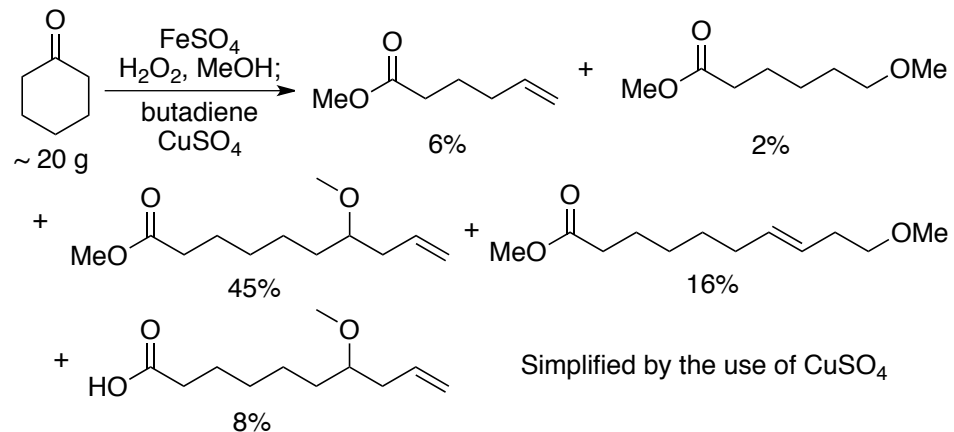


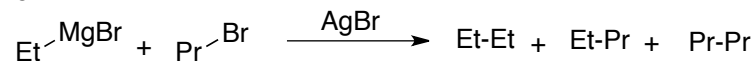


**Early Years - Radical Oxidation**

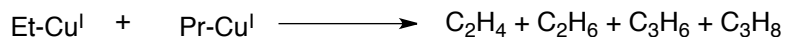
A day in the Kochi Lab:



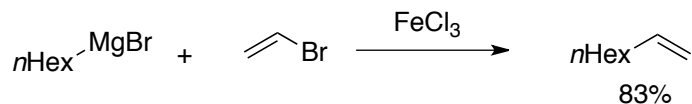
Kochi, J. JACS, 1962, 84, 3946

**Early Years - Kochi cross coupling - Practical outcomes****Silver**

Kochi, J. JACS, 1971, 93, 1483

**Copper**

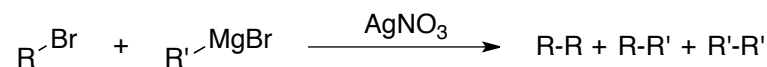
Kochi, J. JACS, 1971, 93, 1485

**Iron**

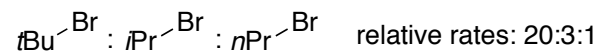
Kochi, J. JACS, 1971, 93, 1487

Radical Based Cross-Coupling**Silver Catalysis - Kochi**Initial studies stoichiometric, found NO<sub>3</sub> oxidizes Ag

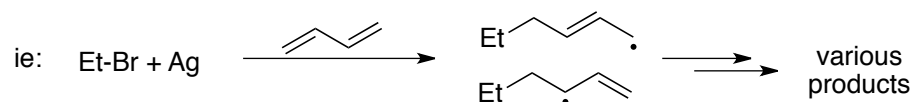
Net Reaction: Catalytic



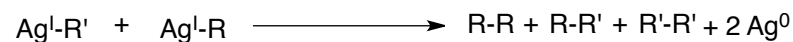
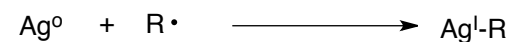
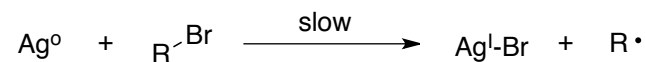
Kinetics: Rate independent of Grignard reagent



R arising from R-Br can be intercepted



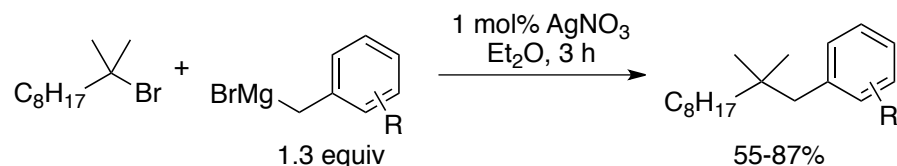
Proposed mechanism:



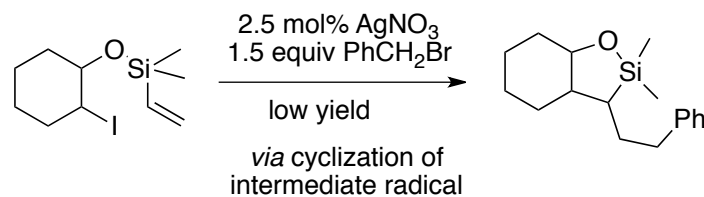
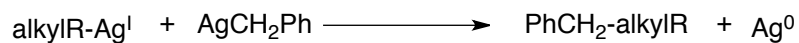
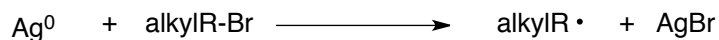
Kochi, J. JACS, 1971, 93, 1483

Radical Based Cross-Coupling**Silver Catalysis - More Synthetic Utility**

But understood?

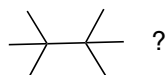
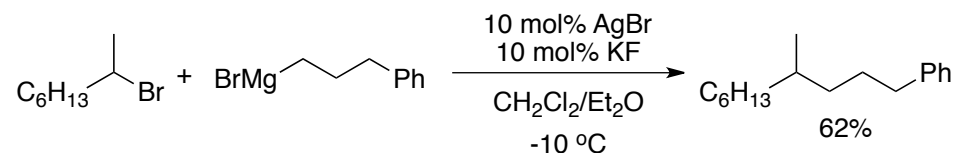


Secondary alkyl bromides also work well  
Primary give low yields

**Silver Catalysis - Oshima's Mechanism**

Authors not sure why cross-coupling predominates

Success due to slow formation of

Oshima, K. *Org. Lett.* **2008**, *10*, 969**Silver Catalysis - More Synthetic Utility**2° and 3° alkyl bromides with **different catalysts**:

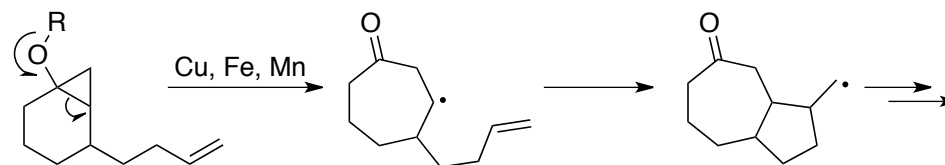
KF proposed to dissociate AgBr aggregates

Oshima, *Tet. Lett.* **2009**, *50*, 3270

2° and 3° alkyl bromides with **alkyl Zincs**: Oshima, *Chem. Asian J.* **2010**, 1487  
with **benzyl- or fluorenyllithiums**: Oshima, *Tetrahedron.* **2010**, *66*, 5993

Radical Oxidation**Silver Catalysis**

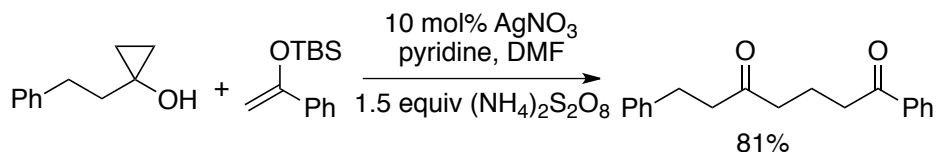
Background - Booker-Milburn cleavage of cyclopropyloxy radicals



de Boer, *Tet. Lett.* **1973**, *14*, 827 - Cu/simple substrates  
Kwon, *J. Org. Chem.* **1992**, *57*, 2399 - Cu/more complex  
Booker-Milburn, *Tet.* **1998**, *54*, 15321 Fe

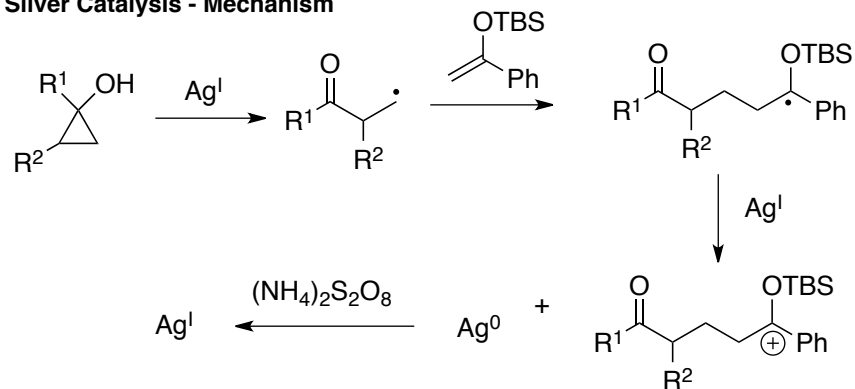
Radical Oxidation -  $\beta$ -keto radicals

Wanted to get away from excess Mn

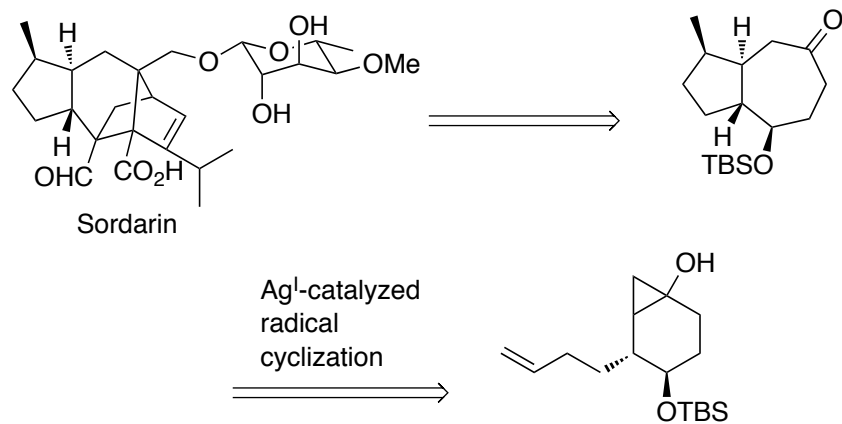


Narasaka, K. *Chem. Lett.* **2006**, *35*, 18

**Silver Catalysis - Mechanism**



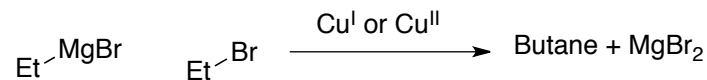
**Silver Catalysis - Application**



Narasaka, K. *J. Am. Chem. Soc.* **2006**, *128*, 6931

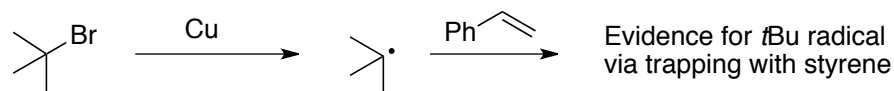
Radical Based Cross-Coupling

**Copper Catalysis - Kochi**



Via 2 electron chemistry - 1° alkylcuprates not intercepted by alkene

Largely in agreement with Whitesides - *JACS*, **1966**, *88*, 4541

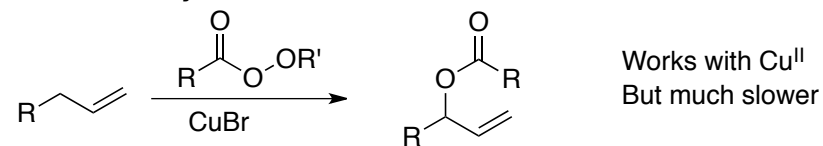


Subsequent Cu-catalyzed cross coupling focused on 2 electron chemistry

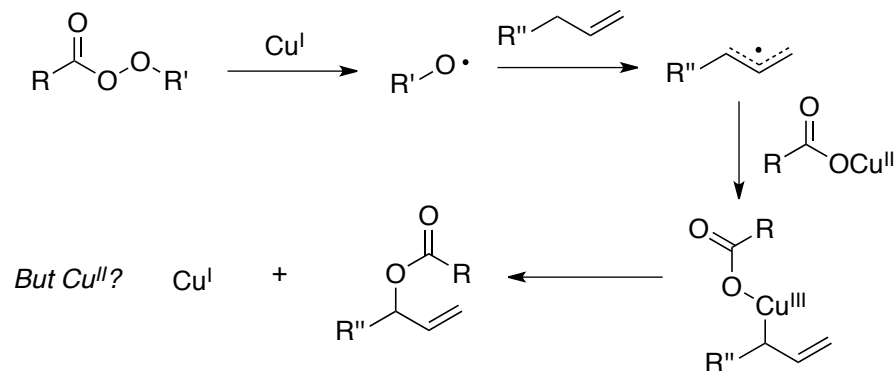
Kochi, J. *J. Am. Chem. Soc.* **1971**, *93*, 1485

Radical Oxidation

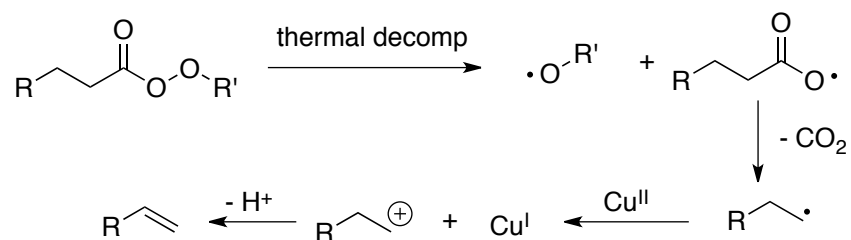
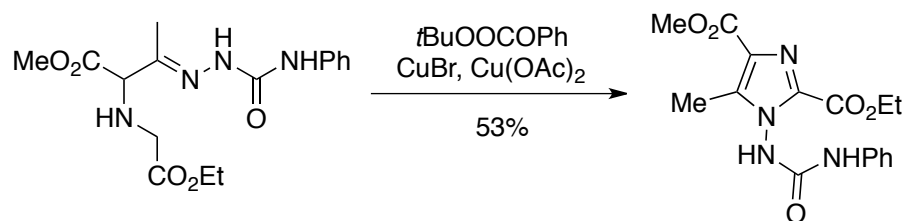
**Kharasch-Sosnovsky**



Kharasch, *JACS*, **1958**, *80*, 756

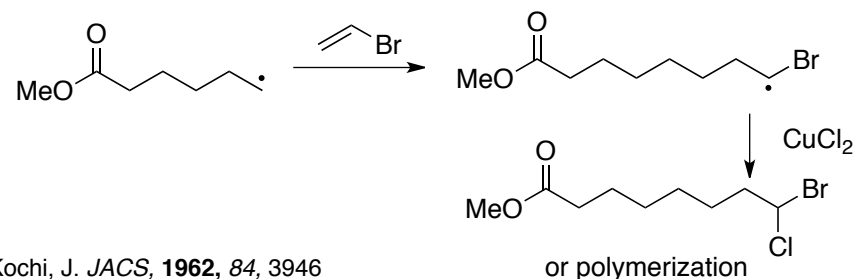
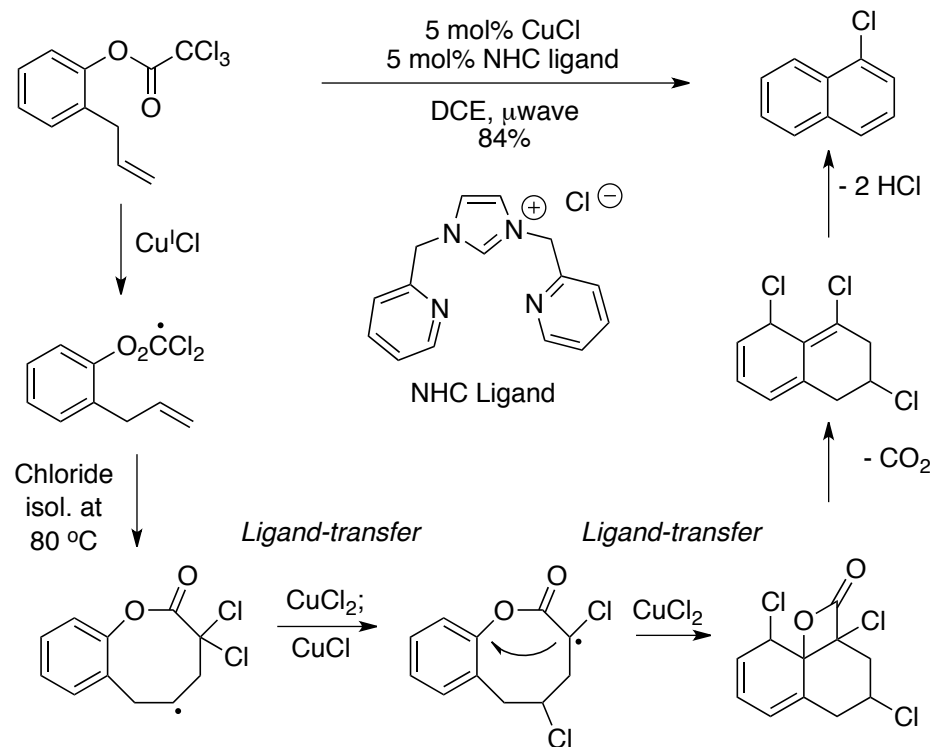


Beckwith, Zavitsas, *JACS*, **1986**, *108*, 8230

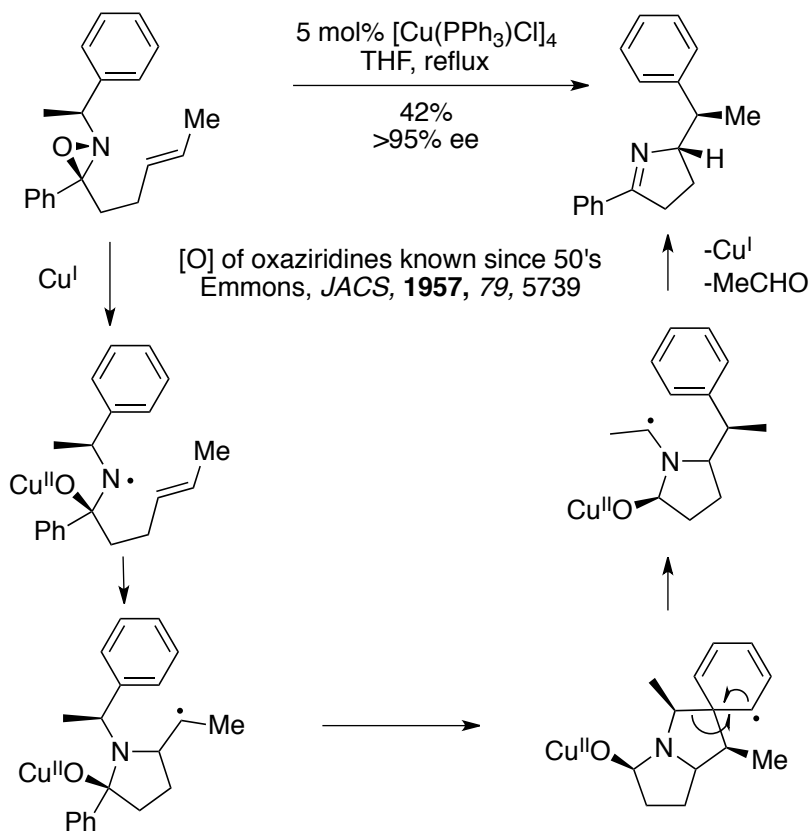
Copper Catalyzed Radical Oxidation**Kharasch-Sosnovsky; Kochi Contribution**How does Cu<sup>II</sup> work? Kinetic studies, detailed analysis of products...Once Cu<sup>I</sup> is formed, oxidation of alkenes becomes very rapidKochi, J. *Tetrahedron* **1968**, *24*, 5099**Kharasch-Sosnovsky like reaction; Application**

Can also be done with base, then heat 2-pot procedure

Mechanism?

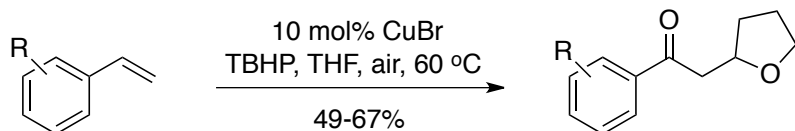
Arcadi, *Tet. Lett.* **1997**, *38*, 2329Copper Catalyzed Transformations - Ligand Transfer**Kochi Precedent****Modern Application**Quayle, *ACIEE*, **2007**, *46*, 1869

Copper Catalyzed Transformations - Heterocycle oxidations



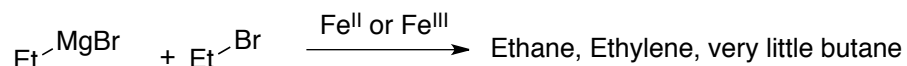
Aube, *JACS*, **1992**, 114, 5466

**THF oxidation**

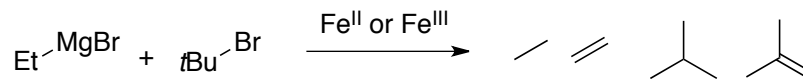


Zhang, *Org Lett.* **2009**, 11, 2908

Iron Catalysis - Alkyl Halides



Like Ag - Rate independent of [Grignard]  
Like Cu - See disproportionation rather than cross coupling - alkyl-Br

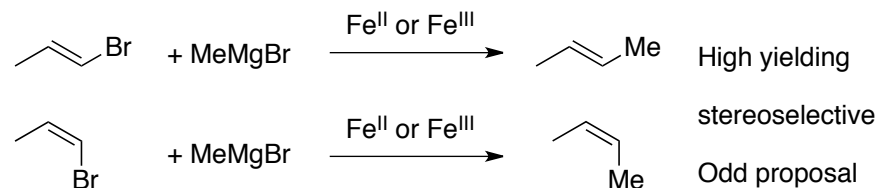


But styrene prevents formation of butane-derived products

Conclusion (by larger community) - alkyl bromides incompatible  
overcome later

Kochi, *J. JACS*, **1971**, 93, 1487

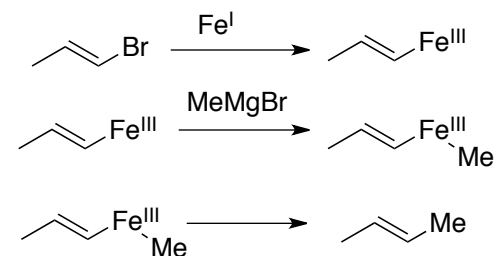
Iron Catalysis - Vinyl Halides



Kochi, *J. JACS*, **1971**, 93, 1487

Iron Catalysis - Vinyl Halides

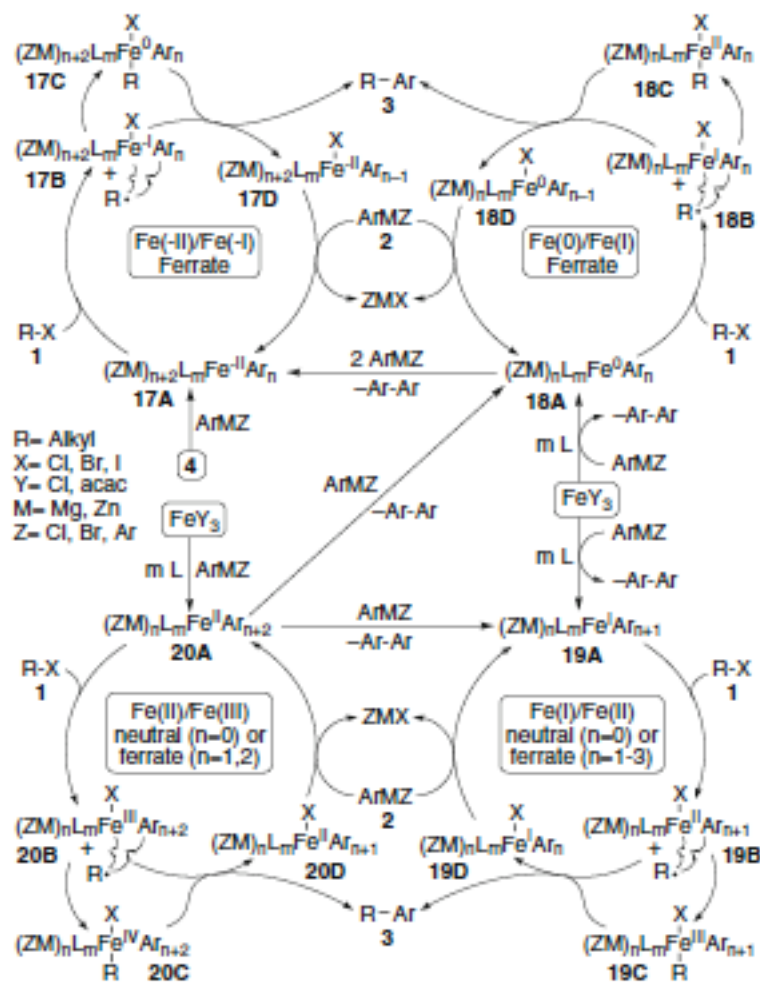
Later proposed



Kochi, *J. JOC*, **1975**, 40, 599  
Kochi, *J. JOC*, **1976**, 41, 502

## Radical Based Cross-Coupling

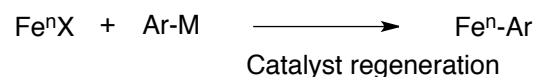
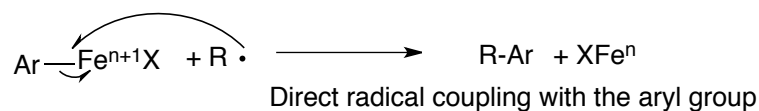
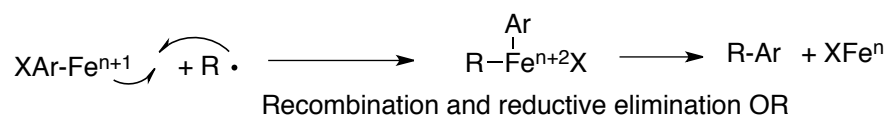
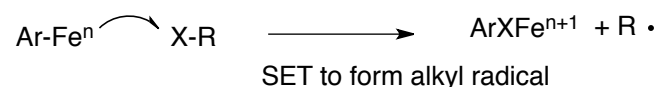
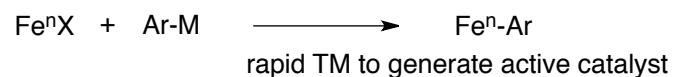
## Iron Catalysis - The mechanism



Kochi, J. and Bogdonovic, *ACIEE*, **2000**, 39, 4610  
 Bedford, *JOC*, **2006**, 71, 1104

Nagashima, *JACS*, **2009**, 131, 6078  
 Makamura, *Chem. Comm.* **2010**, 46, 6054  
 and many others

## The mechanism - Decipherable version



Upshot: 1) If you can get to Ar-Fe, successful catalysis should ensue

2) Transmetalation appears to be facile in all cases studied - so 1) is readily attainable

3) Catalysts can switch between oxidation states via TM-TM-RE

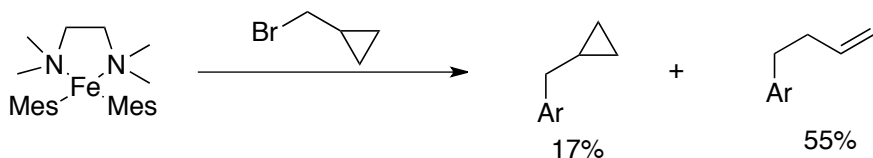
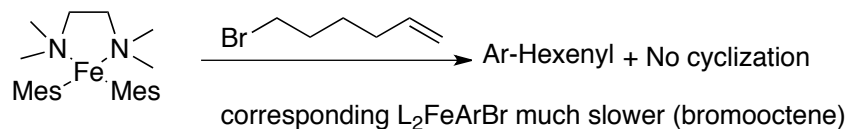
4) Therefore, multiple cycles may be operative in a given pot

5) 2 electron pathways can not be ruled out in all cases

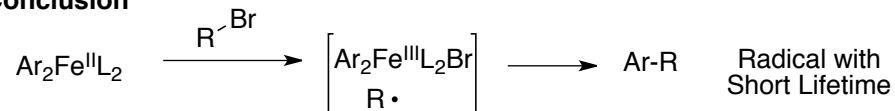
Jahn, *Top. Curr. Chem.* **2012**, 320, 191.

## Radical Based Cross-Coupling

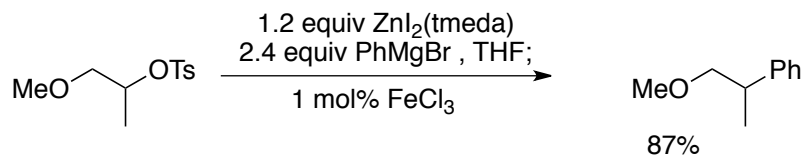
## Iron Catalysis



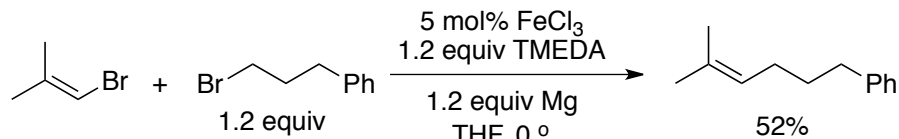
## Conclusion

Nagashima, H. *JACS*, **2009**, *131*, 6078

## Unconventional R-X

Via in situ preparation of R-I  
in situ preparation of Ar-ZnXCompatible with esters, nitriles  
thiophenes, alkynesNakamura, M. *Org. Lett.*, **2009**, *11*, 4306

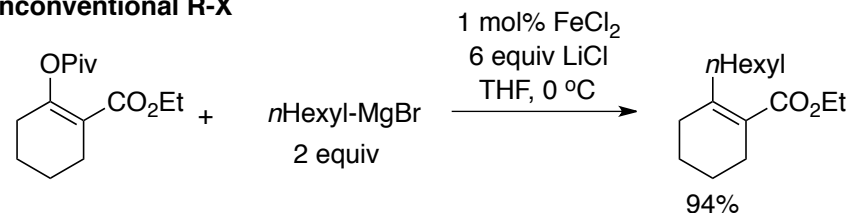
## Unconventional R-X: Avoiding Grignard reagents



Via in situ preparation of alkyl Grignard

von Wangelin, A. J. *ACIEE*, **2009**, *48*, 607

## Unconventional R-X

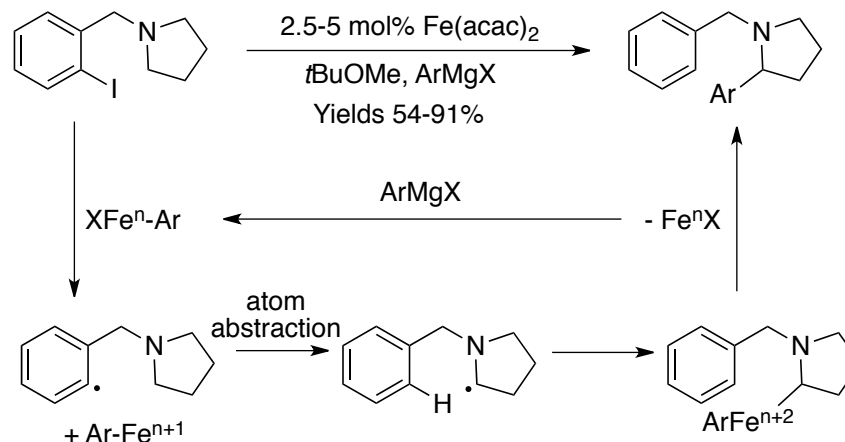


Little mechanistic discussion

Reaction inhibited by TEMPO

Shi, Z. J. *JACS*, **2009**, *131*, 14656

## Radical Transfer

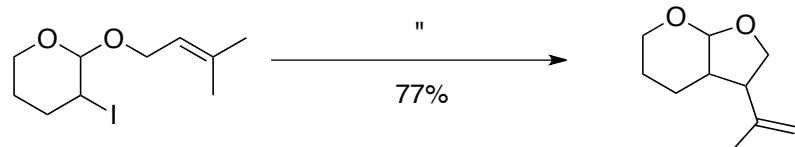
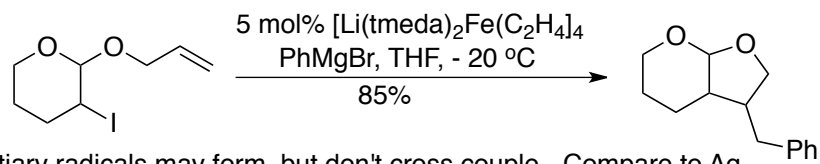
 $Ar_2Zn$  also an effective transmetallating agent

Deuterium labeling supports intramolecular hydrogen transfer

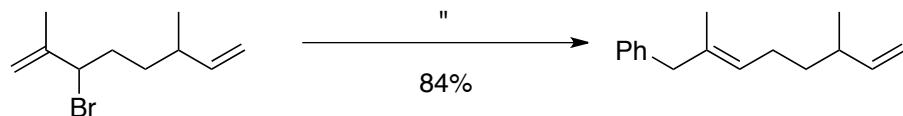
Potential for enantioselective desymmetrizing reaction?

Nakamura, E. *JACS*, **2010**, *132*, 5568

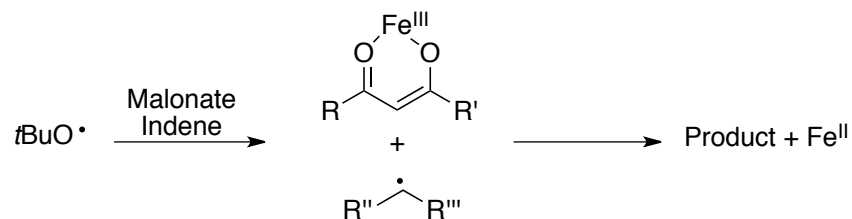
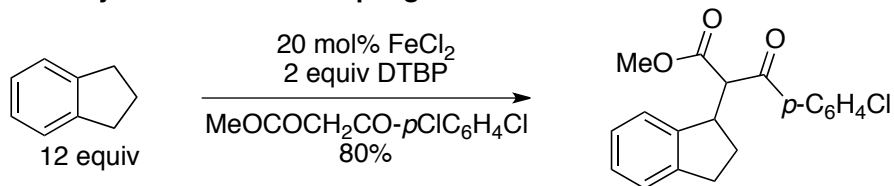


Fe-Catalysis: Iron<sup>II</sup>

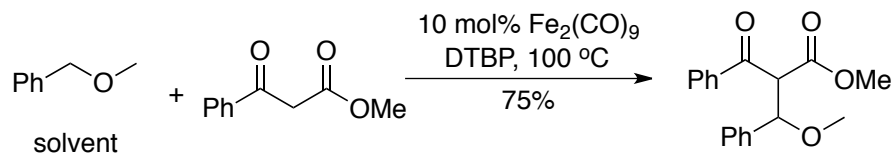
Allylic rearrangement faster than cyclization

Furstner, A. *ACIEE*, 2004, 43, 3955

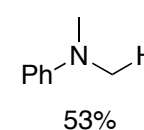
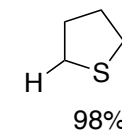
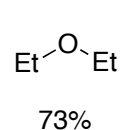
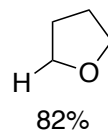
## Fe-Catalysis: C-H Cross Coupling

Li, Z. *ACIEE*, 2007, 46, 6505

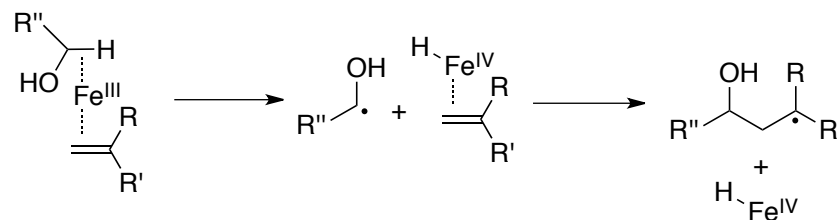
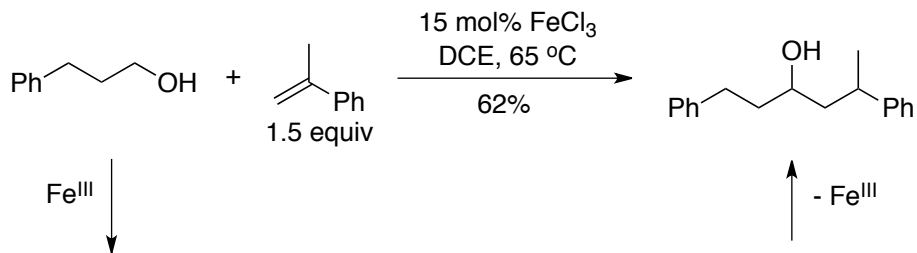
## Fe-Catalysis: C-H Cross Coupling



Other compatible solvents:

Li, Z. *ACIEE*, 2008, 47, 7497

## Fe-Catalysis: C-H Cross Coupling via Hydrogen Transfer

Zhang, Y. Q. *ACIEE*, 2009, 48, 8761

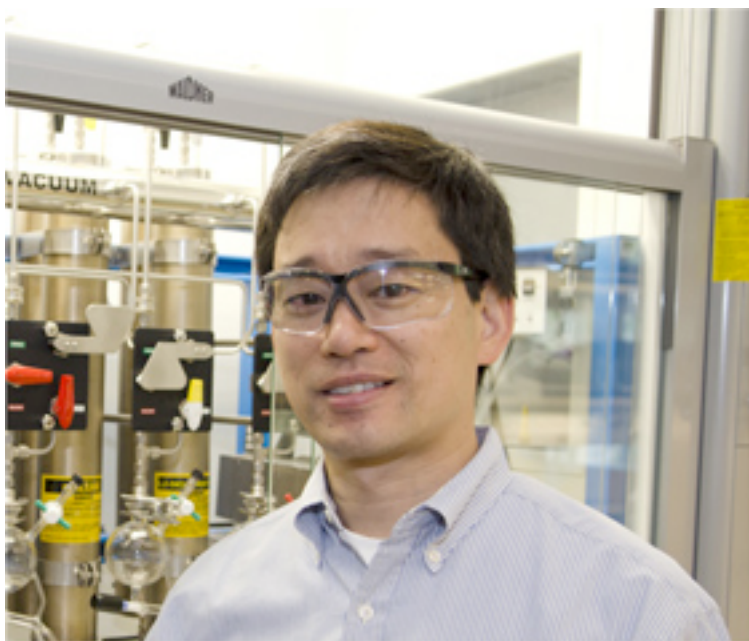
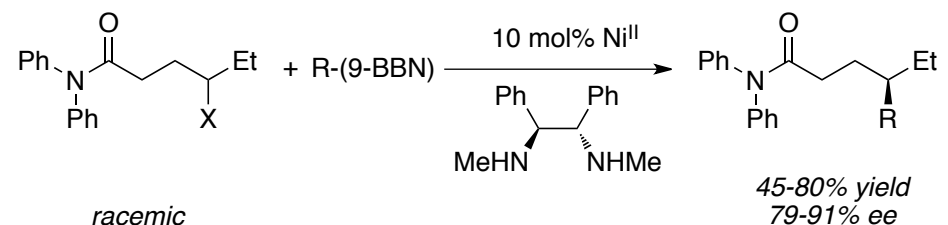
Nickel Cross Coupling

Many groups have investigated mechanism

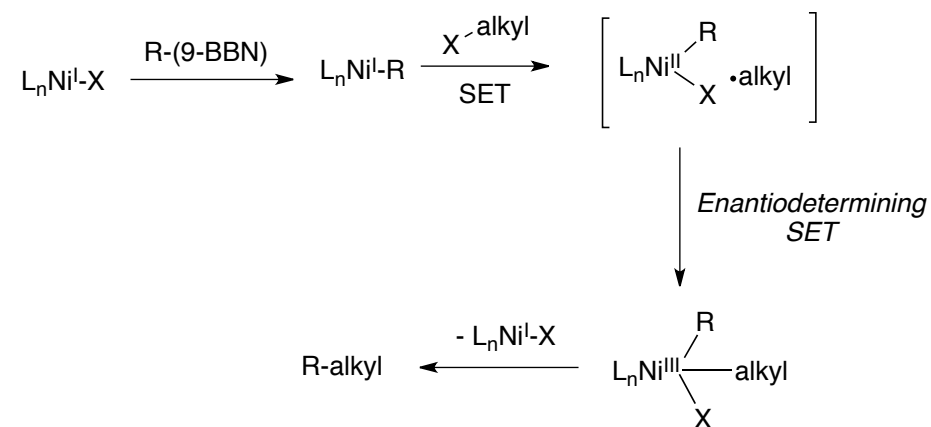
Corey: *JACS*, **1967**, *89*, 2755  
 Hegedus: *JACS*, **1975**, *97*, 459  
 Phillips: *JOC*, **2008**, *73*, 3680  
 Eschavarren: *JACS*, **1994**, *13*, 2262  
 Vicic: *JACS*, **2006**, *128*, 13175  
 Kochi, *JACS*, **1979**, *101*, 6319

Review: Jahn, *Top. Curr. Chem.* **2012**, *320*, 323

Mechanism depends on R-X (Carbon hybridization), ligand, solvent, halide, etc

Gregory FuAsymmetric Suzuki cross couplings to deliver challenging products

R = 1° or 2° alkyl, Ar



**Conclusion:** Kochi an incredibly meticulous physical organic chemist

Invaluable contributions to cross coupling and radical [O] chemistry

Many of his contributions are not covered

More info on radical/TM chem: Jahn, *Top. Curr. Chem.* **2012**, *320*, 121

Fu, G. *JACS*, **2011**, *133*, 15362