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Iron(I) in Negishi Cross-Coupling Reactions

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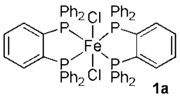
S *Supporting Information*

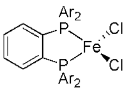
ABSTRACT: Herein we demonstrate both the importance of Fe(I) in Negishi cross-coupling reactions with arylzinc reagents and the isolation of catalytically competent Fe(I) intermediates. These complexes, [FeX(dpbz)$_2$] [X = 4-tolyl (**7**), Cl (**8a**), Br (**8b**); dpbz = 1,2-bis(diphenylphosphino)benzene], were characterized by crystallography and tested for activity in representative reactions. The complexes are low-spin with no significant spin density on the ligands. While complex **8b** shows performance consistent with an on-cycle intermediate, it seems that **7** is an off-cycle species.

The explosion in interest in iron-catalyzed cross-coupling reactions over the past decade[1,2] means there is a growing need to understand the basic mechanisms of these processes, not least to identify the oxidation states of active iron intermediates. Suggested candidates for the lowest oxidation states accessible to iron range from Fe(II) through to Fe(−II).[3,4] Kochi suggested the potential intermediacy of Fe(I) over 40 years ago,[5] and recent indirect evidence in favor of this was provided by Norrby and co-workers on the basis of mechanistic and computational studies.[6] Conversely, Fürstner and co-workers concluded that while Fe(I) is accessible in the allylation of ArMgX, reactions with a model iron(I) complex are too slow to account for the activity, and they suggested an Fe(−II)/Fe(0) manifold instead.[4c,7] Here we demonstrate that Fe(I) is the lowest *kinetically* reasonable oxidation state in a representative Negishi cross-coupling reaction and report the isolation of catalytically relevant iron(I) complexes.

The Negishi coupling of benzyl halides with diarylzinc reagents catalyzed by the preformed iron(II) precursor **1a** was chosen for this study first because the reactions are robust and highly reproducible, and thus amenable to mechanistic study, and second because complex **1a** and the related complexes **2** have shown excellent activity in a range of C−C bond-forming reactions.[8−13]



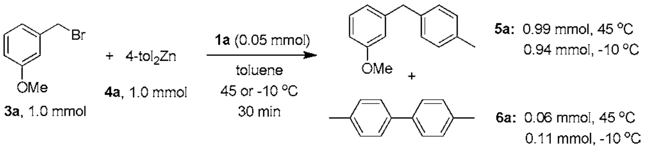
1a



2a: Ar = Ph
b: Ar =3,5-tBu$_2$-C$_6$H$_3$
c: Ar =3,5-(SiMe$_3$)$_2$-C$_6$H$_3$

The reactions of benzyl bromide **3a** with 4-tol$_2$Zn (**4a**) catalyzed by **1a** at both 45 and −10 °C gave not only high yields of the cross-coupled product **5a** but also small amounts of 4,4′-bitolyl (**6a**) (Scheme 1), which was formed very early in the reactions [see Figure S1 in the Supporting Information (SI) for reaction progress against time].[14,15] The formation of bitolyl is a reductive process, liberating two electrons per molecule formed, so it is tempting to conclude that the amounts of bitolyl produced directly correspond to a reduction of the precatalyst **1a** to iron species with average oxidation states of Fe(0) and Fe(−II), respectively. However, reversible redox couples, with the benzyl halide acting as a reoxidant, could also lead to some bitolyl formation, thereby making it difficult to deduce the average oxidation state merely from the amount of bitolyl formed in these reactions.

Scheme 1. Iron-Catalyzed Negishi Coupling of a Benzyl Halide



To circumvent this problem, the reaction was repeated at various temperatures in the *absence* of the electrophile **3a**, as this should give a clear indication of both the average oxidation states accessible under the reaction conditions and, more importantly, whether these oxidation states are accessed fast enough to be relevant in catalysis (Figure 1). It was immediately apparent that at all four temperatures the reduction of Fe(II) to Fe(I) was fast, occurring before the first samples were taken. After this point, further reduction occurred at a much lower, temperature-dependent rate, with the reaction run at 45 °C producing ~0.1 mmol of bitolyl after 15 min. Interestingly this corresponds to an average iron oxidation state of Fe(−II), consistent with Fürstner's suggestion.[4] However, the reductions to oxidation states below Fe(I) appear to be far too slow for them to be involved in the catalytic cycles of the reactions in Scheme 1: turnover leading to at least 50% conversion of substrate was observed in a time shorter than that needed for further reduction in the experiments in Figure 1.[16]

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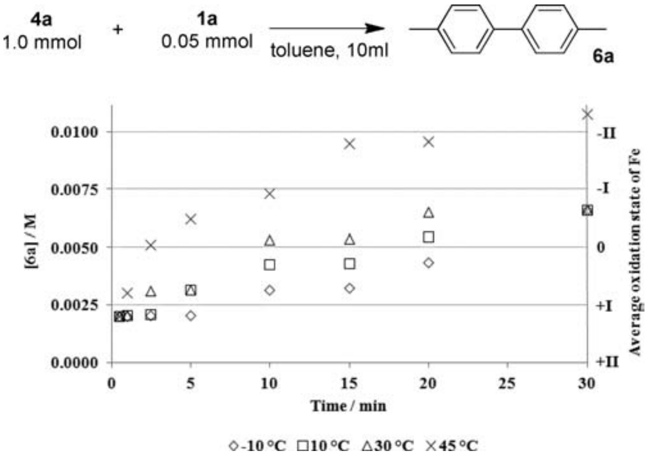
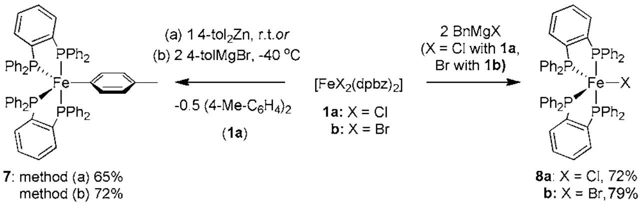


Figure 1. Formation of bitolyl from the reaction of **1a** and excess **4a** at various temperatures and the corresponding average oxidation state of iron.

Fe(I) is one of the more unusual oxidation states of iron, particularly for mononuclear complexes, which can show unusual reactivity, such as the cleavage and coupling of carbon dioxide[17] and the catalytic N−N coupling of aryl azides.[18] Accordingly, isolating catalytic robust potential intermediates became the next focus of our attention.

What are the likely structures of active Fe(I) intermediates in this Negishi reaction? Two obvious candidates are [Fe(*p*-tol)(dpbz)$_2$] (**7**) [dpbz = 1,2-bis(diphenylphosphino)benzene] and [FeX(dpbz)$_2$] (**8**) (X = Cl, Br). The reaction of **1a** with either **4a** at room temperature or 4-tolMgBr at −40 °C furnished complex **7** in good yield (Scheme 2). The formation of **7** was accompanied by the liberation of exactly 0.5 equiv of **6a**, consistent with reduction of the Fe(II) precursor **1a** to Fe(I). Somewhat fortuitously, we were able to isolate the halide complexes **8a** and **8b** by the reaction of **1a** or its bromide counterpart **1b** with excess BnMgX (X = Cl or Br, respectively). All three of these Fe(I) complexes are highly air-sensitive red compounds.[19] Complex **7** is thermally robust: heating it in toluene at 100 °C for 60 min in the absence of **4a** gave no color change and no formation of **6a**.

Scheme 2. Synthesis of Iron(I) Complexes



The X-ray crystal structures of these three complexes were determined and are shown in Figure 2.[14] They display distorted trigonal-bipyramidal geometries with the unique ligand (tolyl or halide) in the equatorial plane. The equatorial planes are tilted by 10.4−11.1° from ideal, while the P_{eq}−Fe−P_{eq} bond angles are more compressed and the P_{eq}−Fe−X angles more obtuse than ideal.[20] Isolated Fe(I)−aryl complexes are very rare,[21] and none of those reported to date are supported solely by phosphine ligands. The Fe−C bond in complex **7** [2.048(2) Å] is in the range of those reported for structurally characterized Fe(I)−aryl complexes (2.029−2.048 Å).[21a,b,d] Similarly, there are very few reported structures for iron(I) halides,[22] and again, none are supported by only phosphine ligands.

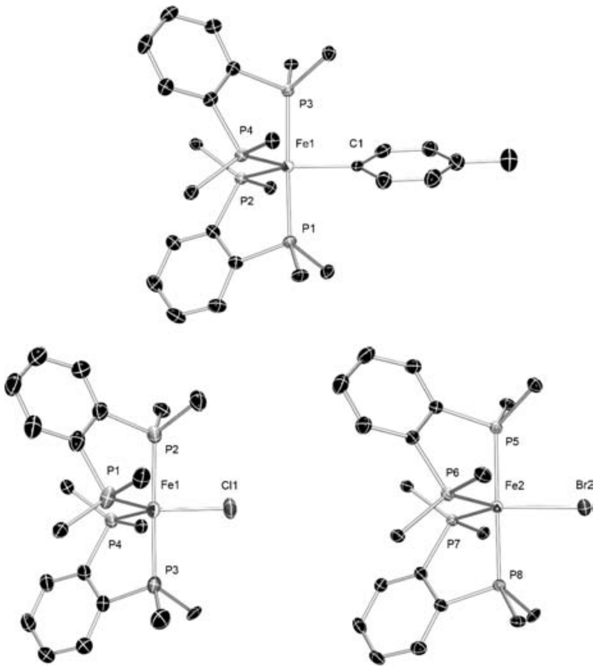


Figure 2. X-ray structures of complexes **7** (top), **8a** (bottom left), and **8b** (bottom right, one of two independent molecules), with the solvate molecules and all but the C_{ipso} atoms of the PPh_2 phenyl residues omitted for clarity. The thermal ellipsoids are set at 50% probability.[14]

The solution magnetic moment (μ_{obs}) of **7** was determined to be 1.8 μ_B at room temperature,[23] while the solid-state μ_{obs} of complexes **8a** and **8b** were determined to be 1.9 and 1.8 μ_B at room temperature, consistent with low-spin ($S = {}^1/_2$) five-coordinate iron(I) centers. The fact that organometallic Fe(I) compounds are rather rare, coupled with the apparent privileged position of phenylene-based bis(phosphines) in iron-catalyzed cross-coupling reactions,[8−12] led us to question whether the unpaired electron is genuinely associated with the metal center or is instead delocalized across the ligands as seen in recently reported, nominally iron(I) complexes with extended conjugated pyridine-based ligands.[24]

The left panel in Figure 3 shows the EPR spectrum of **7** recorded at 10 K and its simulation.[14] The spin Hamiltonian parameters used in the simulation (Table S2 in the SI) are in good agreement with the theoretical calculations based on a low-spin ($S = {}^1/_2$) Fe(I) center.[14] Similarly, a density functional theory (DFT) analysis of the ground-state structure of **7** returned

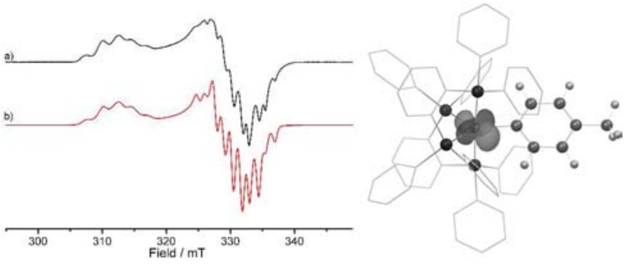
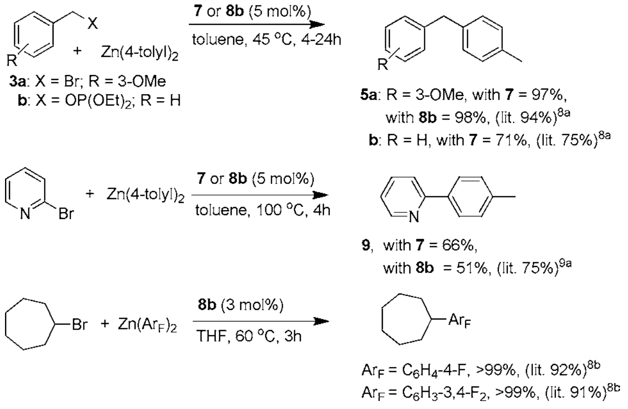


Figure 3. (left) X-band continuous-wave EPR spectrum of **7** recorded at 10 K in THF: (a) experimental; (b) simulated. (right) Calculated SOMO of low-spin complex **7**, with the phosphine ligand residues shown in wireframe.[14]

a geometry and electronic structure consistent with low-spin Fe(I) character (Figure 3, right).[14] The Mulliken spin density corresponding to the unpaired electron is mostly located on Fe (0.88), with very small contributions from the ligating P and C atoms and the other ligand atoms. DFT calculations on **8a** and **8b** gave very similar structures and singly occupied molecular orbitals (SOMOs) (Figure S8), with 0.87 and 0.88 of the unpaired electron located on the iron center, respectively.[14]

Importantly, solutions of both **7** and **8b** proved to be catalytically competent, showing productivities similar to that of the precatalyst **1a** both in representative cross-coupling reactions of ditolylzinc with benzyl halides, benzyl phosphates, and 2-pyridyl halides under our previously reported conditions[8a] and in the reactions of cycloheptyl bromide with fluoroarylzinc reagents as reported by Nakamura (Scheme 3).[8b]

Scheme 3. Representative Cross-Coupling Reactions Catalyzed by 7 (Prepared in Situ) or 8b Compared with the Same Reactions Catalyzed by 1a (Values in Parentheses)



The reaction profile of the coupling of **3a** with **4a** at −10 °C catalyzed by **8b** is essentially identical to that catalyzed by **1a**.[25] This is consistent with the existence of a common intermediate, and the best explanation for this is that **1a** is very rapidly reduced to **8b** in situ, with the latter being an active on-cycle species. In contrast, 7 showed a reaction rate about 5 times lower than that of **1a**, indicating that it is most likely an off-cycle species.[26]

In summary, we have shown that when the precatalyst **1a** is used for cross-coupling reactions of benzyl halides with arylzinc reagents, Fe(I) appears to be the lowest kinetically relevant oxidation state. We are currently undertaking a detailed investigation of the mechanism of the iron-catalyzed Negishi reaction, not least to explain the unusual apparent second-order dependence on the precatalyst,[15] which implies a significantly more complex mechanism than we previously supposed,[8a,9a] and to elucidate the precise roles of the Fe(I) intermediates. Furthermore, we are exploring the possible relevance of our results to iron cross-coupling catalysis using other ligands and other nucleophiles.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental and computational details, kinetic data, EPR spectra, crystallographic information (CIF), and reactivity of complex 7. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent reviews, see: (a) Nakamura, E.; Yoshikai, N. *J. Org. Chem.* **2010**, *75*, 6061. (b) Czaplik, W. M.; Mayer, M.; Cvengroš, J.; von Wangelin, A. J. *ChemSusChem* **2009**, *2*, 396. (c) Sherry, B. D.; Fürstner, A. *Acc. Chem. Res.* **2008**, *41*, 1500. (d) Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.

(2) *Iron Catalysis in Organic Chemistry*; Plietker, B., Ed.; Wiley-VCH: Weinheim, Germany, 2008.

(3) For an example of proposed Fe(II) intermediates, see: Noda, D.; Sunada, Y.; Hatakeyama, T.; Nakamura, M.; Nagashima, H. *J. Am. Chem. Soc.* **2009**, *131*, 6078.

(4) For the suggested intermediacy of Fe(−II), see: (a) Fürstner, A.; Leitner, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 609. (b) Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* **2002**, *124*, 13856. (c) Fürstner, A.; Martin, R.; Krause, H.; Seidel, G.; Goddard, R.; Lehmann, C. W. *J. Am. Chem. Soc.* **2008**, *130*, 8773.

(5) (a) Tamura, M.; Kochi, J. K. *J. Am. Chem. Soc.* **1971**, *93*, 1487. (b) Tamura, M.; Kochi, J. *J. Organomet. Chem.* **1971**, *31*, 289. (c) Tamura, M.; Kochi, J. K. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3063.

(6) Kleimark, J.; Hedström, A.; Larsson, P.-F.; Johansson, C.; Norrby, P.-O. *ChemCatChem* **2009**, *1*, 152.

(7) In this case, the model complexes contained ligands (Cp or Cp*) that were markedly different from those in the most active precatalyst, $[Fe(ethene)_4]^{2-}$, making direct comparison problematic. Under the conditions used for the comparison (−30 °C), all of the complexes with Cp or Cp* ligands performed poorly, irrespective of oxidation state. See ref 4c.

(8) For use with arylzinc reagents, see ref 9a and: (a) Bedford, R. B.; Huwe, M.; Wilkinson, M. C. *Chem. Commun.* **2009**, 600. (b) Hatakeyama, T.; Kondo, Y.; Fujiwara, Y.; Takaya, H.; Ito, S.; Nakamura, E.; Nakamura, M. *Chem. Commun.* **2009**, 1216.

(9) For use with arylboron reagents, see: (a) Bedford, R. B.; Hall, M. A.; Hodges, G. R.; Huwe, M.; Wilkinson, M. C. *Chem. Commun.* **2009**, 6430. (b) Hatakeyama, T.; Hashimoto, T.; Kondo, Y.; Fujiwara, Y.; Seike, H.; Takaya, H.; Tamada, Y.; Ono, T.; Nakamura, M. *J. Am. Chem. Soc.* **2010**, *132*, 10674.

(10) For Al-based nucleophiles, see: Kawamura, S.; Ishizuka, K.; Takaya, H.; Nakamura, M. *Chem. Commun.* **2010**, *46*, 6054.

(11) For alkynylation of alkyl halides, see: Hatakeyama, T.; Okada, Y.; Yoshimoto, Y.; Nakamura, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 10973.

(12) For use with aryl Grignard reagents, see: Hatakeyama, T.; Fujiwara, Y.-i.; Okada, Y.; Itoh, T.; Hashimoto, T.; Kawamura, S.; Ogata, K.; Takaya, H.; Nakamura, M. *Chem. Lett.* **2011**, *40*, 1030.

(13) Complex **1a** is now commercially available from Sigma-Aldrich.

(14) See the SI for details.

(15) At −10 °C with pretreatment of **1a** with **4a**, the reaction was sufficiently slow to allow us to determine the empirical rate law for the catalytic reaction: $d[\mathbf{5a}]/dt = k[\mathbf{1a}]^{(1.9\pm0.3)}[\mathbf{3a}]^{(1.15\pm0.1)}[\mathbf{4a}]^{(1.3\pm0.1)}$. The possibility that the second-order dependence in catalyst is actually due to dissociation of the phosphine was negated by the observation that the reaction is zeroth-order in added dppbz. Repeating the reaction without pretreatment of **1a** with **4a** gave a far higher rate of reaction over the first

2.5 min, after which time the reaction slowed enormously (see Figure S6). Under these conditions, an accurate determination of the rate law using sampling techniques proved difficult, but the data obtained were broadly consistent with the empirical rate law determined above. See the SI for kinetic data.

(16) We observed 50% conversion to product after ~20 s and 12 min in catalytic reactions run at 45 and −10 °C, respectively (compare Figure 1 with Figure S1).

(17) Lu, C. C.; Saouma, C. T.; Day, M. W.; Peters, J. C. *J. Am. Chem. Soc.* **2007**, *129*, 4.

(18) Mankad, N. P.; Müller, P.; Peters, J. C. *J. Am. Chem. Soc.* **2010**, *132*, 4083.

(19) The red color was the same as that observed in the vast majority of catalytic reactions undertaken using **1a** as a precatalyst here and in refs 8a and 9a. The remainder are reddish-brown.

(20) The bite angle and distortions from ideal trigonal-bipyramidal geometry are remarkably similar to those observed in the previously reported isoelectronic cobalt(II) complex [CoCl(dppe)$_2$]SnCl$_3$·C$_6$H$_5$Cl. See: Stalick, J. K.; Corfield, P. W. R.; Meek, D. W. *Inorg. Chem.* **1973**, *12*, 1668.

(21) (a) Ni, C.; Ellis, B. D.; Fettinger, J. C.; Long, G. J.; Power, P. P. *Chem. Commun.* **2008**, 1014. (b) Nguyen, T.; Merrill, W. A.; Ni, C.; Lei, H.; Fettinger, J. C.; Ellis, B. D.; Long, G. J.; Brynda, M.; Power, P. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 9115. (c) Ni, C.; Fettinger, J. C.; Long, G. J.; Brynda, M.; Power, P. P. *Chem. Commun.* **2008**, 6045. (d) Ni, C.; Ellis, B. D.; Stich, T. A.; Fettinger, J. C.; Long, G. J.; Britt, R. D.; Power, P. P. *Dalton Trans.* **2009**, 5401.

(22) Bouwkamp, M. W.; Bart, S. C.; Hawrelak, E. J.; Trovitch, R. J.; Lobkovsky, E.; Chirik, P. J. *Chem. Commun.* **2005**, 3406.

(23) Evans' method was used. See: Evans, D. F. *J. Chem. Soc.* **1959**, 2003.

(24) (a) Bart, S. C.; Chłopek, K.; Bill, E.; Bouwkamp, M. W.; Lobkovsky, E.; Neese, F.; Wieghardt, K.; Chirik, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 13901. (b) Irwin, M.; Jenkins, R. K.; Denning, M. S.; Krämer, T.; Grandjean, F.; Long, G. J.; Herchel, R.; McGrady, J. E.; Goicoechea, J. M. *Inorg. Chem.* **2010**, *49*, 6160.

(25) See Figure S11 for the reaction profiles.

(26) The off-cycle nature of 7 was further indicated by preliminary mechanistic studies on the basis of both its catalytic and stoichiometric reactions with **3a**, **4a**, and related substrates; these are discussed in detail in the SI.