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Additional Information

**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.

Keywords: Cu-MOF catalysis, three-component coupling, indole, imidazopyridine

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 an 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 $[\text{Cu}(2\text{-pymo})_2]$ and $[\text{Cu}(\text{im})_2]$ 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, $[\text{Cu}(2\text{-pymo})_2]$ and $[\text{Cu}(\text{im})_2]$ represent heterogeneous counterparts of the versatile and extensively used homogeneous Cu^{2+} coordination complexes containing 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 homogenous 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: $[\text{Cu}(2\text{-pymo})_2]$ [8], $[\text{Cu}(\text{im})_2]$ [9], $[\text{Cu}(\text{BDC})]$ [15], and $[\text{Cu}_3(\text{BTC})_2]$ [16]. X-ray diffraction (Phillips X’Pert, Cu $\text{K}\alpha$ 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 $[\text{Cu}(\text{2-pymo})_2]$ (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 $[\text{Cu}(\text{2-pymo})_2]$ 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 the rate of formation of the propargylamine depends on the concentration of the alkyne and 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 5 runs (see Fig 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 $[\text{Cu}(\text{2-pymo})_2]$ was found to withstand the reaction conditions without being altered in the least.

< Insert Fig. 1 here >

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 to 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]

< Insert Table 1 here >

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 4h 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 meet in the right orientation within the pores of the MOF, this becoming harder when the size of the components increases. The results presented in Table 1 also show that [Cu(2-pymo)₂] was also able to catalyze the formation of propargylamine from terminal alkylic alkynes, such as 1-octyne (entry 7).

When formaldehyde was replaced by other alkylic aldehydes, such as butyraldehyde (entry 8), the reaction also proceeded smoothly. However, propargylamine is hardly formed when benzaldehyde was reacted (entry 9). We attributed this failure to the difficulty to form the intermediate iminium species by addition of piperidine to benzaldehyde, since this uncatalyzed reaction should require higher temperatures. Indeed, when the reaction temperature was increased from 313 to 373 K and the catalyst loading to 10 mol%Cu (entry 10), full conversion could be achieved.

When piperidine was replaced by another secondary amine, such as dipropylamine (entry 11), the expected product was also formed quantitatively, although the initial reaction rate was lower (compare entries 1 and 12). However, the reaction did not proceed with primary amines, either alkylic or allylic such as n-propylamine or aniline.

3.2. Preparation of indole and imidazopyridines: Tandem three-component coupling and cyclization reactions

We have recently reported on the preparation of indole derivatives catalyzed by supported gold nanoparticles and gold(III)-containing MOFs.[18, 19] The reaction involves the one-pot three-component coupling of aldehydes, amines and N-protected ethynylaniline followed by 5-*endo-dig* cyclization, according to Scheme 1.

< Insert Scheme 1 here >

The above reaction is an example of the versatility of propargylamines as chemical intermediates for the preparation of natural products and drugs, since they can be used, for instance, as starting materials for preparing important molecules such as indole derivatives. Since the formation of the indole passes through an intermediate propargylamine, and given the good performance of [Cu(2-pymo)₂] for propargylamine synthesis, we have studied the application of this and other copper-containing MOFs as catalysts for the preparation of indoles. The results obtained are summarized in Table 2, in which a comparison is also made with a homogenous copper salt and various gold catalysts.

< Insert Table 2 here >

As it can be seen in Table 2, [Cu(2-pymo)₂] was found to be an active and selective catalyst for this tandem reaction to the indole formation: The intermediate propargylamine was not detected at the end of the reaction, and the sole product formed was the indole. The activity of this Cu-MOF catalyst, expressed as turnover frequency (mols of indole formed per mol of copper used per unit of time), was TOF = 7 h⁻¹ (entry 1 in Table 2), which is comparable with that obtained for gold salts (AuCl₃, see entry 2) or supported gold nanoparticles (Au/ZrO₂, entry 3). However, the activity of [Cu(2-pymo)₂] is low compared with CuCl₂ (entry 6) or with that recently reported for Au(III) Schiff base complexes, either as homogenous complexes (entry 4) or as heterogeneized catalysts prepared by post-synthesis modification of an existing MOF (entry 5) [19]. Nevertheless, the crystalline structure of the MOF was not affected by the reaction conditions, and the material can be reused for at least 5 consecutive catalytic cycles without significant loss of activity.

As mentioned above, propargylamines can also be used as intermediates for the preparation of other heterocycles. An interesting example is the preparation of imidazopyridine derivatives, given the presence of this nucleus in a family of anxiolytic drugs, such as alpidem or zolpidem. Imidazopyridines can be prepared from 2-aminopyridine, an aldehyde and a terminal alkyne through a tandem one-pot three-component coupling reaction, leading to the

formation of an intermediate propargylamine, and ensuing 5-*exo-dig* cyclization [20], according to Scheme 2.

< Insert Scheme 2 here >

To investigate the potential of the copper MOF for the preparation of imidazopyridine derivatives, the reaction between 2-aminopyridine, benzaldehyde and phenylacetylene was studied in the presence of [Cu(2-pymo)₂] (10 mol% Cu) at 393 K and toluene as solvent. The amount of catalyst and the relatively elevated temperature needed for this reaction reflect the difficulties for the formation of the intermediate propargylamine from the primary amine, as we already observed with aniline (see above). The results obtained are shown in Fig. 2 and Table 3. Under the reaction conditions used, a maximum conversion of 61% was obtained after 30 h, with quantitative selectivity to the imidazopyridine (entry 1 in Table 3). Although this result is not too far from the values obtained with homogeneous Cu²⁺ and Cu⁺ salts under similar conditions (entries 8-11), we found that the [Cu(2-pymo)₂] catalyst was completely deactivated. Thus, when the catalyst recovered after the reaction was used in a second catalytic cycle, almost no phenylacetylene conversion was observed (less than 6% conversion after 30 h). This deactivation was not due to the instability of the MOF, since its structure was fully preserved (as stated by XRD), but to the irreversible adsorption of reaction products on the copper MOF, since the products inside the pores could not be fully removed by simple washing. Indeed, the XRD pattern of the solid filtered after the reaction seems to indicate an important loss of crystallinity of the material. However, upon thoroughly washing the solid with CH₂Cl₂ to eliminate adsorbed products, an important recovery of the peaks intensities is clearly observed (see Fig. S4).

< Insert Table 3 here >

< Insert Fig. 2 here >

In any case, under these reaction conditions the overall turnover number (TON) attained in the two catalytic cycles over [Cu(2-pymo)₂] was only 6.7 (mols product formed per mol of copper used). This poor performance is not due to a lack of activity of the copper centers but rather to poisoning of the catalyst by irreversible pore blocking. We therefore looked for other copper-containing metal-organic compounds, which would ideally contain the same (or similar) active sites but at the same time should also be less prone to poisoning. Among the different materials tested (viz., [Cu₃(BTC)₂] and [Cu(im)₂]; BTC = benzene tricarboxylate; im = imidazolate), the best results were obtained with the copper terephthalate [Cu(BDC)] (BDC = benzene dicarboxylate) [15]. This material contains the well known paddle-wheel copper

dimers, in which each dimer coordinates to four terephthalate molecules forming sheets which are then bonded through weak stacking interactions. Each copper ion is further coordinated to a DMF molecule in the apical position, which can be thermally removed to expose then a vacant position. When [Cu(BDC)] was used as catalyst for the formation of imidazopyridine under the same reaction conditions, an almost complete conversion was attained (97% imidazopyridine yield after 30 h), with full selectivity with respect to the limiting reagent (phenylacetylene) [21]. Note that this is a significant improvement with respect to [Cu(2-pymo)₂] (compare entries 1 and 4 in Table 3). [Cu(BDC)] shows almost the same activity in a second catalytic run, although the activity sharply decreased in a third cycle (10% yield of the imidazopyridine after 30 h, see entries 5 and 6 in Table 3). The loss of activity of [Cu(BDC)] is accompanied by changes in the crystalline structure of the material upon repeated use (see Fig S5), mainly consisting in the appearance of new diffraction peaks at low angles (7.3° and 8.0° 2θ). It is well known that thermal activation of [Cu(BDC)] produces changes in the X-ray diffraction pattern of the material, which are completely analogous to what we observed upon catalytic use [15]. As reported by Carson et al [15], thermal desorption of the DMF molecules coordinated to the copper sites results in the formation of a new crystalline structure in which the original Cu(BDC) sheets are connected one to another by formation of new bonds between Cu and O belonging to two adjacent layers, according to Scheme 3. Note that, while the lamellar structure contains accessible Cu sites, the structural transformation leaves the copper sites completely blocked by the ligands and inaccessible to the substrates. This explains the low catalytic activity of the new compact structure. The material recovered after two cycles still contains a significant fraction of the lamellar material, while after three cycles the solid consists mainly in the compact structure (see Fig. S5).

< Insert Scheme 3 here >

According to Carson et al. [15], the structural transformation of [Cu(BDC)] from a lamellar to a compact structure upon DMF desorption can be reversed by re-adsorption of molecules containing carbonyl groups, as the authors demonstrated by treating the desolvated solid with *N*-methylpyrrolidone. Analogously, when pure desolvated [Cu(BDC)] was treated with DMF at 405 K for 2 h, we observed that the material showed a diffraction pattern characteristic of the lamellar compound. Thus, we submitted the spent catalyst recovered after three catalytic runs (mainly consisting in the compact structure) to a similar treatment with DMF, with the aim of recovering the pristine lamellar structure (which is the catalytically active phase). This treatment has a twofold effect: On one hand, it effectively yields the lamellar compound according to the XRD pattern (see Fig. S5); i.e., the reverse process in Scheme 3. On the other hand, DMF washes away any possible reaction product that can be adsorbed on the

catalyst surface, as evidenced by the brownish color of DMF at the end of the treatment. Therefore, we found that heating in DMF is an adequate treatment to regenerate the Cu-MOF catalyst. Indeed, regenerated [Cu(BDC)] shows practically the same activity for the production of imidazopyridine that the freshly prepared compound (see Table 3 and Fig. 2).

We carried out an additional set of experiments that revealed a further advantage of using Cu-containing MOFs instead of copper salts as catalysts for the three-component coupling reaction. Note that formation of imidazopyridine following the proposed synthetic procedure implies the use of a terminal alkyne as one of the three components (in our case, phenylacetylene). It is well known that terminal alkynes in the presence of copper salt catalysts and in the presence of air can produce the Glaser's oxidative coupling products, according to Scheme 4. This side reaction could compete with the three-component coupling, resulting in a decrease of the overall imidazopyridine yield. Therefore, when copper salts are used as catalysts for imidazopyridine formation, it is necessary to work under an inert atmosphere and to use degassed solvents to avoid the formation of Glaser's coupling products, as was done in the experiments reported in Table 3 [20]. In order to evaluate the relevance of the competing Glaser reaction, the product distributions were compared when the reaction was performed in either N₂ or air, and using [Cu(BDC)] and various copper salts as catalysts. The results obtained are reported in Table 4.

< Insert Scheme 4 here >

As it can be seen there, when CuCl₂ is used as catalyst the formation of the Glaser product is largely prevented when a N₂ atmosphere is used (see entry 3). However, the amount of undesired product formed increases considerably when N₂ was replaced with air (entry 4), clearly becoming the main reaction product under oxidative conditions. Note that the phenylacetylene conversion after 30 h was also higher when the reaction was performed in the presence of air. The relevance of the Glaser reaction was even larger when copper acetate was used as catalyst. In this case, even with the use of an inert atmosphere, it was very difficult to avoid formation of the byproduct, since traces of O₂ seems to be enough to re-oxidize the Cu⁺ ions formed and to regenerate the catalytic species. Surprisingly, when [Cu(BDC)] was used as catalyst, we hardly observed any difference concerning both phenylacetylene conversion and selectivity to the imidazopyridine, since we did not detect formation of the Glaser product even at the trace level. This result probably indicates that the coordination of the copper centers in the MOF strongly stabilizes the +2 oxidation state of the metal, thus resulting in a completely inactive catalyst for the Glaser reaction. Note in this sense that even when [Cu(BDC)] was contacted with pure phenylacetylene under air and at 393 K (i.e., same reaction conditions but without the other two components necessary for the formation of imidazopyridine), we did not

observe formation of the Glaser product as well. In conclusion, when [Cu(BDC)] is used as catalyst for the formation of the imidazopyridine, the avoidance of O₂ in the reaction medium becomes unnecessary, which largely simplifies the reaction setup.

< Insert Table 4 here >

Conclusions

We have seen that different Cu-MOFs are solid catalysts able to catalyze a three-component coupling reaction to obtain propargylamines with an excellent selectivity and a reasonable scope. Their activity is similar to the reported with other solid catalysts and homogeneous Cu catalysts. Thus, Cu-MOFs have shown to be particularly efficient catalysts for reactions implying the formation of copper-acetylide intermediates.

Owing to the good results obtained for the three-component coupling reaction, two tandem reaction were also attempted that include an additional step to produce indoles and imidazopyridines. [Cu(2-pymo)₂] was active and selective, though it deactivates irreversibly during the synthesis of imidazopyridines, due to pore blocking by the product occluded in the micropores. This problem has been overcome by using [Cu(BDC)]. The material undergoes a progressive structural phase change during the course of the reaction, passing from a catalytically active lamellar structure to a catalytically inactive compact structure, accompanied by the loss of activity after two catalytic cycles. However, this structural phase change can be reversed by treating the solid with DMF under reflux, which recovers the lamellar structure and consequently the catalytic activity of the fresh catalyst. Finally, [Cu(BDC)] was found to be inactive for the Glaser homocoupling reaction of phenylacetylene, which is a side reaction that can otherwise compete with the imidazopyridine formation when copper salts are used as catalysts under oxidizing conditions. This inactivity of [Cu(BDC)] for the Glaser reaction makes unnecessary the use of an inert atmosphere for the three-component coupling reaction, which simplifies the reaction setup as compared to copper salt catalysts.

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- [21] At full phenylacetylene conversion, small amounts (< 5 mol%) of the imine formed between residual aminopyridine and benzaldehyde were also detected by GC.

FIGURE CAPTIONS

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

Fig. 2. Imidazopyridine yield obtained in the presence of different copper salts and Cu-MOF catalysts. The metal loading (mol%) is indicated in parentheses.

SCHEME CAPTIONS

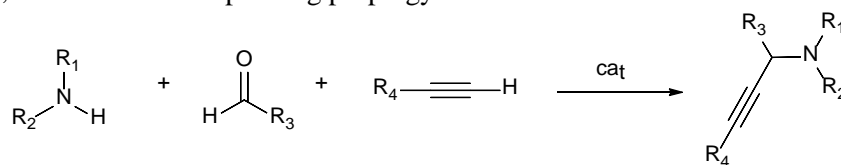
Scheme 1. Indole formation through a three-component coupling and *5-endo-dig* cyclization tandem reaction.

Scheme 2. Formation of imidazopyridine compounds through a three-component coupling and *5-exo-dig* cyclization tandem reaction.

Scheme 3. Reversible crystalline phase transformation of [Cu(BDC)] from the lamellar to the compact structure upon desorption/adsorption of DMF.

Scheme 4. Glaser oxidative coupling of phenylacetylene,

Table 1. Scope of the one-pot three-component coupling reaction between amines, aldehydes and alkynes, to form the corresponding propargylamines.^a



	catalyst (mol% Cu)	R ₁ R ₂ NH	R ₃ COH	R ₄ C≡CH	Temp (K)	% Yield time(h)
1	[Cu(2-pymo) ₂] (1%)		(HCOH) _n		313	60 (4h) 99 (21h)
2	No catalyst	“	“	“	313	4 (22h)
3	Cu(acac) ₂ (1%)	“	“	“	313	45 (6h) 94 (21h)
4	CuCl ₂ (1%)	“	“	“	313	99 (6h)
5	CuI (1%)	“	“	“	313	96 (6h)
6	[Cu(2-pymo) ₂] (1%)	“	“		313	8 (4h) 99 (34h)
7	[Cu(2-pymo) ₂] (1%)	“	“		313	31 (21h) 76 (48h)
8	[Cu(2-pymo) ₂] (1%)	“			313	55 (21h) 99 (48h)
9	[Cu(2-pymo) ₂] (1%)	“		“	313	<1 (21h)
10	[Cu(2-pymo) ₂] (10%)	“	“	“	373	71 (21h) 85 (48h)
11	[Cu(2-pymo) ₂] (1%)		(HCOH) _n	“	313	26 (4h) 99 (21h)

^a Reaction conditions: 1 mmol alkyne, 1.1 mmol aldehyde, 1.1 mmol amine, 1 ml dioxane, N₂ atmosphere.

Table 2. Formation of indole derivatives through domino three-component coupling and 5-*endo-dig* cyclization.^a

Entry	Catalyst	Yield(%) ^b	t(h)	TOF (h ⁻¹)
1	[Cu(2-pymo) ₂]	>95	18	7
2	AuCl ₃ ^c	60	6	3
3	Au/ZrO ₂ ^c	36	14	12
4	Au(III) Schiff base complex ^c	38	14	40
5	IRMOF-3-SI-Au ^c	93	14	52
6	CuCl ₂	>95	2	70

^a Reaction conditions: Ethynylaniline (0.1 mmol), piperidine (0.12 mmol), paraformaldehyde (0.2 mmol), catalyst (1 mol% metal), 1,4-dioxane (1 mL) as solvent at 313 K. ^b Isolated yield based on ethynylaniline. Selectivity to the indole was >99% in all cases. ^c Data taken from reference [19].

Table 3. Formation of imidazopyridine through domino three-component coupling and 5-*exo-dig* cyclization.^a

Entry	Catalyst (mol%Cu)	t(h)	Yield(%)
1	[Cu(2-pymo) ₂] (10)	30	61 ^b
2	[Cu(2-pymo) ₂] (10) (2 nd use)	30	6 ^b
3	No catalyst	30	< 1 ^b
4	[Cu(BDC)] (10)	30	97 ^b
5	[Cu(BDC)] (10) (2 nd use)	30	95 ^b
6	[Cu(BDC)] (10) (3 rd use)	30	10 ^b
7	[Cu(BDC)] (10) (regenerated)	30	93 ^b
8	Cu(OTf) ₂ (5)	16	10 ^c
9	CuCl (10)	16	55 ^c
10	CuCl (50)	16	74 ^c
11	CuCl (5)+ Cu(OTf) ₂ (5)	16	93 ^c

^a Reaction conditions: Phenylacetylene (1 mmol), 2-aminopyridine (1.1 mmol), benzaldehyde (1.2 mmol), toluene (1 mL) at 393 K under inert (N₂) atmosphere. ^b Determined by GC using hexadecane as external standard. ^c Data taken from reference [20].

Table 4. Influence of the atmosphere on the formation of imidazopyridine and Glaser oxidative coupling product.^a

Entry	Catalyst	Atmosphere	Conv (mol%) ^b	%Yield IP ^c	%Yield Glaser ^c
1	[Cu(BDC)]	N ₂	96	96	n.d.
2		Air	97	97	n.d.
3	CuCl ₂	N ₂	60	56	2
4		Air	84	16	34
5	Cu(CH ₃ COO) ₂	N ₂	70	40	15
6		Air	94	30	32

^a Reaction conditions: Phenylacetylene (1 mmol), 2-aminopyridine (1.1 mmol), benzaldehyde (1.2 mmol), toluene (1 mL), Cu-catalyst (10 mol% Cu) at 393 K under either air or N₂ atmosphere. ^b Conversion after 30 h as determined by GC using hexadecane as external standard and referred to the limiting reagent, phenylacetylene. ^c Yield to the imidazopyridine (IP) or to Glaser coupling product (Glaser). Note that formation of the Glaser coupling product requires two equivalents of phenylacetylene, while imidazopyridine consumes only one.

Fig. 1. I Luz *et al.*

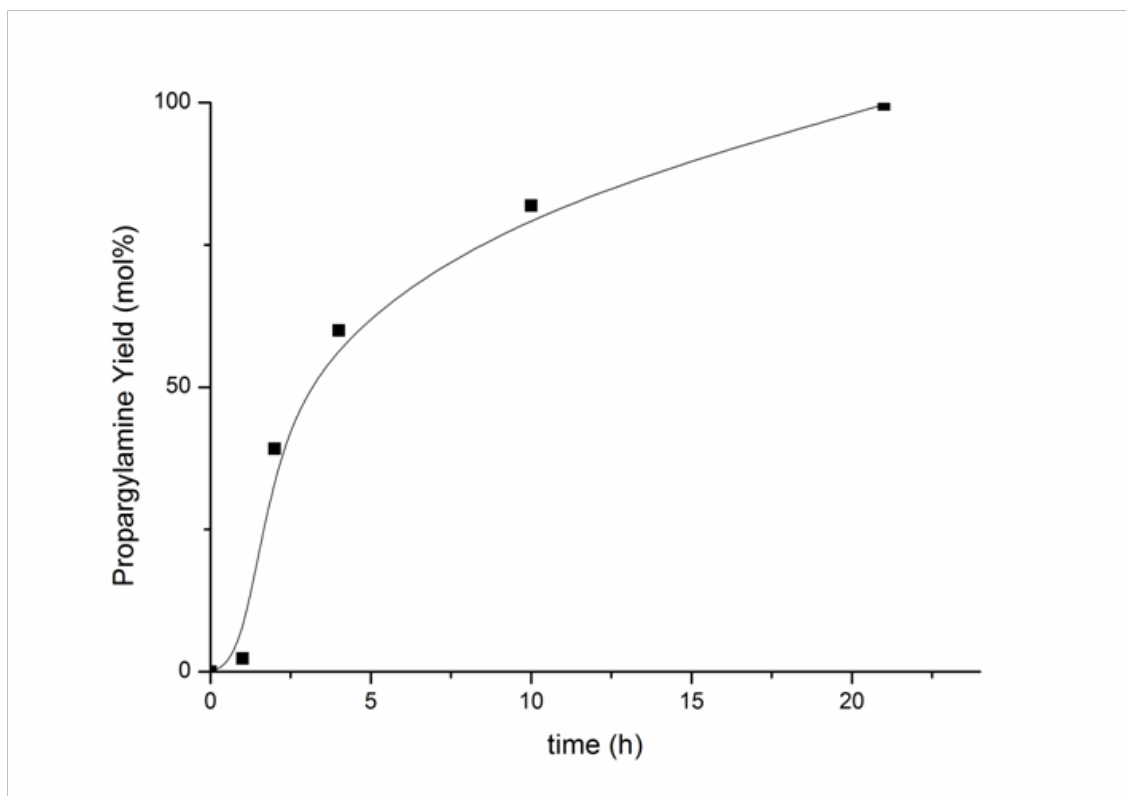
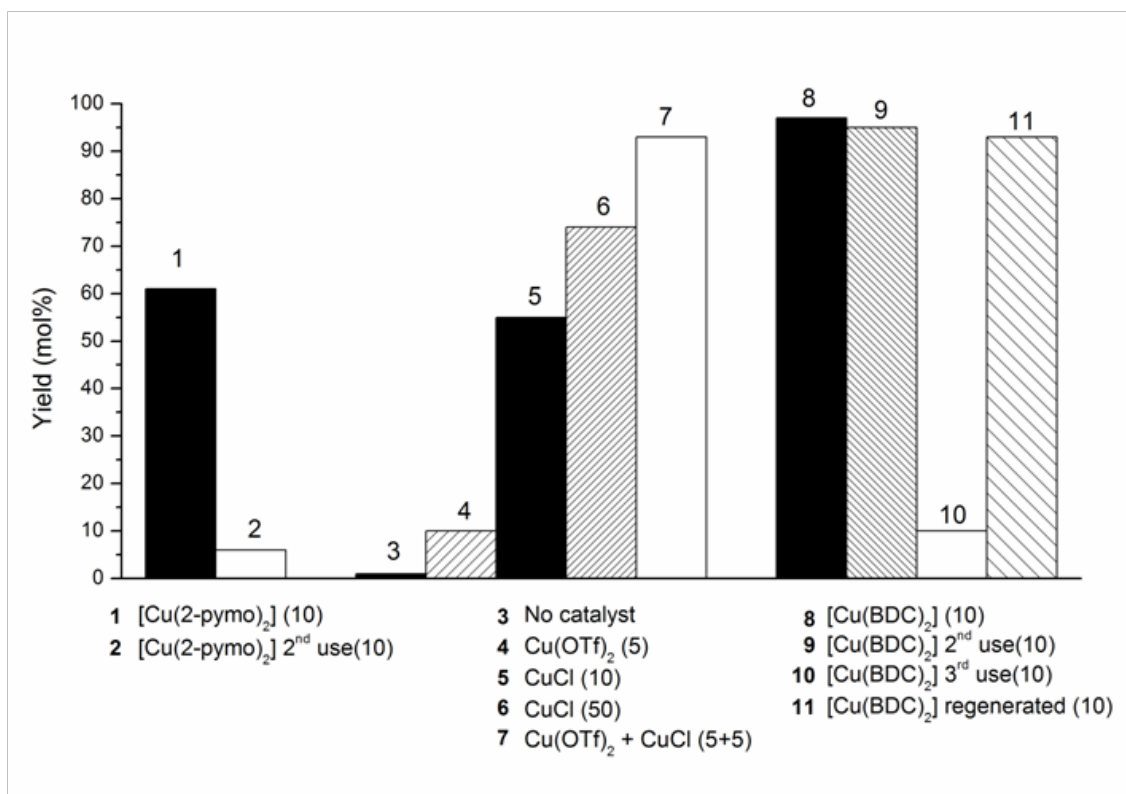
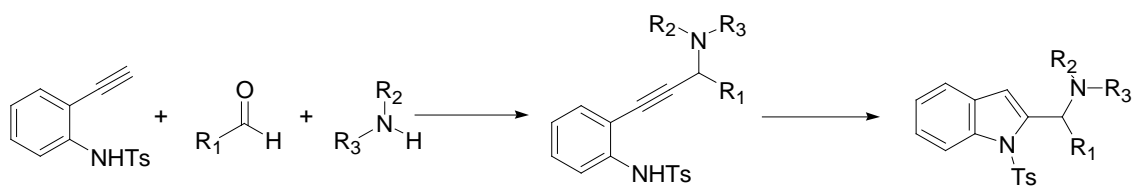
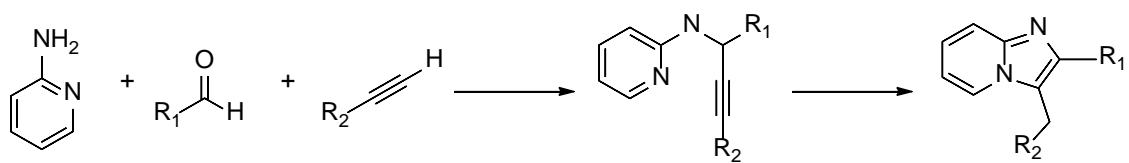


Fig. 2. I Luz *et al.*

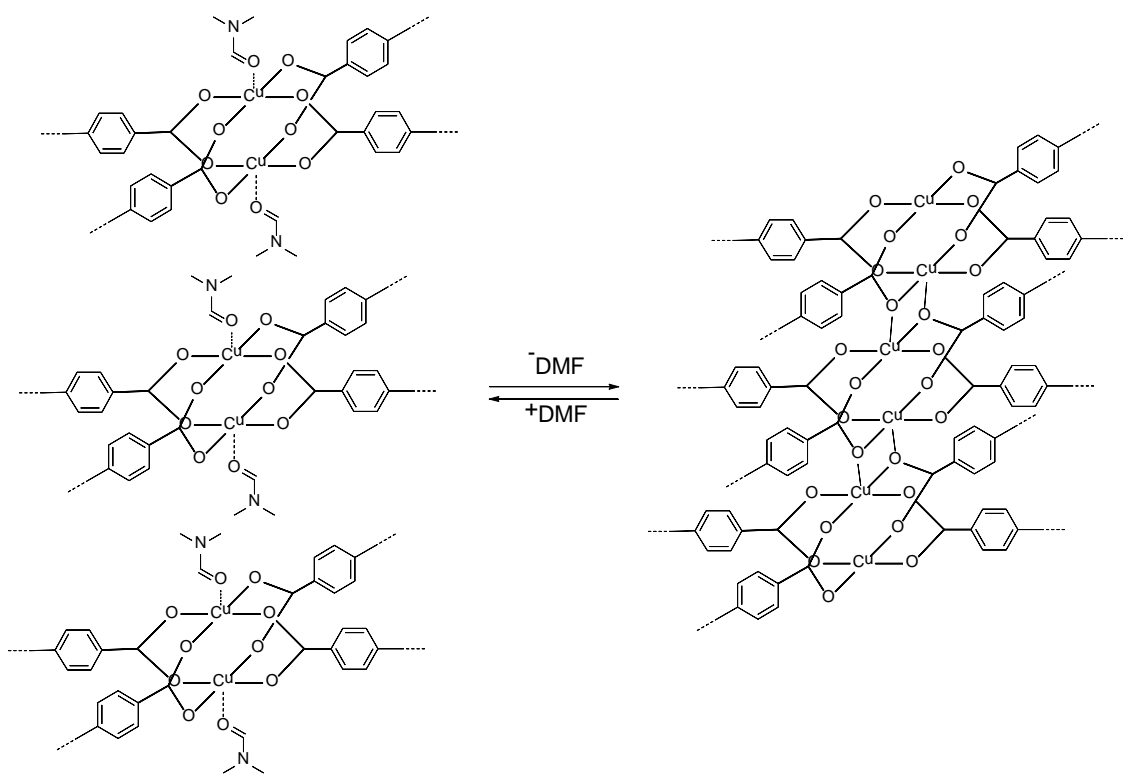




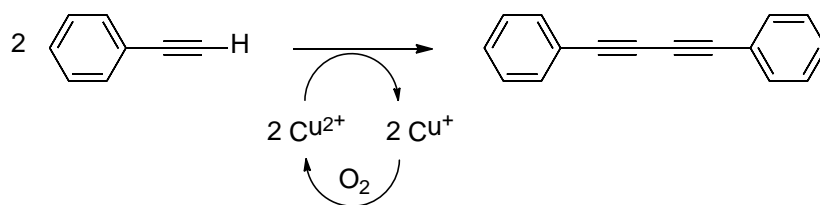
Scheme 1



Scheme 2



Scheme 3



Scheme 4