Simple mixed Fe–Zn catalysts for the Suzuki couplings of tetraarylborates with benzyl halides and 2-halopyridines†

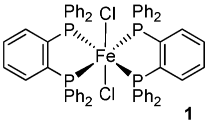
Robin B. Bedford,*[a] Mark A. Hall,[a] George R. Hodges,[b] Michael Huwe[a] and Mark C. Wilkinson[c]

Received (in Cambridge, UK) 4th August 2009, Accepted 10th September 2009
First published as an Advance Article on the web 28th September 2009
DOI: 10.1039/b915945b

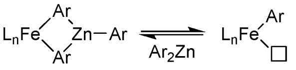
Employing co-catalytic zinc reagents facilitates the iron-catalysed Suzuki cross-coupling of tetraarylborates with both benzyl and 2-heteroaryl halides.

The use of iron catalysis in C–C bond-forming processes (Scheme 1) is undergoing a renaissance due in no small part to the low cost and toxicity of iron compared with palladium.[1] In most cases the organometallic coupling partner employed is a Grignard reagent and whilst these can be used in a wide range of reactions, the application of softer, more substrate tolerant aryl metal nucleophiles remains underdeveloped.[2,3]

We recently found that the preformed catalyst **1** or similar catalysts formed *in situ* show good to excellent activity in the Negishi coupling of arylzinc reagents with benzyl halides and phosphates.[4] Similarly, Nakamura and co-workers demonstrated that **1** can be used in the Negishi coupling of electron-deficient fluoroaryl zinc reagents with alkyl halides.[5]

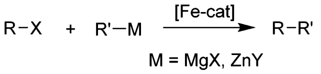


1



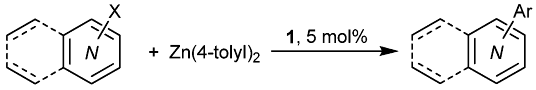
2 **3**

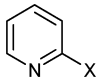
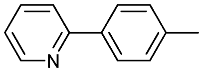
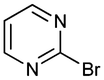
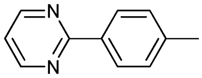
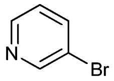
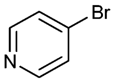
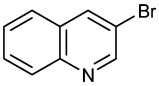
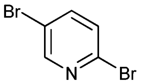
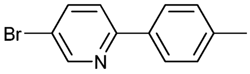
The iron-catalysed Negishi coupling can be extended to 2-halopyridine and pyrimidine substrates, as summarised briefly in Table 1.[6]† Good activity was observed in toluene–THF mixtures; pure THF led to poorer results. Increasing the amount of ditolylzinc beyond 1.2 equiv. gave higher yields of product but also led to substantial quantities of bitolyl impurity. The presence of the catalyst proved to be essential for activity (entry 4). Only 2-halopyridines reacted, in contrast with the previously reported iron-catalysed cross-coupling with aryl Grignard reagents.[6] This allowed for selective 2-arylation, as illustrated in entry 11.



Scheme 1 Iron-catalysed cross-coupling reactions.

Table 1 Fe-catalysed Negishi coupling of halopyridines[a]



Entry	Heteroaryl halide	Product	Spec. yield[b] (%) (isolated)
1			65[c]
2			75 (53)
3			15[d]
4			2[e]
5	X = Cl		35
6	X = I		55
7			58 (58)
8		None	0
9		None	0
10		None	0
11			56 (50)

[a] Conditions: heteroarylhalide (1.0 mmol), Zn(4-tolyl)$_2$ (0.25 M in THF, 4.8 ml), **1** (0.05 mmol), toluene (6 ml), 100 °C, 4 h. [b] Spectroscopic yield determined by ^{1}H NMR (1,3,5-$C_6H_3(OMe)_3$ internal standard). [c] 1 equiv. Zn(4-tolyl). [d] THF only. [e] No catalyst.

Having established the iron-catalysed Negishi coupling of both benzylhalides[4] and 2-halopyridines with diarylzinc reagents, we were keen to see whether this could be extended to analogous Suzuki cross-couplings,[7] however preliminary experiments using arylboronic acids and esters as substrates proved unsuccessful.

We previously postulated that formation of mixed Fe–Zn bimetallic intermediates of the type **2** is important for the success of **1** in the Negishi reaction; the arylzinc reagent helps to stabilise the putative active catalyst **3**, preventing premature catalyst decomposition.[4]

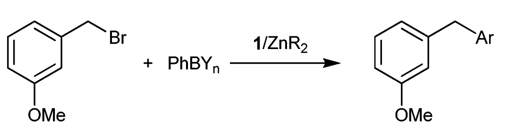
We reasoned that if intermediates of the type **2** are indeed significant then appropriate Fe–Zn mixtures might act as catalysts in other cross-coupling reactions provided the

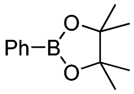
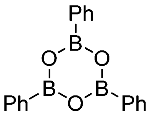
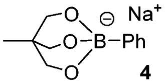
---

[a] *School of Chemistry, University of Bristol, Cantock's Close, Bristol, UK BS8 1TS. E-mail: r.bedford@bristol.ac.uk*
[b] *Syngenta, Jealotts Hill International, Research Centre, Bracknell, Berkshire, UK RG42 6EY*
[c] *Chemical Development, GlaxoSmithKline, Gunnels Wood Road, Stevenage, UK SG1 2NY*

† Electronic supplementary information (ESI) available: Experimental details. See DOI: 10.1039/b915945b

Table 2 Optimisation of Suzuki coupling of benzyl halides[a]



Entry	ZnR_2	$ArBY_n$	Base	Spec. yield[b] (%)
1	$Zn(C_6H_4\text{-}4\text{-}OMe)_2$	$PhB(OH)_2$	None	0
2			K_2CO_3	0
3			None	0
4			K_2CO_3	0
5			None	0
6	Et_2Zn			17
7			K_2CO_3	0
8	*$Zn(C_6H_4\text{-}4\text{-}OMe)_2$*	*$Na[BPh_4]$*	*None*	*96*
9				0^c
10	$Zn(C_6H_4\text{-}4\text{-}Me)_2$			95
11	$Zn(C_6H_4\text{-}4\text{-}OMe)_2$			96^d
12	None			0
13	$ZnCl_2$			48
14	$ZnEt_2$			29
15	$Zn(C_6H_4\text{-}4\text{-}OMe)_2$			93^e
16				71^f
17				0^g
18				24^h
19				44^i
20				59^j
21		$K[4\text{-}tolylBF_3]$		0
22		 **4**		0
23		$Li[PhBBu_3]$		49^k

[a] Conditions: ZnR_2 (0.1 mmol in THF, 0.14–0.34 ml), $ArBY_n$ (1.25 mmol), $3\text{-}MeOC_6H_4CH_2Br$ (1.0 mmol), **1** (0.05 mmol), toluene (8 ml), 85 °C, 4 h. [b] Spectroscopic yield, determined by ^1H NMR ($1,3,5\text{-}C_6H_3(OMe)_3$ internal standard). [c] Solvent = THF. [d] 5 mol% Ar_2Zn. [e] 2.5 mol% Fe. [f] 1 mol% Fe, reflux, 16 h. [g] No catalyst. [h] cat = $[Fe(acac)_3]$, 16 h. [i] cat = $[FeCl_2(dppp)_2]$, 16 h. [j] cat = $[FeCl_2(py)_4]$, 16 h. [k] 39% homocoupled bibenzyl product observed.

nucleophilic coupling partners employed are capable of arylating the zinc centre. Given that aryl boron reagents have been used as stoichiometric arylating species for zinc reagents,[8] we wondered could *co-catalytic* amounts of zinc reagents be exploited to initiate Suzuki cross-coupling?[9]

We focussed initially on the coupling of 3-methoxybenzyl bromide with various aryl boron reagents and these results are summarised in Table 2. Where diarylzinc reagents were employed, these were prepared *in situ* from the appropriate Grignard reagent. Again, no activity was seen with phenylboronic acid or its pinacol ester in either the presence or absence of base (entries 1–4), however some, albeit poor, activity was observed when triphenylboroxine was employed with diethylzinc (entry 6).[10]

The key to success proved to be in the use of tetraarylborate salts as the arylating reagents, with excellent activity observed with sodium tetraphenylborate (entry 8). Changing to pure THF as solvent switched off activity (entry 9), whilst changing the diarylzinc reagent had little impact (entry 10). No difference in yield was obtained on reducing the Zn : Fe ratio from 2 : 1 to 1 : 1 (entry 11), but in the absence of zinc reagents no activity was observed (entry 12). Interestingly, zinc chloride could be used in place of the diarylzinc (entry 13) although the activity was somewhat lower. Diethylzinc also showed some activity (entry 14). When diarylzinc reagents were used as the co-catalysts, essentially no incorporation of their aryl functions into cross-coupled products was observed—presumably the original aryl groups on the zinc were consumed during the reductive activation of the pre-catalyst.

Lowering the iron loading to 2.5 mol% did not have a substantial impact, whilst 1 mol% could be exploited effectively under more forcing conditions (entries 15 and 16). The presence of an iron catalyst proved essential (entry 17). Poorer activities were obtained with $[Fe(acac)_3]$, $[FeCl_2(dppp)_2]$ and $[FeCl_2(py)_4]$ (entries 18–20).

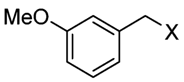
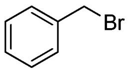
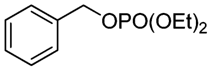
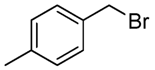
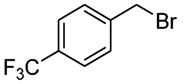
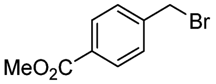
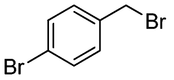
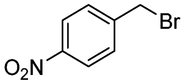
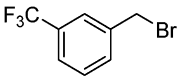
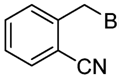
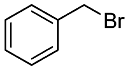
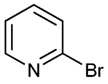
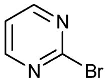
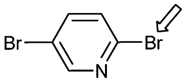
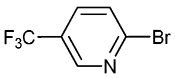
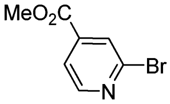
Replacing the tetraarylborate with either an aryltrifluoroborate or the activated aryl triolborate **4**[11] proved unsuccessful (entries 21 and 22). The use of $Li[PhBBu_3]$ formed *in situ* from PhLi and BBu_3 (entry 24) showed promise, but the reaction was accompanied by substantial homocoupling (39%) of the benzyl halide.

Having established that sodium tetraphenylborate gave excellent results, we next examined the coupling of tetraarylborates with a range of benzyl and 2-heteropyridyl halides and these results are summarised in Table 3. In general the reactions with the 2-halopyridines needed to be performed at higher temperature for a longer time in order to maximise conversion, although the conditions for individual reactions were not optimised. Apart from the nitro-function all other functional groups tested on the benzyl halide substrates—cyano, ester and bromide—were tolerated well. Slightly lower activity was observed with a benzyl chloride substrate (entry 2) and contrary to previous findings in the analogous iron-catalysed Negishi reaction,[4] benzyl phosphates proved to be poor substrates (entry 4). As observed in the Negishi coupling, the ability to selectively couple a benzyl bromide decorated with a second bromide on the aromatic ring (entries 8 and 16) is particularly noteworthy as this selectivity would be difficult if not impossible to achieve with palladium catalysis and opens the possibility for further catalytic functionalisation.

Good results were observed when $Na[BPh_4]$ was replaced with $K[B(4\text{-}tolyl)_4]$ (entry 12), unfortunately the less nucleophilic substrate $Na[B(C_6H_4\text{–}Cl)_4]$ displayed very low reactivity.

At present, mechanistic detail is limited, but we note the following observations. The lack of activity in the absence of a zinc co-catalyst supports the supposition that transmetallation occurs from the aryl boron reagent to the iron centre *via* an arylzinc intermediate.[12] Effectively the zinc reagent functions in much the same manner as the copper co-catalyst in Sonogashira coupling reactions.[13] As for the oxidation state of the iron complex when the aryl group is transferred, this has yet to be fully determined but we favour an iron(I)[14,15] species in agreement with the results obtained recently by Norrby and co-workers in the iron-catalysed coupling of aryl halides with alkyl Grignard reagents.[16] Whilst there may be commonality in the transmetallation steps between the reactions reported here and Grignard cross-coupling reactions, there are stark

Table 3 Fe-catalysed Suzuki coupling of RX with M[BAr$_4$][a]

Entry	RX	M[BAr$_4$]	Spec. yield[b] (%)
1		Na[BPh$_4$]	X = Br, 88 (96)
2			X = Cl (75)
3			63 (91)
4			(14)[c]
5			61 (90)
6			(>99)
7			80 (98)
8			79[d] (95)
9			0
10			(>99)
11			73 (85)
12		K[B(4-tolyl)$_4$]	(96)[e]
13		Na[B(4-C$_6$H$_4$Cl)$_4$]	Trace[e]
14		Na[BPh$_4$]	64 (76)
15			51 (69)
16			38 (49)[f]
17			53 (77)
18			52 (94)

[a] Conditions: Zn(C$_6$H$_4$-4-OMe)$_2$ (0.1 mmol in THF, 0.34 ml), M[BAr$_4$] (1.25 mmol), RX (1.0 mmol), **1** (0.05 mmol), toluene (8 ml), 85 °C, 4 h, (benzyl halides) *or* reflux, 16 h (halopyridines). [b] Spectroscopic yield, determined by ^{1}H NMR (1,3,5-C$_6$H$_3$(OMe)$_3$ internal standard). [c] 24 h. [d] ~90% purity. [e] 0.5 mmol scale. [f] Only 2-arylated product observed.

contrasts between the oxidative addition steps. Thus whilst only 2-heteroaryl halides are coupled in the reactions reported here, this is not the case in Grignard cross-coupling reactions.[6] Obviously this dichotomy will need to be explored further.

In summary, simple mixed iron–zinc catalysts formed *in situ* give good activity in the cross-coupling of arylborate salts with both benzyl and heteroaryl halides. We are currently exploring the full scope of these reactions, particularly with regard to increasing the range of aryl boron nucleophiles that can be employed, as well as their mechanisms.

We thank GlaxoSmithKline, Syngenta and EPSRC for funding.

Notes and references

1 Reviews: (*a*) W. M. Czaplik, M. Mayer, J. Cvengroš and A. J. von Wangelin, *ChemSusChem*, 2009, **2**, 396; (*b*) B. D. Sherry and A. Fürstner, *Acc. Chem. Res.*, 2008, **41**, 1500; (*c*) *Iron Catalysis in Organic Chemistry*, ed. B. Plietker, Wiley-VCH, Weinheim, 2008; (*d*) E. B. Bauer, *Curr. Org. Chem.*, 2008, **12**, 1341; (*e*) A. Fürstner and R. Martin, *Chem. Lett.*, 2005, **34**, 624; (*f*) C. Bolm, J. Legros, J. Le Paih and L. Zani, *Chem. Rev.*, 2004, **104**, 6217.

2 For examples of iron-catalysed organocopper couplings see: (*a*) C. C. Kofink, B. Blank, S. Pagano, N. Götz and Paul Knochel, *Chem. Commun.*, 2007, 1954; (*b*) G. Dunet and P. Knochel, *Synlett*, 2006, 407; (*c*) I. Sapountzis, W. Lin, C. C. Kofink, C. Despotopoulou and P. Knochel, *Angew. Chem., Int. Ed.*, 2005, **44**, 1654.

3 For examples of iron-catalysed arylzinc coupling reactions see: (*a*) M. Nakamura, S. Ito, K. Matsuo and E. Nakamura, *Synlett*, 2005, 1794; (*b*) C. K. Reddy and P. Knochel, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 1700.

4 R. B. Bedford, M. Huwe and M. C. Wilkinson, *Chem. Commun.*, 2009, 600.

5 T. Hatakeyama, Y. Kondo, Y. Fujiwara, H. Takaya, S. Ito, E. Nakamura and M. Nakamura, *Chem. Commun.*, 2009, 1216.

6 For examples of iron-catalysed cross-coupling of aryl Grignards with halopyridines see: (*a*) L. Vandromme, H.-U. Reißig, S. Gröper and J. P. Rabe, *Eur. J. Org. Chem.*, 2008, 2049; (*b*) A. Fürstner, A. Leitner, M. Méndez and H. Krause, *J. Am. Chem. Soc.*, 2002, **124**, 13856; (*c*) A. Fürstner and A. Leitner, *Angew. Chem., Int. Ed.*, 2002, **41**, 609; (*d*) J. Quintin, X. Franck, R. Hocquemiller and B. Figadère, *Tetrahedron Lett.*, 2002, **43**, 3547.

7 To the best of our knowledge, the only successful examples of iron-catalysed Suzuki couplings reported previously required very high pressures (15 kbar), see: Y. Guo, D. J. Young and T. S. A. Hor, *Tetrahedron Lett.*, 2008, **49**, 5620.

8 For recent catalytic applications see: (*a*) S. W. Smith and G. C. Fu, *J. Am. Chem. Soc.*, 2008, **130**, 12645; (*b*) C. Jimeno, S. Sayalero, T. Fjermestad, G. Colet, F. Maseras and M. A. Pericàs, *Angew. Chem., Int. Ed.*, 2008, **47**, 1098; (*c*) F. Schmidt, R. T. Stemmler, J. Rudolph and C. Bolm, *Chem. Soc. Rev.*, 2006, **35**, 454.

9 For co-catalytic copper in Fe-catalysed couplings see: (*a*) J. Mao, G. Xie, M. Wu, J. Guo and S. Ji, *Adv. Synth. Catal.*, 2008, **350**, 2477; (*b*) C. M. Rao Volla and P. Vogel, *Tetrahedron Lett.*, 2008, **49**, 5961.

10 For the mechanism and exploitation of arylation of dialkylzinc reagents with triphenylboroxine, see ref. 9*b*.

11 Y. Yamamoto, M. Takizawa, X.-Q. Yu and N. Miyaura, *Angew. Chem., Int. Ed.*, 2008, **47**, 928.

12 For transmetallation from a fourcoordinate boronate to zinc, see ref. 9*b*.

13 For recent reviews of the Sonogashira reaction see: (*a*) R. Chinchilla and C. Nájera, *Chem. Rev.*, 2007, **107**, 874; (*b*) H. Doucet and J.-C. Hierso, *Angew. Chem., Int. Ed.*, 2007, **46**, 834.

14 Reaction (**1**) with Ar$_2$Zn generates a complex corresponding to the formulation "FeAr(dpbz)$_2$" as determined by ESI-MS (see ref. 4). We assumed an oxidation state of Fe(II), but subsequent investigations suggest instead that an uncharged Fe(I) complex is formed. We are currently exploring the reactivity of this complex and the results will be published shortly.

15 For recent examples of Fe(I) aryl complexes see: (*a*) C. Ni, B. D. Ellis, T. A. Stich, J. C. Fettinger, G. J. Long, R. D. Britta and P. P. Power, *Dalton Trans.*, 2009, 5401; (*b*) C. Ni, B. D. Ellis, J. C. Fettinger, G. J. Long and P. P. Power, *Chem. Commun.*, 2008, 1014, and references therein.

16 J. Kleimark, A. Hedström, P.-F. Larsson, C. Johansson and P.-O. Norrby, *ChemCatChem*, 2009, **1**, 152.