshinamoorthy received his postgraduate degree in Chemistry from Loyola College (Autonomous), Chennai, India, with two gold medals in 2002 and later a PhD degree from Madurai Kamaraj University, India, in 2009. He has worked in the group of Prof. Hermenegildo Garcia as a postdoctoral fellow for four years and at present he is working as UGC-Assistant Professor at the School of Chemistry, Madurai Kamaraj University, Madurai, India. He is actively engaged in developing green and sustainable catalysts based on metal–organic frameworks or graphene and its related materials. He has published fifty seven papers, two book chapters and holds one international patent.

Hermenegildo García (Herme) is full Professor and member of the Institute of Chemical Technology at the Technical University of Valencia since 1996. He has co-authored over 500 papers, has supervised over 38 PhDs and holds 14 international patents. His main current interests are green chemistry and catalysis as well as the use of zeolites, metal organic frameworks and mesoporous materials in supramolecular photochemistry, photocatalysis and nanotechnology.