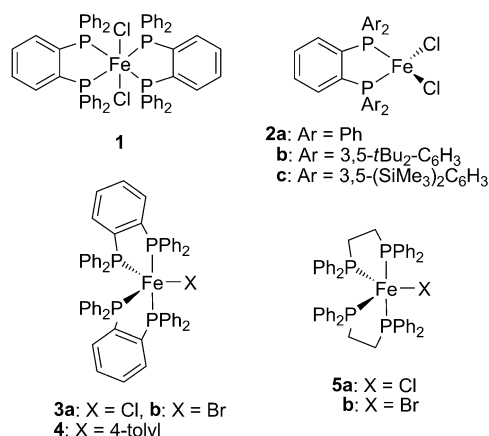


Simplifying Iron–Phosphine Catalysts for Cross-Coupling Reactions**

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Iron–phosphine complexes are emerging as an excellent choice of catalysts in a range of C–C bond-forming processes,^[1] and yet the “rules” for determining selection of the most appropriate phosphine ligands are, at present, far from clear. For example, complexes **1** and **2**, which are based on phenylene bis(phosphine) ligands, seem to occupy a privileged position, displaying, to date, unsurpassed performance in the cross-coupling of alkyl halides in terms of the variety of nucleophilic substrates that they tolerate.^[2–6] But are these systems genuinely unique or can simpler catalysts based on cheaper, more widely available bisphosphines be exploited instead? We now show that an understanding of the likely nature of the active catalyst allows the development of far simpler catalysts based on the widely available and inexpensive ligand bis(diphenylphosphino)ethane (dppe).



Previous screening approaches revealed dppe to be a thoroughly unremarkable ligand in iron-catalyzed cross-coupling reactions,^[1,2a,b] but we now show that, given the

correct choice of pre-catalysts, iron complexes of this simple ligand can show excellent activity across a range of C–C bond-forming processes.

Iron(I) was proposed as a possible active oxidation state in iron-catalyzed cross-coupling reactions by Kochi and Tamura over 40 years ago,^[7] whereas more recent mechanistic and computational evidence in favor of Fe^I was reported by Norrby and coworkers.^[8] We recently showed that Fe^I is the most kinetically reasonable lowest oxidation state in the catalytic cycle for the coupling of aryl zinc reagents with alkyl halides using pre-catalyst **1**.^[9] We isolated the Fe^I complexes **3** and **4**, and demonstrated that **3b** is likely to be an on-cycle intermediate.^[10] In contrast with pre-catalyst **1**, dppe does not readily form a bis-chelate complex, [FeCl₂(dppe)₂],^[11] thus the formation of any putative iron(I) intermediates of the form [FeX(dppe)] (**5**) would require not only reduction of an [FeX₂(dppe)] (**6**) precursor but also the concurrent coordination of another equivalent of dppe. Other iron-based species formed in the meantime may show either poor activity or decreased selectivity towards the cross-coupled product or both. We reasoned that if this is the case, then facilitating the formation of bis-chelate complexes prior to the catalytic reaction may allow good activity.

The data in Table 1 provide support for this hypothesis. In the absence of added dppe, 78 % of the cross-coupled product **9a** was obtained, along with significant amounts of competing homo-coupled products **10** and **11**. Pre-treating **6a** with the diarylzinc reagent prior to addition of the benzyl bromide led to a significant worsening of performance. Employing a mixture of **6a** and one equivalent of dppe gave significantly improved performance and, in this case, pre-reducing the mixture with the diarylzinc reagent improved activity and selectivity further still.

The best performance was seen with the pre-formed Fe(I)–bis(dppe) complex **5a**, which gave excellent conversion to the cross-coupled product **9a**.^[12] Unfortunately, the air-sensitivity of complex **5a** and the relative complexity of its synthesis, detract from its utility. Accordingly, we next examined the use of the easily handled iron(II) bis-dppe complex **12**,^[13] which was readily prepared in one pot from commercially available [Fe(OH₂)₆][BF₄]₂,^[14] and showed no sign of decomposition under air over several days. Complex **12** gave a good amount of **9a**, albeit with slightly reduced selectivity and the need for more forcing reaction conditions (85 vs. 45 °C). The latter may in part be due to the incomplete solubility of the pre-catalyst under the reaction conditions at the lower temperature. Using the formation of bitolyl as a proxy for average oxidation state, the reaction of complex **12** with **8a** at 85 °C revealed that it is rapidly reduced to Fe^I under the reaction conditions.^[15]

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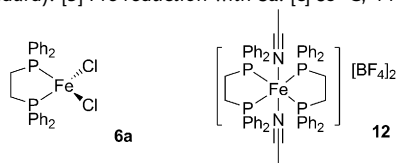
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.201207868>.

Table 1: Optimization of the dppe-based catalyst.

Reaction scheme showing the coupling of **7a** (1.00 mmol) and **8a** (1.00 mmol) using **[Fe]** (5 mol %) in toluene at 45 °C for 16 h. The products are **9a**, **10**, **11**, and **7a**.

| Entry | [Fe], conditions | Products [mmol] ^[a] | | | |
|-------|---|--------------------------------|------|------|------------------|
| | | 9a | 10 | 11 | 7a |
| 1 | 6a , no pre-reduction | 0.78 | 0.15 | 0.23 | 0.07 |
| 2 | 6a , pre-reduction ^[b] | 0.31 | 0.03 | 0.10 | 0.53 |
| 3 | 6a +dppe (1 equiv), no pre-reduction | 0.87 | 0.12 | 0.18 | 0 |
| 4 | 6a +dppe (1 equiv), pre-reduction ^[b] | 0.91 | 0.04 | 0.08 | 0 |
| 5 | 5a | 0.96 | 0.03 | 0.15 | 0 |
| 6 | 12 | 0.93 | 0.07 | 0.10 | 0 ^[c] |

[a] Determined by ¹H NMR spectroscopy (1,3,5-trimethoxybenzene internal standard). [b] Pre-reduction with 8a. [c] 85 °C, 4 h.



Next, we briefly explored the application of both the pre-formed Fe^I complex **5a** and the Fe^{II} complex **12** in a selected range of cross-coupling reactions of benzyl and alkyl halides with various organometallic partners, many of which have previously been shown to be amenable to catalysis using phenylene bis(phosphine)-based catalysts,^[2,3a,4a] and these results are summarized in Table 2. As can be seen, **5a** is highly effective in the coupling of alkyl bromides and chlorides with zinc, aluminium, boron, and indium-based^[16] nucleophiles, with good to excellent spectroscopic yields of the desired cross-coupled products, in most cases. The tolerance of the reactions to sensitive functional groups, such as esters, cyanides, and aryl bromides, is noteworthy. The more easily prepared and handled complex **12** performs at least as well as **5a** in most of the reactions selected for comparison.

These catalytic data demonstrate that dppe-based catalysts can show excellent activity in reactions where previously dpbz-based catalysts (dpbz = 1,2-bis(diphenylphosphino)benzene) were found to be optimal. Does this demonstrate that the active iron(I) species are electronically comparable in both cases, or is the similarity in performance merely coincidental? To address this question, we next turned our attention to ascertaining the molecular and electronic structures of Fe^I-dppe species **5a** and the related bromide complex, **5b**.

Complex **5a** was reported nearly 40 years ago, but no structural information was provided.^[17] We prepared both **5a** and its bromide analogue **5b** in good yields by the reaction of the corresponding [FeX₂(dppe)] complex and dppe with two equivalents of benzylmagnesium chloride and bromide, respectively, in THF.^[14] The X-ray crystal structures of both

Table 2: Cross-coupling reactions catalyzed by Fe–dppe complexes.

| RX + R'M | | [Fe] (5 mol %) | R–R' |
|-------------------|------------------------|---|-----------------------------------|
| Entry | 7 | conditions | 9 |
| | RX | R'M [Fe] | Product, yield [%] ^[a] |
| 1 ^[b] | | Zn(tol) ₂ [5a] | 9a , 96 % |
| 2 ^[c] | 7a | Zn(tol) ₂ [12] | 9a , 93 % |
| 3 ^[d] | | Zn(tol) ₂ [12] | 9a , 91 % |
| 4 ^[c] | | Zn(tol) ₂ [5a] | 9b , 84 % |
| 5 ^[c] | 7c | Zn(tol) ₂ [12] | 9b , 91 % |
| 6 ^[b] | | Zn(tol) ₂ [5a] | 9c , 92 % |
| 7 ^[c] | 7d | Zn(tol) ₂ [12] | 9c , 94 % |
| 8 ^[c] | | Zn(tol) ₂ [5a] | 9d , 79 % |
| 9 ^[c] | 7e | Zn(tol) ₂ [12] | 9d , 78 % |
| 10 ^[e] | 7a | Na[BPh ₄] [5a] | 9e , 83 % |
| 11 ^[e] | 7a | Na[BPh ₄] [12] | 9e , 93 % |
| 12 ^[e] | 7d | Na[BPh ₄] [5a] | 9f , 89 % |
| 13 ^[f] | 7a | MgCl[Al(tol) ₄] [5a] | 9a , 90 % |
| 14 ^[f] | 7a | MgCl[Al(tol) ₄] [12] | 9a , 92 % |
| 15 ^[c] | 7a | MgCl[In(tol) ₄] [5a] | 9a , 73 % |
| 16 ^[c] | 7a | MgCl[In(tol) ₄] [12] | 9a , 81 % |
| 17 ^[g] | | Zn(C ₆ H ₅ F ₂) ₂ [5a] | 9g , 75 % |
| 18 ^[f] | 7f | MgCl[Al(tol) ₄] [5a] | 9h , 90 % |
| 19 ^[f] | 7f | MgCl[Al(tol) ₄] [12] | 9h , 91 % |
| 20 ^[f] | | MgCl[Al(tol) ₄] [5a] | 9i , 83 % |
| 21 ^[f] | bromodecane, 7h | MgCl[Al(tol) ₄] [5a] | 9j , 63 % |
| 22 ^[f] | 7h | MgCl[Al(tol) ₄] [12] | 9j , 78 % |

[a] Yield determined by ¹H NMR spectroscopy (1,3,5-MeO₃C₆H₃ internal standard). [b] 45 °C, 4 h. [c] 85 °C, 4 h. [d] 85 °C, 16 h. [e] Zn(tol)₂ co-catalyst (10 mol %), 85 °C, 4 h. [f] 80 °C, 48 h. [g] 60 °C, 3 h.

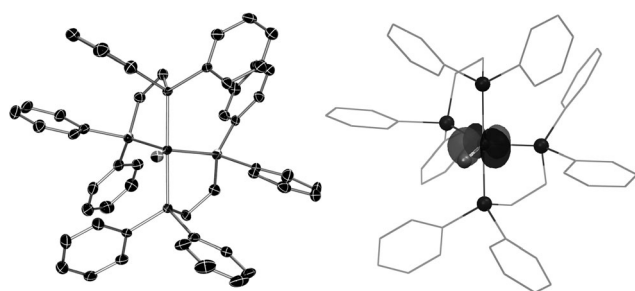


Figure 1. Left: Single crystal X-ray structure of complex **5a**, hydrogen atoms and THF solvate omitted for clarity, thermal ellipsoids set at 50% probability. Right: Calculated SOMO of low-spin complex **5a**, with the phosphine ligand residues shown in wireframe.

complexes were determined and the structure of **5a** is shown in Figure 1 (the isostructural complex **5b** is shown in the Supporting Information, Figure S3).^[14] Both complexes adopt a distorted trigonal bipyramidal structure, which is very similar to those observed for the analogous dpbz-containing complexes **3a** and **3b**,^[9] although in the present molecules, the halide atoms lie much closer to the approximate symmetry axis of the system.

The solid state magnetic moments for complexes **5a** and **b** were determined to be 1.8 and 1.9 BM at room temperature, respectively, which is consistent with a single unpaired electron, thus suggesting that the complexes are low spin in the solid state.

DFT calculations,^[14] assuming a low-spin ($S = 1/2$) character, return optimized structures for both complexes that are in close agreement with the crystal structure data. Figures 1 and S4^[14] show the calculated SOMOs for **5a** and **5b**, respectively. In each case, the Mulliken spin density corresponding to the unpaired electron is mostly located on the iron (0.87 and 0.88 for **5a** and **5b**, respectively), with only very small contributions from the ligating P and halide atoms, and the other ligand atoms.

The low temperature X-band EPR spectra of **5a** and **5b** are shown in Figure 2. The experimental g values (extracted by simulation) and calculated values (determined by DFT

calculations) are listed in Table S3.^[14] The agreement between experiment and theoretical values is excellent, and both reveal a rhombic g tensor, which is consistent with a low spin ($S = 1/2$) Fe^{I} center. Slightly larger Δg shifts were observed in the EPR spectrum of **5b** compared to **5a** ($g_{\text{iso}} = 2.093$ vs. 2.076), and this trend was reflected in the DFT calculations. The EPR spectra are complicated considerably by the numerous and overlapping superhyperfine features originating from the ^{31}P ($I = 1/2$) and $^{35,37}\text{Cl}/^{79,81}\text{Br}$ ($I = 3/2$) nuclei. According to the DFT calculations, the two axial ^{31}P nuclei are equivalent and produce large hyperfine couplings and the two remaining equatorial ^{31}P nuclei possess smaller couplings. These results were confirmed by the EPR spectra for both complexes (Table S4).^[14] Although hyperfine couplings to the Cl or Br nuclei were observed experimentally (Figure 2), the quadrupole couplings could not be determined. However, it appears that the underlying quadrupole interactions may be responsible for the considerable linewidths and distortions observed in the EPR spectra.

In summary, the structural, electronic, DFT, and preliminary catalytic data for the iron(I) dppe complexes bear a very close similarity to the analogous phenylenebis(phosphine)-containing species, thus belying any suggestion that the latter ligands are in any way electronically privileged. We attribute the relatively poor activity associated with dppe in previous reports to the way that the catalysts are formed in situ in screening methods, and caution that such approaches to catalyst discovery may lead to excellent candidates being inadvertently overlooked. This highlights the need to develop a more thorough understanding of the basic mechanisms of iron catalyzed cross-coupling reactions, as this will act as a powerful aid in the rational development of new catalysts and catalyzed processes.

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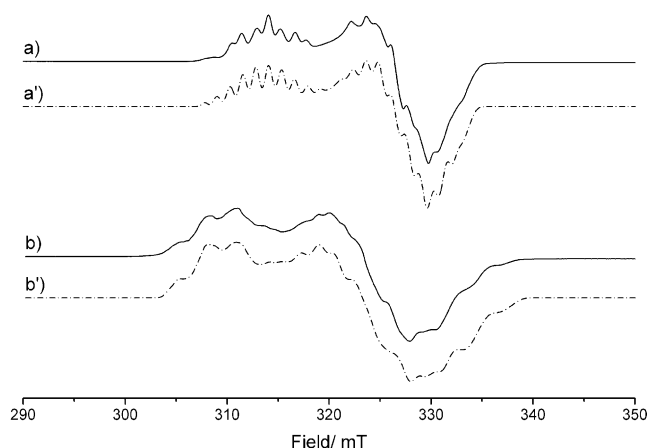


Figure 2. Continuous wave X-band EPR spectra (140 K) of complexes a) **5a** and b) **5b** recorded in a THF/toluene (15:1) solution. The corresponding simulations are shown in a', b'.

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