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Isolation and Identification of the Pre-Catalyst in Iron-Catalyzed Direct

Arylation of Pyrrole with Phenylboronic Acid

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Abstract. Herein we describe the synthesis, charcterization, and role of three dichloric iron(III) complexes, [L1Fe(III)(Cl)₂]ClO₄ (L1Fe), [L2Fe(III)(Cl)₂]ClO₄ (L2Fe), and [L3Fe(III)(Cl)₂]ClO₄ (L3Fe) [L1 (Pyclen)=1,4,7,10-tetra-aza-2,6-pyridinophane; L2 =3,6,9,15-tetraazabicyclo[9.3.1]penta-deca-

1(15),11,13-trien-13-ol; L3 =3,6,9,15-tetra-azabicyclo[9.3.1]penta-deca-1(15),11,13-trien-12-ol], in the coupling of pyrrole and phenylboronic acid to form 2-phenylpyrrole. The oxidation state and spin state of the iron complexes were characterized using X-ray crystallography, UV-vis absorbance spectroscopy, electron paramagnetic resonance spectroscopy, cyclic voltammetry, and mass spectrometry. Electrochemistry results rank ligand L1-L3 as moderate tetra-azamacrocycle donors to iron between cyclen and Me₂EBC-12. Characterization of the iron(III) complexes and subsequent catalytic testing indicates that the complexes enter the C-C coupling catalytic cycle in the high-spin iron(III) oxidation state. Furthermore, the results indicate that the iron(III) complexes are essential for catalytic and regioselective production of the 2-phenylpyrrole product.

KEYWORDS: Iron, cross-coupling, direct Suzuki-Miyaura, heterocycle, catalysis, pyrrole

Introduction

Carbon-Carbon cross-coupling reactions catalyzed by transition metals are invaluable components in a chemist's toolbox.^[1] However, palladium is the most common metal used to facilitate these transformations despite the low availability, toxicity, and cost of the precious metal.^[1-7] Therefore, there is a growing interest in replacing palladium with a more earth abundant element such as iron.^[6-7] While iron catalysts are indeed making strong contributions to the field of cross-coupling reactions, mechanistic insights and thorough catalyst characterizations are much more challenging than the palladium counterparts due to the strong reactivity of iron complexes, unpaired electrons complicating NMR spectroscopy, and transient nature of intermediate species.^[1-7] Nevertheless, iron complexes have proven useful in the synthesis of organic compounds^[1-18] and as model complexes of metalloenzymes.^{[19-} ^{21]} Such work has resulted in reports that iron species, such as Fe(III)OOH, Fe(IV)=O, or Fe(V)=O play a key role in oxidative iron catalysis and mechanistic details are becoming more understood.^[17, 20, 22] However, the studies that investigate iron catalysts for C-C bond formation focus largely on the scope of the catalysts and less on the properties of the active metal center. A compliment to studies of substrate scope would focus on the identification of catalyst oxidation state and spin state (which may be tuned by the ligand scaffold^[23-24]) needed for the desired organic transformation to take place. Thorough understanding of ligand effects on the metal center will aid in designing more efficient catalysts.^[1, 5-7] For example, the White-Chen [Fe(S,S-PDP)] catalyst has been studied for C-H bond activation.^[25] This work focused on regioselectivity derived from substrate properties such as electronics, steric bulk, and directing groups. Talsi et al. have separately probed the nature of the active species in this process using EPR and enantioselectivity studies to show that the oxygen transfer occurs by an Fe(V)-oxo species.^[26] Insight into a previously unknown mechanism resulted from the detailed characterization in this

work.^[27] Furthermore, multi-dentate N-containing ligands have been used to obtain stable Fe(IV)-oxo species, providing invaluable spectroscopic comparisons to metalloenzymes in nature.^[10, 19-20, 28-30]



Figure 1. Tetra-azamacrocycles studied by Wen *et al.* in combination with iron(II) salts to facilitate the coupling of pyrrole and phenylboronic acid to produce 2-phenylpyrrole.^[31]



Figure 2. Iron(III) complexes derived from cyclen, LN₄H₂, and Me₂EBC-12.

Interesting, Bedford and co-workers reported that iron catalysts derived from rigid tetraazamacrocycles, such as **Me₂EBC-12**, resulted in poor yields for the cross-coupling of 4-tolyl magnesium bromide with cyclohexylbromide.^[5] However in 2010, Wen. *et al.* reported that the tetraazamacrocycles shown in Figure 1, when mixed with iron(II) salts in the presence of oxygen, facilitate direct arylation of pyrrole with phenylboronic acid to form 2-phenylpyrrole.^[31] A preliminary mechanism was proposed in which an iron-oxo species acts as the active catalyst; however, no metal oxidation states were assigned or catalyst characterization reported aside from a mass spectrum that proved to be tenuous in its assignment. Since the release of this publication, it has been cited over 70 times ^{[8, 11, 16, 24,} ^{32-97]}. Interestingly, to date the synthesis and characterization of iron complexes derived from two of the four ligands in these original reports, **LN₄H₂** and **cyclen**, have been reported (Figure 2). Both complexes **[(LN₄H₂)Fe(Cl)₂]⁺** and **[(cyclen)Fe(Cl)₂]⁺** were identified as high-spin iron(III) systems.^[98-101] Of the four

mixtures tested for catalytic ability by Wen and co-workers, the mixture containing L1 afforded the highest yield. Therefore and reported here, we identified the spin-state and oxidation state of the complex formed by L1 and iron(II) in the presence of oxygen and compared the structural and electronic properties to [(LN₄H₂)Fe(Cl)₂]⁺, [(cyclen)Fe(Cl)₂]⁺, and others. We have previously explored L1 and its derivatives (L2 and L3, Figure 3) as chelates for Cu(II), Ni(II), and Zn(II); the donor capacity of the ligand was affected by the presence and position of the hydroxyl group.^[102] Therefore, the iron complexes of L2 and L3 were also isolated, characterized, and compared within the series described above. The *bona fide* iron(III) high-spin complexes derived from L1, L2, and L3 were identified as pre-catalysts for *direct* Suzuki-Miyaura coupling of pyrrole and phenylboronic acid to yield 2-phenylpyrrole. Finally, further experiments show that some amine ligands can promote a small amount of background reactivity yielding multiple products, but the iron(III) pre-catalysts are critical for focusing the reactivity to produce only 2-phenylpyrrole, thus validating the need for the intact iron complex as a catalyst.



Figure 3. Chemical structure of ligands **L1-L3** (**L1** = 1,4,7,10-tetra-aza-2,6-pyridinophane,^[103-104] **L2** = 3,6,9,15-tetra-azabicyclo[9.3.1]penta-deca-1(15),11,13-trien-13-ol,^[105] **L3** = 3,6,9,15-tetraazabicyclo[9.3.1]penta-deca-1(15),11,13-trien-12-ol).^[102]

Experimental Section

General Methods. Iron(II) perchlorate was freeze dried prior to use, all other reagents were obtained from commercial sources and used as received, unless noted otherwise. NMR spectra were obtained on a 400-MHz Bruker Advance spectrometer, using deuterated solvents (CDCl₃). NMR spectra were referenced using the corresponding solvent resonance (in parts per million;

 $CDCI_3 \delta = 7.26$).^[106] The following abbreviations were used for proper identification of the NMR signals: s = singlet, d = doublet, t = triplet, m = multiplet. ESI-MS experiments were carried out using an Agilent 6224 Accurate-Mass Time-of-Flight (TOF) mass spectrometer using 175 V to ionize the complexes. Elemental analysis was performed by Canadian Microanalytical Service Ltd. Electronic absorption spectra were recorded on a DU 800 UV-vis spectrophotometer (Beckman Coulter) using a 3 mL quartz cuvette with a 1 cm path length. GC-MS analysis was carried out using a Bruker Scion 436-GC-MS equipped with an auto sampler 8410 and a Br-5ms column 29.9m. *Caution! Perchlorate salts are explosive and should be handled in small quantities. In particular, such compounds should never be heated as solids.*

Synthesis of ligands. Stability of transition-metal complexes containing a tetra-azamacrocycle are facilitated by the macrocyclic effect. The ease with which these processes occur depends upon ring size, the number of donor atoms, electronic characteristics, and other factors.^[104, 107] The formation of 14-membered tetra-azamacrocyclic ligands, for example, typically involves the use of transition metal-ions to template the cyclization step between two independent units to form the ligand. The product of this reaction is, therefore, a transition metal macrocyclic complex. However, tetra-azamacrocyclic amines, comprised of 12 atoms in the ring, form through metal-independent cyclization pathways.^[108-114] Therefore, for the work described herein, the 12-membered pyridine and pyridol based tetra-azamacrocyclic amines ligands, **L1-L3**, were produced previously reported procedures developed in our group and isolated as the corresponding HCl salts.^[102, 105] **Caution!** Perchlorate salts are explosive, and should be handled in small quantities. In particular, such compounds should never be heated as solids.

[L1Fe(III)(CI)₂]CIO₄ (L1Fe): Ligand (L1·3HCI) (101.1 mg, 0.3216 mmol) and Fe(CIO₄)₂ (83.7 mg, 0.330 mmol) were dissolved in 3 mL DI water; the solution was adjusted to pH=6 using 1*M* KOH. The resulting red solution was allowed to stir open to air for 15 hours at 40°C. After 15 hours, a tan precipitate was removed by centrifugation followed by filtration using a 0.45 μ m PTFE filter. The water was removed using an azeotrope formed with acetonitrile. The resulting solid was taken up in CH₃CN and dried with Na₂SO₄. The addition of Et₂O to the CH₃CN solution, followed by centrifugation yielded the product as a brown powder. Yield: 62% (92.8 mg, 0.198 mmol). Yellow X-ray quality crystals were obtained by slow diffusion of ether into DMF at 4°C, CCDC#

1422489. ESI-MS (m/z) Found: 260.1515, $[L1Fe(III)-2H^{+}]^{+}$, (34%); 296.1360, $[L1Fe(III)CI-H^{+}]^{+}$, (58%), 332.1209, $[L1Fe(III)2CI^{-}]^{+}$, (14%). Theoretical: 260.0724, $[L1Fe(III)-2H^{+}]^{+}$, 296.0491, $[L1Fe(III)CI-H^{+}]^{+}$, 332.0258, $[L1Fe(III)2CI^{-}]^{+}$. UV-vis, λ_{max} , ε (M⁻¹·cm⁻¹): 261 nm (3,600), 311 nm (800), 416 nm (170). Elemental analysis: $[L1Fe(III)(CI)_2]CIO_4$ (Formula: $C_{11}H_{18}N_4FeO_4CI_3$); Found (Calculated): C, 30.66 (30.50); H, 4.09 (4.20); N, 13.04 (12.95).

[L2Fe(III)(CI)₂**]CIO**₄ **(L2Fe):** Ligand **(L2·3HCI)** (65.0mg, 0.208 mmol) was dissolved in 2.5 mL DI water. The pH of the solution was adjusted to 5 using 1*M* KOH. Fe(CIO₄)₂ (53.6 mg, 0.211 mmol) was dissolved in 1 mL DI water and added dropwise to the ligand solution; the pH was maintained between 3.5 and 5.2. After all iron(II) solution was added, the pH was adjusted to 5.3. The solution was allowed to stir open to air 2 days resulting in precipitation of a brown solid that was isolated by centrifugation. Yield: 30% (27.4 mg, 0.061 mmol). Yellow crystals suitable for XRD analysis were obtained by slow evaporation of water at room temperature, CCDC # 1422490. ESI-MS (m/z) Found: 276.1529, [L2Fe(III)-2H⁺]⁺ (35%); 312.1377, [L2Fe(III)Cl-H⁺]⁺ (45%). Theoretical: 276.0674, [L2Fe(III)-2H⁺]⁺; 312.0440 [L2Fe(III)Cl-H⁺]⁺. UV-vis, λ_{max} , ε (M⁻¹·cm⁻¹): 249 nm (6,700), 306 nm (4,000), 356 nm (2,700). Elemental analysis: **[L2Fe(III)(Cl)₂]ClO₄** (Formula: C₁₁H₁₈N₄FeO₅Cl₃); Found (Calculated): C, 29.88 (29.46); H, 4.08 (4.05); N, 11.75 (12.49).

[L3Fe(III)(CI)₂]CIO₄ (L3Fe): Ligand (L3·3HCI) (206.4 mg, 0.6223 mmol) was dissolved in 20 mL DI water and the pH was adjusted to 5 using 1*M* KOH. Fe(CIO₄)₂ (164.0 mg, 0.6155 mmol) was dissolved in 10 mL DI water, added drop wise to ligand, and the pH was re-adjusted to 5. The solution was allowed to stir open to air for 2 days at 40°C. The solvent was removed under reduced pressure. The resulting dark brown solid was dissolved in DMF, dried with Na₂SO₄, and filtered. Ether was added to the DMF solution and a red-brown powder was isolated by centrifugation. Yield = 63.2% (235.6 mg, 0.3932 mmol). Brown crystals suitable for XRD analysis were obtained by slow evaporation from water at room temperature, CCDC # 950048. ESI-MS (m/z) Found: 276.1481, [L3Fe(III)-2H⁺]⁺ (30%), 312.1322, [L3Fe(III)CI-H⁺]⁺ (55%). Theoretical: 276.0674, [L3Fe(III)-2H⁺]⁺, 312.0440 [L3Fe(III)CI-H⁺]⁺. UV-vis, λ_{max} , ε (M⁻¹·cm⁻¹): 205 nm (14,000), 219 nm (10,000), 284 nm (5,600), 458 nm (300). Elemental analysis: [L3Fe(III)(CI)₂]CIO₄ (Formula: C₁₁H₁₈N₄FeO₅Cl₃); Found (Calculated): C, 29.03 (29.46); H, 4.05 (4.05); N, 12.57 (12.49).

X-ray Diffraction Analysis. Crystal diffraction data were collected at 100 K on a Bruker D8 Quest Diffractometer. Data collection, frame integration, data reduction (multi-scan), and structure determination were carried out using APEX2 software.^[115] Structural refinements were performed with XSHELL (v 6.3.1), by the full-matrix least-squares method.^[116] All non-hydrogen atoms were refined using anisotropic thermal parameters, while the hydrogen atoms were treated as mixed. The ORTEP molecular plots (50 %) were produced using APEX2 (Version 2014.9-0).

Electrochemistry. Cyclic voltammetry experiments were obtained using 2.2 mM complex and 100 *mM* tetrabutylammonium tetraflouroborate as the supporting electrolyte in DMF. The electrochemical cell was composed of a working glassy carbon electrode, a Pt auxiliary electrode, and a silver wire as the reference electrode. To facilitate solubility, all samples were first dissolved in 1*M* HCl, thoroughly dried, and then dissolved in DMF for electrochemical analysis. The potential was scanned in the negative direction at a rate of 100 mV/s, starting at the open circuit potential. The potential values presented here have been normalized to the half-wave potential of the Fc/Fc⁺ redox couple set equal to 0.00 V. For comparison purposes half-wave potential in cited references were converted to reflect Fc/Fc⁺ = 0 mV; **[(Me₂EBC-12)Fe(Cl)₂]PF₆, (Fc/Fc⁺ = 400 mV), and [(cyclen)Fe(Cl)₂]Cl**, (Fc/Fc⁺ = 515 mV).^[99, 117-118]

X-band EPR Spectroscopy and Analytical Simulations: X-band (9 GHz) EPR spectra were recorded on a Bruker EMX Plus spectrometer equipped with a bimodal resonator (Bruker model 4116DM). Low-temperature measurements were made using an Oxford ESR900 cryostat and an Oxford ITC 503 temperature controller. A modulation frequency of 100 kHz was used for all EPR spectra. All experimental data used for spin-quantitation were collected under non-saturating conditions. Analysis of the EPR spectra utilized the general spin Hamiltonian,

$$\widehat{H} = D\left(\widehat{S}_Z^2 - \frac{S(S+1)}{3}\right) + E\left(\widehat{S}_X^2 + \widehat{S}_Y^2\right) + \beta \mathbf{B} \cdot \boldsymbol{g} \cdot \boldsymbol{S}$$
Equation 1

where *D* and *E* are the axial and rhombic zero-field splitting parameters and *g* is the *g*-tensor.^[119] EPR spectra were simulated and quantified using Spin Count (ver. 5.8.6218.29549), written by Professor M. P. Hendrich at Carnegie Mellon University. The simulations were generated with

consideration of all intensity factors, both theoretical and experimental, to allow concentration determination of species. The only unknown factor relating the spin concentration to signal intensity was an instrumental factor that depended on the microwave detection system. However, this was determined by the spin standard, Cu(EDTA), prepared from a copper atomic absorption standard solution purchased from Sigma–Aldrich.

2-phenylpyrrole Yield Determination: Phenylboronic acid (24 mg, 0.2 mmol) and crystalline material of the iron complex (0.02 mmol) were added to a 5 or 10 mL flask equipped with a stir bar. Pyrrole (1 mL) was added to flask, the mixture was heated to 130° C for 10 hours. The reaction was cooled to room temperature and the pyrrole was removed under vacuum until no visible liquid was present. Increasing the time the reaction was kept under reduced pressure decreased yields. The product mixture was dissolved in a minimum amount of CDCl₃, 5 µL of dimethyldiphenylsilane was added to the solution. The solution was filtered through a 0.2 µm nylon filter and a known amount of sample was added to a pre-weighed NMR tube. Yield determinations were performed using three resonances 6.875, 6.532, and 6.307 ppm corresponding to 2-phenylpyrrole and a resonance at 0.533 ppm corresponding to dimethyldiphenylsilane. The reported values are averages of all resonances; each measurement was run in triplicate.

Control Reactions: Phenylboronic acid (24 mg, 0.2 mmol) and ligand (0.02 mmol), if used, were added to a 2 mL flask equipped with a stir bar, the system was then placed under an atmosphere of nitrogen. Pyrrole (1 mL) was added to flask and the mixture was heated to 130 $^{\circ}$ C for 15 minutes, if used, 10 mL O₂ was injected directly into the pyrrole, the system was closed, and heated for 10 hours. Yields were determined as stated above.

GC-MS Details: Method, 80°C 2 min, ramp 5°C/min to 170°C, ramp 20°C/min to 300°C, hold 5 min. GC-MS Compound Identification **L3** coupling: 3-methyl-4-phenylfuran-2(5H)-one: (trace) RT. 14.909 min. Found (Cal.): M^{+-} 174.1 (174.1); (6%) 3-phenylpyrrole: RT. 15.002 min. Found (Cal.) M^{+-} 142.9 (143.0); (trace) 3-methyl-5-phenylfuran-2(4H)-one: 16.330 min. Found (Cal.) 174.1 (174.1); (16%) 2-phenylpyrrole: RT: 16.460 min Found (Cal.): M^{+-} 142.9 (143.0).

Results and Discussion

Synthesis and Characterization

The corresponding iron complexes of L1-L3, shown in Figure 4, were synthesized in water at pH ~5 to compensate for the protonation of the isolated ligands. The iron(II) salt was used in metalation of L1-L3 and was oxidized in air to iron(III) prior to isolation of the L1Fe-L3Fe complexes. The iron(II) perchlorate salt was exploited to facilitate the growth of X-ray quality crystals, discussed below. Attempts to form complex using Fe(ClO₄)₃ did not afford product in water. The presence and position of the hydroxyl group on the aromatic ring of the ligand affected the metalation efficiency and solubility of the resulting complexes; therefore, divergent synthetic strategies were developed for each complex produced. For example, mixtures of CH₃CN/Et₂O or DMF/Et₂O were used to isolate metal complexes L1Fe (62% yield) and L3Fe (63% yield), respectively, as solids precipitates. L2Fe was easily isolated as a precipitate from the aqueous reaction mixture, albeit with a low yield (30%). Nevertheless, the resulting ferric complexes of L1-L3 were stable to both air and light and can be stored indefinitely once isolated as dark red (L3Fe) or light brown (L1Fe, L2Fe) solids.



Figure 4. Pictorial representation of [L1Fe(III)(Cl)₂]⁺ (L1Fe), [L2Fe(III)(Cl)₂]⁺ (L2Fe), and [L3Fe(III)(Cl)₂]⁺ (L3Fe).

X-ray Crystallography

Figure 5 shows the results of single crystal diffraction analysis on crystalline solids of L1Fe, L2Fe, and L3Fe. Yellow, X-ray quality crystals of L1Fe were obtained through vapor diffusion of ether into a solution of DMF; yellow L2Fe and brown L3Fe crystalline materials were isolated by slow evaporation of aqueous solutions. Table S1 contains the crystal data, intensity collections, and structure refinement parameters; a full list of bond lengths and angles are also located in the supporting information. The structures determined through X-ray diffraction analysis show that

each complex adopts a six coordinate, distorted octahedral geometry (N(2)-Fe-N(4), ~85°; N(1)-Fe-N(3), ~147°). The coordination sphere consists of four nitrogen donors from the ligand set and two chloride ions. Each complex adopts a *cis*-folded geometry due to the rigidity of the 12-membered ligand set in which one chloride is *cis* and the other is *trans* to the pyridol ring.¹⁶ This finding is consistent with previous structure determination of **[L1Fe]BF**₄, reported by Alcock *et al*.^[120] The charge of the $[L_xFe(III)(CI)_2]^+$ systems are balanced by one perchlorate counter ion within the unit cell. The position of the hydroxyl group and the flexibility of the aliphatic portion of the ligand results in an enantiomeric mixture of **L3Fe**. The hydroxyl group was modeled for disorder to account for both enantiomers, as shown in Figure 5c.



Figure 5. ORTEP (50%) representations of **L1Fe** (A), **L2Fe** (B), and **L3Fe** (C). The perchlorate anion has been omitted for clarity; modelling of disorder for **L3Fe** is shown in grey. All complexes take on a *cis*-folded distorted octahedral geometry. The Fe-N bond lengths are greater than 2.0 Å, consistent with other high-spin ferric systems.^[99, 101, 118] A full list of bond lengths and angles are available in Tables S2-7.

Bond	L1Fe	L2Fe	L3Fe
Fe(1)-N(1)	2.1641(6)	2.1787(11)	2.162(2)
Fe(1)-N(2)	2.2001(6)	2.2023(10)	2.181(2)
Fe(1)-N(3)	2.1676(6)	2.1812(11)	2.172(2)
Fe(1)-N(4)	2.1074(5)	2.0970(10)	2.107(2)
N(1)-Fe(1)-N(3)	147.25(2)	146.70(4)	147.17(8)
N(2)-Fe(1)-N(4)	85.56(2)	85.47(4)	85.72(8)

Table 1. Selected bond lengths (Å) and angles (°) of complexes **L1Fe-L3Fe**.

The geometry of complexes L1Fe-L3Fe can be compared to other macrocycles in the literature. For example, N(1)-Fe-N(3) bond angles have been reported for two 12-membered macrocycles (Figure 2), $[(LN_4H_2)Fe(Cl)_2]^+$ (142.41°) and $[(cyclen)Fe(Cl)_2]^+$ (146.40°), where the latter complex provides the closest bond angle to the L1Fe-L3Fe systems.^[101, 117, 121] The L2Fe complex provides slightly longer Fe-N bonds compared to L1Fe and L3Fe. For example, the Fe-N(2) bond of L2Fe was determined to be 2.2023(10) Å, while **L1Fe** and **L3Fe** were slightly shorter with 2.2001(6) and 2.181(2) Å, respectively. The only exception was observed with the Fe-N(4) bond, which was slightly shorter in L2Fe (2.0967(10) Å) compared to L1Fe (2.1074(5) Å) and L3Fe (2.107(2) Å). The difference in the equatorial Fe-N(4) pyridine-derived bond length is consistent with a stronger interaction between the pyridol nitrogen of L2 vs. L1 and L3. Throughout the series, the equatorial Fe-N(2) (pyridine atom) bond is the longest and thus the weakest Fe-N interaction. The Fe-N bond lengths of L1Fe-L3Fe are greater than 2.00 Å (Tables 1-2 and Figure 5) and are consistent with an iron(III) high-spin system.^[122] For example, the iron center of [(LN₄H₂)Fe(Cl)₂]⁺ was assigned as a high-spin iron(III) by EPR, and the Fe-N bond lengths within the high-spin complex were measured as 2.128 and 2.221 Å.^[117, 123] Altogether, the results indicate that ligands L1-L3 stabilize the high-spin iron(III) in similar manners and that L2 is a slightly stronger donor to iron(III) compared to L1 and L3. However, the differences in bond lengths and angles within L1Fe-L3Fe is much smaller than the nickel(II), copper(II), and zinc(II) congeners of L1-L3.^[102]

Mass Spectrometry

Mass spectrometry further confirmed the oxidation state of the iron(III) in L1Fe-L3Fe. The mass spectrum obtained for L1Fe consisted of three isotopic envelopes that correspond to the complex: 260.1519 m/z = [L1Fe(III)-2H⁺]⁺, 296.1358 m/z = [L1Fe(III)Cl⁻-H⁺]⁺, and 322.1209 m/z = [L1Fe(III)2Cl⁻]⁺ (Figure S4). Similar fragmentation patterns were obtained for complexes L2Fe and L3Fe and are detailed in experimental methods related to each complex. Mass spectrometry analysis of the coupling reaction performed by Wen. et al. revealed three isotopic envelopes: m/z = 207.1532, 353.1956, and 369.1956.^[31] The isotopic envelopes were assigned as [L1]⁺, [L1 + Fe +C₂O₄]⁺, and $[L1 + Fe + C_2O_4 + O]^+$, respectively, with no indication of iron oxidation states or charge balance. The isotopic envelope observed at m/z = 207.1532 indeed corresponds to the singly protonated free ligand $[L1 + H^{\dagger}]^{\dagger}$, which we observe as well with studies of free ligand L1. However, the assignment of m/z = 353.1965 as $[L1 + Fe + C_2O_4]^+$ is incorrect, as the exact mass the expected species is modeled to have m/z = 350.0672, three mass units less than the observed ion reported. Similarly, the assignment of m/z = 369.1897 as $[L1 + Fe + C_2O_4 + O]^+$ (Theoretical m/z = 366.0621) as a component of the catalytic reaction does not correlate as well. Therefore, the results reported herein serve as the first validation of the composition and oxidation state of the iron pre-catalyst involved in the C-C coupling chemistry, to be described later.

Spin State Determination

The spin and oxidation states of complexes **L1Fe-L3Fe** were also validated at low temperature via electron paramagnetic resonance (EPR) spectroscopy. As shown in Figure 6 (*left*), the EPR spectra (*solid lines*) for all complexes (**L1Fe - L3Fe**) exhibit features typical of high-spin ferric iron (S = 5/2). For analytical purposes, all data were recorded under non-saturating microwave power. The simulations overlaid on each spectrum (*dashed lines*) consist of contributions from two separate doublets. As indicated by the energy diagram shown in Figure 6 (*right*), the dominant transition for these complexes arises from the ground $m_s = \pm 1/2$ doublet of a S = 5/2 spin state with near axial symmetry (E/D = 0.07). Transitions within this doublet yield the observed *g*-values of 7.6, 4.3, and 1.7. The linewidth of this transition can be reasonably simulated by assuming a Gaussian distribution in rhombicity (E/D) [designated $\sigma_{E/D}$], which broadens the $g \sim 1.7$ resonance significantly. The lower intensity features observed at $g \sim 5.8$ and 1.97 are nearly absent at low temperature (4 K) but reach a maximal intensity near ~ 8 K

before decreasing again as temperature approaches 20 K. The alternating temperature dependence of these features confirm that this signal must originate from the middle $m_s = \pm 3/2$ doublet of the S = 5/2 spin state. The magnitude of the zero-field splitting parameter ($|D| = 0.7 \pm 0.2 \text{ cm}^{-1}$) was determined by plotting the EPR signal intensity of the $m_s = \pm 1/2$ doublet versus 1/T and fitting the data to a Boltzmann population distribution for a 3-level system. Additional corroboration of the axial zero-field splitting term was obtained by simultaneous simulation of EPR spectra collected at temperatures ranging from 4 to 20 K (n = 5). Within this temperature regime, all simulations accurately reproduce the relative intensity for each transition ($\pm 1/2$ and $\pm 3/2 m_s$ -states) using a *D*-value of $0.7 \pm 0.2 \text{ cm}^{-1}$. Within error, all complexes (L1Fe - L3Fe) exhibited equivalent temperature dependence and thus all EPR simulations shown in Figure 6 utilized the same axial zero field splitting term. Indeed, with the exception of minor perturbations in the extent of *E/D*-distribution ($\sigma_{E/D}$), all complexes L1Fe – L3Fe exhibit nearly equivalent EPR spectroscopic properties. The near equivalent of EPR spectra observed for these complexes is understandable given the close agreement in Fe-coordination sphere bond length and coordination geometry observed crystallographically (Table 1).

Table 2. Comparison of spin-state and bond lengths within iron(III) complexes derived from 12-membered tetra-azamacrocyclic ligands.

	*				
Complex	Spin State (S)	Fe-N4 (Å)	Fe-N2 (Å)	N1-Fe-N3 (°)	Ref.
[(cyclen)Fe(Cl) ₂]Cl	5/2	-	2.1461(16)	146.40(6)	[99]
[(LN ₄ H ₂)Fe(Cl) ₂]Cl	*	2.094(1)	2.189(1)	142.41(7)	[101, 117, 121]
[(Me ₂ EBC-12)Fe(Cl) ₂]PF ₆	5/2	-	2.163 (2)	153.20	[118]
[(L1)Fe(Cl) ₂]ClO ₄	5/2	2.1074(5)	2.2001(6)	147.25(2)	‡
[(L2)Fe(Cl) ₂]ClO ₄	5/2	2.0967(10)	2.2023(10)	146.71(4)	‡
[(L3)Fe(Cl) ₂]ClO ₄	5/2	2.107(2)	2.181(2)	147.19(8)	‡
* not reported, ‡ This wo	rk				



Figure 6. X-band EPR spectra of **L1Fe** - **L3Fe** (*left*). Quantitative simulations (dashed lines) are overlaid on each spectrum for comparison. The black circle observed at g ~ 4.92 in **L2Fe** is from a minor (< 10%) high-spin iron(III)-impurity. Instrumental parameters: frequency, 9.643 GHz, microwave power, 6 μ W; modulation amplitude, 0.9 mT; temperature, 10 K. Simulation parameters: S = 5/2; $g_{1,2,3} \sim 2.0$; |D|, 0.7 ± 0.2 cm⁻¹; E/D, 0.07; $\sigma_{E/D}$, 0.01; σ_B , 0.9 mT. Energy level diagram (*right*) illustrating the splitting of doublets within the S = 5/2 spin state along each principle axis (X, *red*; Y, *green*; Z, *black*).

Electrochemistry

Cyclic voltammetry was used to evaluate the electrochemical behavior of L1Fe-L3Fe. The cyclic voltammograms corresponding to the iron(III/II) couple of L1Fe-L3Fe are shown in Figure 7. Of the three complexes, L2Fe ($E_{1/2} = -486$ mV) has the most negative half potential, followed by L3Fe ($E_{1/2} = -468$ mV) and L1Fe ($E_{1/2} = -465$ mV). The difference in the half potentials indicated derivatization of the pyridine ring affects the electron density around the iron center, specifically, L2 is the most donating. Figure 8 compares the electrochemical potentials of iron complexes containing 12-membered tetra-azamacrocycles; a wide range (-865 mV to 20 mV) of half potentials is achieved by changing the donor capacity of the ligand set, LN₄Me₂ < Me₂EBC-12 < L1 \approx L3 < L2 < cyclen.^{94, 105, 122,[124]}

The reversibility of the redox process was investigated by determining the ΔE_p and I_{pa}/I_{pc} . The iron(III/II) redox processes are quasi-reversible (ΔE_p , I_{pa}/I_{pc}): **L1Fe** (105 mV, 1.2583), **L2Fe** (112 mV, 0.7264), and **L3Fe** (101 mV, 0.7485). Lastly, the electrochemical events are diffusion

controlled for all three iron complexes, as shown by the linear relationship between I_p and the square-root of the scan rate (Figure S6).^[125]

It should be noted that an additional ligand based oxidation event around 900 mV is observed in the full solvent window (1.4 to -1.2 mV, Figure S5) for **L1Fe-L3Fe**. We have previously postulated that this event was ligand derived, based on electrochemical analysis of the corresponding zinc(II) complexes providing a similar behavior.^[102] Electrochemical analysis of **L1-L3** in DMF solvent with TBAP electrolyte provide direct confirmation that this positive oxidation wave is ligand based (Figure S5).



Figure 7. Cyclic voltammogram overlay of the $Fe^{III/II}$ couple measured for **L1Fe-L3Fe** in DMF containing 0.1 *M* [Bu₄N][BF₄] as electrolyte, Ag/Ag⁺ reference electrode, glassy carbon working electrode, and platinum auxiliary electrode at a scan rate of 100 mV/sec. All scans were referenced to Fc/Fc⁺ = 0.00 mV.



Figure 8. Iron(III)/(II) halfway potentials of iron complexes in literature containing 12membered tetra-azamacrocycles. The potentials are reported as referenced to $Fc/Fc^{+} = 0.00 \text{ mV}$. ^[99, 117-118, 124, 126]

Table 3. The anodic wave potential (E_{pa}), cathodic wave potential (E_{pc}), peak potential separation (ΔE_p), and halfway potential ($E_{1/2}$) of **L1Fe-L3Fe**. **L2Fe** contains the most stable iron(III) ion in the series according to the $E_{1/2}$ values.

Complex	E _{pc} (mV)	E _{pa} (mV)	E _{1/2} (mV)	ΔE _p (mV)	I _{pc} (μΑ)	I _{pa} (μA)	I _{pa} /I _{pc}
L1Fe	-517	-412	-465	105	10.5837	-13.3181	1.2583
L2Fe	-542	-430	-486	112	18.4176	-13.3791	0.7264
L3Fe	-519	-418	-468	101	11.9661	-8.9570	0.7485



Figure 9. The electronic absorbance spectra of ligands L1-L3 and complexes L1Fe-L3Fe obtained in 1 *M* HCl.

Electronic Absorption Spectroscopy

The spectrophotometric behaviors of **L1Fe-L3Fe** are shown in Figure 9. The aromatic components of the ligands (*sans metal*) result in absorbance bands between 210 and 290 nm when measured in 1 *M* HCl. The iron(III) complexes showed no appreciable shift in the $\pi \rightarrow \pi^*$ region (210-300 nm). Instead, the appearance of MLCT bands were observed at wavelengths greater than 300 nm: **L1Fe** (311 nm), **L2Fe** (306 and 356 nm), **L3Fe** (458 nm), which is consistent with high-spin d⁵ complexes.^[127] These metal based assignments are supported by comparison to the 12-membered macrocycle, **[(cyclen)Fe(NCMe)₂]³⁺** that Hua et *al.* reported to have absorbance bands at 259 and 358 nm and corresponding extinction coefficients below 500 M⁻¹cm⁻¹.^[127]

Furthermore, the difference in the absorbance spectra of L1Fe, L2Fe, and L3Fe is reflected in the visible color of the complexes. The L1Fe and L2Fe complexes are light brown solids, while L3Fe is a red solid; in solution L1Fe and L2Fe are yellow and L3Fe is brown. Low solubility of the complexes in other solvents precluded a full study of solvent effects or at other pH values. Therefore, it should be noted that the iron complex responsible for catalytic activity may vary in the degree of ligand protonation, but the coordination sphere around the iron within the complex does not change. The electronic absorption differences between L3Fe compared to the L1Fe and L2Fe complexes could be attributed to the lack of symmetry originating from the hydroxyl moiety in the meta-position of the pyridine ring of the ligand.

Table 4. Catalytic efficiency of iron complexes to obtain 2-phenylpyrrole from pyrrole

 and phenylboronic acid, achieved using 10% catalyst loading in the presence of air.

H × +	.B(OH) ₂ 	Catalyst ht, 130ºC, 10h	HN
	Catalyst	Yield	
	L1Fe	57 ± 3	
	L2Fe	58 ± 7	
	L3Fe	52 ± 7	

Catalytic Activity of Iron(III) Complexes

Motivated by the report that addition of a tetra-azamacrocycle, iron(II) salt, and oxygen to phenylboronic and pyrrole results in the formation of 2-phenylpyrrole^[31], we explored the oxidation state of the pre-catalyst by testing L1Fe, L2Fe, and L3Fe for catalytic activity. Yields are shown in Table 4. In this series of experiments each catalyst was tested at 10% loading, open to air. The ferric complexes afforded 2-phenylpyrrole in yields of 57% (L1Fe), 58% (L2Fe), and 52% (L3Fe), thereby identifying the oxidation state of the pre-catalyst as an iron(III) species. The realization that the iron(III) complexes enter the catalytic cycle will allow for better foundation to determine the oxidation state and identity of the active catalytic species. The following discussion focuses on the experiments used to validate that the iron +

ligand catalyst species is solely responsible for providing the selective reactivity observed, showing the ligand can catalyze baseline reactions with no regioselectivity, and components necessary for the reaction to proceed.

Table 5. Control reactions used to determine the yield of product in the absence of the high-spin iron(III) complexes.

Test Compound	Oxidant	Yield
*	*	0
*	20 eq. oxygen	0
Fe(ClO ₄) ₃	20 eq. oxygen	0
L1	20 eq. oxygen	0
L2	20 eq. oxygen	Trace
L3	20 eq. oxygen	Trace
L3	Atmosphere	Trace
*Not present		

Control reactions were performed to ensure that the catalytic reactivity observed with **L1Fe**, **L2Fe**, and **L3Fe** was due only to the iron complexes. The substrates, pyrrole and phenylboronic acid, were heated to 130 °C in both the absence or presence of oxygen (Table 5). No reaction was observed under either of these conditions. This indicates that the reaction requires a catalyst to proceed. Additionally, four control reactions consisting of iron(III) perchlorate, **L1**, **L2**, and **L3** were performed in the presence of 10 mL O_2 . Yield of 2-phenylpyrrole was determined by both GC-MS and NMR due to the low quantities observed. Iron(III) perchlorate and **L1** did not afford 2-phenylpyrrole, however, **L2** and **L3** produced trace amounts of 2-phenylpyrrole. Interestingly GC-MS analysis of the control reaction, which included pyrrole, phenylboronic acid, **L3**, and atmospheric air also showed the formation of trace amounts of 2-phenylpyrrole and butenolides was previously observed by Campi *et al.* when 3-phenylprop-2-yn-1-amine is exposed CO/H₂ at 400 psi at 70°C for 20 hours in the presence of a rhodium catalyst. These results indicate

that the ligand is capable of background reactivity thus producing pyrrole derivative. Additionally, it indicates that the derivatives produced are controlled by the composition of the oxidant (O_2 and CO_2) used in the reaction. Importantly, comparison of the products formed in the presence of **L3** and **L3Fe** and atmosphere show that the use of the iron complex is *essential* to obtain catalytic and regioselective production of 2-phenylpyrrole product.

Conclusion

The addition of iron(II) perchlorate to the tetra-azamacrocycles **L1**, **L2**, and **L3** in the presence of oxygen yields high-spin iron(III) complexes **L1Fe**, **L2Fe**, and **L3Fe** as shown by X-ray crystallography and EPR spectroscopy. Furthermore, it was demonstrated that the high-spin iron(III) complexes participate in the coupling of pyrrole and phenylboronic acid to produce 2-phenylpyrrole. Although a small amount of background reactivity was overserved with **L3**, the results show that the iron complexes are responsible for controlling the reaction to produce 2-phenylpyrrole alone. A full study involving a large library of iron macrocyclic derived complexes focused on understanding features of catalytic activity is the topic of a forth coming report. Finally, the characterization of the complexes using electrochemistry, UV-vis spectroscopy and mass spectrometry lays a foundation for mechanistic investigations concerning the oxidation state of the iron center throughout the catalytic process.

Supporting Information

Crystallographic data for L1Fe, L2Fe, and L3Fe (CCDC #: 1422489, 1422490, and 950048, respectively) in both CIF and table format.

Conflicts of interest

There are no conflicts to declare.

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Highlights

- Synthesis of three new dichloric iron(III) tetra-aza macrocyclic complexes. •
- Characterized via X-ray crystallography, UV-vis absorbance spectroscopy, electron • paramagnetic resonance spectroscopy, cyclic voltammetry, and mass spectrometry.
- Pre-catalyst for the coupling of pyrrole and phenylboronic acid to form 2phenylpyrrole.
- Iron(III) state of the complexes is essential for catalytic and regioselective production • of the 2-phenylpyrrole product.