OPEN ACCESS

University of BRISTOL

Avanthay, M., Bedford, R. B., Begg, C. S., Böse, D., Clayden, J., Davis, S. A., Eloi, J. C., Goryunov, G. P., Hartung, I. V., Heeley, J., Khaikin, K. A., Kitching, M. O., Krieger, J., Kulyabin, P. S., Lennox, A. J. J., Nolla-Saltiel, R., Pridmore, N. E., Rowsell, B. J. S., Sparkes, H. A., ... Wilkinson, H. J. (2021). Identifying palladium culprits in amine catalysis. *Nature Catalysis*, *4*, 994-998. https://doi.org/10.1038/s41929-021-00710-1

Peer reviewed version

Link to published version (if available):
10.1038/s41929-021-00710-1

Link to publication record in Explore Bristol Research
PDF-document

This is the accepted author manuscript (AAM). The final published version (version of record) is available online via Nature Research at https://doi.org/10.1038/s41929-021-00710-1.Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research
General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/

Identifying palladium culprits in amine catalysis

Mickaël Avanthay,[1] Robin B. Bedford,[1]*Callum S. Begg,[2] Dietrich Böse,[3] Jonathan Clayden,[1]* Sean A. Davis,[1] Jean-Charles Eloi,[1] Georgy P. Goryunov,[4]* Ingo V. Hartung,[3]* Joseph Heeley,[1] Kirill A. Khaikin,[4] Matthew O. Kitching,*[2] Johannes Krieger,[3] Pavel S. Kulyabin,[4] Alastair J. J. Lennox,[1]* Roberto Nolla-Saltiel,[1] Natalie E. Pridmore,[1] Benjamin J. S. Rowsell,[1] Hazel A. Sparkes,[1] Dmitry V. Uborsky,[4] Alexander Z. Voskoboynikov,[4] Mark P. Walsh[1] and Harry J. Wilkinson[1]

1. School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, U.K.
2. Department of Chemistry, Durham University, Durham, DH1 3LE, U.K.
3. Merck Healthcare KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany
4. Department of Chemistry, Lomonosov Moscow State University, 1/3 Leninskie Gory, 119991 Moscow, Russia

E-mail: r.bedford@bristol.ac.uk; j.clayden@bristol.ac.uk; a.lennox@bristol.ac.uk; matthew.o.kitching@durham.ac.uk; ingo.hartung@merckgroup.com; goryunov@org.chem.msu.ru

The Suzuki coupling reaction (Fig. 1a)[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. 1b) – in particular **1a** – can catalyse the Suzuki reaction to excellent effect under apparently metal-free conditions.[3] We have conducted a reinvestigation of key claims in this paper across multiple academic and industrial laboratories that shows that the observed catalytic activity is not due to the amine but rather to highly robust tricyclohexylphosphine palladium complexes that are readily entrained during the purification of the amine. Unfortunately, the reported organocatalysis of the Suzuki reaction still remains an elusive goal; it is critical that any future endeavours must avoid the use of palladium in the production of the catalyst under investigation.

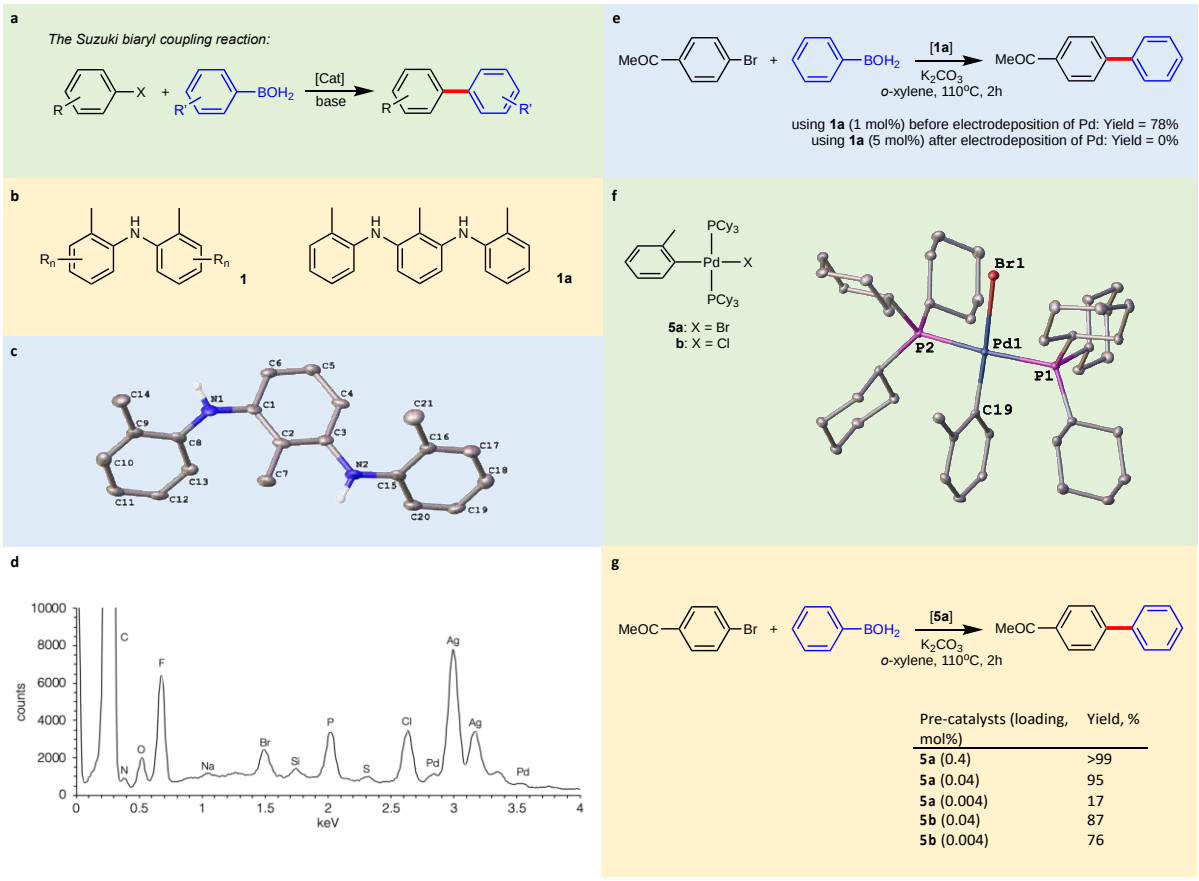


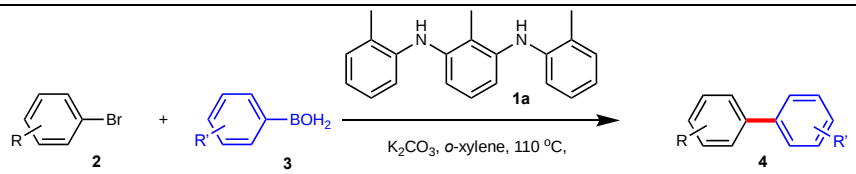
Figure 1. Exploration of the active catalyst species in the Suzuki reaction. a. The Suzuki reaction. **b**. Organocatalysts **1** reported by Yu, Xu and co-workers[3]. **c**. The crystal structure of catalytically inactive **1a** purified by recrystallisation after column chromatography. **d.** EDX spectroscopic analysis of the graphite electrode after electrochemical deposition of palladium from **1a**. **e.** 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). **f.** The palladium complexes **5a** and **b** and the crystal structure of **5a**. **g**. 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.

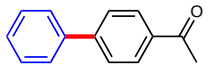
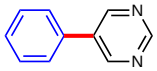
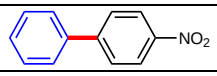
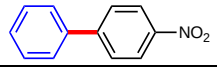
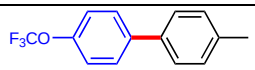
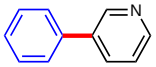
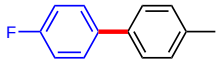
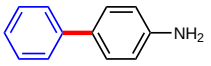
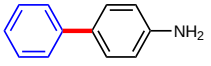
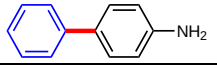
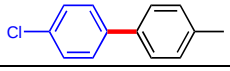
Amine **1a** was independently synthesised by several of us using the palladium-catalysed amination reaction as described[3] (see Supplementary Methods) and then exploited in a number of Suzuki coupling reactions, selected examples of which are shown in Table 1 with the rest given in Supplementary Table 3. Entries 1 – 11 indicate that samples of **1a**, produced as published, can indeed give good to excellent yields of cross-coupled product, activity cannot be due to the amine.

The catalytic performance of **1a** could be significantly improved from the literature protocol by adding water 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] Among our concerns regarding the reported DFT-calculated mechanism (see Computational Studies section in Supplementary Methods) was our suspicion that the key proposed K-Ph intermediate (**Int4**) would undergo competitive intramolecular hydrolysis by a proximate hydroxyl residue. Indeed, a brief computational investigation revealed this hydrolysis to be

very facile and highly favoured (see Extended Data). Clearly, even if a K-Ph-based intermediate could form it would rapidly hydrolyse rather than participate in the proposed steps leading to the activation and coupling of the aryl bromide substrate.

When **1a** was treated with $PhB(OH)_2$ and K_2CO_3 under air, prior to purification, 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 under these conditions. In this regard it should be noted that **1a** prepared as described is catalytically competent in the homocoupling of $PhB(OH)_2$ (see Catalytic Procedures section in Supplementary Methods). Similarly, **1a** recovered from the large-scale Suzuki coupling outlined in entry 10 proved to be catalytically inactive (Suzuki coupling, entry 17; $PhB(OH)_2$ homocoupling, Catalytic Procedures section in Supplementary Methods). We also explored the reactivity obtained with the commercially available amines *o*-toluidine and 3-methylpyridin-4-amine that were reported as active[3] (see Catalytic Runs with Commercial Amines section in 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%

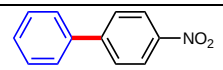
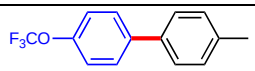
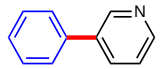
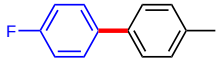
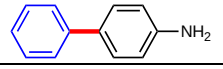
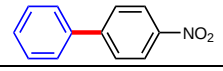
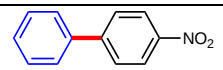
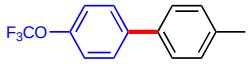
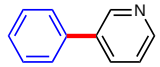
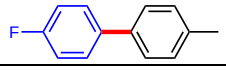
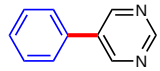
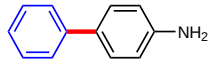
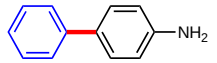
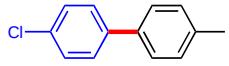
13		Crude **1a** reacted with $PhB(OH)_2$ and K_2CO_3‡ prior to purification. Catalytic conditions as per entry 3.	**No** – NMR and GC-MS show no product
14		Crude **1a** reacted with $PhB(OH)_2$ and K_2CO_3‡ prior to purification. Catalytic conditions as per entry 5.	**Minimal** - ^{1}H NMR* shows 4% 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 purportedly 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: prepare **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 Pd-free Syntheses of **1a** section in Supplementary Methods). 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 (Table 1, entry 25). It seems that the precise form of the palladium contamination determines whether or not it survives during chromatographic purification of **1a**. 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. 1c, 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).

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. 1d) 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. 1e). 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 (see ICP-MS Methods section in 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 Palladium Scavenger Procedure section in 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 Pd-Catalysed Routes to Amine **1a** section, Supplementary Methods) 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 Synthesis of Palladium Complexes section, Supplementary Methods for details). These proved to be the complexes *trans*-[PdX(*o*-tolyl)(PCy_3)$_2$] (**5a**: X = Br, **5b** X = Cl) which could be prepared independently (see Synthesis of Palladium Complexes section, Supplementary Methods) by oxidative addition of the *o*-tolyl halides to appropriate Pd(0)-PCy_3 species. The structure of **5a** was confirmed by X-ray crystallography (Fig. 1f). The HR ESI-MS spectrum showed a peak at m/z = 757.4252 for the ion [**5a**-Br]$^+$ (calcd. *m/z* = 757.4222).

Surprisingly, it appears that the source of the chloride in the conversion of **5a** to **5b** during the preparation of **1a** is the silica used for the chromatographic purification. 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. 1g; 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.

Complex **5b** is remarkably robust, indeed it can be prepared from **5a** by reaction with 10M HCl(aq) under air. Addition of 12M HCl to **5b** followed by sonication under air for about 1.5 hours gave no sign of decomposition, it was only when the sample was heated for 4 hours at 60 °C that hydrolysis occurred to give $[PdCl_2(PCy_3)_2]$ (see Synthesis of Palladium Complexes section, Supplementary Methods). It is therefore not surprising that **5b** so readily survives column chromatography and requires particularly harsh digest conditions for satisfactory ICP-MS analysis.

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 the **1a** produced 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 highly 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 complexes **5** accounting for their poorer performance. 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. All other data are available from the authors upon reasonable request.

References

1. Miyaura, N. & Suzuki, A. Palladium-catalyzed cross-coupling reactions of organoboron compounds. *Chem. Rev.* **95**, 2457–2483 (1995).

2. Lennox, A. J. J., & Lloyd-Jones, G. C. Selection of boron reagents for Suzuki-Miyaura coupling. *Chem. Soc. Rev.*, **43**, 412–443 (2014).
3. Xu, L., Liu, F.-Y., Zhang, Q., Chang, W.-J., Liu, Z.L., Lv, Y., Yu, H.-Z., Xu, J., Dai, J.-J. & Xu, H. J. The amine-catalysed Suzuki–Miyaura-type coupling of aryl halides and arylboronic acids. *Nat. Catal.* **4**, 71–78 (2021).
4. Arvela, R. K., Leadbeater, N. E., Sangi, M. S., Williams, V. A., Granados, P. & Singer R. D. A Reassessment of the Transition-Metal Free Suzuki-Type Coupling Methodology. *J. Org. Chem.*, **70**, 161–168 (2005).
5. Yu, S., Saenz, J. & Srirangam, J. K. Facile Synthesis of N-Aryl Pyrroles via Cu(II)-Mediated Cross Coupling of Electron Deficient Pyrroles and Arylboronic Acids. *J. Org. Chem.*, **67**, 1699–1702 (2002).
6. Sapountzis, I. & Knochel, P. A New General Preparation of Polyfunctional Diarylamines by the Addition of Functionalized Arylmagnesium Compounds to Nitroarenes. *J. Am. Chem. Soc.* **124**, 9390-9391 (2002).
7. Bedford, R. B. & Cazin, C. S. J. High-Activity Catalysts for Suzuki Coupling and Amination Reactions with Deactivated Aryl Chloride Substrates: Importance of the Palladium Source. *Organometallics* **22**, 987-999 (2003).
8. Bedford, R. B., Cazin, C. S. J. & Hazelwood, S. L. Simple Mixed Tricyclohexylphosphane-Triarylphosphite Complexes as Extremely High-Activity Catalysts for the Suzuki Coupling of Aryl Chlorides. *Angew. Chem. Int. Ed.* **41**, 4120-4122 (2002).
9. R. B. Bedford, S. L. Hazelwood & M. E. Limmert. Extremely high activity catalysts for the Suzuki coupling of aryl chlorides: the importance of catalyst longevity. *Chem. Commun.* 2610–2611 (2002).
10. Novák, Zoltán; Adamik, Réka; Csenki, János T.; Béke, Ferenc; Gavaldik, Regina; Varga, Bálint; et al. (2021): Curse or Blessing? Influence of Impurities on Cross-Coupling— Guideline for Elucidating Catalysts. *ChemRxiv*. Preprint. https://doi.org/10.26434/chemrxiv.14071247.v1

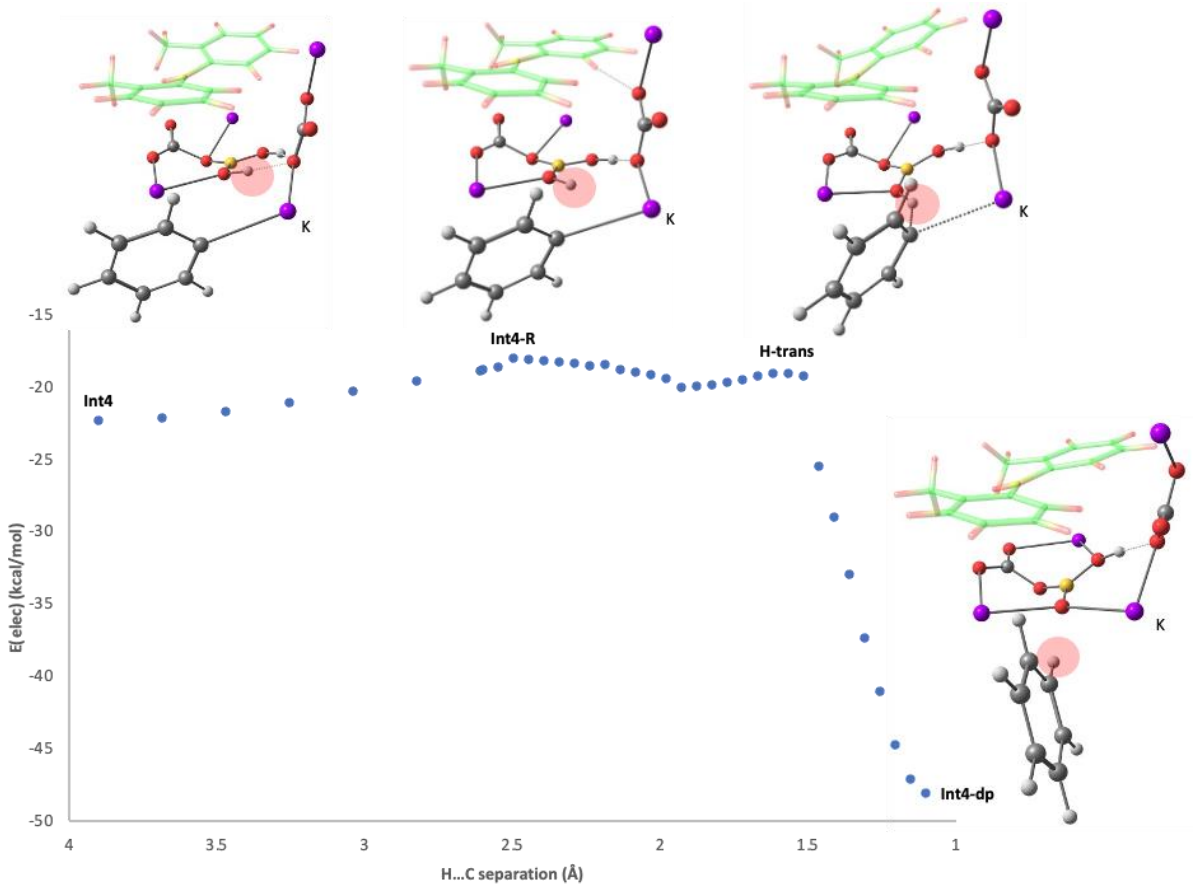
Acknowledgements. We thank Dr. Sven Traxel and his team (Merck Element Analytics) for conducting and evaluating the ICP-MS analysis of **1a**, Dr. Dmitry S. Yufit (Durham) for the structure determination of **1a**, Andrei N. Iashin for conducting NMR experiments (Moscow) and Mikhail I. Sharikov for fruitful discussions. We thank the Chemical Synthesis Centre for Doctoral Training (funded by EPSRC (EP/L015366/1), AstraZeneca, GlaxoSmithKline, Syngenta, UCB, Ziylo and the University of Bristol) for the provision of a PhD studentship (BJSR); the Technology Enhanced Chemical Synthesis Centre for Doctoral Training (funded by EPSRC (EP/S024107/1), AstraZeneca, Astex, Bayer, GlaxoSmithKline, Syngenta, Vertex and the University of Bristol) for the provision of an PhD studentship (JH); GSK (iCASE studentship to MA); the EPSRC (PhD studentship to CSB, EP/T518001/1, project reference 2456710); the UK Catalysis Hub (support provided to RBB, AJJL and RN-S for our membership of the UK Catalysis Hub Consortium, funded by EPSRC grant EP/R027129/1, EP/S018050/1)); the ERC (Advanced Grant 883786 to JC) and the Royal Society (University Research Fellowship to AJJL; Research Fellowship to MOK (UF150536) and equipment grant (RGS\R2\180467)).

Author contributions.
M.A., R.B.B., C.S.B., S.A.D., J.-C.E., G.P.G, J.H., K.A.K., J.K, P.S.K., N.E.P., R.N.-S., H.A.S., B.J.S.R, D.V.U, M.P.W. and H.J.W. performed and analysed experiments. R.B.B., J.C., G.P.G, I.V.H., M.O.K., D.B., A.J.J.L., A.Z.V. and M.P.W. designed and analysed synthetic and catalytic experiments. R.B.B. designed computational experiments. R.B.B. prepared this manuscript.

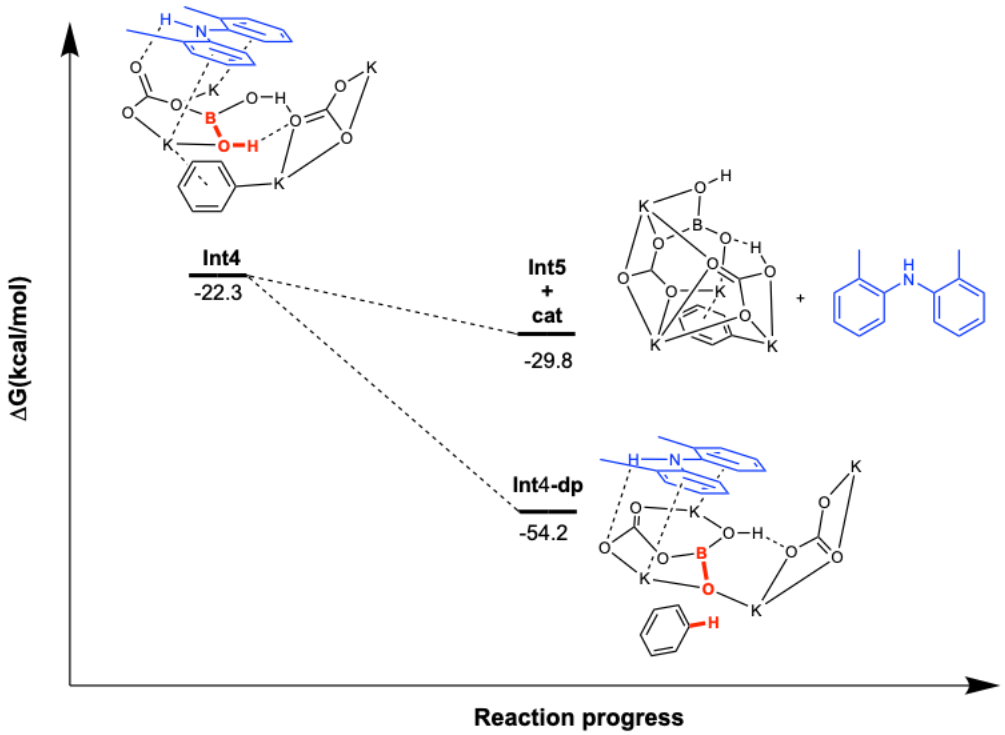
Competing interests
The authors declare no competing interests.

Additional information
Supplementary information is available for this paper at XXXX

Extended Data



Extended Data Figure 1. Computational investigation into the intramolecular hydrolysis of the key proposed phenyl potassium intermediate (Int4). Relaxed PES scan of proton (highlighted) migration to K-Ph from adjacent B-O-H group showing facile cluster rearrangement to **Int4-R** followed by proton transfer (via **H-trans**) to give the hydrolysed product **Int4-dp**. Attempts to model the transition state associated with proton transfer were unsuccessful, which is unsurprising considering the almost flat PES landscape in the region of **H-trans**. The calculations were performed using Orca 4.2 at the B3LYP-D3BJ/def2-svp level of theory (see Computational Studies section, Supporting Methods for full details); $E_{(elec)}$ of **Int4** set to same value as calculated for the ΔG in the literature for comparison purpose; amine group represented as simple tubes, the rest of the cluster as ball-and-stick.



Extended Data Figure 2. 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.** It is clear that hydrolysis is far more favourable than the formation of **Int5** and would occur before **Int5** could participate in the proposed steps leading to the activation and coupling of the aryl bromide substrate. Calculations performed using Gaussian 16 at the B3LYP-D3BJ/6-311+G** level of theory; **Int4**, **Int5** and **cat** reoptimized from the literature coordinates; ΔG for **Int4** set to same value as in the literature. See Computational Studies section, Supporting Methods for full details.