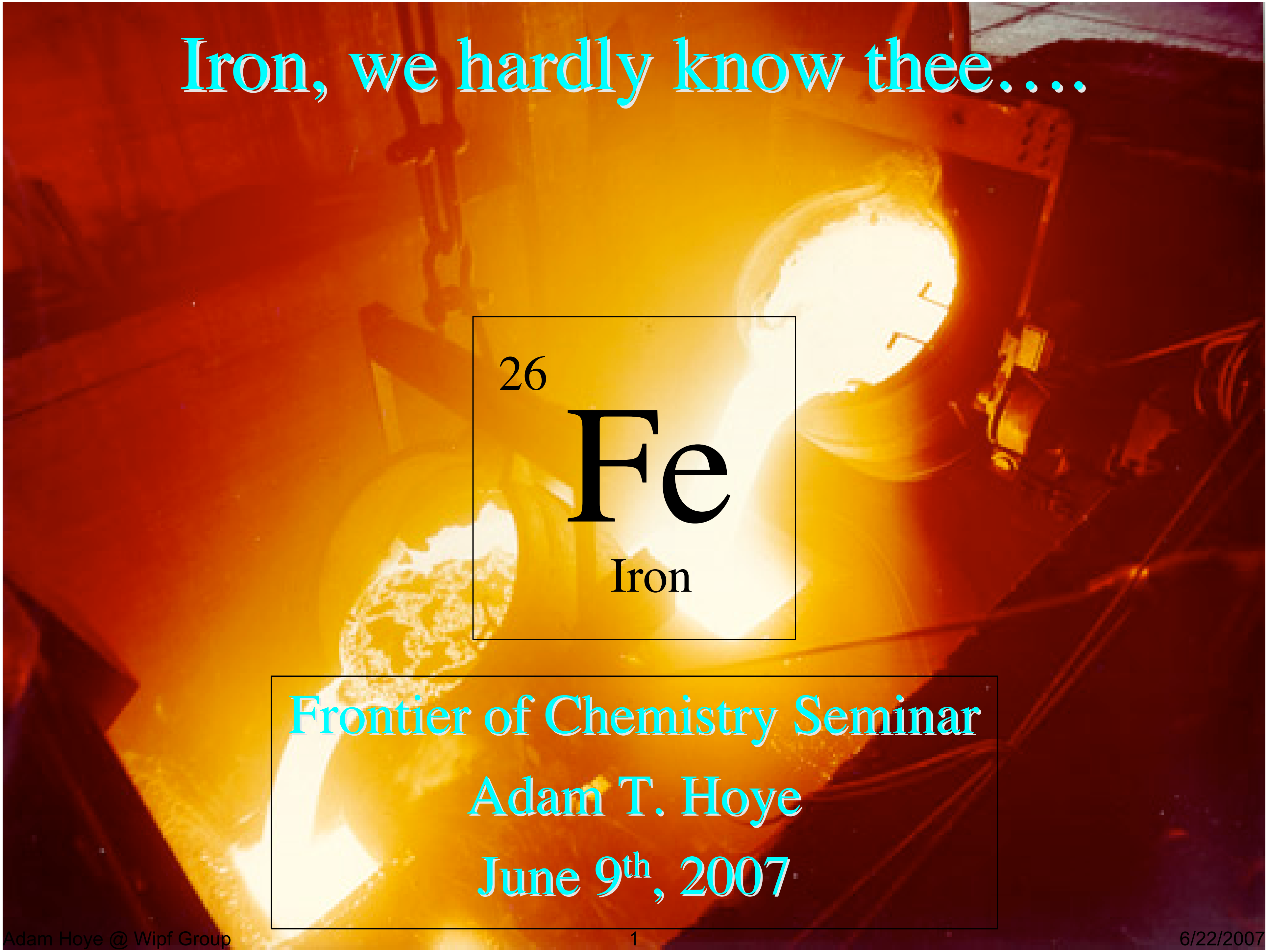


Iron, we hardly know thee….

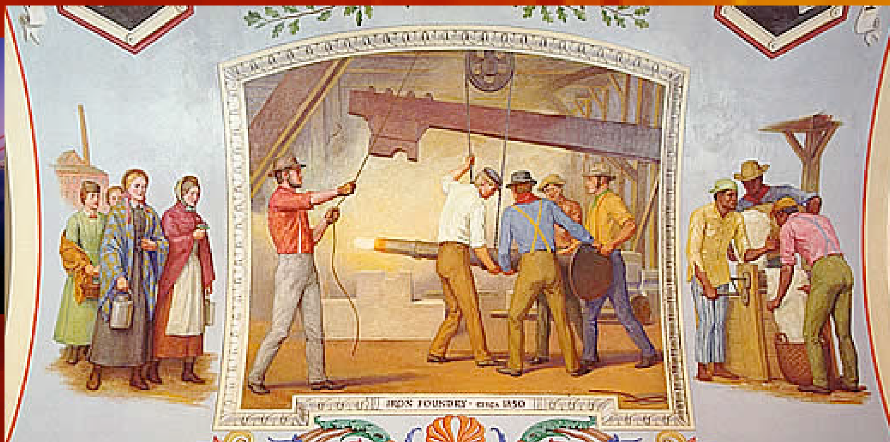
26
Fe
Iron

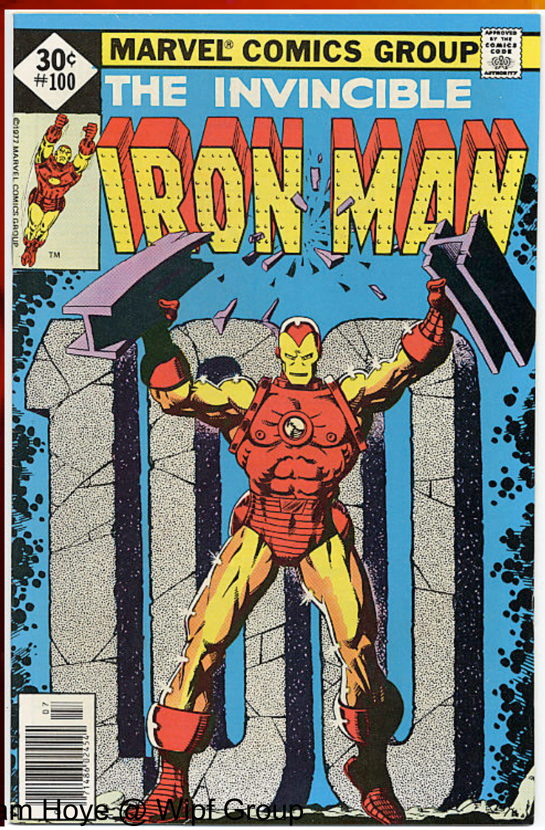
Frontier of Chemistry Seminar

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 prominance in Mesopotamia

This is a Hittite dagger-sword made of iron about 1100 B.C. Much of it has turned to rust over the past three thousand years.

The (Abbreviated) History of Iron

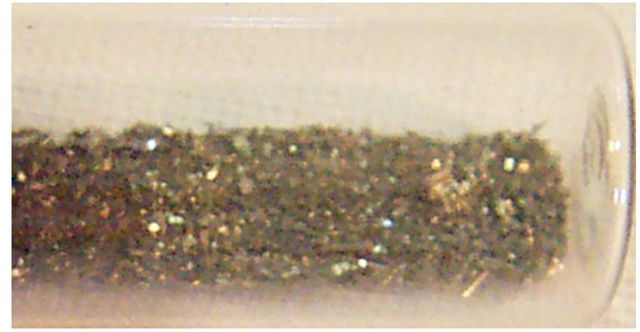
-Around 1200 BCE, during the peak of the Hittites, the kingdom suddenly collapsed (a severe drought seen in the rings of ancient trees?) and forced the Hittites to reveal the secret of iron for their survival.

-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.

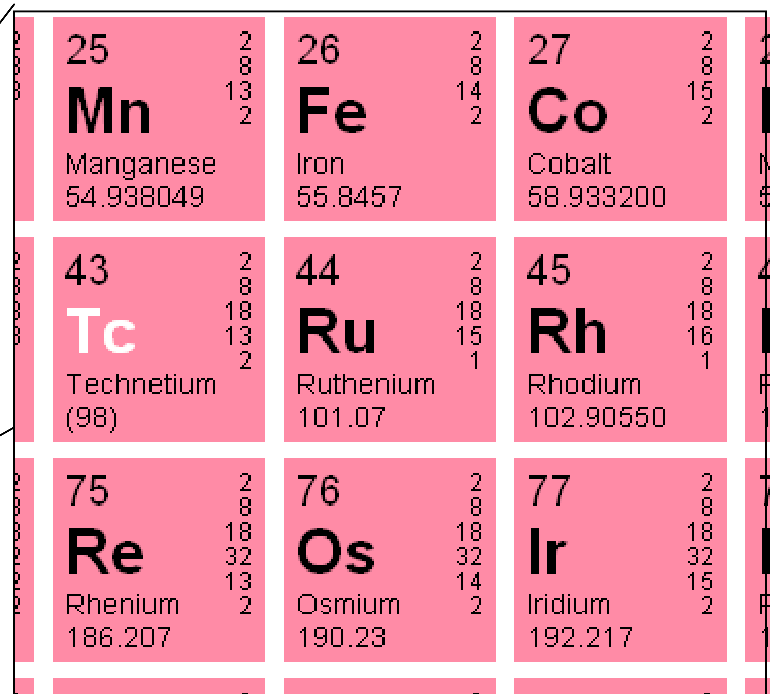
-Through time (and metallurgy), iron would prove itself to be an essential element to human survival and civilization advancement

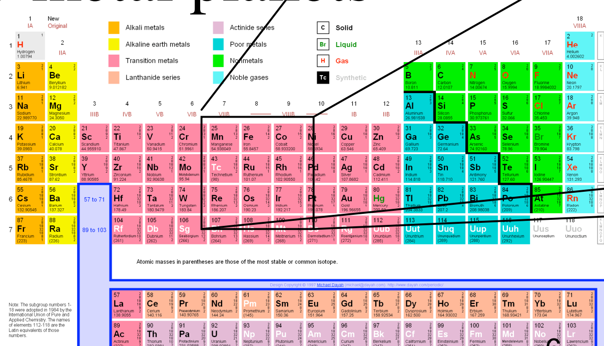
Element 26

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

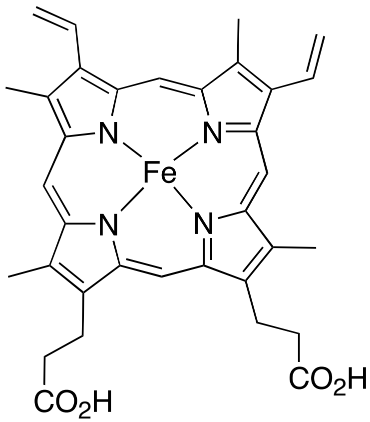
-Concentration of iron ranges from 80% to pure in the Earth's core to 5% in the crust

-Iron is extracted from iron ore; Haematite (Fe_2O_3) $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)

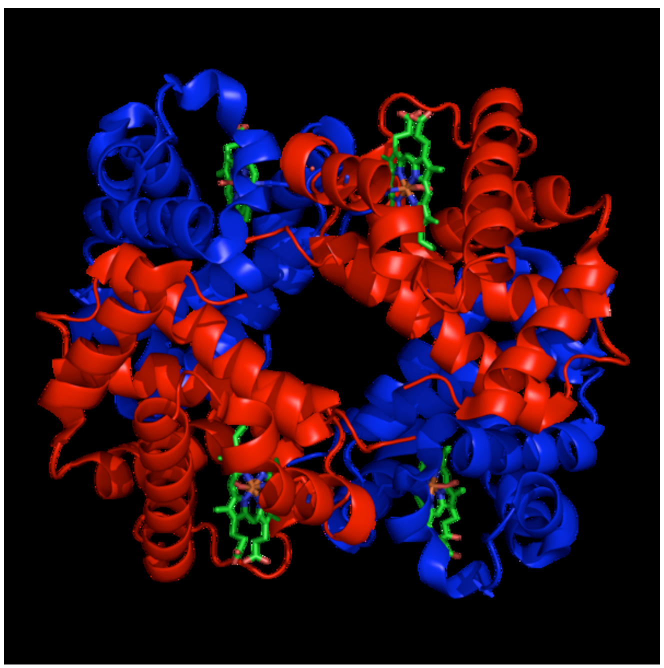
-Iron used in steel and other alloys, automobile manufacturing, and magnetic storage

Heme-Iron and Biological Importance



heme b

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

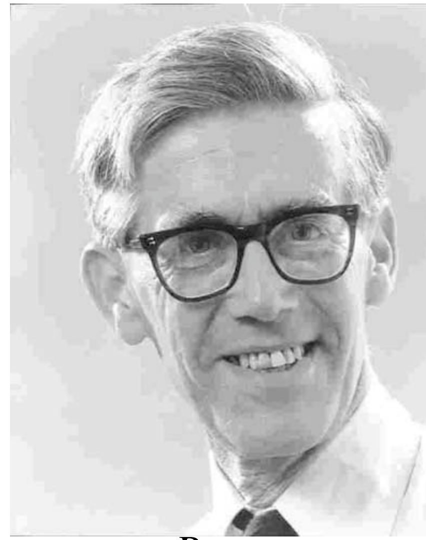


Non-heme iron mostly contained in enzymes such as nitrogenase (ammonia production), methane monooxygenase (methane to methanol), and ribonucleotide reductase (ribose to deoxyribose)

Ferrocene Story

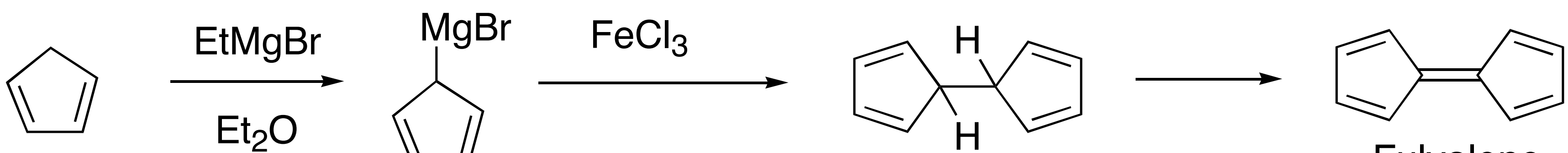
<u>*Paul Pauson & Tom Kealy*</u>

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



Pauson

Kealy



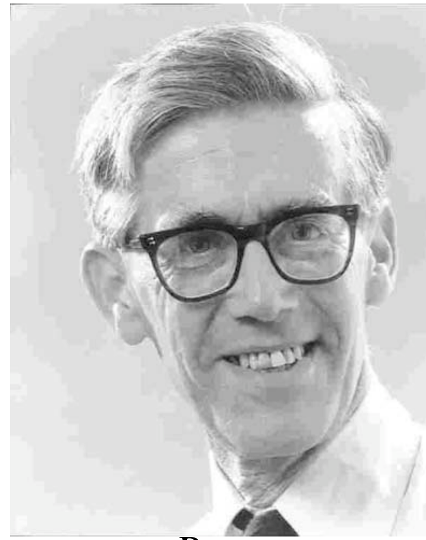
Fulvalene

Pauson, P. L. *J. Organomet. Chem.* **2001**, 3

Ferrocene Story

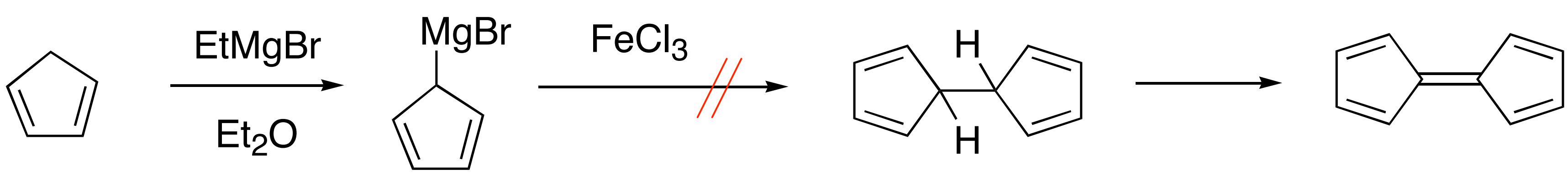
<u>Paul Pauson & Tom Kealy</u>

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

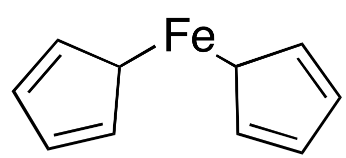


Pauson

Kealy



yellow crystals soluble in organic ethereal solvents;
Elemental analysis indicated $C_{10}H_{10}Fe$

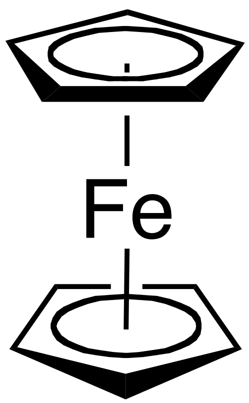


(?)

Pauson, P. L. *J. Organomet. Chem.* **2001**, 3

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).

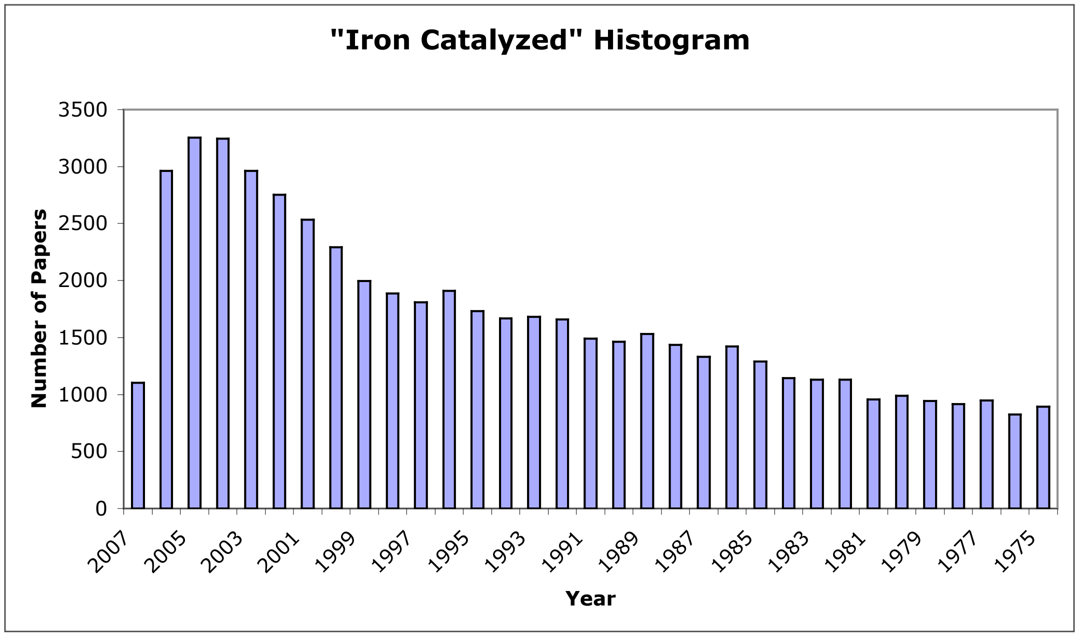
Structure confirmed later by x-ray analysis; Wilkinson and Fischer went on to win the Nobel Prize for their work in sandwich compounds

"At Woodward's suggestion that the compound might be aromatic…"

Pauson, P. L. *J. Organomet. Chem.* **2001**, 3

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

Bolm, C.; Legros, J.; Le Pain, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217

Plan of Attack

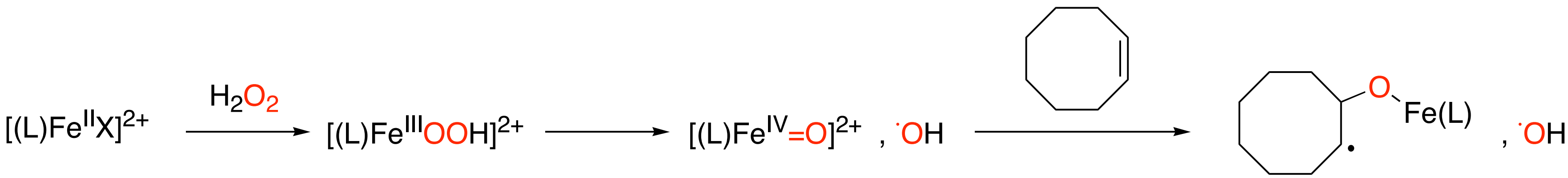
-General Iron-Catalyzed Reactions
- Oxidations
- Reductions
- Olefinations
- Reactions with Sulfur (Iminations)
- Aldol Reactions
- Allylations

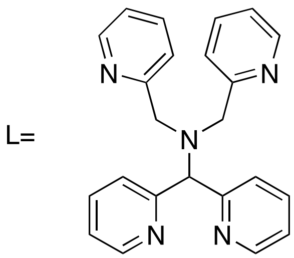
-Carbometallations

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

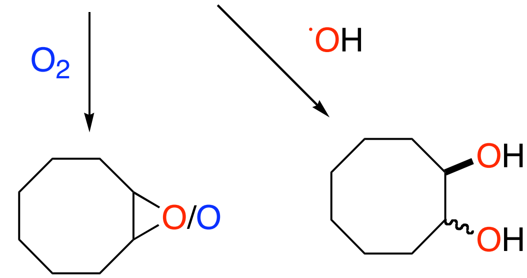
-Cross Coupling Reactions

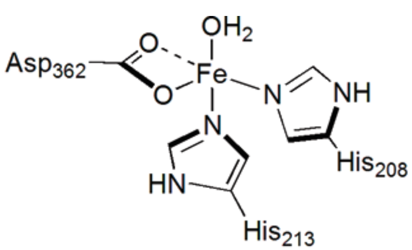
Iron-Catalyzed Oxidations





In air/O_2 or using polar, protic solvents:
100 % epoxide





Olefin Oxidation Products using bio-inspired catalyst

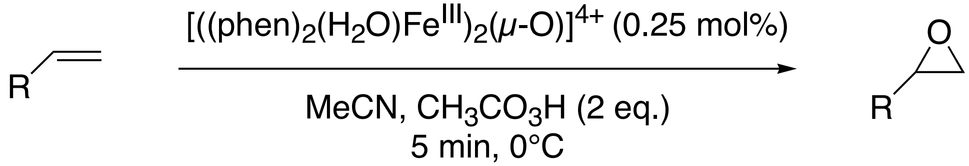
substrate	diol:epoxide
styrene	80:1
cyclooctene	14:1
1-octene	
5 equiv of H2O2	90:1
10 equiv of H2O2	76:1
20 equiv of H2O2	52:1
cyclohexene	9:1
cis-2-heptene	7:1
trans-2-heptene	10:1
ethyl *trans*-crotonate	>100:1
tert-butyl acrylate	>100:1
dimethyl fumarate	>100:1

Reaction Conditions:
10 eq. H_2O_2,
0.35 M in CH_3CN,
5 min

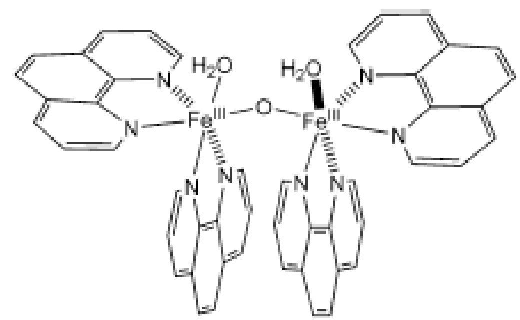
TON (μM product/μM cat.) between 5-10

Que, L. et al. *J. Am. Chem. Soc.* **2005**, *127*, 15672; Que, L. et al. *Angew. Chem. Int. Ed.* **2006**, *45*, 3446

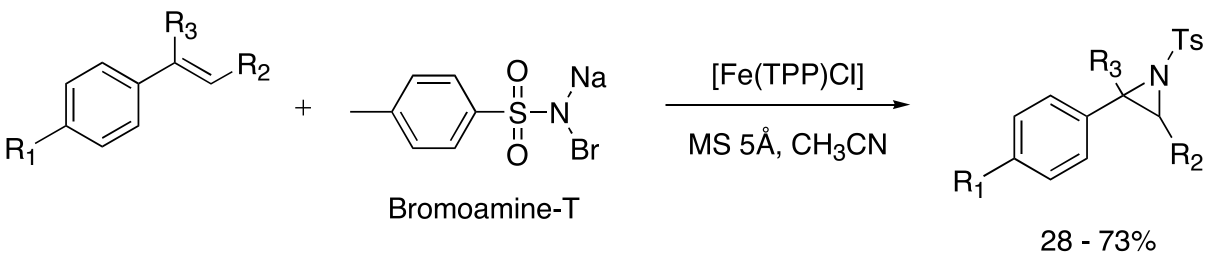
Iron-Catalyzed Oxidations

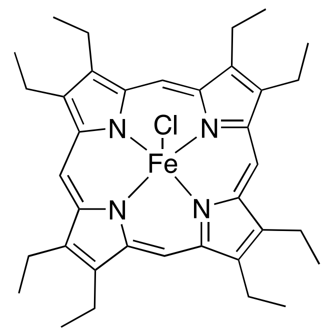


Alkene	yield
cyclooctene	90
cyclohexene	85
1-heptene	88
vinylcyclohexane	90
1-octene	92
trans-methyl styrene	96
trans-methyl-cinnamate	86
ethyl sorbate	89

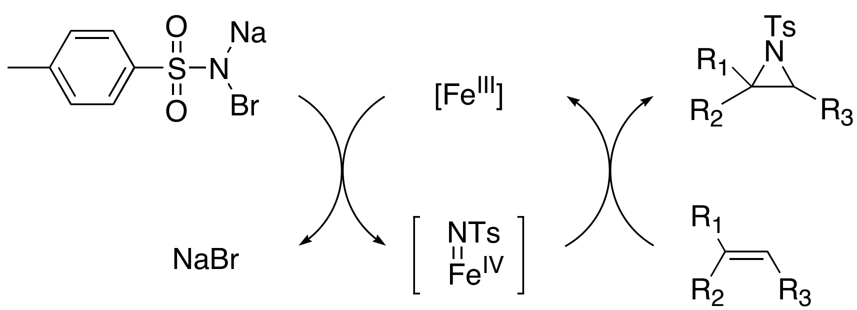


Stack, T. D. P. et al. *Org*. *Lett*. **2003**, *5*, 2469



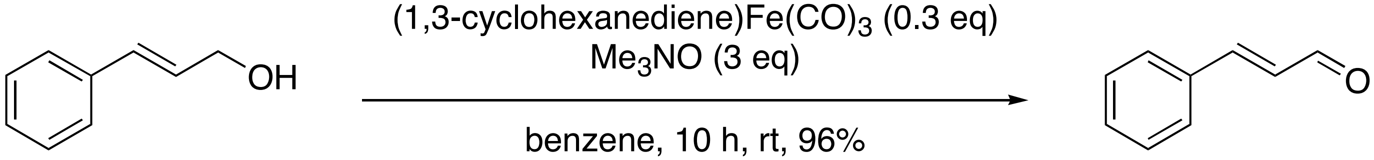


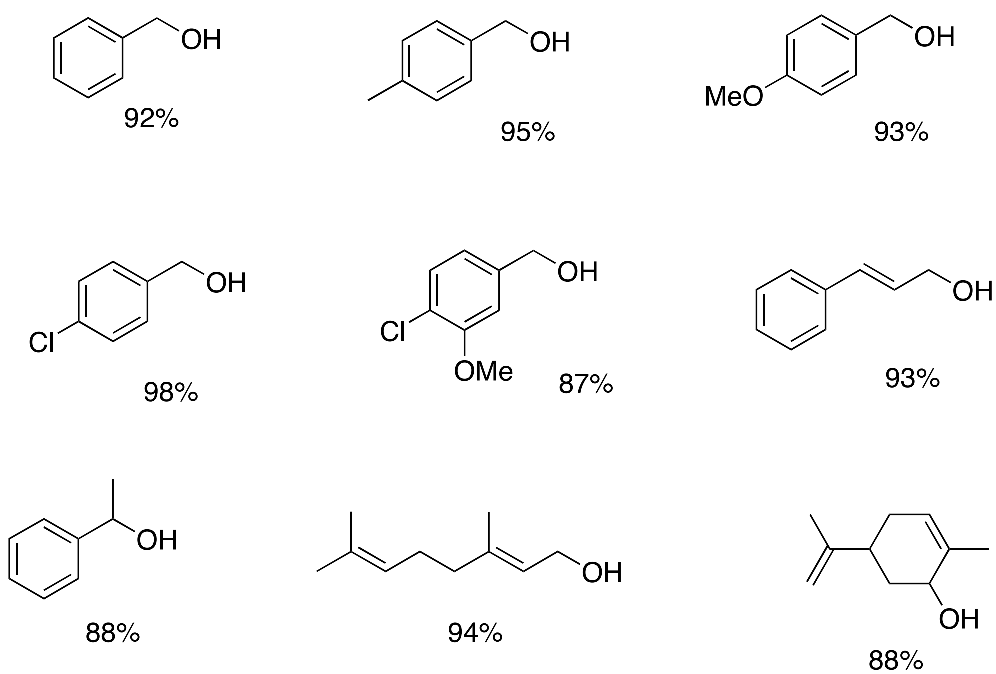
Catalytic Cycle:

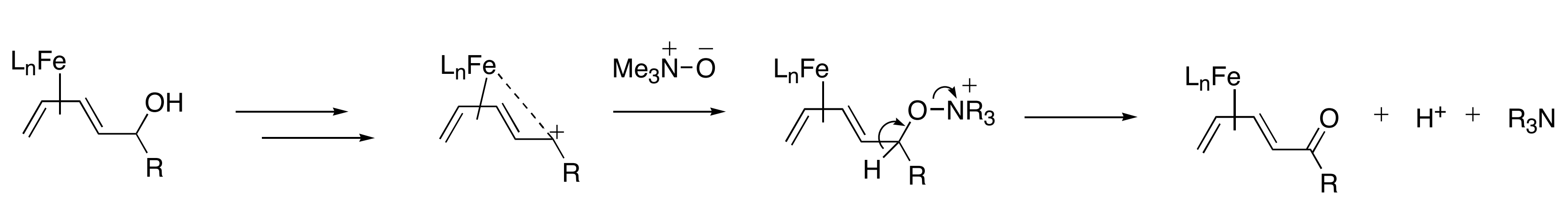


Xang, X. P. et al. *Org*. *Lett*. **2004**, *6*, 1907

Allylic Oxidations

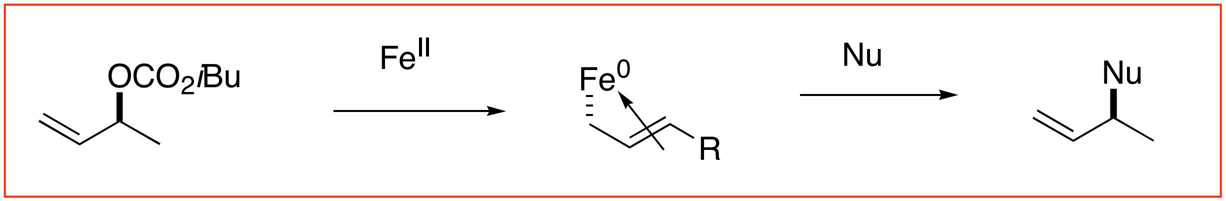


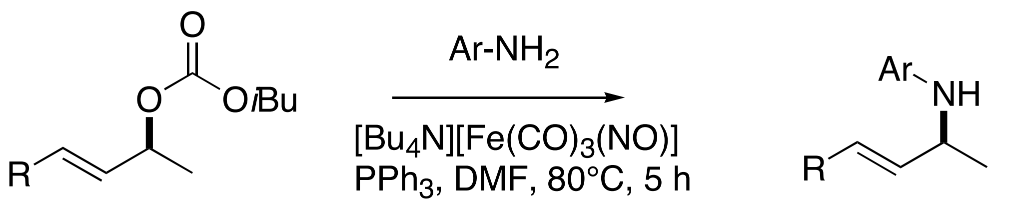




Pearson, A. J.; Kwak, Y. *Tetrahedron Lett*. **2005**, *46*, 5417

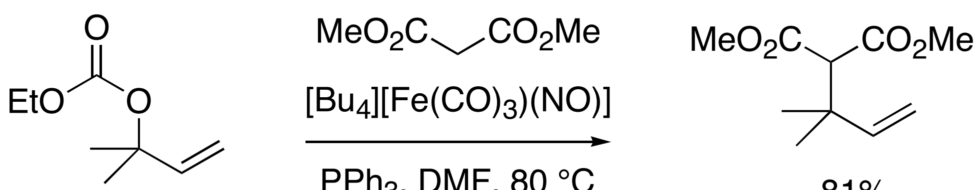
Allylic Substitutions





R= H, Ph

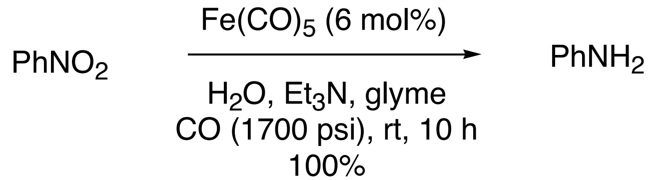
62, 84% yield
86, 87 % *ee*

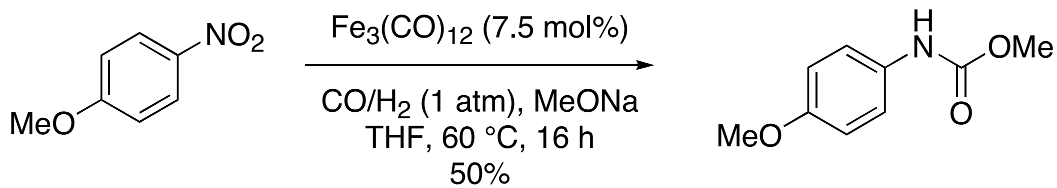


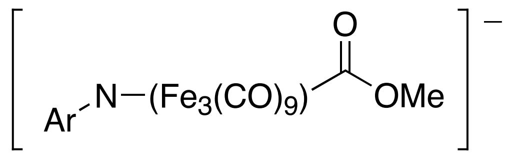
81%

Plietker, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 6053
Plietker, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 1469

Reductions

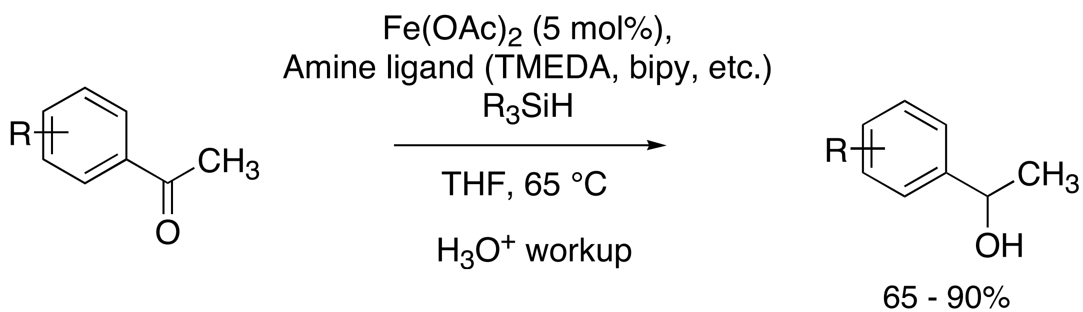




Results suggest:  as intermediate

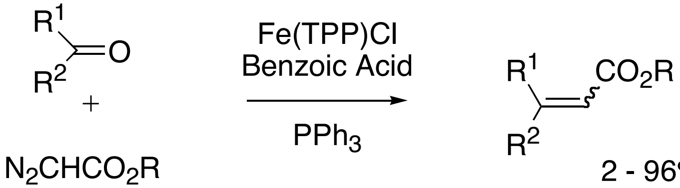
Mechanistic studies show radical anion $[Fe_3(CO)_{11}]^{\cdot -}$ is involved

Cann, K.; Cole, T.; Slegeir, W.; Pettit, R. *J. Am. Chem. Soc.* **1978**, *100*, 3969
Alper, H.; Hashem, K. E. *J. Am. Chem. Soc.* **1981**, *103*, 6514



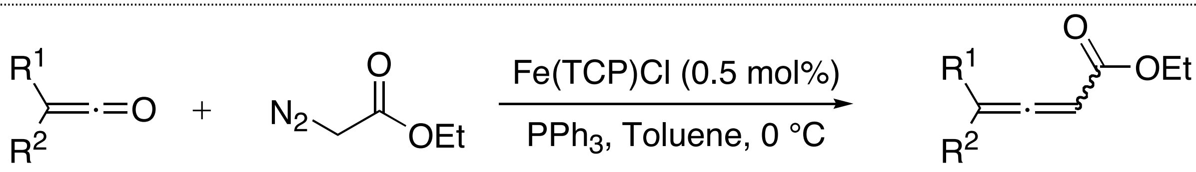
Nishiyama, H.; Furuta, A. *Chem. Commun.* **2007**, 760

Olefinations



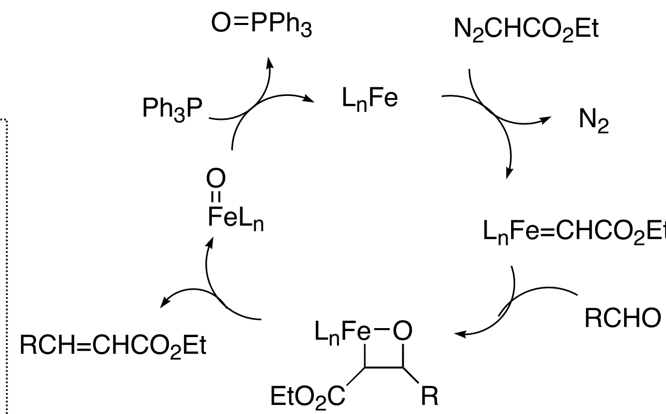
2 - 96% yields

Aromatic, aliphatic, and unsaturated ketones

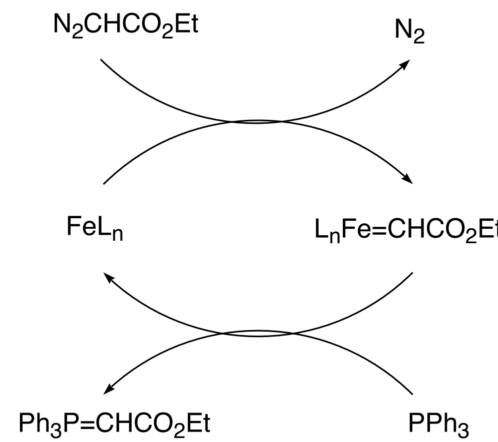


chiral phoshine = chiral allene

	R^1	R^2	Yield (%)
1	Ph	Me	99
2	Ph	Et	99
3	Ph	*i*-Pr	99
4	Ph	*n*-Bu	98
5	*p*-Cl	C_6H_4	98
6	*p*-MeO	C_6H_4	92
7	*o*-Me	C_6H_4	95
8	COOEt	*i*-Bu	83
9	Ph	allyl	53
10	Ph	3-butenyl	75
11	*n*-C_5H_{11}	H	77
12	*n*-$C_{10}H_{21}$	H	80
13	Ph	H	56
14	Br	Me	59
15	*n*-Bu	Et	74



Path A



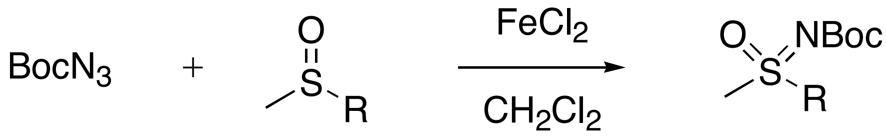
Path B

Chen, Y.; Huang, L.; Zhang, X. P. *Org. Lett.* **2003**, *5*, 2493

Tang, Y. et al. *J. Am. Chem. Soc.* **2007**, *129*, 1494

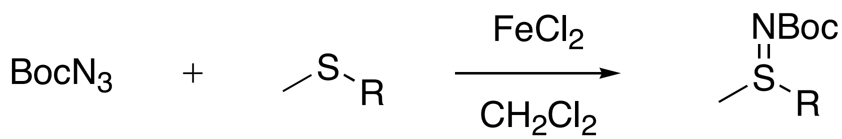
Sulfur Reactions

Sulfoximines:



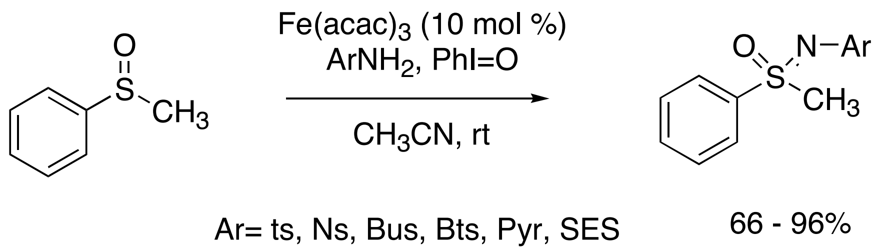
R= Bn, 70%
R= Ph, 45%
R= Me, 64%
R= *p*-MeOPh 52%

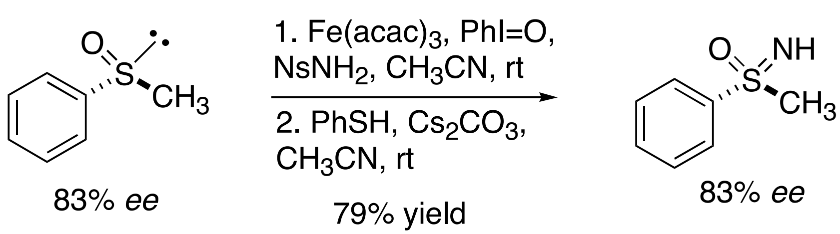
Sulfilimines:



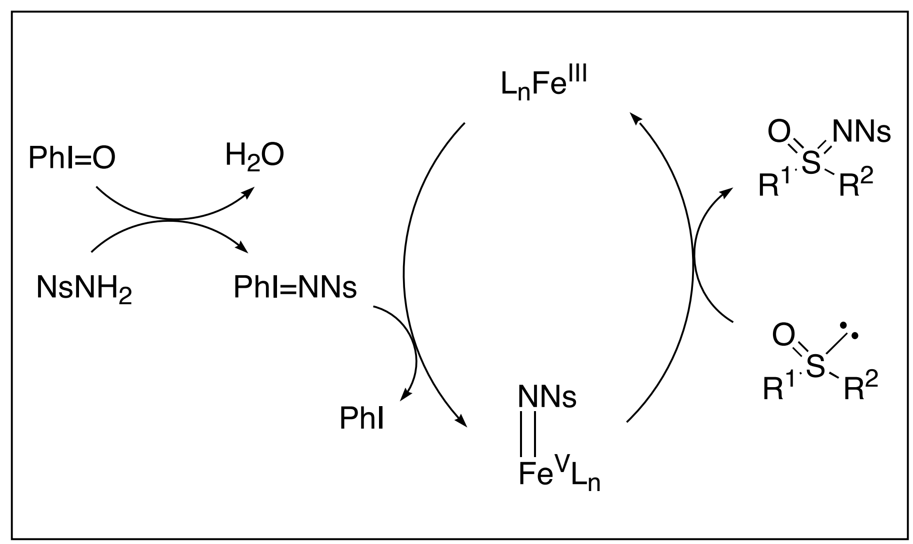
R= Bn, 85%
R= Ph, 70%

Bach, T.; Körber, C. *Tetrahedron Lett*. **1998**, *39*, 5015



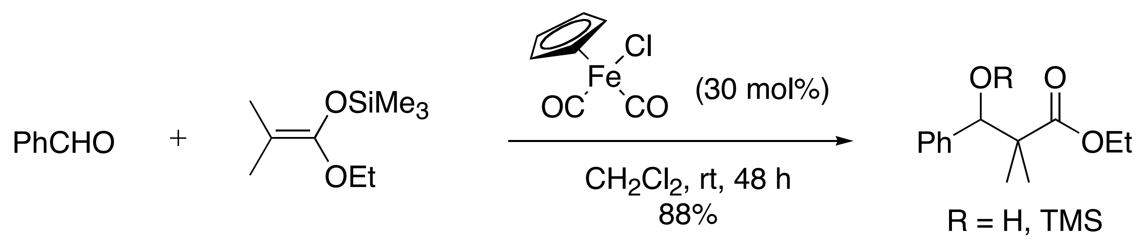


Proposed Mechanism:

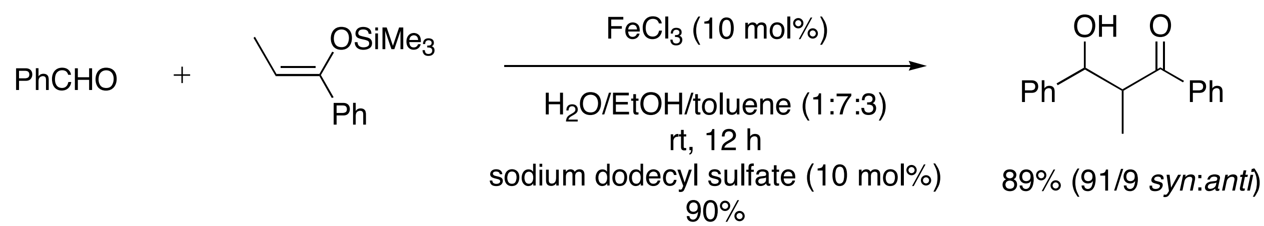


Mancheño, O. G.; Bolm, C. *Org. Lett*. **2006**, *8*, 2349

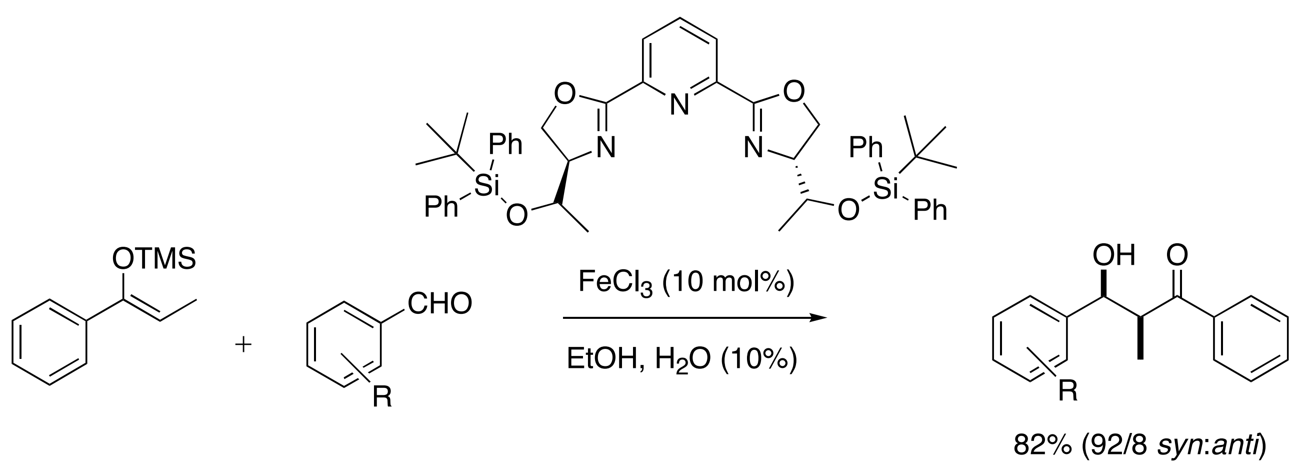
Mukaiyama-Aldol Reactions



Colombo, L.; Ulgheri, F.; Prati, L. *Tetrahedron Lett*. **1989**, *30*, 6435



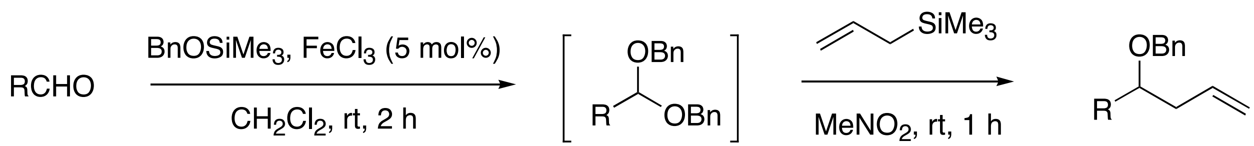
Aoyama, N.; Manabe, K.; Kobayashi, S. *Chem. Lett*. **2004**, *33*, 312



Jankowska, J.; Paradowska, J.; Rakiel, B.; Mlynarski, J. *J. Org. Chem*. **2007**, *72,* 2228

Allylations

One-Pot Acetalization/Allylation

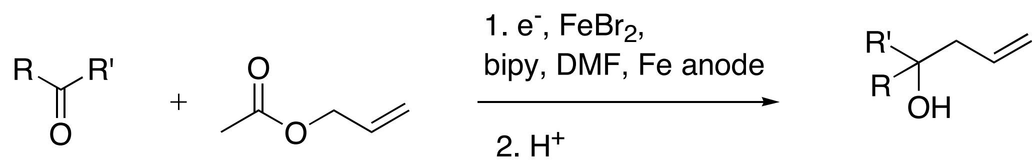


R= Ph, *p*-OMePh, *p*-MeO_2CPh,
$Ph(CH_2)_2$, *c*-C_6H_{11}, *t*-Bu

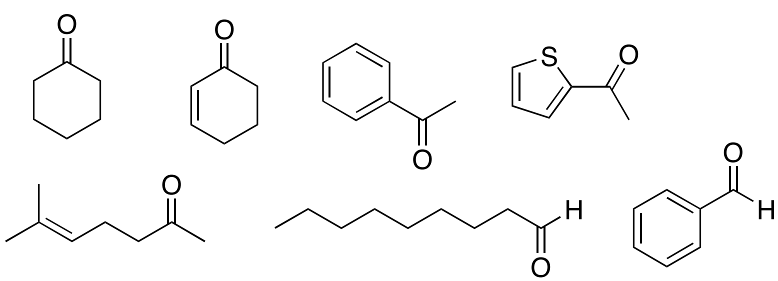
yields 80 - 100%

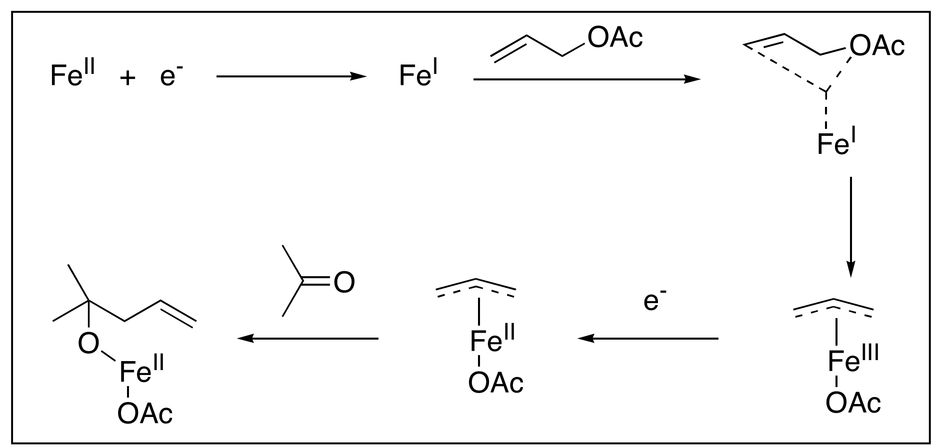
Watahiki, T.; Akabane, Y.; Mori, S.; Oriyama, T. *Org*. *Lett*. **2003**, *5*, 3045

Electrochemical Allylation



yields 39 - 86%

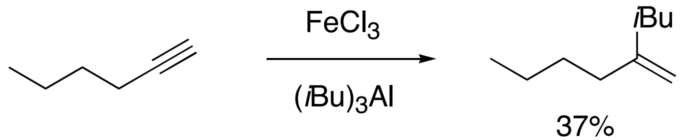




Durrandetti, M.; Meignein, C.; Périchon, J. *J*. *Org*. *Chem*. **2003**, *68*, 3121

Carbometallations

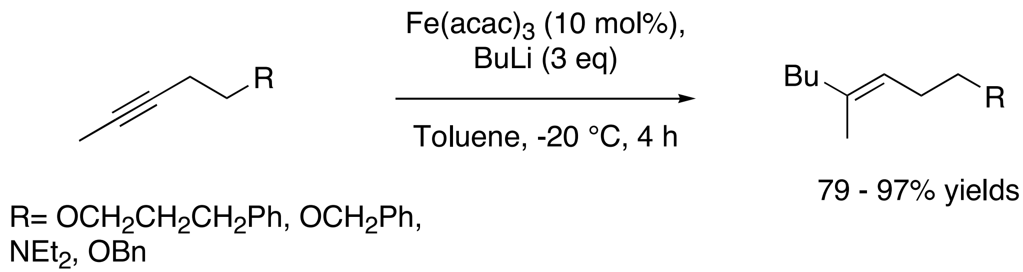
-Initial Fe-catalyzed carbometallation report:



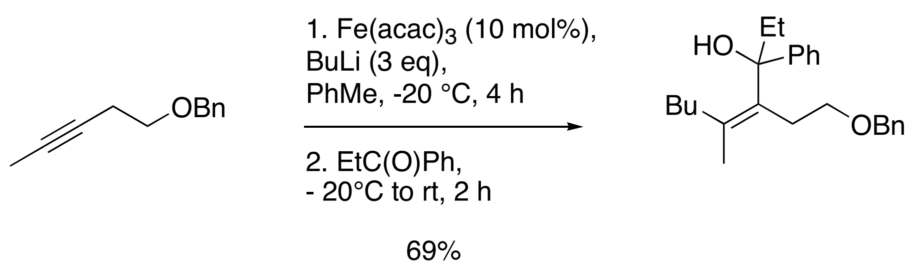
Plus regioisomers and homocoupling products

Caporusso, A. M.; Lardicci, L.; Giacomelli, G. *Tetrahedron Lett*. **1977**, *49*, 4351

-Using alkyllithium reagents provided better results:



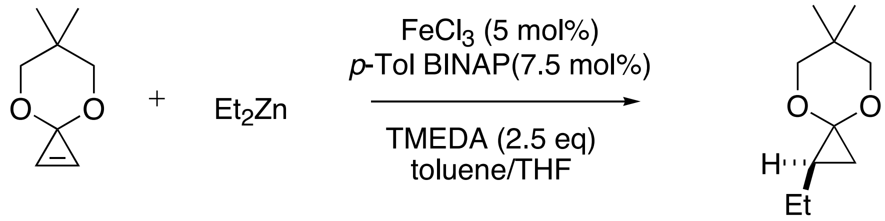
-Intermediate vinyllithium species was postulated and validated based on trapping experiments



Hojo, M.; Murakami, Y.; Aihara, H.; Sakuragi, R.; Baba, Y.; Hosomi, A. *Angew. Chem. Int. Ed.* **2001**, *40*, 621

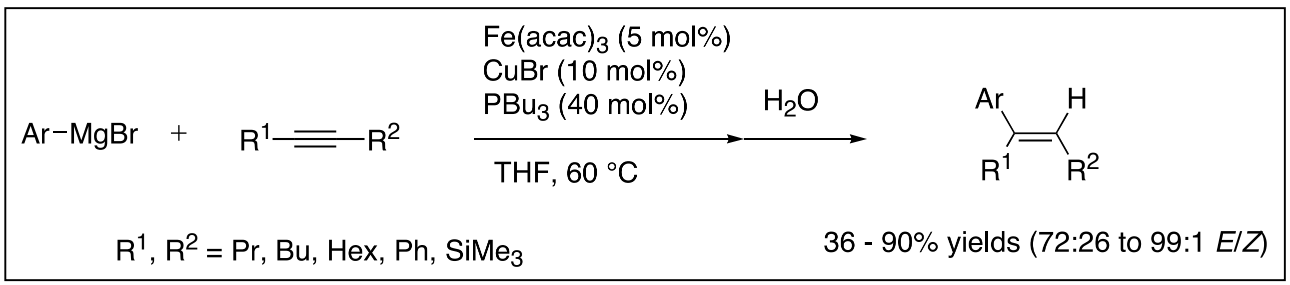
Carbometallations

-Strained alkenes increase reactivity

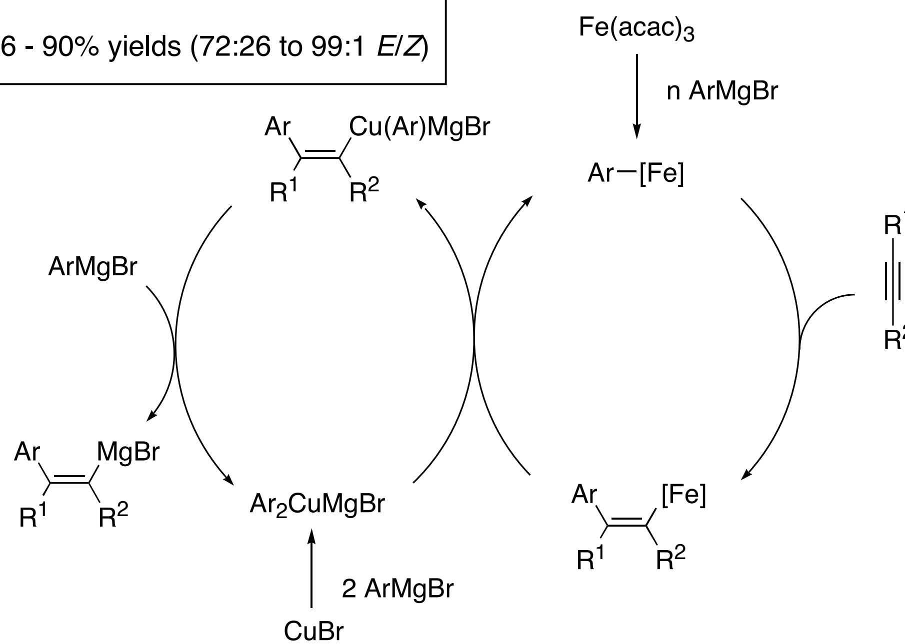


88% yield, 89% *ee*

Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **2000**, *122*, 978



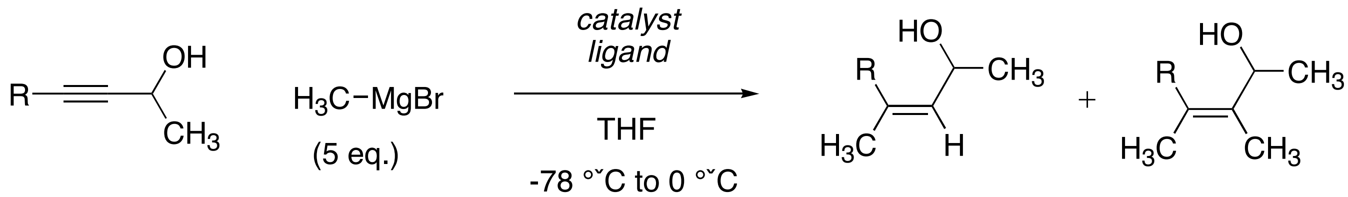
-Cooperative carbometallation met with more positive results:



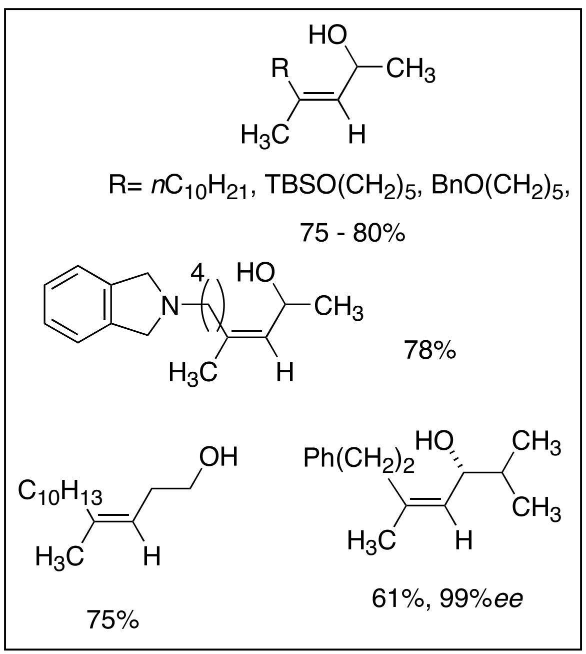
Shirakawa, E.; Yamagami, T.; Kimura, T.; Yamaguchi, S.; Hayashi, T. *J. Am. Chem. Soc.* **2005**, *127*, 17164

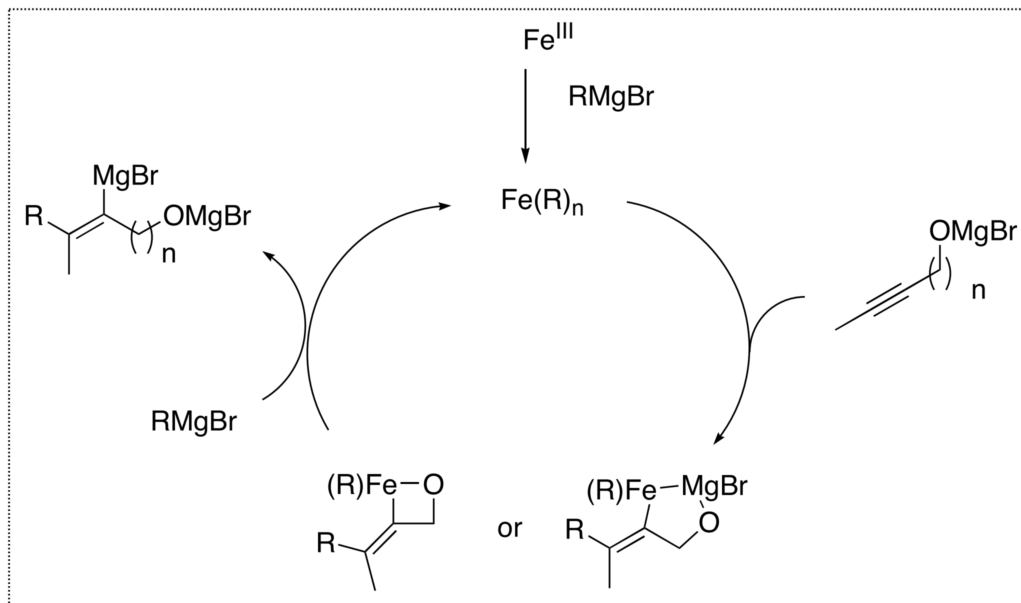
Carbometallations

-Use of intramolecular directing group- propargyl alcohols



Catalyst	Ligand	conversion (%)	ratio of products
$Co(OAc)_2$	-	58	9/1
$Ni(acac)_2$	-	63	9/1
$Fe(acac)_3$	-	98	6/1
$Fe(acac)_3$	dppe	97	21/1

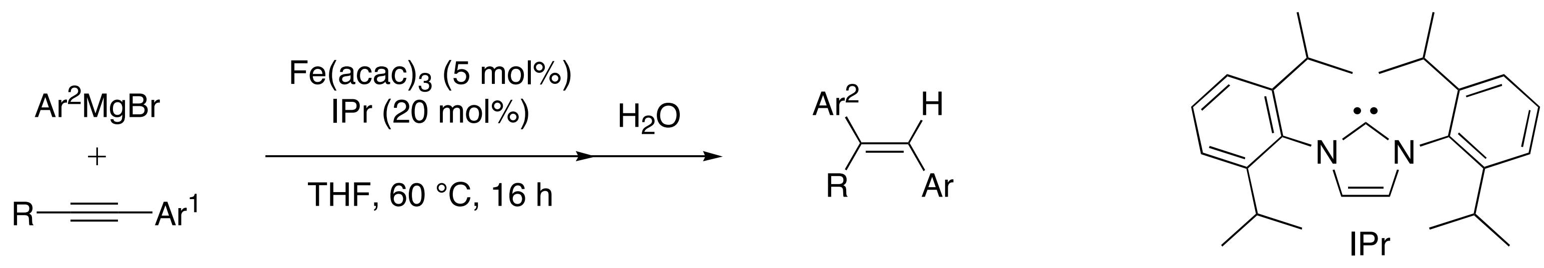




Ready, J. M.; Zhang, D. *J. Am. Chem. Soc.* **2006**, *128*, 15050

Carbometallations

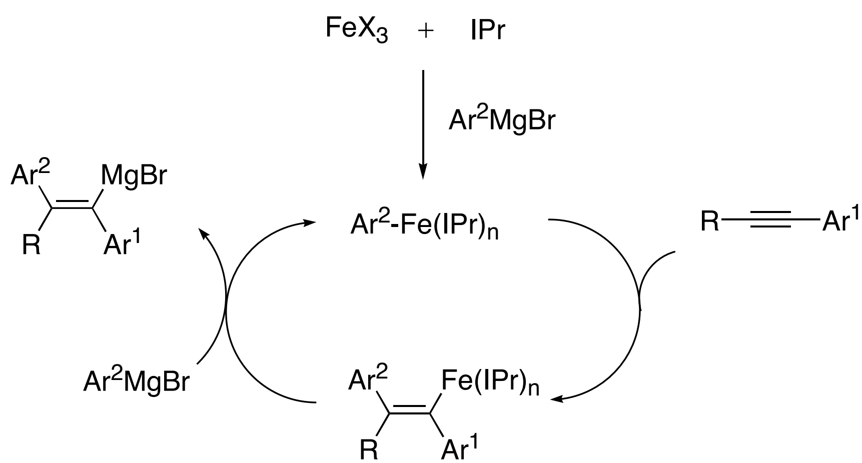
Carbene-Assisted Carbometallation:



R = *n*-Bu, Et, *i*Bu, *i*Pr
Ar^1 = Ph, 4-$MeOC_6H_4$, 3-$MeOC_6H_4$,
4-ClC_6H_4
Ar = 4-$MeOC_6H_4$, 3,5-$Me_2C_6H_4$, 4-FC_6H_4
1-Nap

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

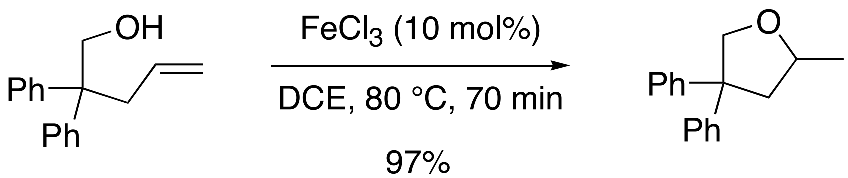
Carbene ligand credited with stabilizing low-valent iron intermediates and preventing decomposition of the alkenyliron species in the catalytic cycle

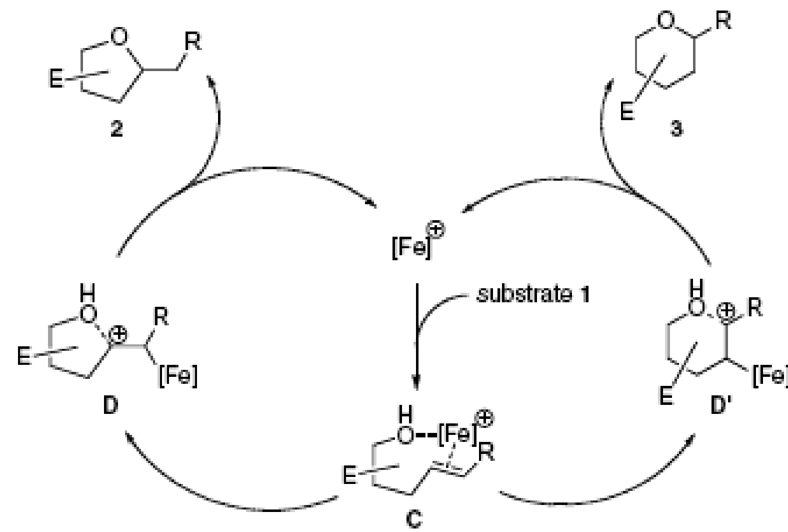


Yamaguchi, T.; Shintani, R.; Shirakawa, E.; Hayashi, T. *Org. Lett.* **2007**, 9, 1045

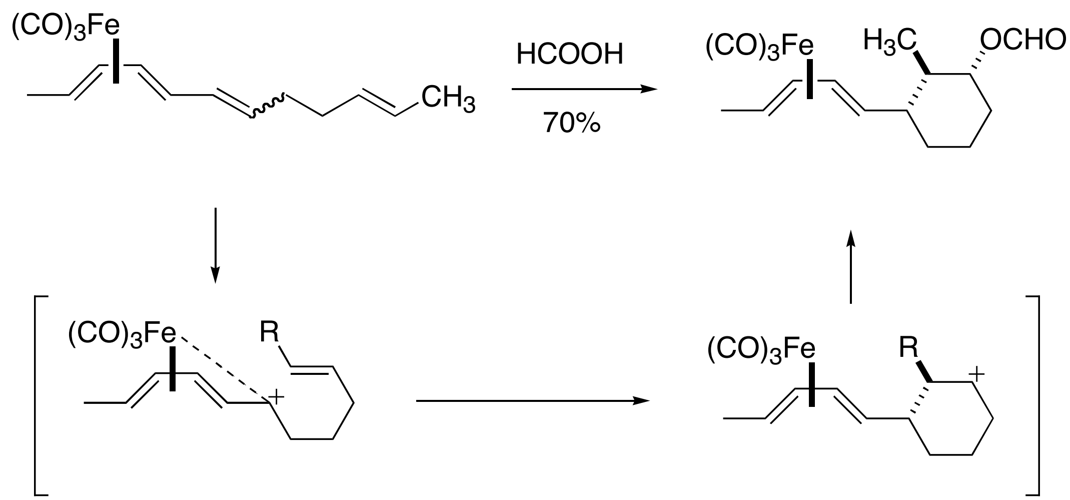
Iron-Catalyzed Cyclization Reactions

-Cationic Cyclizations





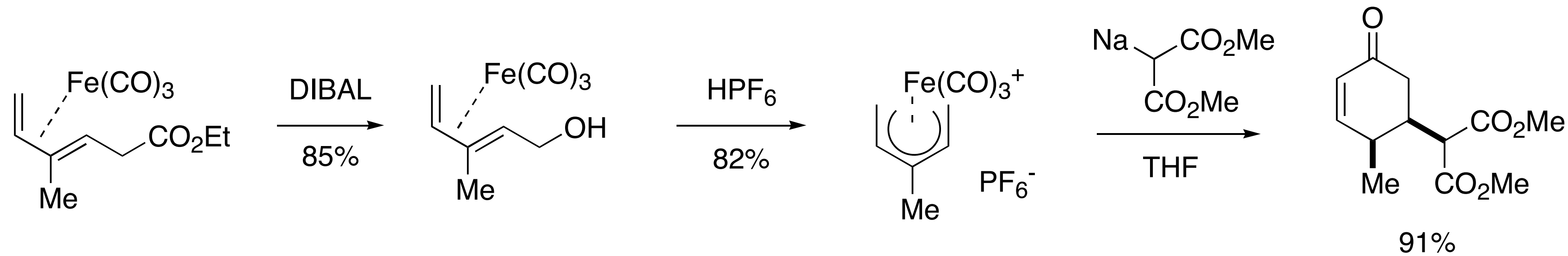
Komeyama, K.; Morimoto, T.; Nakayama, Y.; Takaki, K. *Tetrahedron Lett*. **2007**, *48*, 3259

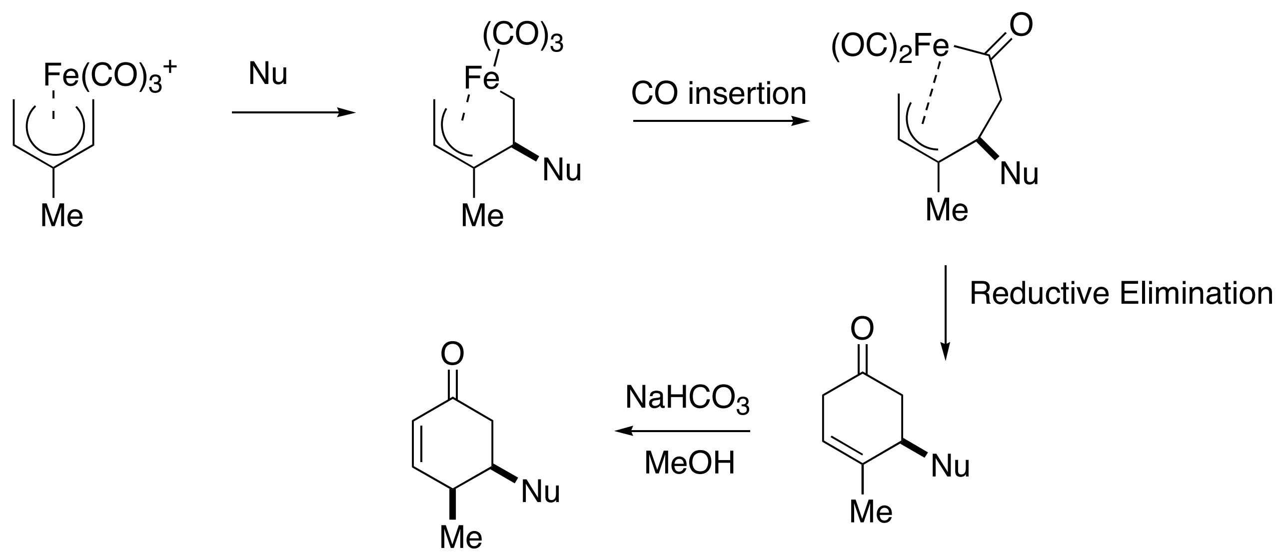


Pearson, A. J.; Ghidu, V. P. *Org. Lett*., **2002**, *4*, 4069

Iron-Catalyzed Cyclization Reactions

-Electrophilic Cyclizations



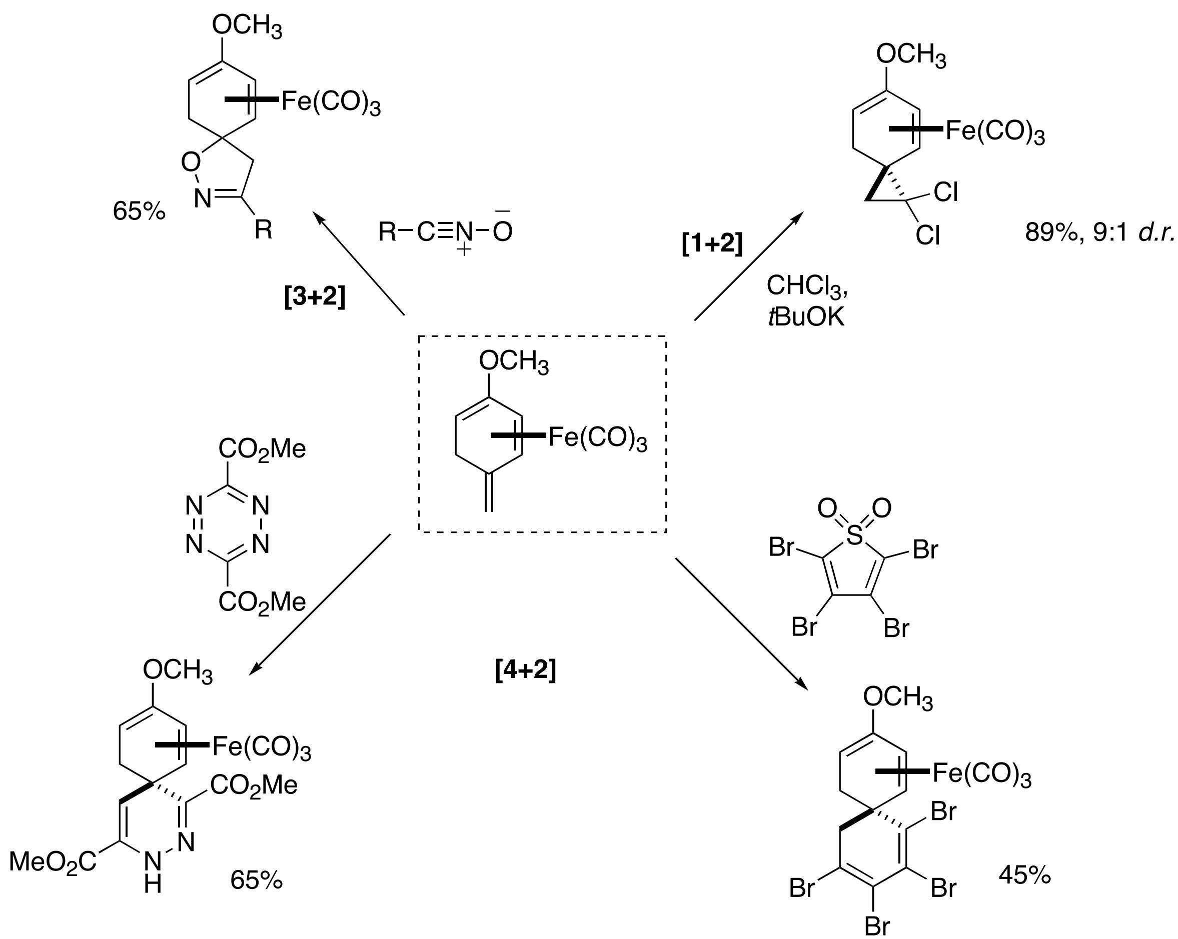


Chaudury, S.; Donaldson, W. A. *J. Am. Chem. Soc.* **2006**, *128*, 5984

Pericyclic Reactions

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

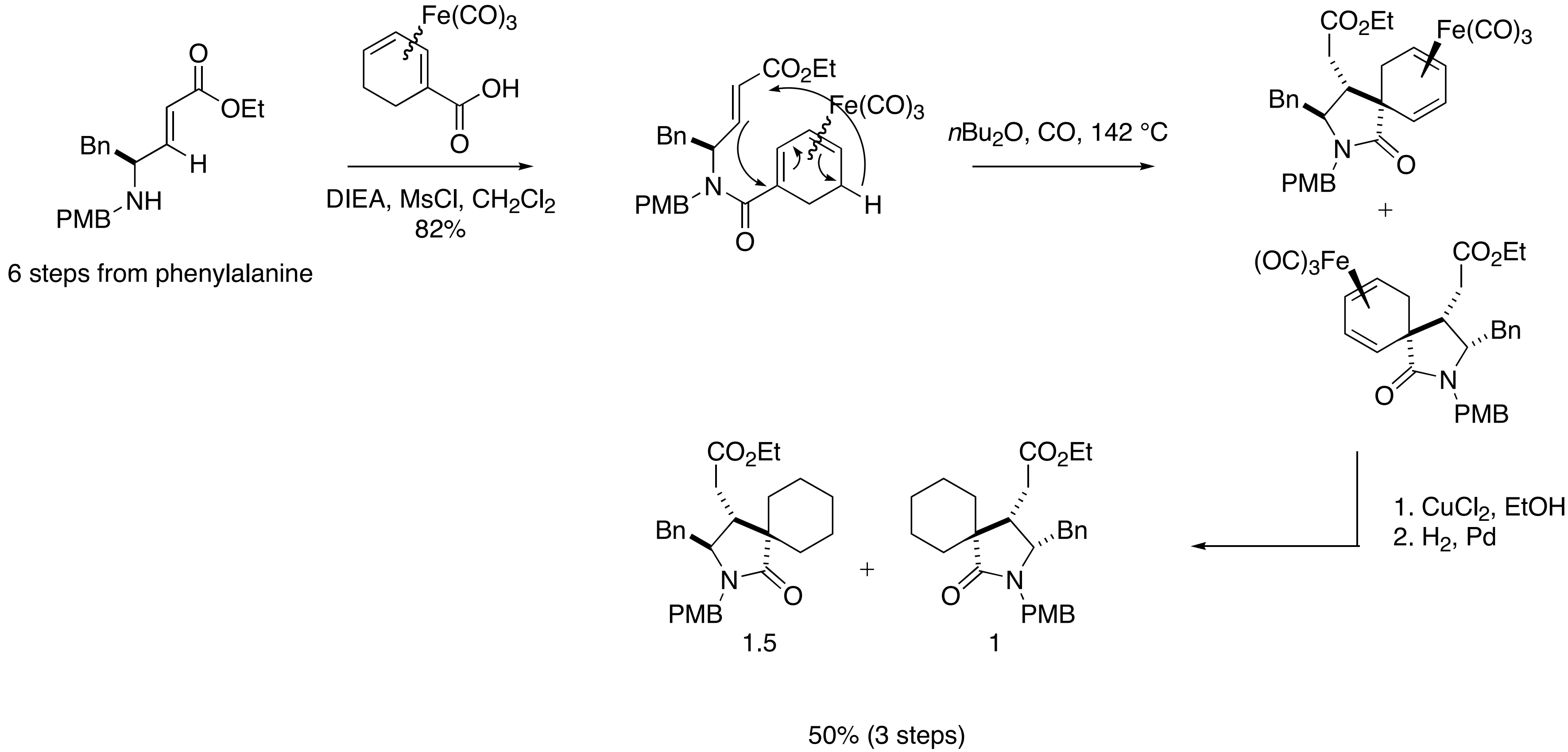
-Fe has been shown to catalyze [2+1], [2+2], [2+2+1], [2+2+2], [4+1], and [4+4] reactions as well



Bolm, C.; Legros, J.; Le Pain, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217
Han, J. L.; Ong, C. W. *Tetrahedron* **2006**, *62*, 8169

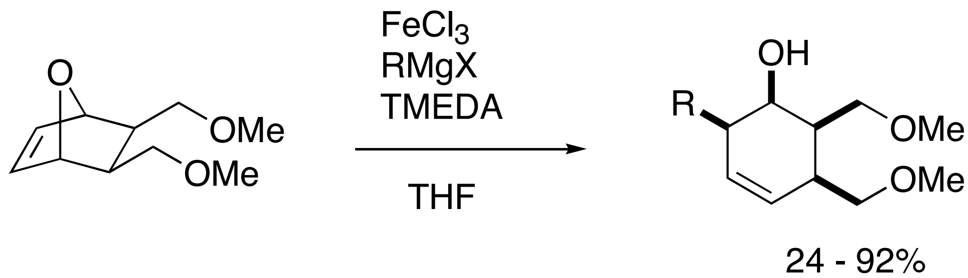
Pericyclic Reactions

-[6+2] ene cyclization



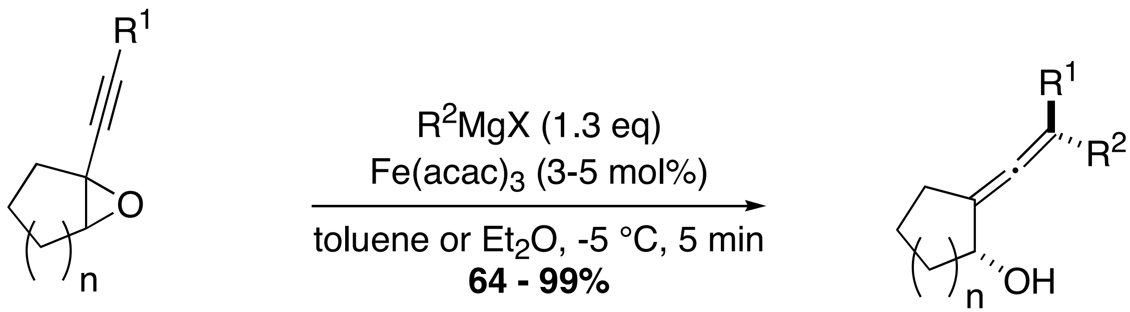
Pearson, A. J.; Sun, H.; Wang, X. *J. Org. Chem.* **2007**, *72*, 2547

Ring-Opening Reactions



R= aryl, alkenyl, or 1° and 2° alkyl

Nakamura, M.; Matsuo, K.; Inoue, T.; Nakamura, E. *Org*. *Lett*. **2003**, *5*, 1373



n = 1, 2, 3, 4

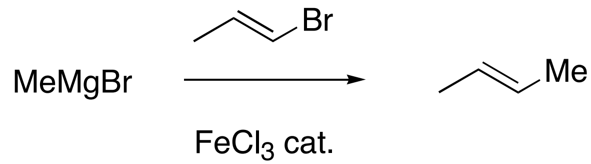
R^1 = H, Me, CH_2OH

R^2 = Me, *i*Pr, C_6H_{13}, Ph

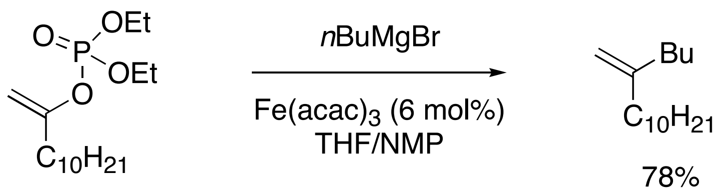
Fürstner, A.; Méndez, M. *Angew*. *Chem*. *Int*. *Ed*. **2003**, *42*, 5355

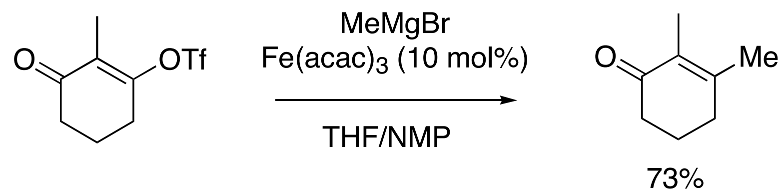
Cross Coupling Reactions Using Fe

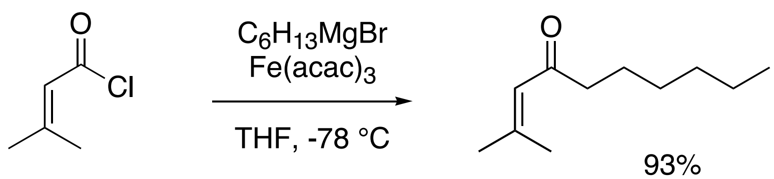
-In 1971 Kochi observed the initial Fe-mediated cross coupling:



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



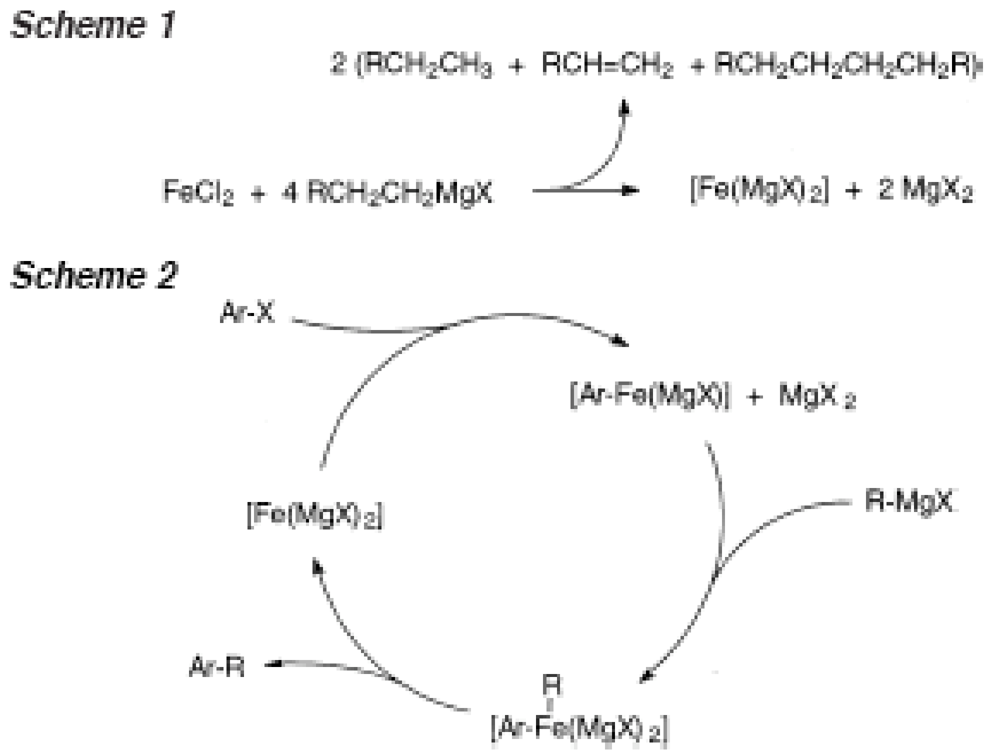




Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624
Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943

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*

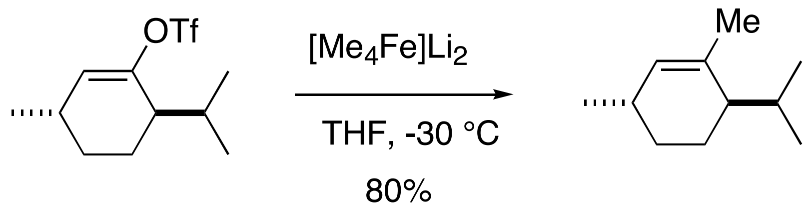


-”Such highly nucleophilic entities lacking any stabilizing ligands are able to oxidatively add to aryl halides”

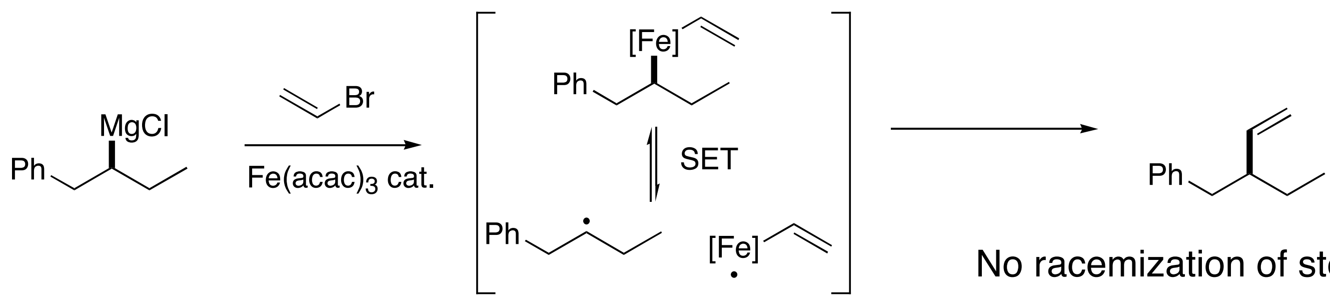
The Plot Thickens…

More than one mechanistic pathway (ate compounds)?

$$5\ MeLi + FeCl_3 \longrightarrow [Me_4Fe]Li_2 + 3\ LiCl + 1/2\ ethane$$



Radical mechanism?

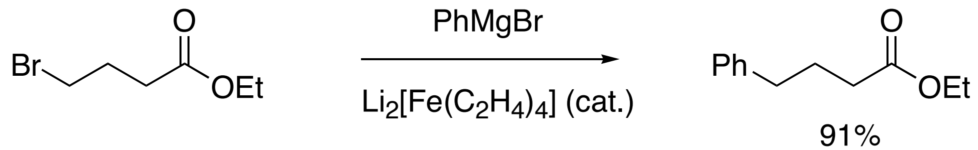


No racemization of stereochemistry

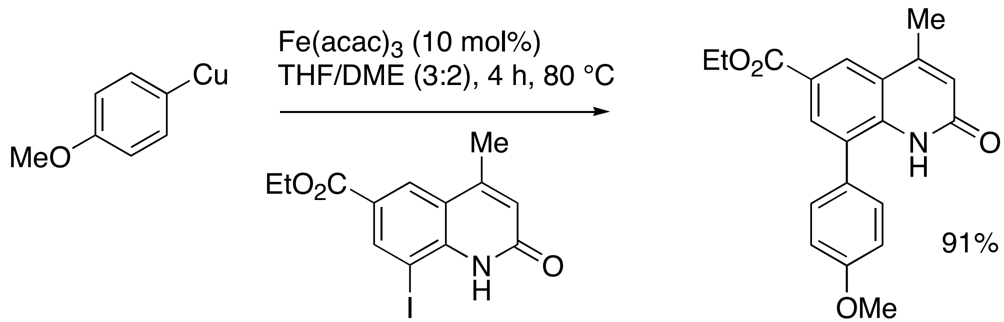
Scheiper, B.; Bonnekessel, M.; Krause, H.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3943
Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624

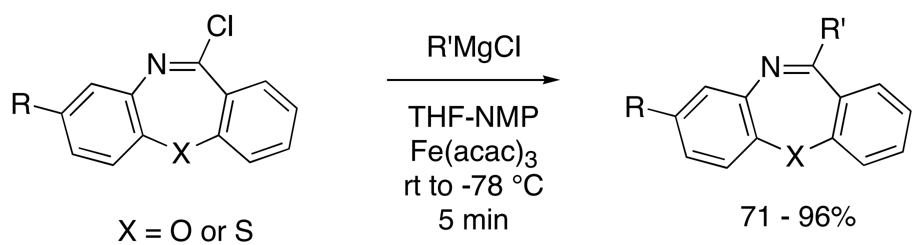
Extension of Coupling Methodology

-Alkyl Halides tolerated



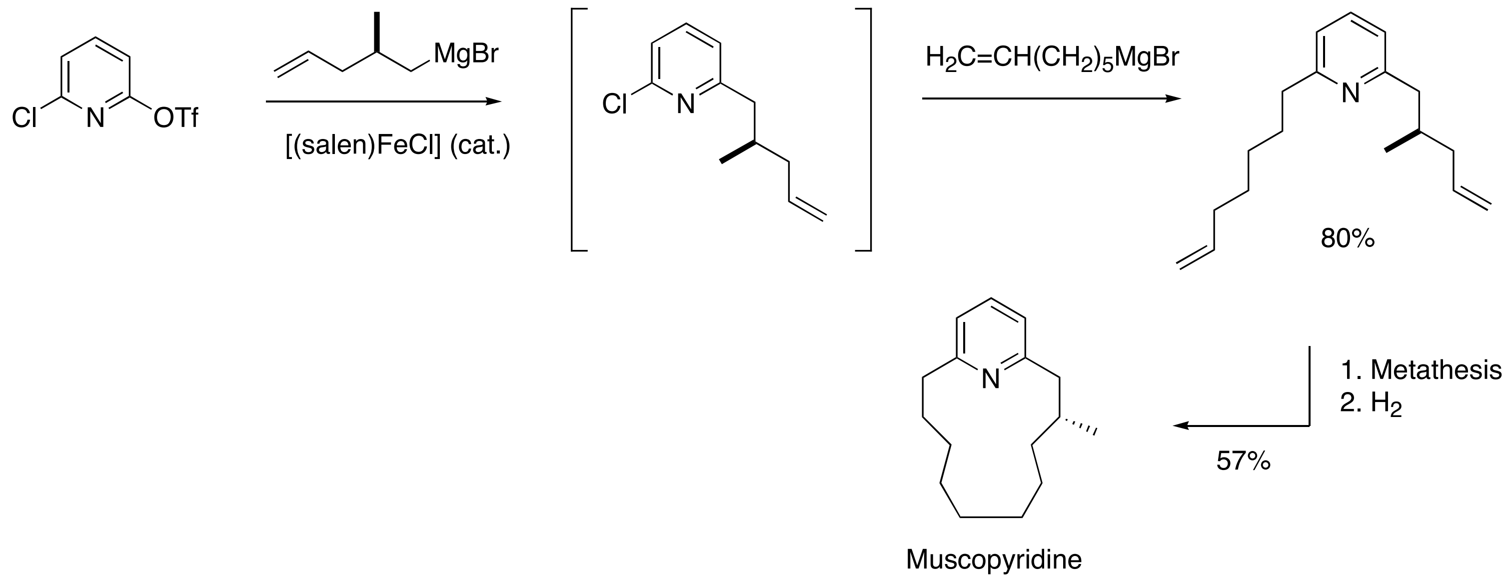
-Expanded Functionality Tolerance

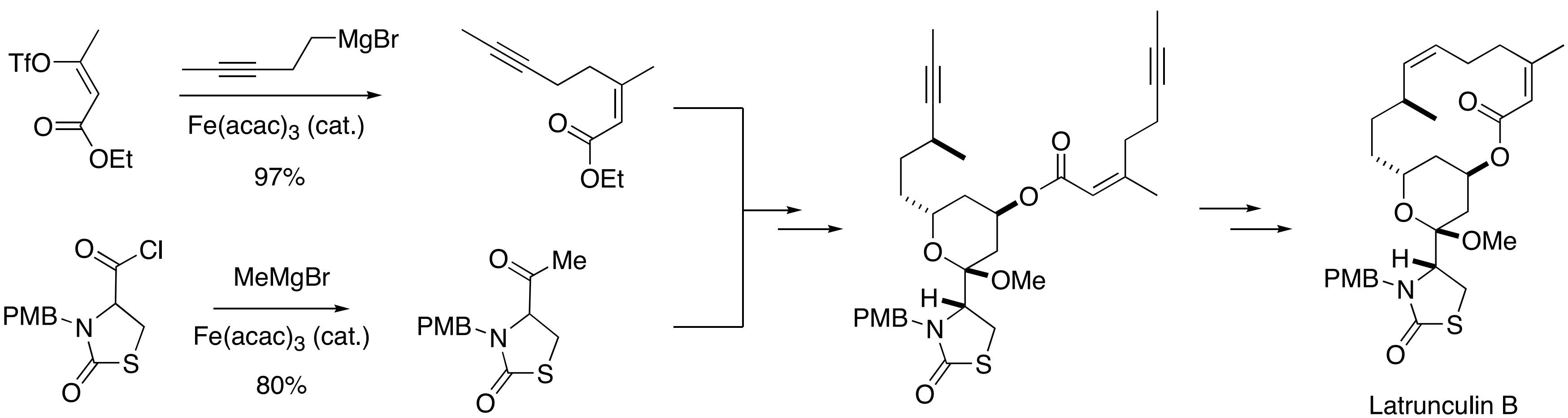




Fürstner, A.; Martin, R. *Chem. Lett.* **2005**, *34*, 624
Kofink, C. C.; Blank, B.; Pagano, S.; Götz, N.; Knochel, P. *Chem. Commun.* **2007**, 1954
Ottesen, L. K.; Ek, F.; Olsson, R. *Org. Lett.* **2006**, *8*, 1771

Applications of Fe-Cross Couplings





Fürstner, A.; Leitner, A. *Angew. Chem. Int. Ed.* **2003**, *42*, 308
Fürstner, A.; De Souza, D.; Parra-Rapado, L.; Jensen, J. *Angew. Chem. Int. Ed.* **2003**, *42*, 5358

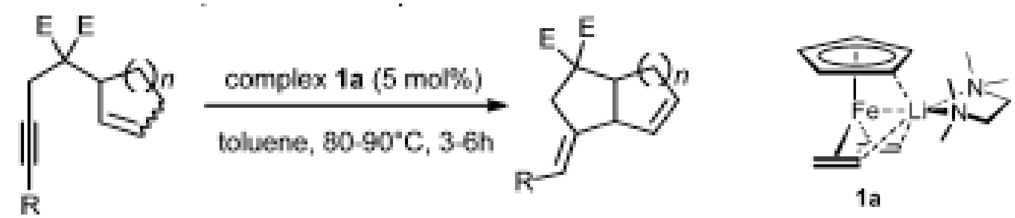
"…this methodology evolved into a routine tool for the preparation of fine chemicals and pharmaceutically active compounds in the laboratory and on the industrial scale, is widely appreciated in the context of parallel synthesis and combinatorial chemistry, and plays a prominent role in a rapidly growing 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