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Highly Functionalized Biaryls via Suzuki–Miyaura Cross-Coupling Catalyzed by Pd@MOF under Batch and Continuous Flow Regimes

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Abstract: A diverse set of more than 40 highly functionalized biaryls was synthesized successfully through the Suzuki–Miyaura crosscoupling reaction catalyzed by Pd nanoparticles supported in a functionalized mesoporous MOF (8 wt% Pd@MIL-101(Cr)-NH_2). This could be achieved under some of the mildest conditions reported to date and a strong control over the leaching of metallic species could be maintained, despite the presence of diverse functional groups and/or several heteroatoms. Some of the targeted molecules are important intermediates in the synthesis of pharmaceuticals and we clearly exemplify the versatility of this catalytic system, which affords better yields than currently existing commercial procedures. Most importantly, Pd@MIL-101-NH_2 was packed in a micro-flow reactor, which represents the first report of metallic nanoparticles supported on MOFs employed in flow chemistry for catalytic applications. A small library of 11 isolated compounds was created in a continuous experiment without replacing the catalyst, demonstrating the potential of the catalyst for large-scale applications.

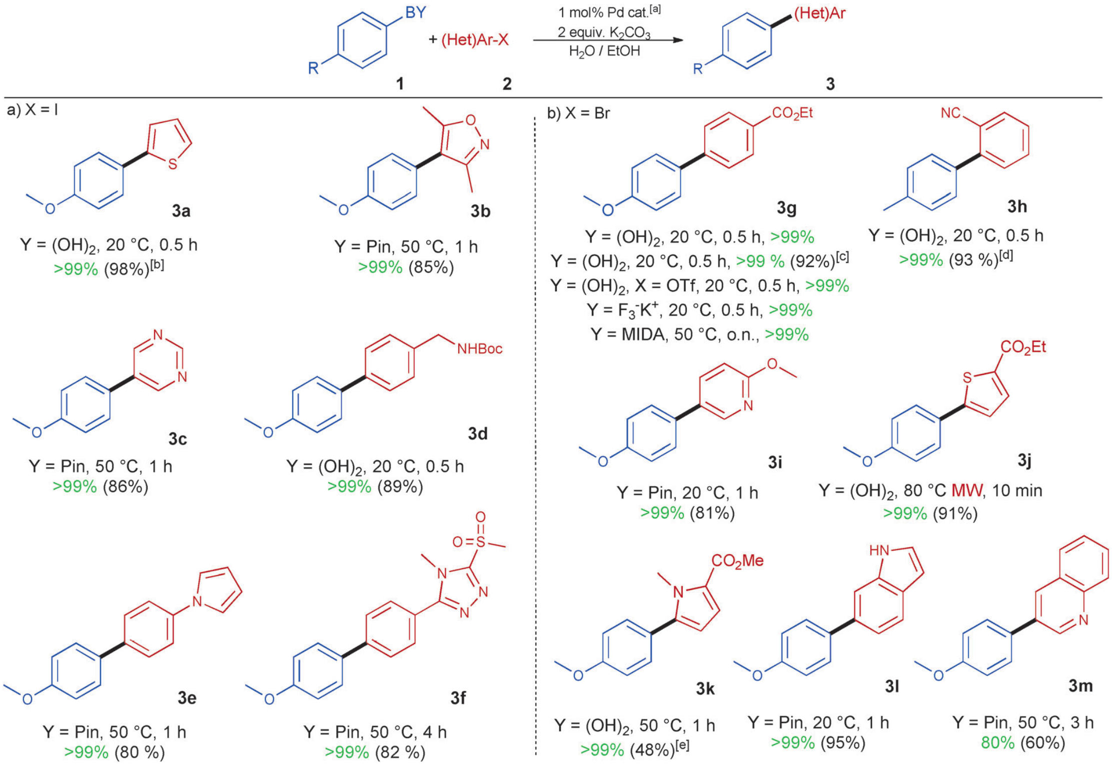
At the center of the rapidly evolving green revolution in chemistry,[1] catalysis plays a pivotal role.[2] Without catalytic processes, it would be unconceivable to aim for a sustainable chemical industry.[3] When it comes to organometallic catalysis, special attention is dedicated to the recycling of metallic species.[4] Aside from the obvious health hazards associated with exposure to heavy metals, resources of palladium or ruthenium are scarce and likely to become increasingly expensive in the future.[5] Solid supports facilitate the recovery of these species and have been used for the immobilization of catalysts as either discrete species[6] or nanometer-scale metal clusters.[7]

Still, a common limitation in heterogeneous transformations is the narrow substrate scope, which often addresses model substrates that do not reflect the challenges of practical applications. Relevant substrates with multiple heteroatoms and competing functional groups are more challenging, so they should be addressed when new heterogeneous catalysts are developed.

Metal–organic frameworks (MOFs),[8] porous crystalline materials with extremely high surface areas, have the potential to fill in this area because they are highly versatile compared to other materials.[9] Since their properties can easily be modulated,[10] they could be applied in advanced organic processes such as tandem and cascade reactions.[11]
Microscale flow chemistry[12] has diffused slowly into academic laboratories, provoking synthetic chemists to face issues traditionally reserved for process chemists and engineers to deal with.[13] The symbiosis between heterogeneous catalysis and flow chemistry became a natural direction of progress in the field, leading to a new generation of packed-bed microreactors.[14] Surprisingly, despite all recent reports on MOF-type catalysts, they have not yet been developed into flow applications. To the best of our knowledge, Galarneau and co-workers[15] were the only ones so far to develop a successful catalytic process at the intersection of flow chemistry and MOFs, using Cu-HKUST-1.[16]
Herein, we report the synthesis of heteroatom-functionalized biaryls through Suzuki–Miyaura cross-couplings catalyzed by Pd nanoparticles supported on MIL-101-NH_2[17] under very mild reaction conditions. The coupling products are potential building blocks of biologically active molecules. Besides a significant expansion of the substrate scope, we discuss in detail some of the particularities of performing this reaction under heterogeneous conditions. We also show the first example of a nanocatalyst supported on a MOF and employed in a packed-bed micro-flow reactor. Pd@MIL-101-NH2 displays good stability under a continuous flow regime, with barely detectable levels of leached metallic species.
A summary of relevant homogeneous Pd catalysts for difficult Suzuki–Miyaura cross-couplings and a comparison of our catalyst with recently developed heterogeneous systems are included in the Supporting Information (Section I). Although the majority of aryl chlorides are still out of reach, the Pd nanocatalyst reported herein has the highest activity amongst the existing heterogeneous systems for this type of applications.

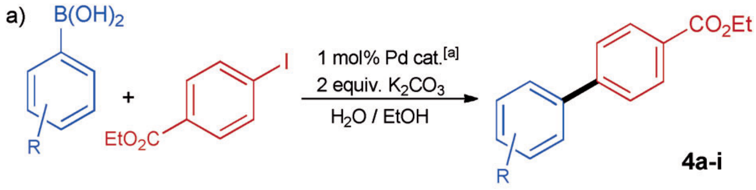
Results and Discussion

We started by investigating the coupling of boronic acids [**1**,Y=$(OH)_2$] or pinacolate esters (**1**, Y= pinacolate = pin) with heteroaryl iodides (**2a–f**) using K_2CO_3 as base (2 equiv) in a mixture of H_2O/EtOH (1:1) as solvent and a catalyst loading of only 1 mol% Pd (Scheme 1a). The material of choice was 8 wt% Pd@MIL-101-NH_2, which we recently reported to have the optimal amount of palladium impregnated in MIL-101-NH2 for this type of applications.[18, 19] The large majority of these functionalized (hetero)aromatic iodides reacted in excellent yields at mild temperatures (20 or 50 ºC) and in very short reaction times (0.5–4 h), leading to the facile synthesis of **3a–f** despite the presence of one or several heteroatoms. Even hindered aryl iodides (**2b**) and lengthy substrates (**2f**) afforded the coupling products **3b** and **3f**, important building blocks in the synthesis of pharmaceutically active intermediates,[20] in high yields (85% and 82 %, respectively) after short reaction times (1 and 4 h, respectively). We then proceeded to the coupling of less reactive aryl bromides (**2g–2m**) while also testing the reactivity of different types of boronates (Scheme 1b). A quantitative yield was obtained in the synthesis of **3g** from *p*-anisylboronic acid (R = OCH3, BY = $B(OH)_2$), even when the catalyst loading was decreased 10 times (0.1 mol% Pd), as well as from the analogous trifluoroborate and MIDA (*N*-methyliminodiacetic acid) ester. The latter, more complex MIDA-boronate gave to our delight an excellent yield, however showed no rate enhancement relative to the other boron derivatives and was therefore not considered further. The same product, **3g**, was also obtained in less than 30 min at 20 ºC when ethyl 4-bromobenzoate (**2g**) was replaced with the corresponding triflate. 2-Bromobenzonitrile (**2h**) could also be coupled with *p*-tolylboronic acid at ambient temperature in only 30 min, affording a quantitative yield of 3h, an intermediate in the synthesis of the cardiovascular drug Valsartan.[21]

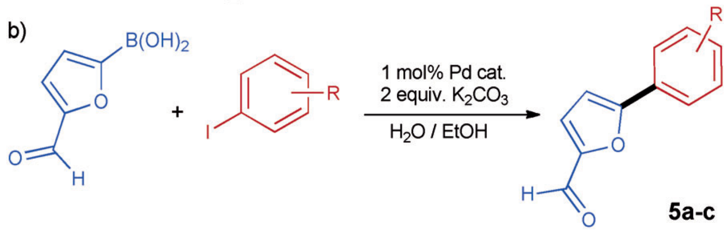


Scheme 1. Couplings of (hetero)aromatic aryl iodides and bromides. [a] Unless otherwise noted, 0.1 mmol of aryl halide and 1.1 equiv of transmetallating agent were used. Conversion determined by LC-MS. Isolated yields in parenthesis. [b] 80% conversion in 4 h from 2-bromothiophene. [c] 0.1 mol% Pd was used. [d] Equimolar amounts of boronic acid were used (1.02 equiv) [e] Low isolated yield due to the hydrolysis of the ester. Pin = pinacolate. MIDA = *N*-methyliminodiacetate.

Methyl 5-bromo-1H-pyrrole-2-carboxylate (**2k**), 6-bromoindole (**2l**), and 3-bromoquinoline (**2m**) were all well tolerated reaction partners despite their coordinating properties and the bulky nature of **2l** and **2m**, and afforded **3k–3m** in good-to excellent yields. The catalytic system displayed very good compatibility under microwave (MW) irradiation conditions (Scheme 1 b, **3j**), as further exemplified in the following sections, which helped to speed up the reaction significantly. The extent to which functional groups can exert a steric hindrance was further examined in more detail (Scheme 2). In the series of trifluoromethylphenylboronic acids (Scheme 2 a), the *ortho* substituted starting material completely inhibited the reaction even at 50 ºC (Scheme 2 a, **4c**). In contrast, the *para* and *meta* analogues afforded **4a–b** in excellent yields. This surprising interference prompted us to examine other *ortho*-substituted phenylboronic acids. When a less bulky chloride replaced the trifluoromethyl functionality at the ortho position, the reactivity returned to normal and **4d** could be obtained in a very good yield. Furthermore, a range of other hindered products were synthesized and isolated successfully (**4e–g**) proving a good tolerance of our catalyst to different ortho substituents (i.e.; OMe, CH2OH and OH). However, 2-formylphenylboronic acid (**4h**) reacted at a slightly reduced rate, while the *o*-methylcarboxylate function (**4i**), inhibited the reaction. This set of experiments indicates that formation of the desired products is suppressed when the boronic acid contains electron-withdrawing groups in addition to bulky *ortho* substituents.



4a: R = *p*-CF_3, 20 °C, 0.5 h, >99% (95%)
4b: R = *m*-CF_3, 20 °C, 0.5 h, >99 % (91%)
4c: R = *o*-CF_3, 20 °C, 1 h, 0%; 50 °C, 3 h, 0%
4d: R = *o*-Cl, 20 °C, 0.5 h, >99% (80%)
4e: R = *o*-OCH_3, 20 °C, 2 h, >99% (98%)
4f: R = *o*-CH_2OH, 20 °C, 2 h, >99% (98%)
4g: R = *o*-OH, 20 °C, 2 h, >99% (98%)
4h: R = *o*-CHO, 20 °C, 3 h, >65% (58%)
4i: R = *o*-CO_2Me, 50 °C, 2 h, 0%



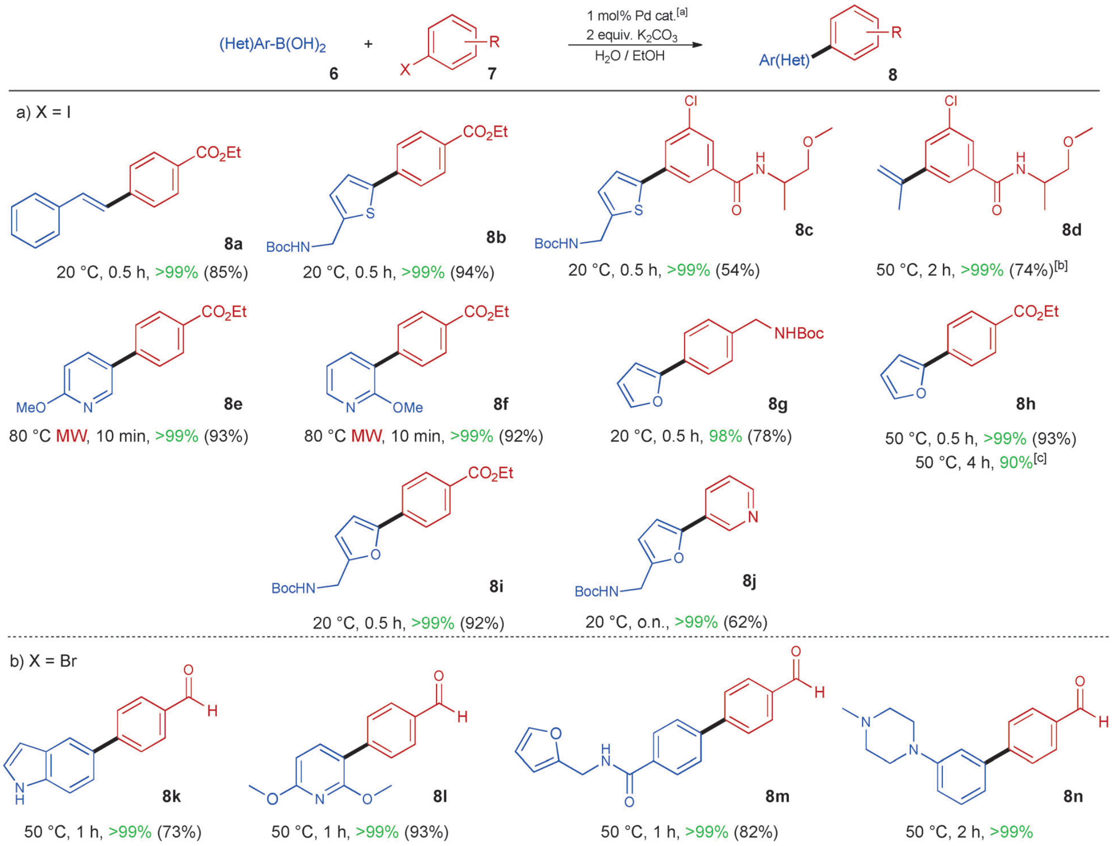
5a: R = *p*-CO_2Et, 20 °C, 0.5 h, >99% (98%)
5b: R = *m*-CO_2Et, 20 °C, 0.5 h, >99% (74%)
5c: R = *o*-CO_2Me, 50 °C, 2 h, 60% (55%)

Scheme 2. Influence of steric effects. [a] 0.1 mmol of aryl halide and 1.1 equiv of transmetallating agent were used. Conversion determined by LC–MS. Isolated yields in parenthesis.

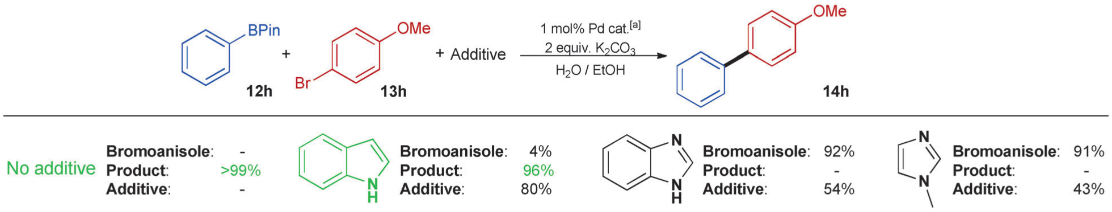
This effect proved to be less pronounced when the bulky, electro-withdrawing functionality was switched to the aryl halide (Scheme 2 b). In this case, methyl *o*-iodobenzoate reacted with (5-formylfuran-2-yl)boronic acid using slightly harsher conditions than the *meta* and *para* ethyl analogues. Consequently, although a significant rate deceleration is observed, this problem can be, in most cases, circumvented at higher temperatures and the catalyst is capable to return an excellent conversion.

Even though the catalytic tests performed so far were rewarding, superior results were obtained when the heterocyclic moiety was located on the boron transmetallating partners. As a general trend, it was observed that this arrangement of reactive groups (boron located on the more functionalized fragment) leads to a better tolerance towards multiple coordinating heteroatoms. A large variety of interesting (hetero)aromatic or vinylboronic acids (6a–6n) were coupled with aryl iodides (Scheme 3a, **7a–j**) and aryl bromides (Scheme 3b, **7k–n**) and afforded biaryls **8a–j** and **8k–n**, respectively, encountering very little difficulties. Notably, **8c** and **8d**, containing a sophisticated motif present in patented antagonists of P2X purinergic receptors,[22] reached full conversion at low temperatures in 30 min and in 2 h, respectively. It was especially interesting to observe that a complex aryl halide such as **7d** could be easily coupled with isoprene-2-yl boronic acid pinacolate ester (6d), which contains a vinylic substituent. Furthermore, boronic acids of pyridines, indoles, furans and thiophenes were well tolerated. The use of MW irradiation was proven once again to be highly effective and led to the isolation of 8e and the sterically hindered **8f** in excellent yields, after merely 10 min of reaction time. More sophisticated products like **8m** and **8n** could also be synthesized and successfully isolated in very good yields from the corresponding aryl bromides at 50 ºC.

In our efforts to determine the tolerance limit that Pd@MIL-101-NH_2 has for complex substrates, it was found that certain classes of heterocycles do not react readily. Halides of pyrazoles, indazoles and benzimidazoles stood out as very challenging substrates. Their poisoning effect was recently discussed in detail by Buchwald and co-workers,[23] who provided evidence for the formation of bridged Pd complexes, which inhibit the Suzuki coupling. A strong influence over the outcome was also attributed to the pKa values of the heterocycles employed. In this context, it was interesting to examine the inhibitory properties of these substrates. In a robustness assessment, as proposed by Glorius et al.,[24] when this type of heterocycles (benzimidazole or 1-methylimidazole) were used as additives in the cross-coupling of two standard substrates, the reaction was completely suppressed and no product formation could be detected (Scheme 4). In contrast, when indole was used as an additive, almost no inhibition could be detected.



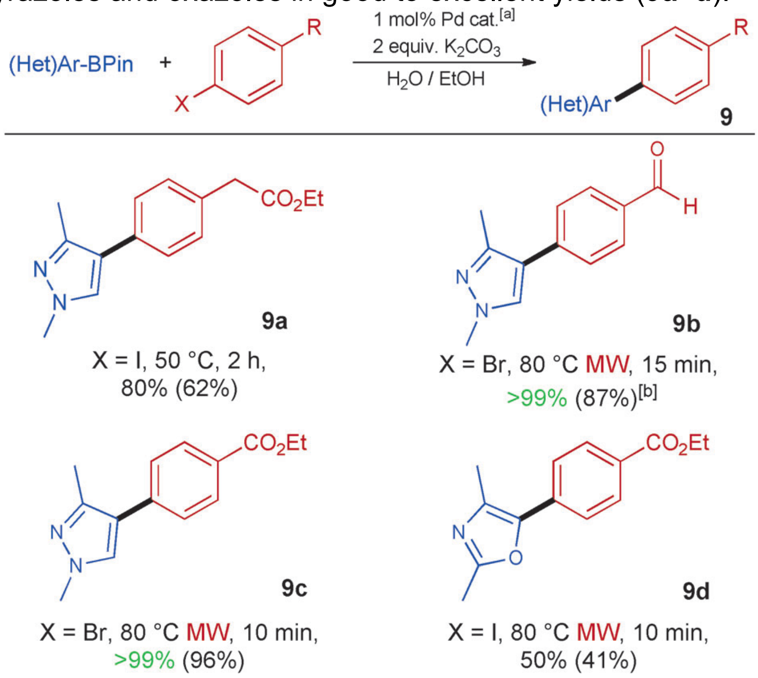
Scheme 3. Couplings of (hetero)aromatic boronic acids. [a] Unless otherwise noted, 0.1 mmol of aryl halide and 1.1 equiv of transmetallating agent were used. Conversion determined by LC-MS. Isolated yields in parenthesis. [b] Using isoprene-2-yl boronic acid pinacolate ester. [c] Using 2-bromofuran.



Scheme 4. Inhibitory effects of heterocycles. [a] 0.1 mmol scale. 1.2 equiv of transmetallating agent and 1 equiv of additive were used. Composition of the reaction mixture after 30 min determined by 1H NMR spectroscopy using 1,2,4,5-tetrachloro-3-nitrobenzene as internal standard. Pin = pinacolate.

Gratifyingly, this problem was partially bypassed using the heterocycles as transmetallating agents under mild conventional heating (Scheme 5, **9a** and **b**) or

MW irradiation conditions. This strategy enabled the synthesis of several aryl substituted pyrazoles and oxazoles in good to excellent yields (**9a–d**).



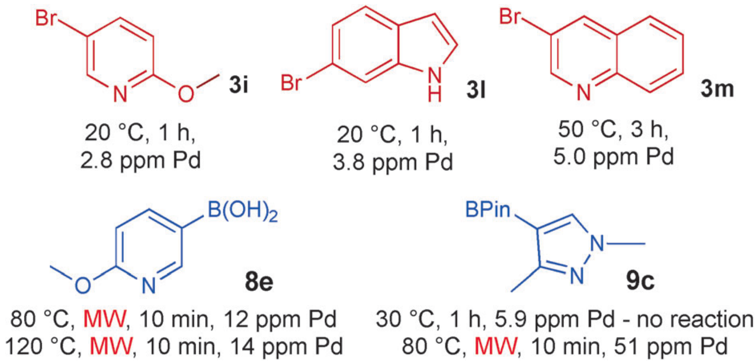
Scheme 5. Coupling of pyrazole and oxazole derived boronic acids. [a] Unless otherwise noted, 0.1 mmol of aryl halide and 1.1 equiv of transmetallating agent were used. Conversion determined by LC–MS. Isolated yields in parenthesis [b] 50% conversion at 50 ºC, conventional heating. Pin = pinacolate.

Although previous reports provide limited evidence that catalysis can occur on the surface of the nanoparticles and inside the pores,[25] homogeneous contributions from leached metallic species must be considered, while the debate on the true nature of the active Pd species is still fiercely active.[26] We consider the character of the dominant mechanism (heterogeneous or homogeneous) to be strongly dependent on the reaction conditions but these two possible pathways can operate simultaneously.[24b] Taking advantage of the good scavenging properties of the MOF, products free of contamination can still be obtained.

Several reactions presented above were repeated in order to assess the extent of Pd leaching and to investigate its dependence on the nature of the substrates and the reaction conditions. When model substrates with no heteroatoms were used, the Pd content in solution after filtration of the catalyst was in most cases below the detection limit of the inductively coupled plasma–optical emission spectrometry (ICP-OES) method (<0.1 ppm). Our attempts to measure precise kinetic profiles of the reaction over several runs were hampered by the insufficient solubility of the starting materials in the solvents mixture and the precipitation of the biaryl product at high concentrations. However, even when the catalyst loading was decreased to 0.1 mol%, the reaction between *p*-bromobenzaldehyde and phenylboronic acid was completed in less than 10 min, over at least 5 recycling runs. The rate in this case was mainly influenced by the rate of solvation of the aryl halide. After repeated recycling runs, some Pd agglomeration becomes evident under TEM.[18] These results suggest that even if Pd leaching occurs, the redeposition process is extremely efficient and products completely free of contamination can be obtained.

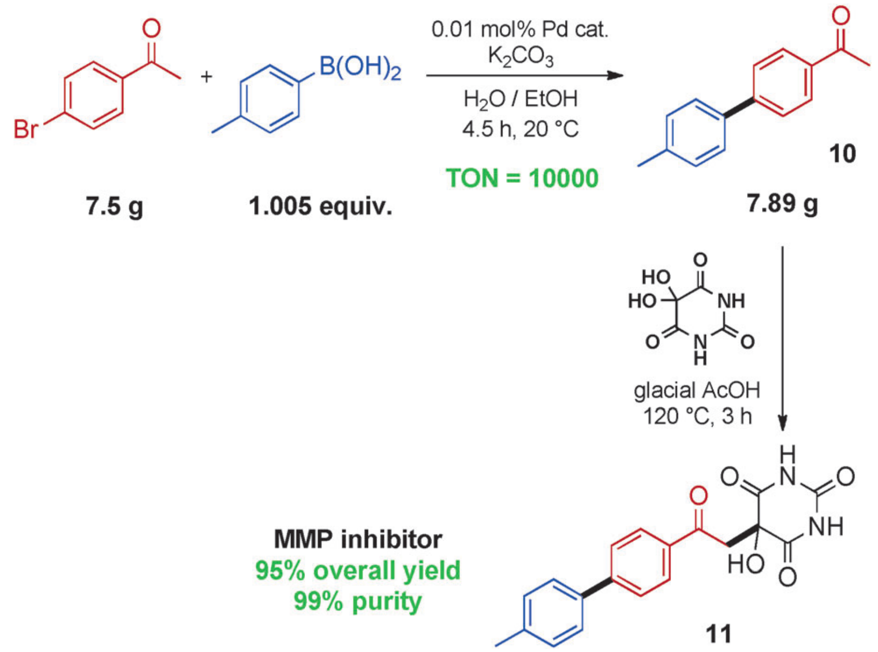
However, when one N atom is present in the aryl halide, leached Pd can be detected in very small amounts (2.8–5.0 ppm) which appear to also be dependent on the reaction time and temperature (Scheme 1 and 6, **3i**, **3l** and **3m**). At elevated temperatures and under MW irradiation (Scheme 3 and 6, **8e**), even higher levels of

Pd can be detected (12–14 ppm), although the MOF keeps the leaching at very reasonable levels for such drastic conditions. The only case where the leaching of Pd was severe was that of pyrazole (Scheme 5 and 6, **9c**). 51 ppm of Pd were detected after 10 min at 80 ºC under MW irradiation, conditions which were required to achieve a complete conversion. When the same set of substrates were reacted for 1 h at 30 ºC, the level of Pd in solution was measured to be only 5.9 ppm but no desired product was observed. This indicates that the presence of a second N atom in the substrate affects the stability of the nanoparticles even more than the harsh conditions employed.



Scheme 6. Pd leaching measured for various *N*-containing substrates.

In order to further demonstrate the applicability of our catalyst, the Pd loading was decreased to 0.01 mol% and 1-(4'-bromophenyl) ethanone was reacted in a 7.5-gram-scale using only an equimolar amount of *p*-tolylboronic acid as transmetallating agent (Scheme 7). The conversion was measured at regular intervals by LC–MS and determined to be complete after 280 min. A simple extraction with EtOAc led to the isolation of the desired biaryl (10) in 99% yield (turnover number TON = 10000) with remarkable purity as proven by the ^{1}H NMR spectrum of the crude mixture (Figure S6). Without further purification, 4-(4'-methylphenyl) acetophenone (**10**) was reacted for 3 h with commercially available alloxan hydrate to obtain compound 11 in a 96% yield after just filtration and washing with water, with no need for chromatographic purification or recrystallization (Scheme 7). This is a drastic improvement on the previously reported synthesis of **11** by Nicolotti et al.[27] (50% overall yield), which has been proposed as an inhibitor for matrix metalloproteinases involved in inflammatory diseases.



Scheme 7. Synthesis of MMP inhibitor **11**.

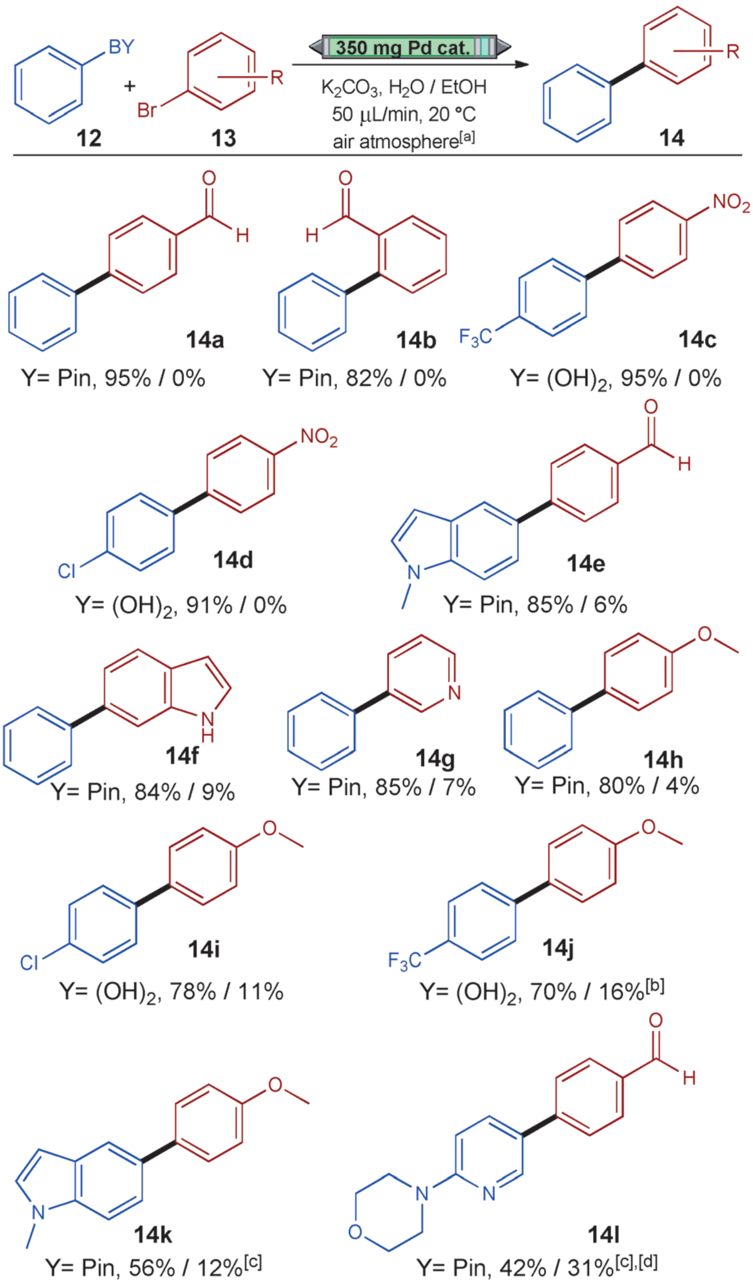
Encouraged by the results presented above and the facile recyclability of this catalyst under batch conditions, previously demonstrated by our group,[18] we proceeded to investigate the behavior of Pd@MIL-101-NH_2 under continuous-flow conditions.[28]

The catalyst was packed in an Omnifit glass column (d = 10 mm; 70 mm max adjustable bed height). For evaluating its performance under flow conditions, an "endurance test" was set up. Thus, 350 mg of catalyst (7.29 wt% Pd@MIL-101-NH_2) was packed as described in the Supporting Information. A vigorously stirred mixture of starting materials (10 mmol of *p*-bromobenzaldehyde,12 mmol of phenylboronic acid pinacolate ester, and 20 mmol of K_2CO_3, in a mixture of 30 mL H_2O and 120 mL EtOH) was passed through the column at an optimized flow rate of 75 μLmin^{-1}. After stabilization of the system, regularly collected samples were analyzed by ^{1}H NMR spectroscopy for measuring the conversion and by ICP-OES for determining the level of leached metallic species. The catalyst displayed a remarkable stability for a considerable period of 54 h, during which the aryl halide was fully converted to the desired product, at a turnover frequency of 1.25 h^{-1} (0.91 h^{-1} calculated from isolated yield), with no formation of by-products and barely detectable levels of metallic species in solution (max. 0.2 ppm of Pd and max. 0.1 ppm of Cr; see Table S1).

After 66 h, it was observed that the outflowing solution had turned from colorless to strongly yellow. This correlated with increased leaching (up to 1.2 ppm of Pd and 0.2 ppm of Cr) while significant amounts of dehalogenated by-product (benzaldehyde) were detected. The experiment was stopped after 70 h and the catalyst was recovered, washed and dried. The XRPD analysis showed a complete amorphization of the recycled material (Figure S4 a). The increased leaching and loss of selectivity are not surprising considering that after the amorphization of the framework, Pd nanoparticles are no longer protected by the MOF pores. In this case, they will agglomerate, forming conglomerates of uncontrolled size and morphology, with inferior catalytic properties.

Satisfied with the determined stability timeframe, we planned to synthesize a small library of more challenging compounds in a single continuous flow experiment. This is an interesting application of flow processes with immobilized catalytic systems in pharmaceutical research. In this manner, focused libraries of drug candidates or drug intermediates can be readily prepared in a sequential procedure, free of contamination by the metal catalyst, through a process easily amenable to automation.[29]

Mixtures of similar concentration (0.3 mmol of aryl halide in 6 mL of solvent, see the Supporting Information) were prepared and passed through an identically packed catalyst column at a reduced flow rate of 50 μLmin^{-1} (see the Supporting Information for detailed procedure). To our delight, 11 coupling products (Scheme 8, **14a–l**), several of which were known to be problematic, could be synthesized before catalytic activity of the system was compromised.
By running the reaction under non-equilibrium conditions specific to continuous flow regimes, some slightly lower yields were obtained compared to batch reactions. Also a minor decrease in activity and selectivity is gradually observed as the column starts to degrade under the stress produced by passing more bulky and heteroaromatic substrates. However, it is not until the 12th product that the operation of the flow column becomes unproductive.[30] As previously observed, a yellow coloration of the outflowing solution started to mark the steep decline in catalytic activity. The recovered catalyst was found to be partially crystalline (Figure S4 b) with a remaining Pd content of 6.81 wt% (initially 7.29 wt%).



Scheme 8. Synthesis of a mini-library of coupling products in one continuous flow

experiment. [a] Products listed in the order they were synthesized. Left: Isolated yields reported. Right: by-products determined by ^{1}H NMR spectroscopy from crude reaction mixtures. [b] Outflowing solution slightly yellow. [c] Outflowing solution strongly yellow. [d] Product not isolated. Pin = pinacolate.

Conclusions

We propose a robust heterogeneous catalytic system for the Suzuki–Miyaura cross-coupling reaction. The system consists of palladium nanoparticles immobilized on the metal–organic framework MIL-101-NH_2, and employs some of the mildest reaction conditions reported to date. Its applicability is demonstrated in the synthesis of a large number of diverse heteroaromatic and highly functionalized biaryls (more than 40 examples). The substrate scope includes motifs frequently encountered in drug molecules and we illustrate the potential to improve existing synthetic routes for commercially relevant products. By adapting this system to operation under continuous flow, we have developed what will hopefully become the first in a rich family of catalysts based on metallic nanoparticles supported on MOFs and applied in packed-bed flow reactors.

After successfully synthesizing a small library of 11 isolated products in a single experiment, we are confident that the set up exemplified in this work demonstrates the potential of Pd@MIL-101-NH_2 to be employed in automated processes under a continuous-flow regime. Fulfilling the main directives of green chemistry through catalysis, efficiency, selectivity and recyclability, we hope that the arguments presented in this report make Pd@MIL-101-NH_2 an attractive solution for large scale applications.

Experimental Section

General procedure for the Suzuki–Miyaura cross-coupling reactions

8 wt% Pd@MIL-101-NH_2 was prepared according to the reported procedure.[18] Unless otherwise stated, in a 20 mL regular vial or Biotage microwave vial, the arylboronic acid (0.83 mmol), the aryl halide (0.158 g, 0.75 mmol), K_2CO_3 (0.207 g, 1.5 mmol), and 8 wt% Pd@MIL-101Cr-NH_2 (10 mg, 7.5 μmol, 1 mol% Pd) were added together with a magnetic stirring bar. EtOH (5 mL) and H_2O (5 mL) were added. The mixture was stirred in a sealed vial at the given temperature under conventional heating or microwave irradiation. The compound was extracted with EtOAc or CH_2Cl_2 (5 mL), the organic phase was separated and the volatile solvents were evaporated to yield the crude product. The product was purified by flash chromatography (see the Supporting Information).

Procedure for experiments under flow regime

For the mini-library experiment, 12 mixtures of starting materials were prepared: consisting of aryl halide (0.3 mmol), boronic acid/ ester (0.45 mmol) and K_2CO_3 (0.6 mmol) in a mixture of H_2O (1.5 mL) and EtOH (4.5 mL). Due to the low solubility of some of the chemicals, the reaction mixture was stirred vigorously during the loading process. Increasing the excess of transmetallating reagent to 1.5 equiv helped to minimize the formation of dehalogenation by-products. Each freshly prepared mixture was passed through the column at 50 $\mu Lmin^{-1}$ corresponding to a residence time of 35–40 min. The column was then flushed with a clean solvent mixture (H_2O/EtOH, 1:3 *v/v*) at the same flow rate for 1 h and at 500 $\mu Lmin^{-1}$ for another 30 min. The outflowing solution was checked by TLC to verify that no residual product is left in the column before switching the inlet needle to the next reaction mixture. For each run, the outflowing solution was collected together with the flushing solvent and extracted with EtOAc. The organic phase was separated, the volatiles were evaporated and the residue was purified by column chromatography (see the Supporting Information).

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