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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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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, especially for the $[Cu(im)_2]$ MOF. The previously reported activity of the Cu²⁺ centers for cumene oxidation allows the use of the MOF as a bifunctional catalyst for olefin epoxidation with O₂. The overall catalytic process consists of 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.

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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 the use of prefunctionalized precursors, thus saving additional preparative steps and increasing the overall atom efficiency of the process while reducing the production of waste.

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 enols (*a*–*a'*) and phenol carbamates (*a*–*b'*) implies 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 is 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*-*b'*) and unsymmetrical acetals (*c*-*a'*), also implying in both cases a direct activation of either the C–H bond of the aldehyde (*b*) or the α -C–H bond of the ether (*c*) (see Scheme 1).

While the development of new efficient metal-catalyzed oxidative coupling reactions 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 homogeneous molecular catalysts for a number of reactions.⁶⁻¹⁰ 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

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ketones. Herein we 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 to effectively react with 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 a 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 $[Cu_3(BTC)_2]$ is 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 ESI.† X-ray diffraction (Philips 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 in the ESI.†

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 the external standard. Particular reaction conditions in each case are indicated in the footnote 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). The presence of a catalyst is necessary

Table 1 Oxidative coupling of 2-hydroxyacetophenone and N,N'-



R-		OOH			
1	l			3	
Entry	Catalyst	ROOH	Time	Yield of $3^b \pmod{b}$	
1	No catalyst	TBHP	24 h	$<\!2$	
2	$Cu(OAc)_2$	TBHP	3 h	95	
3	Cu ²⁺ -ZSM-5	TBHP	3 h	93	
4	Cu ²⁺ -USY	TBHP	30 min	98	
5	Cu ²⁺ –USY (3rd cycle)	TBHP	30 min/1 h	9/24	
6	$[Cu(2-pymo)_2]$	TBHP	3 h	93	
7	$[Cu(2-pymo)_2]$ (3rd cycle)	TBHP	3 h	92	
8	[Cu(im) ₂]	TBHP	30 min/1.5 h	67/97	
9	$[Cu(im)_2]$ (3rd cycle)	TBHP	30 min/1.5 h	60/96	
10	[Cu(BDC)]	TBHP	24 h	71	
11	$Cu(OAc)_2$	CmHP	30 min	97	
12	$[Cu(2-pymo)_2]$	CmHP	30 min	95	
13	$[Cu(im)_2]$	CmHP	30 min	99	
14	$Cu(OAc)_2$ (1 mol% Cu)	CmHP	15 min/30 min/3 h	2/4/75	
15	[Cu(2-pymo) ₂] (1 mol% Cu)	CmHP	15 min/30 min/3 h	1/3/77	
16	$\begin{bmatrix} Cu(im)_2 \end{bmatrix}$ (1 mol% Cu)	CmHP	15 min/30 min/3 h	7/23/74	

^{*a*} Reaction conditions: 1 mmol 2-hydroxyacetophenone (103 μ l), 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 the external standard. TBHP = *tert*-butyl hydroperoxide and CmHP = cumyl hydroperoxide.

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 a catalyst and the copperto-substrate molar ratio was kept constant at 5 mol% (Table 1, entry 6). This demonstrates that this Cu-MOF can successfully replace soluble copper salts as the catalyst 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 Fig. S17 in the ESI[†]), which allowed reuse of 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 evidence: i) maintenance of the crystalline structure of the solid recovered after the catalytic reaction; ii) according to elemental analysis of the liquid filtrate after the reaction, only traces of Cu^{2+} were present (ca. 0.5 mg L⁻¹), 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; and iii) a hot filtration test was also performed (see Fig. S19 in the ESI[†]), showing that once the solid was removed from the reaction medium, no further conversion was observed in the filtrate. This experiment rules out the presence of a 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 the 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 Fig. S18 in the ESI[†]) 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 dimers: viz. $[Cu_3(BTC)_2]$ and [Cu(BDC)]. Although these materials were also found to be active and stable catalysts for this reaction, they were considerably worse performing than the two other 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 metals 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 did not proceed in the presence of other MOFs

containing various metal ions aside 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 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 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 with electron donating adsorbed molecules.¹⁷⁻¹⁹ The larger pore opening of Cu²⁺–USY (7.4 Å) with respect to Cu²⁺–ZSM-5 (5.5 Å) allows easier diffusion of substrates and products and is probably responsible for the higher catalytic activity observed. With respect to the Cu-MOFs, we found that, while Cu^{2+} -ZSM-5 has a catalytic activity similar to $[Cu(2-pymo)_2]$, the performance of Cu^{2+} -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. Fig. 1 shows a comparison of the timeconversion 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.

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 H_2O_2 , urea-hydrogen peroxide (UHP), di-*tert*-butyl peroxide (DTBP), *meta*-chloroperoxybenzoic acid (*m*CPBA) or NaOCl was used as the oxidant.^{3,5} A similar screening of various organic and inorganic oxidants led Barve *et al.* to the same conclusion.⁴ Nevertheless, we wanted to extend the range of applicable oxidants for this reaction to other organic hydroperoxides. Thus, when TBHP was



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

replaced by cumyl hydroperoxide (CmHP), we observed that the oxidative C-O coupling reactions over copper acetate, $[Cu(im)_2]$ and $[Cu(2-pymo)_2]$ were significantly faster than that over 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 making the latter MOF clearly the most active catalyst for this reaction. Nevertheless, the three materials led 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 after 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 thermally 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 the reactions discussed in this work.

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 liquid phase aerobic oxidation of cumene over Cu-MOF catalysts.¹² Thus, taking the idea of the Sumitomo process for the production of propene oxide,20,21 we can envisage a one-pot two-step process in which cumene was oxidized to CmHP using O2 as the oxidant. Then in a second step, CmHP was 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 in air and the oxidative coupling reaction using as the 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.

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.

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 $[Cu-2pymo)_2]$ was selected as the catalyst since we know from previous studies 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, demonstrated the feasibility of applying this Cu-MOF as a bifunctional catalyst for a tandem process in which the copper ions of the MOF produced CmHP, which was 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 yield (*ca.* 80%). Given the excellent results obtained for the synthesis of carbamates by oxidative C–O coupling 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 the reaction of benzaldehyde and 2-hydroxyacetophenone in the presence of copper acetate (5 mol%) and TBHP yielded 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 were better appreciated when the catalyst 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 abilities of each Cu-MOF to coordinate and decompose the hydroperoxide and the relative rate of the 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

Entry

1

2 3

4

5

6

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



^{*a*} Reaction conditions: 1 mmol 2-hydroxyacetophenone (103 µl), 1.1 mmol benzaldehyde (112 µl), 1.5 mmol ROOH, 1 mL of DMSO and Cucatalyst (5 mol% Cu, unless otherwise indicated), 80 °C. ^{*b*} Determined by GC using hexadecane as the external standard.

C–H bond of the 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 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 Fig. 2 summarize the results obtained. According to the 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 best 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

Table 3 Oxidative coupling of 2-hydroxyacetophenone and dioxane ^a								
	$\begin{array}{c} H_{0} \\ \bullet \\$	Н ТВНР						
Entry	Catalyst	ROOH	Time	Yield of $7^b \pmod{6}$				
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	$[Cu(2-pymo)_2]$ (1st run)	TBHP	1.5 h	82				
5	$[Cu(2-pymo)_2]$ (2nd run)	TBHP	1.5 h	78				
6	[Cu(2-pymo) ₂] (3rd run)	TBHP	1.5 h	79				
7	$[Cu(2-pymo)_2]$ (4th run)	TBHP	1.5 h	43				
8	$[Cu(2-pymo)_2]^c$	TBHP	1.5 h	85				
9	$[Cu(im)_2]$ (1st run)	TBHP	0.5 h	83				
10	$\left[Cu(im)_{2}\right]$ (2nd run)	TBHP	0.5 h	84				
11	$\left[Cu(im)_{2}\right]$ (3rd run)	TBHP	0.5 h	80				
12	$\left[Cu(im)_{2}\right]$ (4th run)	TBHP	0.5 h	79				
13	$\left[Cu(im)_{2}\right]$ (5th run)	TBHP	0.5 h	82				
14	$\left[Cu(im)_{2}\right]$ (6th run)	TBHP	0.5 h	81				
15		TBHP	0.5 h	96				

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



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

its activity after the 4th catalytic run, which is associated with a gradual loss in crystallinity and adsorption of the reaction products on the surface of the catalyst, as determined by XRD, FTIR and TG analyses of the used solids (see Fig. S20–S22 in the ESI†). A closer inspection of the catalysts recovered after the first use indicates that product adsorption and loss in crystallinity of the solid occur progressively from the beginning of the reaction, and the effects are observed already after the first cycle. On the contrary, $[Cu(im)_2]$ kept 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 Cu(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 complete exhaustion of the hydroperoxide through spurious decomposition. Thus, it was necessary to increase further the amount of excess TBHP to fully convert 2-hydroxyacetophenone. Alternatively, TBHP can also be slowly and continuously added using a peristaltic pump over the course of the reaction to minimize hydroperoxide decomposition. Thus, when 1.5 eq. of TBHP were added over 60 min (for $Cu(OAc)_2$ and $[Cu(2-pymo)_2]$ or 20 min (for $[Cu(im)_2]$), the final yield of 7 obtained was considerably higher than when the same amount of TBHP was added in one single step. This increase can easily be appreciated by comparing black and white columns in Fig. 2. Also under these conditions, [Cu(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 Cu(OAc)₂ and [Cu(2-pymo)₂], respectively (entries 3 and 8).



Fig. 3 Kinetic data of the oxidative C–O coupling reaction between salicylaldehyde and dioxane over $[Cu(im)_2]$ (\odot) and $[Cu_2(BPDC)_2(BPY)]$ (\blacksquare , data taken from Fig. 16 of ref. 13).

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 $[Cu_2(BPDC)_2(BPY)]$ (BPDC = 4,4'-biphenyldicarboxylate, BPY = 4,4'-bipyridine), and it consists of 2D Cu-BPDC layers pillared by BPY ligands and containing Cu₂ paddle-wheel units.²² In order to establish a fair comparison of the catalytic activity of this MOF and our best performing material, [Cu(im)₂], we selected the experimental conditions used in the original paper by Phan et al. The best results with $[Cu_2(BPDC)_2(BPY)]$ were obtained for the coupling reaction between dioxane and salicylaldehyde with 3 equivalents of TBHP at 100 °C and with 3 mol% catalyst loading. We thus measured the catalytic activity of [Cu(im)₂] under the same reaction conditions. The comparison between the two Cu-MOFs is shown in Fig. 3. As 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 coordinations of the copper sites in each solid, which is more crowded in the case of $[Cu_2(BPDC)_2(BPY)]$ (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

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 study also clearly outperform the very recently reported $[Cu_2(BPDC)_2(BPY)]$ MOF as a catalyst, attaining more than a 6-fold increment of the initial reaction rate (in terms of TOF).

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