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MOFs extend the lifetime of Pd(II) catalyst for room temperature alkenylation of enamine-like arenes

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Abstract. The synthesis of pharmaceutically relevant scaffolds, such as substituted indoles or uracils, through the alkenylation of the "enamine-like" aromatic C-H bond is performed at room temperature using catalytic amounts of $Pd(OAc)_2$ in the presence of redox active, stable and reusable metal-organic microporous frameworks. This is the first time that redox/acid active sites in the porous, non-toxic and earth abundant robust MOF-74 platform are used to avoid the fast deactivation of the cationic Pd species working under ambient conditions.

Keywords: Indole; Uracil; Palladium; MOFs; Alkenylation

Direct alkenylation of aromatic C-H bonds make use of simple, robust compounds, with long shelf life, and without lability issues known for 'traditional' cross-couplings (boronic acids, etc.) eliminating the need for rigorous prefunctionalizations.^[11] In particular, novel synthetic strategies to obtain pharmaceuticals using oxidative-Heck process for alkenylation of nucleophilic "enamine-like" aromatic CH's on an indole core with electrophilic acrylic esters under mild/catalytic conditions are in high demand.^[21] In this sense, suprastoichiometric amounts of acid and/or oxidants capable of effecting the re-oxidation of the Pd sites have been proposed.^[31] However, equipment corrosion, toxicity and environmental impact of the additives employed

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(often in large amounts) requires the development of more safe, efficient and clean synthetic procedures with reduced numbers of transformation steps and minimized chemical waste.^[4]

Here, we propose the use of liquid oxidants (organic peroxides) which allows for a simple reaction set-up, avoiding the use of pressurized gas which complicates the handling, safety and industrial application in a room temperature continuous flow synthesis.^[5] In order to overcome the drawbacks of homogeneous additives, microporous solids such as robust MOF-74 metalorganic framework can be employed as potential active solid and reusable catalytic platform.^[6] The proposed heterogeneous MOF nanoreactor promotes the oxidative cross coupling between two different alkenes to produce pharmaceutically interesting scaffolds (see Scheme 1). Initially, different palladium catalysts were tested for the alkenylation of indole with butyl acrylate in DMSO at room temperature and ambient atmosphere in the absence of the MOF and TBHP oxidant.



Scheme 1. Reusable redox-active Cu(II)-MOF-74 favours the mild alkenylation of enamine-like arenes into pharmaceutical intermediates.^[7]

The homogeneous palladium salt catalysts show TONs (turnover numbers or mol of indole derivative 1 obtained per mol of Pd) that increase in the order PdCl₂ $< Pd(TFA)_2 < Pd(OAc)_2$ (see left part of Fig. 1). When the Pd(OAc)₂ soluble catalyst is employed together with one equivalent of TBHP as an inexpensive oxidant, a twofold increase of the TON of Pd is achieved. Figure 1 shows that the isoreticular $M_2(dobdc)$ (also known as M-MOF-74, M = Cu(II), Co(II), Ni(II), Mg(II), Mn(II); $dobdc^{4-} = 2,5$ -dioxido-1,4- benzenedicarboxylate) solid co- catalysts, enhance the re-oxidation of the electrophilic metal centres, e.g. Pd(OAc)₂. In fact, a linear trend between the TONs and standard reduction potential of the metal ion present in the MOF indicates that more oxidizing cations result in a better catalytic performance of the Pd(II) alkenylation catalyst (see insert in Fig. 1 and Fig. S3). Among all the metalorganic frameworks tested, the Cu₂(dobdc) redox active MOF remarkably extends the lifetime of the $Pd(OAc)_2$ catalyst, since the number of turnovers that a single Pd site may perform is almost three times higher than in the absence of the MOF (see right part of Fig. 1).

The MOFs were used in a second reaction cycle (upon addition of 5 mol% of fresh Pd(OAc)₂) without significant decrease in activity or selectivity (Fig. S2). To our delight, well-reported Cu(OAc)₂ or copper exchanged zeolites do not further improve the catalytic activity of palladium (see Fig. S2a).^[4b] This is probably due to the favoured formation of active Pd(OAc)₂-DMSO clusters and/or hindered formation of insoluble or inactive mixed species in the presence of the Cu-MOF-74 nanoreactor, with respect to the use of soluble oxidants such as Cu(OAc)₂.^[8] The robust M-MOF-74 materials are also more active than the corresponding homogeneous metal nitrates (see Table S1 and Fig. S3) and allow for its reuse with minor loss in activity or



Figure 1. TON values of Pd (5 mol%) in the room temperature alkenylation of indole with butyl acrylate, using 10 mol% of redox active MOFs with respect to indole. The insert shows the dependence of the TON_{Pd} with the standard reduction potential of the MOF cation (M^{2+}) vs SHE. The redox pair (M^{2+}/M^0) was used for Mg, Mn, Ni, Co and the pair Cu²⁺/Cu⁺¹ in the case of copper.

crystallinity in at least four reaction cycles (see Fig. S2 and S4). Neither higher reaction temperatures (60-70 °C) or the use oxygen pressure (up to 20 bar) outperforms the catalytic (TBHP/Cu-MOF-74) system reported here (see Table S2 and Fig. S5a). This could be attributed to the limited solubility of oxygen in DMSO that does not effectively re-oxidise the palladium in contrast to the good solubility of TBHP,^[9] which is further uptaken (up to 0.83 g_{TBHP}/g_{MOF}) by the Cu²⁺-MOF redox active nanoreactor after 10 min RT stirring. Continuous flow catalytic processes have been rarely reported using solid MOFs as heterogeneous catalysts. despite industrial importance.^[10] The easy handling of liquid organic peroxides and the room temperature conditions reported here, allow for the simple operation of a continuous process for the synthesis of 1 (Fig. S7). Given the good results obtained with $Pd(OAc)_2$ in the presence of Cu-MOF-74, this MOF was impregnated with a toluene solution of Pd(OAc)₂, resulting in the heterogeneous catalyst named as Pd(OAc)2@Cu-MOF-74. This solid was able to completely transform a continuous flow of indole and butyl acrylate into the desired product 1 after just five minutes at room temperature (see Fig. 2a, right). The lifetime of the $Pd(OAc)_2$ catalyst (for 50% yield of 1) is increased with more than 270% with respect to using a silica matrix.



Figure 2. (a) Kinetic and deactivation profiles of $Pd(OAc)_2$ containing catalyst (see legend) under batch (5 mol%) or continuous flow (10 mol%) mode. (b) XRD patterns, (c) Arphysisorption, (d) EPR and (e) XAS spectras of Cu-MOF-74 (red), Pd@Cu-MOF-74 before (blue) and after (green) the room temperature alkenylation of indole.

In an attempt to construct a heterogeneous catalyst system with higher activity, the homogeneous Pd(OAc)₂ and H₃PW₁₂O₄₀ polyoxometalate (POM) where encapsulated into the pores of the MOF.^[11] The surface area of the MOF-74 significantly decrease from 1120 to 480 m^2g^{-1} after the pre-loading of POM + Pd(OAc)₂, indicating its encapsulation in the pores of the MOF (compare blue and red isotherms in Fig. 2c). When using this Pd(OAc)₂-POM@Cu-MOF-74 system, a further 290% increase in the catalyst lifetime is achieved. However, the increase in surface area (from $480 \text{ m}^2 \text{ g}^{-1}$ to 790 m² g⁻¹) of the Pd(OAc)₂-POM@Cu-MOF-74 system (green isotherm) after the reaction (see Fig. 2c and S8) suggest the loss of Pd(II) active sites from the pores of MOF-74 (see Table S3). In fact, the activity of the spent Pd(OAc)2-POM@Cu-MOF-74 decreases significantly, requiring the addition of fresh $Pd(OAc)_2$ in subsequent runs. By doing this, the Cu-MOF-74 is reused up to four times with minor loss in the Pd(OAc)₂ activity (TON_{Pd} > 16 in Fig. S6). The Xray diffraction (XRD) patterns (Fig. 2b) show that the recycled Cu-MOF-74 solid co-catalyst maintains its crystalline structure. A slight decrease of the lower angle diffraction peak occurs due to the adsorption of the compounds and solvent during the reaction, in agreement with the Ar physisorption results (Fig. 2c and S8). ICP results (Table S3) and EPR analysis (Fig. 2d) of the spent materials show no major Cu(II) leaching or reduction to Cu(I) or Cu(0) species during the reaction. This is confirmed by the main resonance centered at B_0 = 325 mT, assigned to the Cu^{2+} centers at the MOF nodes in both samples before and after the reaction. The sharp peak at g = 2.005 in the spectrum of the used sample is likely associated with peroxy radicals generated during the reaction.^[12] Finally, X-ray absorption spectroscopy (XAS) of the fresh and spent material (Fig. 2e) reveal that the remaining Pd(OAc)₂ encapsulated in the MOF eventually gets reduced to inactive Pd (0) during the catalytic test, resulting in the deactivation of the catalyst. Besides C-3 indole substituted derivatives, uracil type *N*-heterocyclic arenes are interesting targets since C-5 substituted uracils are found to be potential antitumor and antiviral compounds (Scheme 1).^[13] The reaction rate for the room temperature alkenylation of 1,3dimethyluracil with butyl acrylate to selectively generate compound 2 is also higher when $Pd(OAc)_2$ (30) mol%) is employed in the presence of Cu-MOF-74 with respect to the non-redox active HY zeolite. Although the palladium TON values for the production of substrate 2 are lower than those for the synthesis of



Figure 3. Yields of products 1 and 2 obtained after 24 h of room temperature $Pd(OAc)_2$ catalyzed alkenylation of indoles and uracils in the presence of TBHP and Cu-MOF-74.



Figure 4. NMR spectra (and TOF_{Pd}) of the crude reaction mixture catalysed by 5 mol% of Pd(OAc)₂ (a) in the presence of Cu-MOF-74 (b) and tBuOOH/ Cu-MOF-74 (c) room temperature redox system.

indole **1** (TON₁ ~ 14 vs. TON₂ ~ 4), the initial reaction rate increases from 0.1 mmol·h⁻¹ (in the presence of the HY zeolite) to 0.2 mmol·h⁻¹ (in the presence of 10 mol% Cu-MOF-74). When the amount of MOF present in the reaction is further increased to 40 mol%, the reaction rate for the production of compound **2** also increases up to 0.3 mmol·h⁻¹ (see Fig. S9a), highlighting the beneficial effect of Cu-MOF-74. As reported for indole, the presence of H₃PW₁₂O₄₀ increases the reaction rate with more than 130% with respect to using only the Cu-MOF-74 (see Fig. S9b). A further increase in the yield of **2** is achieved when the reaction is performed at 60 °C, obtaining almost full conversion into product **2**. Based on the experimental results described, we

Based on the experimental results described, we propose a catalytic cycle where both the $Pd(OAc)_2$ and the Cu redox active MOF-74 participate. While palladium catalyzes the C-C coupling between the heteroarene and butyl acrylate, the TBHP/Cu-MOF-74 re-oxidizes the Pd⁰ reduced during the reaction (see in Figure 4 the palladium mirror formed in the absence of and tBuOOH/Cu-MOF-74) to catalytically active Pd²⁺. This results in an increased turnover number of the Pd active sites (extended lifetime) in the presence of the MOF system. It is important to notice that the reaction rate (and turnover frequency, TOF) increases twofold in the presence of the MOF and it is six times higher when TBHP is also present in the media.

In conclusion, earth abundant, non-toxic, redox active metal sites in a stable framework, such as those of MOF-74, improve the performance of Pd(OAc)₂ as efficient catalyst for the room temperature alkenylation of indole or uracil moieties. On the one hand, the highly porous MOF nanoreactor enhances the dispersion of Pd(OAc)₂, which hinders its fast agglomeration and formation of insoluble or inactive mixed species. On the other hand, the use of TBHP as an inexpensive liquid oxidant in the presence of redox active MOF-74, helps to regenerate some of the inactive Pd(0) into catalytically active Pd(II). The Cu-MOF-74 employed here represents an alternative non-harmful solid oxidant co-catalyst that increases the Pd(OAc)₂ lifetime, which will enable faster and safer catalytic process, relevant in

the continuous flow - room temperature synthesis of fine chemicals and pharmaceuticals.

Experimental Section

In a typical synthesis of Cu-MOF-74, a mixture of 2,5dihydroxyterephthalic acid (11.2 mmol) and Cu(NO₃)₂·3H₂O (24.6 mmol) were added over a 20:1 (v/v) solution of DMF and 2-propanol (250 mL). The reaction vial was capped tightly and placed in an oven at 80 °C during 18 hours. The alkenylation reactions were performed as follows: 1 mmol of indole or uracil, 1.2 mmol of butyl acrylate, 1 mmol of *tert*butyl hydroperoxide solution, were added to a glass vessel containing MOF and 1 ml of DMSO. The vials were closed and transferred into an aluminum heating block preheated to 30 °C, the mixture was stirred and sample aliquots were taken at different reaction times. The reaction products were recovered and analyzed by GC-FID (see supporting information for details).

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