Amine-catalysed Suzuki–Miyaura-type coupling? The identification and isolation of the palladium culprits.

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Abstract: A recent report in this journal detailed the potentially paradigm-shifting organocatalysis of Suzuki cross-coupling of aryl halides with aryl boronic acids, catalysed by simple amine species. We have conducted a reinvestigation of key claims in this paper across multiple academic and industrial laboratories that shows that the observed catalytic activity cannot be due to the amine, but rather is due to tricyclohexylphosphine palladium complexes that are readily entrained during the purification of the amine.

The Suzuki coupling reaction (Fig. 1)[1,2] is in the vast majority of cases catalysed by palladium complexes, but there are growing efforts to move away from this expensive, toxic metal. Against this backdrop, Yu, Xu and co-workers very recently reported that a range of di(*o*-tolyl)amine organocatalysts of the type **1** (Fig. 1) – in particular **1a** – can catalyse the Suzuki reaction to excellent effect under apparently metal-free conditions.[3] These findings, if correct, represent a profound and seismic paradigm shift in cross-coupling chemistry and therefore deserved further exploration.

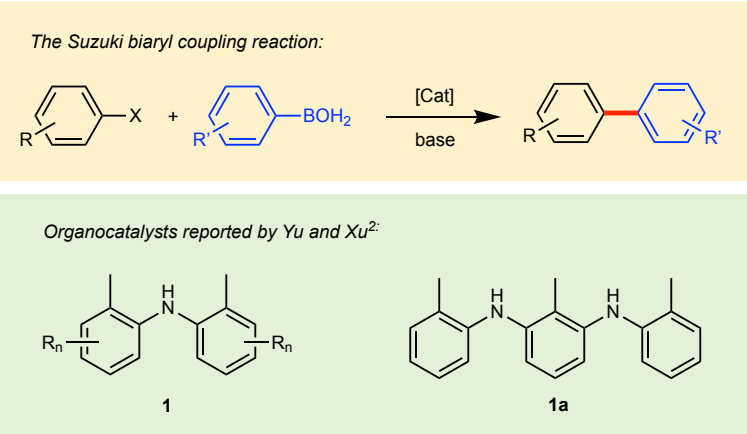


Figure 1. The Suzuki biaryl coupling reactions and the organocatalysts reported by Yu, Xu and co-workers.[3]

Amine **1a** was independently synthesised by several of us using the palladium-catalysed amination reaction described by Yu and Xu[3] (see Supplementary Methods). It was then exploited in a number of Suzuki coupling reactions – selected examples of which are shown in Table 1 with the rest given in Supplementary Table 3. Entries 1 – 11 indicate that samples **1a** produced as published can indeed give good to excellent performance, whereas the results in entries 12 – 26 comprehensively demonstrate that the observed catalytic activity cannot be due to the amine.

Interestingly, we found that the catalytic performance of **1a** could be significantly improved from the literature protocol when water is added as a co-solvent (compare entry 8 with entries 9 and 10): a result entirely at odds with the proposed formation of an organopotassium intermediate.[3] We had several concerns regarding the proposed, DFT-calculated mechanism (see discussion in Supplementary Methods) – however, our main concern regards competitive hydrolysis. It seemed to us highly likely that the K-Ph proposed to form in the proximity of a hydroxyl residue (**Int4**, Fig. 2) would undergo rapid intramolecular hydrolysis. A relaxed PES scan with stepwise reduction in $C_{(Ph)}\cdots H_{(BOH)}$ distance (Fig. 2) revealed a smooth, low energy rearrangement (ΔE_{elec} ~ 4 kcal/mol) of the cluster followed by a very low energy (ΔE_{elec} ~ 1 kcal/mol) proton transfer. Attempts to model the transition states for these two processes were unsurprisingly not successful. The product of this hydrolysis reaction (**Int4-dp**) lies 24.4 kcal/mol downhill of **Int4**. Clearly, even if **Int4** could form it would rapidly hydrolyse rather than participate in the proposed steps leading to the activation and coupling of the aryl bromide substrate.

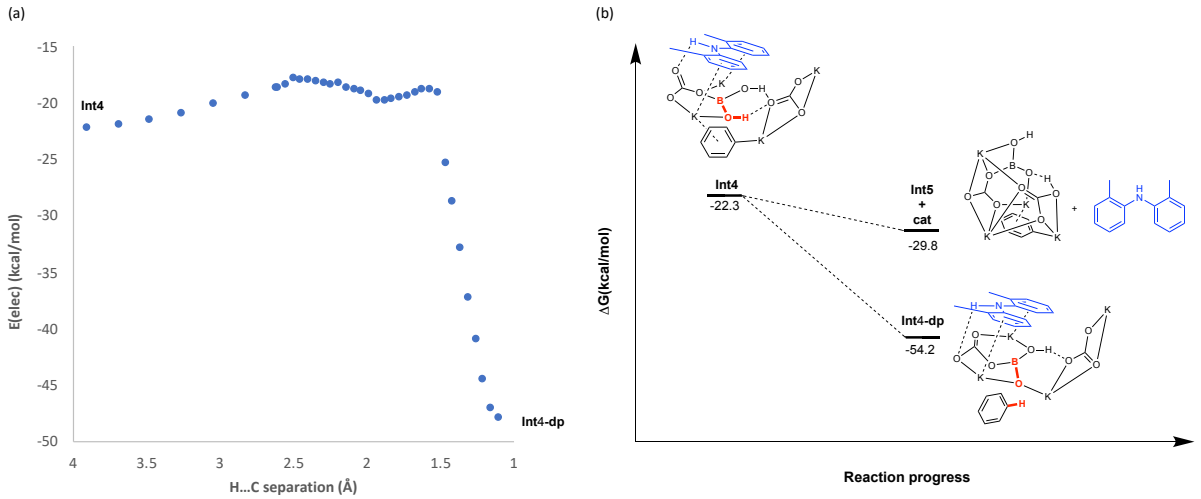
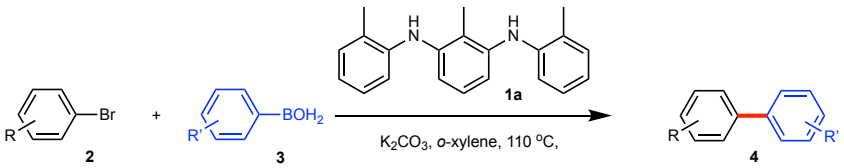
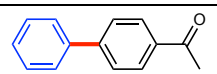
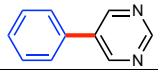
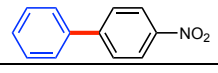
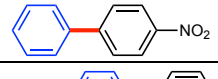
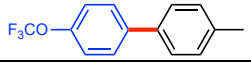
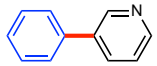


Figure 2. Computational investigation of intramolecular hydrolysis of the key proposed intermediate (Int4). a. Relaxed PES scan of proton migration to K-Ph from adjacent B-O-H group (Orca 4.2, B3LYP-D3BJ/def2-svp, see Supporting Methods for full details). **b.** Comparison of ΔG for intramolecular hydrolysis of K-Ph by adjacent B-O-H group (highlighted in red) versus the originally proposed dissociation of the amine group and formation of **Int5** (Gaussian 16, B3LYP-D3BJ/6-311+G**; **Int4**, **Int5** and **cat** reoptimized; ΔG for **Int4** set to same value as in the literature. See Supporting Methods for full details).

When **1a** was treated with $PhB(OH)_2$ and K_2CO_3 under air, the resultant **1a** gave reduced or no catalytic activity (compare entries 13 – 16 with entries 3 – 7, Table 1) suggesting that **1a** is not the active catalyst, but rather catalysis is due to an impurity that can be 'reacted out'. Similarly, **1a** recovered from the large-scale reaction outlined in entry 10 proved to be catalytically inactive (entry 17). We also explored the reactivity obtained with the commercially available amines *o*-toluidine and 3-methylpyridin-4-amine that were reported as active by Xu and Yu[3] (see Supplementary Methods): none of us were able to reproduce the levels of activity reported.



Entry	Product	Notes	Product observed?
1		**1a** produced and purified according to lit.[3] 16 hour reaction time.	**Yes** – 57% (^{1}H NMR)*
2		**1a** produced and purified according to lit.[3] 4 hour reaction time.	**Yes** – product peak observed by LC-MS
3		**1a** produced and purified according to lit.[3] 16 hour reaction time.	**Yes** – >99% (^{1}H NMR)*
4		**1a** produced and purified according to lit.[3] and provided as a blind sample. 18 hours, 90 °C.	**Yes** – 98% isolated yield
5		**1a** produced and purified according to lit.[3] 16 hour reaction time.	**Yes** – 55% (^{1}H NMR)*
6		**1a** produced and purified according to lit.[3] 16 hour reaction time.	**Yes** – 49% (^{1}H NMR)*

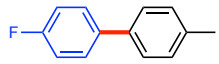
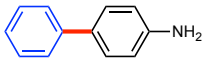
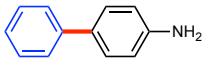
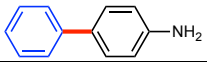
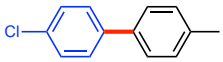
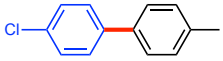
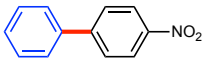
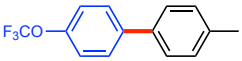
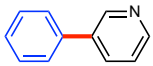
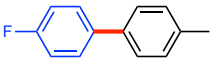
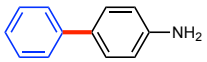
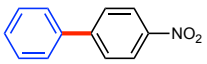
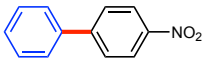
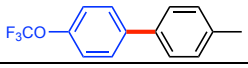
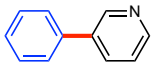
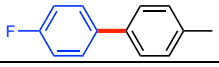
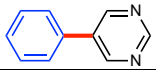
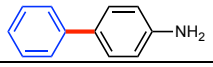
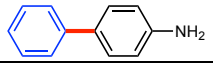
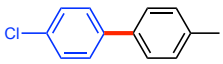
7		**1a** produced and purified according to lit.[3] 16 hour reaction time.	**Yes** – 27% (^{1}H NMR)*
8		**1a** produced and purified according to lit.[3] 2 hour reaction time.	**Yes** – GC-MS shows significant (> 50%) product formation
9		As per entry 8, but solvent = *o*-xylene:water 4:1	**Yes** – GC-MS shows almost quantitative product formation
10		5g 4-bromoaniline scale, *o*-Xylene:H_2O (50:12), overnight.	**Yes** – 98% isolated yield
11		**1a** produced and purified according to lit.[3] 2 hour reaction time.	**Yes** – ^{1}H NMR† 48%
12		As for entry 11, but with **1a** further purified by a second round of column chromatography	**Reduced** – ^{1}H NMR† 42%
13		Crude **1a** reacted with $PhB(OH)_2$ and K_2CO_3‡ prior to purification. Catalytic conditions as per entry 3.	**No** – NMR and GC-MS show no product
14		Crude **1a** reacted with $PhB(OH)_2$ and K_2CO_3‡ prior to purification. Catalytic conditions as per entry 5.	**Minimal** - ^{1}H NMR* shows 4% product
15		Crude **1a** reacted with $PhB(OH)_2$ and K_2CO_3‡ prior to purification. Catalytic conditions as per entry 6.	**No** – NMR and GC-MS shows no product
16		Crude **1a** reacted with $PhB(OH)_2$ and K_2CO_3‡ prior to purification. Catalytic conditions as per entry 7.	**Reduced** - ^{1}H NMR* shows 16% product
17		**1a** recycled from large scale reaction in entry 10	**No** – product peak absent in GC-MS
18		**1a** produced by Cu-catalysed Chan-Lam coupling; conditions identical to entry 3	**No** – ^{1}H NMR and GC-MS show no product
19		**1a** produced by Cu-catalysed Chan-Lam and provided as a 'blind' sample. Conditions identical to entry 4.	**No** – ^{1}H NMR shows no product
20		**1a** produced by Cu-catalysed Chan-Lam coupling; conditions identical to entry 5	**No** – ^{1}H NMR and GC-MS show no product
21		**1a** produced by Cu-catalysed Chan-Lam coupling; conditions identical to entry 6	**No** – ^{1}H NMR and GC-MS show no product
22		**1a** produced by Cu-catalysed Chan-Lam coupling; conditions identical to entry 7	**No** – ^{1}H NMR and GC-MS show no product
23		**1a** produced by Cu-catalysed Chan-Lam coupling; conditions identical to entry 2	**No** – product peak absent in LC-MS
24		**1a** produced by Fe-mediated reductive amination, conditions as per entry 9	**No** – product peak absent in GC-MS
25		**1a** produced using $[Pd(P^tBu_3)_2]$ as catalyst, conditions as per entry 9	**No** – product peak absent in GC-MS
26		**1a** produced and purified according to lit.,[3] then further purified by recrystallisation from ethyl acetate/hexane	**No** – ^{1}H NMR shows no product

Table 1. Investigation into the catalytic performance of amine 1a. Notes: (*) Internal standard = 1,3,5-trimethoxybenzene; (†) Internal standard = biphenyl; (‡) Sample of **1a** heated with $PhB(OH)_2$ (1.3 equiv.) and K_2CO_3 (7.2 equiv.) for 16 hours at reflux in toluene under air and purified by column chromatography.

Yu and Xu undertook eminently sensible experiments in an attempt to rule out possible palladium contamination of **1a**, as has been observed previously in reported 'metal-free' Suzuki coupling,[4] including reacting it with a palladium scavenger and conducting ICP-MS. However, both these approaches are subject to false negatives (see below): the former only works if the palladium is in a form that can be scavenged by the scavenger; the latter requires an appropriate digest. The only guaranteed method to avoid palladium contamination in **1a** is to do the control experiment: make **1a** without using palladium. To this end we prepared **1a** by both copper-catalysed Chan-Lam coupling[5] and iron-mediated reductive amination[6] (see Supplementary Methods for details). Amine **1a** made by these routes is not catalytically competent (Table 1, entries 18 – 24). This indicates that the presence of palladium in **1a** is crucial for activity. Amine **1a** was also prepared by an alternative palladium-catalysed method, using $Pd(P^tBu_3)_2$ as the pre-catalyst. In this case **1a** was obtained in significantly higher yield (89%) than the reported method,[3] but the amine produced was not catalytically active (entry 25); it seems that the presence of palladium in the formation of **1a** is on its own not sufficient for activity after purification by column chromatography. The precise form of the palladium contamination determines whether it is 'entrained' or not during purification – which in turn determines whether or not activity is observed. We note that **1a**, produced as described,[3] but further purified using a second round of column chromatography is still catalytically active, but with slightly reduced activity (Table 1, entry 12); however, if the sample is instead purified by recrystallisation from EtOAc/hexane (the same solvent system used for the chromatographic purification of **1a**)[3] then the resultant **1a** is inactive (Table 1, entry 26). The crystal structure of the catalytically inactive **1a** obtained by this improved purification method is shown in Fig. 3, confirming its identity. Unlike the sample prepared according to the literature method,[3] the recrystallised sample of **1a** is colourless and crystalline (see Supplementary Fig. 17 for comparison).

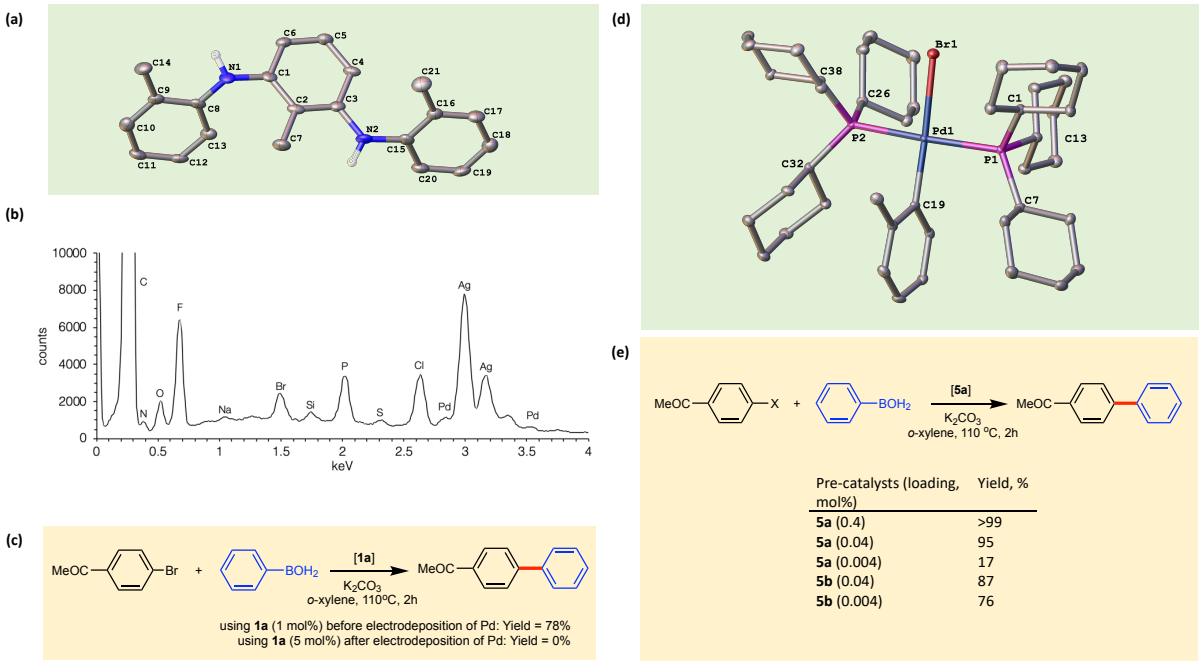


Figure 3. Exploration of the active catalyst species. a. Crystal structure of catalytically inactive **1a** purified by recrystallisation after column chromatography. **b.** EDX spectroscopic analysis of the graphite electrode after electrochemical deposition of palladium from **1a**. **c.** Catalytic data obtained using **1a** before and after electrochemical deposition of palladium

(spectroscopic yield, determined by ^{1}H NMR, 1,3,5-trimethoxybenzene internal standard). **d.** Crystal structure of complex **5a**. **e**. Selected catalytic data obtained using **5a** and **5b** (full data in Supplementary Table 4), spectroscopic yield determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene internal standard.

Direct evidence for palladium contamination was obtained by subjecting a sample of **1a** to reductive electrolysis, in which any metals present should be electrodeposited onto the surface of the graphite electrode. Energy-Dispersive X-ray spectroscopy (Fig. 3b) of this electrode indicated the presence of Pd. A second sample of **1a** was subjected to reductive electrolysis using a larger surface area electrode and the recovered amine **1a** from this experiment was subsequently not catalytically competent (Fig. 3c). The amount of palladium present in a typical sample of **1a** was determined by ICP-MS. Yu and Xu's reported digestion method led them to determine a Pd contamination of < 1 ppb;[3] when we employed a more robust digestion protocol (Supplementary Methods), we obtained a very high value of 7500 µg/g Pd. This corresponds to nearly half of the palladium used in the synthesis of **1a**. We too find that a sample of **1a** remains catalytically competent after treating twice with a palladium scavenger (2-mercaptoethyl ethyl sulfide silica (PhosphonicS); see Supplementary Methods) but we note that the rate of catalysis is significantly reduced after stirring for 2 x 16h. This suggests that there is one or more active palladium species that react only slowly and partially with the scavenger.

Next, we set out to determine the nature of the palladium species entrained in the purification of **1a**. ^{31}P NMR spectra (see Supplementary Information, "Examining Pd impurities formed during the literature synthesis of **1a**") of crude reaction mixtures obtained for the synthesis of **1a** by the reported route[3] – prior to purification by chromatography – show, in addition to signals for free PCy_3 and $OPCy_3$, several other minor peaks including a more significant singlet at 20.4 ppm. Subjecting samples of **1a** to column chromatographic purification as described by Yu and Xu[3] and then running ^{31}P NMR spectra of the 'pure' **1a** obtained showed varying amounts of two species, at 20.4 (**5a**) and 21.5 ppm (**5b**), with the latter species becoming more prevalent the longer the sample was exposed to silica. These palladium species elute just ahead of the amine **1a** (hexane:ethyl acetate, 20:1) allowing isolation of an approximately 1:4 mixture of **5a**/**5b** (see Supplementary Methods for details). The former species, **5a**, proved to be *trans*-[PdBr(*o*-tolyl)(PCy_3)$_2$], which was prepared independently (Supplementary Methods) by oxidative addition of *o*-tolyl bromide to Pd(0)-PCy_3 species. The structure of **5a** was confirmed by X-ray crystallography (Fig. 3d). The HR ESI-MS spectrum showed a peak at m/z = 757.4252 for the ion [**5a**-Br]$^{+}$ (calcd. *m/z* = 757.4222). The second species **5b** is the analogous chloride *trans*-[PdCl(*o*-tolyl)(PCy_3)$_2$], which was prepared independently by reaction of *o*-tolyl chloride with [$Pd_2(dba)_3$] and PCy_3 (see Supplementary Methods for full details). Surprisingly, it appears that the source of the chloride in the formation of **5b** is the silica used for the chromatography. Complex **5a** converts to an approximately 2:1 mixture of **5a**/**5b** on passing through a short plug of silica, but when the silica is first exhaustively washed with water (followed by methanol, then toluene) and the experiment repeated then only a trace of **5b** is obtained (Supplementary Figs. 37 – 39). Interestingly, **5b** is significantly more active than **5a** when used at lower catalytic loading in a representative coupling reaction (selected data Fig. 3e; full data Supplementary Table 4). Meanwhile, **5b** isolated as described above from the formation of **1a** (containing ~20% **5a**) showed very good activity in a range of cross-coupling reactions (See Supplementary Table

4). The good activity observed at very low loadings shows that **1a** contaminated with **5a**/**b** and yet apparently contaminant free by ^{31}P NMR spectroscopy can still be active, as is the case after purifying **1a** twice by column chromatography.

In conclusion, while Yu and Xu undertook sensible experiments to rule out palladium contamination carried over from the synthesis of **1a** (and their other synthesised amines), these experiments were unfortunately susceptible to false negatives. They omitted to undertake the control: to produce **1a** by alternative, palladium-free procedures. When this is done then **1a** is not active. Neither is (crystallographically characterised) **1a** that has been purified by recrystallisation after column chromatography, nor is **1a** produced by an alternative palladium-catalysed route. Unfortunately for the authors, they were highly unlucky in their choice of PCy_3 for the synthesis of **1a**: this gives stable palladium complexes that are readily entrained during the chromatographic purification of the amine **1a** and it is these species that account for the catalysis. In this regard it is worth noting that palladium-based pre-catalysts containing PCy_3 ligands can show very high activity at low loadings in the Suzuki coupling of aryl chlorides.[7-9] The other less active amines synthesised by Yu and Xu may be less efficient at entraining the Pd-PCy_3. During the preparation of this manuscript, a preprint was posted by Novák et al outlining complementary experiments that also demonstrate amine **1a** is not catalytically active.[10]

Data availability

Crystal structure data have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 2070871 and 2070872) and crystallographic data are provided in the Supplementary Information.

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Competing interests
The authors declare no competing interests.

Additional information
Supplementary information is available for this paper at XXXX