C2–H Arylation of Indoles Catalyzed by Palladium-Containing Metal-Organic-Framework in γ-Valerolactone

Ioannis Anastasiou[+],[a] Niels Van Velthoven[+],[b] Elena Tomarelli,[a] Aurora Lombi,[a] Daniela Lanari,[c] Pei Liu,[d] Sara Bals,[d] Dirk E. De Vos,*[b] and Luigi Vaccaro*[a]

An efficient and selective procedure was developed for the direct C2–H arylation of indoles using a Pd-loaded metal–organic framework (MOF) as a heterogeneous catalyst and the nontoxic biomass-derived solvent γ-valerolactone (GVL) as a reaction medium. The developed method allows for excellent yields and C-2 selectivity to be achieved and tolerates various substituents on the indole scaffold. The established conditions ensure the stability of the catalyst as well as recoverability, reusability, and low metal leaching into the solution.

Introduction

C2-arylindoles are regarded as interesting building blocks for biologically active molecules.[1] Therefore, many synthetic strategies have been developed to obtain such molecular scaffolds.[2] The classic approach involves a cross-coupling reaction,[1d, 3] which requires prefunctionalization of the substrates and produces at least a stoichiometric amount of a byproduct. More recently, significant efforts have been made to functionalize the traditionally nonreactive C—H bond to perform a direct C2–H arylation, a more desirable procedure from the point of view of chemical sustainability,[4] as it involves a simpler approach, providing a more step-economical and greener path to C—C bond formation. In particular, this methodology is even more convenient if combined with the use of a heterogeneous catalyst, which further satisfies the target of sustainable chemistry, thanks to the ease of separation and recovery of the

product and catalyst, which eliminates the need for operations such as distillations or extractions. Furthermore, with this type of catalysis the amount of metal leaching into solution is reduced, which is an important benefit especially in the synthesis of pharmaceuticals. Unfortunately, up to now, there has only been a few reports of the direct C—H arylation of indoles using heterogeneous catalysts.[5]

Metal–organic frameworks (MOFs) have emerged as a new promising tool for use in heterogeneous catalysis. This class of porous polymeric materials can be synthesized in a wide variety of forms by the appropriate selection of the organic linkers and inorganic nodes to tune their chemical functionality and cavity size.[6] Their unique features (high surface area, porosity, and chemical tunability) make them potentially suitable for a wide range of applications and the possibility of employing these innovative materials for catalysis[7] has been one of the first proposed, also considering their similarity with zeolites, with which they share a large internal surface, pore uniformity and cavity size. They differ from zeolites because of the presence of organic linkers, which allows a much greater range of potential applications, even though it also limits their thermal stability.

In the last few years, the interaction between the MOF support and the catalytically active metal has been extensively studied because new or enhanced catalytic properties can arise from this combination.[8] In selected cases, improved performance compared with the analogous homogeneous catalysts could be noticed for C—H activation reactions owing to the porosity, large surface area, immobilization, and site isolation that can occur in the heterogeneous MOF catalysts.[7a, d]

As part of our long-lasting effort to define sustainable protocols for the synthesis of key molecules,[9] we envisaged the possibility of using MOFs containing a palladium precursor to catalyze the C2–H arylation of indoles. To make the protocol even more sustainable, γ-valerolactone (GVL) was chosen as the reaction medium. This solvent, produced by hydrogenation of levulinic acid derived from lignocellulosic biomass, is a non-

[a] I. Anastasiou,+ E. Tomarelli, A. Lombi, Prof. Dr. L. Vaccaro
Laboratory of Green SOC, Dipartimento di Chimica, Biologia e Biotecnologie
Università degli Studi di Perugia
Via Elce di Sotto, 8, 06124 Perugia (Italy)
E-mail: luigi.vaccaro@unipg.it
Homepage: http://www.dcbb.unipg.it/greensoc

[b] N. Van Velthoven,+ Prof. Dr. D. E. De Vos
Centre for Membrane Separations, Adsorption, Catalysis and Spectroscopy for Sustainable Solutions (cMACS)
KU Leuven
Celestijnenlaan 200F—box 2454, 3001 Leuven (Belgium)
E-mail: dirk.devos@kuleuven.de

[c] Prof. Dr. D. Lanari
Dipartimento di Scienze Farmaceutiche
Università di Perugia
Via del Liceo, 1, 06123 Perugia (Italy)

[d] P. Liu, Prof. Dr. S. Bals
Electron Microscopy for Materials Science
University of Antwerp
Groenenborgerlaan 171, 2020 Antwerp (Belgium)

[+] These authors contributed equally to this work.

Supporting Information and the ORCID identification number(s) for the author(s) of this article can be found under:
https://doi.org/10.1002/cssc.202000378.

toxic and valid alternative to common polar aprotic solvents such as *N*,*N*-dimethylformamide (DMF), dimethylacetamide, and *N*-methyl-2-pyrrolidone, which are commonly used in cross-coupling reactions,[10] and it has also proven to be a suitable solvent in reactions involving C—H activation[4b, 11] thanks to its ability to reduce metal leaching from a heterogeneous catalyst, thus improving the catalyst recyclability.

Results and Discussion

A series of MOF materials with different metals and linkers were synthesized and fully characterized with the aim to be employed in the presence of a palladium source to enhance its reactivity. The assembly of the MOFs was performed by varying both the inorganic moiety (metal-containing nodes) and the organic linkers to screen a wide variety of possible materials, as reported in Table 1. In all cases, a mixed-linker strategy based on the use of linkers with and without available ligating groups (e.g., carboxylic acid or pyridine moieties) was adopted to achieve a better distribution of the active sites. All MOF ma-
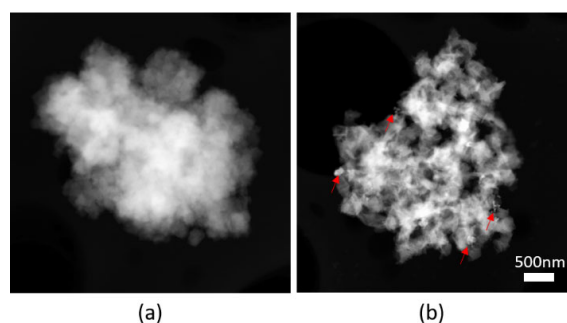
Table 1. Overview of the synthesized MOFs.

Entry	MOF	Ligand moiety	Structural formula[a]
1	UiO-66-PDC	pyridine	$[Zr_6O_4(OH)_4(BDC)_{4.20}(2,5\text{-}PDC)_{1.80}]$
2	CAU-10-PDC	pyridine	$[Al(OH)(iBDC)_{0.58}(3,5\text{-}PDC)_{0.42}]$
3	UTSA-50-PDC	pyridine	$[Cu_6(iBDC)_{4.5}(3,5\text{-}PDC)_{1.5}]$
4	MOF-808-PDC	pyridine	$[Zr_6O_4(OH)_4(BTC)_{1.84}(3,5\text{-}PDC)_{0.16}(CH_3COO)_6]$
5	UiO-67-BPyrDC	bipyridine	$[Zr_6O_4(OH)_4(BPDC)_{4.80}(BPyrDC)_{1.20}]$
6	UiO-66-BTeC	carboxylic acid	$[Zr_6O_4(OH)_4(BDC)_{4.75}(BTeC)_{1.25}]$
7	MIL-101-SO3Na	sulfonate	$[Cr_3F(H_2O)_2O(BDC)_{2.25}(BDC\text{-}SO_3Na)_{0.75}]$

[a] Linkers are abbreviated as: BDC=terephthalate; 2,5-PDC=2,5-pyridinedicarboxylate; iBDC=isophthalate; 3,5-PDC=3,5-pyridinedicarboxylate; BTC=1,3,5-benzenetricarboxylate; BPDC=4,4′-biphenyldicarboxylate; BPyrDC=2,2′-bipyridine-5,5′-dicarboxylate; BTeC=1,2,4,5-benzenetetracarboxylate; BDC-SO₃Na=sodium 2-sulfoterephthalate.

terials were functionalized with palladium(II) acetate (Pd(OAc)₂) in GVL using an "impregnation" methodology,[12] as reported in the Supporting Information. High angle annular dark field scanning transmission electron microscopy (HAADF-STEM) images showed that, in all Pd-loaded samples, the Pd species were homogeneously distributed over the pyridine and carboxylic acid ligand moieties of the MOF crystals before reaction (see Figure 1a and the Supporting Information).

1-Methylindole (**1**) and diphenyliodonium tetrafluoroborate[13] salt (**2**) as arylating agent[10] were employed as test reactants to assess the efficacy of Pd@MOF catalysts for the C2–H arylation of indoles. Diaryliodonium salts are hypervalent iodine compounds that have gained increasing widespread use in a wide range of applications thanks to their selectivity, safety, and nontoxicity,[14] and have been used in numerous arylation reactions on various substrates.[15]

Depending on the type of MOF used, the outcome of the reaction was different, ranging from high yields (when UiO-66-BTeC and CAU-10-PDC were employed, Table 2, entries 1 and 9) to moderate yields. Excellent C2 selectivity was achieved for

Figure 1. HAADF-STEM images of (a) Pd-loaded UiO-66-BTeC before reaction and (b) UiO-66-BTeC after reaction. Pd⁰ nanoparticles that were formed during the reaction are indicated by red arrows.

almost all MOFs, with the exception of MOF UiO-67-BPyrDC, which gave a moderate selectivity, and MOF UTSA-50-PDC, which contained Cu ions in the inorganic units and gave had an inverse selectivity. This might be owing to the reaction proceeding as in thermodynamic, metal-free conditions (Table 2 entry 12), or to the particular behavior of copper, which, depending on the group in the nitrogen atom, gives a different selective arylation in C2 or C3.[4c, 16]

In general, the presence of a MOF enhanced the activity of Pd(OAc)₂ compared with the reaction under homogeneous condition (Pd(OAc)₂ 1 mol%), in which only a 40% yield was observed along with a homocoupling byproduct. Prolonged reaction times led to an increased amount of homocoupling and polymerization products. Increasing the amount of catalyst (2.5 mol%) led to an unchanged yield of the product but increased amount of homocoupling byproduct.

When Pd/C (2.5 mol%) was employed as an alternative source of heterogeneous palladium (Table 2, entry 6) a moderate yield and selectivity were achieved. For comparison, Pd@UiO-66-BTeC, which proved to be the best performing MOF catalyst, was also employed with conventional reaction solvents, that is, toluene and DMF; in each case, the C2 selectivity was complete but the yield was lower than that obtained in GVL.

To evaluate if the phenyliodonium salt **2**, bearing a tetrafluoroborate counterion (BF₄⁻), was the best arylation agent for the arylation of indoles, two other salts, namely phenyliodonium triflate[17] (OTf⁻) and tosylate[18] (OTs⁻) were investigated in the reaction of *N*-methylindole **1** catalyzed by Pd@UiO-66-BTeC in GVL under the best conditions identified in Table 2 (entry 1). The triflate salt gave excellent C2 selectivity but a lower yield (62%), whereas the tosylate salt gave very good yield (90%) but was slightly less selective for the C2 position (98/2) (Table 3). The reason for the lower yield of the reaction performed with the triflate salt could be the different coordinating ability of the anion on the metallic center: both the tosylate and the tetrafluoroborate are weakly coordinating agents that make the palladium intermediate more reactive with these two counterions.[5c] Therefore, the tetrafluoroborate

↖↖ **These are not the final page numbers!**

Table 2. Optimization of direct arylation of N-methylindole **1** with diphenyliodonium salt **2**.[a]

Entry	Catalyst[b] (1 wt%)	Medium	Selectivity C2/C3	Yield[c] [%]
1	Pd@UiO-66-BTeC (3.1)	GVL	>99	94
2	Pd@UiO-66-BTeC (3.1)	toluene	>99	30
3	Pd@UiO-66-BTeC (3.1)	DMF	>99	87
4	Pd@UiO-66-PDC (3.9)	GVL	95/5	50
5	Pd(OAc)₂	GVL	>99	40
6	Pd/C[d]	GVL	98/2	73
7	Pd@UTSA-50-PDC[e] (1.9)	GVL	1/99	40
8	Pd@UiO-67-BPyrDC (3.3)	GVL	94/6	43
9	Pd@CAU-10-PDC (4.2)	GVL	>99	78
10	Pd@MOF-808-PDC (5.2)	GVL	>99	63
11	Pd@MIL-101-SO3Na (1.3)	GVL	>99	40
12	no catalyst	GVL	1/99	40

[a] Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), 1 mol% Pd, 80 °C, 5 h. [b] Values in parentheses correspond to Pd loading in wt%. [c] Isolated yield. [d] 2.5 mol% Pd. [e] catalyst decomposes by dissolving in the reaction conditions.

Table 3. Effect of the anion on the direct arylation of N-methylindole **1** with diphenyliodonium salt **2a**.[a]

| Entry	Counterion	t [h]	Selectivity C2/C3	Yield[b] [%]
1	tetrafluoroborate (BF4⁻)	5	>99	94
2	triflate (OTf⁻)	5	>99	62
3	tosylate (OTs⁻)	5	98/2	90

[a] Reaction conditions: Pd@UiO-66-BTeC (1 mol%), **1** (1 mmol), **2** (1.2 mmol), 80 °C, 5 h. [b] Isolated yield.

counterion was chosen as the best option to be employed in the arylation reactions considering both yield and selectivity.

Tests of the arylation reaction were also performed using iodobenzene as the arylating agent to establish which compound is the actual arylating agent in the reaction, but also to probe whether iodobenzene, which is produced in a stoichiometric quantity, can arylate the indole.[19] No reaction occurred; therefore under these conditions iodobenzene failed to arylate the indole, proving that the diaryliodonium salt, a better arylating agent thanks to its better leaving group, is the actual arylating agent.

The scope of the reaction was extensively studied by varying the indole-based reactants and the substituents on the arylating agents (Scheme 1). Almost every combination of indole/aryliodonium salt used gave good results either in terms of yield or selectivity. Exceptions were the reaction between 2-phenylindole and phenyliodonium salt **2,** which did not yield product **3 m** as expected based on the inherent selectivity of the mechanism, and the reaction between indole-3-carboxaldehyde and phenyliodonium salt **2,** which failed to react to **3 n**, probably owing to steric hindrance at the C3 position.

Catalyst recycling was also investigated to determine the efficiency of this new catalytic system (Table 4). After the first
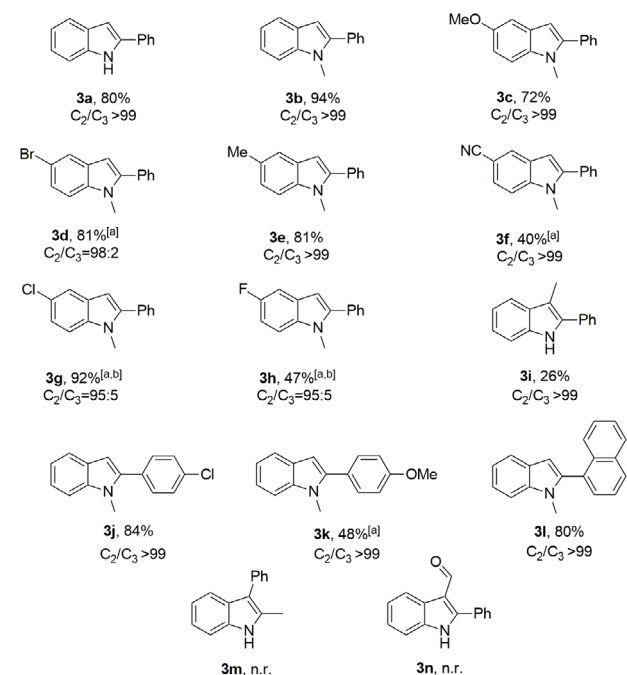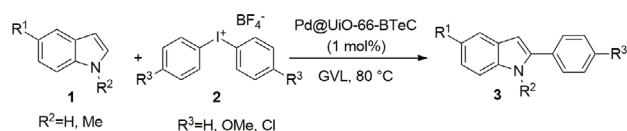
Scheme 1. Scope of C2 arylation of indoles. Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), GVL (1 м), 80 °C, 5 h; isolated yield. [a] 24 h. [b] 2 mmol of **2**.

Table 4. Catalyst recycling for the reaction between N-methylindole **1** and diphenyliodonium salt **2**.[a]

Entry	t [h]	Pd leaching [ppm]	C[b] [%]
1	5	0.7	>99
2	5	0.4	>99
3	5	0.5	>99
4	5	0.4	>99

[a] Reaction conditions: **1** (1 mmol), **2** (1.2 mmol), cat. (1 mol%), GVL (1 м), 80 °C. [b] Conversion to **3**. [c] isolated yields 94%.

run, the catalytic system was filtered off from the reaction mixture, washed, dried, and reused again for a second and a third run. As shown in Table 4, the amount of palladium detected by MP-AES analysis during the three runs was low (≈0.5 ppm) Moreover, if the reaction was performed in DMF, the palladium leaching into the solution was much higher (277 ppm), which confirmed the ability of GVL to reduce metal leaching from a heterogeneous catalyst. After it was used in a reaction, Pd-loaded UiO-66-BTeC was analyzed by HAADF-STEM and energy-dispersive X-ray spectroscopy; migration of the Pd species from the pores and aggregation of Pd⁰ clusters on the surface of the MOF crystals was observed (see Figure 1b and the Supporting Information). This is believed to result in partial deactivation of the catalyst. Interestingly, the Pd⁰ nanoparticles were better distributed over the framework of UiO-66-BTeC

These are not the final page numbers! ⬈⬈

compared with other MOF supports, presumably owing to the plethora of "free" carboxylate ligands in its pores, and this could be the main reason why Pd@UiO-66-BTeC had better catalytic activity. To assess the stability of the MOF material under the reaction and the preloading conditions, powder X-ray diffraction (XRD) analyses were performed on UiO-66-BTeC preloaded with Pd(OAc)$_2$ (Figure 2). The XRD patterns of the MOF after preloading with the metal and after reaction match the pattern of the material after the synthesis, which highlights that no decrease in crystallinity occurred and that the catalyst was stable under the reaction conditions.
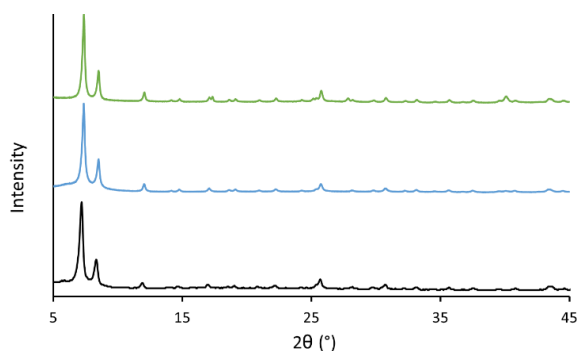

Figure 2. XRD patterns of UiO-66-BTeC after the synthesis (black), the preloading with palladium (blue), and the reaction (green).

To gain more insight into the nature of the catalytic system and on the oxidation state of palladium in the MOF, extended X-ray absorption fine structure (EXAFS) analysis was performed on UiO-66-BTeC functionalized with Pd(OAc)$_2$ (see Figure 3 and the Supporting Information). After preloading, the Pd–O bond length shifted from approximately 1.6 Å for Pd(OAc)$_2$ to 1.9 Å for the preloaded palladium species in the MOF (Pd@UiO-66-BTeC preloaded), which indicated that the ligand of Pd changed during preloading. Because the intensity of the Pd–O interactions is the same in Pd@UiO-66-BTeC as in Pd(OAc)$_2$, it can be assumed that the coordination number of oxygen remained the same and that the acetate ligands of Pd(OAc)$_2$ were exchanged by the "free" carboxylate groups of the
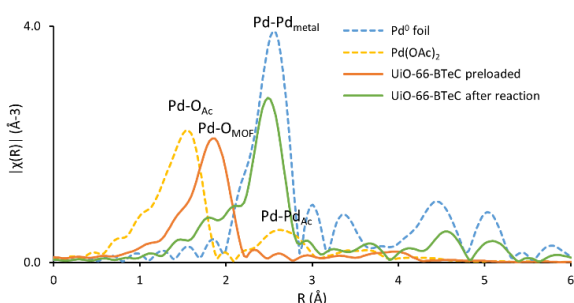
1,2,4,5-benzenetetracarboxylate (BTeC) linker that were abundant in the pores of UiO-66-BTeC (Figure 3).

Furthermore, the Pd–Pd interactions of the trimeric Pd(OAc)$_2$ species at approximately 2.7 Å disappeared after preloading on UiO-66-BTeC, which implied that all Pd(OAc)$_2$ trimers were transformed to monomeric, MOF-supported Pd species. After the reaction, the intensity of the Pd–O interactions decreased and the Pd–Pd interactions appeared, indicating that Pd^0 nanoparticles were formed during the reaction.

Conclusions

An efficient and selective procedure was developed for the direct C2-arylation of various indoles using palladium containing metal–organic frameworks (Pd@MOF) as heterogeneous Pd catalyst and nontoxic biomass-derived GVL as the reaction medium. The UiO-66-BTeC material was identified as the most suitable MOF support. This is a stable material, similar to the well-known UiO-66 Zr-terephthalate MOF. In addition, its pores were lined with pendant —COOH groups, which can provide docking sites for catalytically active Pd species. The presence of the MOF increased the activity of Pd(OAc)$_2$ and allowed higher yields and excellent selectivity for the C-2 position to be achieved compared with the reaction performed under homogeneous conditions. The procedure tolerates various substituents on the indole scaffold in addition to other benefits, such as ease of recoverability, possibility of reuse of the catalyst and low metal leaching into solution. Finally, it was shown that the active Pd@UiO-66-BTeC catalyst retained its crystallinity after reaction and the supported palladium species were characterized before and after the reaction by HAADF-STEM, energy-dispersive X-ray spectroscopy, and EXAFS.

Experimental Section

Unless otherwise stated, all solvents and reagents were used as obtained from commercial sources without further purification. GC analyses were performed by using a Hewlett–Packard HP 5890A equipped with a capillary column DB-35MS (30 m, 0.53 mm), an FID detector and helium as gas carrier. GC-EIMS analyses were performed using a Hewlett–Packard HP 6890N Network GC system/5975 Mass Selective Detector equipped with an electron impact ionizer at 70 eV. NMR spectra were recorded on a Bruker DRX-ADVANCE 400 MHz (^{1}H at 400 MHz, ^{13}C at 100.6 MHz and ^{19}F at 376 MHz) using CDCl$_3$ or [D$_6$]DMSO as solvents and tetramethyl silane as the internal standard. Chemical shifts are reported in ppm with multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constants in Hertz. The amount of palladium leached in solution was measured with a microwave plasma-atomic emission spectrometer MP-AES 4210 from Agilent Technology.

MOF synthesis

UiO-66-PDC was synthesized according to a slightly modified literature procedure.[20] First, 0.733 g 2,5-pyridinedicarboxylic acid, 0.730 g terephthalic acid, and 2.868 g ZrOCl$_2$·8H$_2$O were mixed in 90 mL formic acid and 10 mL deionized water. The mixture was heated at 120 °C under reflux for 3 h. The resulting slurry was fil-

Figure 3. The magnitude of the Fourier transform of the experimental k^2-weighted Pd k-edge EXAFS spectra in R-space of Pd^0 foil (dashed, blue), Pd(OAc)$_2$ (dashed, yellow), Pd@UiO-66-BTeC after preloading (solid, orange) and Pd@UiO-66-BTeC after reaction (solid, green).

↖↖ **These are not the final page numbers!**

trated and washed twice with deionized water and twice with ethanol. Finally, the obtained powder was dried at 115 °C.

CAU-10-PDC was synthesized according to a slightly modified literature procedure.[21] First, 0.40 g 3,5-pyridinedicarboxylic acid, 0.40 g isophthalic acid, and 1.16 g AlCl₃·6H₂O were mixed in 4 mL DMF and 16 mL deionized water. The mixture was heated at 120 °C for 18 h. The resulting slurry was filtrated and washed twice with DMF and twice with ethanol. Finally, the obtained powder was dried at 115 °C.

UTSA-50-PDC was synthesized according to a slightly modified literature procedure.[21] First, 0.172 g 3,5-pyridinedicarboxylic acid, 0.683 g isophthalic acid, and 0.513 g Cu(OAc)₂·H₂O were mixed in 100 mL DMF and 1.1 mL acetic acid. The mixture was heated at 100 °C for 3 days. The resulting slurry was filtrated and washed twice with DMF and twice with ethanol. Finally, the obtained powder was dried at 115 °C.

MOF-808-PDC was synthesized according to a slightly modified literature procedure.[22] First, 0.418 g 3,5-pyridinedicarboxylic acid, 0.525 g 1,3,5-benzenetricarboxylic acid, and 2.425 g ZrOCl₂·8H₂O were mixed in 125 mL DMF and 125 mL formic acid. The mixture was heated at 100 °C for 2 days. The resulting slurry was filtrated and washed twice with DMF and twice with ethanol. Finally, the obtained powder was dried at 115 °C.

UiO-67-BPyrDC was synthesized according to a slightly modified literature procedure.[23] First, 0.132 g 2,2′-bipyridine-5,5′-dicarboxylic acid, 0.741 g 4,4′-biphenyldicarboxylic acid, and 0.909 g ZrCl₄ were mixed in 450 mL DMF and 1.8 mL trifluoroacetic acid. The mixture was heated at 100 °C for 5 days. The resulting slurry was filtrated and washed twice with DMF and twice with ethanol. Finally, the obtained powder was dried at 115 °C.

UiO-66-BTeC was synthesized according to a slightly modified literature procedure.[23] First, 0.115 g 1,2,4,5-benzenetetracarboxylic acid, 0.675 g terephthalic acid, and 0.800 g ZrCl₄ were mixed in 45 mL DMF and 1 mL deionized water. The mixture was heated at 100 °C for 2 days. The resulting slurry was filtrated and washed twice with DMF and twice with ethanol. Finally, the obtained powder was dried at 115 °C.

MIL-101-SO₃Na was synthesized according to a slightly modified literature procedure.[24] First, 0.134 g sodium 2-sulfoterephthalic acid, 0.249 g terephthalic acid, and 0.400 g Cr(NO₃)₃·9H₂O were mixed in 6 mL deionized water and 44 μL 40 % hydrofluoric acid. The mixture was placed in a Teflon-lined stainless steel autoclave and heated at 190 °C for 24 h. The resulting slurry was filtrated and washed twice with deionized water and twice with ethanol. Finally, the obtained powder was dried at 115 °C.

MOF impregnation

The preparation of the MNP/MOF composite was performed by following the solution impregnation approach.[12a] A screw-capped vial equipped with a magnetic stirrer was loaded with Pd(OAc)₂ (0.01 mmol) and GVL or o-xylene. MOF was added and the resulting mixture was slowly stirred (100 rpm) for 8–24 h at RT. After centrifugation, the supernatant liquid was removed and the loaded MOF was washed three times with acetone. The solid was dried under vacuum at room temperature overnight.

General procedure for the MOF-catalyzed synthesis of 2-arylated indoles

A screw-capped vial equipped with a magnetic stirrer was loaded with indole **2** (1 mmol, 1 equiv.), diaryliodonium salt (1.2 mmol, 1.2 equiv.), Pd/UiO-66 (Zr) (1 mol %, 0.01 equiv.), and 1mL of GVL.

The resulting solution was stirred at 80 °C for 5 h. Following completion, the reaction was left to cool to RT and centrifuged for 15 min (6500 rpm). The supernatant liquid was removed and the catalyst was washed three times by adding ethyl acetate (2 mL), centrifugation for 15 min, followed by removal of the supernatant liquid. The crude reaction mixture was concentrated under vacuum and purified by column chromatography to give the 2-aryl-1H-indoles (**3**).

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

Keywords: biomass · green solvents · heterogeneous catalysis · indole · metal–organic framework

[1] a) N. Chadha, O. Silakari, *Eur. J. Med. Chem.* **2017**, *134*, 159–184; b) T. V. Sravanthi, S. L. Manju, *Eur. J. Pharm. Sci.* **2016**, *91*, 1–10; c) J. Roger, A. L. Gottumukkala, H. Doucet, *ChemCatChem* **2010**, *2*, 2053–2063; d) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873–2920; e) F. Alonso, I. P. Beletskaya, M. Yus, *Chem. Rev.* **2004**, *104*, 3079–3159.

[2] a) L. Duan, R. Fu, B. Zhang, W. Shi, S. Chen, Y. Wan, *ACS Catal.* **2016**, *6*, 1062–1074; b) E. T. Nadres, A. Lazareva, O. Daugulis, *J. Org. Chem.* **2011**, *76*, 471–483; c) S. Yanagisawa, T. Sudo, R. Noyori, K. Itami, *J. Am. Chem. Soc.* **2006**, *128*, 11748–11749; d) N. R. Deprez, D. Kalyani, A. Krause, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 4972–4973.

[3] a) N. T. Patil, Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3395–3442; b) D. R. Stuart, E. Villemure, K. Fagnou, *J. Am. Chem. Soc.* **2007**, *129*, 12072–12073; c) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, *106*, 2875–2911; d) S. Chouziera, M. Gruberab, L. Djakovitcha, *J. Mol. Catal.* **2004**, *212*, 43–52.

[4] a) P. Gandeepan, N. Kaplaneris, S. Santoro, L. Vaccaro, L. Ackermann, *ACS Sustainable Chem. Eng.* **2019**, *7*, 8023–8040; b) S. Santoro, F. Ferlin, L. Ackermann, L. Vaccaro, *Chem. Soc. Rev.* **2019**, *48*, 2767–2782; c) L. Ackermann, M. Dell'Acqua, S. Fenner, R. Vicente, R. Sandmann, *Org. Lett.* **2011**, *13*, 2358–2360; d) S. Kirchberg, R. Fröhlich, A. Studer, *Angew. Chem. Int. Ed.* **2009**, *48*, 4235–4238; *Angew. Chem.* **2009**, *121*, 4299–4302; e) N. Lebrasseur, I. Larrosa, *J. Am. Chem. Soc.* **2008**, *130*, 2926–2927; f) X. Wang, D. V. Gribkov, D. Sames, *J. Org. Chem.* **2007**, *72*, 1476–1479; g) B. S. Lane, M. A. Brown, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 8050–8057; h) B. S. Lane, D. Sames, *Org. Lett.* **2004**, *6*, 2897–2900.

[5] a) Y.-B. Huang, Q. Wang, J. Liang, X. Wang, R. Cao, *J. Am. Chem. Soc.* **2016**, *138*, 10104–10107; b) Y.-B. Huang, M. Shen, X. Wang, P. Huang, R. Chen, Z.-J. Lin, R. Cao, *J. Catal.* **2016**, *333*, 1–7; c) J. Malmgren, A. Nagendiran, C.-W. Tai, J.-E. Bäckvall, B. Olofsson, *Chem. Eur. J.* **2014**, *20*, 13531–13535; d) L. Zhang, P. Li, C. Liu, J. Yang, M. Wanga, L. Wang, *Catal. Sci. Technol.* **2014**, *4*, 1979; e) Y. Huang, T. Ma, P. Huang, D. Wu, Z. Lin, R. Cao, *ChemCatChem* **2013**, *5*, 1877–1883; f) Y. Huang, Z. Lin, R.

These are not the final page numbers! ⌐⌐

Cao, *Chem. Eur. J.* **2011**, *17*, 12706–12712; g) L. Wang, W.-B. Yi, C. Cai, *Chem. Commun.* **2011**, *47*, 806–808.

[6] a) A. M. Abdel-Mageed, B. Rungtaweevoranit, M. Parlinska-Wojtan, X. Pei, O. M. Yaghi, R. J. Behm, *J. Am. Chem. Soc.* **2019**, *141*, 5201–5210; b) K. Gao, C. Huang, Y. Yang, H. Li, J. Wu, H. Hou, *Cryst. Growth Des.* **2019**, *19*, 976–982; c) A. Dhakshinamoorthy, A. Santiago-Portillo, A. M. Asiri, H. Garcia, *ChemCatChem* **2019**, *11*, 899–923; d) H.-C. Zhou, S. Kitagawa, *Chem. Soc. Rev.* **2014**, *43*, 5415–5418; e) H.-C. Zhou, J. R. Long, O. M. Yaghi, *Chem. Rev.* **2012**, *112*, 673–674; f) J. R. Long, O. M. Yaghi, *Chem. Soc. Rev.* **2009**, *38*, 1213–1214.

[7] a) F. Ferlin, M. Cappelletti, R. Vivani, M. Pica, O. Piermatti, L. Vaccaro, *Green Chem.* **2019**, *21*, 614–626; b) F. Valentini, H. Mahmoudi, L. A. Bivona, O. Piermatti, M. Bagherzadeh, L. Fusaro, C. Aprile, A. Marrocchi, L. Vaccaro, *ACS Sustainable Chem. Eng.* **2019**, *7*, 6939–6946; c) V. Kozella, F. Rahmania, O. Piermatti, D. Lanari, L. Vaccaro, *Mol. Catal.* **2018**, *455*, 188–191; d) F. Valentini, N. Santillo, C. Petrucci, D. Lanari, E. Petricci, M. Taddei, L. Vaccaro, *ChemCatChem* **2018**, *10*, 1277–1281; e) F. Ferlin, L. Luciani, O. Viteritti, F. Brunori, O. Piermatti, S. Santoro, L. Vaccaro, *Front. Chem.* **2018**, *6*, 659.

[8] a) J.-M. Vincent, M. Contel, G. Pozzi, R. H. Fish, *Coord. Chem. Rev.* **2019**, *380*, 584–599; b) E. Peris, R. Porcar, J. García-Álvarez, M. I. Burguete, E. García-Verdugo, S. V. Luis, *ChemSusChem* **2019**, *12*, 1684–1691; c) R. Babu, J. F. Kurisingal, J.-S. Chang, D.-W. Park, *ChemSusChem* **2018**, *11*, 924–932; d) H.-P. Steinrück, P. Wasserscheid, *Catal. Lett.* **2015**, *145*, 380–397; e) M. Haumann, A. Riisager, *Chem. Rev.* **2008**, *108*, 1474–1497; f) C. R. Mathison, D. J. Cole-Hamilton, *Catal. Met. Complexes* **2006**, *30*, 145–181.

[9] a) D. M. Alonso, S. G. Wettsteinb, J. A. Dumesic, *Green Chem.* **2013**, *15*, 584–595; b) D. M. Alonso, S. G. Wettstein, M. A. Mellmer, E. I. Gurbuz, J. A. Dumesic, *Energy Environ. Sci.* **2013**, *6*, 76–80; c) S. G. Wettstein, D. M. Alonso, Y. Chonga, J. A. Dumesic, *Energy Environ. Sci.* **2012**, *5*, 8199–8203.

[10] a) J. Sherwood, J. H. Clark, I. J. S. Fairlamb, J. M. Slattery, *Green Chem.* **2019**, *21*, 2164–2213; b) H. Mahmoudi, F. Valentini, F. Ferlin, L. A. Bivona, I. Anastasiou, L. Fusaro, C. Aprile, A. Marrocchi, L. Vaccaro, *Green Chem.* **2019**, *21*, 355–360; c) G. Strappaveccia, L. Luciani, E. Bartollini, A. Marrocchi, F. Pizzo, L. Vaccaro, *Green Chem.* **2015**, *17*, 1071–1076.

[11] a) N. Sauermann, R. Mei, L. Ackermann, *Angew. Chem. Int. Ed.* **2018**, *57*, 5090–5094; *Angew. Chem.* **2018**, *130*, 5184–5188; b) F. Ferlin, S. Santoro, L. Ackermann, L. Vaccaro, *Green Chem.* **2017**, *19*, 2510–2514; c) S. Santoro, F. Ferlin, L. Luciani, L. Ackermann, L. Vaccaro, *Green Chem.* **2017**, *19*, 1601–1612.

[12] a) J. Chen, Y. Li, *Chem. Rec.* **2016**, *16*, 1456–1476; b) A.-X. Yan, S. Yao, Y.-G. Li, Z-M. Zhang, Y. Lu, W.-L. Chen, E.-B. Wang, *Chem. Eur. J.* **2014**, *20*, 6927–6933; c) J. Pires, M. L. Pinto, C. M. Granadeiro, A. D. S. Barbosa, L.

Cunha-Silva, S. S. Balula, V. K. Saini, *Adsorption* **2014**, *20*, 533–543; d) M. Sabo, A. Henschel, H. Froede, E. Klemm, S. Kaskel, *J. Mater. Chem.* **2007**, *17*, 3827–3832.

[13] M. Bielawski, D. Aili, B. Olofsson, *J. Org. Chem.* **2008**, *73*, 4602–4607.

[14] a) M. W. S. Chen, X. Jiang, *Chem. Asian J.* **2018**, *13*, 2195–2207; b) Y.-C. Han, C. Zhang, *Tetrahedron Lett.* **2018**, *59*, 3052–3064; c) S. G. Modha, M. F. Greaney, *J. Am. Chem. Soc.* **2015**, *137*, 1416–1419; d) N. Jalalian, T. B. Petersen, B. Olofsson, *Chem. Eur. J.* **2012**, *18*, 14140–14149; e) E. A. Merritt, B. Olofsson, *Angew. Chem. Int. Ed.* **2009**, *48*, 9052–9070; *Angew. Chem.* **2009**, *121*, 9214–9234.

[15] a) J. Malmgren, S. Santoro, N. Jalalian, F. Himo, B. Olofsson, *Chem. Eur. J.* **2013**, *19*, 10334–10342; b) R. J. Phipps, L. McMurray, S. Ritter, H. A. Duong, M. J. Gaunt, *J. Am. Chem. Soc.* **2012**, *134*, 10773–10776; c) A. Bigot, A. E. Williamson, M. J. Gaunt, *J. Am. Chem. Soc.* **2011**, *133*, 13778–13781; d) N. R. Deprez, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 11234–11241.

[16] a) Z. Wang, K. Li, D. Zhao, J. Lan, J. You, *Angew. Chem. Int. Ed.* **2011**, *50*, 5365–5369; *Angew. Chem.* **2011**, *123*, 5477–5481; b) R. J. Phipps, N. P. Grimster, M. J. Gaunt, *J. Am. Chem. Soc.* **2008**, *130*, 8172–8174.

[17] M. Bielawski, M. Zhu, B. Olofsson, *Adv. Synth. Catal.* **2007**, *349*, 2610–2618.

[18] M. Zhu, N. Jalalian, B. Olofsson, *Synlett* **2008**, *4*, 0592–0596.

[19] a) Z. Xua, Y. Xub, H. Lua, T. Yanga, X. Lina, L. Shaob, F. Ren, *Tetrahedron* **2015**, *71*, 2616–2621; b) L. Joucla, N. Batail, L. Djakovitch, *Adv. Synth. Catal.* **2010**, *352*, 2929–2936; c) X. Wang, B. S. Lane, D. Sames, *J. Am. Chem. Soc.* **2005**, *127*, 4996–4997.

[20] S. Waitschat, D. Fröhlich, H. Reinsch, H. Terraschke, K. A. Lomachenko, C. Lamberti, H. Kummer, T. Helling, M. Baumgartner, S. Henninger, N. Stock, *Dalton Trans.* **2018**, *47*, 1062–1070.

[21] A. Cadiau, J. S. Lee, D. D. Borges, P. Fabry, T. Devic, M. T. Wharmby, C. Martineau, D. Foucher, F. Taulelle, C.-H. Jun, Y. K. Hwang, N. Stock, M. F. De Lange, F. Kapteijn, J. Gascon, G. Maurin, J.-S. Chang, C. Serre, *Adv. Mater.* **2015**, *27*, 4775–4780.

[22] H. Furukawa, F. Gándara, Y. B. Zhang, J. Jiang, W. L. Queen, M. R. Hudson, O. M. Yaghi, *J. Am. Chem. Soc.* **2014**, *136*, 4369–4381.

[23] J. H. Cavka, S. Jakobsen, U. Olsbye, N. Guillou, C. Lamberti, S. Bordiga, K. P. Lillerud, *J. Am. Chem. Soc.* **2008**, *130*, 13850–13851.

[24] M. Lammert, S. Bernt, F. Vermoortele, D. E. De Vos, N. Stock, *Inorg. Chem.* **2013**, *52*, 8521–8528.

FULL PAPERS

Biomass-derived selectivity: An effective heterogenous catalyst composed of Pd immobilized on a metal–organic framework was developed for the selective arylation of indoles in γ-valerolactone. The method tolerates various substituents on the indole scaffold to achieve excellent yields and C-2 selectivity.
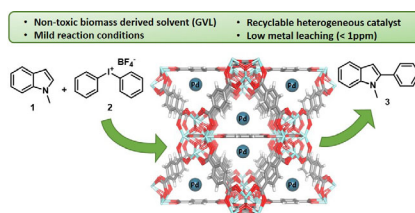
I. Anastasiou, N. Van Velthoven,
E. Tomarelli, A. Lombi, D. Lanari, P. Liu,
S. Bals, D. E. De Vos,* L. Vaccaro*

■■ – ■■

C2–H Arylation of Indoles Catalyzed by Palladium-Containing Metal-Organic-Framework in γ-Valerolactone

These are not the final page numbers! ↗↗