Iron, we hardly know thee....

26

Fe
Iron

Frontier of Chemistry Seminar
Adam T. Hoye
June 9th, 2007
Iron, we hardly know thee?
Iron, we hardly know thee....

...Synthetically

Catching up with an old friend

26

Fe

Iron

Frontier of Chemistry Seminar

Adam T. Hoye

June 9th, 2007
The (Abbreviated) History of Iron

-Oldest iron artifacts are from 7,000 years ago and believed to come from meteorites (first civilized uses 2,500 BCE in China)

-The Hittites (1500 BCE, near modern-day Turkey) were the first people to smelt iron and forge weapons that easily triumphed over the softer bronze weapons of their opponents

-These relatively unknown people grew to rival the great armies of the Egyptians, Syrains, and Persians due to their technological advantage

-Ironworking was kept secret from other civilizations and helped secure the Hittites abnormally fast rise to prominence in Mesopotamia
The (Abbreviated) History of Iron

-Around 1200 BCE, during the peak of the Hittites, the kingdom suddenly collapsed (a severe drought seen in the rings of ancient trees?) and forced the Hittites to reveal the secret of iron for their survival.

-Thus the Iron Age began and due to the expansion of the Roman Empire, civilizations throughout the world learned the secrets and indispensible nature of iron.

-Through time (and metallurgy), iron would prove itself to be an essential element to human survival and civilization advancement
Element 26

Name: Iron, symbol Fe- Ferrum (Latin)
- Group 8, Row 4 element
- Atomic Weight 55.845 g·mol$^{-1}$
- Electron Configuration:
  1s$^2$2s$^2$2p$^6$3s$^2$3p$^6$4s$^2$3d$^6$
- Oxidation states: 2, 3, 4, 6
- Ferromagnetic
- Lustrous, silvery soft metal
- Formed via Stellar Nucleosynthesis; major component of meteorites and cores of dense-metal planets
Element 26

-6th most abundant element in the universe; 4th most abundant on Earth

-Concentration of iron ranges from 80% to pure in the Earth’s core to 5% in the crust

-Iron is extracted from iron ore; Haematite (Fe₂O₃) $0.021 per 100g ($210 per metric ton)

-In 2005, approx. 1.5 Mt (million tons) of iron ore was produced worldwide (China major producer)

-Iron used in steel and other alloys, automobile manufacturing, and magnetic storage
Heme-Iron and Biological Importance

Contained in cytochrome proteins (mediate redox reactions); hemoglobin, myoglobin, and leghemoglobin (oxygen carrier proteins)

Non-heme iron mostly contained in enzymes such as nitrogenase (ammonia production), methane monooxygenase (methane to methanol), and ribonucleotide reductase (ribose to deoxyribose)
Ferrocene Story

*Paul Pauson & Tom Kealy*
At Duquesne University in July 1951, trying to assess the aromaticity of fulvalene

![Chemical reaction diagram]

Paul Pauson & Tom Kealy

Fulvalene
At Duquesne University in July 1951, trying to assess the aromaticity of fulvalene.

Paul Pauson & Tom Kealy

yellow crystals soluble in organic ethereal solvents;
Elemental analysis indicated $\text{C}_{10}\text{H}_{10}\text{Fe}$


Adam Hoye @ Wipf Group
Ferrocene Story

At the 1951 IUPAC conference…

- Pauson gave J. M. Robertson, an x-ray crystallographer and former professor of Pauson’s at Glasgow, a sample of the mysterious crystals

- Results never emerged from the Robertson labs; 2 independent publications put forth the novel “doppelkegel” or “sandwich” structure (Fischer and Pfab- prelim. x-ray data; Wilkinson, Rosenblum, Whiting, and Woodward- IR stretches and diamagnetism).

Structure confirmed later by x-ray analysis; Wilkinson and Fischer went on to win the Nobel Prize for their work in sandwich compounds

“At Woodward’s suggestion that the compound might be aromatic…”
To Fe or not to Fe…

Q: Did Iron use up it’s 15 minutes of fame?
A: No- it used up 40 years!

-Cheap (FeCl$_3$- 100g, $16.30$ Aldrich)
-Non-toxic alternative to other transition metals
-Short reaction times
-In high supply
-Easy large-scale purification
-”Always a bridesmaid, never a bride…”
-Catalyzes a wide range of organic transformations
Reactions Catalyzed by Iron

Michael Additions
Multicomponent Reactions
Barbier-type Reactions
Chloroaminations
Substitution Reactions
Diene Protections
Acetal Formations
Cycloisomerization Reactions
Aza-Prins Reactions
Ferrocene-derived Ligands

Plan of Attack

- General Iron-Catalyzed Reactions
  Oxidations
  Reductions
  Olefinations
  Reactions with Sulfur (Iminations)
  Aldol Reactions
  Allylations

- Carbometallations

- Cyclization Reactions
  Cationic Cyclizations
  Electrophilic Cyclizations
  Pericyclic Reactions
  Ring-Opening Reactions

- Cross Coupling Reactions
Iron-Catalyzed Oxidations

\[
[(L)\text{Fe}^\text{II}X]^2+ + \text{H}_2\text{O}_2 \rightarrow [(L)\text{Fe}^\text{III}\text{OOH}]^2+ \rightarrow [(L)\text{Fe}^\text{IV=O}]^2+ , \cdot\text{OH}
\]

In air/O\textsubscript{2} or using polar, protic solvents: 100 % epoxide

**Olefin Oxidation Products using bio-inspired catalyst**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Diol:Epoxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>styrene</td>
<td>80:1</td>
</tr>
<tr>
<td>cyclooctene</td>
<td>14:1</td>
</tr>
<tr>
<td>1-octene</td>
<td></td>
</tr>
<tr>
<td>5 equiv of H2O2</td>
<td>90:1</td>
</tr>
<tr>
<td>10 equiv of H2O2</td>
<td>76:1</td>
</tr>
<tr>
<td>20 equiv of H2O2</td>
<td>52:1</td>
</tr>
<tr>
<td>cyclohexene</td>
<td>9:1</td>
</tr>
<tr>
<td>cis-2-heptene</td>
<td>7:1</td>
</tr>
<tr>
<td>trans-2-heptene</td>
<td>10:1</td>
</tr>
<tr>
<td>ethyl trans-crotonate</td>
<td>&gt;100:1</td>
</tr>
<tr>
<td>tert-butyl acrylate</td>
<td>&gt;100:1</td>
</tr>
<tr>
<td>dimethyl fumarate</td>
<td>&gt;100:1</td>
</tr>
</tbody>
</table>

**Reaction Conditions:**
10 eq. H\textsubscript{2}O\textsubscript{2}, 0.35 M in CH\textsubscript{3}CN, 5 min

**TON (\mu M \text{ product}/\mu M \text{ cat.})** between 5-10

Iron-Catalyzed Oxidations

\[
\text{Alkene} \quad \text{yield} \\
cyclooctene & 90 \\
cyclohexene & 85 \\
1\text{-heptene} & 88 \\
vinylicyclohexane & 90 \\
1\text{-octene} & 92 \\
trans-methyl styrene & 96 \\
trans-methyl-cinnamate & 86 \\
ethyl sorbate & 89
\]


Catalytic Cycle:

Xang, X. P. et al. Org. Lett. 2004, 6, 1907
Allylic Oxidations

(1,3-cyclohexanediene)Fe(CO)₃ (0.3 eq)
Me₃NO (3 eq)
benzene, 10 h, rt, 96%

Allylic Substitutions

![Chemical Structures]

Reductions

Results suggest:

\[ \text{Ar}^+ \text{N} \text{-(Fe}_3\text{CO)}_9\text{O}\text{Me}^- \] as intermediate

*Mechanistic studies show radical anion [Fe}_3\text{CO)}_11\text{]^- is involved*


Olefinations

\[
\begin{align*}
\text{R}^1 \text{CHO} & \quad \text{Fe(TPP)Cl} \quad \text{Benzoic Acid} \\
+ & \quad \text{PPh}_3 \\
\text{R}^2 \text{CO}_2 \text{R} & \quad 2 \text{ - } 96\% \text{ yields}
\end{align*}
\]

Aromatic, aliphatic, and unsaturated ketones

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Me</td>
<td>99</td>
</tr>
<tr>
<td>Ph</td>
<td>Et</td>
<td>99</td>
</tr>
<tr>
<td>Ph</td>
<td>i-Pr</td>
<td>99</td>
</tr>
<tr>
<td>Ph</td>
<td>n-Bu</td>
<td>98</td>
</tr>
<tr>
<td>p-Cl</td>
<td>C₆H₄</td>
<td>98</td>
</tr>
<tr>
<td>p-MeO</td>
<td>C₆H₄</td>
<td>92</td>
</tr>
<tr>
<td>o-Me</td>
<td>C₆H₄</td>
<td>95</td>
</tr>
<tr>
<td>COOEt</td>
<td>i-Bu</td>
<td>83</td>
</tr>
<tr>
<td>Ph</td>
<td>allyl</td>
<td>53</td>
</tr>
<tr>
<td>Ph</td>
<td>3-butenyl</td>
<td>75</td>
</tr>
<tr>
<td>n-C₅H₁₁</td>
<td>H</td>
<td>77</td>
</tr>
<tr>
<td>n-C₁₀H₂₁</td>
<td>H</td>
<td>80</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>56</td>
</tr>
<tr>
<td>Br</td>
<td>Me</td>
<td>59</td>
</tr>
<tr>
<td>n-Bu</td>
<td>Et</td>
<td>74</td>
</tr>
</tbody>
</table>

Sulfur Reactions

Sulfoximines:

\( \text{BocN}_3 + \text{S}^\text{O}R \xrightarrow{\text{FeCl}_2, \text{CH}_2\text{Cl}_2} \text{O}^\text{NBoc} \text{S}^\text{O}R \)

\( \text{R}= \text{Bn}, 70\% \)
\( \text{R}= \text{Ph}, 45\% \)
\( \text{R}= \text{Me}, 64\% \)
\( \text{R}= \text{p-MeOPh} 52\% \)

Sulfilimines:

\( \text{BocN}_3 + \text{S}^\text{S}R \xrightarrow{\text{FeCl}_2, \text{CH}_2\text{Cl}_2} \text{S}^\text{NBoc} \text{S}^\text{S}R \)

\( \text{R}= \text{Bn}, 85\% \)
\( \text{R}= \text{Ph}, 70\% \)


Proposed Mechanism:

1. \( \text{Fe(acac)}_3, \text{Phl}=\text{O}, \text{NsNH}_2, \text{CH}_3\text{CN}, \text{rt} \)
2. \( \text{PhSH, Cs}_2\text{CO}_3, \text{CH}_3\text{CN}, \text{rt} \)

83\% ee 79\% yield
Mukaiyama-Aldol Reactions


Allylations

One-Pot Acetalization/Allylation

\[
\text{RCHO} \xrightarrow{\text{BnOSiMe}_3, \text{FeCl}_3 \ (5 \text{ mol\%})} \text{CH}_2\text{Cl}_2, \text{rt}, 2 \text{ h} \xrightarrow{\text{SiMe}_3} \text{R} = \text{Ph, } p\text{-OMePh, } p\text{-MeO}_2\text{CPh, } \text{Ph(CH}_2)_2\text{, } c\text{-C}_6\text{H}_{11}, \text{ } t\text{-Bu}
\]


Electrochemical Allylation

\[
\text{R} + \text{R'} \xrightarrow{1. \text{e}^{-}, \text{FeBr}_2, \text{bipy, DMF, Fe anode}} \xrightarrow{2. \text{H}^+} \text{ yields 39 - 86%}
\]

Carbometallations

-Initial Fe-catalyzed carbometallation report:

\[
\begin{align*}
\text{FeCl}_3 & \quad \text{(iBu)}_3\text{Al} \\
& \quad \text{Plus regioisomers and homocoupling products}
\end{align*}
\]


-Using alkyllithium reagents provided better results:

\[
\begin{align*}
\text{Fe(acac)}_3 (10 \text{ mol\%}) , \\
\text{BuLi (3 eq)} \\
& \quad \text{Toluene, -20 °C, 4 h} \\
& \quad \text{R= OCH}_2\text{CH}_2\text{CH}_2\text{Ph, OCH}_2\text{Ph,} \\
& \quad \text{NEt}_2, \text{OBn} \\
& \quad \text{79 - 97\% yields}
\end{align*}
\]

-Intermediate vinyllithium species was postulated and validated based on trapping experiments

Carbometallations

- Strained alkenes increase reactivity

\[
\begin{align*}
\text{MeO} & + \text{Et}_2\text{Zn} \\
\text{FeCl}_3 (5 \text{ mol\%}) & \quad p\text{-Tol BINAP}(7.5 \text{ mol\%}) \\
\text{TMEDA (2.5 eq)} & \quad \text{toluene/THF}
\end{align*}
\]


88% yield, 89% ee

---

\[
\begin{align*}
\text{Ar-MgBr} + \text{R}^1 \equiv \text{R}^2 & \quad \text{Fe(acac)}_3 (5 \text{ mol\%}) \\
\text{CuBr (10 mol\%)} & \quad \text{PBu}_3 (40 \text{ mol\%}) \\
\text{THF, 60 °C} & \quad \text{H}_2\text{O}
\end{align*}
\]

\[
\begin{align*}
\text{Ar} & \quad \text{R}^1 \quad \text{R}^2 \\
\text{36 - 90\% yields (72:26 to 99:1 E/Z)} & \quad 36 - 90\% \text{ yields (72:26 to 99:1 E/Z)}
\end{align*}
\]

R\(^1\), R\(^2\) = Pr, Bu, Hex, Ph, SiMe\(_3\)

---

-Cooperative carbometallation met with more positive results:


Adam Hoye @ Wipf Group

6/22/2007
Carbometallations

-Use of intramolecular directing group- propargyl alcohols

\[
\begin{align*}
R&C\equiv&OH & \text{H}_3C\text{-MgBr} & \text{(5 eq.)} & \text{catalyst} & \text{ligand} & \text{THF} & -78 \, ^\circ\text{C} \text{ to } 0 \, ^\circ\text{C} \\
& & & & & & & & \\
\rightarrow & \text{HO-CH}_3 & + & \text{HO-CH}_3
\end{align*}
\]

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Ligand</th>
<th>conversion (%)</th>
<th>ratio of products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Co(OAc)$_2$</td>
<td>-</td>
<td>58</td>
<td>9/1</td>
</tr>
<tr>
<td>Ni(acac)$_2$</td>
<td>-</td>
<td>63</td>
<td>9/1</td>
</tr>
<tr>
<td>Fe(acac)$_3$</td>
<td>-</td>
<td>98</td>
<td>6/1</td>
</tr>
<tr>
<td>Fe(acac)$_3$</td>
<td>dppe</td>
<td>97</td>
<td>21/1</td>
</tr>
</tbody>
</table>

\[
\begin{align*}
\text{R}= nC_{10}H_{21}, \text{TBSO(CH}_2\text{)}_5, \text{BnO(CH}_2\text{)}_5, \text{75} \text{- } \text{80}\% \\
\text{C}_{10}H_{13} \text{OH} & \text{75}\% \\
\text{Ph(CH}_2\text{)}_2 \text{HO-CH}_3 & \text{61}, \text{99}\% \text{ee}
\end{align*}
\]

Carbene-Assisted Carbometallation:

\[
\begin{align*}
\text{Ar}_2\text{MgBr} + R\equiv\text{Ar}^1 & \quad \text{Fe(acac)}_3 \text{(5 mol\%)} \\
\text{IPr} \text{(20 mol\%)} & \quad \text{H}_2\text{O} \quad \text{THF, 60 °C, 16 h}
\end{align*}
\]

R = n-Bu, Et, iBu, iPr
Ar\(^1\) = Ph, 4-MeOC\(_6\)H\(_4\), 3-MeOC\(_6\)H\(_4\), 4-ClC\(_6\)H\(_4\)
Ar = 4-MeOC\(_6\)H\(_4\), 3,5-Me\(_2\)C\(_6\)H\(_4\), 4-FC\(_6\)H\(_4\)
1-Nap

53 - 91\% yields
72:24 to 95:5 E:Z

Carbene ligand credited with stabilizing low-valent iron intermediates and preventing decomposition of the alkenyliron species in the catalytic cycle

Iron-Catalyzed Cyclization Reactions

-Cationic Cyclizations


Iron-Catalyzed Cyclization Reactions

-Electrophilic Cyclizations

\[
\text{Fe(CO)₃ + DIBAL} \quad \text{85\%} \quad \text{MeCO₂Et} \quad \text{Fe(CO)₃} \quad \text{H₂P} \quad \text{Fe(CO)₃} \quad \text{MeCO₂Me} \quad \text{82\%} \quad \text{THF} \quad \text{91\%}
\]
Pericyclic Reactions

-Fe as a Lewis Acid catalyst for asymmetric Diels-Alder [4+2] reactions is known

-Fe has been shown to catalyze [2+1], [2+2], [2+2+1], [2+2+2], [4+1], and [4+4] reactions as well

Han, J. L.; Ong, C. W. Tetrahedron 2006, 62, 8169
Pericyclic Reactions

-[6+2] ene cyclization

6 steps from phenylalanine

Fe(CO)₃

DIEA, MsCl, CH₂Cl₂

82%

nBu₂O, CO, 142 °C

50% (3 steps)

1. CuCl₂, EtOH
2. H₂, Pd

Pearson, A. J.; Sun, H.; Wang, X. J. Org. Chem. 2007, 72, 2547
Ring-Opening Reactions

R= aryl, alkenyl, or 1° and 2° alkyl


Cross Coupling Reactions Using Fe

-In 1971 Kochi observed the initial Fe-mediated cross coupling:

$$\text{MeMgBr} \quad \text{Br} \quad \text{Me} \quad \text{FeCl}_3 \text{ cat.}$$

-These coupling reactions have been limited to vinyl halides, phosphonates, sulfonates, and acyl chlorides

Fürstner, A.; Martin, R. Chem. Lett. 2005, 34, 624
A Controversial Mechanism…

-Proposed by Fürstner on the basis that FeX$_2$ reacts with 4 equivalents of RMgX to generate an “inorganic Grignard” cluster species, bearing a formally negative charge on iron

”Such highly nucleophilic entities lacking any stabilizing ligands are able to oxidatively add to aryl halides”
The Plot Thickens…

More than one mechanistic pathway (ate compounds)?

\[ 5 \text{MeLi} + \text{FeCl}_3 \rightarrow [\text{Me}_4\text{Fe}]\text{Li}_2 + 3 \text{LiCl} + \frac{1}{2} \text{ethane} \]

Radical mechanism?

Extension of Coupling Methodology

-Alkyl Halides tolerated

\[
\text{Br-COOEt} \xrightarrow{\text{PhMgBr}} \text{Ph-COOEt}
\]

\[\text{Li}_2[\text{Fe(C}_2\text{H}_4)_4]\text{ (cat.)}\]

91%

-Expanded Functionality Tolerance

\[
\text{MeO-Cu} \xrightarrow{\text{Fe(acac)}_3 (10 \text{ mol\%})} \text{EtO}_2\text{C-Ph}[\text{N-Ph}] \xrightarrow{\text{EtO}_2\text{C}} \text{Me}
\]

\[\text{THF/DME (3:2), 4 h, 80 °C}\]

91%

Fürstner, A.; Martin, R. Chem. Lett. 2005, 34, 624
Ottesen, L. K.; Ek, E.; Olsson, R. Org. Lett. 2006, 8, 1771
Applications of Fe-Cross Couplings

\[
\text{Cl-} \begin{array}{c}
\text{Cl} \\
\text{O} \\
\text{Tf}
\end{array}
\overset{\text{[(salen)FeCl] (cat.)}}{\longrightarrow}
\begin{array}{c}
\text{Cl-} \\
\text{O} \\
\text{MgBr}
\end{array}
\text{H}_2\text{C} = \text{CH(})_5\text{MgBr}

\text{80%}

1. Metathesis
2. H_2

\text{Muscopryridine}

\text{TfO} \overset{\text{Fe(acac)}_3 \text{ (cat.)}}{\longrightarrow} \text{MeMgBr} \overset{\text{Fe(acac)}_3 \text{ (cat.)}}{\longrightarrow} \text{Latrunculin B}

97%

80%

“…this methodology evolved into a routine tool for the preparation of fine chemicals and pharmaceutically active compounds in the laboratory and on the industrial scale, is widely appreciated in the context of parallel synthesis and combinatorial chemistry, and plays a prominent role in a rapidly growing number of highly impressive total syntheses of target molecules of utmost complexity.”

-Alois Fürstner
Conclusion and Outlook

- The unique and diverse processes that iron catalyzes offer opportunities for increased investigation and, especially, application

- Reactive intermediates will show clues to novel reactivity

- The demand for Iron catalysts that are cheaper, less toxic and easier to remove, yet perform as well as their transition metal counterparts will be realized - it makes sense!

- Extension of Iron catalyzed reactions into olefin metathesis