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

DOI:
10.1039/C7CC08018B

Document Version
Accepted author manuscript

Link to publication record in Manchester Research Explorer

Citation for published version (APA):

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.
We have discovered that the dba ligand in the commonly used Pd(dba)$_3$Cl catalytic system is susceptible to bismuth 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 aryldeneded by 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). Among the stable and phosphine-free Pd(0) sources, Pd(dba)$_x$ (x = 1, 2; y = 2, 3) complexes are certainly the most commonly used. Although Pd(dba)$_3$ are often considered simple Pd(0) sources, pioneering studies by Amatore and Jutand on the rate of the oxidative addition of Pd(dba)$_3$ complexes with aryl iodides in the presence of phosphines (L), revealed that the coordination ability of dba cannot be overlooked. Indeed, whereas Pd(dba)$_3$ did not undergo oxidative addition, dba-free Pd(0)L$_2$ complexes were instead shown to react with iodoarenes. Therefore, Pd(dba)$_2$ acts as reservoir, which slowly releases the active Pd(0) complexes. In this context, Fairlamb and co-workers reported that Pd(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.

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 Pd$_x$(dba-4,4'-Z)$_y$ complexes, were able to isolate small amounts of mono- and bis-aminated dba-Z ligand from these reaction mixtures. 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 Pd(0)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 Pd(dba)$_3$. 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 Pd(OAc)$_2$ instead of Pd(dba)$_3$ 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...
Pd$_2$(dba)$_3$CHCl$_3$ as the catalyst, a process which occurred under remarkably mild conditions. 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-dbaAr$_2$ 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 arylation 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). A plot comparing formation of product 3aa vs consumption of both starting materials indicated that, while consumption of benzo[b]thiophene ([reactioned 1a] = [1a]$_0$−[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 ([reactioned 2a] = ([2a]$_0$−[2a])−[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 of all of the dba present in the reaction. Intrigued by this possibility, we thoroughly examined the reaction crude after 2 h of reaction. Gratifyingly, we were able to isolate bis-aryltaed dba 4a as a mixture of three stereoisomers, 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. 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](image)

**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 [1a]$_0$−[1a] and [2a]$_0$−[2a], respectively. B) Amount of ArI 2a consumed in bis-arylation of dba, calculated as ([2a]$_0$−[2a])−[3aa].
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. 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 Pd2 as a highly reactive replacement for Pd(dba)2CHCl3 in the couplings between benzo[b]thiophene and aryl iodides. Pd2 may rapidly form Pd(OCH2CF3)2 upon exchange with Ag(dba)2CHCl3 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 Pd2 allowed the desired β-arylated products 3ad-3ao to be formed in good to excellent yields. Pd2 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-o**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield (%)</th>
<th>Reaction Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>3ad</td>
<td>86%</td>
<td>Ag2CO3 (0.75 equiv)</td>
</tr>
<tr>
<td>3ae</td>
<td>89%</td>
<td>Ag2CO3 (0.75 equiv)</td>
</tr>
<tr>
<td>3af</td>
<td>91%</td>
<td>Ag2CO3 (0.75 equiv)</td>
</tr>
<tr>
<td>3ag</td>
<td>85%</td>
<td>Ag2CO3 (0.75 equiv)</td>
</tr>
<tr>
<td>3ah</td>
<td>87%</td>
<td>Ag2CO3 (0.75 equiv)</td>
</tr>
<tr>
<td>3ai</td>
<td>94%</td>
<td>Ag2CO3 (0.75 equiv)</td>
</tr>
<tr>
<td>3aj</td>
<td>89%</td>
<td>Ag2CO3 (0.75 equiv)</td>
</tr>
<tr>
<td>3ak</td>
<td>85%</td>
<td>Ag2CO3 (0.75 equiv)</td>
</tr>
<tr>
<td>3al</td>
<td>81%</td>
<td>Ag2CO3 (0.75 equiv)</td>
</tr>
<tr>
<td>3am</td>
<td>95%</td>
<td>Ag2CO3 (0.75 equiv)</td>
</tr>
<tr>
<td>3an</td>
<td>86%</td>
<td>Ag2CO3 (0.75 equiv)</td>
</tr>
<tr>
<td>3ao</td>
<td>76%</td>
<td>Ag2CO3 (0.75 equiv)</td>
</tr>
<tr>
<td>3ap</td>
<td>73%</td>
<td>Ag2CO3 (0.75 equiv)</td>
</tr>
<tr>
<td>3aq</td>
<td>66%</td>
<td>Ag2CO3 (0.75 equiv)</td>
</tr>
</tbody>
</table>

Reactions carried out on a scale of 0.75 mmol of 1a. Yields given are isolated.

Fig. 2 A) Kinetic reaction profile for the β-arylation of benzo[b]thiophene 1a with 1-bromo-4-nitrotoluene 2d. Reacted 1a and 2d were calculated as [1a]−[1a] and [2d]−[2d], respectively. B) Amount of ArI 2d consumed in bis-arylation of dba, calculated as ([2d]−[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. Fairlamb and Lee have previously reported that, on dba-4,4'-Z (Z = H, EDG, EWG), 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 dbaAr4, 4d is more likely to remain associated to Pd than dbaAr4, 4a (or simple dba), thus negatively affecting the reactivity of the catalyst.44

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)2CHCl3 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 dbaAr4, 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
Iodoarenes were similarly reactive under the two Pd sources, although the corresponding arylated products were obtained in slightly higher yields when PdI₂ 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-arylization of dba-iodin in a Pd₂(dba)₃·CHCl₃ catalyzed process. This undesired arylation results in a modification of the catalytic species. The new species show significantly reduced reactivity when the added aryl groups are electron-deficient. Given the breadth of reported methods that use Pd₃dba, 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 Pd₂(dba)₃·CHCl₃ to PdI₂, 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.J.S.) 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


9 Product 3aa has been obtained in 74% yield after 7 h.

10 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 Pd₂dba₃ 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-arylization 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.

11 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, ¹³C NMR and HSQC).

12 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, ¹³C NMR and HSQC).

13 Geometries, frequency optimizations, Mulliken charge populations were calculated by DFT using Gaussian. B3LYP and 6-311G(dp) were respectively used as functional and basis set for the calculations. See SI for details.


15 For several control experiments on the effects of dba prearylation, see SI.

16 The protocols tested are the ones reported by Fairlamb and co-workers for the synthesis of Pd,(dba-Z), (x = 1, 2; y = 2, 3) complexes [ref. 4c]. In all cases only Pd-black was obtained.