Reaction monitoring reveals poisoning mechanism of Pd₂(dba)₃ and guides catalyst selection

DOI:

[10.1039/C7CC08018B](https://doi.org/10.1039/C7CC08018B)

Document Version

Accepted author manuscript

[Link to publication record in Manchester Research Explorer](#)

Citation for published version (APA):

Colletto, C., Bures Amat, J., & Larrosa, I. (2017). Reaction monitoring reveals poisoning mechanism of Pd₂(dba)₃ and guides catalyst selection. *Chemical Communications*. <https://doi.org/10.1039/C7CC08018B>

Published in:

Chemical Communications

Citing this paper

Please note that where the full-text provided on Manchester Research Explorer is the Author Accepted Manuscript or Proof version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version.

General rights

Copyright and moral rights for the publications made accessible in the Research Explorer are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Takedown policy

If you believe that this document breaches copyright please refer to the University of Manchester's Takedown Procedures [<http://man.ac.uk/04Y6Bo>] or contact uml.scholarlycommunications@manchester.ac.uk providing relevant details, so we can investigate your claim.

Reaction monitoring reveals poisoning mechanism of $\text{Pd}_2(\text{dba})_3$ and guides catalyst selection

Received 00th January 20xx,
Accepted 00th January 20xx

Chiara Colletto, Jordi Burés* and Igor Larrosa*

DOI: 10.1039/x0xx00000x

www.rsc.org/

We have discovered that the dba ligand in the commonly used $\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ cross-coupling pre-catalyst is susceptible to bis-arylation when used in the presence of aryl iodides. The in situ formed dbaAr_2 ligands result in Pd-species with altered catalytic activity. In the case of study, the room temperature C3 arylation of benzo[*b*]thiophenes with aryl iodides, we have observed a marked catalyst deactivation when dba is arylated with electron-deficient aryl iodides, accounting for the poor yields obtained in the C3 arylation reactions with these aryl iodides. Based on these studies, we report a new catalytic system, employing a dba-free Pd catalyst, which allows for the first time the direct C3-arylation of benzo[*b*]thiophenes with electron-deficient aryl iodides at room temperature.

Pd-catalyzed cross-couplings are one of the most powerful tools for the formation of carbon–carbon bonds. These methodologies usually require the employment of Pd(0) catalysts and are often used in combination with ligands such as phosphines or N-heterocyclic carbenes (NHCs).¹ Among the stable and phosphine-free Pd(0) sources, $\text{Pd}_x(\text{dba})_y$ ($x = 1, 2$; $y = 2, 3$) complexes are certainly the most commonly used.² Although $\text{Pd}_x(\text{dba})_y$ are often considered simple Pd(0) sources, pioneering studies by Amatore and Jutand on the rate of the oxidative addition of $\text{Pd}_x(\text{dba})_y$ complexes with aryl iodides in the presence of phosphines (L), revealed that the coordination ability of dba cannot be overlooked.³ Indeed, whereas $\text{Pd}(\text{dba})\text{L}_2$ did not undergo oxidative addition, dba-free $\text{Pd}(0)\text{L}_2$ complexes were instead shown to react with iodoarenes. Therefore, $\text{Pd}(\text{dba})\text{L}_2$ acts as reservoir, which slowly releases the active $\text{Pd}(0)\text{L}_2$ species. In this context, Fairlamb and co-workers reported that $\text{Pd}_x(\text{dba-4,4'-Z})_y$ complexes, featuring more electron-rich ancillary dba-4,4'-Z ligands (where Z = electron-donating substituent), present an enhanced reactivity in cross-coupling reactions. This was attributed to a lowering of the π -accepting character of these dba-4,4'-Z ligands, which

resulted in a more facile formation of catalytically active dba-free Pd(0) species.⁴

On the other hand, the ancillary dba ligand has rarely been reported to itself react under the coupling conditions (Scheme 1). The group of Fairlamb, when studying Buchwald-Hartwig aryl amination reactions with $\text{Pd}_x(\text{dba-4,4'-Z})_y$ complexes, were able to isolate small amounts of mono- and bis-aminated dba-Z ligand from these reaction mixtures.^{4b,5} Contrarily to their previous reports, the electronic nature of dba-4,4'-Z of the Pd(0) source did not significantly influence the catalytic efficiency of the system as the ligand was consumed in situ forming a more electron-rich derivative, with concomitant release of $\text{Pd}(0)\text{L}_2$. Another example of functionalization of dba ligand was described by Liu and Hartwig when investigating the mechanism of α -arylation of azlactones catalyzed by $\text{Pd}(\text{dba})_2$.⁶ A stable Pd(II) complex containing a ligand formed by reaction of dba with the azlactone accounted for the inhibitory effect of dba in the system (Scheme 1b). Indeed, reactions promoted by $\text{Pd}(\text{OAc})_2$ instead of $\text{Pd}(\text{dba})_2$ were reported to take place at lower temperature with a smaller excess of azlactone.

Recently, our group developed a β -selective C–H arylation of (benzo)thiophenes with aryl iodides employing

Scheme 1 In situ dba-modification in Pd couplings

^a School of Chemistry, The University of Manchester, Oxford Road, Manchester, M13 9PL. Email: igor.larrosa@manchester.ac.uk; jordi.bures@manchester.ac.uk

[†] Electronic Supplementary Information (ESI) available: Experimental procedures, NMR. See DOI: 10.1039/x0xx00000x

$\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3$ as the catalyst, a process which occurred under remarkably mild conditions.^{7,8} Notably, the first experimental evidence supporting a Heck-type pathway for the C–H activation step in the arylation of heteroarenes was also disclosed. When investigating the scope of this methodology we realized that, while electron-rich iodoarenes reacted smoothly at room temperature, electron-deficient aryl iodides reacted sluggishly in yields of 10–42% under the standard conditions (Scheme 2).

Herein we report mechanistic investigations showing that an in situ arylation of the dba ligand in the Pd-precatalyst results in a catalytic system with altered reactivity (Scheme 1c). The reactivity of the resulting Pd-dbaAr₂ complex markedly depends on the nature of the aryl iodide employed in the reaction and is responsible for the sluggish performance of electron-deficient aryl iodides. Based on these investigations, a new catalytic system has been identified capable of arylating benzo[*b*]thiophenes with electron-deficient aryl iodides at room temperature in good to excellent yields.

We began our mechanistic investigation by examining the kinetic profile of the reaction of benzo[*b*]thiophene **1a** and 4-iodotoluene **2a**, an aryl iodide displaying high reactivity (Fig. 1).⁹ A plot comparing formation of product **3aa** vs consumption of both starting materials indicated that, while consumption of benzo[*b*]thiophene ($[\text{reacted } \mathbf{1a}] = [\mathbf{1a}]_0 - [\mathbf{1a}]$) is consistent with formation of product **3aa**, an abnormally high consumption of the aryl iodide **2a** was observed (Fig. 1a). Interestingly, a second plot showing only the aryl iodide consumed in excess to that required to form product **3aa** (*ie* $([\mathbf{2a}]_0 - [\mathbf{2a}]) - [\mathbf{3aa}]$) revealed that this additional consumption occurred exclusively during the first 1–2 h of reaction (Fig. 1b). Importantly, the aryl iodide consumed in excess totals 0.15 equiv, the exact amount that would be employed in bis-arylation all of the dba present in the reaction.¹⁰ Intrigued by this possibility, we thoroughly examined the reaction crude after 2 h of reaction. Gratifyingly, we were able to isolate bis-arylated dba **4a** as a mixture of three stereoisomers,¹¹

accounting for the observed consumption of aryl iodide **2a**. A closer look at the reaction profile shown in Fig. 1a suggests that bis-arylation of dba with 4-iodotoluene **2a** does not have any significant effect in the efficiency of the catalytic system, with product **3aa** obtained in 87% yield after 16 h.

We then moved on to study the reaction between **1a** and 1-iodo-4-nitrobenzene **2d**, an aryl iodide poorly reactive under our standard reaction conditions. Interestingly, a similar excess consumption of the aryl iodide was observed (Fig. 2a). A plot of excess aryl iodide consumed suggests that for this substrate the bis-arylation of dba also occurs quantitatively within the first 2 h of reaction (Fig. 2b). Also in this case, we were able to isolate bis-arylated dba **4d** as a mixture of three stereoisomers.¹² In contrast to the reaction with the electron-rich aryl iodide **2a**, analysis of the kinetic profile of the reaction with **2d** clearly shows a significant decrease in reactivity of the catalytic system after the first 2 h, with 24% of product **3ad** being formed in that period, compared to only an additional 14% produced between 2 and 8 h. In fact, comparison of initial rates of reaction between the systems in Fig. 1 and 2 would suggest that the reaction with the electron-deficient aryl iodide **2d** is initially approximately twice as fast as that with aryl iodide **2a**, but significantly slows down as dba arylation progresses.

In order to gain further insights on the possible effect of

Scheme 2 Different reactivity of aryl iodides in room temperature Pd-catalyzed β -arylation of benzo[*b*]thiophene

Fig. 1 A) Kinetic reaction profile for the β -arylation of benzo[*b*]thiophene **1a** with 4-iodotoluene **2a**. Reacted **1a** and **2a** are calculated as $[\mathbf{1a}]_0 - [\mathbf{1a}]$ and $[\mathbf{2a}]_0 - [\mathbf{2a}]$, respectively. B) Amount of ArI **2a** consumed in bis-arylation of dba, calculated as $([\mathbf{2a}]_0 - [\mathbf{2a}]) - [\mathbf{3aa}]$.

Fig. 2 A) Kinetic reaction profile for the β -arylation of benzo[*b*]thiophene **1a** with 1-iodo-4-nitrobenzene **2d**. Reacted **1a** and **2d** are calculated as $[1a]_0 - [1a]$ and $[2d]_0 - [2d]$, respectively. B) Amount of Aryl **2d** consumed in bis-arylation of dba, calculated as $[(2d)_0 - (2d)] - [3ad]$.

bis-arylation on the Pd-coordinating ability of dba, we evaluated *in silico* the Mulliken charge localized on the C=C bonds of compounds **4a** and **4d**.¹³ Fairlamb and Lee have previously reported that, on dba-4,4'-Z (Z = H, EDG, EWG),^{4d} this charge can be correlated with the reactivity of the Pd-catalyst, with higher charge leading to higher reactivity. This is explained by a lower capacity in coordinating Pd(0) as charge increases, through decreased π -back-bonding. Our calculations show that there is a marked decrease in C=C charge population upon bis-arylation with aryl iodide **2d** (-0.063) when compared to **2a** (-0.076), in line with the experimentally observed lower reactivity of the system when dba **4d** is formed. These experimental and computational results suggest that upon bis-arylation dbaAr₂ **4d** is more likely to remain associated to Pd than dbaAr₂ **4a** (or simple dba), thus negatively affecting the reactivity of the catalyst.¹⁴

We hypothesised that if bis-arylated dba **4a** could be formed first, the resulting catalytic system would display higher reactivity with electron-deficient aryl iodide **2d**, as formation of dba **4d** would be avoided. Thus, we treated 2.5 mol % Pd₂(dba)₃CHCl₃ with 0.15 equiv of 4-iodotoluene **2a** (2 equiv of **2a** per dba) in the presence of Ag₂CO₃ for 1.5 h, leading to the *in situ* formation of dbaAr₂ **4a** and consumption of aryl iodide **2a** (Scheme 3). To this 'pre-activated' catalyst we then added benzo[*b*]thiophene **1a** and the normally poorly reactive electron-deficient aryl iodide **2d**. Remarkably, this protocol led to the formation of the desired product **3ad** in an excellent yield of 74% at room temperature in 16 h compared to the previously observed 30%, and confirming our hypothesis.¹⁵

Scheme 3 Effect of pre-arylation dba with aryl iodide **2a**, in the coupling between **1a** and **2d**. Reaction performed on a scale of 0.25 mmol of **1a** with 0.75 equiv of Ag₂CO₃, 1.5 equiv of **2d** and HFIP [0.25 M] at 24 °C. Yield given is calculated by ¹H-NMR analysis using an internal standard.

Based on these results, we envisioned that a Pd(0) pre-catalyst containing a bis-arylated dba species such as **4a** would allow us to develop a general, high yielding room temperature coupling of benzo[*b*]thiophene **1a** with electron-deficient iodoarenes. Unfortunately, attempts to synthesise such a complex were unsuccessful.¹⁶ As an alternative, we speculated that a dba-free Pd(II) source able to readily undergo reduction to Pd(0) under the reaction conditions may be a suitable alternative pre-catalyst for this transformation. Based on this, an assessment of Pd-species allowed us to identify PdI₂ as a highly reactive replacement for Pd₂(dba)₃CHCl₃ in the couplings between benzo[*b*]thiophene and aryl iodides. PdI₂ may rapidly form Pd(OCH(CF₃)₂)₂ upon exchange with AgOCH(CF₃)₂ which then may readily decompose to form Pd(0). With this new catalyst, we tested a variety of electron-deficient aryl iodides (Table 1).

Gratifyingly, the use of PdI₂ allowed the desired β -arylated products **3ad-3ao** to be formed in good to excellent yields. PdI₂ clearly exhibiting superior reactivity with respect to the dba-containing Pd source (yields in brackets) in the cases where electron-withdrawing substituents were present at the para (**3ad-3af**) and meta positions (**3ag-3ak**). Surprisingly, ortho-substituted

Table 1 Direct C–H arylation of benzo[*b*]thiophene **1a** with electron-poor iodoarenes **2d-oa**^a

^a Reactions carried out on a scale of 0.75 mmol of **1a**. Yields given are isolated. ^b Yields in brackets are using Pd₂(dba)₃CHCl₃ (2.5 mol %) instead of PdI₂ and calculated by ¹H-NMR analysis using an internal standard. C3/C2 ratios were determined by GC-MS analysis of the crude reaction mixture and were greater than 98:2 in all cases.

iodoarenes were similarly reactive under the two Pd sources, although the corresponding arylated products were obtained in slightly higher yields when PdI_2 was employed (**3am-3ao**). We speculate that the increased steric hindrance provided by the ortho-substituent may lead to a poorly coordinating bis-arylated dba, thus resulting in a more highly reactive Pd species. Finally, in the coupling with 1-iodo-4-nitro-benzene **2d**, a reduced loading of 1.0 equiv of aryl iodide was tested without significantly affecting the formation of desired product **3ad** (82%).

In summary, we have described mechanistic studies showing the first example of an in situ bis-arylation of dba-ligand in a $\text{Pd}_2(\text{dba})_3\text{CHCl}_3$ catalyzed process. This undesired arylation results in a modification of the catalytic species. The new species show significantly reduced reactivity when the added aryls groups are electron-deficient. Given the breadth of reported methods that use Pd_xdba_y catalysts in combination with aryl iodide coupling partners, we speculate that this in situ catalyst modification could be a widespread phenomenon. Thus researchers developing new methods using these common Pd-catalyst precursors should take into account whether any alterations of dba occur and their possible impact on catalytic efficiency of the system. In the reaction under study, the room temperature arylation of benzo[*b*]thiophene, we found that high reactivity with electron-deficient aryl iodides can be achieved by switching the Pd catalyst from $\text{Pd}_2(\text{dba})_3\text{CHCl}_3$ to PdI_2 , thus avoiding any issues with dba-arylation and in situ catalyst modification.

Acknowledgements

We gratefully acknowledge the European Research Council for a Starting Grant (to I.L.) and the EPSRC (EP/K039547/1). We thank Dr Ralph Adams (UoM) for the NMR experiments related to the identification of the bis-arylated dba compounds **4a** and **4d**.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- (a) A. de Meijere, F. Diederich, *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH, Weinheim, 2004; (b) S. P. Nolan, *N-Heterocyclic Carbenes in Synthesis*, Wiley-VCH, Weinheim, 2006, pp. 1-304; (c) F. Glorius, *N-Heterocyclic Carbenes in Transition Metal Catalysis*, Springer-Verlag, Berlin, 2006, pp. 1-218.
- For selected applications of $\text{Pd}_x(\text{dba})_y$ ($x = 1, 2$; $y = 2, 3$) complexes see: (a) A. F. Littke, G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4176-4211; (b) M. Cong, Y. Fan, J.-M. Raimundo, J. Tang, L. Peng, *Org. Lett.*, 2014, **16**, 4074-4077; (c) S. S. Zaleskiy, V. P. Ananikov, *Organometallics*, 2012, **31**, 2302-2309.
- (a) C. Amatore, A. Jutand, F. Khalil, M. A. M'Barki, L. Mottier, *Organometallics*, 1993, **12**, 3168-3178; (b) C. Amatore, A. Jutand, G. Meyer, *Inorg. Chim. Acta*, 1998, **273**, 76-84; (c) C. Amatore, A. Jutand, *Coord. Chem. Rev.*, 1998, **178-180**, 511-528.
- (a) I. J. S. Fairlamb, A. R. Kapdi, A. F. Lee, *Org. Lett.*, 2004, **6**, 4435-4438; (b) I. J. S. Fairlamb, A. R. Kapdi, A. F. Lee, G. P. McGlacken, F. Weissburger, A. H. M. de Vries, L. Schmieder-van de Vondervoort, *Chem. Eur. J.*, 2006, **12**, 8750-8761; (c) Y. Macé, A. R. Kapdi, I. J. S. Fairlamb, A. Jutand, *Organometallics*, 2006, **25**, 1795-1800; (d) I. J. S. Fairlamb, A. F. Lee, *Organometallics*, 2007, **26**, 4087-4089; (e) I. J. S. Fairlamb, *Org. Bio. Chem.*, 2008, **6**, 3645-3656; (f) P. Sehnal, H. Taghzouti, I. J. S. Fairlamb, A. Jutand, A. F. Lee, A. C. Whitwood, *Organometallics*, 2009, **28**, 824-829.
- J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy, L. M. Alcazar-Roman, *J. Org. Chem.*, 1999, **64**, 5575-5580.
- X. Liu, J. F. Hartwig, *Org. Lett.*, 2003, **5**, 1915-1918.
- C. Colletto, S. Islam, F. Juliá-Hernández, I. Larrosa, *J. Am. Chem. Soc.*, 2016, **138**, 1677-1683.
- For selected examples of β -arylation of (benzo)thiophenes in the absence of directing groups, see: (a) K. Ueda, S. Yanagisawa, J. Yamaguchi, K. Itami, *Angew. Chem., Int. Ed.*, 2010, **49**, 8946-8949; (b) S. Kirchberg, S. Tani, K. Ueda, J. Yamaguchi, A. Studer, K. Itami, *Angew. Chem., Int. Ed.*, 2011, **50**, 2387-2391; (c) K. Funaki, T. Sato, S. Oi, *Org. Lett.*, 2012, **14**, 6186-6189; (d) D.-T. D. Tang, K. D. Collins, F. Glorius, *J. Am. Chem. Soc.*, 2013, **135**, 7450-7453; (e) K. Yuan, H. Doucet, *Chem. Sci.*, 2014, **5**, 392-396; (f) D.-T. D. Tang, K. D. Collins, J. B. Ernst, F. Glorius, *Angew. Chem., Int. Ed.*, 2014, **53**, 1809-1813; (g) Z. Wang, Y. Li, B. Yan, M. Huang, Y. Wu, *Synlett*, 2015, **26**, 531-536; (h) Y. Maki, T. Goto, N. Tsukada, *ChemCatChem*, 2016, **8**, 699-702.
- Product **3aa** has been obtained in 74% yield after 7 h.
- The plot also shows that 0.10 equiv of aryl iodide **2a** are consumed very fast, whereas a further 0.5 are consumed more slowly. This suggests that two out of the three dba in the Pd_2dba_3 precatalyst are bis-arylated faster than the remaining one. This can be explained by considering the initial formation of 0.05 equiv of Pd(0)-dba and 0.025 equiv of free dba, followed by fast bis-arylation of the Pd-bound dba, which would consume 0.10 equiv of **2a**. Slow ligand exchange with the remaining free-dba is then required before it is bis-arylated using further 0.05 equiv of **2a**.
- 4a** was obtained as a mixture of (*E,E*):(*Z,E*):(*Z,Z*) isomers in ratio 6:1:traces as confirmed by NMR techniques (^1H NMR, COSY, selective 1D NOESY, ^{13}C NMR and HSQC).

- 4d** was obtained as a mixture of (*E,E*):(*Z,E*):(*Z,Z*) isomers in ratio 0.9:1:<0.1 as confirmed by NMR techniques (^1H NMR, COSY, selective 1D NOESY, selective 1D TOCSY, ^{13}C NMR and HSQC).

- Geometries, frequency optimizations, Mulliken charge populations were calculated by DFT using Gaussian. B3LYP and 6-311G(d,p) were respectively used as functional and basis set for the calculations. See SI for details.
- A. A. Sabino, A. H. L. Machado, C. R. D. Correia, M. N. Eberlin, *Angew. Chem., Int. Ed.*, 2004, **43**, 2514-2518.
- For several control experiments on the effects of dba prearylation, see SI.
- The protocols tested are the ones reported by Fairlamb and co-workers for the synthesis of $\text{Pd}_x(\text{dba}-Z)_y$ ($x = 1, 2$; $y = 2, 3$) complexes [ref. 4c]. In all cases only Pd-black was obtained.