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Luz Minguez, I.; Corma Canós, A.; Llabrés I Xamena, FX. (2014). Cu-MOFs as active, selective and reusable catalysts for oxidative C O bond coupling reactions by direct C H activation of formamides, aldehydes and ethers. *Catalysis Science and Technology*. 4(6):1829-1836. doi:10.1039/c4cy00032c.



The final publication is available at

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Additional Information

Cu-MOFs as active, selective and reusable catalysts for oxidative C-O bond coupling reactions by direct C-H activation of formamides, aldehydes and ethers

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Abstract

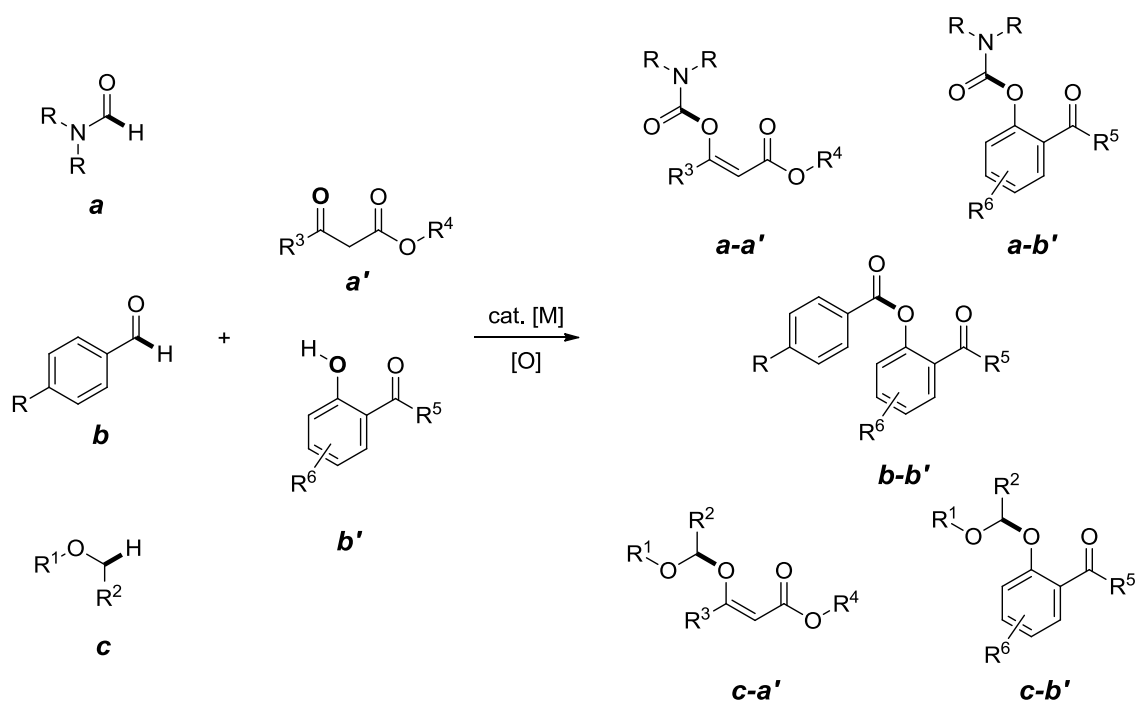
MOFs with Cu²⁺ centers linked to four nitrogen atoms from azaheterocyclic compounds, i.e., pyrimidine [Cu(2-pymo)₂] and imidazole [Cu(im)₂], are active, stable and reusable catalysts for oxidative C-O coupling reactions by direct C-H activation of formamides, aldehydes and ethers. The measured catalytic activities are clearly superior to other homogeneous cupric salts, specially for the [Cu(im)₂] MOF. The previously reported activity of the Cu²⁺ centers for cumene oxidation allows using the MOF as a bifunctional catalyst for olefin epoxidation with O₂. The overall catalytic process consists in a cascade reaction in which the Cu-MOF first produces cumyl hydroperoxide and then the same Cu²⁺ centers catalyze the oxidative C-O coupling reaction using the generated hydroperoxide as the oxidant.

1. Introduction

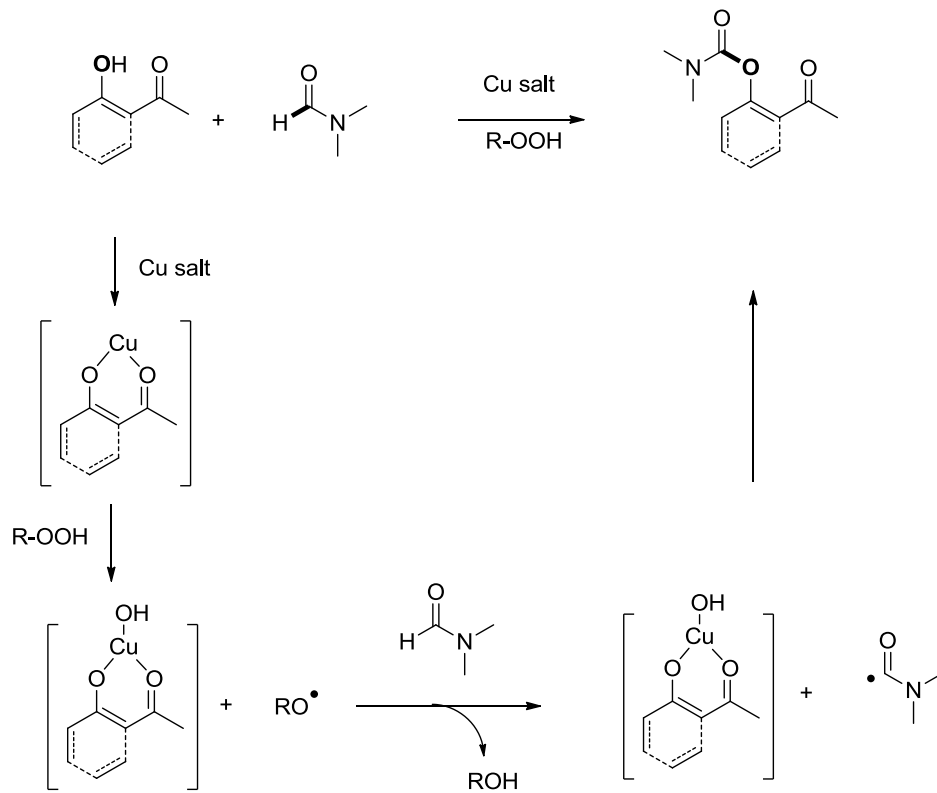
Transition metal catalyzed C-C and C-heteroatom coupling reactions are essential tools for the preparation of fine chemicals and key intermediates ^{1, 2}. These reactions usually rely on the use of pre-functionalized compounds (e.g., halogenated compounds and Grignard or organolithium reagents), and the reaction is usually carried out in the presence of an organic or inorganic base. An interesting possibility that has attracted great attention is the coupling reaction by direct activation of C-H bonds. This avoids using pre-functionalized precursors, thus saving additional preparative steps and increasing the overall atom efficiency of the process while reducing the production of wastes.

In this sense, Kumar et al. ³ and Barve et al. ⁴, have recently shown that various copper salts can catalyze the oxidative C-O coupling reaction of dialkyl formamides (**a**) with either β -keto esters (**a'**) or 2-carbonyl-substituted phenols (**b'**) using *tert*-butyl hydroperoxide (TBHP) as the oxidant (see Scheme 1). This synthetic route leading to enol (**a-a'**) and phenol carbamates (**a-b'**) implies the direct activation of the C-H bond of the formamide, and it was proposed as a phosgene-free alternative to the use of amines and isocyanates or chloroformates. The authors concluded that the presence of a carbonyl group adjacent to the hydroxy group was essential for the success of the oxidative C-O coupling. This was attributed⁴ to the tendency of dicarbonyl compounds to form a bidentate complex with the copper ions that facilitates the homolytic cleavage of the TBHP O-O bond. The reaction was proposed to proceed through the formation of a formamide radical species, as shown in Scheme 2. Kumar et al. also demonstrated that both β -keto esters (**a'**) and 2-carbonyl-substituted phenols (**b'**) can be coupled with either aldehydes (**b**) ³ or ethers (**c**) ⁵, leading respectively to phenol esters (**b-b'**) or ethers (**c-b'**) and unsymmetrical acetals (**c-a'**), also implying in both cases a direct activation of a C-H bond of either an aldehyde (**b**) or a α -C-H bond of an ether (**c**) (see Scheme 1).

Scheme 1



Scheme 2



While the development of new efficient metal-catalyzed oxidative couplings based on direct C-H activation is a significant step towards more eco-friendly processes, it is evident that the use of heterogeneous catalysts introduces additional advantages concerning product isolation and catalyst recovery and reuse. In this sense, it has been demonstrated that metal organic frameworks can replace homogenous molecular catalysts for a number of reactions⁶⁻¹⁰. In particular, we have shown that copper-MOFs containing CuN₄ centers with either imidazolate or 2-oxypyrimidinolate ligands ([Cu(im)₂] and [Cu(2-pymo)₂]) are highly active catalysts for the liquid phase aerobic oxidation of activated alkanes (viz., tetralin, ethylbenzene and cumene)^{11, 12}, which implies the effective generation of hydroperoxides and conversion to the corresponding alcohols and ketones. Herein we will show that these Cu-MOFs can also catalyze the oxidative coupling reactions of the compounds shown in Scheme 1, which also rely on the ability of the materials for effectively reacting hydroperoxides, as shown in Scheme 2. It is worth mentioning that during the preparation of this manuscript, Phan et al.¹³ have successfully applied a Cu-MOF as catalyst for the oxidative coupling of ethers and *ortho*-substituted phenolic compounds, following an analogous procedure as that depicted in Scheme 1 for the preparation of *c-b'* type compounds.

2. Materials and methods

2.1. Preparation of the Cu-MOFs

The Cu-MOFs were prepared according to the corresponding procedures reported in the original references for [Cu(2-pymo)₂],¹⁴ [Cu(im)₂],¹⁵ and [Cu(BDC)].¹⁶ The [Cu₃(BTC)₂] was a Basolite C300 commercial sample purchased from Sigma-Aldrich. Copper-exchanged zeolites used for comparison were prepared by conventional cationic exchange of commercial samples purchased from Zeolyst International, as described in detail in the Supporting Information. X-ray diffraction (Phillips X'Pert, Cu K α radiation) was used to confirm the expected crystalline structure of all the materials. Characterization of the samples by elemental analysis, TGA, FTIR and N₂ adsorption is provided as Supporting Information.

2.2. Catalytic reactions

Time evolution of products was determined in all cases by GC analysis of the samples (Varian 3900, capillary column HP-5) using *n*-hexadecane as external standard.

Particular reaction conditions in each case can be found at the foot of the corresponding Tables.

3. Results and Discussion

3.1. Synthesis of carbamates by direct C-H activation of formamides

When 2-hydroxyacetophenone (**1**) was contacted with TBHP (1.5 eq) in a large excess of *N,N*-dimethylformamide (DMF, 2 mL, *ca.* 26 eq), no reaction took place even after 24 h at 80°C (Table 1, entry 1). It was necessary the presence of a catalyst in the reaction medium to assist the oxidative coupling between the phenol derivative and DMF to form the corresponding carbamate **3**. As already reported by Kumar et al.,³ various Cu^I and Cu^{II} salts can catalyze this reaction. Thus as expected, when the reaction was carried out under the same reaction conditions and in the presence of copper acetate (5 mol% Cu), carbamate **3** was quantitatively formed after 3 h (Table 1, entry 2), in good agreement with the results previously reported^{3,4}. Very similar results were obtained when the Cu-MOF [Cu(2-pymo)₂] was used as catalyst and keeping constant the copper-to-substrate molar ratio at 5 mol% (Table 1, entry 6). This demonstrates that this Cu-MOF can successfully replace soluble copper salts as catalysts for this reaction, with the additional advantage that the solid MOF can be easily separated from the reaction products by simple filtration or centrifugation. Moreover, the solid recovered at the end of the reaction was found to remain intact, as determined by comparing the XRD pattern with that of the fresh catalyst (see Figure S17 in Supporting Information), which allowed reusing the material without significant loss of activity for at least 3 catalytic cycles (Table 1, entry 7). The heterogeneity of the catalytic process is supported by the following evidences: i) The maintenance the crystalline structure of the solid recovered after the catalytic reaction ii) According to the elemental analysis of the liquid filtrate after the reaction, only traces of Cu²⁺ were present (*ca.* 0.5 mg/L), showing that no significant amount of copper (less than 0.03% of the total amount of Cu) leached from the solid to the reaction medium during the reaction; iii) A hot filtration test was also performed (see Fig. S19 in Supporting Information), showing that once the solid is removed from the reaction medium, no further conversion is observed in the filtrate. This experiment rules out the presence of significant amount of homogeneous (soluble) catalytic species coming from the solid MOF.

Better results were obtained when the [Cu(im)₂] MOF was used as catalyst, since in this case the time needed for full phenol conversion was halved to only 1.5 h (Table 1, entry 8). Also the crystalline structure of [Cu(im)₂] was maintained during the reaction (see Figure S18 in Supporting Information) and the material was reusable for at least 3 catalytic cycles (Table 1, entry 9). We also evaluated the catalytic activity of other Cu-MOFs containing Cu₂ paddle-wheel dimmers: viz. [Cu₃(BTC)₂] and [Cu(BDC)]. Although these materials were also found to be active and stable catalysts for this reaction, they were considerably less performing than the above two Cu-MOFs containing CuN₄ centers. For instance, a maximum yield of 71% was attained over [Cu(BDC)] after 24 h of reaction (Table 1, entry 10). It is also worth mentioning that this reaction seems to be exclusively catalyzed by copper ions, while other metal give no reaction under similar conditions. In this sense, Barve et al. reported a preliminary screening of various substances that are known to catalyze radical reactions, including Fe₂O₃ or ZnCl₂, but none of them was able to catalyze this C-O coupling reaction.⁴ Analogously, we observed that the reaction between 2-hydroxyacetophenone and DMF does not proceed in the presence of other MOFs containing various metal ions different from copper, including Cr-MIL-101 and CPO-27 materials of Mn, Co and Ni.

To the best of our knowledge, no reports exist on other Cu-containing heterogeneous catalysts for this coupling reaction. Therefore, in order to put the activity of the Cu-MOFs into perspective, we have extended our study to Cu-exchanged zeolites of medium (MFI-type) and large pore (FAU-type) zeolites. The results are reported in Table 1 (entries 3 and 4). As it can be seen, both zeolites are active catalysts, as expected due to the typically high degree of coordinative unsaturation of the Cu²⁺ counterions in zeolites and their ability to coordinate to electron donating adsorbed molecules¹⁷⁻¹⁹. The larger pore openings of Cu²⁺-USY (7.4 Å) with respect to Cu²⁺-ZSM-5 (5.5 Å) allows an easier diffusion of substrates and products and is probably responsible for the higher catalytic activity observed. With respect to the Cu-MOFs we have found that, while Cu²⁺-ZSM-5 has a catalytic activity similar to [Cu(2-pymo)₂], the performance of Cu²⁺-USY is superior to that of [Cu(im)₂]. However, Cu²⁺-USY loses most of its catalytic activity after one catalytic cycle due to leaching of Cu²⁺ counterions to the liquid medium. Figure 1 shows a comparison of the time-conversion plots obtained for fresh and reused Cu²⁺-USY and [Cu(im)₂]. Therefore, in spite of the high initial activity of Cu²⁺-USY, the lack of long term stability and limited reusability make

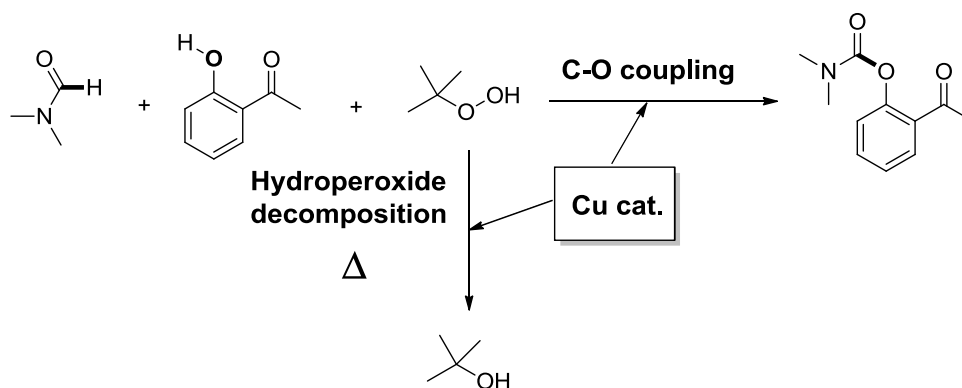
the Cu-zeolite a poor catalyst for this oxidative coupling reaction in comparison with the Cu-MOFs.

<Insert Figure 1 here>

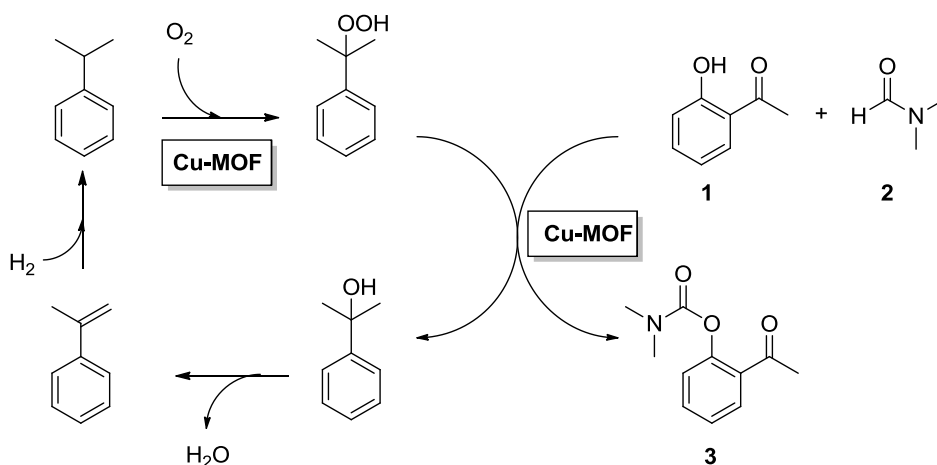
As reported by Kumar et al., the selection of TBHP as the oxidant for this oxidative C-O coupling reaction was found to be essential: no product formation was observed by these authors when H₂O₂, urea-hydrogen peroxide (UHP), di-*tert*-butyl peroxide (DTBP), *meta*-chloroperoxybenzoic acid (*m*CPBA) or NaOCl were used as the oxidant^{3,5}. A similar screening of various organic and inorganic oxidants led Barve et al. to the same conclusion⁴. Nevertheless, we wanted to extend the range of applicable oxidants for this reaction to other organic hydroperoxides. Thus, when TBHP was replaced by cumyl hydroperoxide (CmHP), we observed that the oxidative C-O coupling reaction over copper acetate, [Cu(im)₂] and [Cu(2-pymo)₂] was significantly faster than with TBHP, attaining full conversion of **1** to carbamate **3** in only 30 min in all cases (Table 1, entries 11-13). In order to appreciate the differences between copper acetate and the two Cu-MOFs, the reaction was repeated using only 1 mol% of copper with respect to phenol. Under these conditions, [Cu(im)₂] clearly outperformed the other Cu-MOF and copper acetate at short reaction times (23% yield after 30 min for [Cu(im)₂] vs. 3-4% for copper acetate and [Cu(2-pymo)₂], Table 1, entries 14-16). The corresponding turnover frequencies, (*TOFs*) calculated for the catalysts were 1 h⁻¹, ~5 h⁻¹ and ~28 h⁻¹ for [Cu(2-pymo)₂], Cu(OAc)₂ and [Cu(im)₂], respectively, thus being the latter MOF clearly the most active catalyst for this reaction. Nevertheless, the three materials lead to very similar *ca.* 75-80% product yields after 3 h. It is worth mentioning that the reaction stops before full phenol conversion due to the complete consumption of CmHP. Indeed, when a larger excess of CmHP was used (3 eq), carbamate **3** was quantitatively formed in 3 h. The reason for this spurious consumption of the hydroperoxide is the occurrence of a decomposition side reaction competing with the oxidative C-O coupling, which can be either a thermically activated process or it can also be catalyzed by the same copper centers, as shown in Scheme 3. Thus the amount of carbamate **3** formed will be determined by the relative reaction rates of both competing reactions, and this, in turn, will depend on the relative stability of the hydroperoxide used (either TBHP or CmHP), the substrates of the C-O coupling

reaction, the reaction temperature and, of course, the local structure of the copper active centers of the catalyst. This holds true for the rest of reactions discussed in this work.

Scheme 3



Besides the higher reaction rate attained as compared to TBHP, the use of CmHP as the oxidant for the C-O coupling reaction is interesting, since we have previously shown that CmHP can be generated *in situ* by the liquid phase aerobic oxidation of cumene over Cu-MOFs catalysts¹². Thus, taking the idea of the Sumitomo process for the production of propene oxide^{20, 21}, we can envisage a one-pot two-steps process in which cumene is oxidized to CmHP using O₂ as the oxidant. Then in a second step, CmHP is used to perform the oxidative C-O coupling of DMF and 2-hydroxyacetophenone. Eventually, the cumyl alcohol generated in the second step could be reconverted into cumene through dehydration and hydrogenation. The whole process is depicted in Scheme 4. Note that the Cu-MOF catalyzes both, cumene oxidation with air and the oxidative coupling reaction using as oxidant the CmHP generated in the first step. Thus, in this sense, the Cu-MOF acts as a bifunctional catalyst, even though the active centers are the same Cu²⁺ ions for both reactions.



Scheme 4

Following the process shown in Scheme 4, we contacted 1 mL of cumene (ca. 7 mmol) with [Cu(2-pymo)₂] (5 mol% Cu) at 80°C under an O₂ atmosphere for 2 h to produce CmHP in ca. 20% yield, whereupon 1 mmol of 2-hydroxyacetophenone and 1 mL of DMF were added at the same reaction temperature. [Cu-2pymo)₂] was selected as catalyst since we know from previous works that this material is highly selective to CmHP at low cumene conversions^{11,12}. Under these conditions, the carbamate product **3** was quantitatively formed in 97% yield after 1.5 h of reaction. This experiment, though being far from a practical application, demonstrates the feasibility of applying this Cu-MOF as a bifunctional catalyst for a tandem process in which the copper ions of the MOF produce CmHP, which is used by the same Cu active centers to catalyze the oxidative C-O coupling of a formamide and a 2-carbonyl-substituted phenol (**a** and **b'** in Scheme 1).

3.2. Synthesis of phenol esters by direct C-H activation of aldehydes

Besides formamides, copper catalysts can also activate C-H bonds of aldehydes, as reported by Kumar et al.³ These authors have studied the reaction between 2-hydroxyacetophenone and benzaldehyde in the presence of TBHP, leading to phenol esters (**b-b'** in Scheme 1) in good yields (ca. 80%). Given the excellent results obtained for the synthesis of carbamates by oxidative C-O couplings over copper MOFs, we wanted to investigate if these materials are also able to catalyze the direct C-H activation of aldehydes. The results obtained are summarized in Table 2.

In line with the results reported earlier by Kumar et al.,³ reaction of benzaldehyde and 2-hydroxyacetophenone in the presence of copper acetate (5 mol%) and TBHP yields 80% of the corresponding ester, **5**, after about 1.5 h (entry 2, Table 2). However, when copper acetate was replaced by [Cu(2-pymo)₂], the reaction was considerably slower, attaining only 36 mol% of **5** after the same reaction time (entry 3). Much better results were obtained with the other Cu-MOF studied, [Cu(im)₂], which afforded practically full conversion and full selectivity to **5** (entry 4), thus improving the results obtained with Cu(OAc)₂. The different catalytic performances of both Cu-MOFs are better appreciated when the catalysts loading was lowered to 1 mol% Cu (entries 5 and 6, Table 2): *TOFs* of 4 h⁻¹ and 84 h⁻¹ were obtained for [Cu(2-pymo)₂] and [Cu(im)₂], respectively. These large differences most probably arise from the different ability of each Cu-MOF to coordinate and decompose the hydroperoxide and the relative rate of oxidative C-O coupling reaction.¹² Also in this case, both MOFs were found to be stable under the reaction conditions and can be reused without significant loss of activity.

3.3. Synthesis of phenol ethers by direct α -C-H activation of ethers

As first reported by Kumar et al.,⁵ and then also by Phan et al.,¹³ various copper catalysts can directly activate the C-H bond of an alpha carbon of an ether, producing phenol ethers upon reaction with suitable *ortho*-substituted phenolic compounds. Very recently, Phan et al. have shown that this reaction can also be catalyzed by a copper-containing MOF. Thus, we have studied the reaction between 2-hydroxyacetophenone, **1**, and dioxane, **6**, in the presence of our two Cu-MOFs and using TBHP as the oxidant. Table 3 and Figure 2 summarize the results obtained. According to these results, [Cu(2-pymo)₂] was found to be more active than copper acetate for this reaction, attaining 82% yield of phenol ether **7** after 1.5 h (73% yield was obtained with copper acetate under identical conditions). As we have already shown for the two reactions described above, [Cu(im)₂] was again the most performing catalyst (compare entries 2, 4 and 9 in Table 3). Both Cu-MOFs were stable under reaction conditions and both can be fairly reused. However, [Cu(2-pymo)₂] started to lose significantly its activity after the 4th catalytic run, which is associated with a gradual loss of crystallinity and adsorption of reaction products on the surface of the catalyst, as determined by XRD, FTIR and TGA analysis of the used solids (see Figures S20-S22 in Supporting Information). A closer inspection of the catalysts recovered after the first use indicate that product adsorption and loss of

crystallinity of the solid occurs progressively from the beginning of the reaction, and the effects are observed already after the first cycle. On the contrary, $[\text{Cu}(\text{im})_2]$ keep its catalytic activity for (at least) 6 catalytic cycles, thus providing a cumulative *turnover number* (*TON*) of at least 98 moles of product formed per mol of Cu after 6 catalytic cycles (as compared with the maximum *TON* of 14.6 attained with the non-recoverable $\text{Cu}(\text{OAc})_2$ catalyst).

As commented above, full conversion of 2-hydroxyacetophenone was never attained when only a slight excess of TBHP (1.5 eq) was used, due to the complete exhaustion of the hydroperoxide through spurious decomposition. Thus, it is necessary to increase further the excess of TBHP to fully convert 2-hydroxyacetophenone. Alternatively, TBHP can also be slowly and continuously added with a peristaltic pump over the course of the reaction to minimize hydroperoxide decomposition. Thus, when 1.5 eq of TBHP were added during 60 min (for $\text{Cu}(\text{OAc})_2$ and $[\text{Cu}(2\text{-pymo})_2]$) or 20 min (for $[\text{Cu}(\text{im})_2]$), the final yield of **7** obtained was considerably higher than when the same amount of TBHP was added in one single stroke. This increase can easily be appreciated by comparing black and white columns in Figure 2. Also in these conditions, $[\text{Cu}(\text{im})_2]$ was the most active catalyst, with 96% yield of **7** produced in only 30 min (entry 15). For comparison, note that maximum yields of 79% and 85% were obtained after 1.5 h of reaction for $\text{Cu}(\text{OAc})_2$ and $[\text{Cu}(2\text{-pymo})_2]$, respectively (entries 3 and 8).

<Insert Figure 2 here>

As we have previously mentioned, Phan et al. have recently reported the use of a copper-containing MOF as a heterogeneous catalyst for the oxidative C-O coupling reaction of ethers and various 2-carbonyl-substituted phenols.¹³ The MOF used by these authors was $[\text{Cu}_2(\text{BPDC})_2(\text{BPY})]$ (BPDC = 4,4'-biphenyldicarboxylate, BPY = 4,4'-bipyridine), and it consists of 2D Cu-BPDC layers pillared by BPY ligands and containing Cu_2 paddle-wheel units.²² In order to establish a fair comparison of the catalytic activity of this MOF and our best performing material, $[\text{Cu}(\text{im})_2]$, we selected the experimental conditions used in the original paper by Phan et al. The best results with $[\text{Cu}_2(\text{BPDC})_2(\text{BPY})]$ were obtained for the coupling reaction between dioxane and salicylaldehyde with 3 equivalents of TBHP, at 100°C and with a 3 mol% catalyst loading. We thus measured the catalytic activity of $[\text{Cu}(\text{im})_2]$ under the same reaction

conditions. The comparison between the two Cu-MOFs is shown in Figure 3. As it can be seen, [Cu(im)₂] clearly outperforms the catalytic activity of [Cu₂(BPDC)₂(BPY)] under identical conditions, providing more than a 6-fold increment of the corresponding turnover frequency (TOF). The differences between the two catalysts most probably arise from the different local coordination of the copper sites in each solid, which is more crowded in the case of [Cu₂(BPDC)₂(BPY)] (each Cu ion is coordinated to 4 oxygen atoms from 4 carboxylate ligands and 1 N from a bpy molecule). On the contrary, copper ions in [Cu(im)₂] are surrounded by 4 N from 4 imidazolate ligands in a highly distorted square planar configuration, and the crystalline framework is highly adaptable to readily accommodate changes in the coordination sphere of copper ions that are necessary during the catalytic reaction, including ligand expansions, as we have previously shown.¹²

< Insert Figure 3 here >

4. Conclusion

In summary, we have shown herein that copper MOFs containing azaheterocyclic ligands, viz., pyrimidine [Cu(2-pymo)₂] and imidazole [Cu(im)₂], are active, stable and reusable catalysts for oxidative C-O coupling reactions by direct C-H activation of formamides, aldehydes and ethers. This represents a clear advantage with respect to other homogeneous catalysts reported so far for this reaction concerning product isolation and catalyst recovery and reuse. The materials used in the present work also clearly outperform the results reported very recently using the [Cu₂(BPDC)₂(BPY)] MOF as catalyst, attaining more than a 6-fold increment of the initial reaction rate (in terms of *TOF*).

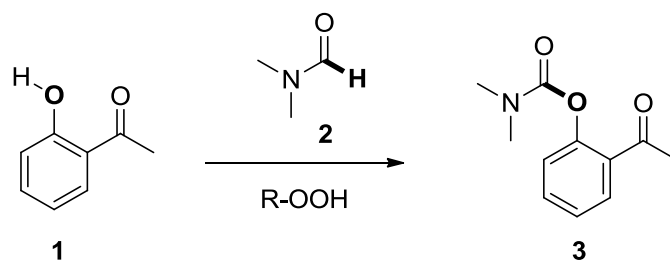
Acknowledgements

Financial support by Consolider-Ingenio 2010 (project MULTICAT), Severo Ochoa program, and the Spanish Ministry of Science and Innovation (project MAT2011-29020-C02-01) is gratefully acknowledged. Prof. Eduardo Palomares is gratefully acknowledged for providing the Cu-exchanged zeolites.

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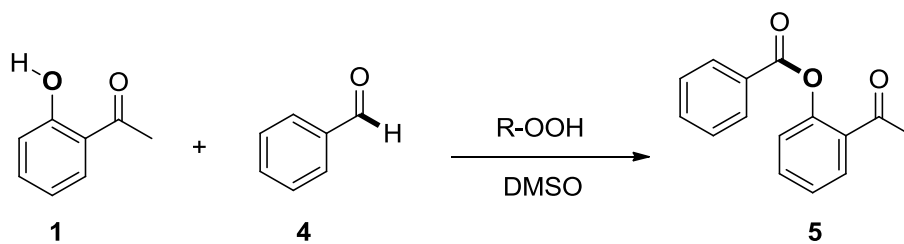
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Table 1. Oxidative coupling of 2-hydroxyacetophenone and *N,N*'-dimethylformamide.^a

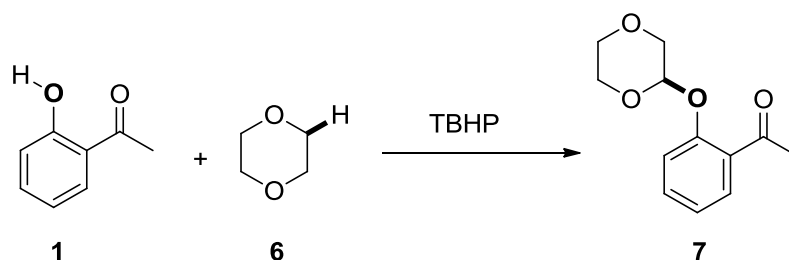
Entry	Catalyst	ROOH	Time	Yield of 3 (mol%) ^b
1	No catalyst	TBHP	24h	< 2
2	Cu(OAc) ₂	TBHP	3h	95
3	Cu ²⁺ -ZSM-5	TBHP	3h	93
4	Cu ²⁺ -USY	TBHP	30min	98
5	Cu ²⁺ -USY (3 rd cycle)	TBHP	30min/1h	9/24
6	[Cu(2-pymo) ₂]	TBHP	3h	93
7	[Cu(2-pymo) ₂] (3 rd cycle)	TBHP	3h	92
8	[Cu(im) ₂]	TBHP	30min/1.5h	67/97
9	[Cu(im) ₂] (3 rd cycle)	TBHP	30min/1.5h	60/96
10	[Cu(BDC)]	TBHP	24h	71
11	Cu(OAc) ₂	CmHP	30min	97
12	[Cu(2-pymo) ₂]	CmHP	30min	95
13	[Cu(im) ₂]	CmHP	30min	99
14	Cu(OAc) ₂ (1 mol% Cu)	CmHP	15min/30min/3h	2/ 4/ 75
15	[Cu(2-pymo) ₂] (1 mol% Cu)	CmHP	15min/30min/3h	1/ 3/ 77
16	[Cu(im) ₂] (1 mol% Cu)	CmHP	15min/30min/3h	7/ 23/ 74

^a Reaction conditions: 1 mmol 2-hydroxyacetophenone (103μl), 1.5 mmol ROOH, 2 mL of DMF and Cu-catalyst (5 mol% Cu, unless otherwise indicated), 80°C. ^b Determined by GC using hexadecane as internal standard. TBHP = *tert*-butyl hydroperoxide, CmHP = cumyl hydroperoxide.

Table 2. Oxidative coupling of 2-hydroxyacetophenone and benzaldehyde.^a

Entry	Catalyst	ROOH	Time	Yield of 5 (mol%) ^b
1	No catalyst	TBHP	24h	< 2
2	Cu(OAc) ₂	TBHP	1.5h	80
3	[Cu(2-pymo) ₂]	TBHP	1.5h	36
4	[Cu(im) ₂]	TBHP	1.5h	92
5	[Cu(2-pymo) ₂] (1 mol% Cu)	TBHP	15min/30min/3h	1/ 4/ 7
6	[Cu(im) ₂] (1 mol% Cu)	TBHP	15min/30min/3h	21/ 28/ 55

^a Reaction conditions: 1 mmol 2-hydroxyacetophenone (103 μ l), 1.1 mmol benzaldehyde (112 μ l), 1.5 mmol ROOH, 1 mL of DMSO and Cu-catalyst (5 mol% Cu, unless otherwise indicated), 80°C. ^b Determined by GC using hexadecane as internal standard.

Table 3. Oxidative coupling of 2-hydroxyacetophenone and dioxane.^a

Entry	Catalyst	ROOH	Time	Yield of 7 (mol%) ^b
1	No catalyst	TBHP	5 h	< 2
2	Cu(OAc) ₂	TBHP	1.5 h	73
3	Cu(OAc) ₂ ^c	TBHP	1.5 h	79
4	[Cu(2-pymo) ₂] (1 st run)	TBHP	1.5 h	82
5	[Cu(2-pymo) ₂] (2 nd run)	TBHP	1.5 h	78
6	[Cu(2-pymo) ₂] (3 rd run)	TBHP	1.5 h	79
7	[Cu(2-pymo) ₂] (4 th run)	TBHP	1.5 h	43
8	[Cu(2-pymo) ₂] ^c	TBHP	1.5 h	85
9	[Cu(im) ₂] (1 st run)	TBHP	0.5 h	83
10	[Cu(im) ₂] (2 nd run)	TBHP	0.5 h	84
11	[Cu(im) ₂] (3 rd run)	TBHP	0.5 h	80
12	[Cu(im) ₂] (4 th run)	TBHP	0.5 h	79
13	[Cu(im) ₂] (5 th run)	TBHP	0.5 h	82
14	[Cu(im) ₂] (6 th run)	TBHP	0.5 h	81
15	[Cu(im) ₂] ^d	TBHP	0.5 h	96

^a Reaction conditions: 1 mmol 2-hydroxyacetophenone (103μl), 1.5 mmol TBHP, 2 mL dioxane and Cu-catalyst (5 mol% Cu), 100°C. ^b Determined by GC using hexadecane as internal standard. ^c 1.5 eq ROOH were continuously added with a peristaltic pump over the first 1 h of reaction. ^d 1.5 eq ROOH were continuously added with a peristaltic pump over the first 20 min of reaction.

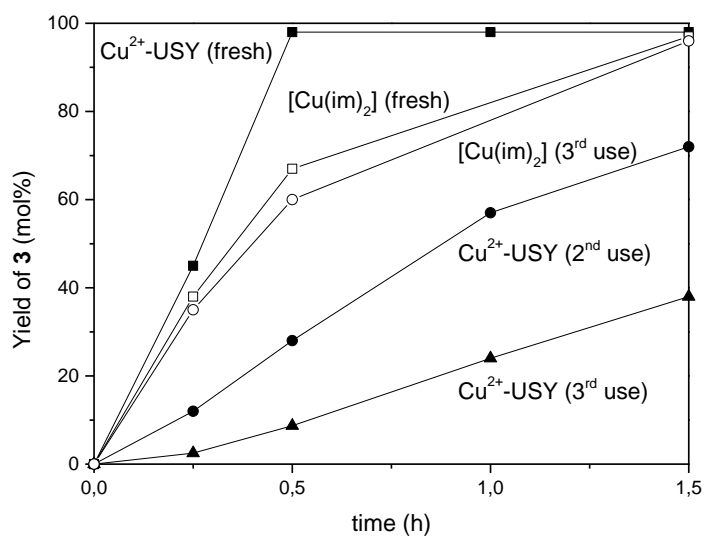


Figure 1. Kinetic data of the oxidative C-O coupling reaction between 2-hydroxyacetophenone and DMF over fresh and reused $[\text{Cu}(\text{im})_2]$ and Cu^{2+} -USY.

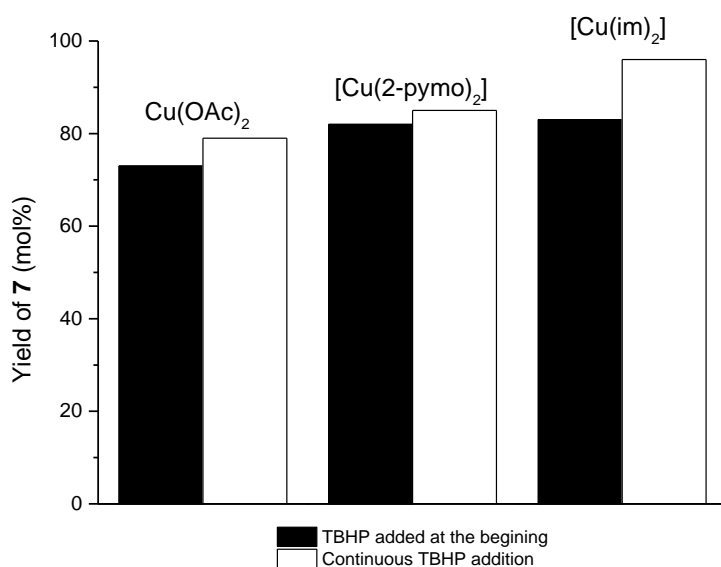


Figure 2. Comparison of the maximum yield of phenol ether **7** attained with the different copper catalysts when 1.5 eq of hydroperoxide were added in one single stroke at the beginning of the reaction (black columns) or when the same amount of hydroperoxide was slowly added with a peristaltic pump (white columns). See text for details.

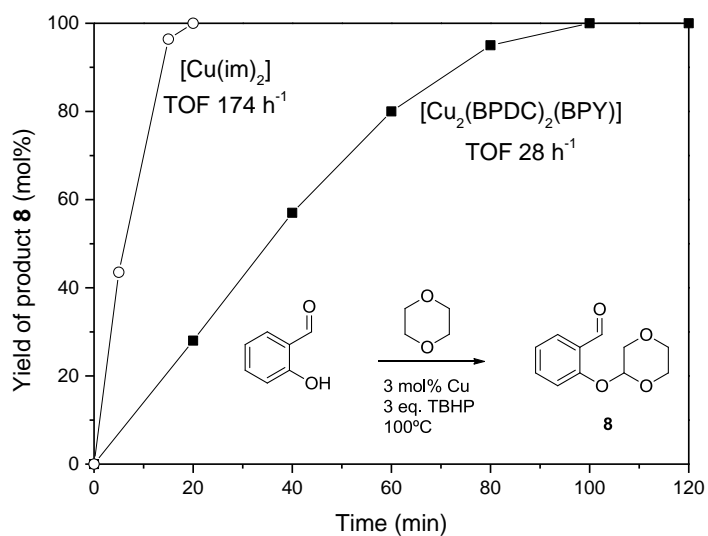


Figure 3. Kinetic data of the oxidative C-O coupling reaction between salicylaldehyde and dioxane over [Cu(im)₂] (○) and [Cu₂(BPDC)₂(BPY)] (■, data taken from Figure 16 of reference ¹³).