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Iron-catalysed Suzuki coupling? A cautionary tale

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ABSTRACT

In our hands, Fe(II) or (III) pyridine complexes show no activity in Suzuki biaryl cross-coupling reactions, except in one irreproducible instance when complete conversion was observed. A comparison with palladium acetate under the same conditions showed that complete conversion can be obtained in a S:C ratio of 1,000,000:1 and therefore extreme caution must be exercised to prevent 'false-positives' arising from trace Pd-contaminants.

Traditionally, biaryl cross-coupling reactions are catalysed by palladium, but the cost of this metal and the requirement to remove palladium residues in pharmaceuticals and agrochemicals to the low ppm level have led to the investigation of other metals. Iron is particularly attractive as it is cheap and has both low toxicity and environmental impact.[1] The iron-catalysed Suzuki reaction therefore represents something of a 'holy grail' in coupling chemistry. In late 2008, it appeared that this highly desirable goal had been achieved when Franzén and co-workers published their work on the use of *trans*-tetrakis(pyridine) dichloroiron(II), complex **1**, in the coupling of aryl bromides with phenylboronic acid, Scheme 1.[2,3]

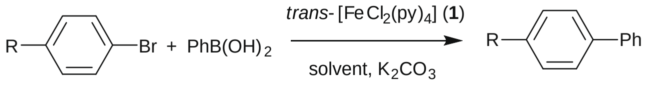
Our groups were highly interested in this potentially very valuable report and set about examining this catalyst system. Complex **1** was best prepared using the method described by Clarke and Long from iron(II) chloride tetrahydrate.[4] We re-examined the single crystal X-ray structure of **1** and found the crystal data to be identical to those reported previously.[2,4]

Contrary to our expectations we observed no catalytic activity with **1**; representative reactions and conditions studied are presented in Table 1 (entries 1–14). We then moved on to an analogous iron(III)-pyridine complex, *mer*-$[FeCl_3(py)_3]\cdot py$, **2**.[5] Complex **2** was suggested by Professor Franzén and co-workers after a closer inspection and overhaul of their results revealed that the catalyst isolated from a complex product mixture might be this iron(III) complex.[6]

Complex **2** can be described as a clathrate, in which the $[FeCl_3(py)_3]$ core is the host and the non-coordinated pyridine is the guest. Ogienko et al. demonstrated that on loss of the pyridine guest in the solid state, a facile process that readily occurs at 347 K, the host is unstable with respect to formation of $[FeCl_3(py)_2]$.[7] Indeed, we found that red microcrystals of approximate composition $[FeCl_3(py)_3]$, **2′**, formed by a modification of the literature procedure,[5a,8] readily underwent loss of pyridine, unless kept wet, generating an orange complex **3**,[7] with an Fe:py ratio of approx. 1:1.7 (as determined by elemental analysis) assigned as $[FeCl_3(py)_2]$. We also prepared a genuine sample of complex **2** by a modification of the literature procedure,[9] and re-determined the X-ray structure which was found to be identical to that reported previously.[5b] Interestingly, when data were collected at room temperature on a second sample stored for approx. one month, the reported temperature-dependent phase change was not observed. Instead the unit cell proved to be very similar to that recorded at 100 K.

X-ray quality crystals of complex **2** were tested in selected reactions (entries 15 and 16), but again no catalytic activity was observed. The considerably more unstable microcrystals **2′** were also tested (entries 17–20). Whilst no activity was observed in all other cases, we were delighted to find quantitative conversion in one reaction using the activated substrate 4-bromoacetophenone (entry 21). Unfortunately, when we attempted to repeat it, no activity was observed, even after ten attempts.

It is apparent that one of the coordinated pyridine ligands in **2** is very labile, and is readily lost under mild conditions to give the



Scheme 1.

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Table 1
Selected, representative attempted Suzuki couplings of phenylboronic acid with aryl bromides[a]

Entry	Catalyst	Aryl bromide	Solvent[b]	Conditions[c]
1	**1**	4-Bromoacetophenone	EtOH	Inert
2				Aerobic
3			EtOH/H_2O	
4				Inert
5			EtOH/H_2O + TBAB	
6			H_2O	Aerobic
7				Inert
8			H_2O + TBAB	Aerobic
9		4-Bromoanisole	EtOH	Inert
10			H_2O	
11			EtOH/H_2O + TBAB	
12			H_2O + TBAB	
13		4-Bromonitrobenzene	EtOH/H_2O	
14			EtOH/H_2O + TBAB	
15	**2**		EtOH/H_2O + TBAB	Aerobic
16			EtOH/H_2O + TBAB	
17	**2′**		EtOH	Aerobic
18				Inert
19			EtOH/H_2O + TBAB	
20		4-Bromoanisole	H_2O + TBAB	
21[d]		**4-Bromoacetophenone**	**EtOH/H_2O + TBAB**	
22	**3**		EtOH/H_2O + TBAB	
23			EtOH	Inert
24		4-Bromoanisole	H_2O + TBAB	Aerobic
25		4-Bromoacetophenone	EtOH/H_2O + TBAB	
26	**4**		EtOH/H_2O + TBAB	
27		4-Bromonitrobenzene		

[a] Conditions: ArBr (0.56 mmol), $PhB(OH)_2$ (0.728 mmol), K_2CO_3 (1.68 mmol), Fe complex, (1 mol %), solvent (3 mL), 80 °C, 24 h. Conversion to coupled product was probed by a combination of ^1H NMR spectroscopy, GC and GC–MS with appropriate internal standards against genuine samples of cross-coupled products. In all cases, unless otherwise stated, no cross-coupled products were obtained.

[b] EtOH:H_2O, 1:1; TBAB, 1.3 equiv with respect to aryl bromide.

[c] Inert atmosphere = argon or nitrogen using a glovebox or standard Schlenk line techniques.

[d] This reaction once gave complete conversion to coupled product. This reaction was then repeated a further 10 times and no cross-coupled product was observed.

complex **3**[8] which is also catalytically inactive (entries 22–25).[10] This lability may conceivably account for the very poor reproducibility. In order to circumvent the facile decomposition by ligand dissociation, we briefly examined the analogous terpy complex, [$FeCl_3$(terpy)], **4**, which has a related structure and similar magnetic properties to **2** but is stable with respect to loss of the terpy ligand. Unfortunately, it too showed no activity (entries 26 and 27).

It is possible that microcrystalline **2′** is an active but exceptionally capricious catalyst, but it is perhaps more likely that palladium contamination occurred in the one case where activity was observed despite our best efforts to prevent it.[11] It is worth noting in this regard that pre-formed palladium catalysts can show activity with this substrate at ppb levels.[12] Similarly, it has recently been shown that the activity reported in iron-catalysed C–N, C–O and C–S bond forming reactions may in fact be due to copper contaminants in the $FeCl_3$.[13]

In order to probe just how effective a palladium contaminant could be, the reaction in entry 21 was repeated with progressively lower loadings of palladium acetate with no additional ligands. Remarkably, given that the reaction is performed under air in aqueous ethanol, quantitative conversion to 4-acetylbiphenyl was observed at a substrate to catalyst ratio of one million.[14] Thus the observed, irreproducible catalytic activity could well be accounted for by trace palladium contamination either on the glassware or stirrer bar, or in the catalyst.

In conclusion, the iron-catalysed Suzuki biaryl coupling reaction appears to be, for the moment at least, out of reach. Fleeting glimpses of potential activity are tantalising; however, they must be treated with extreme caution given how exceptionally active simple palladium species are under the same reaction conditions.

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8. Under a nitrogen atmosphere anhydrous iron(III) chloride (Alfa-Aesar, 98%, 1.0 g, 6.17 mmol) was treated with anhydrous pyridine (9 mL, 0.11 mol). **CARE**: the reaction is accompanied by a significant heat production. Within 20 min red microcrystals precipitated. The supernatant layer was removed to give red microcrystals of **2′** which need to be stored wet in order to prevent loss of pyridine. Elemental analysis: Calcd for $FeCl_3py_3$: C, 45.1; H, 3.8; N, 10.5. Found: C, 45.6; H, 4.2; N,10.1. μ_{obs} = 5.86 B.M. (lit. μ_{obs} for **2** = 5.8 B.M).[4a] Drying **2′** in vacuo yielded the orange microcrystalline solid **3**, assigned as [$FeCl_3(py)_2$]. Yield 1.76 g, 89%. μ_{obs} = 4.72 B.M.
9. *Complex* **2**: As above except that after formation of the red precipitate of **2′**, a further 9.9 mL of pyridine was added and the mixture was heated to 60 °C to give a dark brown solution. The solution was then allowed to cool slowly to room temperature to give large, red crystals of **2**, suitable for X-ray analysis. X-ray data were collected on a Bruker Apex II diffractometer with graphite-monochromated MoKα (k = 0.71073 Å) radiation at 100 K. The structure was found to be the same as previously reported (see Ref. 4b). $C_{20}H_{20}Cl_3FeN_4$, orthorhombic, space group $C222_1$, $a = 8.8565(9)$, $b = 16.6659(16)$, $c = 14.2754(14)$, $b = 15.945(2)$ Å, $c = 17.278$ (3) Å. Room temperature data set: orthorhombic, space group $C222_1$ $a = 8.9730(7)$, $b = 16.8433(14)$, and $c = 14.4058(12)$. Crystallographic data (excluding structure factors) for the room temperature structure of **2** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC 738763. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk).
10. It is also worth considering the stability of **2** in water, under air at 80 °C. Under these conditions complex **2** underwent a rapid (seconds) change to a 'rusty' solid. This too was tested in catalysis as per the conditions in Table 1, entry 18, but no activity was observed.
11. For an example of trace palladium impurities catalysing the Suzuki reaction see: Arvela, R. K.; Leadbeater, N. E.; Sangi, M. S.; Williams, V. A.; Granados, P.; Singer, R. D. *J. Org. Chem.* **2005**, *70*, 161.
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14. A Radley's Carousel tube was charged with $Pd(OAc)_2$ (5.6×10^{-7} mmol as a solution in CH_2Cl_2, prepared by multiple volumetric dilutions) and the solvent removed under reduced pressure. Phenyl boronic acid (0.728 mmol), 4-bromoacetophenone (0.56 mmol), tetrabutylammonium bromide (0.56 mmol) and K_2CO_3 (1.68 mmol) were added. The solvent was added (3 mL, H_2O/EtOH 1:1) and the mixture was heated at 80 °C under nitrogen for 24 h. The solution was allowed to cool, then CH_2Cl_2 (5 mL) was added. The mixture was extracted with water (3×5 mL) and dried over $MgSO_4$ before being concentrated to dryness. The spectroscopic yield was determined as >99% by ^1H NMR spectroscopy (1,3,5-trimethoxybenzene as an internal standard).