ChemPubSoc Europe

DOI: 10.1002/chem.201502918

CHEMISTRY
A European Journal
Full Paper

Metal–Organic Frameworks |*Very Important Paper*|

Selective Heterogeneous C–H Activation/Halogenation Reactions Catalyzed by Pd@MOF Nanocomposites

Vlad Pascanu,[a, c] Fabian Carson,[b, c] Marta Vico Solano,[a, c] Jie Su,[b, c] Xiaodong Zou,[b, c] Magnus J. Johansson,[d] and Belén Martín-Matute*[a, c]

Abstract: A directed heterogeneous C–H activation/halogenation reaction catalyzed by readily synthesized Pd@MOF nanocatalysts was developed. The heterogeneous Pd catalysts used were a novel and environmentally benign Fe-based metal–organic framework (MOF) (Pd@MIL-88B-NH_2(Fe)) and the previously developed Pd@MIL-101-NH_2(Cr). Very high conversions and selectivities were achieved under very mild reaction conditions and in short reaction times. A wide variety of directing groups, halogen sources, and substitution patterns were well tolerated, and valuable polyhalogenated compounds were synthesized in a controlled manner. The synthesis of the Pd-functionalized Fe-based MOF and the recyclability of the two catalysts are also presented.

Introduction

C–H functionalization represents an attractive and straightforward method to introduce diverse functional groups into a molecule.[1] Not relying on leaving groups to direct a transformation brings significant benefits in terms of time and costs.[2] This simplifies late-stage transformations in the synthesis of target molecules,[3] and can positively impact the environmental output of the chemical industry. However, the activation of relatively inert C–H bonds while accurately distinguishing between several bonds with similar activation energies, is challenging.[4] Moreover, methods for the activation of C–H bonds using heterogeneous catalysts are still scarce.[5]

Halogenated compounds are very useful in various branches of chemistry (e.g., agrochemistry,[6] pharmaceuticals,[7] supramolecular chemistry[8]). They can also be further functionalized to synthesize more diverse structures. Halogenation through selective C–H functionalization is an engaging concept, but few catalysts have proved capable of realizing this challenging goal efficiently as well as in a selective manner.[9] If such a protocol could be based on a heterogeneous catalyst, this would represent an attractive way to synthesize a wide range of functionalized molecules.

Metal–organic frameworks (MOFs) are porous materials with extremely high surface areas that have been shown to be useful heterogeneous supports for transition-metal nanocatalysts.[10] MOFs can impede the aggregation of supported nanoparticles during a reaction, thereby prolonging their lifetime.[11] The confined environment found inside the pores of MOFs can lead to surprising reactivity or selectivity, which would otherwise be difficult to achieve in homogeneous systems.[12] Their inherent structural features allow MOFs to discern between substrates of various shapes and sizes, meaning that they could potentially be used as supports for catalysts for selective C–H activation reactions.[13] In addition, MOFs can facilitate the catalyst recycling and prevent metal contamination of the reaction products.

An interesting first report on aromatic C–H activation/halogenation under heterogeneous catalysis was recently published by Fei and Cohen.[14] A molecular Pd catalyst was immobilized in a modified UiO-66 framework by post-synthetic ligand exchange. The heterogeneity and recyclability of the catalyst were demonstrated for a limited number of substrates that do not raise selectivity issues. For other substrates containing a directing group that allows activation of two equivalent C–H bonds, such as phenylpyridines and related molecules, it is very challenging to stop the reaction after the first functionalization, and activation of the second C–H bond results in low selectivities towards the monofunctionalized product.[15] Indeed, excellent conversions can be achieved using $Pd(OAc)_2$[16] or even Cu salts[15a] as the catalyst, but a mixture of mono- and difunctionalized products is formed under these conditions, which necessitates tedious purification steps. To-

---

[a] V. Pascanu, Dr. M. V. Solano, Prof. B. Martín-Matute
Department of Organic Chemistry, Stockholm University
Stockholm, 10691 (Sweden)
E-mail: belen.martin.matute@su.se

[b] Dr. F. Carson, Dr. J. Su, Prof. X. Zou
Department of Materials and Environmental Chemistry
Stockholm University, Stockholm, 10691 (Sweden)

[c] V. Pascanu, Dr. F. Carson, Dr. M. V. Solano, Dr. J. Su, Prof. X. Zou, Prof. B. Martín-Matute
Berzelii Center EXSELENT on Porous Materials, Stockholm University
Stockholm, 10691 (Sweden)

[d] Dr. M. J. Johansson
CVMD iMed, Medicinal Chemistry
AstraZeneca R&D, Mölndal, 43183 (Sweden)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201502918.

Part of a Special Issue "Women in Chemistry" to celebrate International Women's Day 2016. To view the complete issue, visit: http://dx.doi.org/chem.v22.11.

wards this goal it is still necessary to develop methods that afford the synthesis of either mono- or dihalogenated aromatics selectively, and that could be scaled up and applied in large-scale processes.

Our group has developed efficient procedures for Suzuki cross-coupling[10i–j] and alcohol oxidation reactions[10k] using Pd nanoparticles supported in the MIL-101-NH_2(Cr) and MIL-88B-NH_2(Cr) MOFs, respectively. Although these systems show extremely low metal leaching and very good recyclability, the presence of Cr clusters in the frameworks raises concerns over health issues in potential industrial large-scale applications. To address this issue, in this paper we report the synthesis of a related catalyst based on a benign Fe MOF, dubbed Pd@MIL-88B-NH_2(Fe). This new heterogeneous catalyst is cheaply and easily synthesized, which makes it extremely attractive for catalytic applications.

We report here a reliable and selective heterogeneous C–H halogenation method using palladium nanoparticles immobilized into porous heterogeneous MOFs, Pd@MIL-88B-NH_2(Fe) and Pd@MIL-101-NH_2(Cr). Both MOFs showed excellent selectivity for the formation of monofunctionalized products from starting materials in which two competing positions were available, under exceptionally mild and environmentally friendly conditions. Conversely, the difunctionalized products could also be obtained selectively by adjusting the reaction parameters. This heterogeneous system is considerably more efficient in terms of yields, and even more importantly selectivity, using lower catalyst loadings and temperatures than any of those previously described.[14,15,16b,17] We found the reaction to have a wide substrate scope, which demonstrates both catalysts are versatile, and can be used with various directing groups, substitution patterns, and halogen sources. We also investigated the recyclability of the two MOFs, which revealed some differences in their behavior.

Results and Discussion

1. Catalysts synthesis

The two catalysts utilized for this study, Pd@MIL-101-NH_2(Cr) and Pd@MIL-88B-NH_2(Fe), are shown in Figure 1. Pd@MIL-101-NH_2(Cr) containing 8 wt % of Pd (cat. 1) was synthesized according to a procedure previously developed and reported by our group.[10i,j]

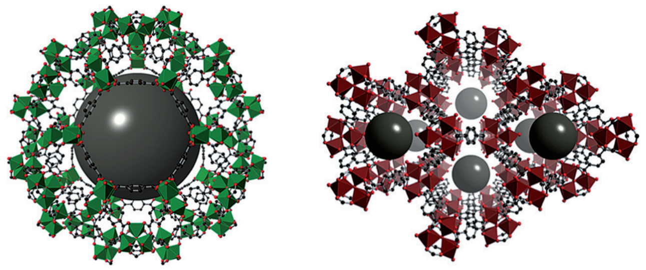


Figure 1. Illustrative representation of palladium nanoparticles supported in MIL-101-NH_2(Cr) cages (left, green), and MIL-88B-NH_2(Fe) channels (right, red) (note: The nanoparticles in both materials are of similar dimensions).

For cat. 2 a new procedure was developed. The supporting framework, MIL-88B-NH_2(Fe), was synthesized by adapting a protocol reported by Serre et al.[18] using ethanol as the solvent and without hazardous additives. The stability of the MOF in acidic and basic aqueous solutions (ranging from pH 1 to 14) was investigated in order to determine the appropriate functionalization conditions. According to the X-ray powder diffraction (XRPD) data, the material is stable between pH 1 to 11. At higher pH (pH 12 to 13), significant mass loss was observed, which correlated with a decrease in crystallinity and a color change from dark brown to pale orange. At pH 14, the structure transformed into another crystalline phase, possibly a MIL-53-type structure (see the Supporting Information, Figure S1). This behavior makes MIL-88B-NH_2(Fe) an ideal heterogeneous support for applications that require stability under acidic conditions such as C–H activation reactions, which are typically carried out in an acidic environment.

Despite the flexible nature of the MOF, impregnation with a palladium precursor was successfully achieved, using a strategy that we had previously developed for the Cr analogue of MIL-88B-NH_2.[10k] Na_2PdCl_4 was found to be an optimal Pd source, and MeOH proved to be an adequate solvent for keeping the flexible structure of the MOF in an open conformation during the impregnation process. Analysis of the impregnated material, Pd^{II}@MIL-88B-NH_2(Fe), by inductively-coupled-plasma optical emission spectrometry (ICP-OES) confirmed the successful loading of Pd (10.89 wt % Pd) and the complete removal of Na (see the Supporting Information, Section S2 for a detailed procedure). The use of $NaBH_4$ to reduce the Pd^{II} resulted in amorphization of the material, even when the reaction was carried out at $-5\,^{\circ}C$. This led us to explore milder reducing agents. We found that the crystallinity of the MOF was preserved when either a mixture of Na citrate/L-ascorbic acid or $NaBH(OAc)_3$ were used as the reducing agents. To verify the efficiency of these conditions for the synthesis of Pd nanoparticles and the ability of these reagents to access the Pd sites within the pores of the MOF, XPS was carried out after the reduction step. This revealed Pd^0/Pd^{II} ratios of 70:30 and 90:10, respectively, when sodium citrate/L-ascorbic acid and $NaBH(OAc)_3$ were used as reducing agents (Figure 2b, top right). Therefore we chose to use $NaBH(OAc)_3$ as the reducing agent for the synthesis of the nanoparticles (see the Supporting Information for further details). TEM micrographs confirmed the formation of Pd nanoparticles with an average size of 2 nm that were uniformly distributed throughout the MOF (Figure 2c, bottom). Specific rod-shaped crystals could be observed, ranging in size from 500 nm to several micrometers. Pd^0@MIL-88B-NH_2(Fe) synthesized in this way had a Pd loading of 11.46 wt %.

The XRPD data confirmed that the framework remained crystalline after the functionalization procedure (Figure 2a, top left). The peaks progressively shifted to lower 2θ angles and the unit cell volume increased in Pd^{II}@MIL-88B-NH_2(Fe) and Pd^0@MIL-88B-NH_2(Fe) compared to MIL-88B-NH_2(Fe), which indicates that the framework expanded during the impregnation

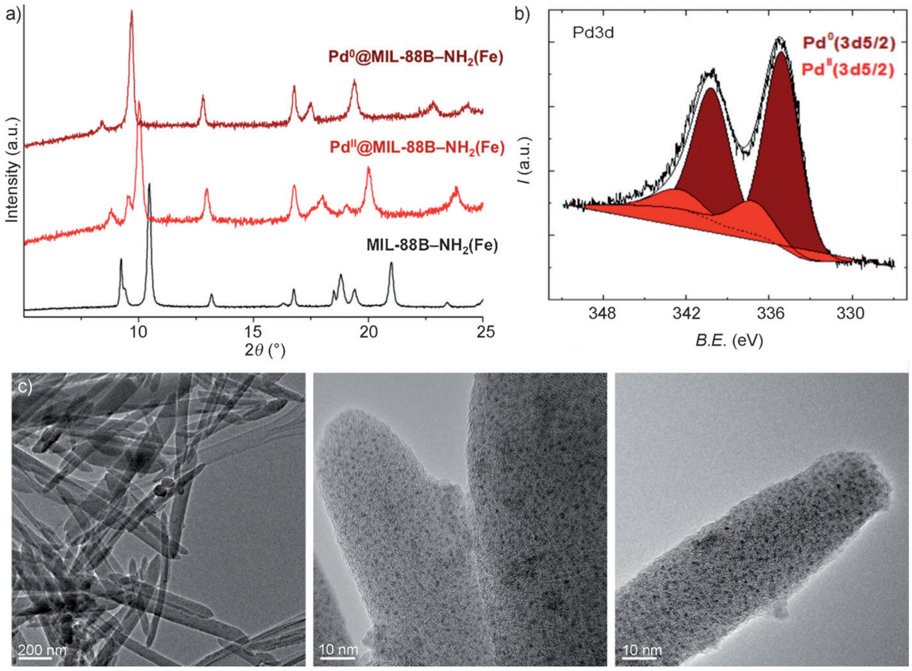
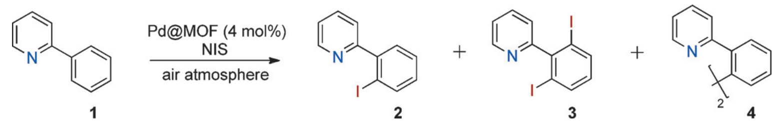


Figure 2. a) XRPD patterns of MIL-88B-NH_2(Fe), Pd^{II}@MIL-88B-NH_2(Fe), and Pd^0@MIL-88B-NH_2(Fe); b) XPS analysis of Pd^0@MIL-88B-NH_2(Fe); c) TEM micrographs of Pd^0@MIL-88B-NH_2(Fe).

with Pd and again during the formation of the Pd nanoparticles. LeBail fitting of the XRPD data gave unit cell parameters of $a=10.891(1)$, $c=19.181(2)$ Å; $V=1970.4(3)$ Å^3 for MIL-88B-NH_2(Fe); $a=11.691(2)$, $c=18.705(4)$ Å; $V=2214.2(6)$ Å^3 for Pd^{II}@MIL-88B-NH_2(Fe); and $a=12.243(3)$, $c=18.429(6)$ Å; $V=2392.1(9)$ Å^3 for Pd^0@MIL-88B-NH_2(Fe) using a hexagonal space group ($P\bar{6}2c$) (see the Supporting Information, Figures S2–S4). TGA results confirmed that Pd^{II}@ and Pd^0@MIL-88B-NH_2(Fe) were thermally stable up to 300 °C in air, which is similar to the thermal stability of MIL-88B-NH_2(Fe) (see the Supporting Information, Figure S6).

Table 1. Optimization of the selective mono a di-iodination of 2-phenylpyridine (**1**).[a]



Entry	Catalyst	T [°C]	t [h]	NIS [equiv]	Solvent	Additive	Yield [%]		
							2	3	4
1	Pd@MIL-101-NH_2(Cr)	50	7	1.2	AcOH	–	58	2	8
2	Pd@MIL-101-NH_2(Cr)	50	7	2.3	AcOH	–	74	1	3
3	Pd@MIL-101-NH_2(Cr)	40	7	3.0	AcOH	–	52	0	0
4	Pd@MIL-101-NH_2(Cr)	80	2.25	3.0	THF	PTSA	0	93	3
5	Pd@MIL-101-NH_2(Cr)	80	16	3.0	DCE	PTSA	0	98	0
6	Pd@MIL-88B-NH_2(Fe)	50	7	2.3	AcOH	–	81	7	3
7	Pd@MIL-88B-NH_2(Fe)	80	16	3.0	DCE	PTSA	0	99	0
8	Pd/C (10 wt %)	50	7	2.3	AcOH	–	16	0	0

[a] Experiments were carried out under an air atmosphere on a 0.1 mmol scale, using Pd@MOF or Pd/C (4 mol % Pd) and 3 mL of solvent. Conversions were monitored by GC. 0.5 mmol additive was used in entries 4, 5, and 7. PTSA = p-toluenesulfonic acid; DCE = 1,2-dichloroethane.

2. Reaction optimization

The iodination of unsubstituted 2-phenylpyridine using N-iodosuccinimide (NIS) as a halogenating agent was chosen as a model reaction to explore the reactivity and selectivity obtained with the two Pd@MOF catalysts. Preliminary investigations were carried out using Pd@MIL-101-NH_2(Cr) (Table 1). A step-by-step approach led to the identification of suitable reaction conditions for the synthesis of either 2-(2-iodophenyl)pyridine (**2**) or 2-(2,6-diiodophenyl)pyridine (**3**) in high yields and with excellent selectivity. Complete details of the optimization procedure are given in the Supporting Information (Section S4). The first experiments were aimed at obtaining 2-(2-iodophenyl)pyridine (**2**). The choice of acetic acid as an environmentally friendly and cheap solvent also simplifies the protocol as addition of an acid additive is therefore not needed. Moreover, it creates a polar environment, which favors the diffusion of the reagents into the pores of MIL-101-NH_2. After 7 h, a good conversion and high selectivity were achieved, even though the temperature was as mild as 50 °C (Table 1, entry 1). Surprisingly, along with traces of dihalogenated product **3**, small amounts of a dimeric product (**4**) were formed.[19] This result could be significantly improved by using 2.3 equivalents of NIS, which gave a higher conversion while keeping products **3** and **4** in trace amounts (entry 2). Remarkably, the product (**2**) could also be obtained at a temperature as low as 40 °C (entry 3). These are some of the mildest conditions ever reported for an efficient Pd-catalyzed C–H activation. Further experiments carried out at 50 and 60 °C with various reaction times and equivalents of reagents did not give improved product distributions (see the Supporting Information, Table S2).

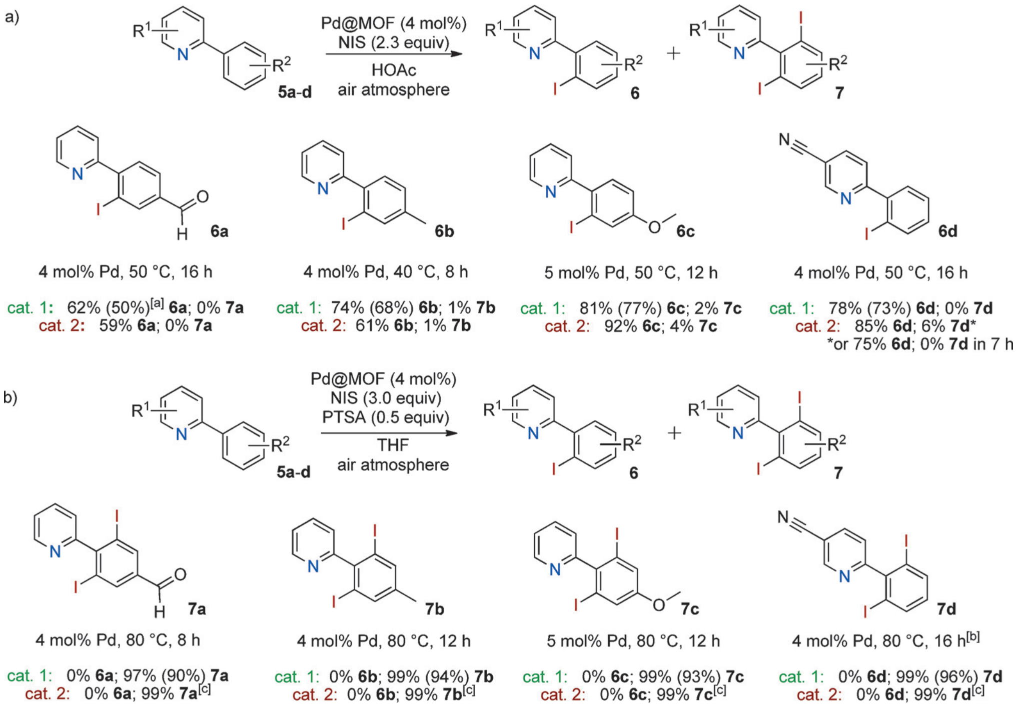
We then set out to find optimal conditions that would favor the formation of the dihalogenated product, 2-(2,6-diiodophenyl)pyridine (**3**). Increasing the temperature to 80 °C promoted the activation of the monohalogenated ring for a second functionalization step. Switching to THF, which is a less polar solvent, along with *p*-toluenesulfonic acid as an additive was also an important step in the right direction, and the balance of products shifted considerably towards **3** (see the Supporting Information, Table S2). Increasing the excess of halogenating agent to 3 equivalents was decisive, and the reaction proceeded to full conversion into **3**. It was interesting to observe that in THF at 80 °C, the reaction was extremely fast, and it was complete in approximately 2 h (Table 1, entry 4) due to the high pressure created in the sealed vial, at a temperature above the boiling point of the solvent (THF b.p. = 66 °C). Switching to 1,2-dichoroethane (DCE b.p. = 84 °C) led to a decrease in the rate, and the reaction required overnight stirring to reach completion, but formation of byproduct **4** was inhibited and complete selectivity for **3** was achieved (entry 5). Other solvents and additives were screened, but none of them improved the reaction outcome (see the Supporting Information, Table S2), while with Pd/C only a modest conversion was obtained (entry 8).

The optimal conditions for the formation of both mono- and di-iodinated products were also tested in experiments using Pd@MIL-88B-NH_2(Fe). At 50 °C in AcOH, the Fe-based catalyst (cat. 2) was found to be even more reactive than the Cr one (cat. 1), and the selectivity was marginally lower (Table 1, entry 6). At 80 °C in DCE, the Fe-based catalyst gave a full and clean conversion within 16 h, and no traces of dimer **4** were found in the reaction mixture (entry 7). Importantly, control experiments confirmed that in the absence of a catalyst, as well as in the presence of MOFs without supported Pd, no conversion was observed for either the first or the second halogenation step.

It can therefore be concluded that the selective synthesis of either monohalogenated **2** or dihalogenated **3** compounds can be well controlled with both cat. 1 and cat. 2. The selectivity is mostly dependent on the reaction temperature, the polarity, and pH of the reaction solvent. It is also influenced by the excess of the halogenating agent, albeit to a far lesser extent. We then investigated the influence of various substitution patterns on the functionalization of 2-phenylpyridine derivatives under these optimized reaction conditions (**5a**–**d**, Scheme 1 a).

3. Scope in terms of symmetrical phenylpyridines

The activation of the C–H bond in electron-poor 2(4-formylphenyl)pyridine (**5a**) proved to be more difficult, and the reactions were allowed to stir overnight. This lower reactivity meant that we obtained conversions of approximately 60% with both catalysts, but a complete selectivity for the desired product (**6a**) could be achieved (Scheme 1 a). 2-(4-Tolyl)pyridine (**5b**) was more reactive, giving up to 10% of **7b** at 50 °C. However, by decreasing the temperature to 40 °C the selectivity could be completely restored while maintaining a very good conversion (74%) (Scheme 1 a). The electron-rich 2-(4-methoxylphenyl) pyridine (**5c**) was converted into **6c** in 81 and 92% yield with both catalysts (Scheme 1 a). A functional group grafted on the pyridyl moiety did not affect its directing prop-



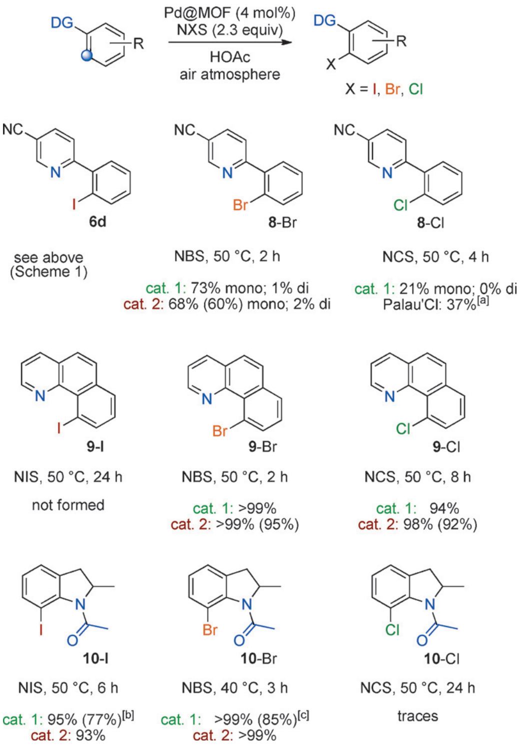
Scheme 1. a) Selective monoiodination of substituted 2-phenylpyridines; b) Selective diiodination of substituted 2-phenylpyridines. Unless otherwise specified, experiments were carried out on a 0.1 mmol scale, using 3 mL of solvent. Conversions were monitored by ^1H NMR spectroscopy. Reactions were scaled up to 0.4 mmol for isolation purposes. Isolated yields are reported in parentheses. [a] Low isolated yields of monoiodinated products due to difficult separation from the remaining starting material. [b] 3.5 equiv NIS was used. [c] DCE was used as the solvent, 24 h.

erties and 6-phenylnicotinonitrile (**5d**) gave the monoiodinated product in high yields (78 to 85 %, Scheme 1 a). These results (Scheme 1 a) show that the outcome of the reaction is not highly dependent on the electronic nature of the substituents, and both electron-withdrawing and -donating groups are well tolerated. The variations in reactivity observed are most likely caused by the differences in size and polarity between the substrates; this behavior is typical with porous catalysts such as the ones investigated.

Under the second set of reaction conditions (Scheme 1 b), all the substrates (**5a**–**d**) were quantitatively converted into diiodinated products using Pd@MIL-101-NH_2(Cr) (cat. 1). For the second MOF (cat. 2), dichloroethane (DCE) proved again to be a more suitable solvent and a quantitative yield was achieved in all cases within 24 h. The formation of dimers was not observed with these larger substituted 2-phenylpyridines, which is expected for a reaction carried out in a size-limiting environment.

4. Bromination and chlorination reactions and diverse directing groups

The next step in our investigation was to test whether our method was also applicable to bromination and chlorination reactions (Scheme 2). We found that under similar mild conditions, brominated products could be obtained in excellent yields within much shorter reaction times than their iodinated counterparts. 6-Phenylnicotinonitrile (**5d**) could be selectively monobrominated (Scheme 2, **8**-Br) using *N*-bromosuccinimide (NBS) and cat. 1. A 73 % yield was achieved within 2 h. Pd@MIL-88B-NH_2(Fe) (cat. 2) gave a similar high yield and selectivity. The analogous chlorination reaction using *N*-chlorosuccinimide (NCS) and cat. 1 gave significantly worse results. Only 21 % of the product (**8**-Cl) could be obtained after 4 h, and the reaction did not progress further. Replacing the halogenating agent with the newly developed Palau'chlor[20] led to a more efficient chlorination, but it also triggered the decomposition (disolution) of both MOFs.



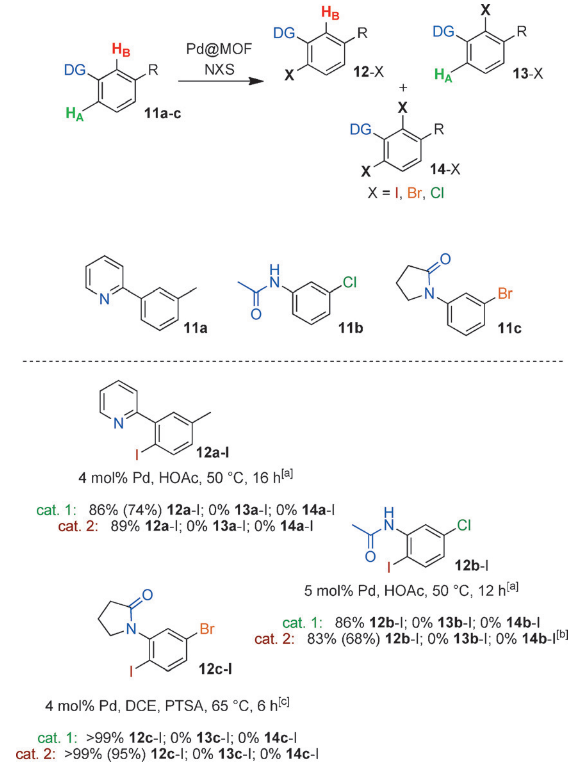
Scheme 2. Evaluation of other halogenation agents and different directing groups. Unless otherwise specified, experiments were carried out under an air atmosphere, on a 0.1 mmol scale, using 3 mL of solvent. Conversions were monitored by ^1H NMR spectroscopy. Isolated yields are reported in parentheses. DG = directing group. [a] MOF decomposition leading to a homogeneous reaction mixture; [b] 18 % oxidation to indole-type byproducts; [c] 14 % oxidation to indole-type byproducts.

We also investigated the behavior of other directing groups in the reaction. Substrates bearing rigid directing groups (**9**, **10**) were readily halogenated. 7,8-Benzoquinoline (**9**), which showed no reactivity in iodination reactions due to steric limitations (**9**-I), could be rapidly and efficiently brominated yielding **9**-Br and even chlorinated (**9**-Cl). *N*-acetyl-2-methylindoline (**10**) is another interesting target molecule for directed C–H activation, but it is highly susceptible to oxidation yielding undesired indole-type products. We were pleased to see that the mild conditions used in the methodology described here enabled C7-iodination and bromination of **10** efficiently, yielding products **10**-I and **10**-Br for the first time in very good yields. Both catalysts showed a good tolerance towards the amide-directing group and they displayed similar levels of performance. Iodine (to give **10**-I, at 50 °C) and bromine (to give **10**-Br, at 40 °C) atoms could be successfully grafted onto the phenyl ring using either of the two catalysts. All four of these reactions proceeded to completion in a directed fashion and within very short reaction times. On the other hand, only traces of desired product were formed in the corresponding chlorination reactions (**10**-Cl).

5. *meta*-Substituted substrates

A more interesting case in our study was that of *meta*-substituted phenyl rings (Scheme 3, **11a**–**c**). With these substrates three halogenated products may be formed: the functionalization at either one of the two available positions *ortho* to the directing group would lead to the formation of two different monohalogenated isomers, and in addition, the corresponding dihalogenated arene can be formed.

As expected, at low temperatures the introduction of a large iodine substituent proceeded exclusively through activation of the less crowded C–H bond (i.e., H_A). This behavior was observed with all the substrates tested, regardless of the size or the electronic properties of the R group (Scheme 3). Products **12a**-I and **12b**-I could be isolated in very good to excellent yields from the standard conditions (AcOH, 50 °C). When the R group was replaced by a bulkier bromine atom, as in the case of *N*-(3-bromophenyl)pyrrolidin-2-one (**11c**), the substrate became less reactive. Little or no product formation could be observed in either AcOH or THF. This behavior, which contrasts with that observed for phenylpyridines, may be explained by the coordinating nature of THF. This solvent did not affect the



Scheme 3. *meta*-Substituted substrates **11 a–c** (top); synthesis of products **12 a**-I to **12 c**-I (bottom). Unless otherwise specified, all experiments were carried out under an air atmosphere, on a 0.1 mmol scale, using 3 mL of solvent. Conversions were monitored by ^{1}H NMR spectroscopy. Isolated yields in parentheses. [a] 2.3 equiv NIS was used. [b] Low isolated yield of **12 b**-I due to difficult separation from remaining starting material; [c] 0.5 equiv PTSA and 3.0 equiv NIS were used. Only 17 % conversion in AcOH at 50 °C. DG = directing group.

reactivity of the strongly coordinating pyridines, but it can compete with the less strongly coordinating amides and lactams, disrupting their directing ability. Gratifyingly, when the solvent was replaced with DCE, a non-coordinating solvent, the function of the directing group was restored, and product **12 c**-I was obtained quantitatively at 65 °C.

Intrigued by this behavior, we attempted the corresponding bromination of *N*-(3-bromophenyl)pyrrolidin-2-one (**11 c**). Indeed, the smaller and more reactive Br atom could access and functionalize both of the C–H bonds *ortho* to the directing lactam group (Figure 3, top). At 50 °C in AcOH, full conversion was recorded within 4 h, but both regioisomers **12 c**-Br and **13 c**-Br were present in the reaction mixture in a ratio of approximately 2.7:1. When the temperature was decreased to 40 °C, the bromination could still be carried out efficiently, although 6 h were necessary for full conversion to be achieved (Figure 3, top). However, the selectivity was only slightly improved. Similarly, a mixture of the two chlorinated regioisomers was obtained when NCS was used, and slightly harsher conditions were required (Figure 3, bottom).

By a strategy similar to that described above (Section 3), we attempted to switch the selectivity towards the formation of diiodinated products. This approach proved suitable for substrate **11 a**, which gave 2-(2,6-diiodo-3-methylphenyl)pyridine

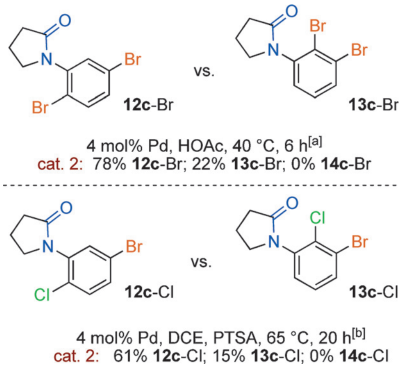


Figure 3. Selectivity in the functionalization of *N*-(3-*b*romophenyl)pyrrolidin-2-one (**11 c**). Experiments were carried out under an air atmosphere, on a 0.1 mmol scale, using 3 mL of solvent. Conversions were monitored by ^{1}H NMR spectroscopy. [a] 2.3 equiv NBS was used. At 50 °C, a ratio of 73:27:0 was recorded. [b] 0.5 equiv PTSA and 3.0 equiv NCS were used. No conversion was recorded in AcOH at 50 °C.

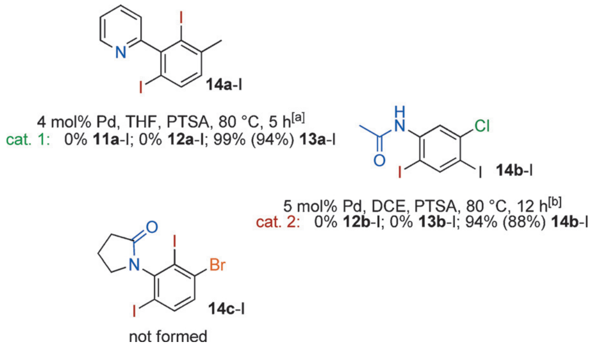
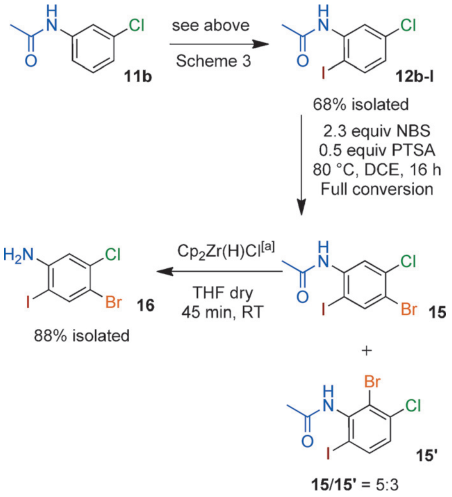


Figure 4. Synthesis of diiodinated, *meta*-substituted products **14 a-I** to **14 c-I**. Experiments were carried out under an air atmosphere, on a 0.1 mmol scale, using 3 mL of solvent. Conversions were monitored by ^{1}H NMR spectroscopy. Isolated yields in parentheses. [a] 0.5 equiv PTSA and 3.0 equiv NIS were used. [b] 0.5 equiv PTSA and 3.5 equiv NIS were used.

14 a-I in excellent yield in THF at 80 °C in only 5 h (Figure 4, top). We tested *N*-(3-chlorophenyl)acetamide (**11 b**), and a difunctionalized product (**14 b**-I) was also obtained here. However, upon closer inspection, we found that in this case the insertion of the second iodine atom took place in an undirected fashion at the *para* position (Figure 4, middle). This was further confirmed in a control experiment performed in the absence of palladium, which afforded similar yields of the product. Finally, in the case of **11 c**, a diiodinated product was not observed under any of the conditions tested (Figure 4, bottom).

Observing the different preferences in substitution patterns for different halogen atoms, we attempted to illustrate the utility of this protocol by synthesizing a polyhalogenated amine product **16**, which is a highly valuable synthetic intermediate. Each one of the four different anchors present on the aromatic ring can be selectively targeted in order to access an immense variety of functionalized molecules. After the initial directed iodination step catalyzed by Pd@MOF, product **12 b**-I was brominated under similar conditions in the absence of a Pd catalyst. A mixture of regioisomers **15** and **15′** was obtained in a ratio



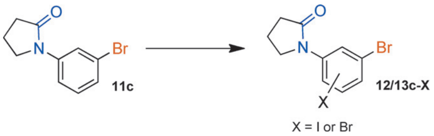
Scheme 4. Synthetic route to multifunctionalized amine **16**. [a] Experiment carried out on a 0.1 mmol scale under an Ar atmosphere. 2 equiv Zirconocene chloride hydride and 1 mL THF were used.

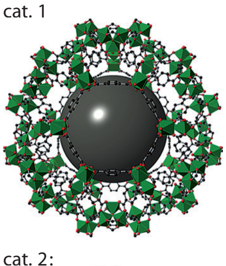
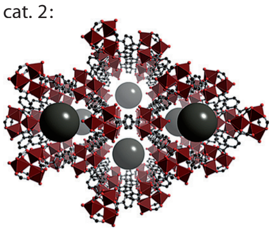
of 5:3 (Scheme 4). The major component (**15**) was isolated and subjected to a mild diacetylation reaction using Schwartz reagent,[21] which gave the polyhalogenated amine **16** in a very high isolated yield. The experiments described in this section demonstrate the wide applicability of our protocol for selective C–H activation/halogenation reactions using Pd@MOF catalysts.

6. Recyclability

We studied the stability of the catalysts upon repeated recycling, under the conditions described above (Section 5). *N*-(3-Bromophenyl)pyrrolidin-2-one (**11 c**) was chosen as a model substrate, using Pd@MIL-101-NH_2(Cr) (cat. 1) and Pd@MIL-88B-NH_2(Fe) (cat. 2) in a parallel study. The two catalysts were subjected to iodination and bromination reactions alternatively to test their ability to withstand changes in the reaction environment. The results are described below in Table 2. The detailed procedure is available in the Supporting Information (Section S5).

Table 2. Recyclability of Pd@MOF catalysts.



Entry	Catalyst	Conditions	Run	X	Conv. [%]	Pd leaching [ppm]
1	cat. 1 	for X=I:	1	I	>99%[a]	0.5
2		65 °C, 6 h	2	I	>99%[a]	0.1
3		2.5 equiv NIS,	3	Br	98%[b]	0.3
4		0.5 equiv PTSA, DCE	4	Br	97%[b]	0.2
5		or	5	I	>99%[a]	0.3
6	cat. 2: 		1	I	>99%[a]	1.5
7		for X=Br:	2	I	>99%[a]	0.3
8		40 °C 6 h	3	Br	>99%[b]	5.0
9		2.5 equiv NBS, AcOH	4	Br	>99%[b]	6.7
10			5	I	>99%[a]	0.9

[a] Selective formation of **11 c**-I; [b] Mixture of products **11 c**-Br and **12 c**-Br formed.

Both MOFs were capable of giving full conversion for several runs. Since in the presence of coordinating directing groups, some metal leaching can be expected, the Pd content in the reaction solution was measured after each run by ICP-OES analysis. In the first run, the amount of Pd in the supernatant was found to be slightly higher than expected for both of the catalysts. This is due to small amounts of Pd that are inevitably present on the surface of the MOFs (Table 2, entries 1 and 6). During further runs leaching was kept to a minimum in the case of the Cr-MOF (cat. 1), which could easily withstand the change of reaction solvent between the iodination (i.e., 65 °C, PTSA, DCE; Table 2 entries 2 and 5) and bromination conditions (i.e., 40 °C, AcOH; entries 3 and 4).

The Fe MOF (cat. 2) was also stable under the iodination conditions (Table 2, entry 7). However, when the solvent was switched to AcOH for the bromination reaction, the Pd leaching increased despite the reaction being run at a lower temperature (entries 8 and 9). Interestingly, when the conditions were reverted to the iodination protocol, the MOF was capable of regaining control over the Pd leaching (entry 10). Despite the loss of small amounts of Pd during runs 3 and 4, the catalyst was still active, and full conversion was obtained in all runs. This behavior suggests that the Fe framework is not destroyed during the reaction, but that it is less effective at protecting Pd nanoparticles in the presence of polar solvents. In this situation, the different behaviors of the two materials (entries 3 and 4 for cat. 1 vs. entries 8 and 9 for cat. 2) may be explained by the different structural features of the two MOFs; cages (MIL-101) are more suitable for protecting Pd nanoparticles than channels (MIL-88B). Additionally, Cr-MOFs are in general more stable than Fe-MOFs.[22]

XRPD analysis of the recycled catalysts revealed changes in the crystallinity of the materials. Pd@MIL-88B-NH_2(Fe) remained crystalline after catalysis, with the peaks in the XRPD pattern shifting to lower 2θ angles, which suggests an expansion of the framework. In contrast, most of the peaks in the XRPD pattern of Pd@MIL-101-NH_2(Cr) after catalysis had disappeared, indicating loss of long-range order (see the Supporting Information, Figure S8).

The recycled materials were also studied by TEM. In both cases, significant agglomeration of Pd could be observed on the surface of the MOF crystals (see the Supporting Information, Figures S11 and S12). The aggregated Pd nanoparticles suggest that a rapid leaching–redeposition mechanism could be predominant. This hypothesis was supported by additional hot filtration experiments (Supporting Information, Figures S13 and S14), which are consistent with the results of the recycling study. Thus, in the case of 2-phenylpyridine (**1**), which is a non-recyclable substrate, a hot-filtration test from AcOH at 50 °C led to just a partial inhibition of the reaction rate and a moderate yield could still be achieved. In contrast, under identical conditions (AcOH, 50 °C) a hot-filtration experiment performed for a substrate bearing an amide directing group (**11 b**), led to a nearly complete inhibition of the reaction. This result suggests that the rate of the redeposition process is strongly influenced by the coordinating strength of the directing group and is consistent with the behavior observed during recycling studies (see the Supporting Information, Section S5.4). A weaker coordinating directing group leads to a much faster redeposition process, which in turn makes the recycling of the catalyst possible. N_2 sorption isotherms of Pd@MIL-101-NH_2(Cr) after catalysis revealed that the material was still porous, although the BET surface area and pore volume were now 332 $m^2 g^{-1}$ and 0.20 $cm^3 g^{-1}$ (see the Supporting Information, Figure S9).

We anticipated that the MOFs could undergo halogenation during catalysis, therefore, in a separate experiment, Pd@MIL-88B-NH_2(Fe) (cat. 2) was subjected to three consecutive iodination runs (i.e. under the reaction conditions shown in Table 2 but in the absence of the substrate). The material was then thoroughly washed, dried, and subsequently digested for analysis. ^{1}H NMR analysis of the digested MOF revealed incorporation of one iodine atom into 68 % of the linker molecules (see the Supporting Information, Section S5 for a detailed procedure of the digestion experiments). As a control experiment, we also subjected dimethyl aminoterephthalate to the to the same conditions and observed that a full conversion into dimethyl 2-iodoaminoterephthalate was obtained after 12 h. Pd@MIL-101-NH_2(Cr) is a rigid MOF and iodination of the framework seems to result in partial collapse of the framework, whereas introduction of iodine into the linker of Pd@MIL-88B-NH_2(Fe) leads to a swelling of the flexible MOF structure to accommodate the bulky iodine group. This is consistent with observations by Serre and co-workers who showed that functionalization of the linker in MIL-88B(Fe) with halogen atoms (Cl, Br and F) led to expansion of the respective frameworks.[19] This highlights the benefit of using a flexible MOF as an advanced catalytic material. The halogenation of the framework linkers also explains the need for an excess of halogenating agent in the catalytic tests. Fortunately, halogenation of the Pd@MOF composites does not reduce their catalytic properties.

Conclusion

We present in detail the development of one of the first efficient and highly selective heterogeneous procedures for C–H activation/halogenation reactions. For this purpose we also report the facile synthesis of a catalyst based on a benign and robust Fe MOF, namely Pd@MIL-88B-NH_2(Fe). This composite material together with the well-known Pd@MIL-101-NH_2(Cr) were used to catalyze the directed C–H halogenation of a wide range of aromatic substrates. Both Pd@MOF catalysts perform remarkably well. Excellent conversions can be achieved under very mild conditions, and the selectivity between mono- and dihalogenated products can be fully controlled. The catalysts show high versatility, tolerating various halogen sources, directing groups, and different reaction conditions. In most cases, the Fe MOF and Cr MOF give similar results and show similar catalytic activity, which demonstrates that robust heterogeneous procedures can also be developed using less harmful materials. The MOFs can also be recycled, maintaining their activity for several runs.

Experimental Section

Procedure for the monohalogenation experiments

Typically, in a 10 mL vial the starting material (0.1 mmol), NXS (2.3 equiv; X = I, 52 mg; X = Br, 41 mg or X = Cl, 31 mg) and Pd@MOF (4 mol % Pd) (5.0 mg of 8.40 wt %-Pd@MIL-101-NH_2(Cr) or 3.7 mg of 11.46 wt %-Pd@MIL-88B-NH_2(Fe)) were added together with a magnetic stirring bar. AcOH (3 mL glacial) was added, and the vial was sealed with a lid and stirred vigorously at 50 °C. The progress of the reaction was monitored until completion by regular sampling followed by GC or ^{1}H NMR analysis.

Procedure for the dihalogenation experiments

Typically, in a 10 mL vial the starting material (0.1 mmol), NXS (3.0 equiv; X = I, 68 mg; X = Br, 54 mg or X = Cl, 40 mg), PTSA monohydrate (0.5 equiv, 9.5 mg) and 4 mol % Pd cat. (5.0 mg 8.40 wt % Pd@MIL-101-NH_2(Cr) or 3.7 mg 11.46 wt % Pd@MIL-88B-NH_2(Fe)) were added together with a magnetic stirring bar. THF or DCE (3 mL) was added, and the vial was sealed with a lid and stirred vigorously at 80 °C. The progress of the reaction was monitored until completion by regular sampling followed by GC or ^{1}H NMR analysis.

For isolation or recycling purposes, the reactions were scaled up to 0.4 mmol of starting material. The crude reaction mixture was extracted in an appropriate organic solvent (EtOAc or $CHCl_3$ depending on the solubility of the product) and washed with brine. The organic phase was separated, dried over $MgSO_4$, and the volatiles were evaporated under reduced pressure. The solid residue was purified by column chromatography. Mixtures of petroleum ether/EtOAc were used as the standard mobile phase but in cases of insufficient solubility, $CHCl_3$ was added as a coeluent.

Acknowledgements

This project was supported by the Swedish Governmental Agency for Innovation Systems (VINNOVA) and AstraZeneca through the Berzelii Center EXSELENT, by the Swedish Research Council (VR), the MATsynCELL project through the Röntgen Ångström Cluster and by the Knut and Alice Wallenberg Foundation (Catalysis in Selective Organic Synthesis and 3DEMNATUR). B.M.-M. was supported by VINNOVA through a VINNMER grant and M.V.S. was supported by the Carl Trygger foundation through a postdoctoral grant. The authors thank Dr. H. Zheng at Stockholm University, Stockholm, Sweden for TEM analyses and Dr. T. Radu at the National R&D Institute for Isotopic and Molecular Technologies, Cluj-Napoca, Romania, for XPS analyses.

Keywords: C–H activation · halogenation · heterogeneous catalysis · metal–organic frameworks · nanocatalysts

[1] a) D. Kalyani, N. R. Deprez, L. V. Desai, M. S. Sanford, *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331; b) Z. Shi, B. Li, X. Wan, J. Cheng, Z. Fang, B. Cao, C. Qin, Y. Wang, *Angew. Chem. Int. Ed.* **2007**, *46*, 5554–5558; *Angew. Chem.* **2007**, *119*, 5650–5654; c) B. Liu, Y. Huang, J. Lan, F. Song, J. You, *Chem. Sci.* **2013**, *4*, 2163–2167; d) L. G. Mercier, M. Leclerc, *Acc. Chem. Res.* **2013**, *46*, 1597–1605; e) A. McNally, B. Haffemayer, B. S. L. Collins, M. J. Gaunt, *Nature* **2014**, *510*, 129–133; f) K. D. Collins, R. Honeker, S. Vásquez-Céspedes, D.-T. D. Tang, F. Glorius, *Chem. Sci.* **2015**, *6*, 1816–1824.

[2] a) M. Schnurch, N. Dastbaravardeh, M. Ghobrial, B. Mrozek, M. D. Mihovilovic, *Curr. Org. Chem.* **2011**, *15*, 2694–2730; b) P. Novák, A. Correa, J. Gallardo-Donaire, R. Martin, *Angew. Chem. Int. Ed.* **2011**, *50*, 12236–12239; *Angew. Chem.* **2011**, *123*, 12444–12447; c) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 10236–10254; *Angew. Chem.* **2012**, *124*, 10382–10401.

[3] J. Wencel-Delord, F. Glorius, *Nat. Chem.* **2013**, *5*, 369–375.

[4] a) S. E. Bromberg, H. Yang, M. C. Asplund, T. Lian, B. K. McNamara, K. T. Kotz, J. S. Yeston, M. Wilkens, H. Frei, R. G. Bergman, C. B. Harris, *Science* **1997**, *278*, 260–263; b) C. Cheng, J. F. Hartwig, *Science* **2014**, *343*, 853–857; c) B. Su, Z.-C. Cao, Z.-J. Shi, *Acc. Chem. Res.* **2015**, ##DOI: 10.1021/ar500345f; d) L. Maidich, G. Dettori, S. Stoccoro, M. A. Cinellu, J. P. Rourke, A. Zucca, *Organometallics* **2015**, *34*, 817–828.

[5] For a Minireview on initial achievements in C–H activation/arylation catalyzed by supported Pd, see: a) L. Djakovitch, F.-X. Felpin, *ChemCatChem* **2014**, *6*, 2175–2187; then see: b) D.-T. D. Tang, K. D. Collins, F. Glorius, *J. Am. Chem. Soc.* **2013**, *135*, 7450–7453; c) D.-T. D. Tang, K. D. Collins, J. B. Ernst, F. Glorius, *Angew. Chem. Int. Ed.* **2014**, *53*, 1809–1813; *Angew. Chem.* **2014**, *126*, 1840–1844; d) S. Vásquez-Céspedes, A. Ferry, L. Candish, F. Glorius, *Angew. Chem. Int. Ed.* **2015**, *54*, 5772–5776; *Angew. Chem.* **2015**, *127*, 5864–5868.

[6] P. Jeschke, *Pest. Manag. S.* **2010**, *66*, 10–27.

[7] a) K. Mueller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881–1886; b) M. Z. Hernandes, S. M. T. Cavalcanti, D. R. M. Moreira, W. Filgueira de Azevedo Jr. , A. C. L. Leite, *Curr. Drug Targets* **2010**, *11*, 303–314; c) Z.-J. Xu, Z. Liu, T. Chen, T.-T. Chen, Z. Wang, G.-H. Tian, J. Shi, X.-L. Wang, Y.-X. Lu, X.-H. Yan, *J. Med. Chem.* **2011**, *54*, 5607–5611.

[8] P. Metrangolo, F. Meyer, T. Pilati, G. Resnati, G. Terraneo, *Angew. Chem. Int. Ed.* **2008**, *47*, 6114–6127; *Angew. Chem.* **2008**, *120*, 6206–6220.

[9] a) N. Schröder, J. Wencel-Delord, F. Glorius, *J. Am. Chem. Soc.* **2012**, *134*, 8298–8301; b) N. Kuhl, N. Schröder, F. Glorius, *Org. Lett.* **2013**, *15*, 3860–3863; c) L. Wang, L. Ackermann, *Chem. Commun.* **2014**, *50*, 1083–1085; d) N. Schröder, F. Lied, F. Glorius, *J. Am. Chem. Soc.* **2015**, *137*, 1448–1451.

[10] For comprehensive reviews of reports of MOF-supported nanoparticles in catalysis, see: a) A. Dhakshinamoorthy, H. Garcia, *Chem. Soc. Rev.* **2012**, *41*, 5262–5284; b) A. Aijaz, Q. Xu, *J. Phys. Chem. Lett.* **2014**, *5*, 1400–1411; for more recent examples of MOF-supported nanoparticles, see: c) H. Liu, Y. Li, H. Jiang, C. Vargas, R. Luque, *Chem. Commun.* **2012**, *48*, 8431–8433; d) T. T. Dang, Y. Zhu, J. S. Y. Ngiam, S. C. Ghosh, A. Chen, A. M. Seayad, *ACS Catal.* **2013**, *3*, 1406–1410; e) Y.-Z. Chen, Y.-X. Zhou, H. Wang, J. Lu, T. Uchida, Q. Xu, S.-H. Yu, H.-L. Jiang, *ACS Catal.* **2015**, *5*, 2062–2069; f) B. Gole, U. Sanyal, P. S. Mukherjee, *Chem. Commun.* **2015**, *51*, 4872–4875; g) T. Wen, D.-X. Zhang, J. Liu, H.-X. Zhang, J. Zhang, *Chem. Commun.* **2015**, *51*, 1353–1355; h) H. Liu, L. Chang, L. Chen, Y. Li, *J. Mater. Chem. A* **2015**, *3*, 8028–8033; i) V. Pascanu, Q. Yao, A. Bermejo Gómez, M. Gustafsson, Y. Yun, W. Wan, L. Samain, X. Zou, B. Martín-Matute, *Chem. Eur. J.* **2013**, *19*, 17483–17493; j) V. Pascanu, P. Hansen, A. Bermejo Gómez, C. Ayats, A. E. Platero-Prats, M. J. Johansson, M. À. Pericàs, B. Martín-Matute, *ChemSusChem* **2015**, *8*, 123–130; k) V. Pascanu, A. Bermejo Gómez, C. Ayats, A. E. Platero-Prats, F. Carson, J. Su, Q. Yao, M. À. Pericàs, X. Zou, B. Martín-Matute, *ACS Catal.* **2015**, *5*, 472–479; l) F. Carson, V. Pascanu, A. Bermejo Gómez, Y. Zhang, A. E. Platero-Prats, X. Zou, B. Martín-Matute, *Chem. Eur. J.* **2015**, *21*, 10896–10902.

[11] a) J. Zhang, C. Feng, Y. Deng, L. Liu, Y. Wu, B. Shen, C. Zhong, W. Hu, *Chem. Mater.* **2014**, *26*, 1213–1218; b) G. Collins, M. Schmidt, C. O'Dwyer, J. D. Holmes, G. P. McGlacken, *Angew. Chem. Int. Ed.* **2014**, *53*, 4142–4145; *Angew. Chem.* **2014**, *126*, 4226–4229.

[12] a) Z. Guo, C. Xiao, R. V. Maligal-Ganesh, L. Zhou, T. W. Goh, X. Li, D. Tesfagaber, A. Thiel, W. Huang, *ACS Catal.* **2014**, *4*, 1340–1348; b) X. Li, Z. Guo, C. Xiao, T. W. Goh, D. Tesfagaber, W. Huang, *ACS Catal.* **2014**, *4*, 3490–3497; c) K. Na, K. M. Choi, O. M. Yaghi, G. A. Somorjai, *Nano Lett.* **2014**, *14*, 5979–5983; d) A. Aijaz, Q.-L. Zhu, N. Tsumori, T. Akita, Q. Xu, *Chem. Commun.* **2015**, *51*, 2577–2580; e) J. Huo, J. Aguilera-Sigalat, El-S. Hankari, D. Bradshaw, *Chem. Sci.* **2015**, *6*, 1938–1943.

[13] N. Chang, X.-P. Yan, *J. Chromatogr. A* **2012**, *1257*, 116–124.

[14] H. Fei, S. Cohen, *J. Am. Chem. Soc.* **2015**, *137*, 2191–2194.

[15] a) Z.-J. Du, L.-X. Gao, Y.-J. Lin, F.-S. Han, *ChemCatChem* **2014**, *6*, 123–126; b) P. Zhang, L. Hong, G. Li, R. Wang, *Adv. Synth. Catal.* **2015**, *357*, 345–349.

[16] a) D. Kalyani, A. R. Dick, W. Q. Anani, M. S. Sanford, *Tetrahedron* **2006**, *62*, 11483–11498; b) F. Kakiuchi, T. Kochi, H. Mutsutani, N. Kobayashi, S. Urano, M. Sato, S. Nishiyama, T. Tanabe, *J. Am. Chem. Soc.* **2009**, *131*, 11310–11311; c) R. B. Bedford, M. F. Haddow, C. J. Mitchell, R. L. Webster, *Angew. Chem. Int. Ed.* **2011**, *50*, 5524–5527; *Angew. Chem.* **2011**, *123*, 5638–5641.

[17] S. Korwar, K. Brinkley, A. R. Siamaki, B. F. Gupton, K. C. Ellis, *Org. Lett.* **2015**, *17*, 1782–1785.

[18] P. Horcajada, F. Salles, S. Wuttke, T. Devic, D. Heurtaux, G. Maurin, A. Vimont, M. Daturi, O. David, E. Magnier, N. Stock, Y. Filinchuk, D. Popov, C. Riekel, G. Férey, C. Serre, *J. Am. Chem. Soc.* **2011**, *133*, 17839–17847.

[19] J. J. Topczewski, M. S. Sanford, *Chem. Sci.* **2015**, *6*, 70–76.

[20] R. A. Rodriguez, C.-M. Pan, Y. Yabe, Y. Kawamata, M. D. Eastgate, P. S. Baran, *J. Am. Chem. Soc.* **2014**, *136*, 6908–6911.

[21] P. R. Sultane, T. B. Mete, R. G. Bhat, *Org. Biomol. Chem.* **2014**, *12*, 261–264.

[22] a) T. Devic, C. Serre, *Chem. Soc. Rev.* **2014**, *43*, 6097–6115; b) M. Bosch, M. Zhang, H.-C. Zhou, *Adv. Chem.* **2014**, ID. 182327, DOI: 10.1155/2014/182327.

Received: July 24, 2015