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# Iron Catalyzed Cross Coupling: Mechanism and Application

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# Long Induction Period: Early History Of Iron Catalyzed Cross Coupling

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- 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
- 1972-1997: Occasional reports, including use of vinyl halides (1983) and allylic phosphonates (1991)
- 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.

Kharasch, M. S.; Fields, E. K. *J. Am. Chem. Soc.* **1941**, *63*, 2316–2320.

Vavon, G.; Chaminade, C.; Quesnel, G. *Hebd. Seances Acad. Sci.* **1945**, *220*, 850–852.

Tamura, M.; Kochi, J. K. Vinylation of Grignard reagents. Catalysis by iron. *J. Am. Chem. Soc.* **1971**, *93*, 1487–1489.

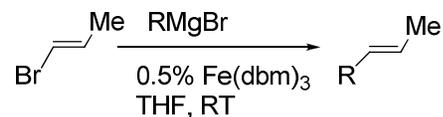
Molander, G. A.; Rahn, B. J.; Shubert, D. C.; Bonde, S. E.; *Tet. Lett.* **1983**, 5449

Yanagisawa, A.; Nomura, N. Yamamoto, H. *Synlett*, **1991**, 514

Fürstner, A.; Leitner, A.; Mendez, M.; Krause, H. *JACS*, **2002**, *124*, 13856

# Cross-Coupling of Vinyl Halides: Overview

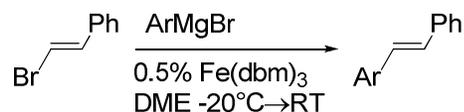
Earliest studies: Kochi



Stereospecific

Drawback: Several equiv. of bromide used

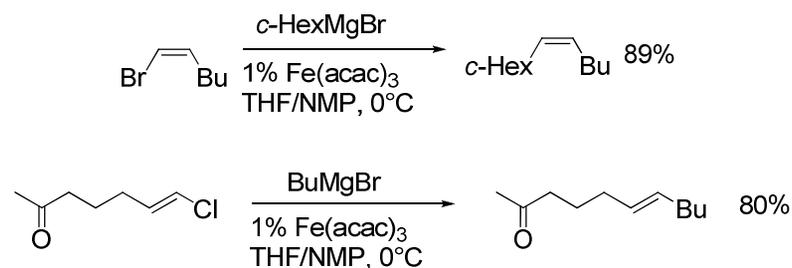
Molander's Modification



1:1 Stoichiometry

*E*-bromides give *E,Z* mixtures

Cahiez's Modification



Broad scope

Stereospecific

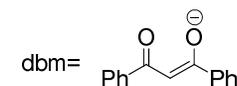
Insensitive to choice of halide



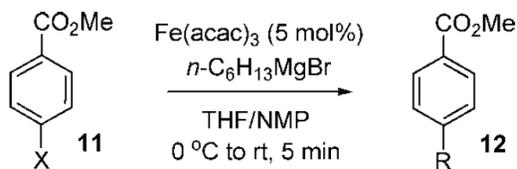
Tamura, M.; Kochi, J. K. *JACS*, **1971**, *93*, 1487.

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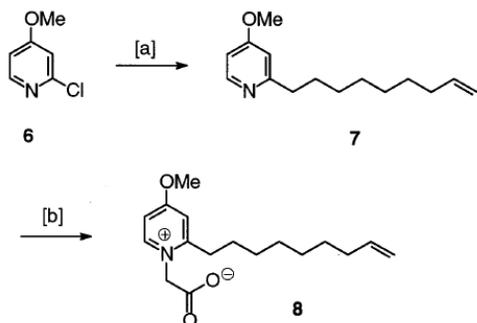
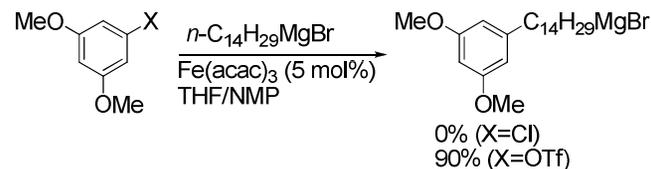
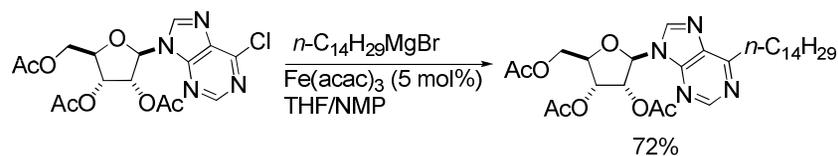
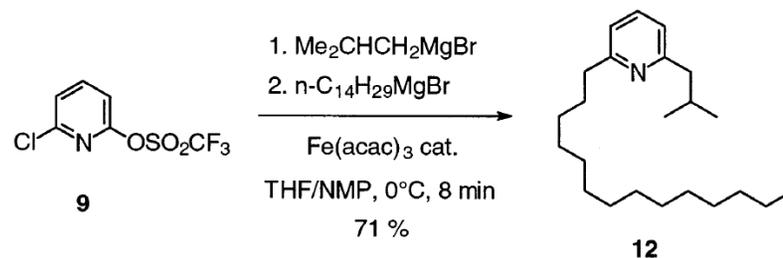
Cahiez, G.; Avedissian, H. *Synthesis*, **1998**, 1199



# Alkylation of Aryl Halides



entry	X	yield, % (R = <i>n</i> -C <sub>6</sub> H <sub>13</sub> )	yield, % (R = H)
1	I	27	46
2	Br	38	50
3	Cl	> 95	
4	OTf	> 95	
5	OTs	> 95	



<sup>a</sup> (a) 8-Nonenylmagnesium bromide, Fe(acac)<sub>3</sub> (5 mol %), THF/NMP, 0 °C → rt, 81%. (b) (i) BrCH<sub>2</sub>COOtBu, 40 °C; (ii) F<sub>3</sub>CCOOH, Et<sub>3</sub>SiH, CH<sub>2</sub>Cl<sub>2</sub>, 74%.

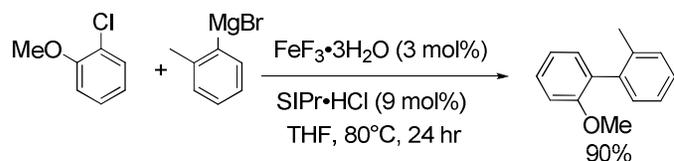
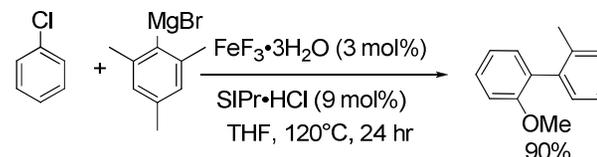
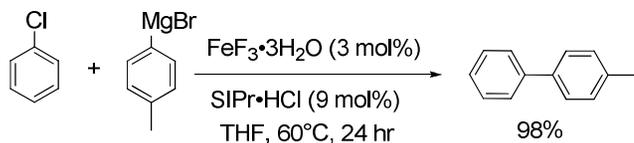
Electron-poor aryl chlorides and alkyl Grignards are excellent coupling partners

Electron rich arenes require OTf

# Arylation of Aryl Halides

More challenging, homocoupling of Grignard problematic

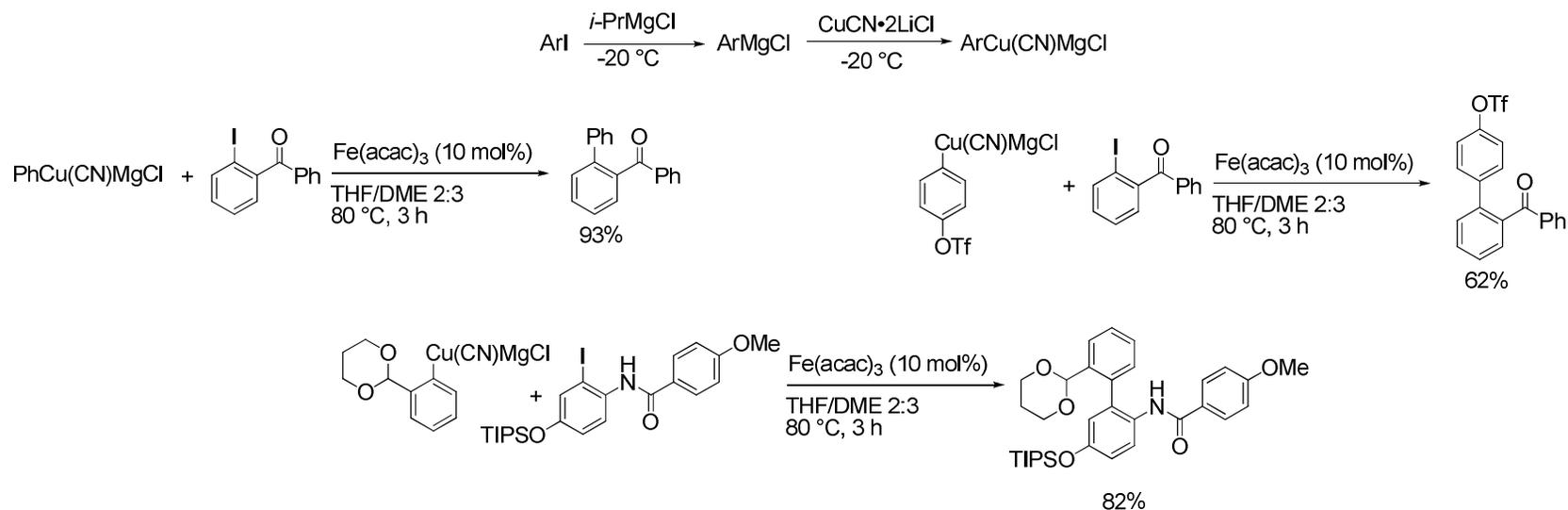
Two methods known:



$\text{FeF}_3$  suppresses homocoupling

Catalyst pretreated with  $\text{EtMgBr}$  @ 0 – 23 °C for 4 h

Thermal stability of active species is remarkable



Electron-rich iodides are unreactive

Hatakeyama, T.; Nakamura, M. *JACS*, **2007**, *129*, 9844.

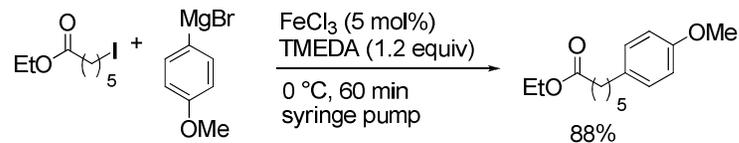
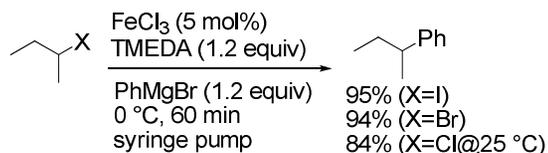
Sapountzis, I.; Lin, W.; Kofink, C.; Despotoulou, C.; Knochel, P. *ACIE*, **2005**, *44*, 1654.

Kofink, C.; Blank, B.; Pagano, S.; Götz, N.; Knochel, P.; *ChemComm*, **2007**, 1954..

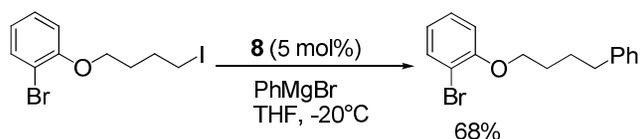
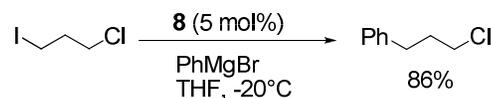
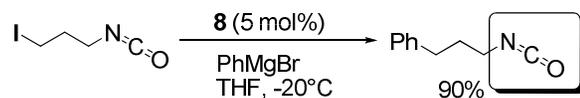
# Cross Coupling of Alkyl Halides

## Arylation of Alkyl Halides

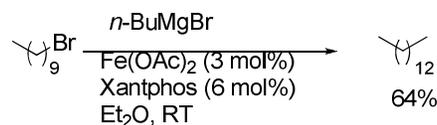
### Amine ligands



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



## Alkylation of Alkyl Halides

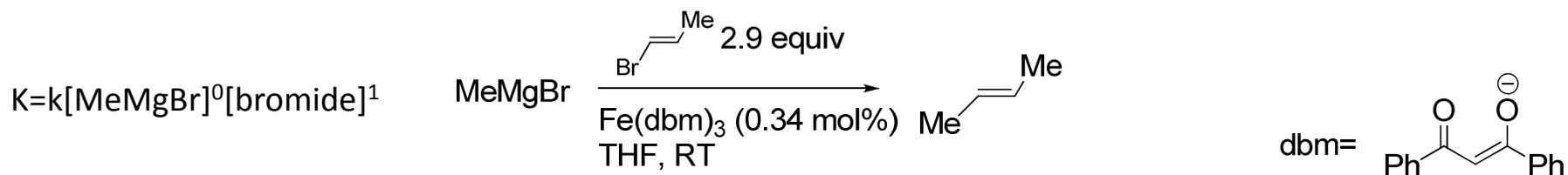


Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *JACS*, **2004**, *126*, 3686.

Martin, R.; Fürstner, A.; *Angew. Chem.*, **2004**, *116*, 4045.

Dongol, K.; Koh, H.; Sau, M.; Chai, C. *Adv. Synth. Catal.* **2007**, *349*, 1015

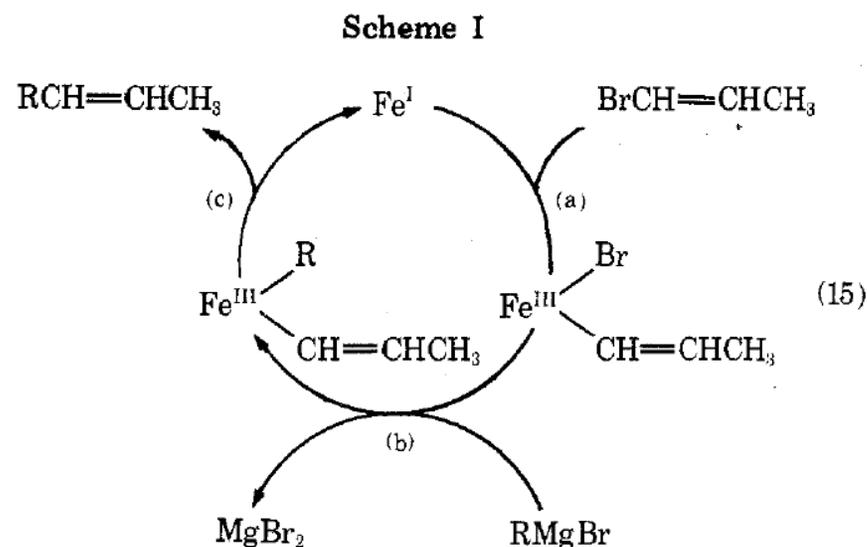
# Cross Coupling of Vinyl Halides: Kochi's pioneering studies



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)<sub>3</sub> shows broad signal at  $\langle g \rangle = 2.085$

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

- Smith, R. S.; Kochi, J. K. JOC, **1976**, *41*, 502.  
 Tamura, M.; Kochi, J. K. JACS, **1971**, *93*, 1487.  
 Neumann, S. M.; Kochi, J. K. JOC, **1975**, *40*, 599.  
 Kwan, C. L.; Kochi, J. K. JACS, **1976**, *98*, 4903.

# 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.



**Table IV**  
**Reduction of Iron(III) by Methylmagnesium Bromide<sup>a</sup>**

Iron(III) complex	CH <sub>3</sub> MgBr, (10 <sup>2</sup> mmol)	CH <sub>3</sub> <sup>-</sup> MgBr/ Fe(III)	CH <sub>4</sub> , (10 <sup>2</sup> mmol)	C <sub>2</sub> H <sub>6</sub> , (10 <sup>2</sup> mmol)	n <sup>b</sup>
Fe(acac) <sub>3</sub>	20	4	6.15	1.16	1.7
Fe(acac) <sub>3</sub>	30	6	3.41	3.29	2.0
FeCl <sub>3</sub> (PPh <sub>3</sub> )	30	6	4.53	2.48	1.9
Fe(acac) <sub>3</sub>	50	10	1.40	3.54	1.7
Fe(acac) <sub>3</sub>	125	25	1.96	2.66	1.5

<sup>a</sup> In THF solutions containing  $5 \times 10^{-2} M$  iron(III). <sup>b</sup>  $n = (\text{CH}_4 + 2\text{C}_2\text{H}_6)/5$ .

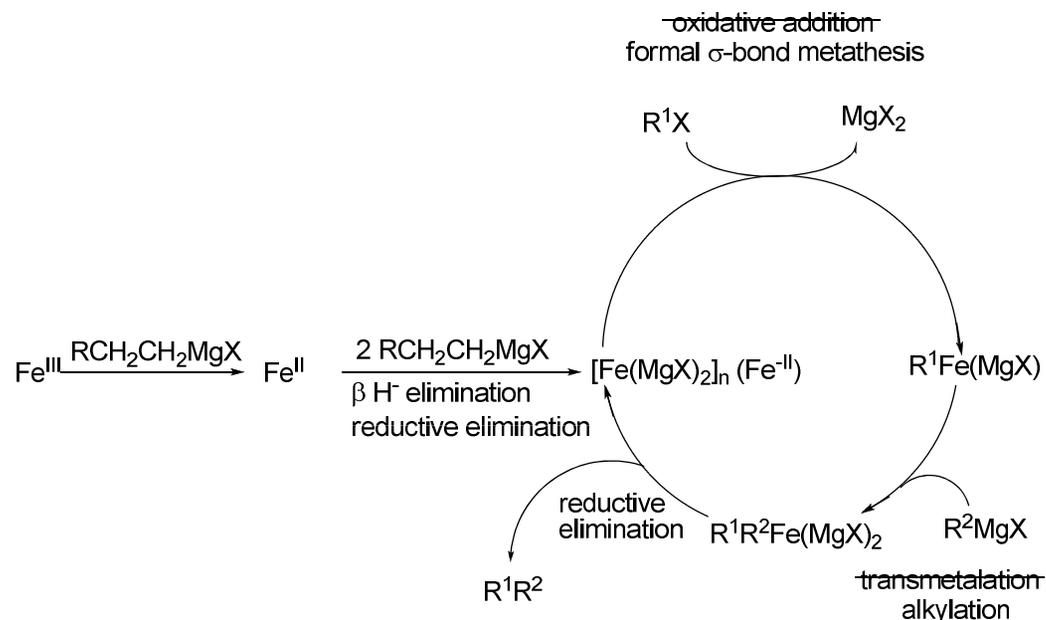
# Mechanisms of Iron Catalyzed Cross-coupling

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

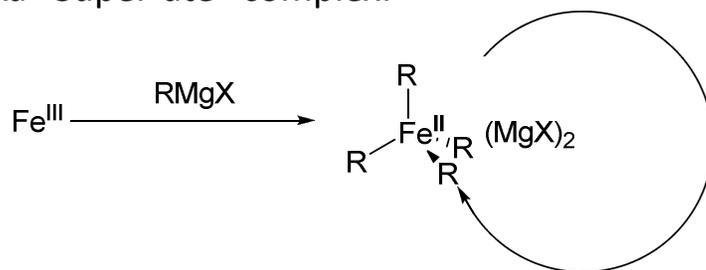
Fe(0) – Fe(-II) cycle:

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

Requires  $\beta$ -hydride elimination  
or other initiation mechanism



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

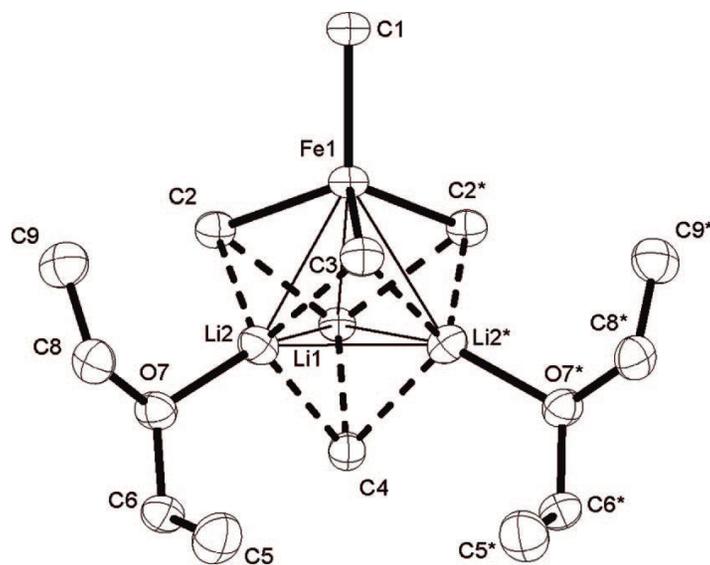
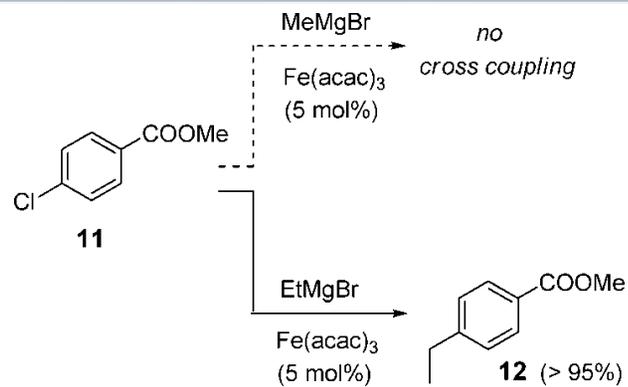


Bright yellow solutions

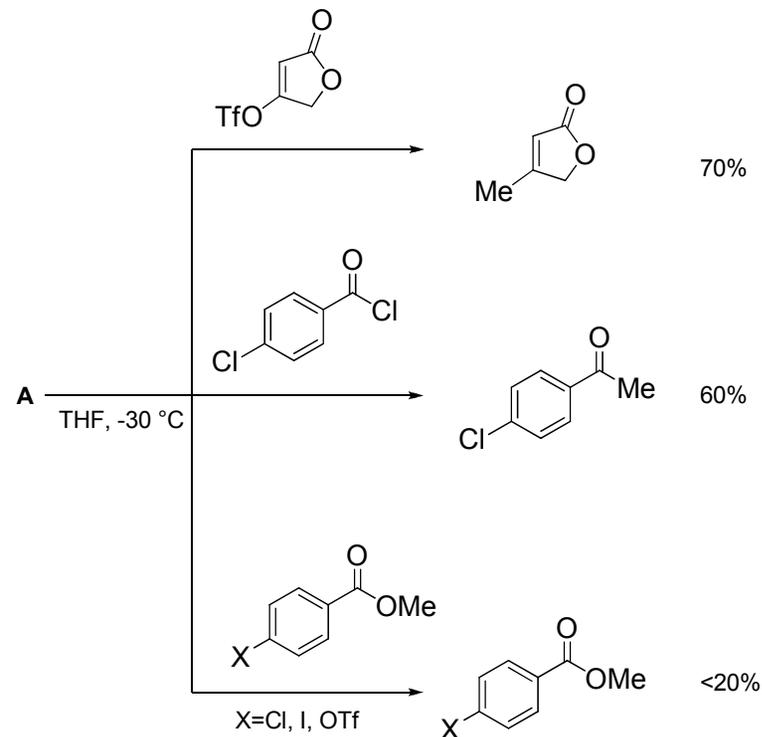
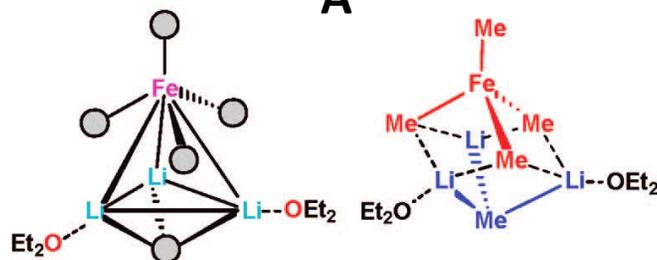
Occurs in absence of  $\beta$ -hydride e.g.  $\text{MeMgBr}$

# Evidence for Ferrate Manifold

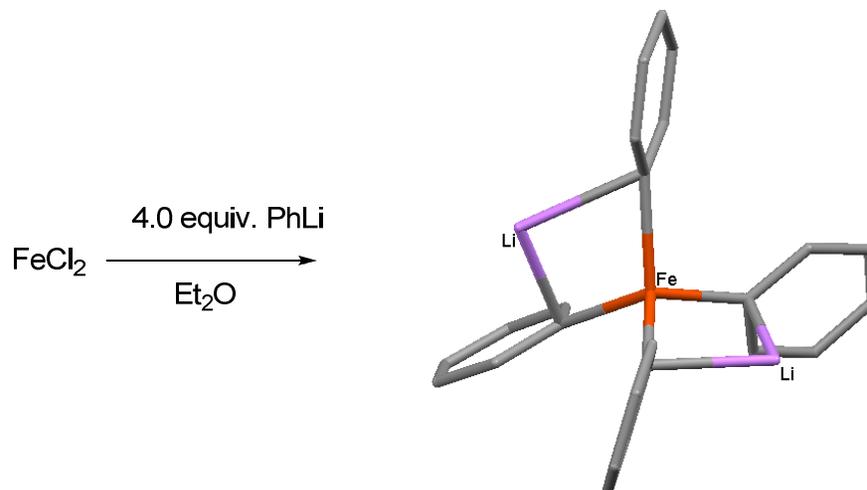
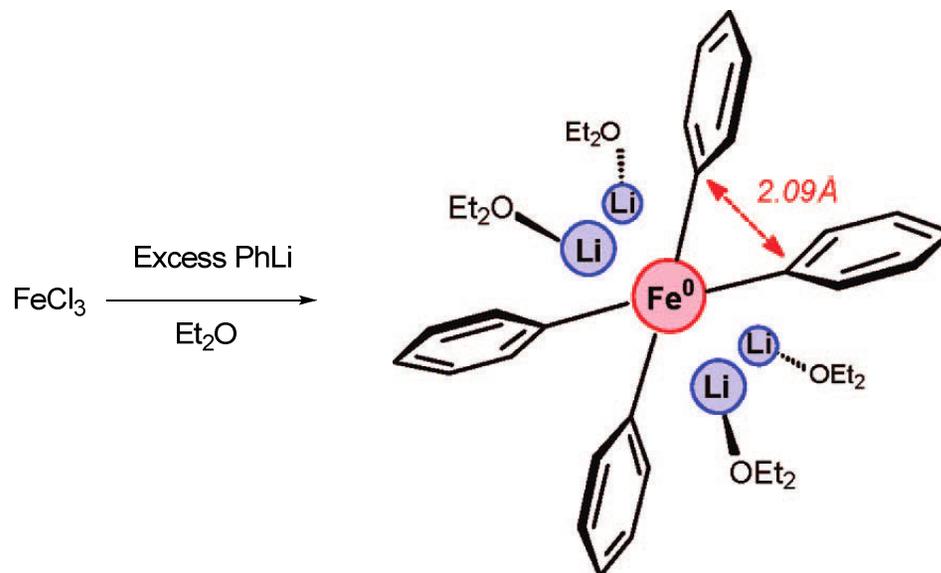
Different Reactivity of MeMgBr:



**A**



# Complications with Phenyl Analogs

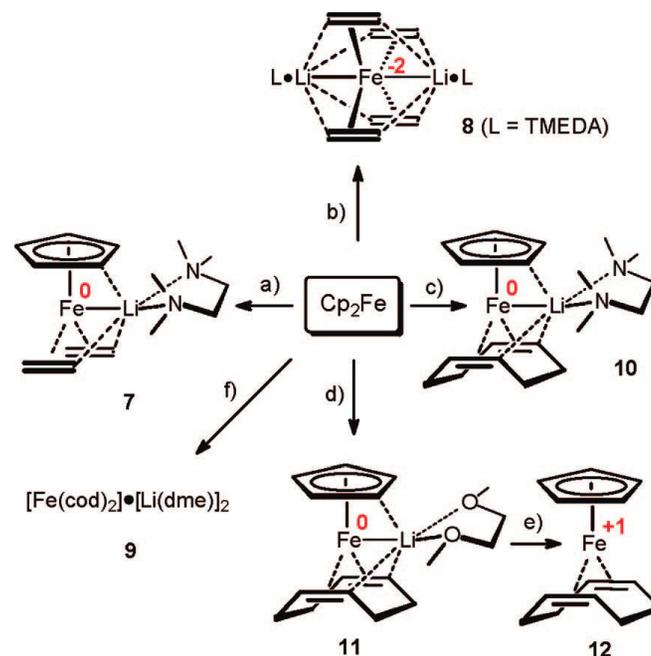


Both decompose thermally, producing biphenyl

# Non-Ferrate Manifold

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

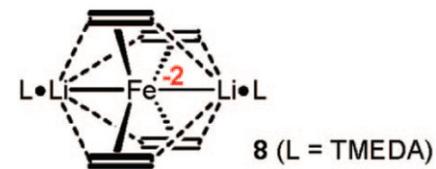
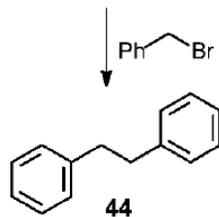
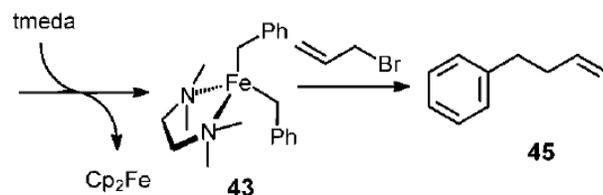
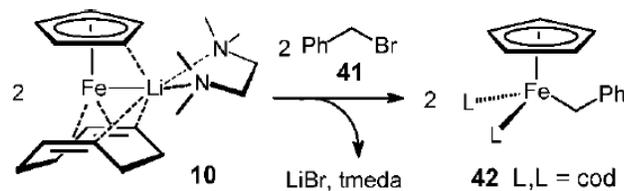
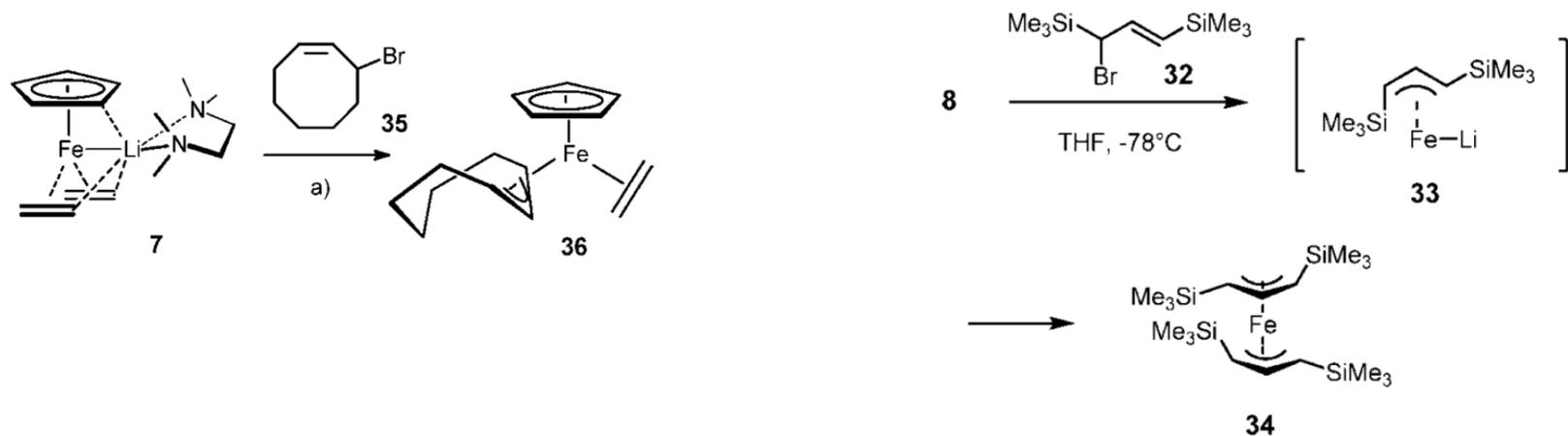
Wide range of plausible oxidation states  
Model systems required



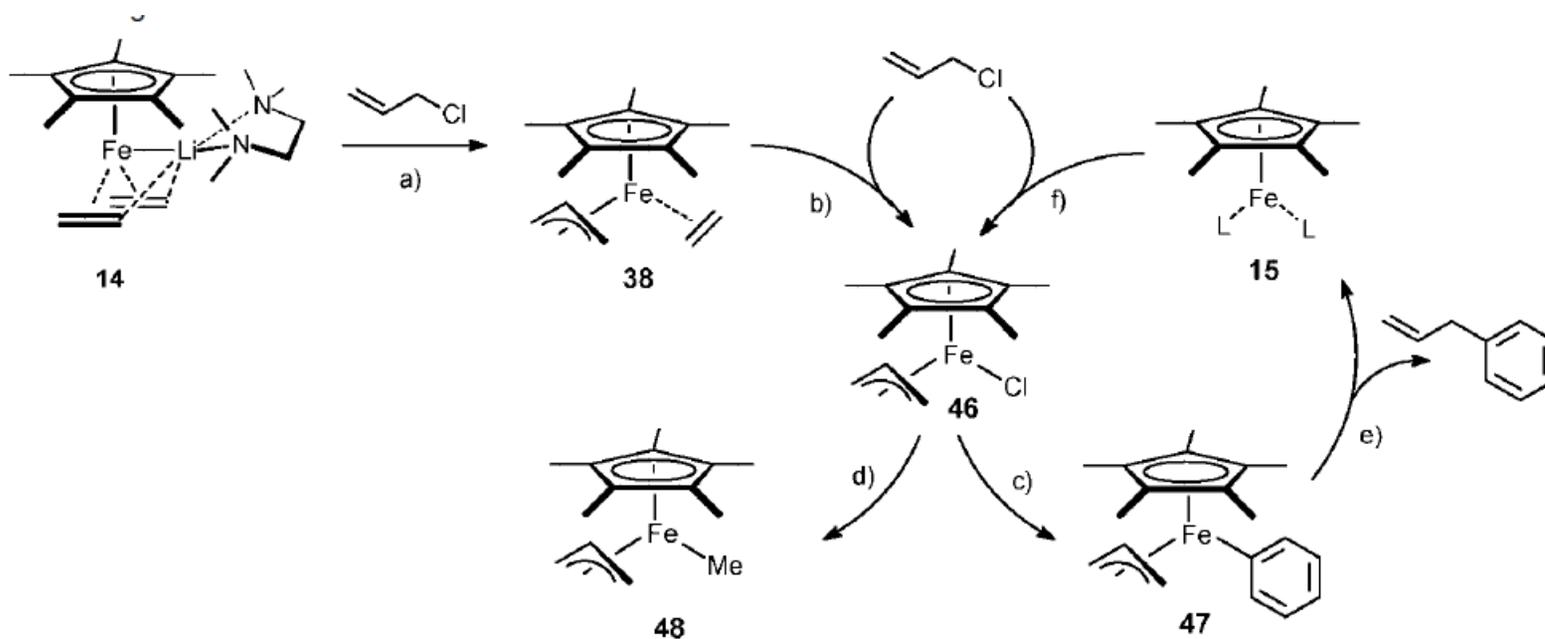
<sup>a</sup> The red numbers indicate the *formal* oxidation states of the iron centers.  
<sup>b</sup> Reagents and conditions: (a) Li, ethylene (1 bar), THF, -50 °C → 0 °C, then *N,N,N',N'*-tetramethylethylenediamine (tmeda); 45% (23 g scale); (b) Li, ethylene (5–8 bar), 20 °C, then tmeda, 43% (12 g scale); (c) (i) Li, COD, THF, -50 °C, (ii) tmeda, Et<sub>2</sub>O, RT, 75%; (d) Li, COD, DME, -50 °C → RT, 97% (85 g scale) [50% after recrystallization, 11 g scale]; (e) Ph<sub>3</sub>CCl, pentane, -35 °C → RT, 70%; (f) Li, DME, ethylene (4–6 bar), RT, then COD, 70 °C, 22% (>27 g scale).

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

# Stoichiometric $\sigma$ -Bond Metathesis in Model Systems

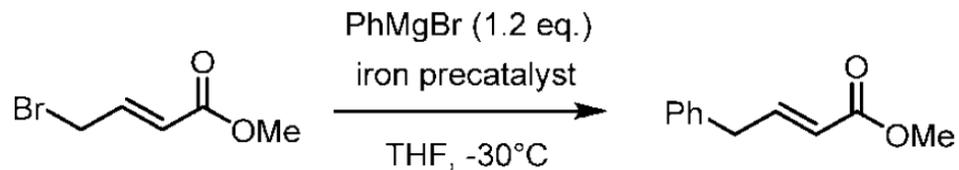


# Potential Fe(I)-Fe(III) cycle



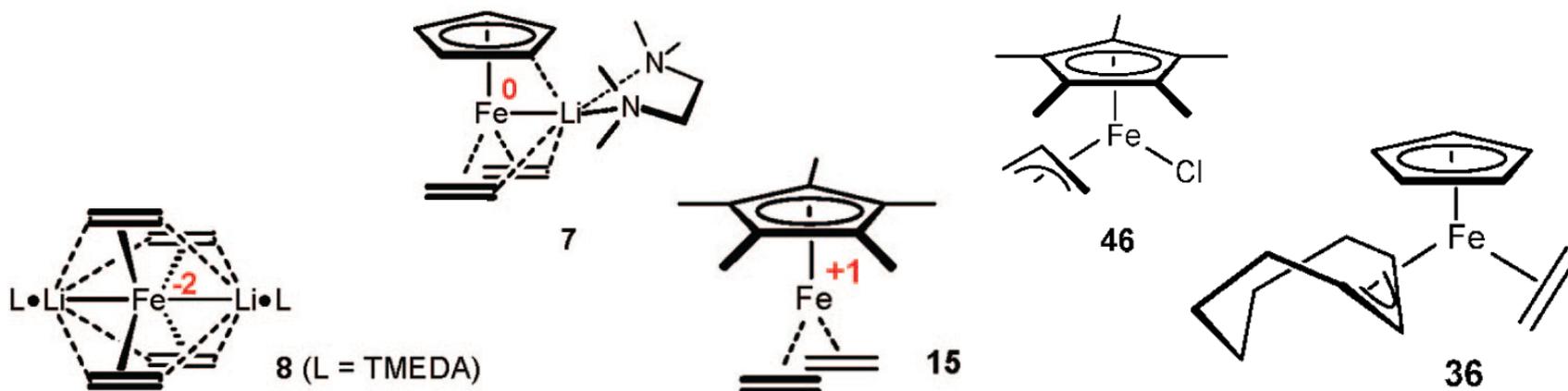
<sup>a</sup> Reagents and conditions: (a) allyl chloride, pentane,  $-20\text{ }^{\circ}\text{C} \rightarrow 0\text{ }^{\circ}\text{C}$ , 16 h, 43%, cf. Scheme 9; (b) allyl chloride,  $\text{Et}_2\text{O}$ ,  $0\text{ }^{\circ}\text{C}$ , 24 h, 61%, cf. Scheme 13; (c) PhLi or PhMgBr,  $\text{Et}_2\text{O}$ ,  $-35\text{ }^{\circ}\text{C}$ , 2 h; (d) MeLi, pentane,  $-78\text{ }^{\circ}\text{C} \rightarrow 0\text{ }^{\circ}\text{C}$ , ca. 70%; (e)  $\text{THF-}d_8$ , ethene (1 atm), ambient temperature, 46% (NMR, allylbenzene), see text; (f) allyl chloride,  $\text{Et}_2\text{O}$ ,  $-40\text{ }^{\circ}\text{C}$ , 20 h, 58%.

# Relative Catalytic Activity of Model Complexes



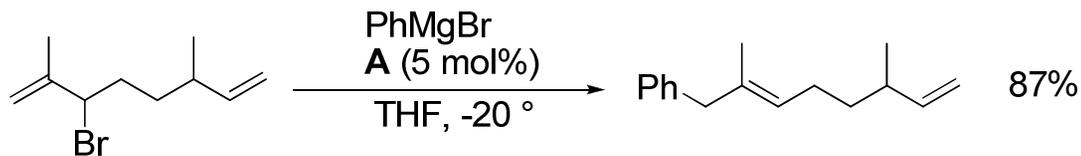
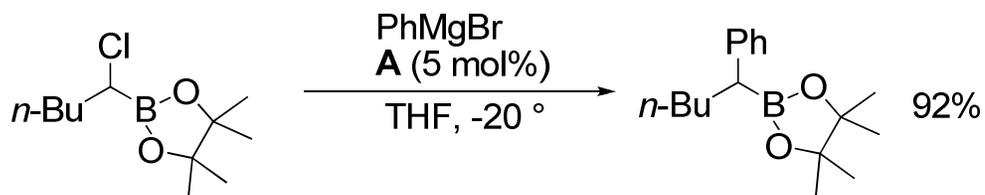
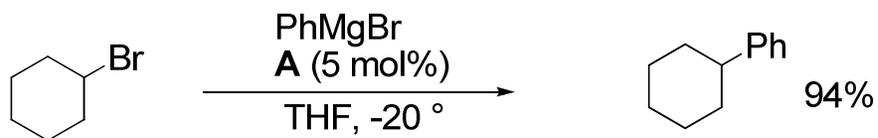
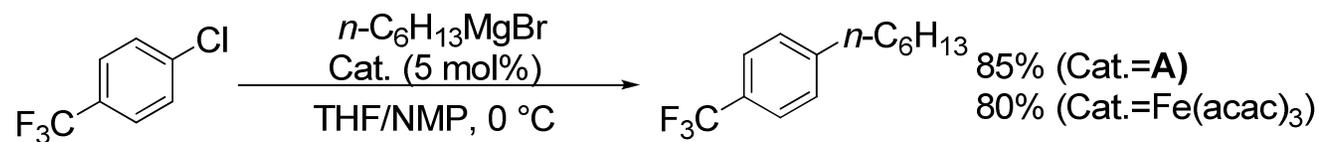
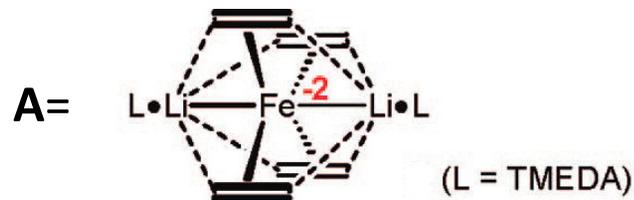
entry	complex (loading)	formal oxidation state	$t^a$	yield <sup>b</sup>
1	<b>8</b> (5%)	-2	<10 min	94%
2	<b>7</b> (5%)	0	30 min	45%
3	<b>15</b> (10%)	+1	30 min	50%
4	<b>36</b> (10%)	+2	30 min	46%
5	<b>46</b> (10%)	+3	30 min	73%

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

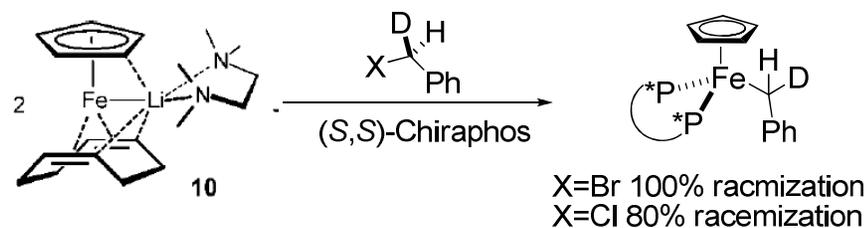
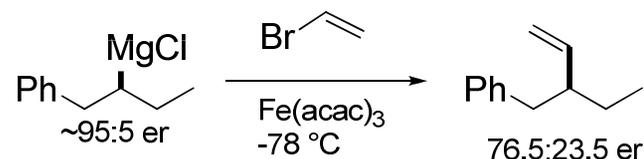
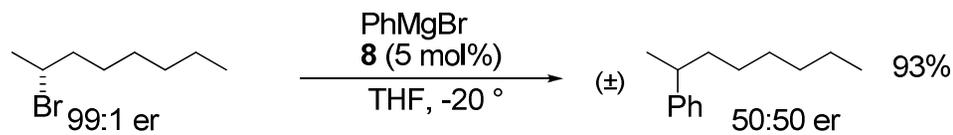
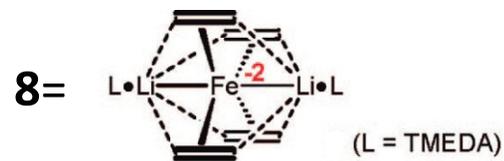
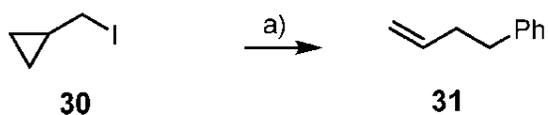
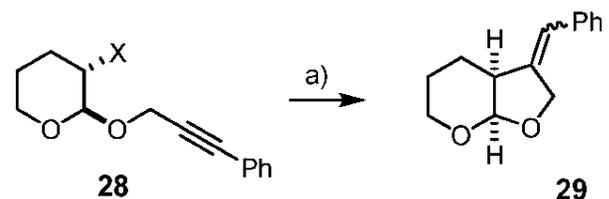
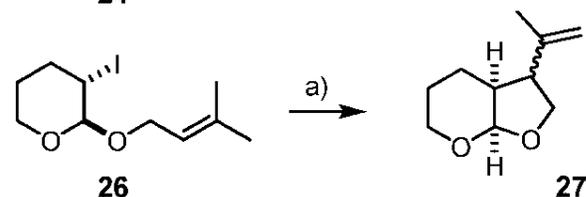
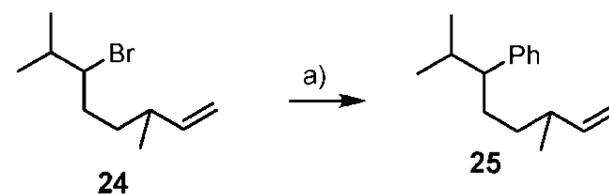
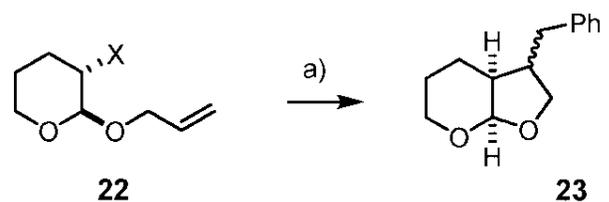


# Catalytic activity of complexes

Selected examples:



# Evidence for Radical Intermediate



<sup>a</sup> Reagents and conditions: complex **8** (5 mol%), PhMgBr, THF, 0 °C;  
 85% (**23**, X = I, dr = 10:1); 54% (**23**, X = Br, dr = 10:1); 89% (**25**); 77%  
 (**27**, dr = 1.8:1); 73% (**29**, dr = 4:1); quant. (**31**, GC).

Evidence against: no reaction with 3° halides

# Conclusions

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Iron-catalyzed cross couplings at low temperature likely occur by an Fe(-II) catalyzed process, preceded by catalyst activation through a  $\beta$ -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  $\beta$ -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.