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

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/adsc.201#####>. ((Please delete if not appropriate))

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.^[1] 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.^[2] In this sense, supra-stoichiometric amounts of acid and/or oxidants capable of effecting the re-oxidation of the Pd sites have been

proposed.^[3] However, equipment corrosion, toxicity and environmental impact of the additives employed (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 metal-organic framework can be employed as potential active solid and reusable catalytic platform.^[6] The role of this MOF in the oxidative cross coupling between two different alkenes to produce pharmaceutically interesting scaffolds is highlighted in Scheme 1. Initially, different palladium catalysts were tested for the alkenylation of indole with butyl acrylate in DMSO at room temperature and ambient atmosphere.

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

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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 $\text{PdCl}_2 < \text{Pd}(\text{TFA})_2 < \text{Pd}(\text{OAc})_2$ (see left part of Fig. 1). When the $\text{Pd}(\text{OAc})_2$ soluble catalyst is employed together with one equivalent of TBHP as an inexpensive oxidant, a twofold increase of the TON of Pd is achieved. The isorecticular $\text{M}_2(\text{dobdc})$ (also known as M-MOF-74, M = Cu(II), Co(II), Ni(II), Mg(II), Mn(II); $\text{dobdc}^{4-} = 2,5$ -dioxido-1,4- benzenedicarboxylate) solid co- catalysts, enhance the re-oxidation of the electrophilic metal centres, e.g. $\text{Pd}(\text{OAc})_2$. 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 metal-organic frameworks tested, the $\text{Cu}_2(\text{dobdc})$ redox active MOF remarkably extends the lifetime of the $\text{Pd}(\text{OAc})_2$ 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 $\text{Pd}(\text{OAc})_2$) without significant decrease in activity or selectivity (Fig. S2). To our delight, well-reported $\text{Cu}(\text{OAc})_2$ 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 $\text{Pd}(\text{OAc})_2$ -DMSO clusters and/or hindered formation of insoluble or inactive mixed species in the case of the Cu-MOF-74 porous solid with respect to the use of soluble oxidants such as $\text{Cu}(\text{OAc})_2$.^[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

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 $t\text{-BuOOH}$.^[9] 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**. Given the good results obtained with $\text{Pd}(\text{OAc})_2$ in the presence of Cu-MOF-74, this MOF was impregnated with a toluene solution of $\text{Pd}(\text{OAc})_2$, resulting in the heterogeneous catalyst named as $\text{Pd}(\text{OAc})_2@ \text{Cu-MOF-74}$. 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). The lifetime of the $\text{Pd}(\text{OAc})_2$ catalyst (for 50% yield) is increased with more than 270% with respect to using a silica matrix. A further 290% increase in the catalyst lifetime is achieved by supporting polyoxometalates (POMs) in the Cu-MOF-4 catalyst.^[11] This MOF can be reused up to four times with minor loss in the $\text{Pd}(\text{OAc})_2$ activity ($\text{TON}_{\text{Pd}} > 16$, see Fig. S6). The X-ray diffraction (XRD) pattern shows that the recycled Cu-MOF-74 solid co-catalyst maintains its crystalline structure (Fig. 2b). 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. S8).

Figure 1. Figure Caption. 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 $\text{Cu}^{2+}/\text{Cu}^{+1}$ in the case of copper.

Figure 2. Kinetic and deactivation profiles of $\text{Pd}(\text{OAc})_2$ containing catalyst under batch (5 mol%) or continuous flow (10 mol%) mode (a), XRD pattern (b) and EPR spectra (c) of the $\text{Pd} @ \text{Cu-MOF-74}$ before (blue) and after 2 h (green) of the room temperature alkenylation of indole.

ICP results (Table S3) and EPR analysis (see Fig. 2c) 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]

Besides from 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 1,3-dimethyluracil with butyl acrylate to selectively generate compound **2** is also higher when the $\text{Pd}(\text{OAc})_2$ (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 indole **1** ($\text{TON}_1 \sim 14$ vs. $\text{TON}_2 \sim 4$), the initial reaction rate increases from $0.1 \text{ mmol} \cdot \text{h}^{-1}$ (in the presence of the HY zeolite) to $0.2 \text{ mmol} \cdot \text{h}^{-1}$ (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 $0.3 \text{ mmol} \cdot \text{h}^{-1}$ (see Fig. S9a), highlighting the beneficial effect of Cu-MOF-74. As reported for indole, the presence of $\text{H}_3\text{PW}_{12}\text{O}_{40}$ 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 dimethyl uracil conversion into product **2**.

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

Regarding to the reaction mechanism, we propose a catalytic cycle where both the $\text{Pd}(\text{OAc})_2$ and the Cu redox active MOF-74 participate (see Figure 4). While palladium catalyzes the C-C coupling between the heteroarene and butyl acrylate, the TBHP/Cu-MOF-74 re-oxidizes the Pd^0 reduced during the reaction (see in Figure 4 the palladium mirror formed in the absence of and $\text{tBuOOH}/\text{Cu-MOF-74}$) to catalytically active Pd^{2+} . This eventually 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 is six times higher when TBHP is also present in the media.

Figure 4. NMR spectra (and TOF_{Pd}) of the crude reaction mixture catalysed by 5 mol% of $\text{Pd}(\text{OAc})_2$ (a) in the presence of Cu-MOF-74 (b) and $\text{tBuOOH}/\text{Cu-MOF-74}$ (c) room temperature redox system.

In conclusion, earth abundant, non-toxic, redox active metal sites in a stable framework, such as those of MOF-74, improve the performance of $\text{Pd}(\text{OAc})_2$ as efficient catalyst for the room temperature alkenylation of indole or uracil moieties. On the one hand, the highly porous MOF enhances the dispersion of $\text{Pd}(\text{OAc})_2$, 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 $\text{Pd}(0)$ into catalytically active $\text{Pd}(\text{II})$. The Cu-MOF-74 employed here represents an alternative non-harmful solid oxidant co-catalyst that increases the $\text{Pd}(\text{OAc})_2$ 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 2,5-dihydroxyterephthalic acid (11.2 mmol) and $\text{Cu}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$ (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 0.05 mmol $\text{Pd}(\text{OAc})_2$, 0.1 mmol of metal 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).

Acknowledgements

F.G.C. kindly acknowledges the European Commission-Horizon 2020 under the Marie Skłodowska-Curie Individual Fellowship grant agreement number 750391 (Project acronym SINMOF) for financial support. The FWO and Spanish Ministry of Science and innovation are also acknowledged for funding.

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Extending the lifetime of Pd(II) alkenylation catalyst through redox-active metal-organic frameworks

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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