Part I: Discovery, Structure, and Bonding Properties

a) Elucidating ferrocene structure

- In 1951, Paulson and Kealy were the first to synthesize ferrocene, unintentionally, in an attempt to synthesize fulvalene.

\[
\begin{align*}
\text{MgBr} & \quad \text{FeCl}_2 \quad \text{Metalloccenes} \\
\text{Cyclopentadiene} & \quad \text{Fe} & \quad \text{Cyclopentadiene} \\
\end{align*}
\]


- Coincidentally, another group at British Oxygen Co. synthesized ferrocene in an attempt to perform a modified Haber process using iron and ammonia

\[
\begin{align*}
\text{Fe}^0 & \quad \text{Cyclopentadiene} \quad \text{O}_2, \text{NH}_3 (g) \\
\end{align*}
\]


- Both groups reported the incorrect structure!

- After the reported syntheses of ferrocene, R. B. Woodward and G. Wilkinson theorized a more reasonable structure based on the following properties:

1. When subjected to IR spectroscopy, a sharp band at 3.25 µ was detected, indicating only one type of C–H bond.
2. The net dipole of the compound was calculated to be 0.
3. The total electron count should be 18.


1. Contour maps via X-ray diffraction showed a "sandwich complex."
2. Ten-bonded structure excluded because lack of s, p, and d orbitals to show correct symmetry.
4. C–Fe bond length = 2.0 Å

Part I: Discovery, Structure, and Bonding Properties

- Impressively, Woodward and Wilkinson also correctly predicted the staggered conformation of the cyclopentadienes as being lower in energy, thus more stable.

- A more accurate orbital diagram is depicted below:

- Orbital symmetry is most likely a combination of the diagram above.


b) Cyclopentadiene as a ligand

- Cyclopentadiene (Cp), when considered η^5, is an L_2X-type ligand because it occupies three facially oriented coordination sites on the metal center.

- Cp binds very tightly in metallocene systems because of an additional electrostatic interaction between the cationic metal center and the anionic Cp.

- In Cp-metal complexes, it is very rare for full dissociation of Cp from the metal to occur.

\[ \Delta H = 79 \text{ kcal/mol} \]

- Generally, there are four classes of Cp complexes:

Note: Cp* indicates methylated Cp
Part I: Discovery, Structure, and Bonding Properties

c) Synthesis and functionalization of ferrocenes

- In addition to the aforementioned methods, some common methods for ferrocene synthesis are:

- Although Friedel–Crafts-type reactions are utilized in the derivatization of ferrocenes, there are two potential problems:
  1. Iron is capable of performing a single-electron oxidation, rendering nitration, halogenation, and sulfonation difficult
  2. Competitive electrophilic attack between Fe and Cp

- Ferrocenes are often functionalized for chiral ligand development due to the stabilization of the positive charge at the α-position of the Cp ring
Ferrocene: Catalyzing Interest in Organometallic Chemistry

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Part I: Discovery, Structure, and Bonding Properties

- Strong bases are also used to deprotonate and, subsequently, functionalize the Cp ring(s) of ferrocene.

- Monolithiation of ferrocene is a difficult process, as most strong bases carry out unbiased deprotonation at both sites. Interestingly, use of t-BuLi and trapping with stannyl electrophile yields selective monolithiated product:

- Ferrocenes with oxazoline, sulfoxide, or aminoalkyl substitution can undergo ortho-lithiation with very high selectivity — strong directing effect from heteroatoms


- These properties allow for synthesis of unique and complex ligands for other transition metals:

- Several properties make ferrocene a powerful ligand in catalysis:

1. Backbone is rigid enough to provide an efficient chiral environment
2. Simple to derivatize - ferrocene reacts $3 \times 10^6$ times faster than benzene!
3. Planar chirality and appropriate steric bulk to govern enantio- and stereocontrol
4. Stable to oxygen and moisture
5. Commercially available for low price ($4.50/g from Sigma-Aldrich)


a) **Amination** (Hartwig, J.F., et al., JACS 1998, 120.)

- J. F. Hartwig utilized diphosphinoferrocene (dpf) ligands in his work on palladium-catalyzed amination of aryl halides and aryl tosylates
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Part II: Ferrocene as a Ligand in Transition-Metal Catalysis

- Demonstrated utility of diphosphinoferrocene ligands as electron-rich alkyl phosphines that promote necessary ligand dissociation

b) Direct α-Arylation of Ketones (Hartwig, J. F., et al., JACS 1997, 119)

- In an attempt to effect amination of aryl bromides, Hartwig observed an interesting side reaction when acetone was used as solvent
- Displayed the utility of diphosphinoferrocene ligands in their ability to prohibit β-hydride elimination via occupation of coordination sites

- Increasing electron density at the metal center shown to promote the oxidative addition step, which involves bent, chelated Pd⁰ complex
- Alkyl phosphines too electron-rich and tightly bound to promote ligand dissociation
Part II: Ferrocene as a Ligand in Transition-Metal Catalysis

Proposed Catalytic Cycle

\[ \text{Y}X + R'CO\text{R''} \xrightarrow{\text{10\% Pd(dba)\_2, DPPF/DTPF}} \text{ArCO\text{R'}} \]

- Observed that more sterically hindered ferrocene ligands (DTPF vs. DPPF) give faster reaction rates and higher overall yields by strongly promoting reductive elimination over \( \beta \)-hydride elimination.

Examples:

- 85% yield for t-Bu 4-Ph-CO
- 84% yield for Ph 4-Ph-CO
- 55% yield for Ph 3-Ph-CO
- 94% yield for 4-Ph-CO

\[ \text{Ph} \xrightarrow{\text{84\%}} \text{Ph} \xrightarrow{\text{55\%}} \text{Ph} \xrightarrow{\text{94\%}} \]

- 79% yield for 4-Ph-CO (Me)
Part II: Ferrocene as a Ligand in Transition-Metal Catalysis

c) Olefin Polymerization (Long, N., et al., Organometallics 2006, 25.)

- Terdentate bis(imino)pyridine ligands commonly employed in development of olefin polymerization catalysts, however, bis-chelate complexes proved to be problematic for the propagation of polymerization

- Ferrocene adds effective steric bulk, preventing formation of the 2:1 ligand:Fe complex
Part II: Ferrocene as a Ligand in Transition-Metal Catalysis

- It was observed that these ferrocenyl derivatives also contributed to the increased rate of propagation, thus, increasing the molecular weight of the resulting polymer.

- Inclusion of ferrocene influences activity and selectivity of the active center via redox-active properties (oxidation of ferrocene at remote site can change reactivity of active transition-metal center).

- For ferrocenyl derivative, two oxidation and reduction waves were observed.
- Ferrocenyl iron atoms easier to oxidize than central iron atom, and this increase in electrophilicity aids in ethylene binding.

\[ \text{d) C–H Imidation of Heteroarenes} \ (\text{Baran, P.S., et al., JACS, 2014, 136.}) \]

- Ferrocene shown to act as "electron shuttle" in radical mechanism responsible for addition of imides to aromatic systems.

- Imidated products could be deprotected to aniline derivatives in one pot.

\[ \text{Imidated products} \rightarrow \text{Aniline derivatives} \]
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Part II: Ferrocene as a Ligand in Transition-Metal Catalysis

Proposed Catalytic Cycle

\[
\begin{align*}
\text{R} - \text{Het} & \quad \text{NSP} \quad \xrightarrow{\text{Cp}_2\text{Fe (5 mol%)}} \quad \text{R} - \text{Het} \quad \text{NO} \\
& \quad \text{DCM, 50 °C} \quad \xrightarrow{-\text{tBuO}^-} \quad \text{HC} - \text{CO}_2 \quad \xrightarrow{+e^-} \quad \text{Het} \quad \text{Fe}^{\text{II}} \\
& \quad \text{Fe}^{\text{III}} \quad \text{Ot-Bu} \quad \xrightarrow{-e^-} \quad \text{Het} \quad \text{NO} \\
\end{align*}
\]

40%, 60%, 44%, A:B=2.5:1
Part III: Other Applications of Ferrocene

a) Perturbation of ferrocene via metal-metal interactions

(Diaconescu, P. L., et al., Organometallics 2008, 27.)

- Strong interaction detected between uranium and iron atoms via calculated distances from one metal center to the other (Fe–U distance = 3.08 Å)

- In crystal structure and corresponding geometry optimization model, ferrocene is perturbed such that the "sandwich-complex" becomes bent

- A bent ferrocene complex could be a potentially useful conformation for both ligand design and in iron catalysis, as it makes the metal center more accessible
Ferrocene: Catalyzing Interest in Organometallic Chemistry

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Part III: Other Applications of Ferrocene

b) Using ferrocene for analytic methods in total synthesis
(Burn, N. Z., et al., JACS 2015, 137.)

- In Burns’ synthesis of (+)-Halomon, a ferrocene derivative of one precursor was synthesized in order to form a crystalline solid that could be subjected to X-ray crystallography for determination of absolute and relative configuration.

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} & \quad \text{Br} & \quad \text{O} & \quad \text{Fe} \\
\text{Cl} & \quad \text{Br} & \quad \text{OH} & \quad \text{Cl} & \quad \text{Fe}
\end{align*}
\]

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} & \quad \text{Br} & \quad \text{Fe} & \quad \text{O} \\
\text{Br} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Fe}
\end{align*}
\]

\[
\begin{align*}
\text{HN} & \quad \text{Fe} & \quad \text{N} \\
\text{Cl} & \quad \text{Fe}
\end{align*}
\]

ferroquine (FQ)

c) Ferrocene as a potential drug candidate
(Fraisse, L., et al., Parasite, 2011, 18.)

- A set of antimalarial drugs known as the quinoline class has utilized ferrocene in developmental antimalarial treatment.

- Ferroquine (FQ) is efficacious against chloroquinoline (CQ) targets, as well as CQ-resistant strains.

- FQ is more rigid than CQ, and it carries out a reversible one-electron redox reaction to counter the harsh oxidizing environment of the parasite.

- FQ mode of actions involves the inhibition of β-hematin via complexation.
Part III: Other Applications of Ferrocene

d) Asymmetric Catalysis using planar-chirality of ferrocene derivatives

(Fu, G.C., Acc. Chem. Res. 2004, 37.)

- "Planar-chiral" ferrocene derivatives act as unique nucleophilic catalyst to effect various transformations in an asymmetric fashion.

- Catalyst can perform nucleophilic addition to carbonyls and effect the stereochemistry via formation of a chiral enolate intermediate (similar reactivity with other functional groups).

- Other derivatives include pyrrolidine and/or methyl substitution on remaining Cp.

- Various asymmetric transformations have been realized:

1. Addition of alcohols to ketenes

   \[
   \text{MeOH} + \text{O=C} - \text{R} \xrightarrow{\text{cat.}^*} \text{MeO} - \text{H} - \text{Ar} \]

2. Rearrangement of O-acylated enolates

   \[
   \text{BnO} - \text{O} \xrightarrow{\text{cat.}^*} \text{BnO} - \text{O} - \text{Me} \]

3. Acylation of alcohols by anhydrides

   \[
   \text{Ar} - \text{OH} + \text{Me} - \text{O} - \text{O} \xrightarrow{\text{cat.}^*} \text{Ar} - \text{O} - \text{Me} \]