### Cross-Coupling

# Expedient Iron-Catalyzed Coupling of Alkyl, Benzyl and Allyl Halides with Arylboronic Esters

Robin B. Bedford,<sup>\*[a]</sup> Peter B. Brenner,<sup>[a]</sup> Emma Carter,<sup>[b]</sup> Thomas W. Carvell,<sup>[a]</sup> Paul M. Cogswell,<sup>[a]</sup> Timothy Gallagher,<sup>[a]</sup> Jeremy N. Harvey,<sup>[a]</sup> Damien M. Murphy,<sup>[b]</sup> Emily C. Neeve,<sup>[a]</sup> Joshua Nunn,<sup>[a]</sup> and Dominic R. Pye<sup>[a]</sup>

**Abstract:** While attractive, the iron-catalyzed coupling of arylboron reagents with alkyl halides typically requires expensive or synthetically challenging diphosphine ligands. Herein, we show that primary and secondary alkyl bromides and chlorides, as well as benzyl and allyl halides, can be coupled with arylboronic esters, activated with al-kyllithium reagents, by using very simple iron-based catalysts. The catalysts used were either adducts of inexpensive and widely available diphosphines or, in a large number of cases, simply [Fe(acac)<sub>3</sub>] with no added coligands. In the former case, preliminary mechanistic studies highlight the likely involvement of iron(I)–phosphine intermediates.

Iron-catalyzed cross-coupling reactions have recently enjoyed a renaissance, having spent most of the seventy years since their initial publication in relative obscurity.<sup>[1,2]</sup> One particularly attractive aspect of iron-catalyzed cross-coupling processes, aside from the obvious advantages of the low cost and benign nature of iron, is that they can often tolerate both primary and secondary alkyl halide substrates, for instance in coupling reactions with aryl nucleophiles.

While the most widely studied variants of these reactions are based on aryl Grignard reagents, recently, there has been a shift towards exploiting more substrate- and media-tolerant nucleophiles. To this end, we<sup>[3]</sup> and Nakamura and co-workers<sup>[4]</sup> have developed a range of diphosphine-based systems for the iron-catalyzed coupling of organoboron-based nucleophiles. Unfortunately, the high cost or the protracted syntheses of the most effective chelating diphosphine ligands detract from the synthetic appeal of the resultant catalytic processes. Herein, we now report that very simple catalysts based on either inex-

Main Building, Park Place, Cardiff CF10 3AT (UK)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201402174.

Chem. Eur. J. **2014**, 20, 1–5

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pensive, readily available diphosphines (1,2-bis(diphenylphosphino)ethane (dppe) and 1,3-bis(diphenylphosphino)propane (dppp)) or, in a large number of cases, phosphine-free systems can catalyze the coupling of nucleophiles derived in situ from arylboron pinacol esters and a wide range of primary and secondary alkyl halides.

Nakamura's iron-catalyzed coupling of pinacol esters 1 (activated with alkyllithium reagents) with alkyl halides 2 (Scheme 1)<sup>[4a]</sup> is a particularly useful process, representing the



**Scheme 1.** Suzuki coupling of alkyl halides. Catalytic reaction conditions:<sup>[6]</sup> [a] 40 °C, 3–4 h (1 mol% Fe); [b] 25 °C, 4 h (5 mol% Fe); [c] 40 °C, 3 h (1 mol% Fe); [d] RT, 24 h (1 mol% Fe, 1 equiv dppp added); 40 °C, 1 h (5 mol% Fe); [e] 40 °C, 1 h (5 mol% [Fe(acac)<sub>3</sub>]).

current state of the art, since pinacol esters of arylboronic acids are widely commercially available and easily synthesized from the parent acids. Therefore, we were delighted to find that the trivially simple complexes [FeCl<sub>2</sub>(dppe)] and [FeCl<sub>2</sub>-(dppp)] (with an added equivalent of dppp) give excellent yields of the cross-coupled product 3a,<sup>[5]</sup> not only with cycloheptyl bromide (2a), but also with the more challenging chloride analogue 2b. Even more surprising was the observation that excellent conversion to 3a could be obtained from 2a by using 5 mol% [Fe(acac)<sub>3</sub>] (acac=acetylacetonate) with no added phosphine ligand. [Fe(acac)<sub>3</sub>] is an inexpensive, free-flowing, air-and moisture-stable solid, making it a particularly attractive precatalyst.

Table 1 summarizes the catalytic reactions investigated in the presence and absence of phosphine ligands. Gratifyingly, under phosphine-free conditions, cyclic and open-chain secondary alkyl bromides were well tolerated (entries 1, 4, 5, and 9),

<sup>[</sup>a] Prof. Dr. R. B. Bedford, Dr. P. B. Brenner, T. W. Carvell, P. M. Cogswell, Prof. Dr. T. Gallagher, Prof. Dr. J. N. Harvey, Dr. E. C. Neeve, J. Nunn, D. R. Pye School of Chemistry, University of Bristol Cantock's Close, Bristol, BS8 1TS (UK) E-mail: r.bedford@bristol.ac.uk
[b] Dr. E. Carter, Prof. Dr. D. M. Murphy School of Chemistry, Cardiff University

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[a] Conditions: A) RX (1 mmol), Li[pinBAr(tBu)] (formed in situ from pinBAr and tBuLi at 0 °C, 1.4 mmol), MgBr<sub>2</sub> (0.2 mmol), [Fe(acac)<sub>3</sub>] (5 mol%), RT, 1 h. B) As A, 40 °C. C) As A with [FeCl<sub>2</sub>(dppe)] (1 mol%), 40 °C, 3 h. D) As C with [FeCl<sub>2</sub>(dppe)] (3 mol%). E) As A with [FeCl<sub>2</sub>(dppp)] and dppp (1 mol% each), RT, 24 h. F) As E with [FeCl<sub>2</sub>(dppp)] and dppp (3 mol% each). [b] Determined by <sup>1</sup>H NMR spectroscopy (1,3,5-(MeO)<sub>3</sub>C<sub>6</sub>H<sub>3</sub> as internal standard).

giving good to excellent conversions to the desired cross-coupled products. While  $[Fe(acac)_3]$  was routinely exploited,  $FeCl_3$  also worked reasonably well.<sup>[7]</sup>

To the best of our knowledge, the iron-catalyzed coupling of allyl halides with arylboron nucleophiles has not been reported previously,<sup>[8]</sup> but was achieved readily under phosphine-free conditions (entries 15 and 16). Benzyl bromides and chlorides also performed well (entries 17–20) under phosphine-free conditions, but, in general, the reactions with open-chain primary alkyl bromides or cycloalkyl chlorides fared better in the pres-

ence of either dppe or dppp (entries 3, 11, 13, and 14). Primary alkyl chlorides remain a challenge, with only 50% conversion to the cross-coupled product observed with *n*-octyl chloride in the presence of dppp (entry 12). Esters and cyano groups were well tolerated (entries 13, 14, and 20).

With regard to the mechanism of the catalytic processes, in the presence of diphosphines, red homogeneous reaction mixtures were observed throughout the reaction. By contrast, under phosphine-free conditions, black suspensions of iron nanoparticles formed during the reactions<sup>[9]</sup> after a variable length of time, dependent on the nature of the alkyl halide substrate. Thus, with benzyl bromide 2m, 89% of the crosscoupled product was obtained before nanoparticle formation was observed,<sup>[10]</sup> which is suggestive of a homogeneous catalytic manifold, but with alkyl bromides and allyl or benzyl chlorides, the nanoparticles formed early in the coupling reaction. Examining the reaction-time profile for the coupling of cycloheptyl bromide (2a) with 1a, we observed an induction period of around 2 min, which is coincident with the time necessary for the reaction mixture to change from pale yellow to black.<sup>[10]</sup> A black suspension was also formed on leaving out the electrophile, however, when the magnesium salt was also omitted, the reaction mixture remained as an orange homogeneous solution, suggesting that the salt is necessary for efficient transmetalation.

To simplify the mechanistic investigations, we focused on the dppe-containing catalyst system for the rest of the study, because this remains homogeneous and shows a faster rate in the coupling of **2a** with the preformed borate Li[pinBPh(tBu)] (**5a**)<sup>[11]</sup> than the catalyst derived from [Fe(acac)<sub>3</sub>] (see Figure S4 in the Supporting Information).<sup>[10]</sup> The EPR spectrum (recorded at 140 K, Figure 1) of a catalytic reaction between **2a** and **5a**, catalyzed by [FeBr<sub>2</sub>(dppe)] and one equivalent of dppe,<sup>[10]</sup> revealed the presence of the previously reported iron(I) complex [FeBr(dppe)<sub>2</sub>] (**6a**, Scheme 2).<sup>[3b]</sup> Similarly, **6a** or the related iron(I) chloride complex **6b** were observed on reaction of [FeX<sub>2</sub>(dppe)] (X = Cl or Br) and dppe with excess **5a**/MgCl<sub>2</sub>.<sup>[10]</sup>



**Figure 1.** EPR spectra (140 K) of a) a sample removed from the catalytic reaction between **2a** and **5a** catalyzed by  $[FeBr_2(dppe)]$  at 40 °C and b) a genuine sample of  $[FeBr(dppe)_2]$  **6a**.

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Scheme 2. Observation of iron(I).

magnesium salt, but to a lesser extent, suggesting that the salt facilitates transmetalation.<sup>[10]</sup>

Isolated **6b** is not only catalytically competent, but it also appears to show no induction period when used as a catalyst in the coupling of **2a** and **5a** and shows the same initial rate of reaction as [FeCl<sub>2</sub>(dppe)] with one equivalent of dppe.<sup>[10]</sup> The appearance of significant amounts of **6a** in the catalytic reaction is consistent with it being involved in the catalytic cycle, prior to the rate-determining step. If this is the case, then **6a** could be either the iron-containing intermediate immediately before the rate-determining step, or it could be in pre-equilibrium with such a species. To differentiate between these two possibilities, kinetic studies were undertaken.

The rate of reaction of **2a** with **5a** catalyzed by [FeCl<sub>2</sub>(dppe)] was found to show a first-order dependence on the iron complex and an inverse first-order dependence on added dppe, up to about eight equivalents per Fe, after which point the effect began to tail off.<sup>[10]</sup> This suggests that the active catalyst contains only *one* dppe ligand in the rate-determining step of the catalytic reaction. The observed rate showed a zero-order dependence on [**5a**], but an approximately first-order dependence on [**2a**],<sup>[12]</sup> indicating that the rate-determining step is associated with the reaction of the alkyl halide with the iron center. The reaction was accelerated by the addition of up to 0.20 equivalents (with respect to **2a**) of MgBr<sub>2</sub>, after which point it was retarded.<sup>[13]</sup>

We propose that the rate-determining step in the catalytic cycle is associated with the sequence outlined in Scheme 3, wherein a pre-equilibrium between the five-coordinate Fe<sup>1</sup> spe-



Scheme 3. The proposed sequence incorporating the rate-determining step.

cies **6** and a three-coordinate  $Fe^{1}$  species **7** a is followed by the comparatively slow reaction of **7** a with the alkyl halide. Providing that the pre-equilibrium favors **6**, the proposed process is consistent with: a) the observation of **6** a under catalytic conditions, b) the inverse order dependence on added dppe, c) the approximately first-order dependence on the alkyl halide, and d) the intermediacy of organic radicals, as supported by the products observed from the radical probe experiments in entries 21 and 22 of Table 1.

While so far we have not been able to observe the putative low-coordinate Fe<sup>1</sup> intermediate **7a** directly, owing to its high lability,<sup>[14]</sup> we reasoned that the bulkier, more conformationally rigid diphosphine ligand **4a** may allow the observation of analogous but more stable low-coordinate Fe<sup>1</sup> species. This indeed appears to be the case: the EPR spectra recorded of reaction mixtures of [FeBr<sub>2</sub>(**4a**)] with either 20 equivalents of borate **5a** and four equivalents of MgBr<sub>2</sub> (comparable with catalytic conditions but in the absence of an electrophile) or with excess PhMgBr<sup>[15]</sup> showed signals consistent with the formation of a low-spin  $S = \frac{1}{2}$  species, with non-equivalent P environments, very tentatively assigned as [FePh(**4a**)] (**7b**).<sup>[10,16]</sup>

Once generated, there are at least two potential fates for the organic radical produced in the rate-determining step shown in Scheme 3: it could react with either  $[FeX_2(dppe)]$  to generate an organoiron(III) intermediate or with a second equivalent of **6** to generate an organoiron(II) intermediate, either of which could then react with the nucleophile and ultimately close the catalytic cycle.<sup>[17]</sup> At present, it is not possible to distinguish between these (or other)<sup>[18]</sup> possibilities and work is ongoing to establish the full details of the catalytic manifold.

In summary, we have developed a highly attractive, expedient coupling of arylboronic esters with alkyl, benzyl and allyl halides. When chelating diphosphines are employed, the evidence suggests that the reaction proceeds via iron(I) as the lowest oxidation state in the manifold.<sup>[19]</sup> We are currently further investigating the full scope and mechanism of the reaction under both phosphine-containing and phosphine-free conditions.

#### Acknowledgements

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We thank the EPSRC and Pfizer for funding under both the collaborative EPSRC Programme for Synthetic Organic Chemistry with AZ-GSK-Pfizer (E.C.N) and for funding from Bristol Chemical Synthesis Centre for Doctoral Training (P.M.C. and D.R.P.) and the EPSRC for student (J.N.) and post-doctoral (P.B.B., E.C.) support and for funding from the Bristol Centre for Functional Nanomaterials (T.W.C.).

**Keywords:** alkyl halides · catalysis · cross-coupling · iron · Suzuki coupling

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- [6] **1 a** and *t*BuLi were premixed in THF  $(-40-0^{\circ}C)$  to yield Li[pinBPh(*t*Bu)] in situ; then, this mixture was added to the THF solution of the precatalyst, alkyl halide and magnesium bromide.
- [7] Repeating the reaction in Table 1, entry 1 with FeCl<sub>3</sub> gave 87% of 3a. The equivalent reaction with high-purity FeCl<sub>3</sub> (99.99%) gave 89% of 3a. Leaving the iron precatalyst out gave no activity, while using [Fe(acac)<sub>3</sub>], tBuLi, magnesium bromide diethyl etherate and substrates from more than one supplier in each case did not give an appreciable change in performance.
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- [9] For TEM image and EDX analysis, see the Supporting Information.
- [10] For details, see the Supporting Information.
- [11] Nakamura and co-workers demonstrated the formation of the borates Li[pinBR(Ar)] 5 from 1 and lithium reagents under catalytically relevant conditions, see Ref. [4].
- [12] Rate dependence on  $[{\bf 2}\,{\bf a}]$  determined to be  $\approx 0.7$  order.
- [13] As yet, we have not been able to establish why the [MgBr<sub>2</sub>] (or any Grignard reagent produced in situ from it) has an accelerating influence on the rate-determining step, at least at lower loadings.
- [14] [FeX(dppe)] species appear to be unstable with respect to ligand redistribution. Thus, the reaction of [FeCl<sub>2</sub>(dppe)] with **5** a shows [FeCl-(dppe)<sub>2</sub>] (**6** b) and not [FeCl(dppe)] in the EPR spectrum (see Figure S7 in the Supporting Information).

- [15] In this case, we also saw signals in the EPR spectrum for a second minor component that was also  $S = \frac{1}{2}$ , but showed no hyperfine coupling to phosphorus. The spectrum was very similar to one recorded previously for the reaction of FeCl<sub>3</sub> with 4-tolMgCl (see: R. B. Bedford, P. B. Brenner, E. Carter, P. M. Cogswell, M. F. Haddow, J. N. Harvey, D. M. Murphy, J. Nunn, C. H. Woodall, *Angew. Chem.* **2014**, *126*, 1835–1839; *Angew. Chem. Int. Ed.* **2014**, *53*, 1804–1808) and identical to a spectrum obtained on reacting FeBr<sub>2</sub> with 20 equivalents PhMgBr, suggesting that the ligand **4a** can be displaced by a large excess of Grignard to give a phosphine-free iron(I) complex. Interestingly, the last experiment also revealed that a soluble iron(I) species is accessible under conditions in which Fe nanoparticles are formed.
- [16] The inequivalence of the P-donors could be due to the adoption of T-shaped geometry, but is more likely to be due to either coordination of solvent or a secondary interaction with one of the ligands. For a review of related effects in 3-coordinate Pt<sup>II</sup> complexes, see: M. A. Ortuño, S. Conejero, A. Lledós, *Beilstein J. Org. Chem.* 2013, *9*, 1352; for an example of a secondary interaction in a low-coordinate iron(I) complex, see: C. Ni, B. D. Ellis, T. A. Stich, J. C. Fettinger, G. J. Long, R. D. Britta, P. P. Power, *Dalton Trans.* 2009, 5401.
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Received: February 13, 2014 Published online on ■■ ■, 0000

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## COMMUNICATION

More irons in the fire: Primary and secondary alkyl, benzyl and allyl halides were coupled with arylboronic esters by using very simple iron-based catalysts. These were either adducts of inexpensive and widely available diphosphines or, in a large number of cases, simply [Fe(acac)<sub>3</sub>] with no added co-ligands (see scheme; acac=acetylacetonate). In the former case, preliminary mechanistic studies highlight the likely involvement of low-coordinate iron(I)–phosphine intermediates.



(n = 1.2)

#### Cross-Coupling

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