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A Physical-Inorganic Approach for the Elucidation of Active Iron Species and Mechanism in Iron-Catalyzed Cross-Coupling

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Abstract

Detailed studies of iron speciation and mechanism in iron-catalyzed cross-coupling reactions are critical for providing the necessary fundamental insight to drive new reaction development. However, such insight is challenging to obtain due to the prevalence of mixtures of unstable, paramagnetic organoiron species that can form in this chemistry. A physical-inorganic research approach combining freeze-trapped inorganic spectroscopic studies, organometallic synthesis and GC/kinetic studies provides a powerful method for studying such systems. Mössbauer, EPR and MCD spectroscopy enable the direct investigation of *in situ* formed iron species and, combined with GC analysis, the direct correlation of reactions of specific iron species to the generation of organic products. This review focuses on a description of the key methods involved in this physical-inorganic approach, as well as examples of its application to investigations of iron-SciOPP catalyzed cross-coupling catalysis.

Keywords

Iron; cross-coupling; Mössbauer spectroscopy; magnetic circular dichroism

1. Introduction

The selective formation of C–C bonds is of fundamental importance in the synthesis of pharmaceuticals, natural products and bio-active molecules for both health related research and clinical use. Iron-catalyzed C–C cross-coupling has emerged as a highly promising alternative to traditional precious metal catalysis, offering reduced cost, low toxicity and novel reactivities.^[1–6] Some of the first insight into the potential of iron in C–C cross-coupling is found in the work of Kochi, who discovered that simple ferric salts catalyze the stereoselective coupling of alkenyl halides and alkyl Grignard reagents (Scheme 1).^[7–11] Despite this significant early success with iron, from the 1980s onward interest in precious metal cross-coupling catalysis exploded while the analogous iron chemistry remained largely unexplored. In the late 1990s, interest in iron began to resurface, where the studies of Cahiez and co-workers helped reinvigorate the field of iron-catalyzed C–C cross-coupling. Their work pushed iron cross-coupling towards its current, highly productive state, broadening the substrate scope of Fe cross-couplings while highlighting the sensitivity of the

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reactivities of Fe(II) and Fe(III) salts to additives, such as NMP.^[12] More recently, reaction additives (TMEDA,^[13–15] NHCs^[16–21], bisphosphines^[20,22–25]) and well-defined mononuclear iron complexes have been employed to generate more robust cross-coupling systems with a broad substrate scope in Kumada, Negishi and Suzuki-Miyaura type cross-couplings. Additionally, studies by Fürstner and coworkers, as well as Hayashi and Nagano, explored the scope of Grignard reagents and electrophiles that can be utilized in iron-catalyzed cross-coupling reactions.^[26–29] Recent reviews further highlight the success of iron catalysts in organic synthesis to obtain cross-coupled products.^[30–31]

In these reactions, a detailed understanding of active catalyst structure, ligand and additive effects, and mechanism can provide both a key fundamental framework for improvements in current catalytic systems and the inspiration for the development of new catalysts and methodologies that will greatly expand the scope and utility of iron in C–C cross-coupling. Unfortunately, a detailed understanding of iron cross-coupling catalysis has remained largely elusive, and even systems derived from well-defined iron precursors have yielded little molecular-level insight. Historically, no consensus could be reached with regard to mechanism or fundamental catalyst structure, and even aspects as basic as the oxidation state of iron along a given reaction manifold have proven contentious. For example, a brief survey of the literature reveals that Fe(–II)/Fe(0),^[1,32–33] Fe(0)/Fe(II),^[10,34] Fe(I)/Fe(III)^[10] and Fe(II)/Fe(III)^[35] redox couples have been proposed for similar systems. This lack of consensus and fundamental insight underscores 1) the broad range of plausible reaction mechanisms for paramagnetic iron complexes in cross-coupling catalysis (including both one and two electron pathways) and 2) the experimental challenges associated with characterizing paramagnetic iron complexes. These challenges have historically presented a barrier to understanding the basic science that governs iron cross-coupling catalysis, generally precluding the rational, mechanistic driven catalyst development that has proven widely successful in palladium chemistry.

To address these challenges, our group has recently developed a physical-inorganic approach centered on the use of inorganic spectroscopic methods (e.g. Mössbauer spectroscopy, electron paramagnetic resonance (EPR), variable-temperature, variable-field magnetic circular dichroism (VTVH-MCD)) to evaluate *in situ* iron speciation, reactivity and mechanism in iron-catalyzed cross-coupling. The spectroscopic methods at the heart of this approach enable the identification and quantification of *in situ* formed iron species, including complex mixtures of paramagnetic iron species, providing the necessary insight into iron speciation to probe catalysis. Furthermore, these physical-inorganic methods are well suited to freeze-trapped, time-resolved studies, enabling evaluation of the time evolution of catalyst structure in solution, the identification of short-lived intermediates, and direct correlation between changes in iron speciation and product/side-product generation. While central to understanding mechanism, the inorganic spectroscopic studies alone are insufficient for obtaining a complete understanding of structure, reactivity and mechanism. Thus, these techniques are combined with anaerobic inorganic syntheses, reaction/GC and kinetic studies in order to fully define the on-cycle and off-cycle iron species present in catalysis. This combined experimental approach has proven to be a powerful approach to understanding iron cross-coupling catalysis, including the definition of the active iron species in iron-bisphosphine catalyzed cross-couplings of aryl nucleophiles and alkyl halides

as well as direct insight into the iron species prevalent in cross-coupling with simple ferric salts.

This review focuses on the utilization of this physical-inorganic approach for understanding iron speciation and mechanism in cross-coupling. Following the description of some of the key inorganic spectroscopic methods utilized in this methodology, the review details the application of this approach in two case studies related to iron-SciOPP catalyzed cross-coupling. While this review focuses exclusively on cross-coupling catalysis, this physical-inorganic approach also offers the potential to have a profound impact on mechanistic studies across a range of iron-catalyzed reactions in organic synthesis.

2. Inorganic Spectroscopic Methods

The combination of Mössbauer, EPR, and MCD spectroscopies in conjunction with low temperature, inert atmosphere synthesis, density functional theory, and gas chromatography represents a particularly powerful approach for the identification of *in situ* formed and reactive iron species in iron-catalyzed cross-coupling. As the information content available from the key inorganic spectroscopic methods is central to this approach, a brief introduction to each technique is provided followed by a description of how these methods are combined with synthesis and reaction studies to probe iron-catalyzed cross-coupling reactions.

2.1 Mössbauer Spectroscopy

Based upon the Mössbauer effect first described by R. L. Mössbauer in the late 1950's, [36–38] Mössbauer spectroscopy involves the recoil-free absorption of γ -rays for transitions between nuclear ground and excited states in a Mössbauer active nucleus. While numerous nuclei are amenable to Mössbauer spectroscopy (e.g. ^{119}Sn , ^{197}Au), ^{57}Fe Mössbauer spectroscopy is by far the most widely utilized due to factors including the natural abundance and stability of ^{57}Fe , the use of a source material with a reasonable half-life (^{57}Co , half-life~270 days) and the excited state lifetime properties of the ^{57}Fe excited state enabling well-resolved absorption features. Due to recoil effects from the absorption (or emission) of γ radiation in a free atom or molecule, a non-zero recoil-free fraction is required restricting Mössbauer measurements to solid or frozen solution samples. Due to the narrow linewidths for ^{57}Fe Mössbauer transitions observed, small changes in the Mössbauer transitions due to interactions between the nucleus and its surrounding environment can be observed, manifested as hyperfine interactions. Three hyperfine interactions contribute to Mössbauer spectra: (1) monopole interaction (leading to the isomer shift), (2) magnetic dipole interaction (leading to the magnetic splitting), and (3) electric quadrupole interaction (leading to the quadrupole splitting). The isomer shift (δ) arises from Coulombic interaction between the nucleus and surrounding electrons, where the *s*-electrons can penetrate the nucleus (Figure 1). The shift provides information regarding changes in the electron density of the Mössbauer active nucleus. Information from the isomer shift can provide insight into the oxidation state and spin state of a given compound.^[39] Quadrupole splitting (E_Q) occurs when a Mössbauer nucleus has a measurable electric quadrupole moment due to a nonspherical nuclear charge distribution, as is the case for ^{57}Fe , which interacts with the local electric field gradient around the nucleus to remove the degeneracy of the M_I levels of

the excited state (Figure 1). Quadrupole splitting is observed as a doublet in the absence of a magnetic interaction and provides additional insight into symmetry, oxidation state, and spin state of a compound. The magnetic hyperfine interaction (E_M) occurs when a nucleus has a magnetic dipole moment that interacts with a magnetic field (internal or applied). However, magnetic hyperfine splitting is not observed in most iron catalyzed cross-coupling Mössbauer studies, which are performed in the absence of an applied external magnetic field. Further information regarding magnetic hyperfine splitting, as well as the general theory behind Mössbauer spectroscopy, can be found in various books and reviews.^[39–52]

Mössbauer spectroscopy is a powerful tool for studying iron catalyzed cross-coupling systems as all iron species are observable regardless of spin or oxidation state. Thus, this method enables the identification and quantification of all the iron species formed *in situ* in frozen solution measurements. However, the low natural abundance of ^{57}Fe (2.1%) requires enrichment of iron salts or precatalyst samples with ^{57}Fe for studies of iron speciation at catalytically relevant concentrations. Importantly, the two parameters obtained from a zero-field Mössbauer experiment (isomer shift and quadrupole splitting) are unique for each iron compound in a mixture (Figure 1). Thus, combination with inert atmosphere synthesis, and/or additional spectroscopic measurements, enables the definitive assignment of individual components. Lastly, the use of freeze-quenched, time-resolved Mössbauer studies of reactions enables the study of the evolution of iron speciation as a function of time and reaction temperature, as well as detailed studies correlating iron speciation changes to product and side product formation in reaction studies with electro-phile, even at very short reaction times.

2.2 Electron Paramagnetic Resonance Spectroscopy

Electron paramagnetic resonance (EPR) spectroscopy is a widely used technique in inorganic chemistry for studies of paramagnetic species that probes the absorption of microwave radiation for transitions between Zeeman split M_s sublevels. Unlike more traditional absorption techniques, in EPR the microwave energy is fixed while the applied magnetic field is varied. While multiple microwave energies can be used, X-band EPR ($\sim 0.3\text{ cm}^{-1}$) is typically employed for most EPR experiments in a perpendicular mode set-up (i.e. applied magnetic field perpendicular to the oscillating magnetic field of the electromagnetic radiation). In this standard configuration, EPR experiments are the most useful for studying transition metal complexes having Kramers doublet ground states (i.e. the total spin is a half integer value), as non-Kramers systems (i.e. integer total spin) are usually EPR silent. While this review briefly highlights EPR, many excellent reviews and books discuss the theory and practical applications of EPR in further detail.^[39,51–60]

As previously described, the magnetic field is varied at a fixed microwave frequency during an EPR experiment. Zeeman splitting resulting from the applied magnetic field removes the degeneracy of the M_s sublevels of the ground state (i.e. $M_s = \pm 1/2$ for a $S=1/2$ ground state) leading to a difference in energy between these sublevels. This energy separation corresponds to $E=g\beta H$, where the g -value for a free electron is 2.0023, β is the electron Bohr magneton, and H is the applied magnetic field.^[51] However, EPR spectra of transition metal complexes exhibit deviations from the spin only g value of 2.0023 due to spin orbit

coupling (SOC). Many transition metal complexes exhibit anisotropic g values (i.e. g_x , g_y and g_z can all be different) due to the coupling between spin angular momentum and orbital angular momentum. If $g_x = g_y = g_z$, then an isotropic spectrum is observed; if $g_x = g_y \neq g_z$, then an axial spectrum is observed (see Figure 2 for an example axial spectrum); if $g_x \neq g_y \neq g_z$, then a rhombic spectrum is observed. In systems where $S > 1/2$ (i.e. $S = 3/2$ or $5/2$), effective g -values significantly different than $g = 2$ can be observed depending on the spin-state and zero-field splitting (ZFS) present. ZFS results from low symmetry distortions and SOC, and is described by the ZFS Hamiltonian given in Eq. 1.

$$H_{ZFS} = D \left[\hat{S}_z^2 - \frac{1}{3} S(S+1) \right] + E (\hat{S}_x^2 - \hat{S}_y^2) \quad (1)$$

Both axial (D) and rhombic (E) ZFS parameters are described by this Hamiltonian, where $|E/D| \leq 1/3$, and a purely axial system has $|E/D| = 0$ whereas a purely rhombic system has $|E/D| = 0.33$. Due to the Boltzmann population over the ZFS ground state, EPR intensity varies at a given temperature depending on the sign and magnitude of D and, hence, variable temperature studies can be used to experimentally determine the value of D for a specific complex (Figure 2).^[51] In addition to Zeeman effects and SOC, EPR spectra can also exhibit fine structure due to metal hyperfine and ligand hyperfine (i.e. superhyperfine) coupling interactions. While these topics are not covered in this review, further information can be found in many books and reviews.^[39,51–52,61]

For iron-catalyzed cross-coupling, X-band EPR spectroscopy is particularly useful for the identification of iron(I) and iron(III) mononuclear species as both have Kramers ground states and are EPR active (high-spin iron(I), $S = 3/2$; low-spin iron(I), $S = 1/2$; high-spin iron(III), $S = 5/2$; etc.). By contrast, mononuclear iron(II) species are generally EPR silent due to the presence of non-Kramers ground states for high-spin ($S = 2$) and intermediate-spin ($S = 1$) iron(II) (Note that low-spin iron(II) is $S = 0$ and, hence, EPR silent). Furthermore, for binuclear iron species exchange coupling (e.g. antiferromagnetic or ferromagnetic coupling) can also lead to EPR silent species even when iron(I) or iron(III) are present. In contrast to Mössbauer spectroscopy, not all iron species that may be present *in situ* can be observed by EPR. EPR spectroscopy is a useful method for determining the spin-state (and insight into the oxidation state) of isolated organoiron species of relevance to a particular cross-coupling reaction. As with freeze-trapped Mössbauer spectroscopy, freeze-trapped samples for EPR can also be taken as a function of time during a catalytic or stoichiometric reaction (i.e. with nucleophile or electrophile) in order to evaluate the potential formation or consumption of EPR active iron species. Due to the high sensitivity of EPR, *in situ* formed EPR active species can be observed even when they are present in very low concentrations (i.e. even species present as $< 1\%$ of the total iron concentration can be readily observed by EPR). Thus, this high sensitivity necessitates spin quantitation of observed EPR signals in order to determine their relative amounts with respect to total iron concentration in solution. Correlations between EPR active species and specific iron components observed by Mössbauer spectroscopy can also be performed based upon the amounts observed by each method.

2.3 Magnetic Circular Dichroism Spectroscopy

Magnetic circular dichroism (MCD) spectroscopy is a powerful method for the evaluation of electronic transitions and electronic structure in paramagnetic metal containing complexes. While this review briefly covers MCD spectroscopy, there are reviews and books which offer an in-depth explanation of the theory behind MCD spectroscopy.^[39,61,63–74] Briefly, circular dichroism (CD) spectroscopy probes the difference in absorption of left and right circularly polarized light. Observed transitions in CD are both electric dipole and magnetic dipole allowed, and only chiral molecules fulfil the requirements to observe transitions in CD. MCD combines a typical CD experiment with a magnetic field, where the magnetic field is parallel to the direction of the circularly polarized light. Furthermore, due to the Faraday effect, all molecules will exhibit MCD intensity, even if they are achiral. MCD intensity is described by Eq. 2

$$\frac{\Delta A}{E} = (3.27 \times 10^{38}) \frac{\alpha^2 C \ell}{n} \beta H \left[A_1 \left(-\frac{\partial f(E)}{\partial E} \right) + \left(B_0 + \frac{C_0}{kT} \right) f(E) \right] \quad (2)$$

where ΔA is the field-dependent difference in absorption of left and right circularly polarized light, $E = h\nu$, α is the electric permeability, C is concentration, ℓ is the path length, n is the index of refraction, β is Bohr magneton, H is the applied magnetic field, $f(E)$ is an absorption band shape and $f'(E) = \partial f(E) / \partial E$ is its derivative, A_1 is the A -term, B_0 is the B -term, and C_0 is the C -term.^[39] The A -, B - and C -terms relate to specific mechanisms through which MCD intensity arises. For paramagnetic species at extremely low temperatures, C -terms dominate (they are several orders of magnitude more intense than A - or B -terms) and are directly proportional to magnetic field and inversely proportional to temperature. The C -term intensity mechanism requires a degenerate ground-state where the degeneracy is removed due to Zeeman splitting in the presence of a magnetic field (Figure 3A). The temperature dependence observed in C -terms is due to the Boltzmann population of the Zeeman split ground state. Therefore, typical MCD experiments are run at liquid helium temperatures and high magnetic fields (up to 7 T) to maximize the C -term intensity (Figure 3B). Importantly, the ground state degeneracy requirement can be met via spin degeneracy for orbitally non-degenerate ground states, as are commonly present in lower symmetry complexes. However, spin degeneracy can only produce a non-zero C -term through SOC, and SOC governs the C -term intensity. Since transition metal ions have larger SOC parameters (ζ) than ligands, transitions involving orbitals with significant metal character will have enhanced C -term MCD intensity. Hence, $d \rightarrow d$ excited states will have more intensity than ligand-based charge transfer states, and show more low temperature MCD intensity relative to absorption intensity. The ratio between the intensities in electronic absorption and MCD is given by Eq. 3

$$\frac{C_0}{D_0} = \frac{kT}{\beta H} \left(\frac{\Delta \epsilon}{\epsilon} \right) \quad (3)$$

where D_0 is the dipole strength defined by the electric dipole transition moment integral for electronic absorption.^[39] The magnitude of the C/D ratio can be used to assign ligand field and charge transfer bands, respectively. SOC between states can also produce a temperature-dependent pseudo A -term that is comprised of two equal, but opposite signed, C -terms. Lastly, variable-temperature, variable-field MCD (VTVH-MCD), or saturation magnetization, is also a useful tool to determine the spin Hamiltonian parameters of the ground state (including the spin state and ZFS of the complex). At high magnetic field and low temperature, the C -term MCD intensity is dependent on both field and temperature. MCD intensity will increase linearly as the lowest ground state sublevel is populated and will eventually saturate and no longer produce linear MCD intensity. Fits of this data enable the determination of the spin Hamiltonian parameters of the ground state. An example of this can be seen in Figure 3C.^[75]

MCD spectroscopy is a powerful tool in studies of iron-catalyzed cross-coupling reactions, both for the analysis of isolated organoiron species and for the study of freeze-trapped, *in situ* generated iron species. For isolated iron complexes, MCD enables detailed studies of ligand-field transitions which provides insight into the oxidation and spin state of the complex as well as its geometry (via ligand-field analysis). MCD is also very useful for studies of charge-transfer transitions and, combined with TD-DFT calculations, can provide insight into the nature of specific transitions which relate to electronic structure and bonding. VTVH-MCD studies enable determination of the spin-state of a given iron species, a much higher resolution method than typical measurements of effective magnetic moments due to the greater information content obtainable for the ground state. Importantly, MCD spectroscopy is well-suited to studies of any paramagnetic iron species, thus providing a critical tool for detailed studies of systems with non-Kramers ground states (including mononuclear iron(II) species).

Freeze-trapped, time-resolved MCD studies can also provide insight into the nature of *in situ* formed iron species, as well as changes in iron speciation in reactions. For such applications, MCD offers significant advantages over traditional electronic absorption studies. Since C -term MCD is significantly more intense for paramagnetic species, contributions from paramagnetic iron complexes are observed whereas contributions from diamagnetic molecules such as organic substrates and products (which can dominate electronic absorption spectra particularly at high energy) are not observable. This enables detailed studies focusing specifically on the *in situ* formed iron species. Furthermore, the signed nature of MCD transitions facilitates the resolution of complex, overlapping transitions. Lastly, ligand-field transitions often fall in the near-infrared region, are weak in intensity and obscured by solvent overtones in absorption spectroscopy. By contrast, C -term MCD results in enhanced intensity for ligand-field transitions (due to SOC), facilitating the observation of these transitions.

2.4 Coupling Inorganic Spectroscopic Methods with Synthesis, Kinetics, and Density Functional Theory Studies in Mechanistic Investigations of Iron-Catalyzed Cross-Coupling Reactions

The combination of Mössbauer, EPR and MCD spectroscopies provide a critical means for assessing *in situ* formed iron speciation, evaluating changes in iron speciation with time, and identifying the transformation of specific iron species upon reactions with nucleophile and electrophile in iron-catalyzed cross-coupling reactions. While these methods are central to the success of the physical-inorganic approach for studying these reactions, the spectroscopic methods alone are insufficient for fully evaluating reactive iron species and mechanisms in these systems. Coupling spectroscopic data with inorganic synthesis, kinetic studies, and density functional theory (DFT) is important to fully elucidate structure and reactivity in cross-coupling.

While the nature of *in situ* formed iron species in cross-coupling can often be elucidated via spectroscopic studies, X-ray structural studies of key *in situ* formed iron species provides further information regarding ligation, geometric distortions and, in certain cases, identification of unusual structures previously unreported in the literature. While successfully obtaining structural data on organoiron species relevant to cross-coupling is challenging due to the air and temperature sensitivity of many of the transient species formed *in situ*, capabilities to grow and handle crystals at low temperature, including direct liquid nitrogen feeds into anaerobic glove boxes and cryogenic transfer equipment (combined with a patient crystallographer!) can facilitate such studies.

The coupling of direct reaction studies of isolated organo-iron species and *in situ* formed iron species with electrophile to product and side-product formation is critical to assessing (1) if a given organoiron species is reactive, (2) whether its reactions with electrophile leads to selective formation of cross-coupled product (or side products) and (3) whether such reactions occur at catalytically relevant rates. To address these questions, the combination of chemically quenched GC studies as a function of reaction time are essential. Importantly, since time resolved GC studies can be coupled with freeze-trapped spectroscopic studies at analogous reaction time points (to correlate changes in iron speciation with organic product formation), an unambiguous assignment of reactivity to an iron species can be made in order to address concerns regarding the potential reactivity of only non-iron impurities.

DFT is an additional method used to study electronic structure and bonding in structurally defined organoiron species in cross-coupling. DFT can be used to evaluate the spin state of isolated (and postulated) iron species compared to experimental data, as well as provide critical insight into the key frontier molecular orbitals relevant to catalysis. Molecular orbital (MO) calculations can be complemented by more advanced analyses focused on the evaluation of Mayer bond order and charge donation analyses to evaluate metal-ligand bonding in greater detail.^[76–77] Time-dependent DFT (TD-DFT) calculations can be invaluable in assigning electronic transitions observed by MCD spectroscopy, including ligand-field and charge transfer transitions. Importantly, since extensive spectroscopic data is available for each iron species of interest in this research approach, the DFT calculations can be refined to reproduce the experimental observables (termed spectroscopically calibrated

DFT). Such DFT models can then be utilized for more detailed reaction studies including the evaluation of reaction coordinates relevant to catalysis.

Lastly, additional spectroscopic techniques can also be used as complementary methods for the study of iron-catalyzed cross-coupling reactions. Of note is X-ray absorption spectroscopy (XAS), including X-ray absorption near-edge structures (XANES) and extended X-ray absorption fine structure (EXAFS) studies, which can provide insight into oxidation state and molecular structure. However, care must be taken when employing this method as XAS is a bulk technique which complicates the analysis of complex mixtures of iron species. While not covered in this review, Nakamura and Nagashima have previously described the use of XAS in iron-catalyzed cross-coupling reactions.^[78–79]

3. Mechanistic Studies of Iron-SciOPP Catalyzed Cross-Coupling

The $\text{FeCl}_2(\text{SciOPP})$ precatalyst developed by Nakamura and co-workers (Scheme 2) is an extremely versatile system, capable of catalyzing Kumada^[80] and Suzuki-Miyaura^[81–82] type cross-coupling of aryl nucleophiles with alkyl halides as well as cross-couplings employing alkynyl Grignards,^[83] in high yield and good selectivity towards heterocoupling over homocoupling. Early applications of the physical-inorganic approach developed by Neidig and co-workers for studying iron-catalyzed cross-coupling focused on these systems. The mechanistic studies of iron-SciOPP Kumada cross-coupling of mesitylmagnesium bromide (MesMgBr) and primary alkyl halides and the iron-SciOPP catalyzed Kumada and Suzuki-Miyaura cross-couplings of phenyl nucleophiles and secondary alkyl halides are presented herein as demonstrations of this experimental approach.^[84–85]

3.1 Iron-SciOPP Catalyzed Cross-Coupling of MesMgBr and Primary Alkyl Halides

Initial studies focused on the identification of the mesitylated iron-SciOPP species that can form *in situ* from reactions of $\text{FeCl}_2(\text{SciOPP})$ and various equivalents of MesMgBr . By utilizing ^{57}Fe -labeled precatalyst, freeze-trapped Mössbauer analysis of the *in situ* iron species could be performed at catalytically relevant concentrations of iron. Combining Mössbauer spectroscopy with independent synthesis of mesitylated-iron(II)-SciOPP species, it was identified that reaction of $\text{FeCl}_2(\text{SciOPP})$ with 1 equiv. MesMgBr formed $\text{FeMesBr}(\text{SciOPP})$, reaction with 2 equiv. MesMgBr predominately formed $\text{FeMes}_2(\text{SciOPP})$ (Scheme 3). Further addition of MesMgBr led to the formation of FeMes_3^- , in which the SciOPP ligand is lost. No EPR active species were observed to form in these reactions and all transmetalated species were found to be stable towards reductive elimination or disproportionation. Addition of free SciOPP ligand to *in situ* generated FeMes_3^- (from FeCl_2 and MesMgBr) was also shown by Mössbauer spectroscopy to generate $\text{FeMes}_2(\text{SciOPP})$ and MesMgBr .

To determine the nature of the iron species present during catalytic turnover, freeze-trapped Mössbauer of the reaction mixture during catalysis was performed. While it is not generally expected that the active iron species would be observable during catalysis, such studies do enable the determination of whether additional iron species might form during catalysis beyond those identified in stoichiometric reactions. From such a study, it was found that nearly all iron during catalysis was mono-mesitylated with a minor amount of

FeMes₂(SciOPP) also present. The highly undertransmetalated nature of iron during catalysis was consistent with the slow rate of MesMgBr required for high cross-coupling yields. TD-DFT calculations were used to assign the observed transitions in the UV-Vis electronic absorption and MCD spectra of both FeBrMes(SciOPP) and FeMes₂(SciOPP) and further DFT calculations evaluated the electronic structure and bonding in these complexes.

Having identified all of the key transmetalated iron(II)-SciOPP species, reaction studies were performed combining freeze-trapped Mössbauer and MCD spectroscopies (to track changes in iron speciation) and chemical quench GC studies (to track product generation) at analogous reaction time points. Whereas FeMesBr(SciOPP) was found to be unreactive towards 1-iododecane, pseudo first-order reaction of FeMes₂(SciOPP) with electrophile resulted in the selective formation of cross-coupled product at a kinetically relevant rate together with the consumption of FeMes₂(SciOPP) to generate FeMesI(SciOPP) (Figure 4A). The iron(II) product of this reaction was found to be FeMesI(SciOPP) based on the Mössbauer and MCD parameters of the iron product (Figure 4B). Overall, these reaction studies were consistent with an FeMes₂(SciOPP) active species (Figure 4C) and an Fe(II)/Fe(III) reaction cycle (Figure 4D), a mechanism analogous to that previously proposed by Nakamura. An iron(IV) intermediate was determined to be unlikely in this chemistry due to the radical clock experiments of Nakamura demonstrating radical character along the reaction coordinate as well as the bisphosphine ligation present, which would disfavor oxidation to iron(IV).

Lastly, FeMes₃⁻ was also found to be reactive towards electrophile at a rate similar to that observed for reactions with FeMes₂(SciOPP). However, FeMes₃⁻ was found to be far less selective, generating nearly equal amounts of cross-coupled product and β-hydrogen eliminated side product in pseudo first-order reactions. It was found that the reaction protocol itself serves to prevent the formation of unselective FeMes₃⁻ via slow addition of nucleophile to favor undertransmetalated iron(II)-SciOPP and through the addition of excess free SciOPP to favor FeMes₂(SciOPP) over FeMes₃⁻.

3.2 Iron-SciOPP Catalyzed Cross-Coupling of Phenyl Nucleophiles and Secondary Alkyl Halides

While the mechanistic studies of iron-SciOPP catalyzed cross-coupling with MesMgBr provided the definitive demonstration of an iron(II) active species for cross-coupling, simple phenyl nucleophiles represent a more synthetically useful system. However, mechanistically simple phenyl systems are far more challenging to study. Whereas mesitylated iron(II)-bisphosphine species were known in the literature, no structurally characterized Fe(Ph)₂(bisphosphine) or Fe(Ph)X(bisphosphine) (X=halide) has been reported. Such bisphenylated iron(II)-bisphosphines would likely be unstable and could decompose via reductive elimination reactions to generate iron(0) or iron (I) (via a cooperative reductive elimination). Furthermore, mono-phenylated iron(II)-bisphosphines could also be susceptible to disproportionation reactions. Thus, unlike the mesityl case, phenylated iron(II)-SciOPP intermediates would likely be unstable and evolve as a function of time. Lastly, the phenyl nucleophile cross-couplings with FeCl₂(SciOPP) are much faster reactions than those with MesMgBr, where the Kumada cross-coupling of PhMgBr and

secondary alkyl halides turns over 200 times in 20 min at RT. Despite these significant challenges, the application of the physical-inorganic based approach ultimately proved successful for such systems.

Initial studies focused on the identification of the trans-metalated iron(II)-SciOPP species formed *in situ* upon reaction of $\text{FeCl}_2(\text{SciOPP})$ and PhMgBr (2 or 20 equiv) or 20 equiv. Ph-borate/MgBr_2 (Suzuki-Miyaura transmetalation conditions) resulted in the formation of a single major iron species (Figure 5A). Identified through X-ray crystallography as $\text{Fe}(\eta^6\text{-biphenyl})(\text{SciOPP})$ (Figure 5B), this iron(0) species was found to be an acceptable precatalyst for cross-coupling though with a lag phase. While pseudo first-order reactions of $\text{Fe}(\eta^6\text{-biphenyl})(\text{SciOPP})$ with electrophile demonstrated that a reaction was possible, this occurred at a rate far too slow to be catalytically relevant and led selectively to the formation of only cycloheptene side product. Thus, the iron(0) species was found to be off-cycle. However, the iron product of this reaction was $\text{FeX}_2(\text{SciOPP})$ ($\text{X} = \text{halide}$), the normal precatalyst for catalysis, explaining the ability of the iron(0) species to serve as a precatalyst with a lag phase. Lastly, a very minor $S=1/2$ species also formed upon reaction of $\text{FeCl}_2(\text{SciOPP})$ with phenyl nucleophile (Figure 5A, inset), but exhibited no reaction towards electrophile over the course of 45 min at RT indicating that it was either unreactive or far less reactive than $\text{Fe}(\eta^6\text{-biphenyl})(\text{SciOPP})$ and, hence, also off-cycle.

Freeze-trapped Mössbauer and MCD studies enabled the identification of phenylated-iron(II)-SciOPP species formed prior to reductive elimination to iron(0). $\text{Fe}(\text{Ph})\text{X}(\text{SciOPP})$ ($\text{X} = \text{Br}$ or Cl due to halide exchange) and $\text{Fe}(\text{Ph})_2(\text{SciOPP})$ are accessible in this chemistry, and both are highly reactive with electrophile with rates consistent with catalysis ($k_{\text{obs}} > 12 \text{ min}^{-1}$) (Figure 5C). The main reactive species in this chemistry could be assigned to $\text{Fe}(\text{Ph})\text{X}(\text{SciOPP})$ (Figure 5D) as the product distribution of its reaction with electrophile is highly selective and analogous to the product distribution in catalysis (whereas reaction of $\text{Fe}(\text{Ph})_2(\text{SciOPP})$ was only ~ 50% selective to cross-coupled product following two turnovers with respect to iron). This observation is consistent with the requirement in catalysis to add the nucleophile very slowly via a syringe pump which serves to favour formation of $\text{Fe}(\text{Ph})\text{X}(\text{SciOPP})$ *in situ*. Lastly, the reaction of $\text{Fe}(\text{Ph})\text{X}(\text{SciOPP})$ with electrophile led to formation of $\text{FeX}_2(\text{SciOPP})$ as determined by freeze-quenched Mössbauer (Figure 5E), consistent with an analogous Fe(II)/Fe(III) redox cycle as previously determined for cross-coupling of MesMgBr with iron-SciOPP.

4. Summary and Outlook

Fundamental insight into *in situ* formed and reactive iron species in iron-catalyzed cross-coupling is critical for the rational design and development of new iron-catalyzed methodologies. While detailed insight into reactivity and mechanism in Pd and Ni cross-coupling have enabled tremendous advances in such systems, analogous insight into iron-catalyzed cross-coupling has been largely undeveloped in part due to the challenges in studying potentially complex mixture of unstable, paramagnetic organoiron species that might form *in situ*.

A physical-inorganic methodology combining freeze-trapped inorganic spectroscopic studies, organometallic synthesis and GG/kinetic studies is a powerful method for overcoming these inherent challenges for studies of iron-catalyzed cross-coupling reactions. In particular, the ability to track both changes in iron speciation (via freeze-trapped spectroscopy) and organic products (via chemically quenched GC) at analogous time points enables the direct correlation of the reaction of specific iron species to the generation of organic product distributions. This research approach has enabled unprecedented insight into the nature of the *in situ* formed and reactive iron species, where studies of iron-SciOPP catalysed cross-coupling of aryl nucleophiles and alkyl halides has demonstrated the important role of iron(II) reactive species in catalysis. The continued application of this methodology across the breadth of iron-catalyzed cross-coupling reactions and to other iron-catalyzed transformations in organic synthesis will continue to define the key reactive iron species involved in effective catalysis. Such insight provides an important fundamental foundation from which to rationally design new iron-based catalysts for organic synthesis.

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Figure 1. Mössbauer spectroscopy. (A) Electric monopole and electric quadrupole effects on the $I=1/2$ ground state and $I=3/2$ excited state of ^{57}Fe . (B) Example Mössbauer spectra indicating the isomer shift (δ) and quadrupole splitting (ΔE_Q) parameters (top) and a mixture in which two iron species are present (bottom). Spectra adapted with permission from [75] and [84]. Copyright 2014 and 2016, American Chemical Society.

Figure 2. 10 K EPR spectrum of $S=3/2$ $[\text{FeMe}_4]^-$ as an example of an axial $S=3/2$ EPR spectrum. The inset shows the temperature dependence of the EPR intensity and its fit to determine the axial ZFS parameter D for the complex. Adapted with permission from [62]. Copyright 2014, American Chemical Society.

Figure 3.

MCD spectroscopy. (A) MCD C -term mechanism with (left) no applied magnetic field resulting in no observed MCD intensity and (right) at low temperature where $kT \sim g_g \beta H$ (where $g_g \beta H$ = ground state Zeeman splitting) and the two states are unequally populated resulting in an MCD transition with an absorption bandshape. (B) Ligand-field transitions in the near-infrared MCD spectrum of $FeCl_2(dpbz)$ collected at $T=5 K$, $H=7 T$. (C) Saturation magnetization data of $FeCl_2(dpbz)$ collected at $6536 cm^{-1}$ fit to a $-ZFS$ $S=2$ ground-state model with $D = -9 \pm 2 cm^{-1}$ and $|E/D| = 0.29 \pm 0.02$. Spectra adapted with permission from [75]. Copyright 2016, American Chemical Society.

Figure 4.

Iron-SciOPP catalyzed Kumada cross-coupling of MesMgBr and primary alkyl halides. Freeze-trapped (A) Mössbauer spectroscopy and (B) near-infrared MCD spectroscopy of *in situ* iron speciation as a function of time for the reaction of *in situ* generated FeMes₂(SciOPP) with 20 equiv. 1-iododecane. (C) X-ray crystal structure of the FeMes₂(SciOPP) active species. (D) Proposed mechanistic cycle for iron-SciOPP cross-coupling of MesMgBr and primary alkyl halides. Adapted with permission from [84]. Copyright 2014, American Chemical Society.

Figure 5.

Iron-SciOPP catalyzed cross-coupling of PhMgBr and secondary alkyl halides. (A) 80 K Mössbauer spectroscopy of *in situ* formed iron species from reaction of $\text{FeCl}_2(\text{SciOPP})$ and (top) 20 equiv. *t*BuPh-borate/6.7 equiv. MgBr_2 and (bottom) 2 equiv. PhMgBr at 25 °C. The inset shows the minor $S=1/2$ component (~5% of all iron) observed by 10 K EPR spectroscopy. (B) X-ray crystal structure of $\text{Fe}(\eta^6\text{-biphenyl})(\text{SciOPP})$. (C) GC analysis of reactions of *in situ* generated mono- and bis-phenylated iron(II)-SciOPP with bromocycloheptane. (D) X-ray crystal structure of the reactive $\text{Fe}(\text{Ph})\text{Br}(\text{SciOPP})$ species. (E) 80 K Mössbauer spectroscopy demonstrating the formation of $\text{FeX}_2(\text{SciOPP})$ ($\text{X}=\text{Cl}$ or Br) upon reaction of $\text{Fe}(\text{Ph})\text{X}(\text{SciOPP})$ with 20 equiv. bromocycloheptane. Adapted with permission from [85]. Copyright 2015, American Chemical Society.

Kochi (1971)

Cahiez (1998)

Bedford (2012)

Nakamura (2007)

Nakamura (2012)

Nakamura (2004)

Scheme 1.
Examples of Iron-Catalyzed Cross-Coupling Reactions

Aryl-alkyl cross-coupling (2011)

Aryl-alkyl cross-coupling (2011)

Aryl-alkyl cross-coupling (2010)

Alkynyl-alkyl cross-coupling (2011)

Scheme 2.
Iron-SciOPP Catalyzed Cross-Coupling Reactions.

Scheme 3.

In Situ Iron Speciation from Reaction of FeCl₂(SciOPP) with MesMgBr. Reproduced with permission from [84]. Copyright 2014, American Chemical Society.