



Bridging homogeneous and heterogeneous catalysis with MOFs: Cu-MOFs as solid catalysts for three-component coupling and cyclization reactions for the synthesis of propargylamines, indoles and imidazopyridines

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ABSTRACT

Copper-containing MOFs are found to be active, stable and reusable solid catalysts for three-component couplings of amines, aldehydes and alkynes to form the corresponding propargylamines. Two tandem reactions, including an additional cyclization step, leads to the effective production of indoles and imidazopyridines. In particular, the lamellar compound [Cu(BDC)] (BDC = benzene dicarboxylate) is highly efficient for the preparation of imidazopyridines, although a progressive structural change of the solid to a catalytically inactive compact structure is produced, causing deactivation of the catalyst. Nevertheless, the phase change can be reverted by refluxing in DMF, which recovers the original lamellar structure and the catalytic activity of the fresh material. The use of [Cu(BDC)] for this reaction also prevents the formation of Glaser/Hay condensation products of the alkyne, even when the reaction is performed in air atmosphere. This is a further advantage of [Cu(BDC)] with respect to other homogeneous copper catalysts, for which the use of an inert atmosphere is necessary.

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1. Introduction

Transition metal complexes are successful homogeneous catalysts with well defined single active sites. Their heterogeneization allows having solid recyclable molecular catalysts with well defined and predesigned active centers. In this sense much effort has been done to develop adequate supports and heterogeneization procedures that allow, not only preserving the catalytic characteristics of the starting homogeneous catalyst but, sometimes, even improving their behavior by a cooperative effect between the transition metal complex and the support [1]. Other possibilities to transform homogeneous catalysts based on transition metal complexes into solid heterogeneous catalysts involve the synthesis of hybrid organic–inorganic structured porous materials [2,3] and the preparation of coordination polymers [4–7]. One type of coordination polymers are the so-called metal–organic frameworks (MOFs) in where metal nodes are connected by organic linkers through strong coordination bonds in a tridimensional net, forming crystalline, hybrid microporous materials. It appears then that by properly selecting the metal and the organic linkers it should be possible to obtain a heterogeneous counterpart of some homogeneous catalysts.

We have recently reported on the catalytic application of metal–organic frameworks featuring Cu^{2+} ions coordinated to four N atoms belonging to heterocyclic rings, thus forming CuN_4 centers. Examples of such materials are [Cu(2-pymo)₂] and [Cu(im)₂] (2-pymo = 2-hydroxypyrimidinolate; im = imidazolate) [8,9]. In these compounds, each heterocycle (pyrimidine or imidazole) is coordinated to two Cu^{2+} ions, leading in both cases to a neutral and highly flexible 3D distorted sodalite-type framework [10]. We have recently found that the coordination and electronic properties of the Cu^{2+} ions in these MOFs are analogous to those of N-heterocyclic copper coordination complexes [11,12]. Moreover, the high flexibility of the framework allows copper ions to coordinate to adsorbed molecules, either by expanding the coordination sphere of copper ions or by displacing one heterocyclic ligand, without causing structure collapse. Therefore, given the similarities between the copper sites in the above described MOFs, and the N-heterocyclic copper coordination complexes, it is not surprising that both [Cu(2-pymo)₂] and [Cu(im)₂] could be heterogeneous active catalysts for reactions that occur in the presence of those copper complexes. Indeed, we have seen this similarity for the liquid phase allylic oxidation of a number of substrates [11], as well as for the 1,3-dipolar cycloaddition of azides to alkynes (“click” reaction) [12], which involves the formation of a copper-acetylide intermediate. In this sense, [Cu(2-pymo)₂] and [Cu(im)₂] represent heterogeneous counterparts of the versatile and extensively used homogeneous Cu^{2+} coordination complexes containing

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N-heterocyclic ligands. Following this idea, in the present work, we have studied a more complex reaction such as the one-pot three-component coupling reaction between alkynes, aldehydes and amines, as a means to prepare the corresponding propargylamines with a series of copper-containing MOFs as catalysts. The interest of this reaction lies on the versatility of propargylamines as synthetic intermediates in organic synthesis and as important structural elements in natural products and therapeutic drug molecules [13,14]. Given the recognized catalytic activity of copper N-heterocyclic coordination complexes for this reaction, we have anticipated that these homogeneous catalysts could be replaced by Cu-MOFs as heterogeneous alternatives. We have examined the scope of the reaction and the various conditions in which the reaction can proceed, and good yields have been obtained without altering the crystalline structure of the materials. We have also prepared indole derivatives in good yield, by a tandem one-pot three-component coupling reaction followed by a 5-*endo-dig* cyclization. Following a similar reaction scheme, the imidazopyridine nucleus, analogous to that found in a family of anxiolytic drugs, such as alpidem or zolpidem, has also been prepared. To the best of our knowledge, this work is the first attempt to prepare the imidazopyridine nucleus using a heterogeneous copper catalyst in a one-pot multi-component process.

2. Materials and methods

The Cu-MOFs were prepared according to the corresponding procedures reported in the original references: [Cu(2-pymo)₂] [8], [Cu(im)₂] [9], [Cu(BDC)] [15], and [Cu₃(BTC)₂] [16]. X-ray diffraction (Phillips X'Pert, Cu K α radiation) was used to confirm the expected crystalline structure of the materials. Benzaldehyde (Aldrich, 99.5%) was freshly distilled prior to use, while all other substances and reagents used were commercially available and used as received. The reaction and analytic methodology are given in [Supplementary material](#).

All the catalytic reactions described in the text were carried out in batch reactors. Aliquots were taken during the course of the reaction and analyzed by GC using hexadecane as external standard. Specific conditions for each reaction (amounts of catalyst and reagents, temperature, etc.) are indicated in the corresponding Tables.

3. Results and discussion

3.1. Formation of propargylamines by one-pot three-component coupling reactions

Reaction between piperidine, paraformaldehyde, and phenylacetylene at 313 K in the presence of [Cu(2-pymo)₂] (1 mol%Cu) gave 99% yield of the corresponding propargylamine (see [Fig. 1](#) and [Table 1](#), entry 1). The short induction period observed is not related with the formation of the iminium ion (the primary product of the reaction) since this step is very fast and not catalyzed by the MOF. Its presence rather reflects the time needed for the activation of phenylacetylene by the Cu-MOF. Indeed, we recently reported the presence of a similar induction period in the 1,3-dipolar cycloaddition of alkynes and azides catalyzed by Cu-MOFs [12]. However, when the catalysts were pre-treated with the alkyne for a certain time period (up to 4 h) before adding the azide, the induction period gradually disappeared. A similar behavior was also observed in the present case of propargylamine formation. Incubation of [Cu(2-pymo)₂] with phenylacetylene for 2 h before adding the amine and the aldehyde completely suppressed the induction time. Note also in [Fig. 1](#) that after the initial induction period, the time-conversion plot roughly follows a second order law, since

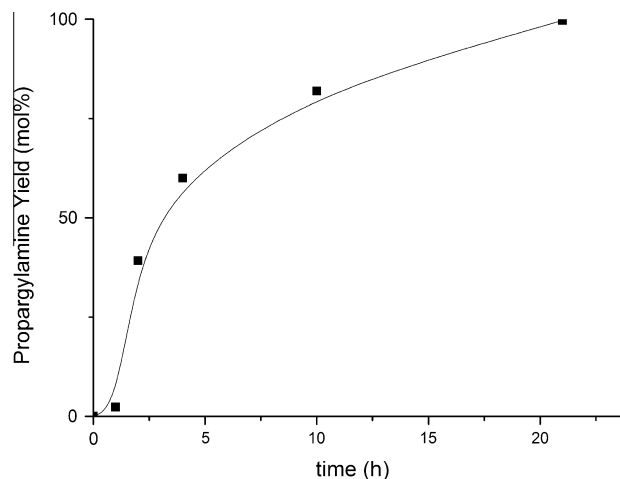


Fig. 1. Formation of propargylamine in the presence of [Cu(2-pymo)₂] as catalyst ([Table 1](#), entry 1).

the rate of formation of the propargylamine depends on the concentration of the iminium ion, being the formation of the iminium ion comparatively very fast.

After the reaction of propargylamine formation, the solid catalyst was recovered by filtration and washed with dioxane and acetone and dried at room temperature in a desiccator. No significant losses of crystallinity and activity were observed after five runs (see [Figs. S1 and S2](#)). No leached Cu was detected in the solution. Nevertheless, the contribution of homogeneous catalysis by eventually leached species after hot filtration was studied and the results in [Fig. S3](#) show negligible activity in the filtrate. These verifications were made for all the reactions studied here, and in all cases [Cu(2-pymo)₂] was found to withstand the reaction conditions without being altered in the least.

Since the reaction between the amine and the aldehyde produces a stoichiometric amount of water, we were prompted to study the possible effect of water on the catalyst efficiency. To do that, we repeated the reaction in the presence of either 1 or 5 equivalents of water intentionally added to the reaction medium. Not only the presence of water has no negative effects on the reaction, but it is even observed a clear shortening of the induction period upon addition of 5 equivalents of H₂O.

Blank experiments in the absence of catalyst produced only very small amounts of propargylamine ([Table 1](#), entry 2), and the activity of [Cu(2-pymo)₂] was comparable with that of homogeneous copper salts (entries 3–5). This indicates that incorporation of the Cu²⁺ ions into framework positions to form the MOF does not cause a significant decrease in the activity of copper to catalyze this reaction. The activity of [Cu(2-pymo)₂] is also comparable with 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 under similar reaction conditions (8 mol%Cu, 353 K, solvent free) [17].

To explore the scope of [Cu(2-pymo)₂] as catalyst, different catalyzed multi-component coupling reactions of aldehydes, amines, and alkynes have been studied. Thus, when phenylacetylene was replaced by an aromatic alkyne larger than phenylacetylene, the reaction rate slightly decreased. Thus, the yield of propargylamine obtained after 4 h of reaction in the case of phenylacetylene was 60%, while in the case of 1-ethynyl-naphthalene was only 8% (entry 6), and a longer time is required to attain full conversion. These differences in reactivity probably reflect the higher diffusion problems of the bulkier propargylamine to leave from the inner surface of the MOF. This is not surprising if one considers that, for the reaction to proceed it is necessary that the three molecules

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