Iron Catalyzed Cross Coupling: Mechanism and Application

Matthew Burk
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Long Induction Period: Early History Of Iron Catalyzed Cross Coupling

- 1941: Effect of metal impurities on homocoupling during Grignard formation investigated by Kharasch
- Followed by coupling of alkyl Grignards with benzyl bromide (1945), acetyl chloride (1953)
- 1971: Extensive studies on coupling with vinyl halides by Kochi
- 1998: Cahiez reports *practical* method of coupling alkyl Grignards and vinyl halides
- 2002: Fürstner reports highly practical coupling of alkyl Grignards with aryl halides
- 2002-present: Many reports by many groups.

Molander, G. A.; Rahn, B. J.; Shubert, D. C.; Bonde, S. E.; *Tet. Lett.* 1983, 5449
Cross-Coupling of Vinyl Halides: Overview

Earliest studies: Kochi

\[
\text{Br} \quad \text{Me} \quad \text{R} \quad \text{MgBr} \quad \frac{0.5\% \text{Fe(dbm)}_3}{\text{THF, RT}} \quad \text{Me} \quad \text{R} \\
\]

Stereospecific
Drawback: Several equiv. of bromide used

Molander’s Modification

\[
\text{Br} \quad \text{Ph} \quad \text{Ar} \quad \text{MgBr} \quad \frac{0.5\% \text{Fe(dbm)}_3}{\text{DME, -20°C} \rightarrow \text{RT}} \quad \text{Ph} \\
\]

1:1 Stoichiometry
E-bromides give \( E,Z \) mixtures

Cahiez’s Modification

\[
\text{Br} \quad \text{Bu} \quad \text{c-HexMgBr} \quad \frac{1\% \text{Fe(acac)}_3}{\text{THF/NMP, 0°C}} \quad \text{c-Hex} \quad \text{Bu} \quad 89\% \\
\]

Broad scope
Stereospecific
Insensitive to choice of halide

\[
\text{Br} \quad \text{Ph} \quad \text{BuMgBr} \quad \frac{1\% \text{Fe(acac)}_3}{\text{THF/NMP, 15 to 20°C}} \quad \text{Ph} \\
\]

60%

Molander, G. A.; Rahn, B. J.; Shubert, D. C.; Bonde, S. E.; *Tet. Lett.* 1983, 5449
Cahiez, G.; Avedissian, H. *Synthesis*, 1998, 1199
Alkylation of Aryl Halides

Electron-rich arenes require OTf

Electron-poor aryl chlorides and alkyl Grignards are excellent coupling partners

Electron rich arenes require OTf

Arylation of Aryl Halides

More challenging, homocoupling of Grignard problematic

Two methods known:

FeF$_3$ suppresses homocoupling
Catalyst pretreated with EtMgBr @ 0 – 23 °C for 4 h
Thermal stability of active species is remarkable

Electron-rich iodides are unreactive

Cross Coupling of Alkyl Halides

Arylation of Alkyl Halides

Amine ligands

**Preformed Fe (-2) complex (Much more on this later)**

**Alkylation of Alkyl Halides**

Cross Coupling of Vinyl Halides: Kochi’s pioneering studies

\[
\begin{align*}
K &= k[\text{MeMgBr}]^0[\text{bromide}]^1 \\
\text{MeMgBr} &\xrightarrow{2.9 \text{ equiv}} \text{Me} \\
\text{Fe(dbm)}_3 (0.34 \text{ mol\%}) \text{ THF, RT} \\
\end{align*}
\]

Poor results obtained with higher alkyl Grignards due to elimination, homocoupling and reduction.

Measures all conversions based on Grignard reagent

Proposes a Fe(I)-Fe(III) cycle (but won’t rule out Fe(0)-Fe(II))

Evidence: analysis of headspace gases (1.5 to 2.0 equiv MeMgBr consumed during catalyst activation)
ESR of activated complex formed from EtMgBr + Fe(dbm)_3 shows broad signal at \(g=2.085\)

Determined that dbm (and acac) ligands are reduced to radical dianions, disproving his interpretation of UV/Vis spectra.

Problem

Propose an alternative oxidation state (not Fe(I)) for Kochi’s intermediate that explains the total stoichiometry (n) of gases observed during catalyst activation.

\[
\text{Fe(acac)}_3 + n \text{MeMgBr} \xrightarrow{\text{THF}} [\text{Fe}]^? + \text{CH}_4 + \text{C}_2\text{H}_6
\]

**Table IV**

Reduction of Iron(III) by Methylmagnesium Bromide\(^a\)

<table>
<thead>
<tr>
<th>Iron(III) complex</th>
<th>(\text{CH}_3\text{MgBr}, \text{MgBr}_2/\text{MgBr}_2) ((10^2 \text{ mmol}))</th>
<th>(\text{CH}_3^+), (\text{MgBr}_2/\text{MgBr}_2) ((10^2 \text{ mmol}))</th>
<th>(\text{CH}_4, \text{C}_2\text{H}_6) ((10^2 \text{ mmol}))</th>
<th>(n) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{Fe(acac)}_3)</td>
<td>20</td>
<td>4</td>
<td>6.15</td>
<td>1.16</td>
</tr>
<tr>
<td>(\text{Fe(acac)}_3)</td>
<td>30</td>
<td>6</td>
<td>3.41</td>
<td>3.29</td>
</tr>
<tr>
<td>(\text{FeCl}_5(\text{PPh}_3))</td>
<td>30</td>
<td>6</td>
<td>4.53</td>
<td>2.48</td>
</tr>
<tr>
<td>(\text{Fe(acac)}_3)</td>
<td>50</td>
<td>10</td>
<td>1.40</td>
<td>3.54</td>
</tr>
<tr>
<td>(\text{Fe(acac)}_3)</td>
<td>125</td>
<td>25</td>
<td>1.96</td>
<td>2.66</td>
</tr>
</tbody>
</table>

\(^a\) In THF solutions containing \(5 \times 10^{-2} \text{ M iron(III)}\). \(^b\) \(n = (\text{CH}_4 + 2\text{C}_2\text{H}_6)/5\).
Mechanisms of Iron Catalyzed Cross-coupling

The Fürstner model: at least two classes of mechanisms exist (<0 to -20 °C)

Fe(0) – Fe(-II) cycle:

\[
[\text{Fe(MgX)}_2]_n, \text{aka “inorganic Grignard”}
\]
Black-brown, unstable solutions

Requires β-hydride elimination or other initiation mechanism

Fe(II) Ferrate, aka “Super-ate” complex:

Occurs in absence of β-hydride e.g. MeMgBr

Evidence for Ferrate Manifold

Different Reactivity of MeMgBr:

X-ray structure of Li – analog A:

Complications with Phenyl Analogs

Both decompose thermally, producing biphenyl

Non-Ferrate Manifold

Active catalyst is not stable (except in under certain conditions)

Wide range of plausible oxidation states
Model systems required

Mechanistic Hypothesis:  Active catalyst is Mg/Fe clusters of composition \([\text{Fe}(\text{MgX})_2]^n\)

Stoichiometric σ-Bond Metathesis in Model Systems


Potential Fe(I)-Fe(III) cycle

Reagents and conditions: (a) allyl chloride, pentane, $-20^\circ C \rightarrow 0^\circ C$, 16 h, 43%, cf. Scheme 9; (b) allyl chloride, Et₂O, 0 $^\circ C$, 24 h, 61%, cf. Scheme 13; (c) PhLi or PhMgBr, Et₂O, $-35^\circ C$, 2 h; (d) MeLi, pentane, $-78^\circ C \rightarrow 0^\circ C$, ca. 70%; (e) THF-d₈, ethene (1 atm), ambient temperature, 46% (NMR, allylbenezene), see text; (f) allyl chloride, Et₂O, $-40^\circ C$, 20 h, 58%.

Relative Catalytic Activity of Model Complexes

Only 8 (Fe(-II)) accounts for very high rates observed in catalytic reactions

Catalytic activity of complexes

Selected examples:

\[ A = \begin{array}{c}
\text{Fe}^2 \\
\text{L} \end{array} \]

(L = TMEDA)

\[ \begin{array}{ccc}
\text{F}_3\text{C} & \text{Cl} & \text{Ph} \\
\text{Br} & \text{Br} & \text{Br}
\end{array} \]

\[ n\text{-C}_6\text{H}_{13}\text{MgBr} \quad \text{Cat. (5 mol\%)} \quad \text{THF/NMP, 0 °C} \]

\[ \begin{array}{c}
\text{F}_3\text{C} \\
\text{n-C}_6\text{H}_{13}
\end{array} \]

85% (Cat.=A)

80% (Cat.=Fe(acac)₃)

\[ \text{PhMgBr} \quad \text{A (5 mol\%)} \quad \text{THF, -20 °} \]

\[ \text{Ph} \]

94%

\[ \text{n-Bu} \]

92%

\[ \text{PhMgBr} \quad \text{A (5 mol\%)} \quad \text{THF, -20 °} \]

\[ \text{Ph} \]

87%

Evidence for Radical Intermediate

Evidence against: no reaction with 3° halides

Conclusions

Iron-catalyzed cross couplings at low temperature likely occur by an Fe(-II) catalyzed process, preceded by catalyst activation through a β-hydride elimination/reductive elimination pathway.

An alternative Fe(I) – Fe(III) cycle appears to be too slow to account for the observed catalytic rates, but could possibly participate under some combination of conditions.

In the absence of a β-hydride on the Grignard reagent, the active species may be a tetraalkyl ferrate (Fe(II)).

Insertion into alkyl C-X bonds involves a radical intermediate.

At higher temperatures (>-20 to 0 °C) little is known.