How Low Does Iron Go? Chasing the Active Species in Fe-Catalyzed Cross-Coupling Reactions

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S *Supporting Information*

CONSPECTUS: The catalytic cross-coupling reactions of organic halides or related substrates with organometallic nucleophiles form the cornerstone of many carbon–carbon bond-forming processes. While palladium-based catalysts typically mediate such reactions, there are increasing concerns about the long-term sustainability of palladium in synthesis. This is due to the high cost of palladium, coupled with its low natural abundance, environmentally deleterious extraction (∼6 g of metal are produced per ton of ore), toxicity, and competition for its use from the automotive and consumer electronics sectors.

Therefore, there is a growing interest in replacing palladium-based catalysts with those incorporating more earth-abundant elements.

With its low cost, high natural abundance, and low toxicity, iron makes a particularly appealing alternative, and accordingly, the development of iron-catalyzed cross-coupling is undergoing explosive growth. However, our understanding of the mechanisms that underpin the iron-based catalytic cycles is still very much in its infancy. Mechanistic insight into catalytic reactions is not only academically important but also allows us to maximize the efficiency of processes or even to develop entirely new transformations.

Key to the development of robust mechanistic models for cross-coupling is knowing the lowest oxidation state in the cycle. Once this is established, we can explore subsequent redox processes and build the catalytic manifold. Until we know with confidence what the lowest oxidation state is, any cycles proposed are largely just guesswork.

To date, Fe(−II), Fe(−I), Fe(0), Fe(I), and Fe(II) have been proposed as contenders for the lowest-oxidation-state species in the cycle in iron-catalyzed cross-coupling; the aim of this Account is to pull together the various pieces of evidence in support, or otherwise, of each of these suggestions in turn.

There currently exists no direct evidence that oxidation states below Fe(0) are active in the catalytic cycle. Meanwhile, the reactivity required of the lowest-oxidation-state species has been observed with model compounds in higher oxidation states, implying that there is no need to invoke such low oxidation states. While subzero-valent complexes do indeed act as effective precatalysts, it is important to recognize that this tells us that they are efficiently converted to an active catalyst but says nothing about the oxidation states of the species in the catalytic cycle.

Zero-valent heterogeneous iron nanoparticles can be formed under typical catalytic conditions, but there is no evidence to suggest that homogeneous Fe(0) complexes can be produced under comparable conditions. It seems likely that the zero-valent nanoparticles act as a reservoir for soluble higher-oxidation-state species.

Fe(II) complexes can certainly be formed under catalytically relevant conditions, and when bulky nucleophilic coupling partners are exploited, potential intermediates can be isolated. However, the bulky reagents act as poor proxies for most nucleophiles used in cross-coupling, as they give Fe(II) organometallic intermediates that are kinetically stabilized with respect to reductive elimination. When more realistic substrates are exploited, reduction or disproportionation to Fe(I) is widely observed, and while it still has not been conclusively proved, this oxidation state currently represents a likely candidate for the lowest one active in many iron-catalyzed cross-coupling processes.
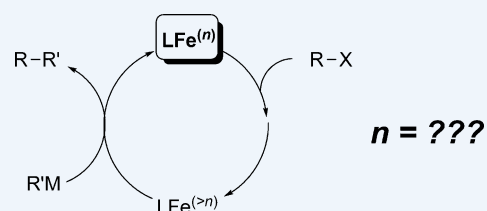
INTRODUCTION

Transition-metal-catalyzed cross-coupling reactions (Scheme 1) form the bedrock of many carbon–carbon bond-forming processes. By far the most routinely exploited catalysts used in these processes are based on palladium, but after a protracted period of dormancy,[1] iron-catalyzed cross-coupling processes are being developed at a rapid pace. The development of iron catalysts and their applications have recently been comprehensively reviewed and will not be dealt with here.[2] Instead, the focus of this Account is on the hunt for the lowest oxidation state adopted by iron in the catalytic cycles of iron-catalyzed cross-coupling reactions.

Scheme 1. Cross-Coupling Reactions
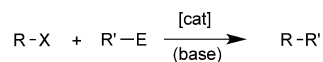
R, R' = aryl, alkenyl, alkynyl, vinyl ...
X = halide, pseudohalide leaving group ...
E = Mg, Zn, Sn, B ...

In cross-coupling chemistry, the electrophilic substrate acts as an oxidant for the metal center, while the nucleophilic substrate acts as a reductant. Scheme 2 very broadly summarizes the four

Scheme 2. Broad Classifications of On- and Off-Cycle Species in Cross-Coupling Reactions and Their Oxidation States
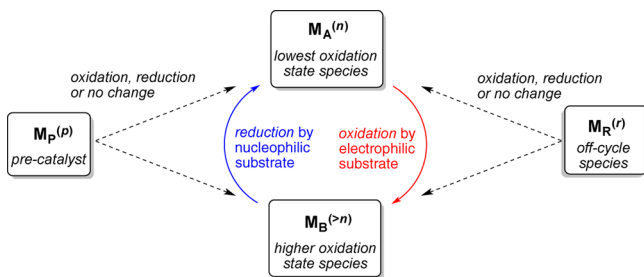
simplest "silos" into which metal species fall in the catalytic manifolds of cross-coupling processes and the redox processes that link these species. M_A represents the lowest-oxidation-state species—the species of interest here. M_P is the precatalyst added to the reaction, and M_R represents all other off-cycle species, such as catalyst resting states. The oxidation of M_A to M_B is complicated with iron because the metal can undergo facile single-electron transfer (SET) processes in addition to classical two-electron oxidative addition pathways. Before we can fully delineate these steps, it is obviously critically important to determine the oxidation state of the most reduced active species, M_A. However, as yet there is no general consensus in the literature as to what this oxidation state may be, with suggestions ranging from Fe(−II) to Fe(II). The aim of this Account is to pull together and critically examine the various strands of evidence that have been presented in the search for the lowest kinetically relevant oxidation state.

Before embarking on this journey, three general points that have a bearing on the discussion need to be made:

(a) We must distinguish between the precatalyst (M_P) and a catalytically active species. The precatalyst added to a reaction is highly unlikely to be an active catalyst itself. Instead, it undergoes an activation process that, in the presence of both oxidants (RX) and reductants (R'E) (Scheme 1), may be a redox process, giving an active species in an oxidation state different from that in M_P. It cannot be assumed that the oxidation state of a precatalyst has any bearing on the oxidation state of M_A.

(b) If a particular species is observed during catalysis, it cannot be assumed to be on-cycle; it may be an off-cycle resting state (M_R) or a side product of no relevance. Such species may also undergo a redox process before rejoining the catalytic cycle.

(c) Having both an oxidant and a reductant present makes a priori judgment of M_A almost impossible. Reaction of the precatalyst (M_P) with the reductant (R'E) alone can help determine the lowest thermodynamically accessible oxidation state, but it does not tell us whether this is

kinetically relevant in catalysis, as the reduction to the thermodynamically favored oxidation state may be too slow to be involved in the catalytic reaction.

With these considerations in hand, we can now turn our attention to the evidence presented in the field.

■ SUBZERO-VALENT IRON?

From the outset it is important to note that iron-catalyzed cross-couplings with aryl halides can be problematic. For instance, simple catalyst systems based on iron chlorides or [Fe(acac)₃] can facilitate cross-coupling of ArX with alkyl Grignards bearing β-hydrogens, but the equivalent reactions with aryl Grignards are rarely seen. It has been suggested that in the former case subzero-valent complexes are produced and that these are responsible for the increased reactivity with ArX.[3] On the basis of the cycle shown in Scheme 3a, proposed for the iron-catalyzed

Scheme 3. Proposed Fe(−II)-Based Cycles for (a) Aryl Grignard Formation and (b) Cross-Coupling
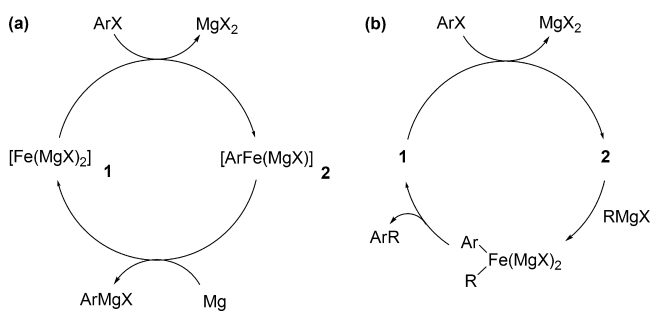
formation of ArMgX from ArX,[4] Fürstner and co-workers suggested a related Fe(−II)/Fe(0) manifold for cross-coupling (Scheme 3b).[3]

Direct evidence in support of the subzero-valent "inorganic Grignard" **1** remains elusive, although formally zero-valent iron complexes **3** and **4** with unsupported Fe−Mg bonds have been structurally characterized.[5,6] Furthermore, the reaction in Scheme 3a contains Mg(0), a powerful reductant, while the cycle in Scheme 3b does not, and currently there is no evidence to suggests that Grignard reagents are capable of reducing iron below Fe(0).
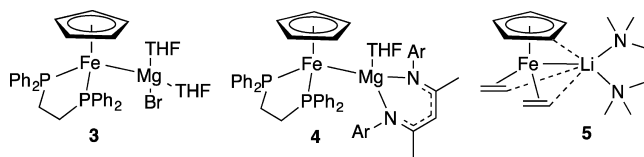

Is an oxidation state below zero necessary for the oxidative addition of an aryl halide? The zero-valent complex **5** reacts with PhCl to yield a small amount of [CpFePh(PMe₃)₂] upon trapping with trimethylphosphine,[7] suggesting that the answer is no. Furthermore, while preprepared Fe(−II) and Fe(−I) complexes can act as functioning precatalysts in cross-coupling reactions,[7,8] it must be remembered that this has no bearing on the oxidation state of the active species, M_A. Finally, iron/N-heterocyclic carbene precatalysts can be used to good effect in the coupling of aryl Grignards with ArX, provided that fluoride or alkoxide ligands (which tend to favor higher oxidation states) are also present in the coordination sphere of the iron.[9]

To summarize, while subzero-valent iron species have been invoked as active intermediates when β-hydrogen-containing alkyl Grignards are exploited in cross-coupling, there is currently scant evidence in support of this hypothesis. The true nature of the lowest-oxidation-state species in these instances is very much an open question, although a recent electron paramagnetic resonance (EPR) spectroscopic study revealed the presence of a low-spin iron(I) species.[10] Significantly more research aimed at trying to identify the intermediates formed from aryl Grignards or related nucleophiles without β-hydrogens has been undertaken, and this will form the focus of the rest of the discussion.

■ IRON(II) MESITYL COMPLEXES AS MODELS

N,N,N′,N′-Tetramethylethylenediamine (TMEDA) is useful additive in the cross-coupling of alkyl halides with aryl Grignard reagents in both greater than stoichiometric (with respect to the Grignard reagent)[11] and cocatalytic quantities.[12,13] Therefore, TMEDA-containing organoiron complexes make appealing targets for mechanistic studies, and accordingly, Nagashima and co-workers probed the coupling of mesityl Grignard with bromooctane catalyzed by a mixture of FeCl$_3$ and TMEDA as a model reaction.[14] At 5 mol % catalyst loading, this gives the cross-coupled product after 18 h at room temperature, albeit in rather low yield (32%). It is worth noting here that this low rate of catalysis and poor yield are atypical of such catalytic processes with smaller, more representative Grignard reagents. A mixture of FeCl$_3$ and TMEDA reacts with 3 equiv of MesMgBr to yield the bismesityl complex **6**, which was characterized by X-ray crystallography.[14] Complex **6** reacts with bromooctane to generate the monomesityl complex **7** and the cross-coupled product. In turn, complex **7** reacts with MesMgBr to regenerate **6**, leading the authors to propose the catalytic cycle shown in Scheme 4. However, there remained two unanswered questions:

Scheme 4. Observed Reactivity and Proposed Catalytic Cycle
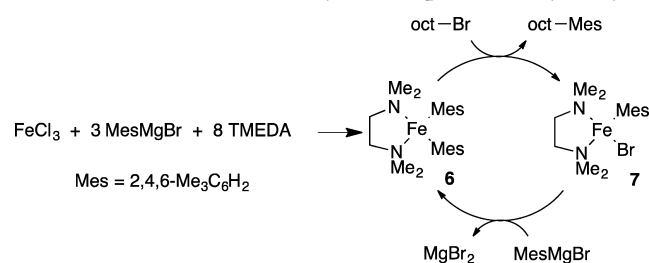
(i) what happens in a control experiment when TMEDA is left out of the catalytic reaction and (ii) is **6** still formed in the presence of excess MesMgBr, as would be present in the catalytic reaction?

We set out to answer these questions and found first that the control reaction gave a slightly higher yield of the cross-coupled product (36%) but with slightly less recovered bromooctane and slightly more octane and octene side products.[15] This suggests that TMEDA may not be important in the primary catalytic cycle but may instead suppress competing, less selective side pathways. A reinvestigation of the paramagnetic species observable by ^{1}H NMR spectroscopy upon reaction of FeCl$_3$/TMEDA with varying amounts of MesMgBr revealed that while complex **6** is indeed present at lower Grignard loadings, increasing the amount leads to increasing amounts of the homoleptic "ate" complex **8**, until by 8 equiv complex **8** is the only paramagnetic

Scheme 5

x = 3:	major
x = 5:	minor
x = 8:	none

minor
major
sole species
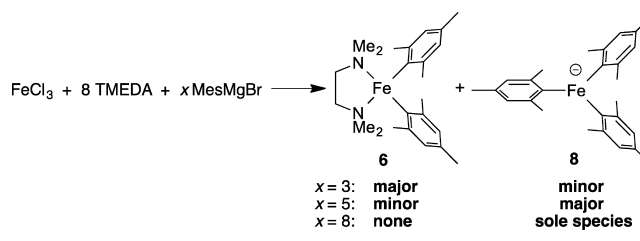
species seen (Scheme 5). Indeed, **8** is the only paramagnetic species observed by ^{1}H NMR spectroscopy during catalysis.

While the equilibrium between complexes **6** and **8** lies firmly in favor of **8** under catalytic conditions, the Curtin−Hammett principle dictates that **6** could still be the key catalytic intermediate if it reacts more rapidly with the electrophile. However, this proved not to be the case. Instead, **8** reacts far faster,[15,16] yielding the cross-coupled product and a paramagnetic species tentatively assigned as [FeBr(Mes)$_2$]$^-$ (**9**). Scheme 6 outlines a revised catalytic manifold in which the

Scheme 6. Revised Catalytic Pathways for the Coupling of MesMgBr with OctBr
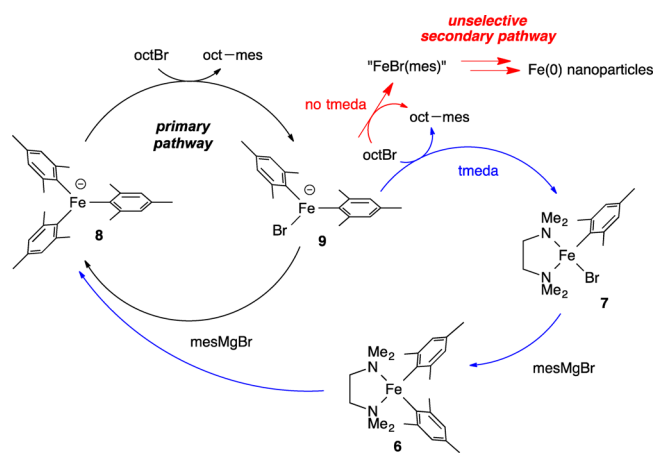
principal catalytic cycle revolves around intermediates **8** and **9**. In this scenario, the role of TMEDA is to act as a "chaperone", stabilizing off-cycle iron species as TMEDA adducts before they are reintroduced into the primary cycle by reaction with the Grignard, thus preventing the population of less-selective pathways, in particular the formation of iron nanoparticles (see below).

While the data point to TMEDA-free iron centers in the primary catalytic cycle, is this the case with more strongly coordinating bidentate ligands? The diphosphines **10** and **11** can be exploited in the cross-coupling of bulky aryl Grignards with alkyl halides;[17−19] ligand **11a** works particularly well, while the bulkier analogues **11b** and **11c** give slightly more of the competitive alkene side product.[19]

10

| **11a**: R = Et |
| **b**: R = ^{i}Pr |
| **c**: R = ^{t}Bu |
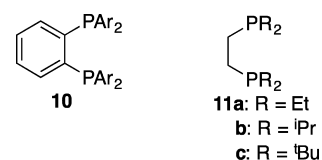
The phosphine complexes **12** react with MesMgBr to yield either dimeric monoaryl complexes **13** (Scheme 7) or the "ate"

Scheme 7
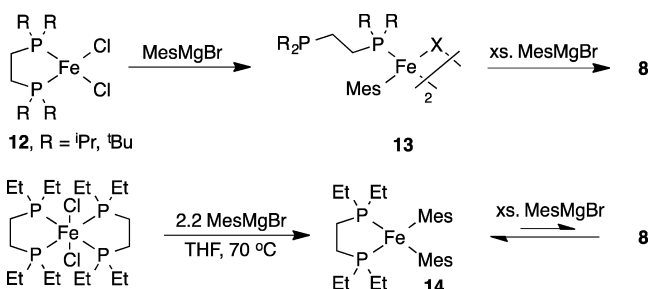
complex **8**, depending on the amount of Grignard added, while with the smaller phosphine **11a**, the bisaryl complex **14** can be accessed. We recently found that complex **14** reacts with excess MesMgBr to give an equilibrium between **14** and **8**.[20] With 20 equiv of Grignard reagent, comparable to the catalytic conditions, the equilibrium lies in favor of **8**. However, in this case the rate of formation of the cross-coupled product upon reaction of bromooctane with either **14** or **8** is lower when the "ate" complex is employed.

The phenylene-bridged diphosphines **10** should give more stable complexes than **11**. Even so, Neidig[21] showed that in the presence of excess MesMgBr, the isolated complex [Fe(Mes)$_2$(**10**)] (**15**) (Ar = 3,5-^{t}Bu$_2$C$_6$H$_3$) is in equilibrium with the "ate" complex **8** and that **15** and **8** show similar initial rates of reaction with a representative alkyl bromide. The observed increased selectivity for the cross-coupled product obtained in catalytic reactions performed using slow addition of the Grignard reagent was explained by the fact that the relatively low instantaneous concentration of the Grignard prevents the buildup of **8** and hence inhibits competitive, less selective pathways.

Scheme 8 summarizes the equilibria observed upon reaction of chelate complexes of iron dihalides with MesMgX. It is clear that

Scheme 8. Equilibria between Chelate Complexes and 8
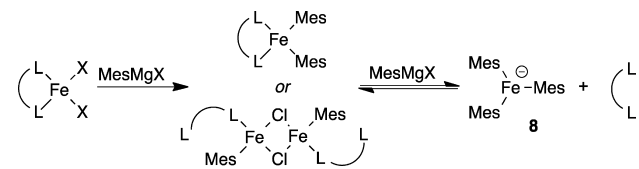
the balance between chelate complexes with mesityl ligands and the "ate" complex **8** is dependent on both the stability of the chelate and the relative concentration of the Grignard. With regard to the catalytic processes, when chelating diamines are used as coligands, it appears that the primary catalytic cycle proceeds via amine-free "ate" complexes and that the role of amine ligand is to prevent population of less-selective side manifolds. In the presence of more strongly chelating diphosphine ligands, it seems that the ligand is most likely coordinated during the primary catalytic cycle, particularly when the Grignard reagent is added slowly in order to prevent the formation of complex **8**.

■ IRON(II) ORGANOMETALLICS FROM SMALLER GRIGNARD REAGENTS

In all of the cases described in the preceding section, iron(II) appears to be a sensible candidate for **M$_A$** when bulky aryl Grignards are used as model substrates. However, it is critically

important to recognize that in all of these reactions, the bulky nucleophiles employed are not representative of the vast majority of smaller aryl Grignard reagents used in most cross-coupling processes. Not only do they give very low relative rates of catalysis, but they also yield kinetically stable, often isolable, Fe(II) intermediates. By contrast, any such species formed with smaller aryl groups would be highly unstable with respect to further reductive elimination, a point graphically illustrated in Figure 1a, where the photograph on the left shows the reaction
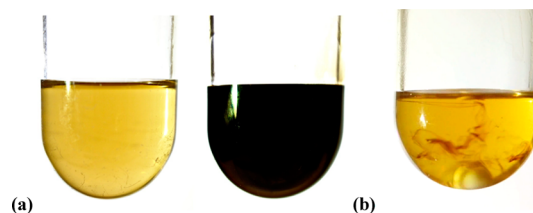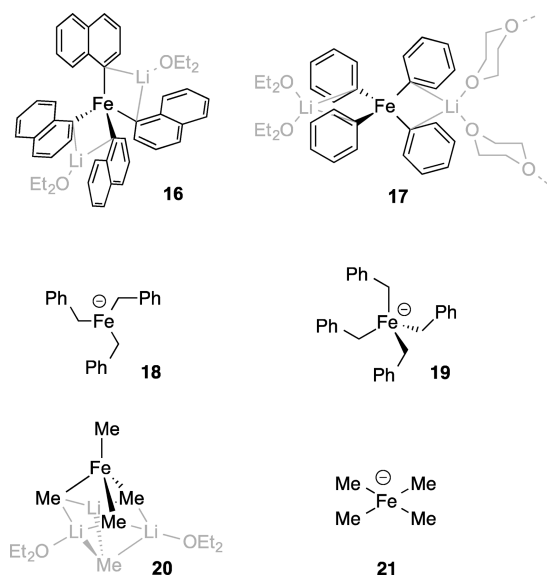

Figure 1. (a) Reactions of FeCl$_2$/TMEDA (10 equiv) with 10 equiv of ArMgBr: (left) Ar = Mes; (right) Ar = 4-tolyl. (b) Still from a video showing the dropwise addition of (4-tolyl)MgBr to CyBr in a coupling reaction catalyzed by 5 mol % FeCl$_2$ in the presence of a large excess of TMEDA.

mixture obtained upon addition of 10 equiv of MesMgBr to FeCl$_2$/TMEDA in tetrahydrofuran (THF) while that on the right shows the comparable mixture obtained with (4-tolyl)-MgBr, where further rapid reduction occurs to give iron nanoparticles. In order to prevent such over-reduction, some cross-coupling protocols call for slow addition of the Grignard reagent,[22] but this is not always necessary, as in many cases the iron nanoparticles formed are themselves active (pre)catalysts (see below).[23]
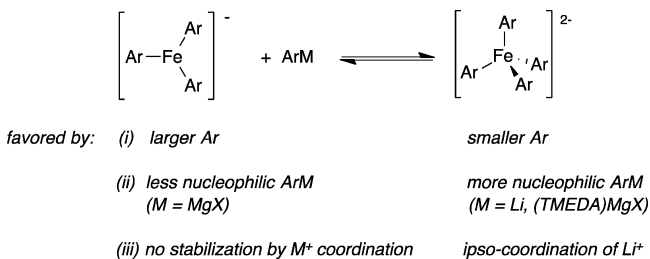
Catalytic reactions that exploit the slow addition of ArMgX typically proceed via the formation of transient, highly colored intermediates, as illustrated by the short-lived red species shown in Figure 1b.[15,24] The precise structure of this intermediate remains elusive, although ^{1}H NMR spectroscopic studies on mixtures of FeCl$_2$ and (4-tolyl)MgBr at −30 °C suggest that it may be the Fe(II) complex [Fe(4-tolyl)$_3$]$^-$, analogous to complex **8**, while addition of excess TMEDA to the mixture leads to a species tentatively assigned as [Fe(4-tolyl)$_4$]$^{2-}$, analogous to the structurally characterized complexes **16** and **17**.[25,7] No paramagnetically shifted signals for TMEDA are observed, indicating that it is not coordinated to the iron center. Interestingly, EPR spectra of these reaction mixtures revealed the presence of an $S = ^1/_2$ Fe(I) species.

Clearly there is fine balance between three- and four-coordinate mono- and dianionic "ate" complexes, with the equilibria dependent on (a) the size of the aryl group, (b) the nucleophilicity of ArM, and (c) the presence or absence of *ipso*-C-bonded M$^+$ (Scheme 9). Li counterion coordination, seen in **16** and **17**, apparently favors the formation four-coordinate complexes, but this stabilization may be deleterious to the catalyst performance, as evidenced by the fact that iron-catalyzed cross-coupling reactions with aryllithium reagents are far more sluggish than those with their Grignard counterparts.[7,15]

The balance between three- and four-coordinate complexes is further demonstrated by the structures of organoiron species obtained from alkyl Grignard or lithium reagents. With BnMgX, we found that the structurally characterized complex **18** is formed from Fe(II) or Fe(III) chloride precursors.[15] Complex **18** is susceptible to disproportionation to the tetrabenzyliron(III)

Scheme 9. Equilibria between Three- and Four-Coordinate "Ate" Complexes

favored by:		
(i)	larger Ar	smaller Ar
(ii)	less nucleophilic ArM (M = MgX)	more nucleophilic ArM (M = Li, (TMEDA)MgX)
(iii)	no stabilization by M⁺ coordination	ipso-coordination of Li⁺

"ate" complex **19** and an as yet uncharacterized Fe(I) species that can be trapped as a bischelating diphosphine adduct.[15] While Fürstner showed that tetraorganoferrate **20** is formed from FeCl₃ when MeLi is employed as the nucleophile,[7] Neidig found that when MeMgBr is used instead, the iron(III) complex **21**, akin to **19**, is formed.[26] Warming **21** again leads to the formation of an as yet uncharacterized low-spin Fe(I) species.

To summarize, homoleptic organometallic complexes can be formed upon reaction of Fe(II) or Fe(III) precursors with smaller Grignard regents. However, unlike with the mesityl ligand, these complexes are subject to facile reduction and/or disproportionation processes, both of which can generate iron species in oxidation states below Fe(II). The nature of these species and their possible relevance to the catalytic manifold are addressed in the next section.

■ FE(0) AND FE(I) SPECIES

As shown in Figure 1a, rapid addition of smaller Grignard reagents at ambient temperature leads to the production of zerovalent iron nanoparticles. These have been isolated, characterized, and shown to be catalytically competent in cross-coupling reactions,[23] demonstrating that heterogeneous Fe(0) can be accessed in cross-coupling reactions. Treatment of FeCl₃ with a large excess of PhLi was reported to generate the zerovalent complex [FePh₄]⁴⁻ (**22**), suggesting that homogeneous Fe(0) complexes may also be accessible under cross-coupling conditions.[7] However, the identification of **22** was based on a crystal structure reported before by Shilov,[27] which Girolami had already shown to be solved in the incorrect space group;[28] he

proposed that complex **22** is in fact the Fe(II) complex [Li(Et₂O)]₄[FeH₂Ph₄].

While there remains no conclusive evidence that homogeneous organometallic Fe(0) complexes can be accessed by Grignard reagents, Fe(0) nanoparticles are readily produced. Although these show catalytic activity,[22] they may well be an off-cycle resting state (**M_R**) rather than the active species (**M_A**). Indeed, dropwise addition of the nanoparticles to a large excess of a representative alkyl bromide gives a homogeneous solution[24] wherein the soluble iron complex produced presumably has an oxidation state higher than Fe(0). Furthermore, EPR spectra of the nanoparticle suspensions formed from the reaction of iron halides with excess (4-tolyl)MgCl or PhMgBr exhibited signals consistent with an $S = {}^{1}/_{2}$ Fe(I) species.[15,29] As described earlier, low-spin Fe(I) species are also seen in the disproportion of **18**,[15] the spontaneous reduction of **21**,[26] the red solutions formed upon reaction of (4-tolyl)MgBr with FeCl₃ at low temperature,[15] and the reaction of Fe(II) with alkyl Grignard reagents,[10] all of which point to iron(I) species being contenders for potential catalytic intermediates.

Iron(I) was first proposed as the possible low oxidation state in iron-catalyzed cross-coupling reactions by Kochi,[30] supported by the observation of $S = {}^{1}/_{2}$ species by EPR spectroscopy.[31] More recent mechanistic and computational evidence in favor of Fe(I) was reported by Norrby and co-workers.[32] Their density functional theory (DFT)-based comparison of Fe(I)/Fe(III) and Fe(0)/Fe(II) manifolds for the coupling of PhCl with EtMgCl showed that oxidative addition to Fe(0) is more challenging than to Fe(I) and that the reductive elimination from Fe(II) is prohibitively high in energy, strongly disfavoring the Fe(0)/Fe(II) pathway.[32b]

What might these Fe(I) species look like? A significant limitation on proposed structures for the intermediates observed by EPR spectroscopy is that they must be low-spin ($S = {}^{1}/_{2}$) rather than high-spin ($S = {}^{3}/_{2}$) complexes. Lefèvre and Jutand[33] proposed the square-planar complex [FePh(acac)(THF)]⁻ as the structure of the low-spin iron(I) species observed by EPR spectroscopy upon reaction of [Fe(acac)₃] with PhMgBr and predicated their subsequent computational analysis of reactions with representative electrophiles on this structure. However, a reexamination revealed that a trigonal-pyramidal geometry with a high-spin ($S = {}^{3}/_{2}$) electronic structure is preferred by over 20 kcal/mol.[34] This concurs with the results of a previous study by Norrby and co-workers, who showed computationally that the iron(I) etherates [FeX(DME)$_n$]⁻ (X = Br, Ph), suggested to form from iron bromide and PhMgBr, are high-spin irrespective of the number of coordinated solvent molecules.[32a] The high-spin states are again preferred by more than 20 kcal/mol, and yet the EPR studies described above for the reactions of iron halides or [Fe(acac)₃] with Grignard reagents show that some low-spin Fe(I) species must be formed. It is apparent that significantly more work is required before we can state with any confidence what the spectroscopically observed low-spin Fe(I) species are and determine the relative importance or otherwise of both high- and low-spin Fe(I) species in the catalytic manifold.

While the structures proposed for iron(I) intermediates observed in the absence of stabilizing coligands remain somewhat debatable, there have been a growing number of studies based on the reactivity of isolated iron(I) complexes with appropriate coligands. The first of these was an elegant study by Fürstner and co-workers, who showed that the crystallographically characterized Fe(I) complex **23** reacts with allyl chloride at low temperature to give iron(III) complex **24**, which

was also crystallographically characterized.[7] While the reactions summarized in Scheme 10 do not constitute a catalytic cycle, they

Scheme 10. Model Steps in a Plausible Cycle
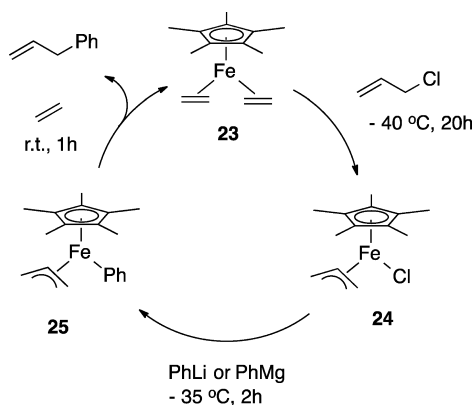
serve as an excellent model for one. However, the authors dismissed this rather appealing model in favor of an Fe(−II)-based manifold, arguing that the Fe(−II) complex **26** shows higher conversions in far shorter reaction times than **23**, **24**, or the other model compounds tested (**5** and **27**) when subjected to stoichiometric reactions with allyl halides or when used as precatalysts in the coupling of allyl halides with aryl Grignards.
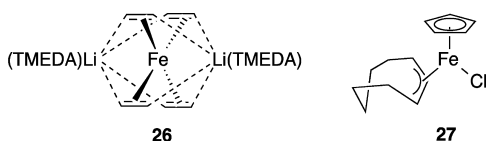
An alternative and perhaps more likely interpretation of the observed data is that the introduction of a cyclopentadienyl (Cp) or pentamethylcyclopentadienyl (Cp*) ligand significantly retards the reactivity of iron complexes **23**, **24**, **5**, and **27** compared with the highly labile Cp-ligand-free "ate" complex **26**, irrespective of the oxidation state of the iron. Furthermore, it must be remembered that while the catalytic studies tell us that the highly labile complex **26** is a better precatalyst (M_P) than any of the Cp- or Cp*-containing analogues, this has no bearing on the oxidation state of the low-valent active species (M_A). Indeed, all that can be said conclusively at this stage is that catalytic cycles comprising intermediates with Cp or Cp* give far lower rates of catalysis than those that do not contain these ligands.

Obviously it would be beneficial to move the focus away from studying model complexes and toward more realistic systems based on precatalysts that are actually exploited in a variety of processes. Iron–phosphine complexes offer real promise in this regard, as they not only are active precatalysts for Grignard cross-

coupling reactions[35,17−19] but also can be exploited in the cross-coupling of alkyl halides and related substrates with aryl-Zn-,[36−38] -Al-,[38−40] -B-,[40−45,37,29] -Ga-,[40] -In-,[37,40] and -Tl-based[40] nucleophiles. Furthermore, they can be used in the catalytic borylation of alkyl halides with diboron reagents.[46] Thus, they represent a robust family of precatalysts that display more wide-ranging activity than any other class of iron-based catalysts, and any mechanistic details that may be gleaned from their study are likely to offer insights into the mechanisms of a variety of catalytic transformations.

As descried above, the reaction of mesityl Grignard with selected iron–phosphine precatalysts leads to the formation of both phosphine-containing and phosphine-free iron(II) mesityl complexes, but such species are not representative of the wider range of nucleophiles employed because they are stable with respect to reductive elimination. Our interest has focused on the reaction of iron–phosphine complexes with smaller, more realistic aryl and related nucleophilic reagents, specifically with the aim of trying to address what oxidation states can be accessed in a kinetically relevant time frame. Titration studies of complex **28**, an active precatalyst in Negishi cross-couplings,[36,37] with a representative diarylzinc reagent showed that while lower average oxidation states may be accessed, only Fe(I) is produced on a time scale commensurate with the rates of catalysis under the same conditions.[47] Similar results were obtained when the diarylzinc was replaced with $[M(4\text{-tolyl})_4]^-$ (M = Al, In) under conditions relevant to the cross-coupling reactions of these nucleophiles.[40] Scheme 11 summarizes the Fe(I) complexes isolated upon reaction of the precursor **28** with a range of nucleophiles relevant to cross-coupling.[47,40] Either the halide complexes **29** or the aryl complex **30** is formed depending on the amount and relative nucleophilicity of the main-group organometallic. It is apparent that the Fe(I) halides are formed before the Fe(I)–aryl complexes, which implies that reduction from Fe(II) occurs from a monoaryl intermediate, LFeX(Ar), and not a bisaryl species, LFe(Ar)$_2$, and that the Fe(I)–aryl complex is formed by a comparatively slow transmetalation reaction of the Fe(I)–halide complex.

Complexes **29** and **30** have been characterized by X-ray crystallography, as have the 1,2-bis(diphenylphosphino)ethane (dppe)-containing complexes **31** formed form Mg- and B-based nucleophiles[38,29,40] and the Fe(I)–boryl complex **32**.[46] EPR spectroscopy of these complexes demonstrated that they are all low-spin ($S = ^1/_2$) species, while magnetic measurements showed that they contain a single unpaired electron. DFT computational analysis of the low-spin structures showed in all cases that the Mulliken spin density corresponding to the unpaired electron resides predominantly on the iron center.[47,38,40,46]

The isolated complexes **29b**, **30**, and **31a** are catalytically competent in a range of cross-coupling processes with aryl-Zn-,

Scheme 11. Formation of Fe(I)−Phosphine Complexes

31a: X = Cl
b: X = Br
c: X = Ph
d: X = 4-tolyl

32
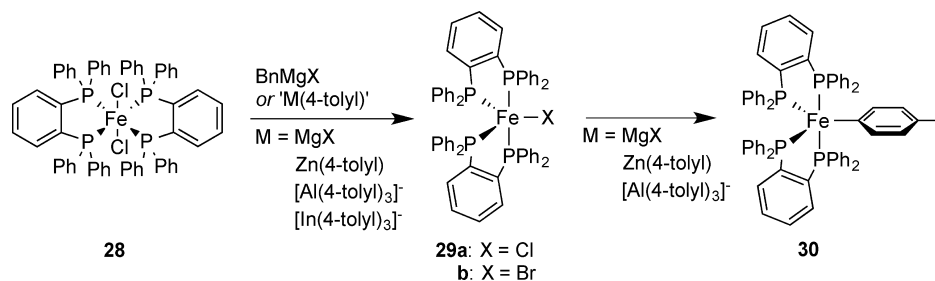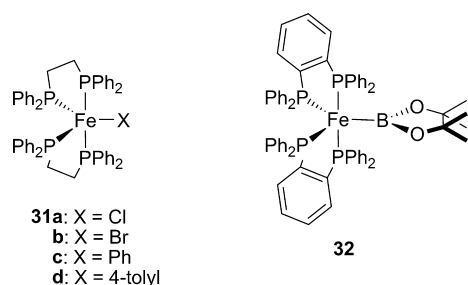
-B-, and -Al-based nucleophiles, in all cases showing productivities comparable to those of the equivalent Fe(II) precatalysts.[47,38] Importantly, when we compared the rates of Negishi reactions catalyzed by **28** and **29b**, we found that the iron(I) bromide complex showed a reaction profile essentially identical to that of the precatalyst, consistent with **29b** being either on-cycle or in equilibrium with an on-cycle species. By contrast, the aryl complex **30** showed a far lower rate, suggesting that it is not relevant to the catalytic cycle. Moreover, EPR spectra run on samples removed from representative iron-catalyzed cross-coupling reactions with B-, Al-, Ga-, and In-based nucleophiles revealed the presence of Fe(I)−phosphine complexes.[29,40]

In summary, it is apparent that (i) reduction of Fe(II)−phosphine precatalysts to Fe(I) species occurs on catalytically relevant time scales, while further reduction is much too slow to be involved; (ii) isolated Fe(I)-phosphine complexes are not only catalytically competent, but can also catalyze the reactions rapidly enough to be considered as likely intermediates; and (iii) EPR spectra of catalytic reaction mixtures show that the isolated Fe(I) species are present. Taken together, these observations strongly suggest that Fe(I)−phosphine complexes have to be considered as sensible candidates for the lowest-oxidation-state species, M_A, in a wide variety of cross-coupling processes. Future investigations are likely to focus on whether the five-coordinate Fe(I)−phosphine complexes are on-cycle or, as suggested by recent mechanistic investigations, are off-cycle resting states in equilibrium with lower-coordinate Fe(I) species, such as the tentatively assigned monodiphosphine complexes **33**.[29,40]

33: Ar = 3,5-(SiMe₃)₂C₆H₃;
X = halide, aryl
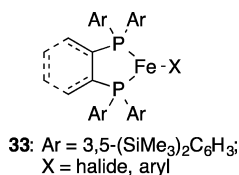
■ CONCLUSIONS AND OUTLOOK

Mechanistic studies not only give us deeper insight into existing processes, but can also allow us to develop entirely new transformations. Determining the lowest, kinetically relevant oxidation state on iron in cross-coupling is the crucial first step in an ongoing process and is the foundation stone on which mechanistic edifices will be built.

Probing organometallic mechanistic pathways is a challenging endeavor at the best of times and is made all the more entertaining in the case of iron because of its paramagnetic nature and variation in spin multiplicity and the extreme sensitivity of many of the potential intermediates. Against this backdrop, some remarkable results have been obtained, not least in the isolation of highly sensitive potential intermediates. It is important now that the community focuses on addressing the kinetic relevance

of these possible intermediates, specifically exploring whether the rates of fundamental oxidative reactions with the isolated species are consistent with rate data obtained from catalytic reactions. While it is still too early to say definitively what such studies will reveal about the lowest kinetically relevant oxidation state accessed, if I were a gambling man I would not bet against Fe(I) being found to be the culprit in many processes.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Computational details. 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.

Biography

Robin B. Bedford is a Professor of Catalysis at the University of Bristol. His research focuses on homogeneous catalysis using organometallic species, particularly replacing platinum-group-metal catalysts with those based on iron.

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