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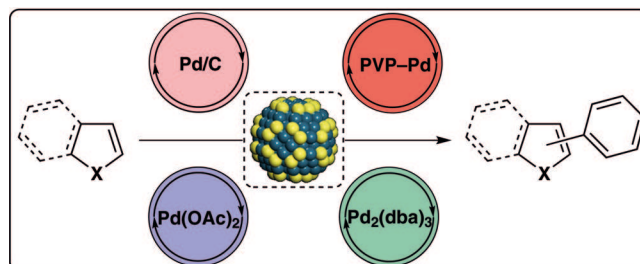
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Catalyst Efficacy of Homogeneous and Heterogeneous Palladium Catalysts in the Direct Arylation of Common Heterocycles

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Abstract The direct arylation of several common heterocycles, using homogeneous and heterogeneous palladium (pre)catalysts, has been examined by initial rate analysis. The study reveals that apparently distinct palladium catalysts can display similar activities in such transformations, implying formation of a comparable active palladium catalyst phase. A substrate dependence was noted for the palladium catalysts examined.

Key words catalysis, palladium, homogeneous, heterogeneous, arylation, heterocycles

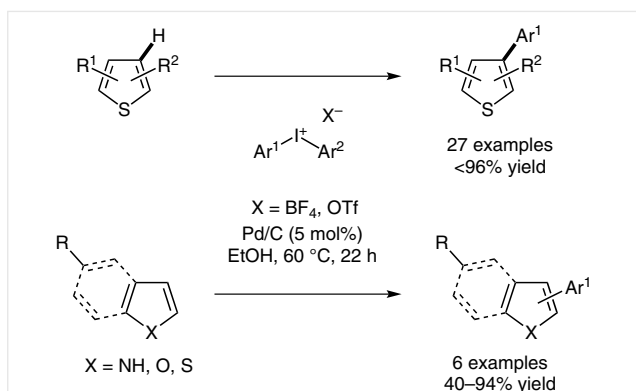
The importance of palladium-mediated cross-coupling reactions in organic synthesis is without question, as the ability to selectively form C–C bonds in the presence of other molecular functionality is unparalleled in its utility.² While highly useful from a synthetic viewpoint, a significant drawback to traditional cross-coupling reactions is the requirement for substrate pre-functionalisation with activating groups such as organoboronic acids or organostannanes, among others. Recent advances in direct C–H bond functionalisation chemistry have addressed this issue, as many mild and selective methods can now be used to cleave and generate C–H bonds directly without pre-functionalisation, significantly expanding the toolkit of the synthetic chemist.³

One issue that remains is the elemental sustainability of rare and precious metals, which increasingly leads to prohibitive costs and issues surrounding the criticality of supply chains.⁴ One approach to obviate this concern is to determine whether current palladium catalysts can be used more effectively, by recycling the precious metal from each reaction and preventing it from entering waste streams.⁵ Central to this approach is the understanding that many

ubiquitous palladium (pre)catalysts often display heterogeneous-type catalytic behaviour, typically through speciation to form higher-order palladium colloids or nanoparticles (PdNPs) under commonly found experimental conditions. This is evident in traditional palladium-mediated cross-couplings⁶ and more recently in C–H bond functionalisation reactions.⁷

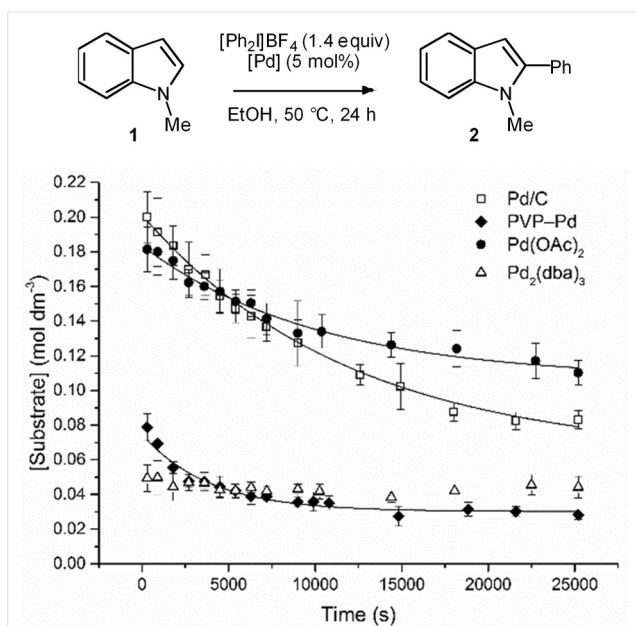
Glorius and co-workers reported the regioselective direct arylation of 2-*n*-butylthiophene and other simple heterocycles, using the heterogeneous catalyst Pd/C (Scheme 1).⁸ It was noted that Pd/C, obtained from different commercial sources, demonstrated profoundly different activities. Several established tests for heterogeneous catalysis were performed and revealed no evidence for active homogeneous palladium species, although poor catalyst recyclability was observed suggesting palladium leaching, or palladium catalyst restructuring, could have occurred under the oxidising conditions. Our group has previously investigated the nature of the active catalyst in similar direct arylation reactions, where the activity of pre-formed ‘stabilised’ PdNP catalysts can be compared to that of PdNPs formed in situ from nominally homogeneous precursors such as Pd(OAc)₂.⁹ With these observations in mind, we proposed that kinetic examination, using ex situ GC analysis, would provide valuable insight into the behaviour of these and similar reactions.¹⁰

To begin our studies, we identified four palladium catalyst sources which provide a useful test of two ubiquitous precatalysts, a supported catalyst and well-defined palladium nanoparticulate catalyst, namely: Pd₃(OAc)₆ hereafter Pd(OAc)₂ (>99% purity), Pd₂(dba)₃·CHCl₃ [dba = (*E,E*)-dibenzylideneacetone], hereafter Pd₂(dba)₃ (91% purity, based on Ananikov’s method),¹¹ Pd/C (5 wt%, Sigma Aldrich, catalogue number 205680, lot number 06230AJ-298) and PVP–Pd (PVP = polyvinylpyrrolidinone). The latter catalyst, PVP–Pd, is an established polymer-supported PdNP catalyst, the



Scheme 1 Direct arylation using Pd/C of thiophenes and related heterocycles⁸

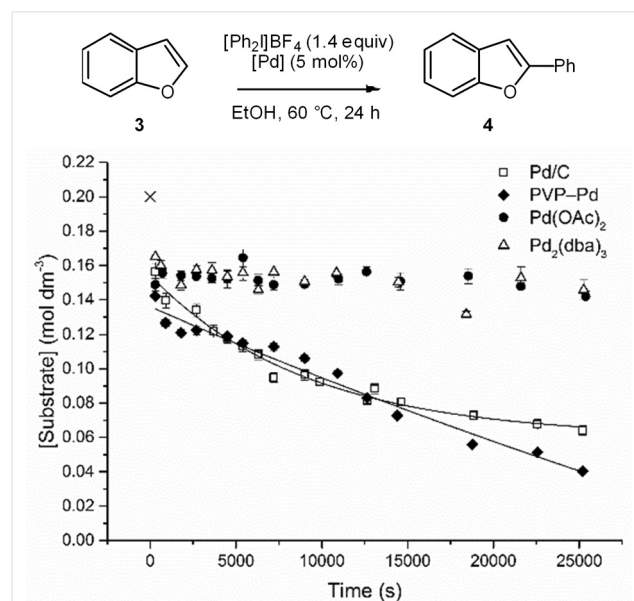
synthesis of which provides well-controlled, regular nanoparticles typically between 2–4 nm in diameter (see Supporting Information).¹² These four catalysts were initially applied to the direct arylation of *N*-methylindole (**1**) under the conditions shown in Scheme 1.¹³ Substrate **1** demonstrated high reactivity under these conditions, with all four palladium catalysts rapidly producing the C-2 arylated product **2**.¹⁴ The reaction temperature was lowered to 50 °C to provide improved discrimination between the activity of these catalysts, and reactions followed ex situ by GC analysis (Scheme 2). During this process a novel method of sample quenching by centrifugation with Celite™ was developed to give reliable data (see Supporting Information for details).



Scheme 2 Direct arylation of *N*-methylindole at 50 °C over 24 h. Data is fitted to a first-order exponential decay equation. Detailed analysis over the initial 7 h shown, final conversions by GC after 24 h; Pd/C: 83%, PVP-Pd: 100%, Pd(OAc)₂: 66%, Pd₂(dba)₃: 88%.

Under the conditions shown in Scheme 2, Pd₂(dba)₃ and PVP-Pd proved the most active catalysts, with rapid conversion of substrate **1** within the first five minutes of substrate turnover (the first recorded data point). This implies a similarity between the active catalytic species in these reactions, despite the apparently highly dissimilar starting catalysts. Pd/C and Pd(OAc)₂ exhibited markedly different reactivity, although these two catalysts were broadly similar in their activity. These results suggest that if PdNPs are catalysing this reaction, the nanoparticles produced from Pd(OAc)₂ and Pd/C are similar, yet distinct from the nanoparticles produced by Pd₂(dba)₃ and PVP-Pd. It is also interesting to note that of the catalysts tested, only PVP-Pd led to complete consumption of substrate **1** after 24 hours. Despite its relatively slow initial rate, Pd/C eventually provides conversion that parallels Pd₂(dba)₃, which is more active in the early stages of the reaction. However, Pd(OAc)₂ does not achieve these levels of conversion; the activity of this catalyst eventually drops off, despite matching the initial turnover rates of Pd/C. This type of behaviour can be rationalised if the deactivating agglomeration of PdNPs is more facile in the absence of a supporting matrix such as activated carbon, even if the PdNPs originally formed from Pd(OAc)₂ and Pd/C are similar. Conversely, little difference is seen in the reaction profiles when using either Pd₂(dba)₃ or PVP-Pd as the catalyst.

The four palladium catalysts shown above were examined further in the reaction of benzofuran (**3**) at 60 °C; kinetic profiles are shown in Scheme 3. Overall, substrate **3**



Scheme 3 Direct arylation of benzofuran at 60 °C over 24 h. Data is fitted to a first-order exponential decay equation for Pd/C and PVP-Pd. Detailed analysis over the initial 7 h shown, final conversions by GC after 24 h; Pd/C: 88%, PVP-Pd: 91%, Pd(OAc)₂: 31%, Pd₂(dba)₃: 31%. X = starting concentration of substrate at t = 0.

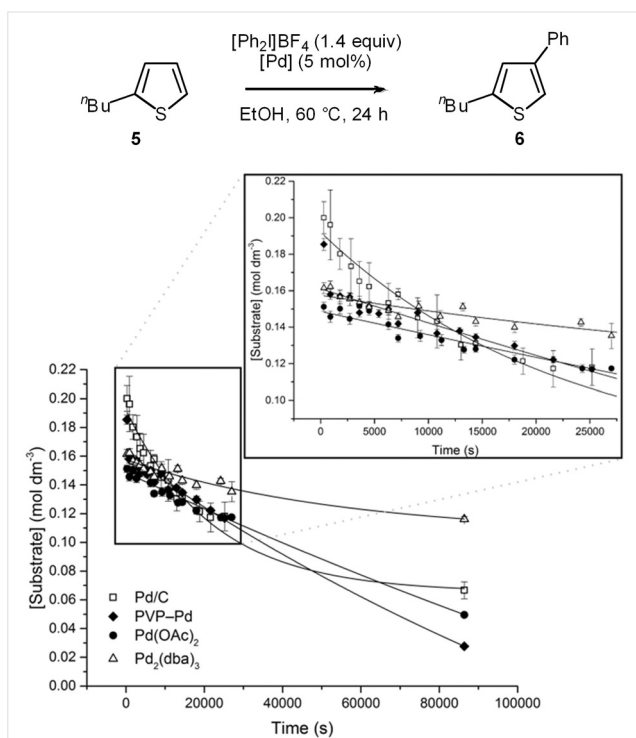
demonstrated lower activity towards arylation than *N*-methylindole (**1**). PVP-Pd proved to be the most active catalyst, providing ca. 29% conversion to the C-2 arylated product **4** within five minutes, and >90% after 24 hours.¹⁵ Interestingly, Pd/C performed similarly to PVP-Pd, in stark contrast to its poor initial activity when using *N*-methylindole **1** as a substrate. Pd(OAc)₂ and Pd₂(dba)₃ displayed poor catalyst activity for this arylation. Comparing arylations **1** → **2** and **3** → **4** we can see that there is a substrate dependence on the catalytic activity for this transformation; whether this is due to variation in PdNP formation or behaviour, or rather a difference in palladium leaching rates/catalyst restructuring, is unclear at this stage.

2-*n*-Butylthiophene (**5**), the key substrate in the previous study reported by Glorius and co-workers,⁸ was also examined under these conditions (Scheme 4). 2-*n*-Butylthiophene (**5**) demonstrated catalyst activity lower than that of either *N*-methylindole (**1**) or benzofuran (**3**), as expected, but did reach 86% conversion to the C-3 arylated product **6** after 24 hours, using PVP-Pd as a catalyst (which was again the most reactive catalysts of those tested).^{15,16} Little difference between palladium catalysts was observed during early substrate turnover, which had earlier provided a discrimination between catalysts *vide supra*. However, the final

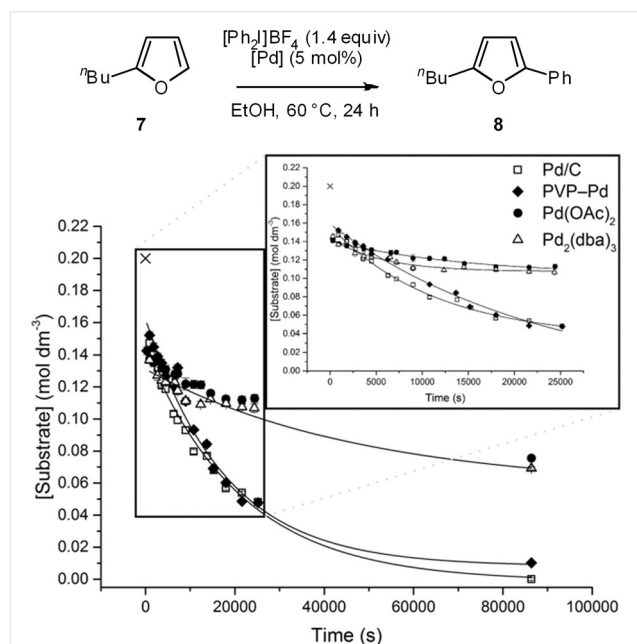
conversion varied significantly, that is, between worst-performing catalyst, Pd₂(dba)₃ (42%), and best-performing catalyst, PVP-Pd (86%).

The substrates tested thus far were all reported by Glorius and co-workers to be active under their conditions, when using Pd/C as the catalyst.⁸ We hypothesised that 2-*n*-butylfuran (**7**) should also prove effective in this protocol, but the original publication states that reaction of this substrate with [Ph₂I]BF₄ using Pd/C leads to degradation of the starting materials. Conversion to the desired arylated product is feasible using a strongly electron-deficient diaryliodonium salt.⁸

We pursued further studies with substrate **7** (Scheme 5). Reaction of **7** under the standard arylation conditions¹³ using the four palladium catalysts led to substrate turnover of **7**. Reactivity not dissimilar to that of benzofuran (**3**) was realised, with PVP-Pd and Pd/C proving the most effective catalysts; complete conversion was recorded after 24 hours at 60 °C. Pd(OAc)₂ and Pd₂(dba)₃ were less effective, with ca. 60–65% conversion after 24 hours.



Scheme 4 Direct arylation of 2-*n*-butylthiophene at 60 °C over 24 h. Data is fitted to a first-order exponential decay equation. Final conversions by GC after 24 h; Pd/C: 66%, PVP-Pd: 86%, Pd(OAc)₂: 75%, Pd₂(dba)₃: 42%.

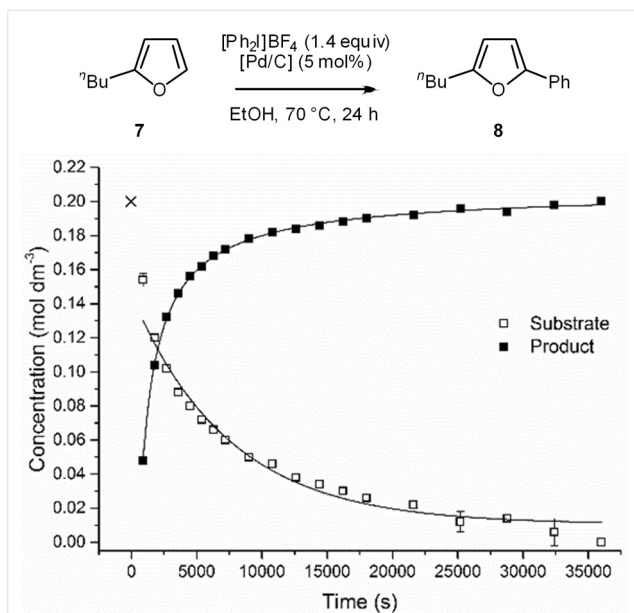


Scheme 5 Direct arylation of 2-*n*-butylfuran at 60 °C over 24 h. Data is fitted to a first-order exponential decay equation [with the exception of Pd(OAc)₂ which showed more complex behaviour under the reaction conditions]. Final conversions by GC after 24 h; Pd/C: 100%, PVP-Pd: 95%, Pd(OAc)₂: 62%, Pd₂(dba)₃: 65%. X = starting concentration of substrate at *t* = 0.

The activity of these four palladium catalysts is similar over the first hour of the reaction, but a distinction between the palladium catalysts tested is apparent after this time point.

In order to gain a detailed picture of the reactivity of **7** under conditions catalysed by Pd/C, the reaction was repeated at a higher temperature (70 °C) and samples taken at

regular intervals until reaction completion after ca. ten hours. Loss of substrate **7** was concomitant with formation of the C-2 arylated product **8**, with no observable side products (Scheme 6).¹⁷



Scheme 6 Direct arylation of 2-*n*-butylfuran at 70 °C over 10 h. Data is fitted to a first-order exponential decay (substrate) or logarithmic growth (product) equation. X = starting concentration of substrate at $t = 0$.

It is not obvious why substrate **7** provides excellent reactivity in our hands. It may be that the different sources of Pd/C used provide unique forms of catalytically active palladium. Alternatively, an impurity such as those reported for other commercially available palladium catalysts may be present,¹⁸ which manifests itself when using this substrate. It was noted during our investigations that purification of the arylated product **8** from the Pd/C-catalysed reactions was challenging. Attempted purification of several reactions catalysed by Pd/C afforded inseparable mixtures of the desired product **8** and biphenyl, confirmed by TLC, GC–

MS (EI), and ¹H NMR spectroscopic analysis. Iodobenzene is also present as a major byproduct of [Ph₂I]BF₄ (bp 188 °C), which complicates the matter due to the relatively low boiling point of **8** (95 °C).¹⁹ Purification of **8** by silica gel column chromatography of a separate reaction, catalysed by PVP–Pd, enabled its isolation in pure form in 45% yield, confirmed as the C2-arylated regioisomer **8** by ¹H NMR analysis.¹⁷ Degradation of Ar^{III}X₂ species to give ArI in similar reactions has been reported previously.²⁰

The detailed analysis of the initial stages of reaction using these substrates allowed fitting of first-order exponential decay equations, as shown in the appropriate Schemes 2–6. Good fits were obtained in the majority of cases; where line fitting could not be performed this is suspected to be the result of rapid initial reactivity followed by loss of catalytic activity, for example, the reaction of benzofuran with Pd(OAc)₂ as catalyst. These analyses allowed calculation of the initial rate of reaction (k_{obs}) for the majority of substrate and catalyst combinations; these are shown in Table 1. Errors in these values are calculated from the standard deviation of a linear regression of the initial reaction rates, (least-squares method). These rate constants are broadly similar to one another, lying between ca. $1 \cdot 10^{-6}$ and $1 \cdot 10^{-5} \text{ s}^{-1}$ for all the catalyst/substrate combinations tested. By comparison, a pseudo-first-order rate constant of $3.5(2) \cdot 10^{-4} \text{ s}^{-1} \text{ M}^{-1}$ for the arylation of 2-methylthiophene has been reported, measured directly with [PdAr(μ -OAc)(PPh₃)₂] in 1,4-dioxane at 90 °C.²¹

In conclusion, the effects of four nominally distinct palladium catalysts in direct arylation reactions, mediated by homogeneous and heterogeneous palladium, have been examined.⁸ Initial-rate kinetic analysis showed similarities in catalytic behaviour between apparently distinct palladium catalysts, implying that dissimilar catalyst structures can function as precatalysts for the formation of a comparable active catalyst phase; speciation to form PdNPs or clusters is proposed as one possible mechanism for this process, under the reaction conditions tested. It may be that PdNPs are not actively catalysing these reactions (i.e., acting as a palladium reservoir),²² the active species instead consisting of

Table 1 Observed Pseudo-First-Order Rate Constants (k_{obs}) for Direct Arylation Reactions Mediated by Pd/C, PVP–Pd, Pd(OAc)₂, and Pd₂(dba)₃^a

	Pd/C	PVP–Pd	Pd(OAc) ₂	Pd ₂ (dba) ₃
<i>N</i> -methylindole (1)	$(9.2 \pm 0.5) \cdot 10^{-6}$	$(1.3 \pm 0.1) \cdot 10^{-5}$	$(9.7 \pm 0.4) \cdot 10^{-6}$	–
benzofuran (3)	$(6.3 \pm 0.8) \cdot 10^{-6}$	$(2.1 \pm 0.5) \cdot 10^{-6}$	–	–
2- <i>n</i> -butylthiophene (5)	$(6.1 \pm 0.6) \cdot 10^{-6}$	$(1.6 \pm 0.2) \cdot 10^{-6}$	$(1.9 \pm 0.3) \cdot 10^{-6}$	$(2.6 \pm 0.3) \cdot 10^{-6}$
2- <i>n</i> -butylfuran (7) (at 60 °C)	$(7.1 \pm 0.6) \cdot 10^{-6}$	$(4.8 \pm 0.5) \cdot 10^{-6}$	$(1.6 \pm 0.1) \cdot 10^{-6}$	$(3.3 \pm 0.5) \cdot 10^{-6}$
2- <i>n</i> -butylfuran (7) (at 70 °C)	$(9.3 \pm 0.9) \cdot 10^{-6}$	N/A	N/A	N/A
5-phenyl-2- <i>n</i> -butylfuran (8) (at 70 °C) ^b	$(9.4 \pm 1.6) \cdot 10^{-6}$	N/A	N/A	N/A

^a Rate constants calculated from initial rates using a fitted first-order decay, using at least five recorded data points with $\geq 90\%$ correlation. All rates are shown in s^{-1} . In many cases, rapid conversion occurs within ca. five minutes (the first recorded data point), which has not been considered in these data. Hyphens indicate those reactions which cannot be fitted to a first-order exponential decay.

^b Rate constant for product formation calculated from initial rates using a fitted first-order logarithmic growth (Scheme 6).

leached mononuclear/lower-order palladium species. If this is the case, then perhaps the parallels between catalyst types manifest as a result of similar leaching rates. Notably, following the initial stages of reactivity more pronounced differences between catalysts were seen, which is indicative of catalyst deactivation.^{10d} It is important to recognize that whether these results are due to variation in active palladium nanoparticle formation/behaviour, or a difference in palladium leaching rates, is not clear at this stage. In-depth mechanistic studies are required to address these questions.

A pronounced substrate effect has been revealed in these studies, which suggests that reaction conditions, including substrate choice, could be as important as the particular palladium (pre)catalyst used. It is commonplace to see reaction optimisation of a single benchmark reaction in palladium-catalysed direct arylation chemistry, with catalyst type and other reaction conditions varied. We suggest, based on the observations detailed herein, that it is worth also varying substrate type against several palladium catalysts, before reaching a definite conclusion about which particular palladium catalyst is best for subsequent advanced substrate-scoping studies.

2-*n*-Butylfuran (**7**), reported to be unstable under direct arylation reaction conditions using Pd/C as the catalyst,⁸ has been shown to react effectively to provide the desired direct arylation product **8** with four palladium catalysts in ~100% conversion. This example represents an illustration of the dichotomy in outcomes that can be observed when using Pd/C, which can be poorly defined. We suggest that such an issue might manifest itself on the scale-up of direct arylation processes using Pd/C. On a general note, our studies highlight the value of simple kinetic analysis of these types of direct arylation reactions, as opposed to the more common practice of evaluating catalyst performance as a function of yield.²³

Acknowledgment

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Supporting Information

Supporting information for this article is available online at <http://dx.doi.org/10.1055/s-0035-1561436>.

References and Notes

- (1) Leibniz Institute for Catalysis, Albert-Einstein-Str. 29a, 18059 Rostock, Germany. Email: lydia.neumann@catalysis.de
- (2) (a) Nicolaou, K. C.; Bulger, P. J.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 4442. (b) Kambe, N.; Iwasaki, T.; Terao, J. *Chem. Soc. Rev.* **2011**, *40*, 4937.
- (3) (a) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792. (b) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960.
- (4) Hunt, A. J.; Farmer, T. J.; Clark, J. H. In *Element Recovery and Sustainability*; Vol. 1; Hunt, A. J., Ed.; RSC Publishing: Cambridge, **2013**, 1.
- (5) Blaser, H.-U.; Indolese, A.; Schnyder, A.; Steiner, H.; Studer, M. *J. Mol. Catal. A: Chem.* **2001**, *173*, 3.
- (6) (a) Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133. (b) Molnár, Á. *Chem. Rev.* **2011**, *111*, 2251. (c) Balanta, A.; Godard, C.; Claver, C. *Chem. Soc. Rev.* **2011**, *40*, 4973.
- (7) (a) Djakovitch, L.; Felpin, F.-X. *ChemCatChem* **2014**, *6*, 2175. (b) Cano, R.; Schmidt, A. F.; McGlacken, G. P. *Chem. Sci.* **2015**, *6*, 5338.
- (8) Tang, D.-T. D.; Collins, K. D.; Ernst, J. B.; Glorius, F. *Angew. Chem. Int. Ed.* **2014**, *53*, 1809.
- (9) (a) Baumann, C. G.; De Ornellas, S.; Reeds, J. P.; Storr, T. E.; Williams, T. J.; Fairlamb, I. J. S. *Tetrahedron* **2014**, *70*, 6174. (b) Reay, A. J.; Fairlamb, I. J. S. *Chem. Commun.* **2015**, *51*, 16289.
- (10) (a) Widegren, J. A.; Bennett, M. A.; Finke, R. G. *J. Am. Chem. Soc.* **2003**, *125*, 10301. (b) Widegren, J. A.; Finke, R. G. *J. Mol. Catal. A: Chem.* **2003**, *198*, 317. (c) Crabtree, R. H. *Chem. Rev.* **2012**, *112*, 1536. (d) Crabtree, R. H. *Chem. Rev.* **2015**, *115*, 127. (e) Mower, M. P.; Blackmond, D. G. *J. Am. Chem. Soc.* **2015**, *137*, 2386.
- (11) (a) Zaleskiy, S. S.; Ananikov, V. P. *Organometallics* **2012**, *31*, 2302. (b) Kapdi, A. R.; Whitwood, A. C.; Williamson, D. C.; Lynam, J. M.; Burns, M. J.; Williams, T. J.; Reay, A. J.; Holmes, J.; Fairlamb, I. J. S. *J. Am. Chem. Soc.* **2013**, *135*, 8388.
- (12) (a) Ellis, P. J.; Fairlamb, I. J. S.; Hackett, S. F. J.; Wilson, K.; Lee, A. F. *Angew. Chem. Int. Ed.* **2010**, *49*, 1820. (b) Lee, A. F.; Ellis, P. J.; Fairlamb, I. J. S.; Wilson, K. *Dalton Trans.* **2010**, *39*, 10473. Other supported PdNPs are available for direct arylation, e.g. Pd@PPy, which are highly active and appear to operate as molecular/colloidal Pd species at higher reactions temperatures (150 °C), see: (c) Zinovyeva, V. A.; Vorotyntsev, M. A.; Bezverkhyy, I.; Chaumont, D.; Hierso, J.-C. *Adv. Funct. Mater.* **2011**, *21*, 1064. ; also see ref. 9a High turnover numbers can be achieved in direct arylations using Pd(OAc)₂ at higher reaction temperatures, see: (d) Požgan, F.; Roger, J.; Doucet, H. *ChemSusChem* **2008**, *1*, 404.
- (13) **General Conditions for Direct Arylation Reactions**
To a microwave vial fitted with magnetic stirrer bar was added [Ph₂]BF₄ (309 mg, 0.84 mmol, 1.4 equiv), Pd catalyst (5 mol%), and EtOH (3 mL). To initiate the reaction, substrate (0.6 mmol, 1 equiv) was added, the vial sealed with a septum, and the reaction stirred at the given temperature for 24 h in a pre-heated solid heating block. Under these conditions the isolated product yields were: **2** [32 mg, 51%, using Pd(OAc)₂], **4** [18 mg, 31%, using Pd(OAc)₂], **6** (45 mg, 69%, using PVP-Pd), and **8** (27 mg, 45%, using PVP-Pd) (nonoptimized).
- (14) **1-Methyl-2-phenylindole (2)**
¹H NMR (400 MHz, CDCl₃): δ = 7.64 (d, *J* = 8.0 Hz, 1 H), 7.56–7.46 (m, 4 H), 7.45–7.36 (m, 2 H), 7.28–7.23 (m, 1 H), 7.18–7.12 (m, 1 H), 6.57 (s, 1 H), 3.76 (s, 1 H). ¹³C NMR (101 MHz, CDCl₃): δ = 141.7, 138.5, 133.0, 129.5, 128.6, 128.1, 128.0, 121.8, 120.6, 120.0, 109.7, 101.8, 31.3.

(15) **2-Phenylbenzofuran (4)**

^1H NMR (400 MHz, CDCl_3): δ = 7.92–7.87 (m, 2 H), 7.63–7.59 (m, 1 H), 7.57–7.53 (m, 1 H), 7.50–7.44 (m, 2 H), 7.40–7.35 (m, 1 H), 7.31 (ddd, J = 8.0, 7.0, 1.5 Hz, 1 H), 7.26 (ddd, J = 8.0, 7.0, 1.5 Hz, 1 H), 7.05 (d, J = 1.0 Hz, 1 H). ^{13}C NMR (101 MHz, CDCl_3): δ = 156.0, 155.0, 130.6, 129.3, 128.9, 128.7, 125.1, 124.4, 123.1, 121.0, 111.3, 101.4. GC-MS (EI): m/z (ion) = 194 [$\text{C}_{14}\text{H}_{10}\text{O}$] $^+$; HRMS (EI): m/z calcd for $\text{C}_{14}\text{H}_{10}\text{O}$: 194.0732; found: 194.0720 [$\text{C}_{14}\text{H}_{10}\text{O}$] $^+$.

(16) **4-*n*-Butyl-2-phenylthiophene (6)**

^1H NMR (400 MHz, CDCl_3): δ = 7.61–7.56 (m, 2 H), 7.42–7.36 (m, 2 H), 7.31–7.25 (m, 1 H), 7.24 (d, J = 1.5 Hz, 1 H), 7.09 (dt, J = 1.5, 1.0 Hz, 1 H), 2.87 (t, J = 7.5 Hz, 2 H), 1.77–1.67 (m, 2 H), 1.50–1.38 (m, 2 H), 0.97 (t, J = 7.5 Hz, 3 H). ^{13}C NMR (101 MHz, CDCl_3): δ = 146.8, 141.9, 136.4, 128.8, 127.0, 126.4, 123.5, 117.9, 33.9, 30.0, 22.4, 14.0. ESI-MS: m/z (ion) = 217 [$\text{C}_{14}\text{H}_{17}\text{S}$] $^+$; ESI-HRMS m/z calcd for $\text{C}_{14}\text{H}_{17}\text{S}$: 217.1045; found: 217.1024 [$\text{C}_{14}\text{H}_{17}\text{S}$] $^+$.

(17) **5-*n*-Butyl-2-phenylfuran (8)**

^1H NMR (400 MHz, CDCl_3): δ = 7.68–7.63 (m, 2 H), 7.40–7.34 (m, 2 H), 7.23 (tt, J = 7.5, 1.0 Hz, 1 H), 6.56 (d, J = 3.0 Hz, 1 H), 6.08 (dt, J = 3.0, 1.0 Hz, 1 H), 2.70 (app t, J = 7.5 Hz, 2 H), 1.70 (tt, J = 7.5, 6.5 Hz, 2 H), 1.44 (app sext, J = 7.5 Hz, 2 H), 0.97 (t, J = 7.5 Hz, 3 H). ^{13}C NMR (101 MHz, CDCl_3): δ = 156.6, 152.2, 131.4, 128.7, 126.8, 123.4, 107.0, 105.8, 30.4, 28.0, 22.4, 14.0. GC-MS (EI): m/z (ion) = 200 [$\text{C}_{14}\text{H}_{16}\text{O}$] $^+$. HRMS (EI): m/z calcd for $\text{C}_{14}\text{H}_{16}\text{O}$: 200.1201; found: 200.1202 [$\text{C}_{14}\text{H}_{16}\text{O}$] $^+$.

(18) Bajwa, S. E.; Storr, T. E.; Hatcher, L. E.; Williams, T. J.; Baumann, C. G.; Whitwood, A. C.; Allan, D. R.; Teat, S. J.; Raithby, P. R.; Fairlamb, I. J. S. *Chem. Sci.* **2012**, *3*, 1656.

(19) Pridgen, L. N.; Jones, S. S. J. *Org. Chem.* **1982**, *47*, 1590.

(20) Williams, T. J.; Fairlamb, I. J. S. *Tetrahedron Lett.* **2013**, *54*, 2906.

(21) Wakioka, M.; Nakamura, Y.; Wang, Q.; Ozawa, F. *Organometallics* **2012**, *31*, 4810.

(22) Fairlamb, I. J. S.; Lee, A. F. In *C–H and C–X Bond Functionalization: Transition Metal Mediation*; Ribas, X., Ed.; RSC Publishing: Cambridge, **2013**, Chap. 3, 72.

(23) Kozuch, S.; Martin, J. M. L. *ACS Catal.* **2012**, *2*, 2787.