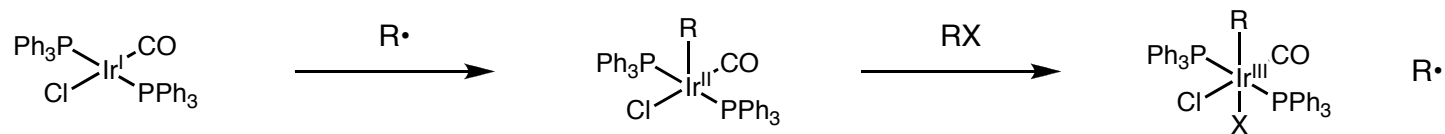


## Interaction of Organic Radicals with Transition Metals

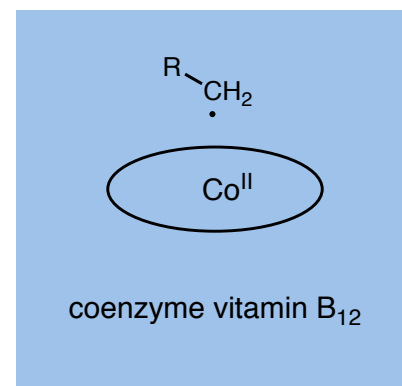
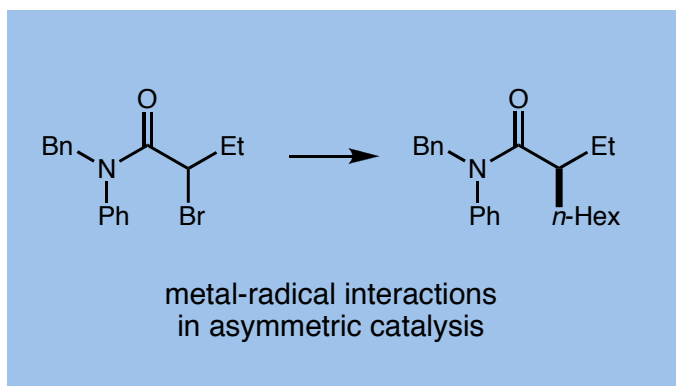
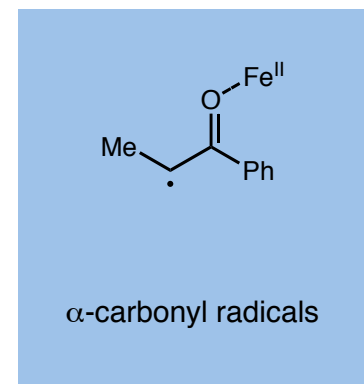
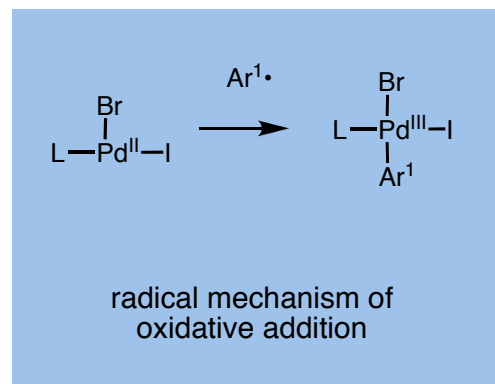
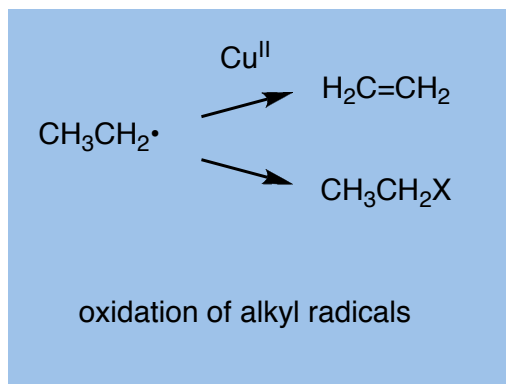


Chris Prier

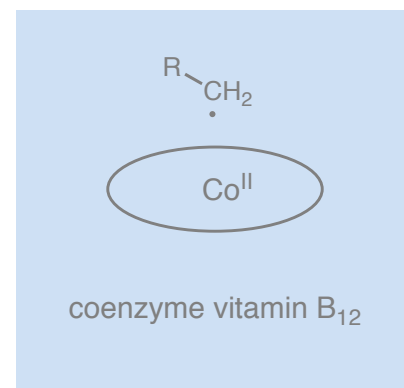
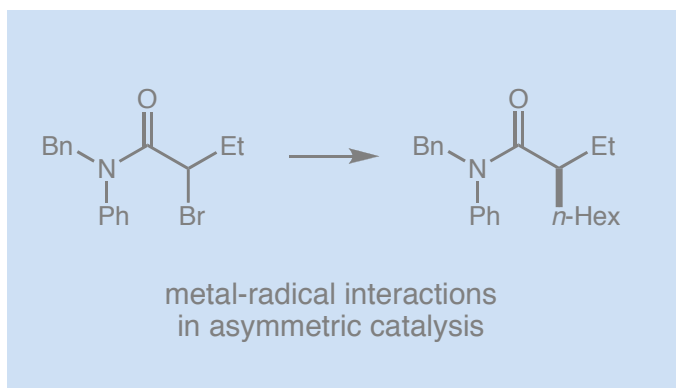
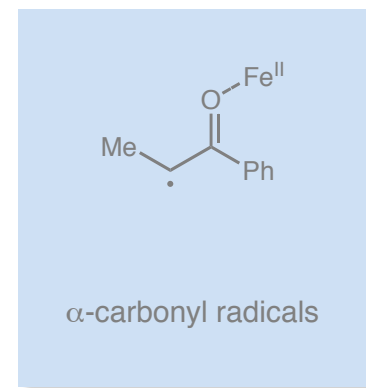
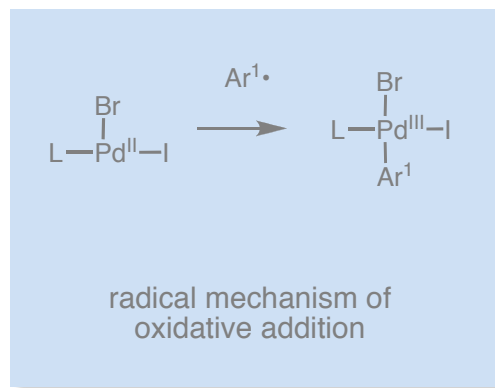
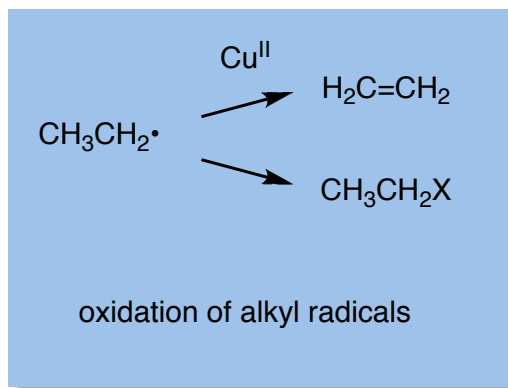
MacMillan Group Meeting

March 23, 2011

## Interaction of Organic Radicals with Transition Metals

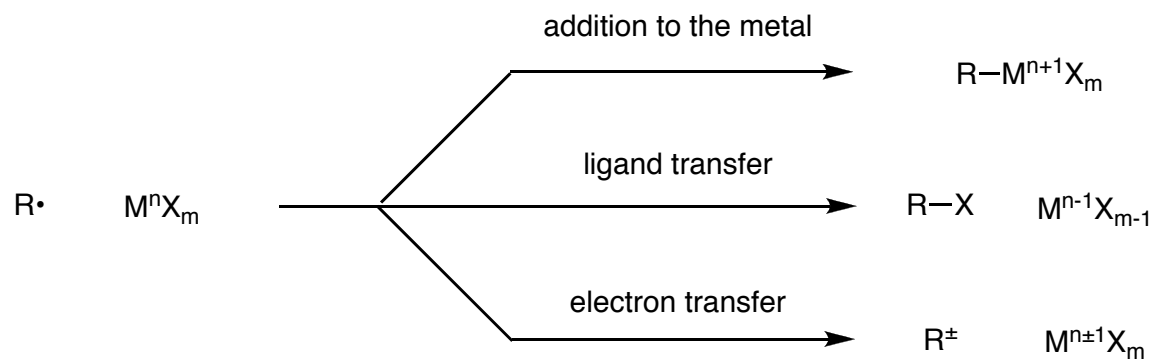


## Interaction of Organic Radicals with Transition Metals



## Transition Metals and Organic Radicals

- What are the mechanisms by which an alkyl radical can interact with a transition metal?



- Different  $Cu^{II}$  sources show divergent reactivity with respect to ethyl radical

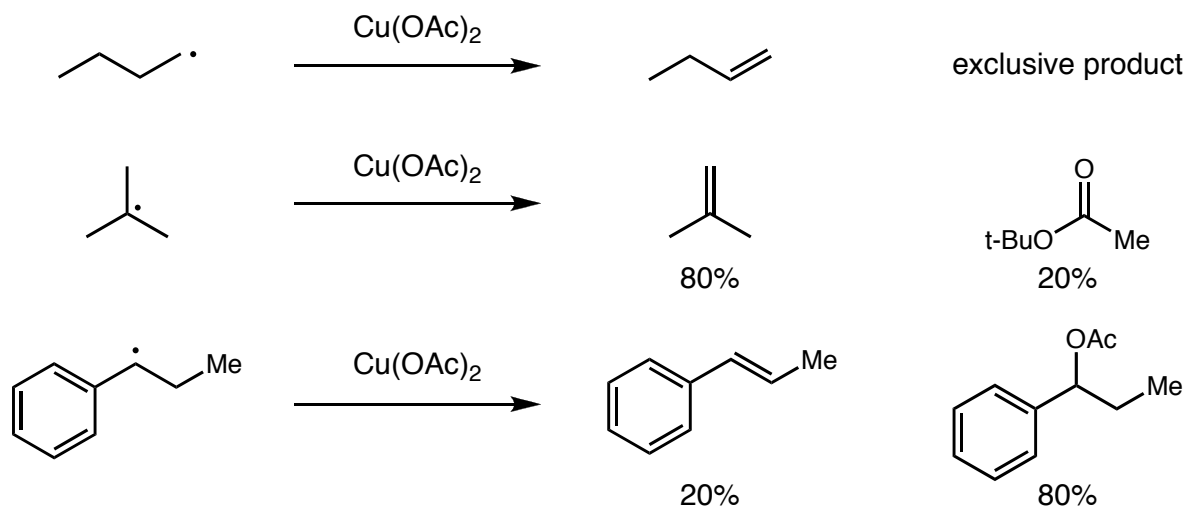


## Oxidation of Alkyl Radicals by Cu<sup>II</sup>

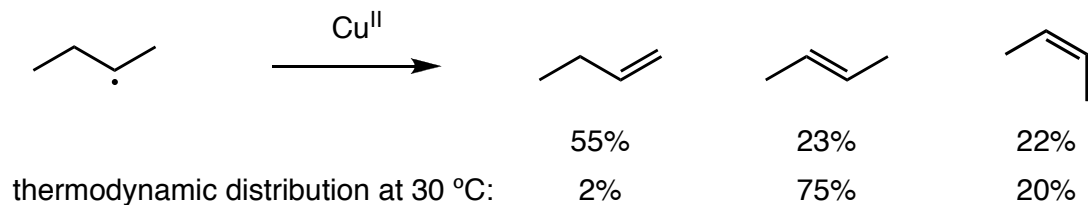
- Oxidation by CuSO<sub>4</sub> is an electron transfer processes (outer-sphere)



- Radicals which would give more stabilized carbocations give more substitution product

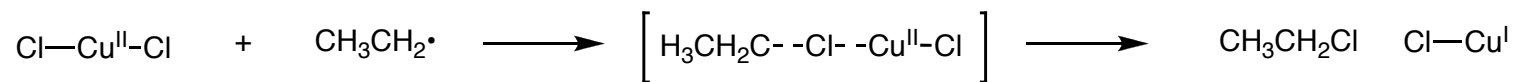


- Stabilities of the oxidation products do not control the selectivity of oxidative elimination

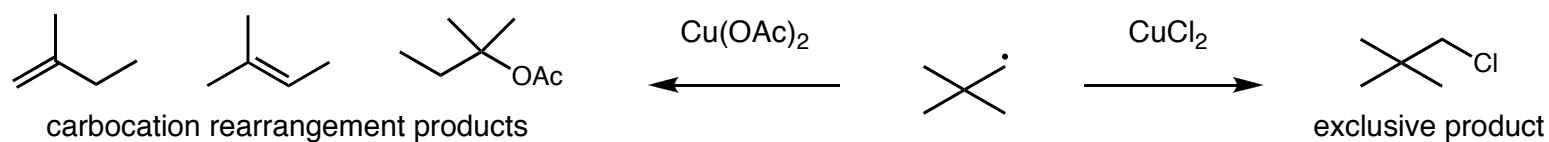


## Oxidation of Alkyl Radicals by Cu<sup>II</sup>

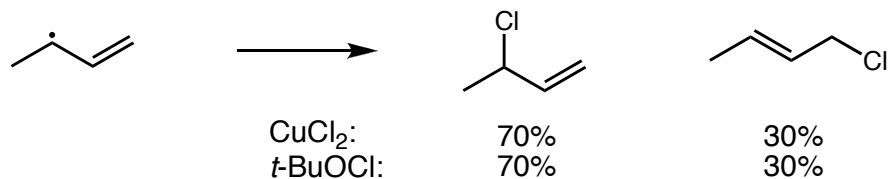
- Oxidation by CuCl<sub>2</sub> is a ligand transfer processes (inner-sphere)



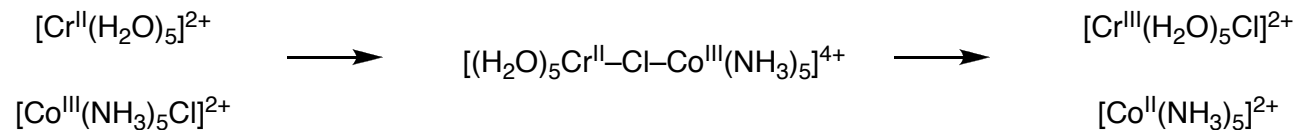
- Oxidation of neopentyl radical gives no rearranged products with CuCl<sub>2</sub>



- Product ratios match those obtained with atom transfer reagents



- Analogy with Taube inorganic ligand transfer process



## Metal-Alkyl Bond Strengths

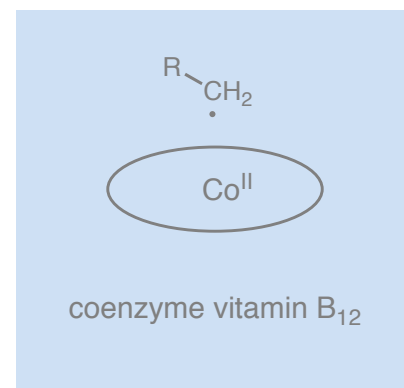
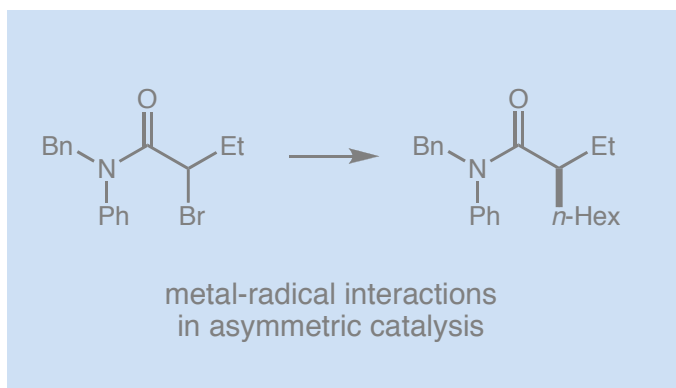
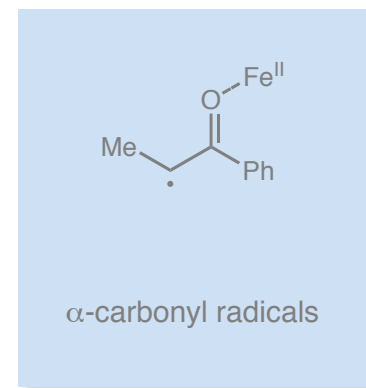
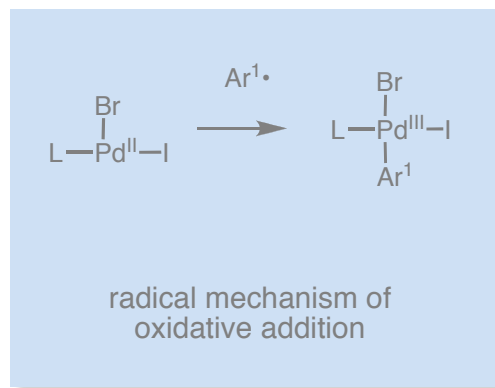
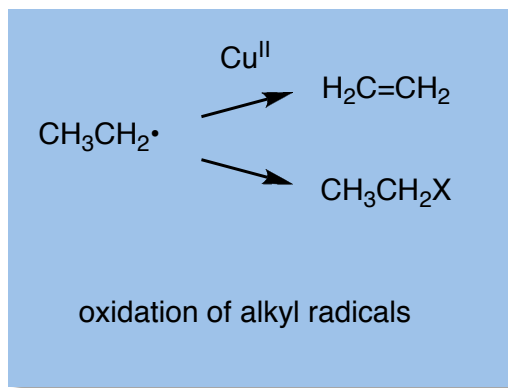
- Metal-alkyl bonds are characteristically weak, correlate with degree of steric crowding

	bond dissociation energy (kcal/mol)
(py)(SALOPH)Co-CH <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	25
(py)(SALOPH)Co-CH(CH <sub>3</sub> ) <sub>2</sub>	20
(py)(SALOPH)Co-CH <sub>2</sub> C(CH <sub>3</sub> ) <sub>3</sub>	18
(py)(SALOPH)Co-CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	22
(PMe <sub>2</sub> Ph)(DH) <sub>2</sub> Co-CH(CH <sub>3</sub> )C <sub>6</sub> H <sub>5</sub>	24
(PEtPh <sub>2</sub> )(DH) <sub>2</sub> Co-CH(CH <sub>3</sub> )C <sub>6</sub> H <sub>5</sub>	19
(PPh <sub>3</sub> )(DH) <sub>2</sub> Co-CH(CH <sub>3</sub> )C <sub>6</sub> H <sub>5</sub>	17
(CO) <sub>5</sub> Mn-CH <sub>3</sub>	37
(CO) <sub>5</sub> Mn-CF <sub>3</sub>	41
(CO) <sub>5</sub> Mn-C <sub>6</sub> H <sub>5</sub>	41
(CO) <sub>5</sub> Mn-CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	21
(CO) <sub>5</sub> Mn-COC <sub>6</sub> H <sub>5</sub>	21
(CO) <sub>5</sub> Re-CH <sub>3</sub>	53

SALOPH = N,N'-disalicylidene-*o*-phenylenediamine, (DH)<sub>2</sub> = dimethylglyoxime

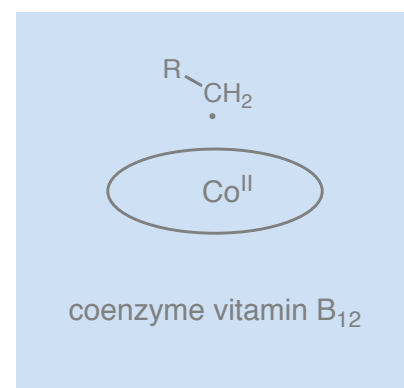
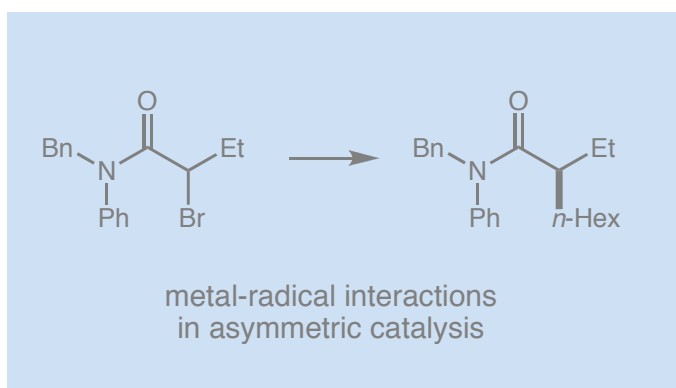
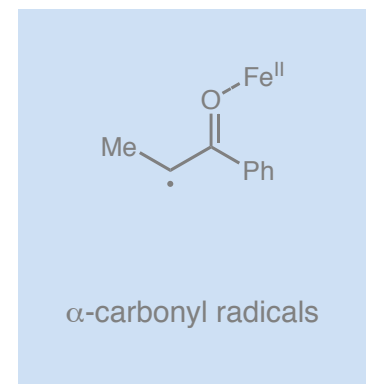
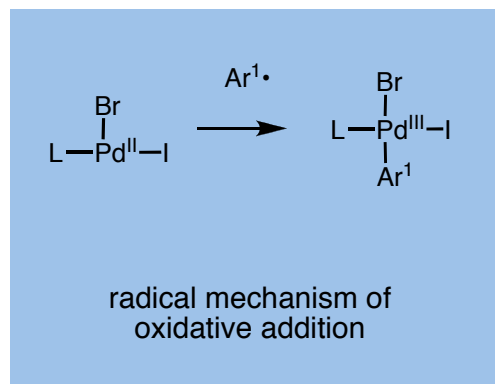
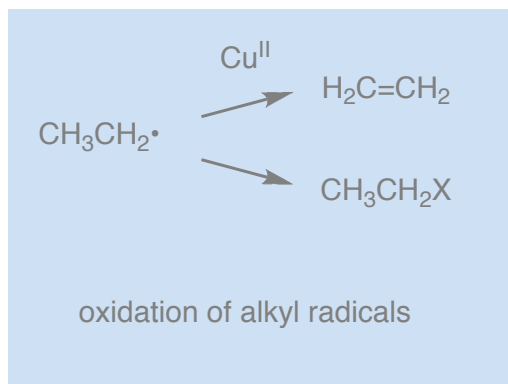
Halpern, J. *Inorg. Chim. Acta.* **1985**, *100*, 41-48.  
Brown, D. L. S.; Connor, J. A.; Skinner, H. A. *J. Organomet. Chem.* **1974**, *81*, 403-409.  
Connor, J. A. et al. *Organometallics.* **1982**, *1*, 1166-1174.

## Interaction of Organic Radicals with Transition Metals



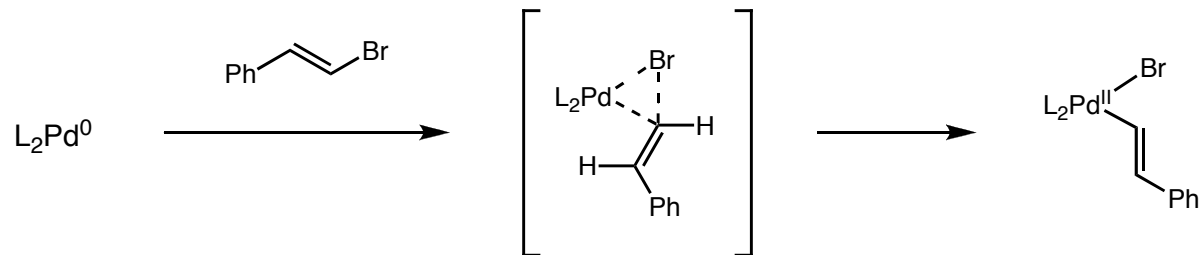


## Interaction of Organic Radicals with Transition Metals

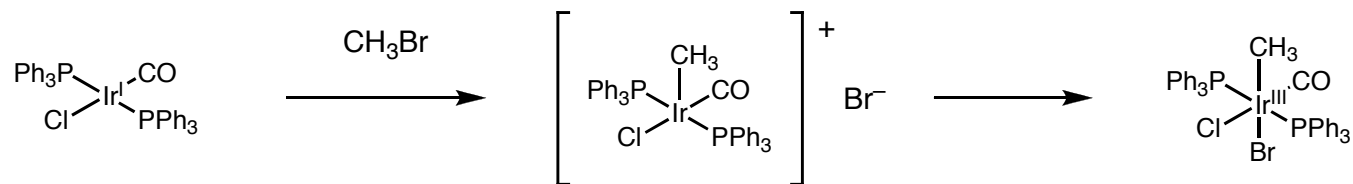


## Two-Electron Mechanisms of Oxidative Addition

- Concerted pathway: *cis* insertion via a three-center, two-electron bond

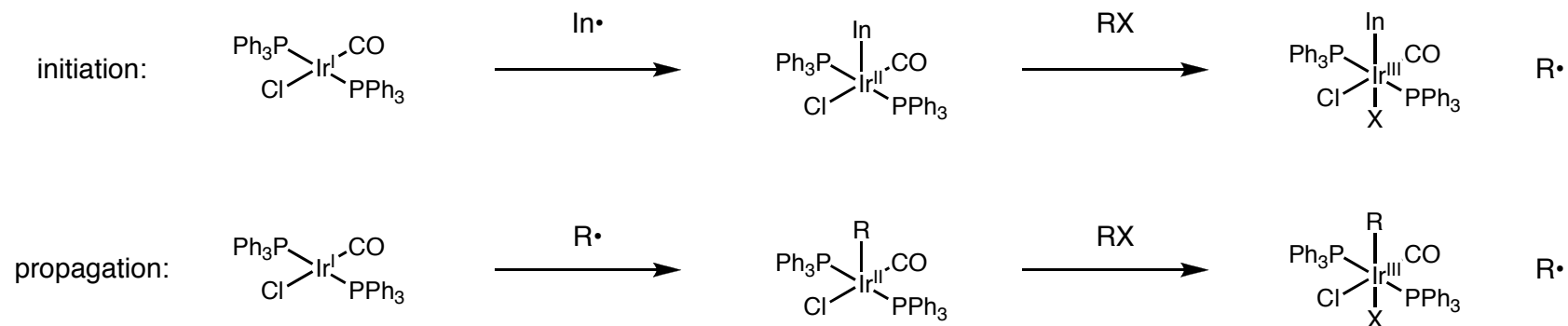


- $S_N2$ -type substitution: highly nucleophilic metal complexes attack primary or secondary halides



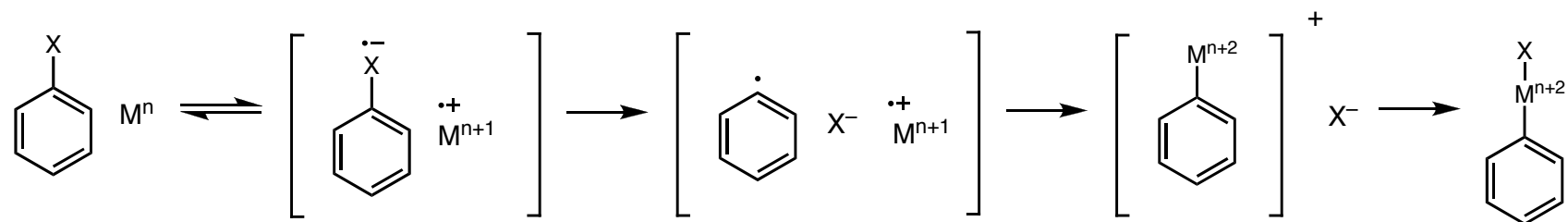
## One-Electron Mechanisms of Oxidative Addition

### ■ Radical pathway (two inner sphere one-electron processes)



Labinger, J. A.; Osborn, J. A.; Coville, N. J. *Inorg. Chem.* **1980**, *19*, 3236-3243.

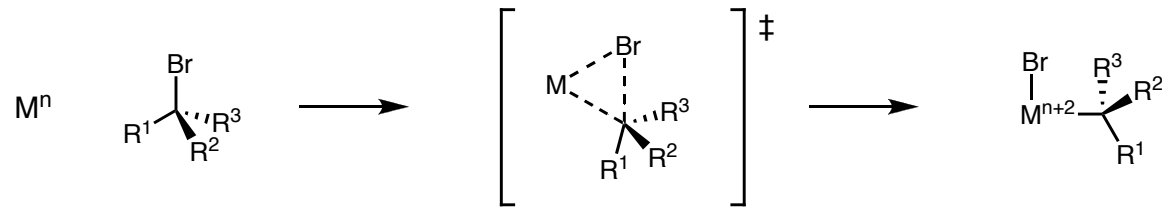
### ■ Electron-transfer mechanism (outer sphere one-electron process, then inner sphere one-electron process)



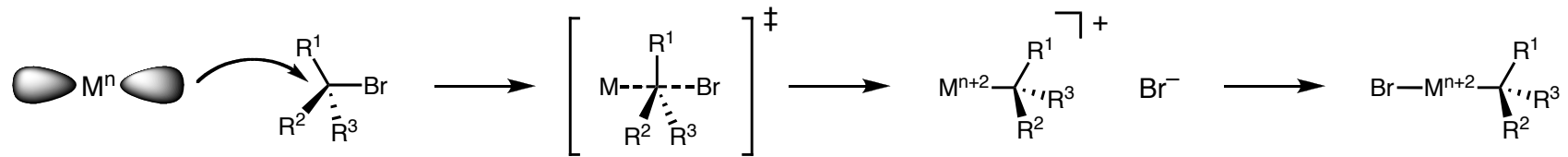
Tsou, T. T.; Kochi, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 6319-6332.

## Stereochemical Consequence of Oxidative Addition Pathways

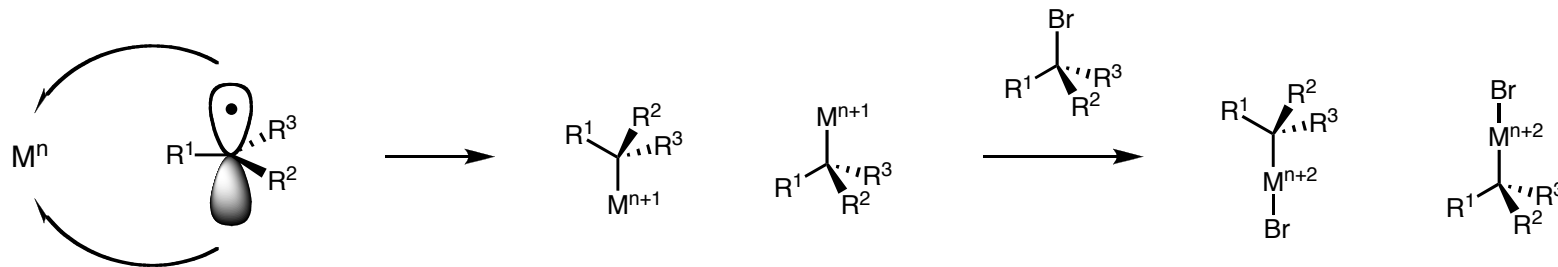
- Concerted pathway: requires retention of configuration



- $S_N2$ -type substitution: requires inversion of configuration

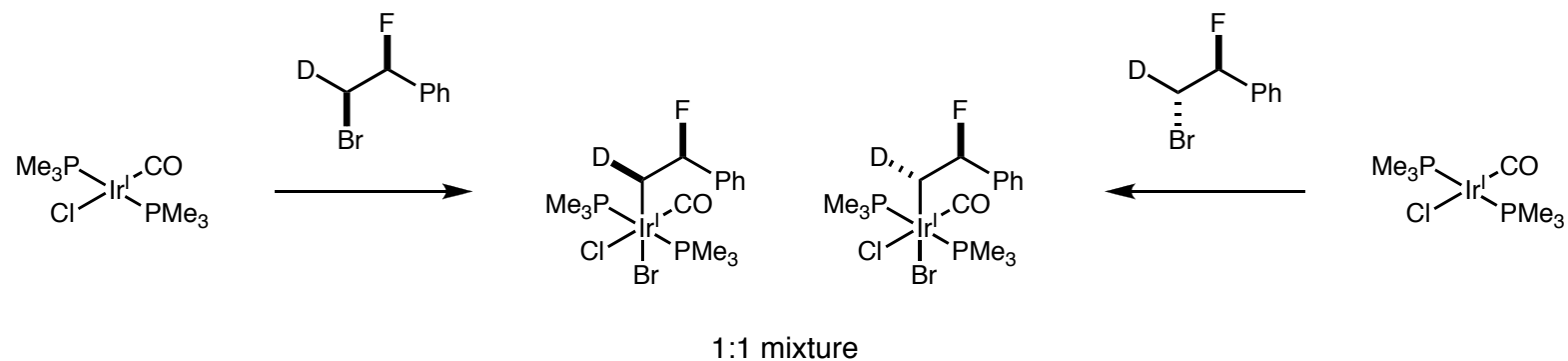


- Radical pathways: likely to proceed with loss of stereochemistry



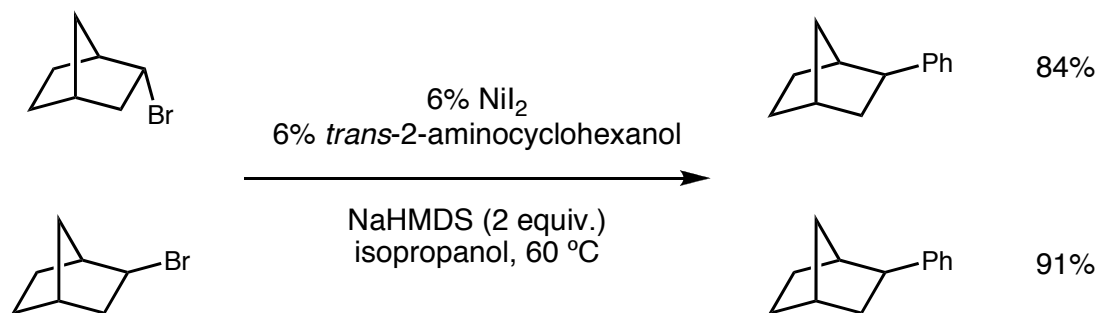
## Stereochemical Consequence of Oxidative Addition Pathways

- Oxidative addition of alkyl halides to an Ir<sup>I</sup> complex proceeds with loss of stereochemistry



Labinger, J. A.; Osborn, J. A. *Inorg. Chem.* **1980**, *19*, 3230-3236.

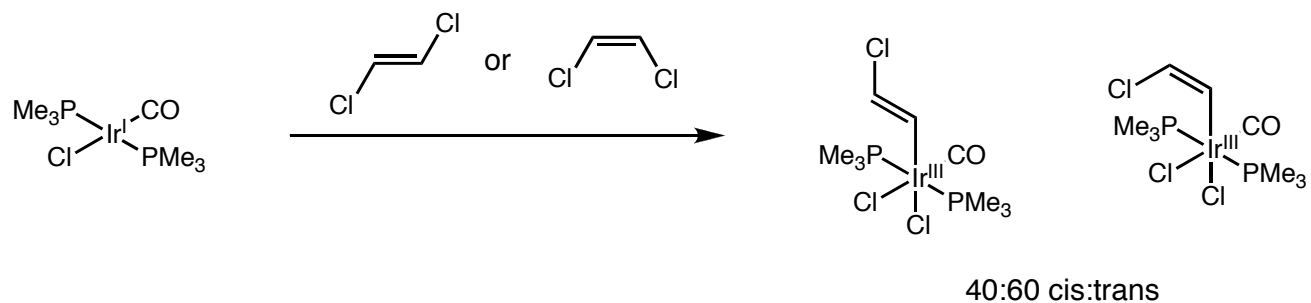
- Cross-coupling of *endo*- and *exo*-2-norbornane leads to the same *exo* product



González-Bobes, F.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 5360-5361.

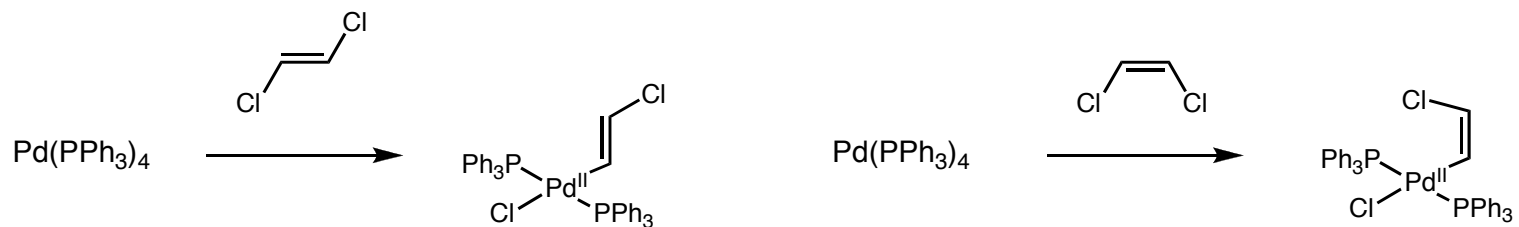
## Evidence for Radical Chain Process

- *Cis*- and *trans*-1,2-dichloroethylene give the same isomeric mixture of oxidative addition product



Labinger, J. A.; Osborn, J. A.; Coville, N. J. *Inorg. Chem.* **1980**, *19*, 3236-3243.

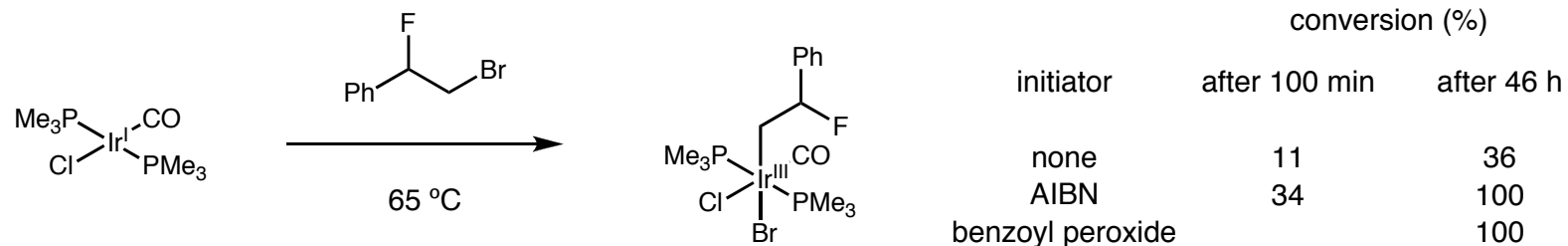
- Complete retention of configuration is observed in the oxidative addition to  $\text{Pd}(\text{PPh}_3)_4$



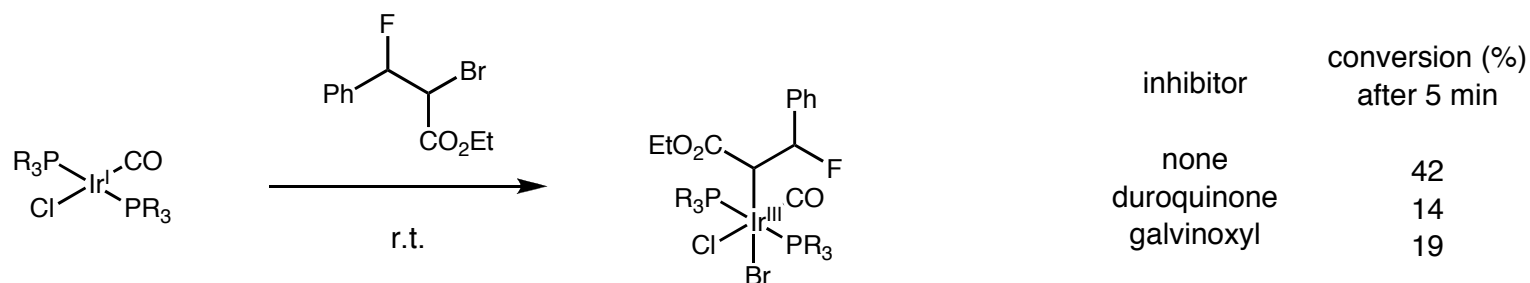
Fitton, P.; McKeon, J. E. *Chem. Commun.* **1968**, 4-6.

## Evidence for Radical Chain Process

- Radical initiators promote the oxidative addition of alkyl halides to Ir<sup>I</sup> complexes

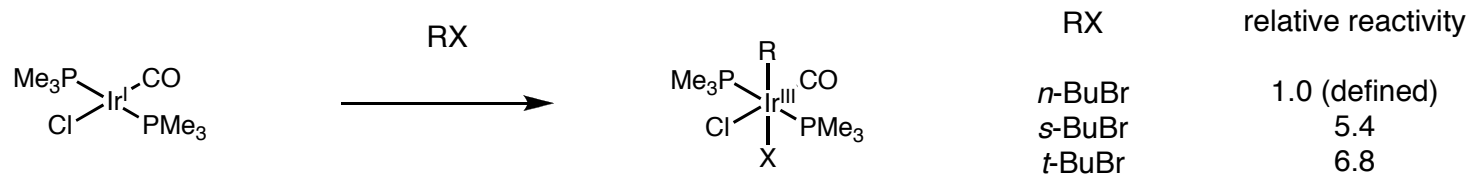


- Radical inhibitors depress the oxidative addition of alkyl halides to Ir<sup>I</sup> complexes

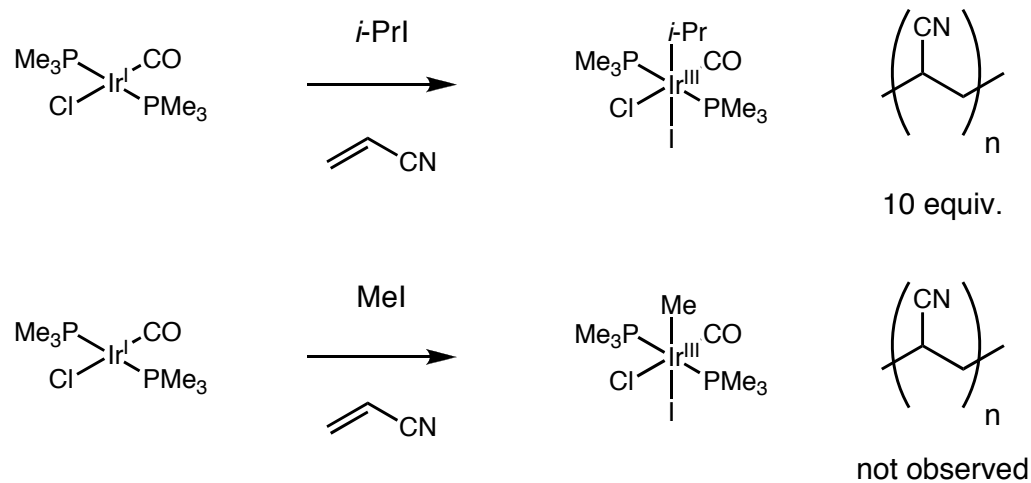


## Evidence for Radical Chain Process

- Rate of reactivity of alkyl halides is consistent with radical process, inconsistent with  $S_N2$



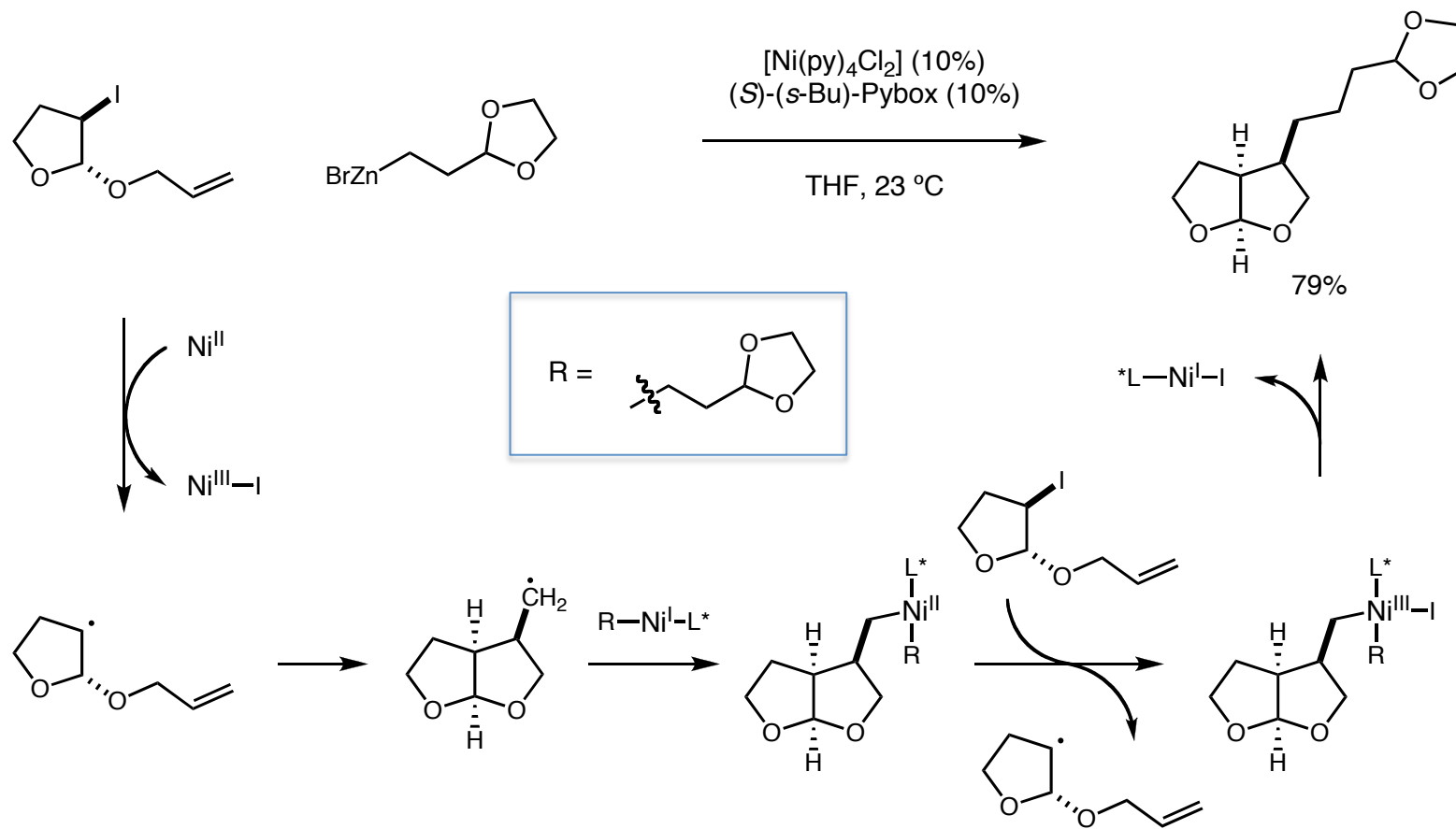
- Trapping of radical intermediates with acrylonitrile





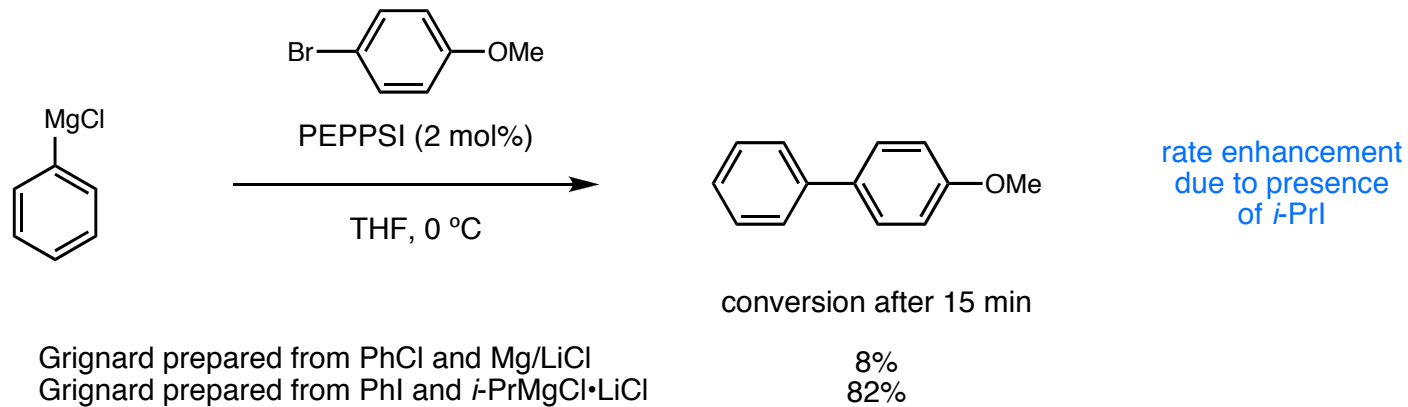
## Radical Cyclizations in Oxidative Addition

- Alkyl iodides bearing tethered alkenes undergo radical cyclization concomitant with oxidative addition

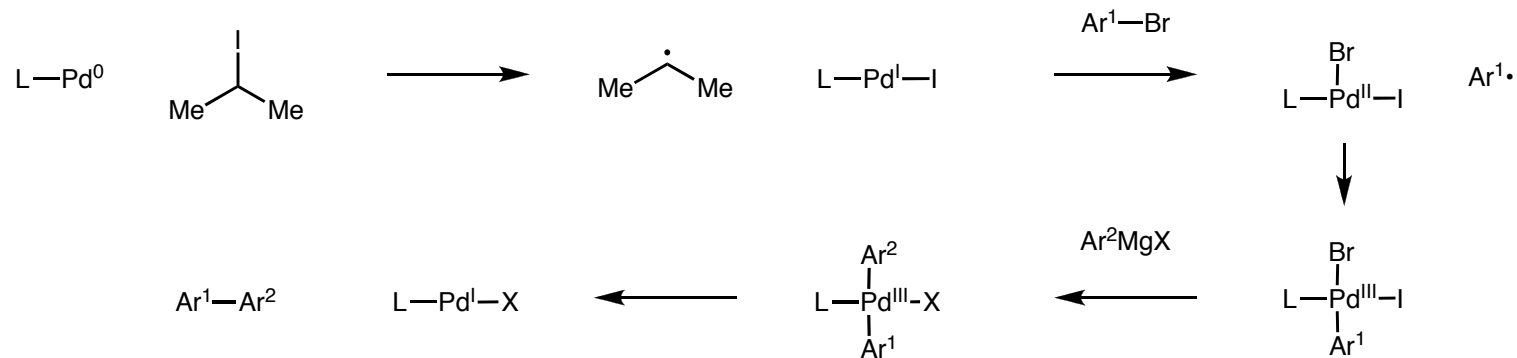


## Alkyl Iodide Accelerated Kumada Couplings

- Isopropyl iodide accelerates the Kumada cross-coupling of aryl Grignard reagents

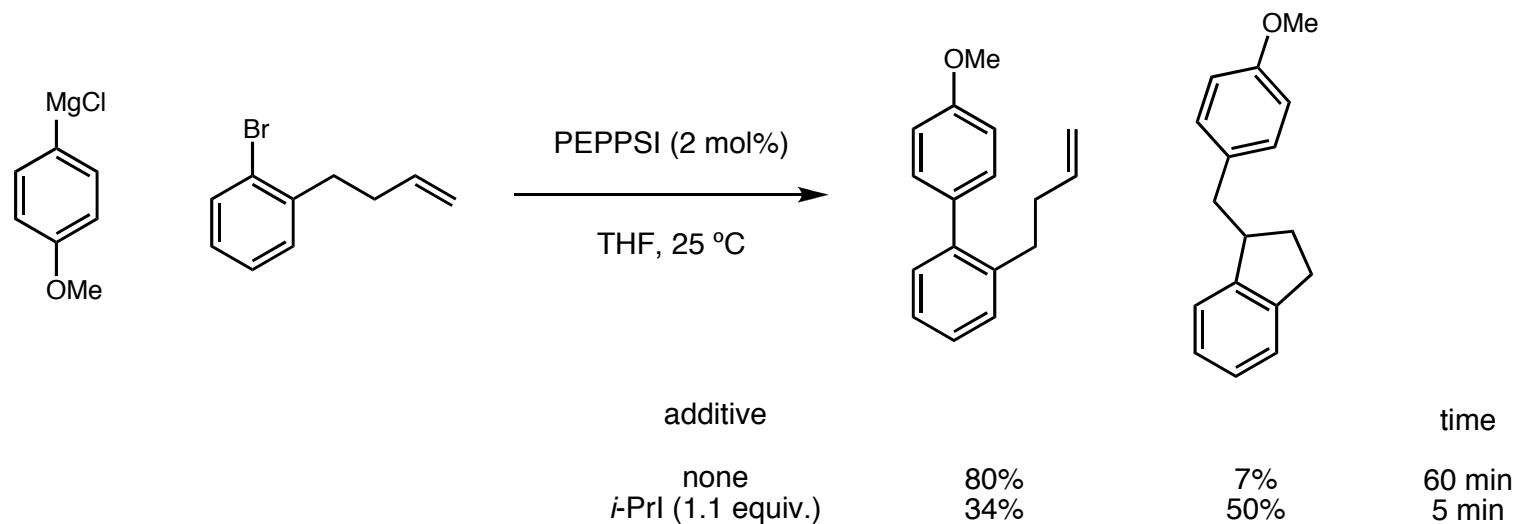


- Rate acceleration arises from initiation of radical pathway by isopropyl iodide

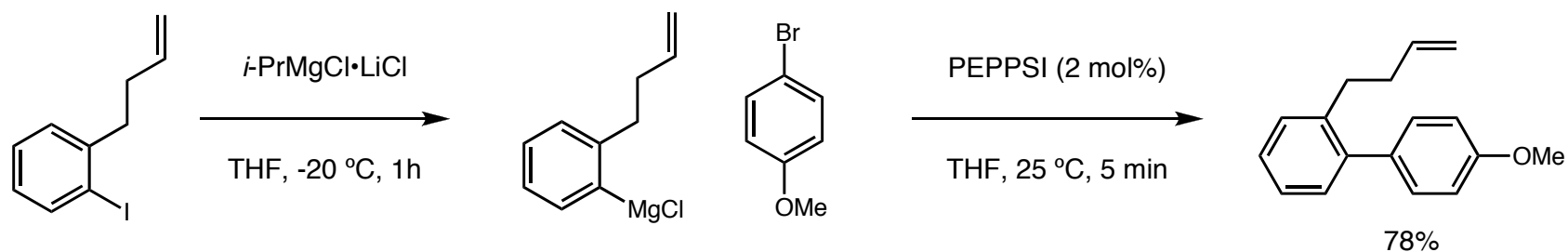


## Radical Cyclizations in the Accelerated Kumada Coupling

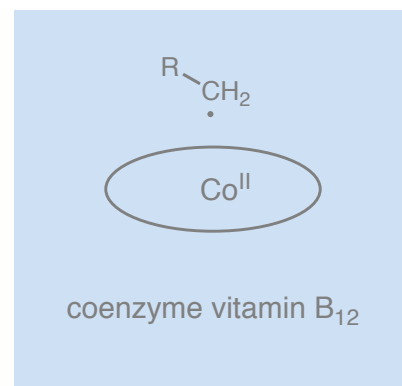
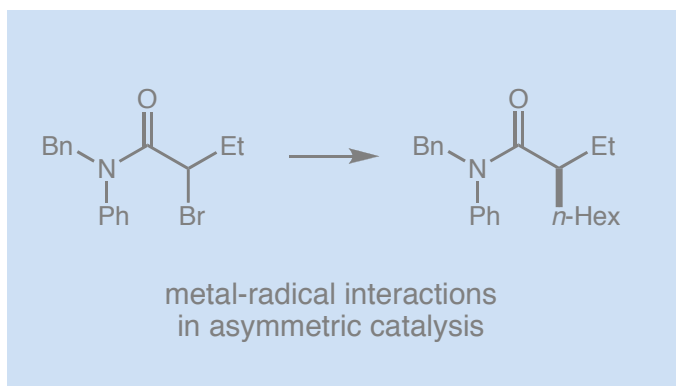
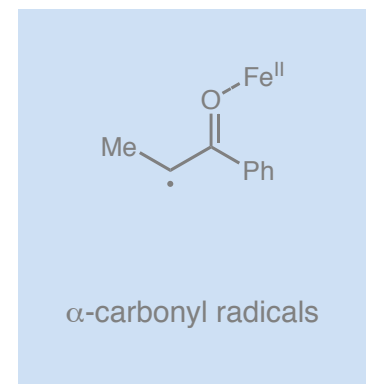
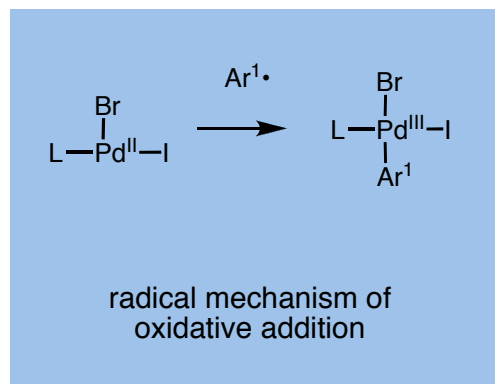
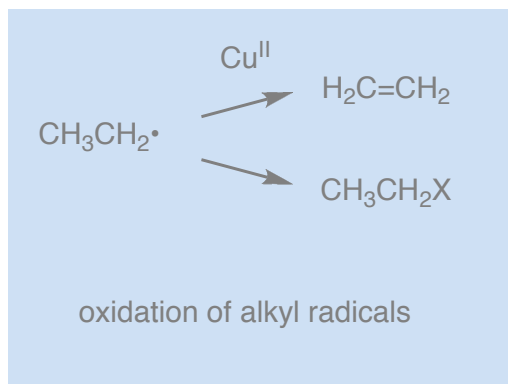
- Aryl halides bearing an alkene tether undergo radical cyclization



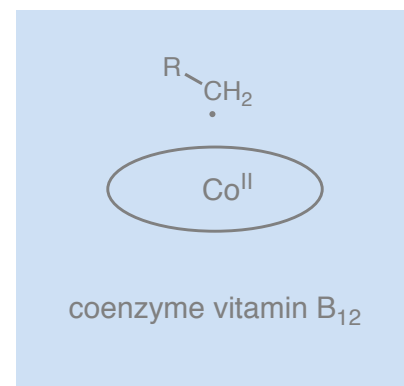
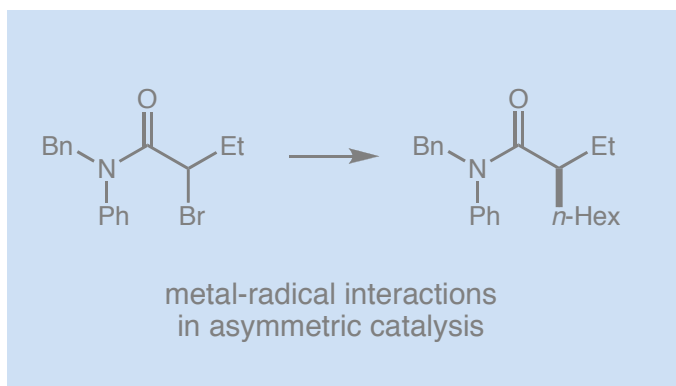
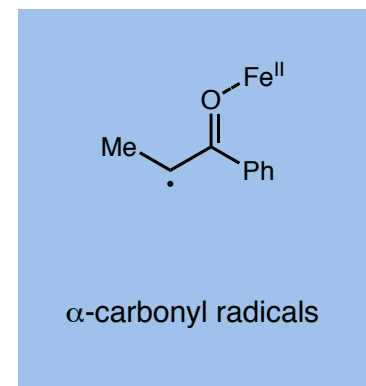
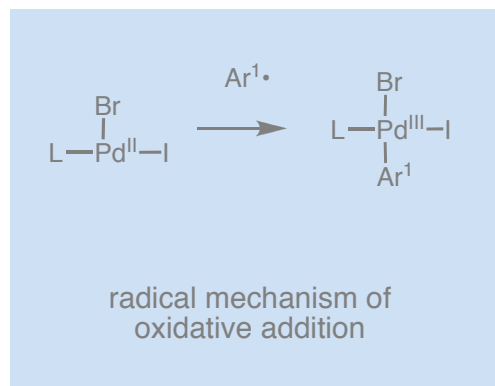
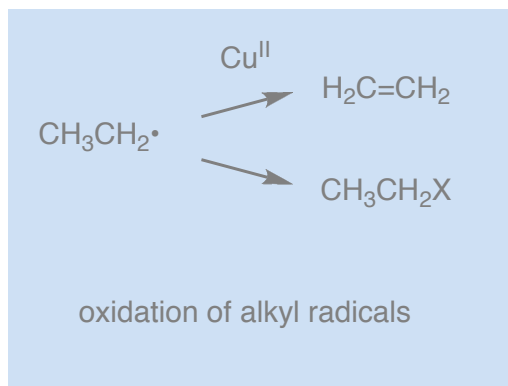
- No cyclized products are observed when the alkene tether is on the Grignard reagent



## Interaction of Organic Radicals with Transition Metals

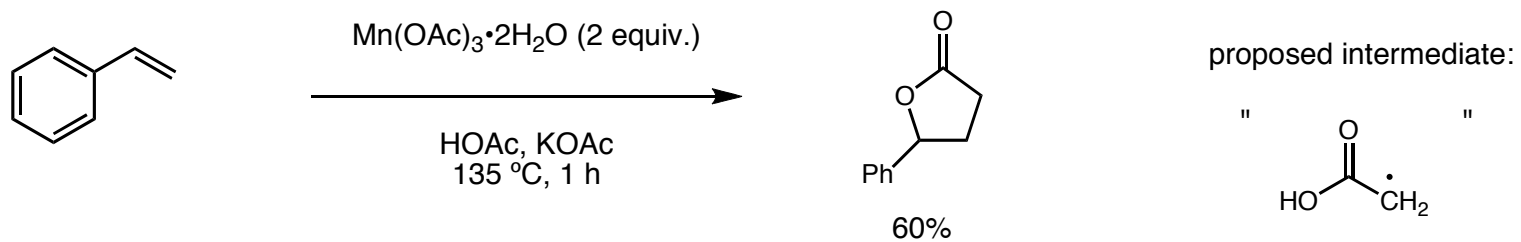


## Interaction of Organic Radicals with Transition Metals



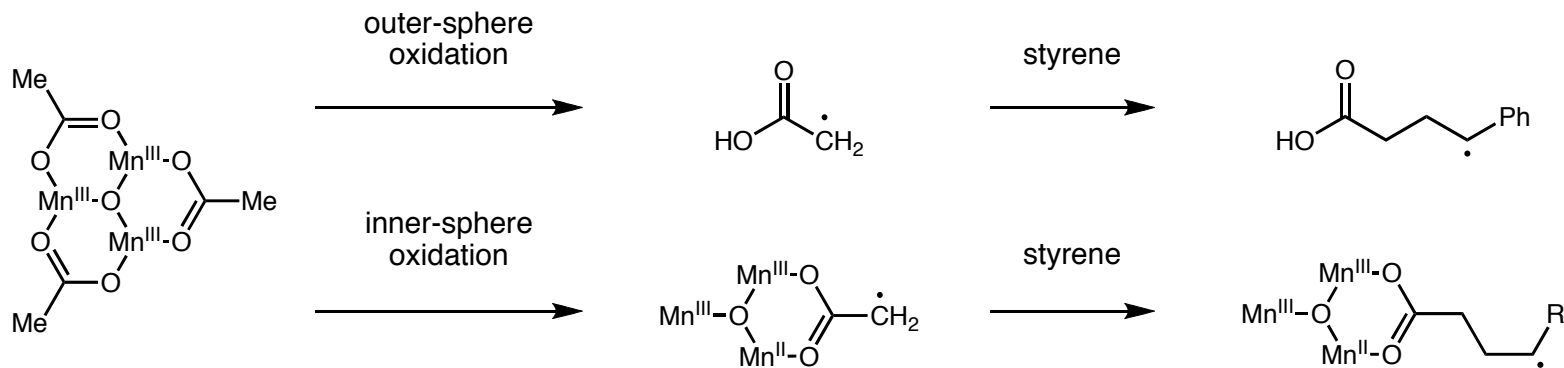
## Oxidative Reactions with Manganese(III) Acetate

### ■ Synthesis of $\gamma$ -lactones by reaction of $\text{Mn}(\text{OAc})_3$ with olefins



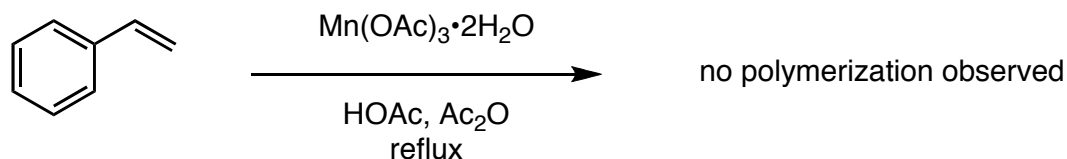
Heiba, E. I.; Dessau, R. M.; Koehl, W. J. *J. Am. Chem. Soc.* **1968**, *90*, 5905-5906.  
Heiba, E. I.; Dessau, R. M.; Rodewald, P. G. *J. Am. Chem. Soc.* **1974**, *96*, 7977-7981.

### ■ Key mechanistic question: Is the species that adds to the olefin a free or metal-complexed radical?



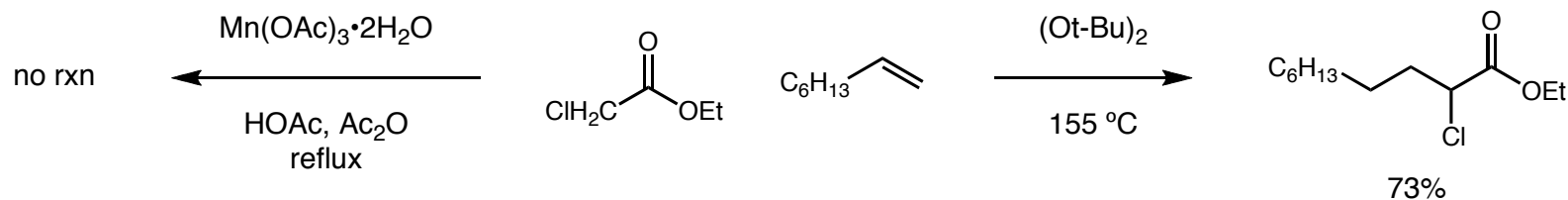
## Evidence Against Intermediacy of Discrete Radicals

### ■ No polymerization of styrene observed



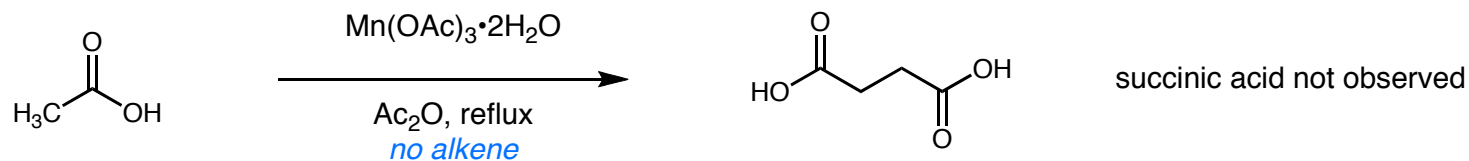
Bush, J. B., Jr.; Finkbeiner, H. J. *J. Am. Chem. Soc.* **1968**, *90*, 5903-5905.

### ■ Acetate esters add to olefins upon initiation with (Ot-Bu)<sub>2</sub>, but not Mn(OAc)<sub>3</sub>·2H<sub>2</sub>O



Bush, J. B., Jr.; Finkbeiner, H. J. *J. Am. Chem. Soc.* **1968**, *90*, 5903-5905.  
Allen, J. C.; Cadogan, J. I. G.; Hey, D. H. *J. Chem. Soc.* **1965**, 1918-1932.

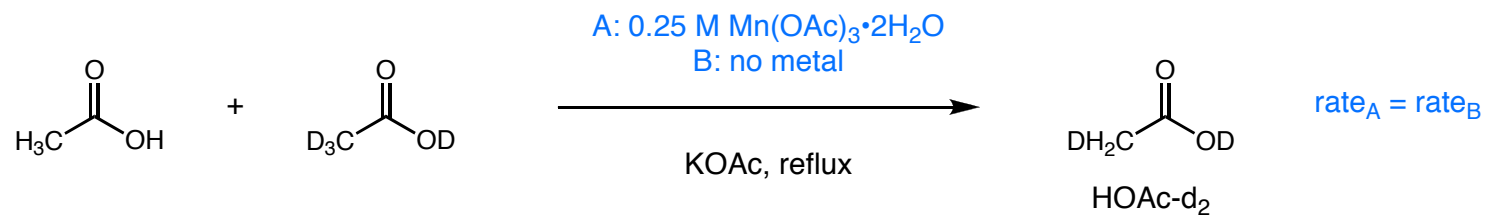
### ■ No dimerization of acetic acid radicals observed



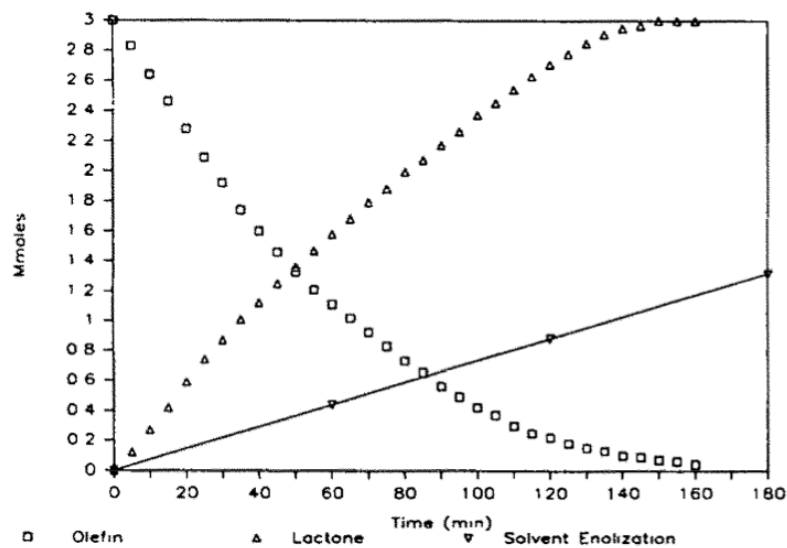
Fristad, W. E.; Peterson, J. R.; Ernst, A. B.; Urbi, G. B. *Tetrahedron.* **1986**, *42*, 3429-3442.

## Evidence for Metal-Complexed Radical

- H/D exchange experiments show no rate dependence on the metal



- $\gamma$ -lactone formation exceeds total solution H/D exchange

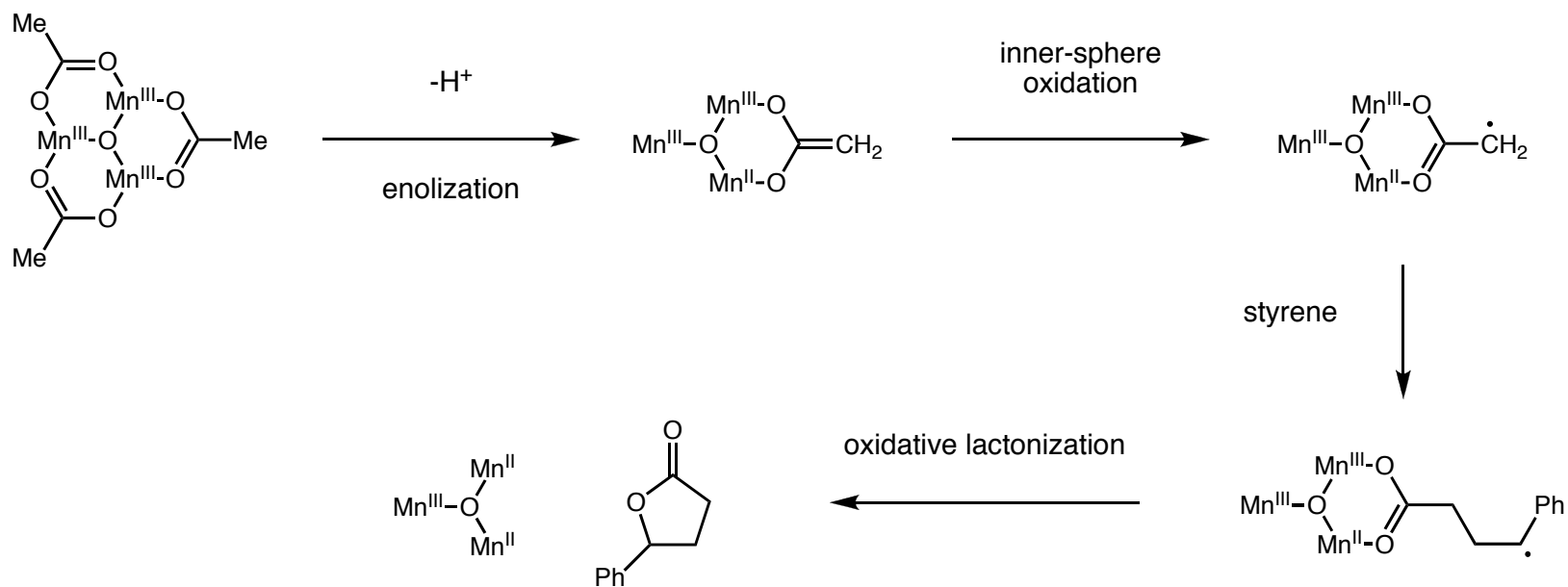


- Results are only consistent with rate-determining enolization of complexed acetate



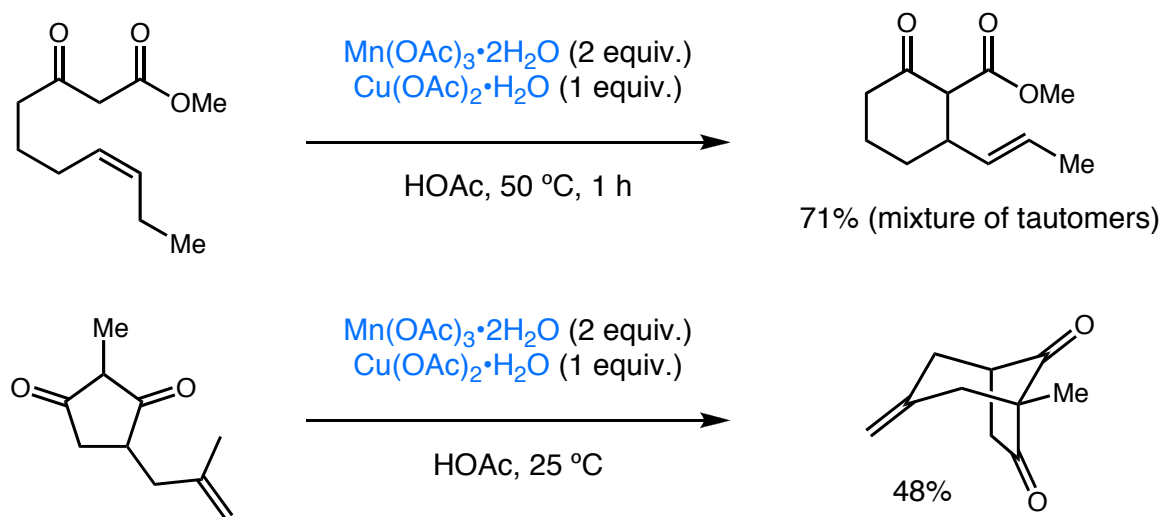
## Consensus Mechanism of Manganese(III) Acetate Oxidation

- Rate-determining enolization followed by single-electron oxidation generates metal-bound radical

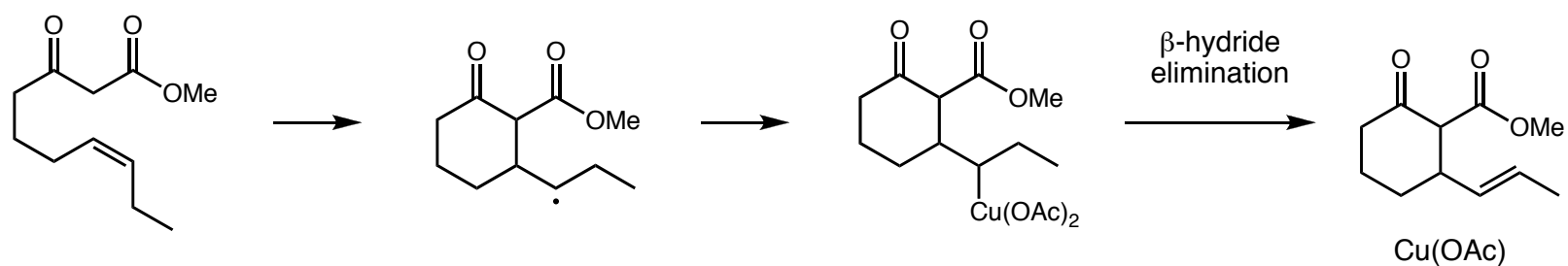


## Oxidative Cyclization of $\beta$ -Dicarbonyls

- $\text{Mn}(\text{OAc})_3$  initiates radical cyclizations of  $\beta$ -keto esters and 1,3-diketones

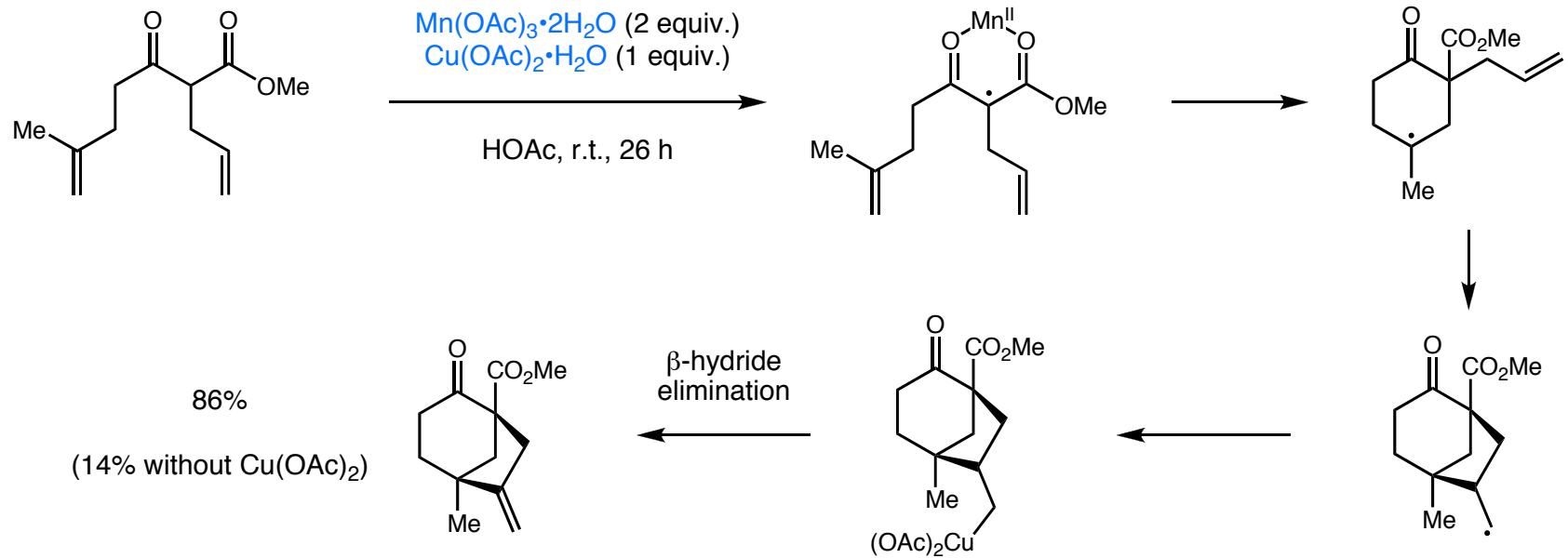


- $\text{Cu}(\text{OAc})_2$  is used to oxidize the alkyl radical to the alkene

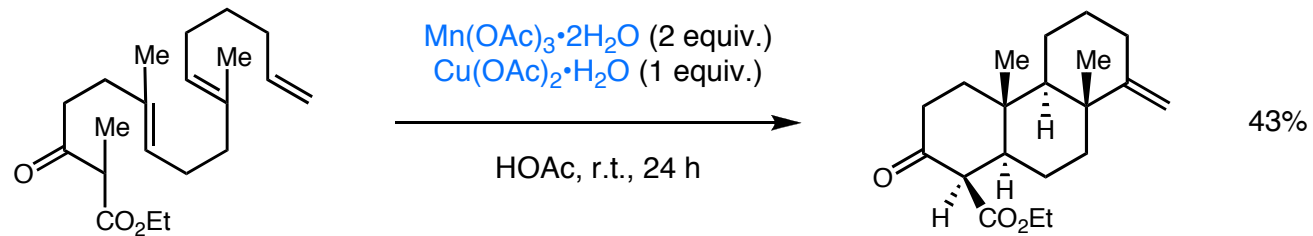


## Oxidative Radical Cascade Cyclizations

■  $\text{Mn}(\text{OAc})_3$  can initiate radical cascade cyclizations



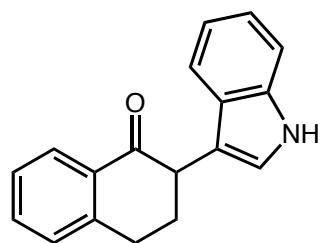
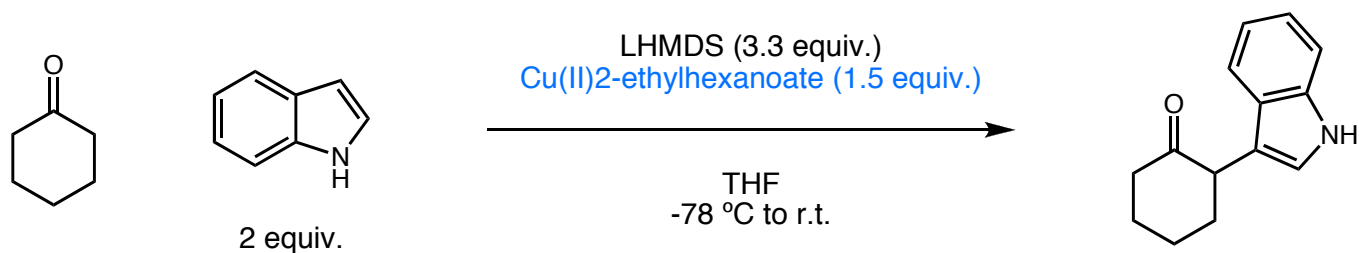
Dombroski, M. A.; Kates, S. A.; Snider, B. B. *J. Am. Chem. Soc.* **1990**, *112*, 2759-2767.



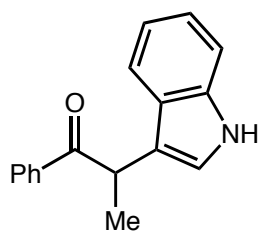
Zoretic, P. A.; Shen, Z.; Wang, M.; Riberio, A. A. *Tetrahedron Lett.* **1995**, *36*, 2925-2928.

## Indole Coupling via $\alpha$ -Carbonyl Radicals

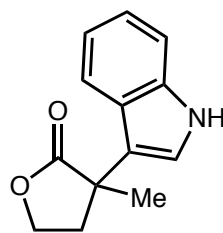
### ■ Baran's Cu(II)-mediated indole-carbonyl coupling



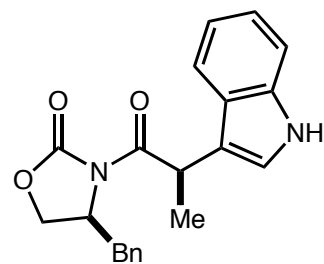
43%



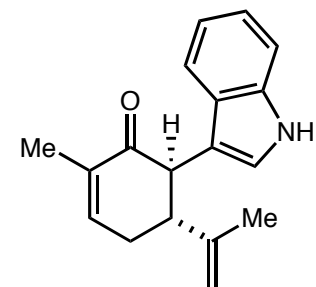
30%



51%



54%, 5:1 d.r.

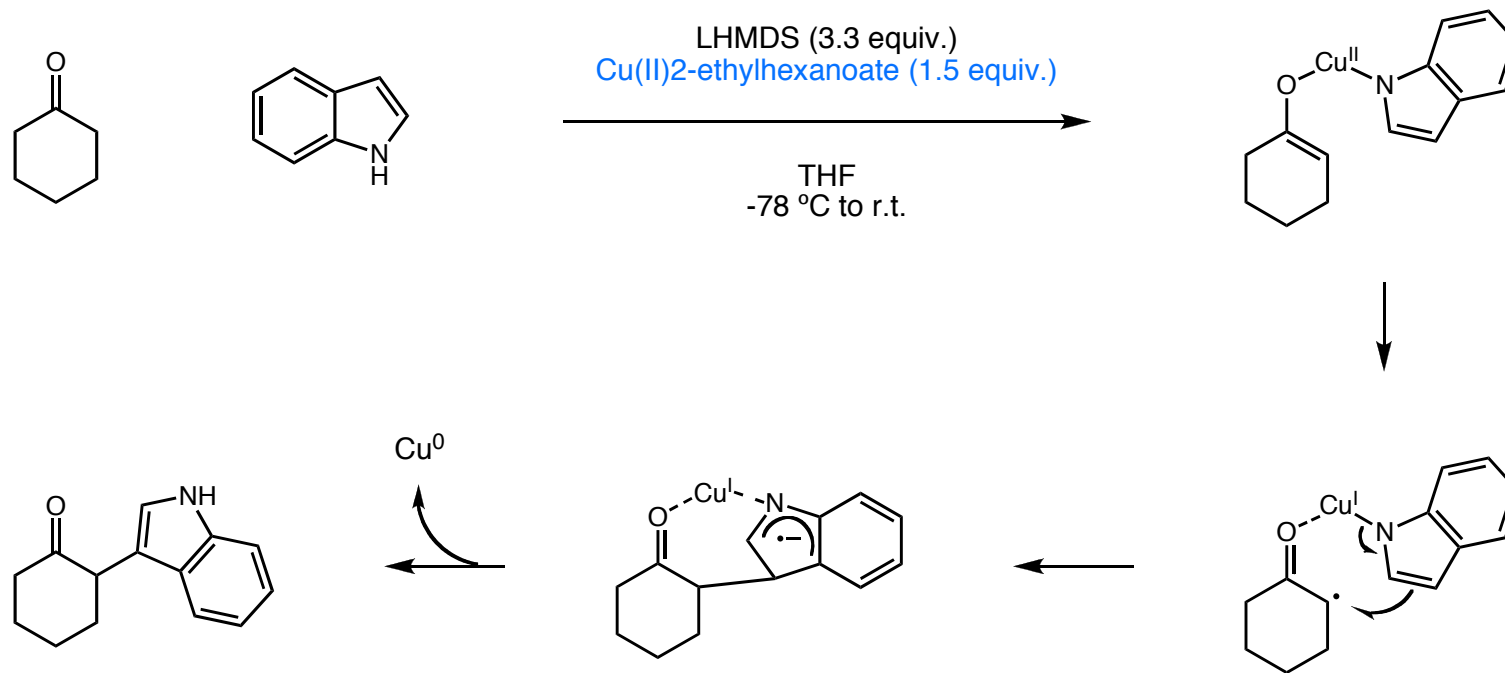


53%, single diastereomer  
(5 equiv. indole: 77%)

Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450-7451.  
Baran, P. S.; Richter, J. M.; Lin, D. W. *Angew. Chem. Int. Ed.* **2005**, *44*, 609-612.  
Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857-12869.

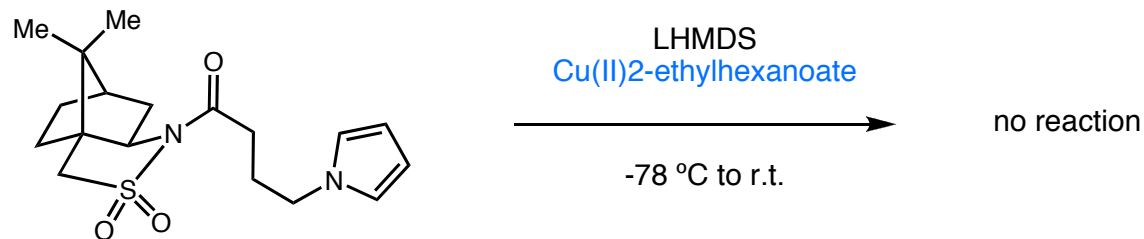
## Proposed Mechanism of Indole-Carbonyl Coupling

- Oxidation of enolate to  $\alpha$ -keto radical enables coupling with copper-coordinated indole

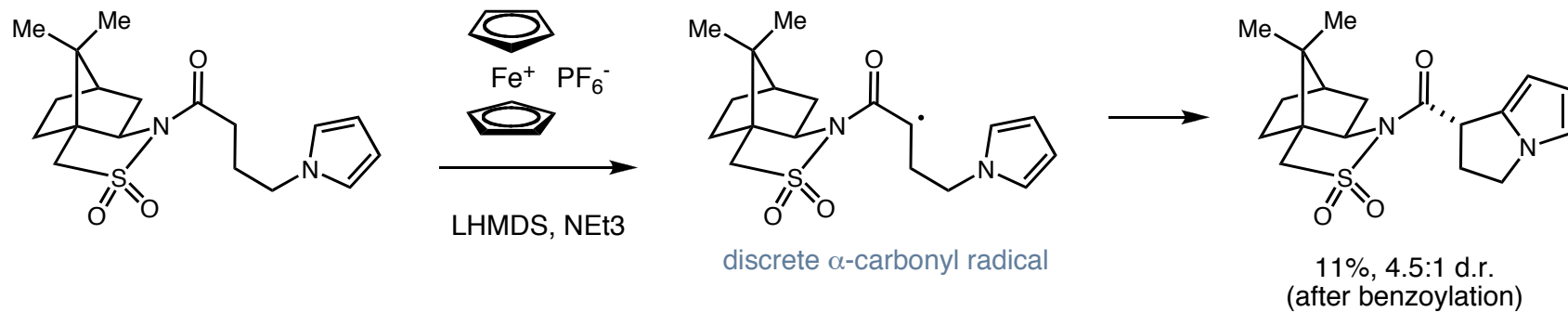


## Evidence for Electron Transfer via Copper Enolate

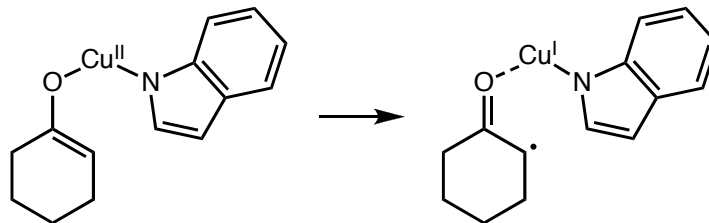
- Free N-H is required for reactivity under copper conditions



- Reaction proceeds with a known outer-sphere oxidant

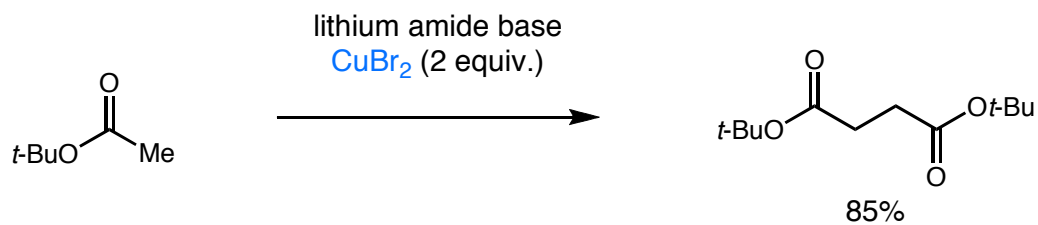


*implicates inner-sphere oxidation via indole-bound copper enolate:*

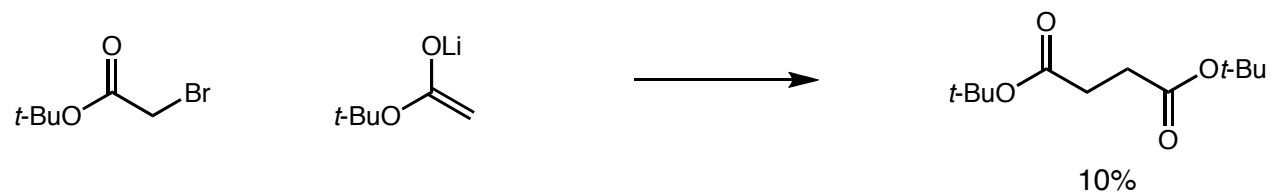


## Oxidative Enolate Coupling

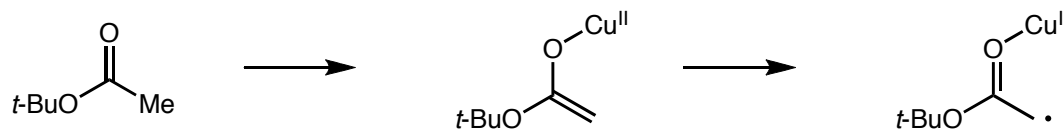
- Enables the synthesis of 1,4-dicarbonyl compounds via  $\alpha$ -carbonyl radicals



- Reaction does not proceed via formation of the  $\alpha$ -bromoester

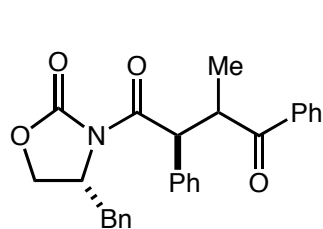
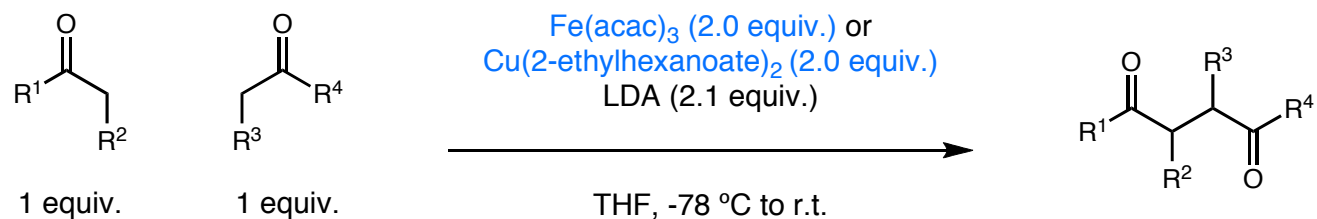


- Proposed to proceed via single-electron oxidation of enolate to  $\alpha$ -carbonyl radical

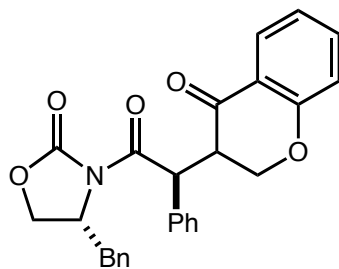


## Oxidative Enolate Coupling

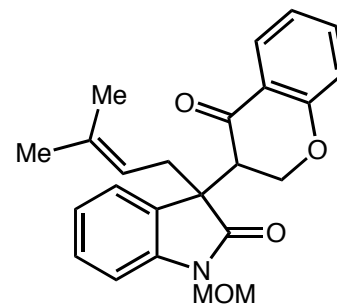
- Heterocoupling can be achieved in the coupling of imides or amides with ketones or esters



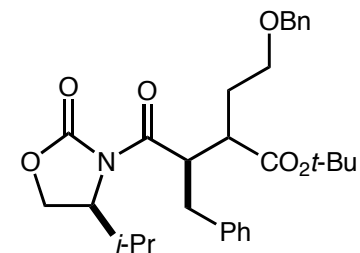
Fe(III): 57%, 1.8:1 d.r.  
Cu(II): 55%, 1:1.6 d.r.



Fe(III): 60%, 2.6:1 d.r.



Fe(III): 73%, 2:1 d.r.

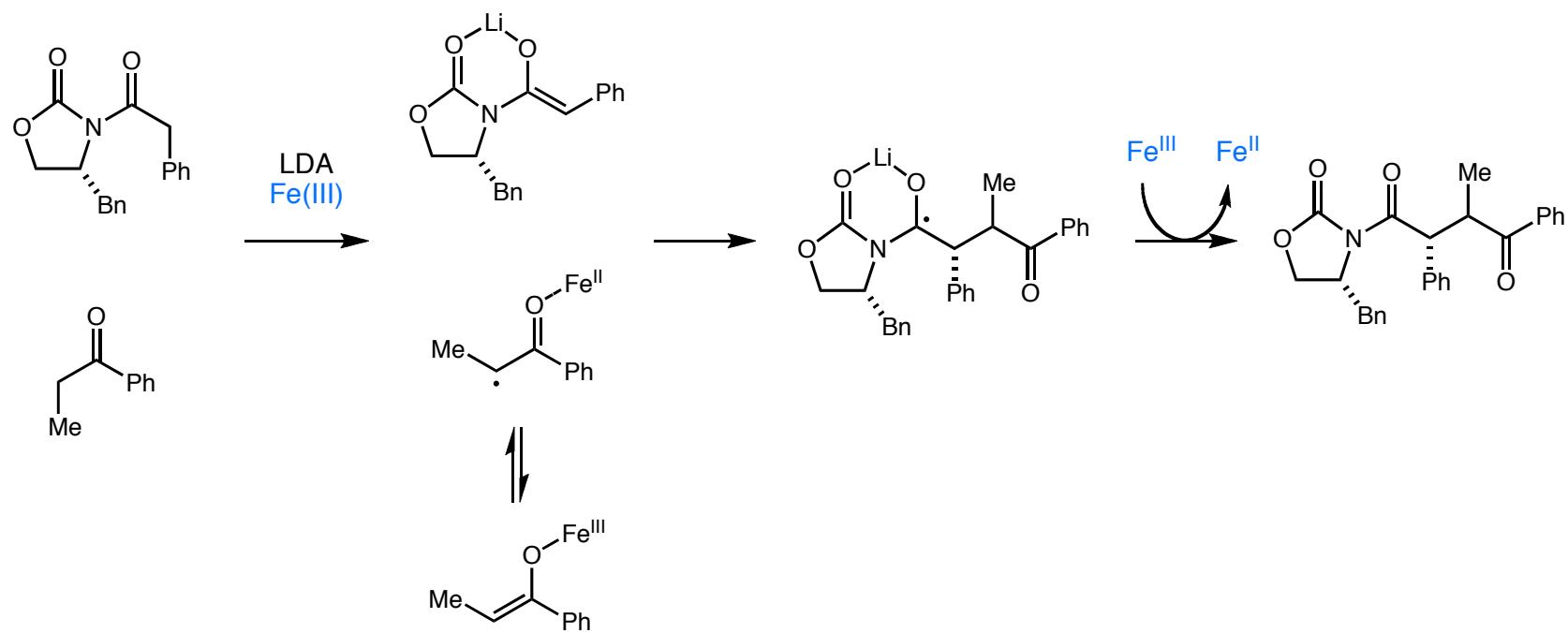


Cu(II): 62%, 1.2:1 d.r.  
(1.75 equiv. ester)



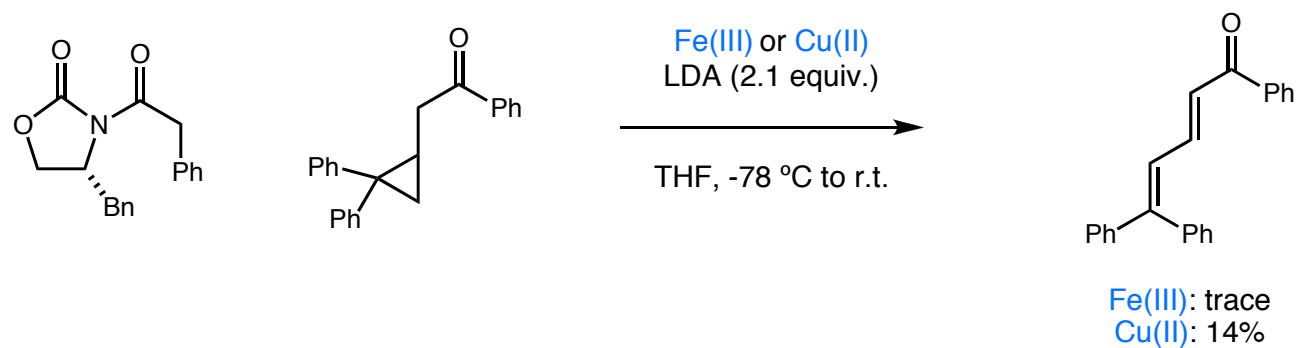
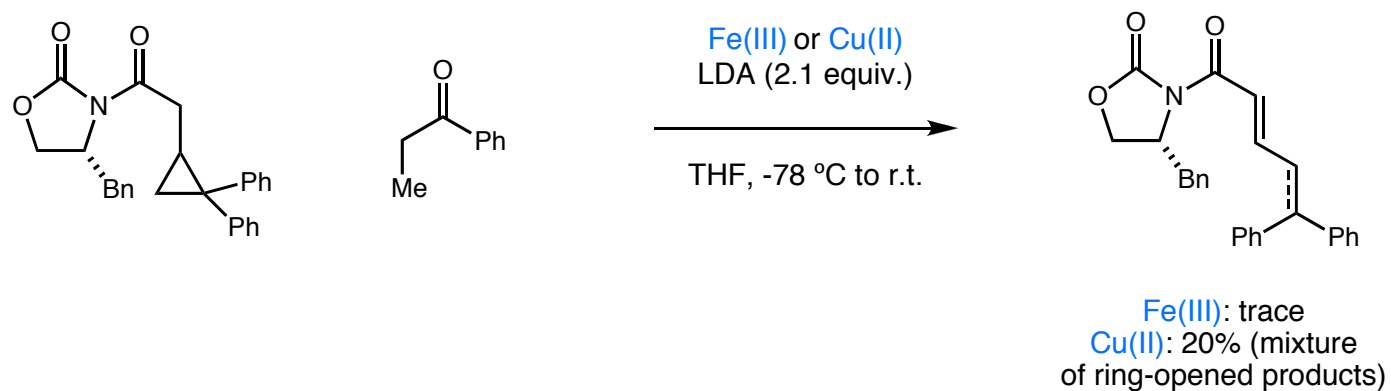
## Proposed Mechanism of Oxidative Enolate Coupling

- Formation of ketone-iron enolate followed by single-electron oxidation furnishes  $\alpha$ -carbonyl radical



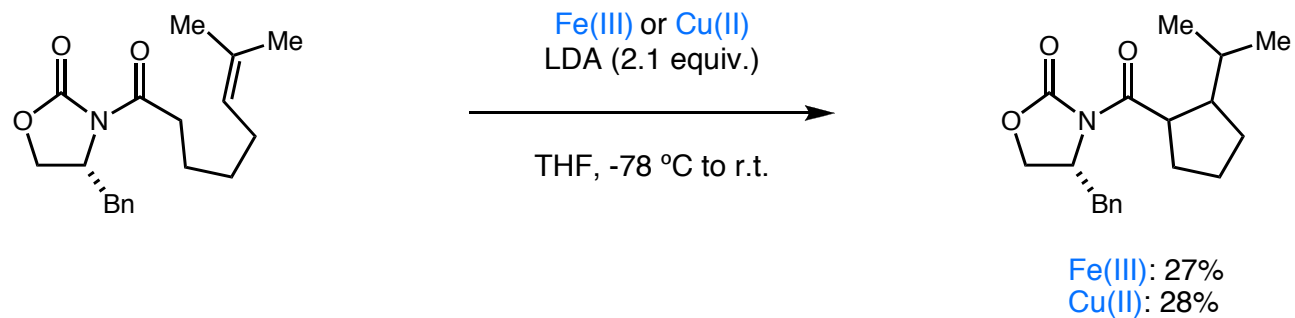
## Mechanism of Oxidative Enolate Coupling

- Fe(III) and Cu(II) show divergent reactivity in cyclopropane radical clock studies



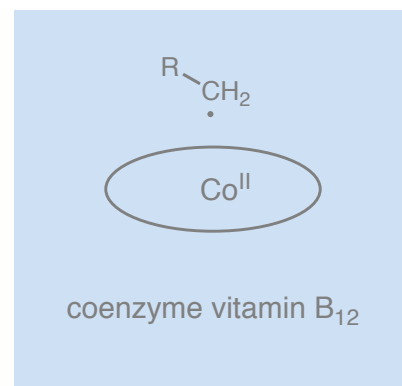
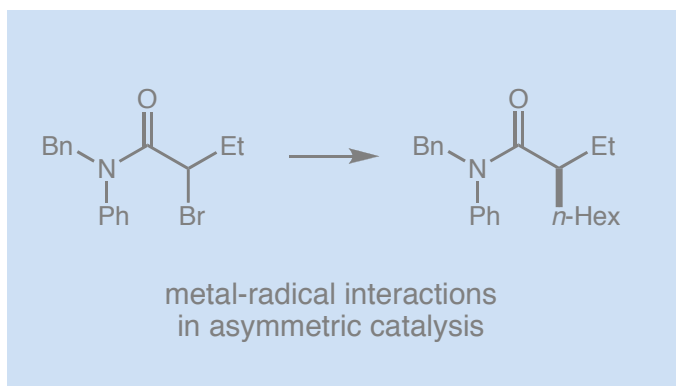
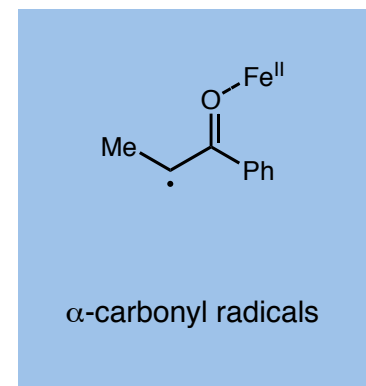
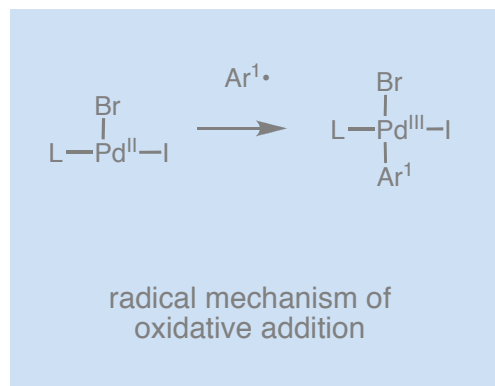
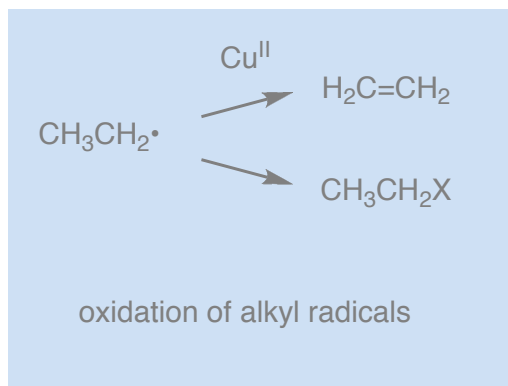
## Mechanism of Oxidative Enolate Coupling

- Fe(III) and Cu(II) promote cyclization with tethered olefins

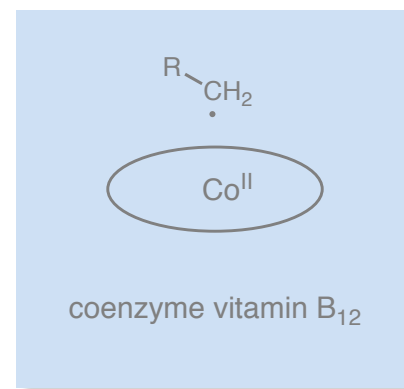
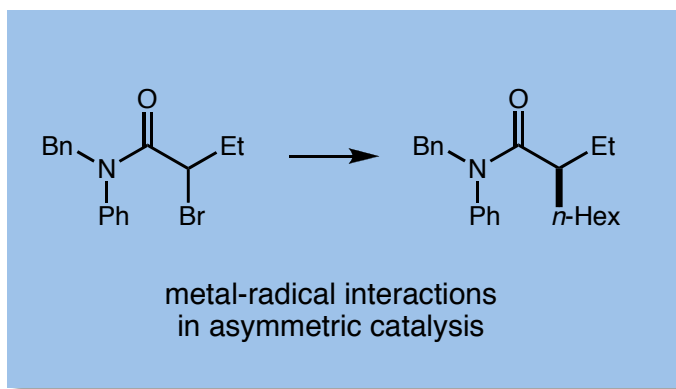
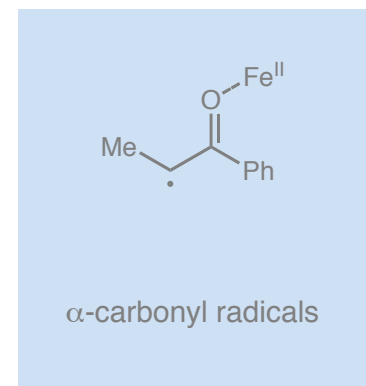
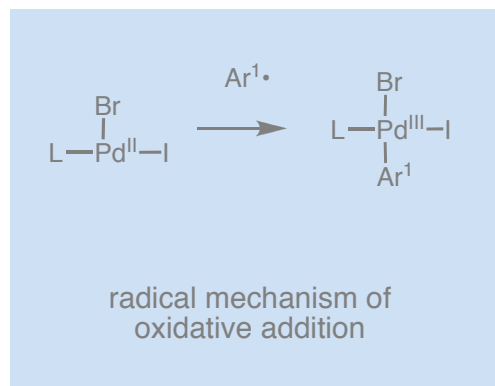
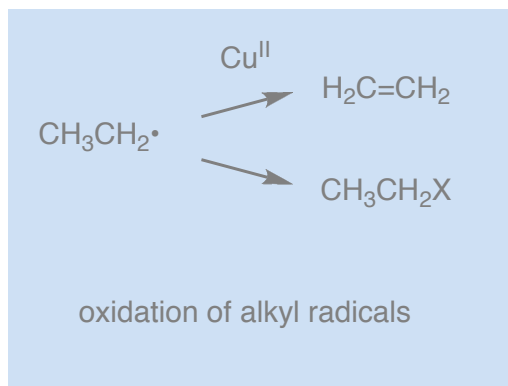


DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546-11560.

## Interaction of Organic Radicals with Transition Metals

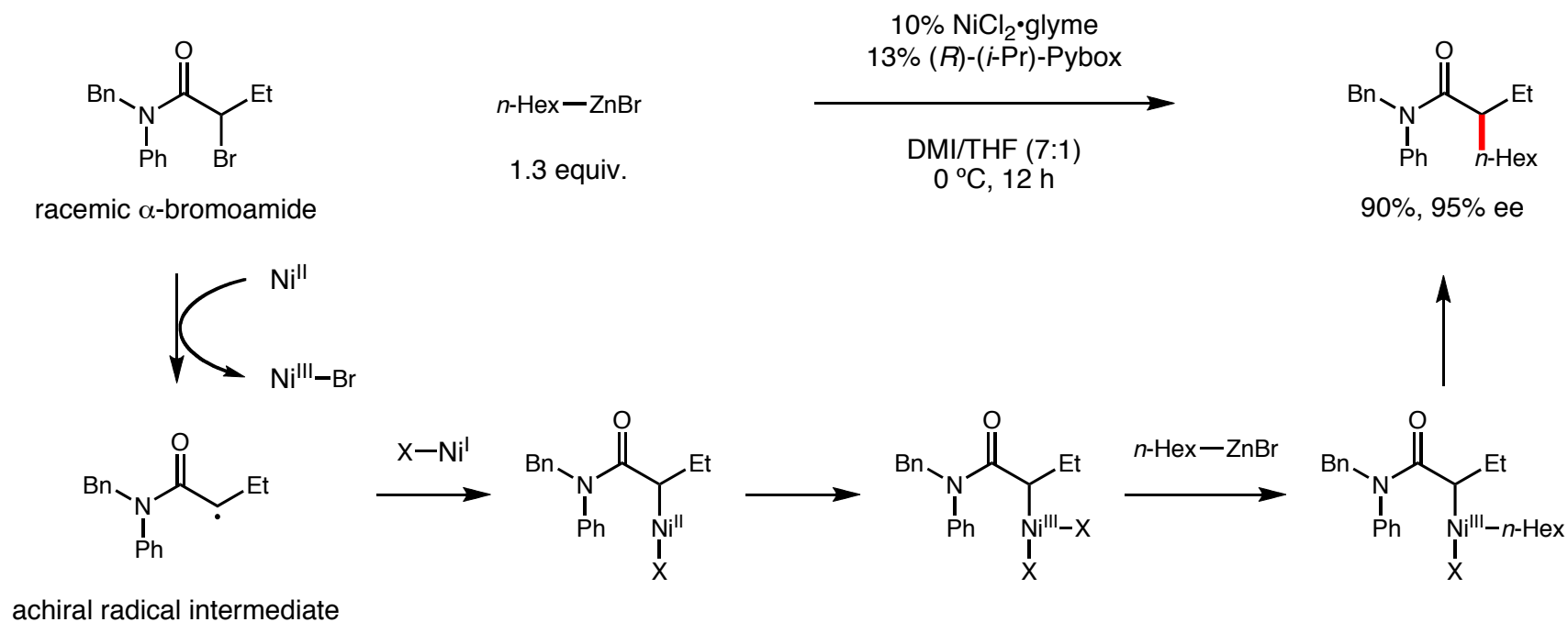


## Interaction of Organic Radicals with Transition Metals



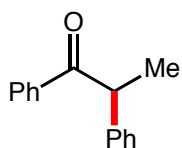
## Asymmetric Negishi Coupling of $\alpha$ -Bromoamides

- Racemic starting material is converted to single enantiomer product via radical intermediate



## Asymmetric Cross Coupling of Alkyl Halides

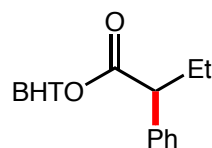
- Wide range of asymmetric cross couplings of racemic secondary alkyl halides has been developed



81%, 92%

$\alpha$ -bromoketones

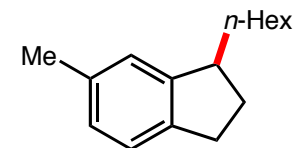
*Angew. Chem. Int. Ed.* **2009**, 48, 154-156.  
*J. Am. Chem. Soc.* **2010**, 132, 1264-1266.



80%, 99% ee

$\alpha$ -bromoesters

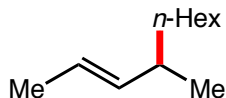
*J. Am. Chem. Soc.* **2008**, 130, 3302-3303.



89%, 96% ee

secondary benzylic halides

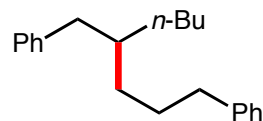
*J. Am. Chem. Soc.* **2005**, 127, 10482-10483.



95%, 87% ee

secondary allylic chlorides

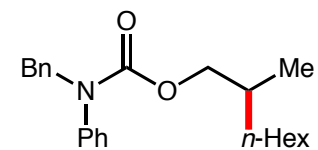
*J. Am. Chem. Soc.* **2008**, 130, 2756-2757.



84%, 94% ee

homobenzylic halides

*J. Am. Chem. Soc.* **2008**, 130, 6694-6695.



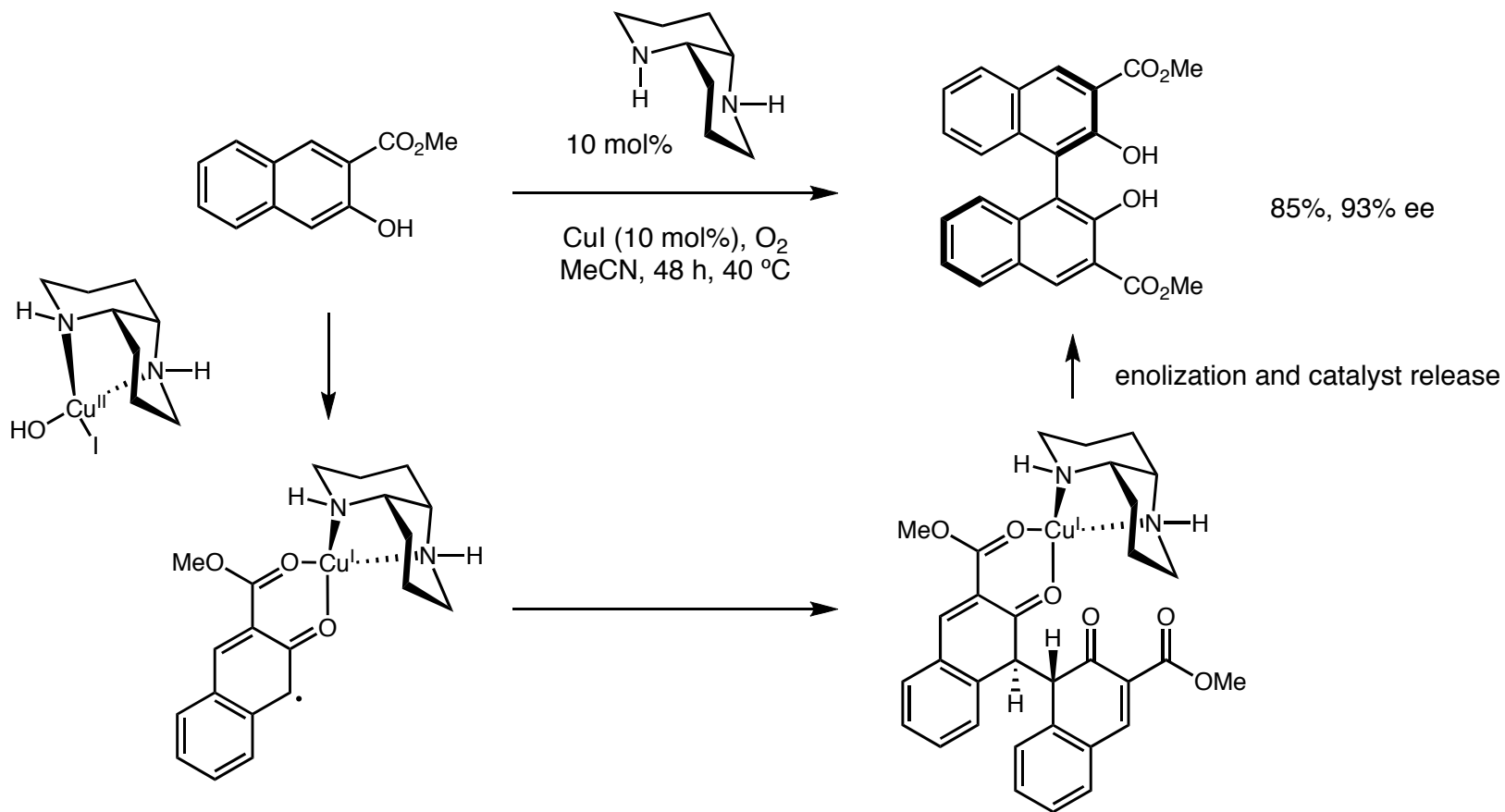
80%, 94% ee

acylated halohydrins

*J. Am. Chem. Soc.* **2010**, 132, 11908-11909.

## Enantioselective Oxidative Biaryl Coupling

- A copper/chiral diamine catalyst controls the dimerization of 2-naphthol derivatives

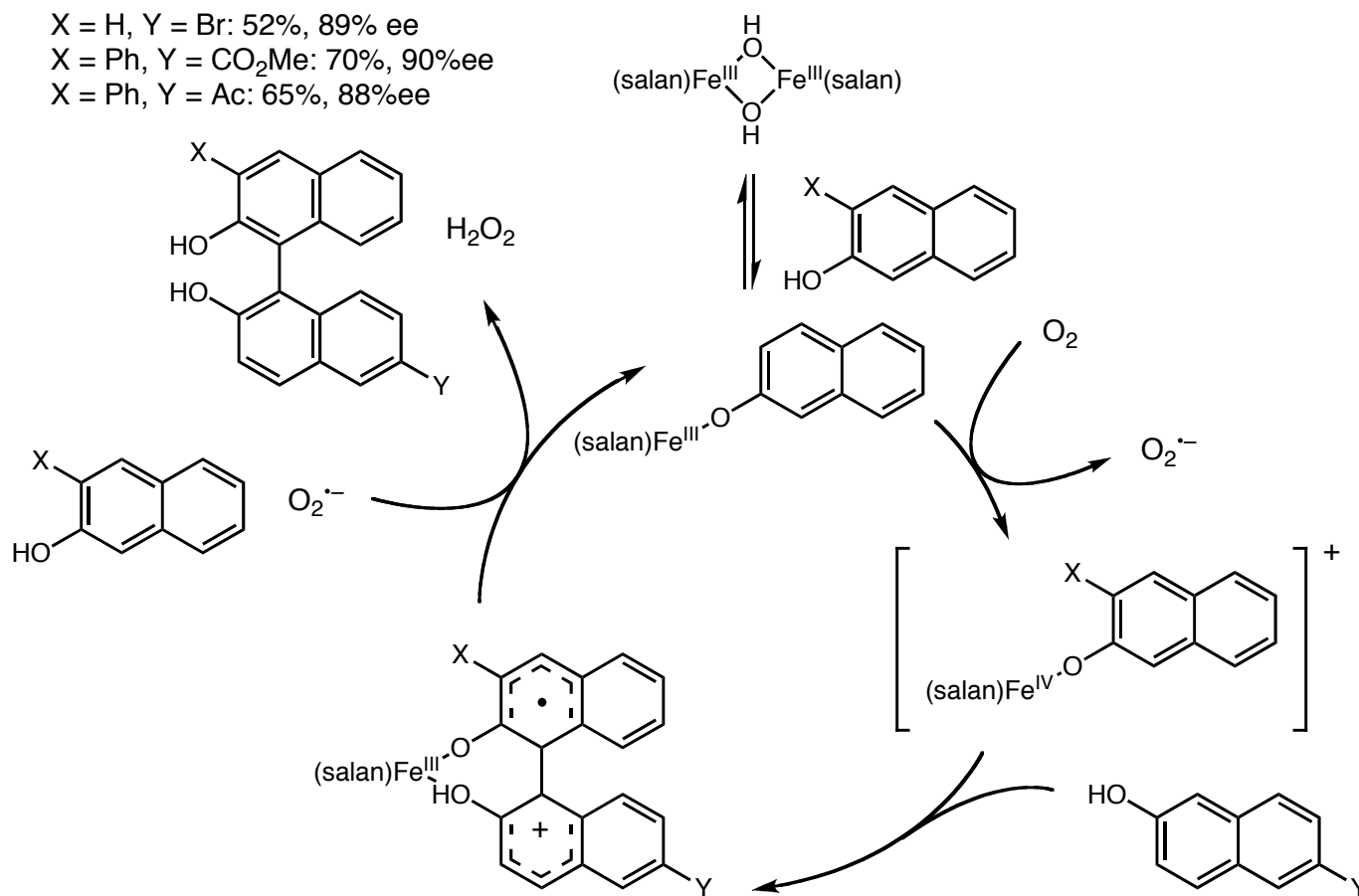


Li, X.; Yang, J.; Kozlowski, M. C. *Org. Lett.* **2001**, *3*, 1137-1140.  
Hewgley, J. B.; Stahl, S. S.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 12232-12233.



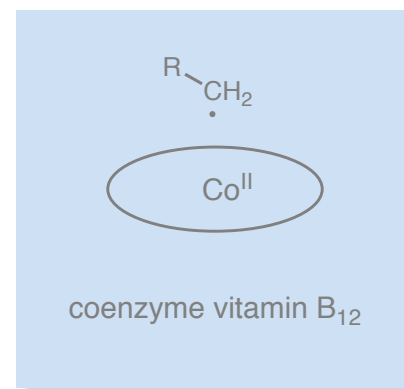
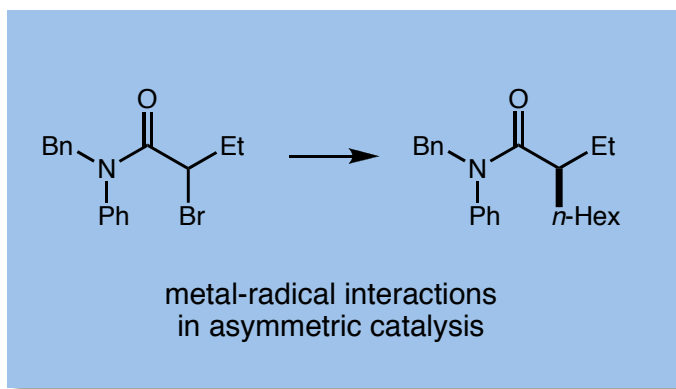
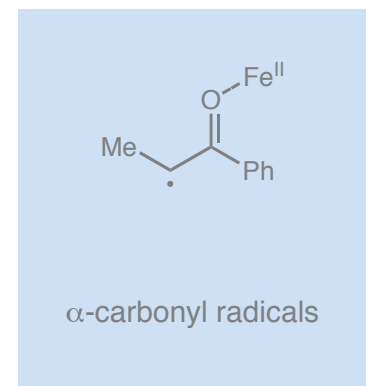
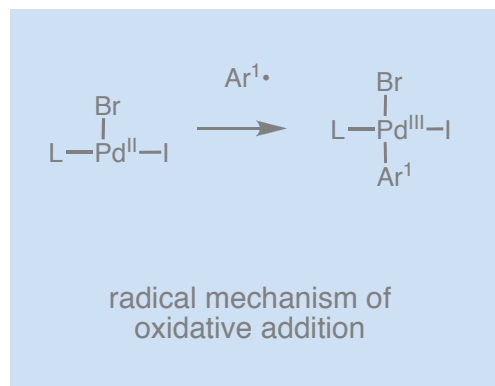
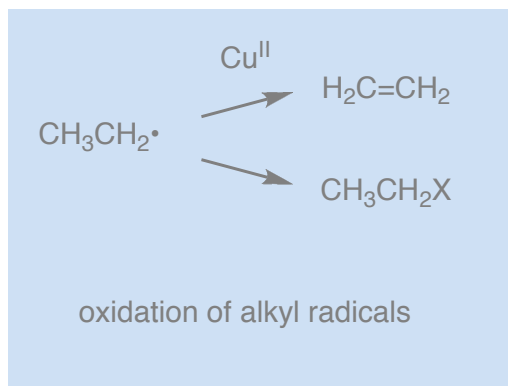
## Enantioselective Oxidative Biaryl Coupling

### Iron(salan)-catalyzed process enables oxidative biaryl heterocoupling

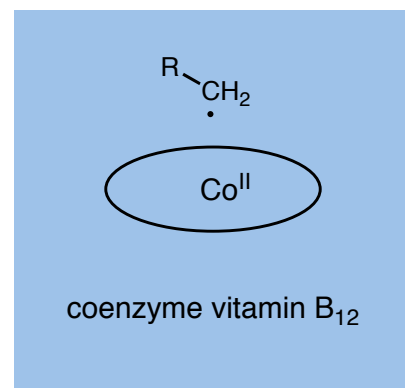
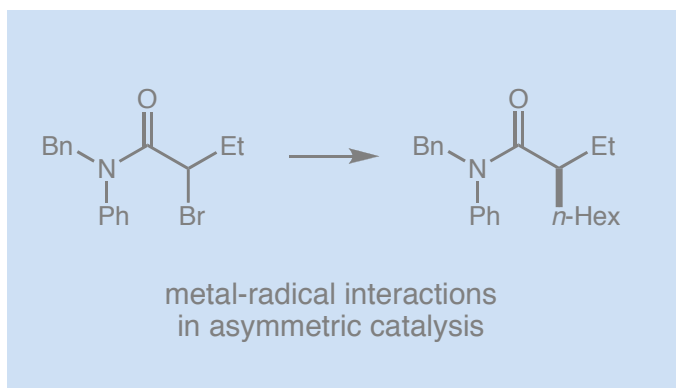
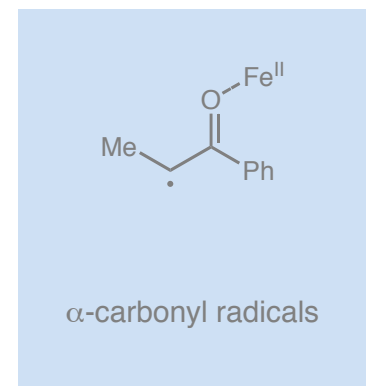
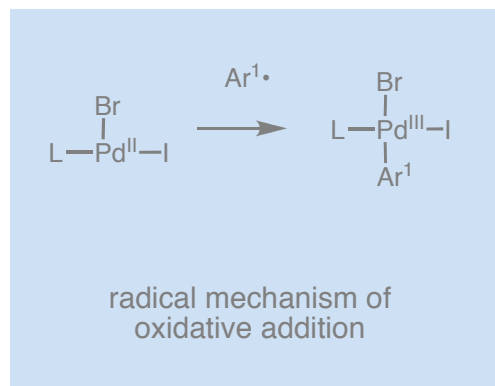
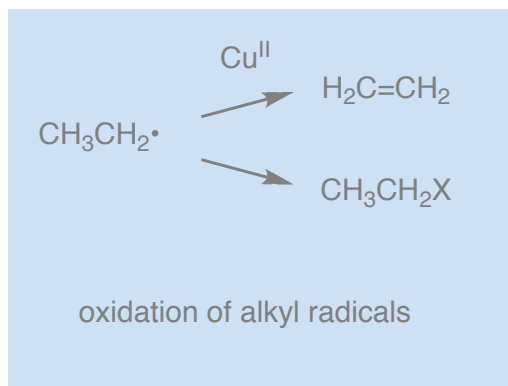


Egami, H.; Matsumoto, K.; Oguma, T.; Kunisu, T.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *132*, 13633-13635.

## Interaction of Organic Radicals with Transition Metals

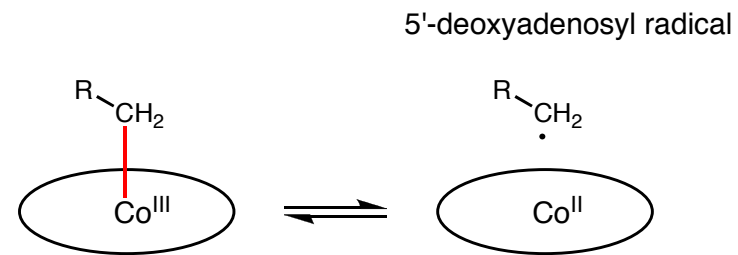
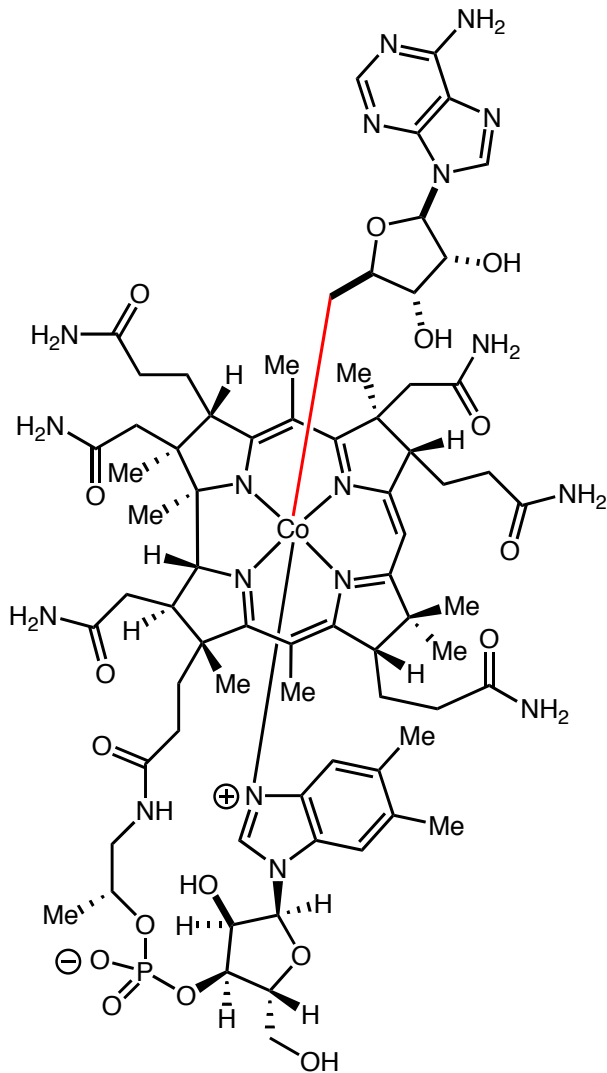


## Interaction of Organic Radicals with Transition Metals



## Coenzyme Vitamin B<sub>12</sub> is a Source of Radicals

- Homolysis of cobalt-carbon bond generates carbon-centered radical capable of performing catalysis



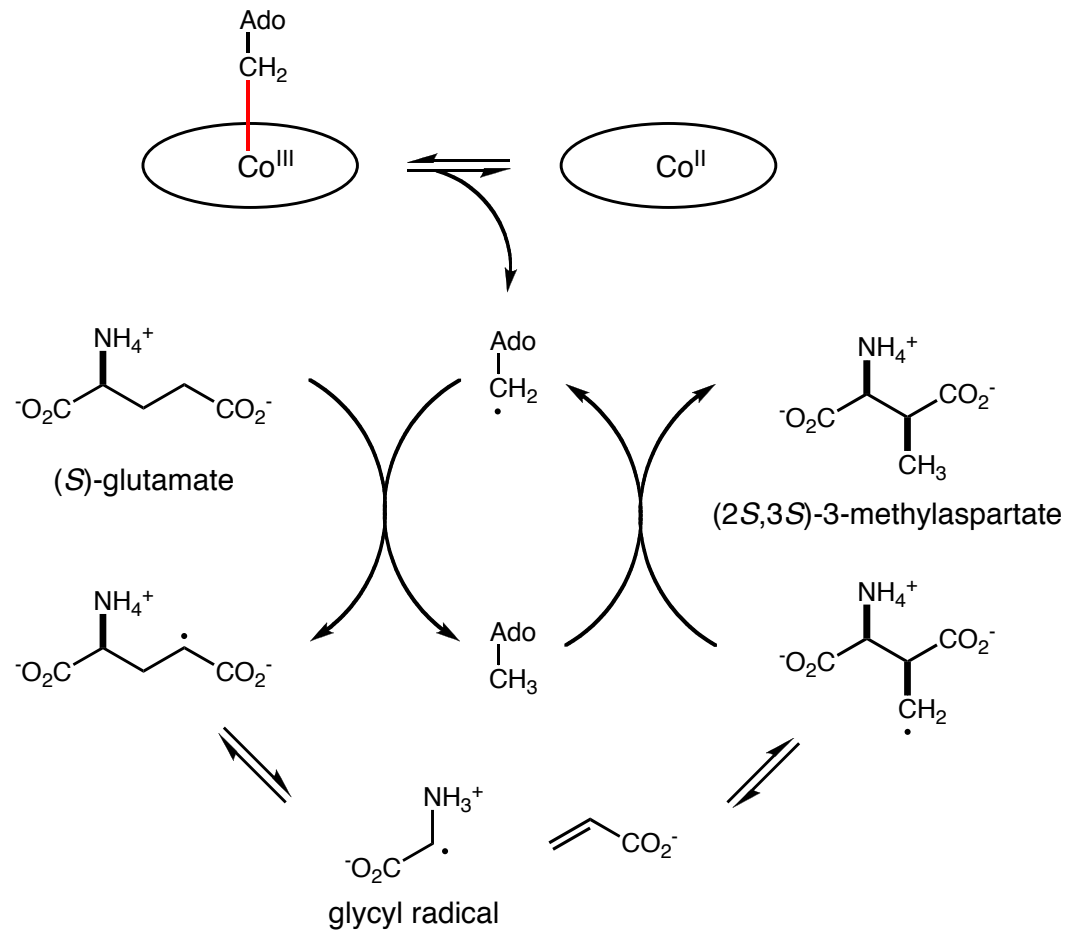
BDE = 30 kcal/mol

"latent radical reservoir"

Buckel, W.; Golding, B. T. *Annu. Rev. Microbiol.* **2006**, *60*, 27-49.

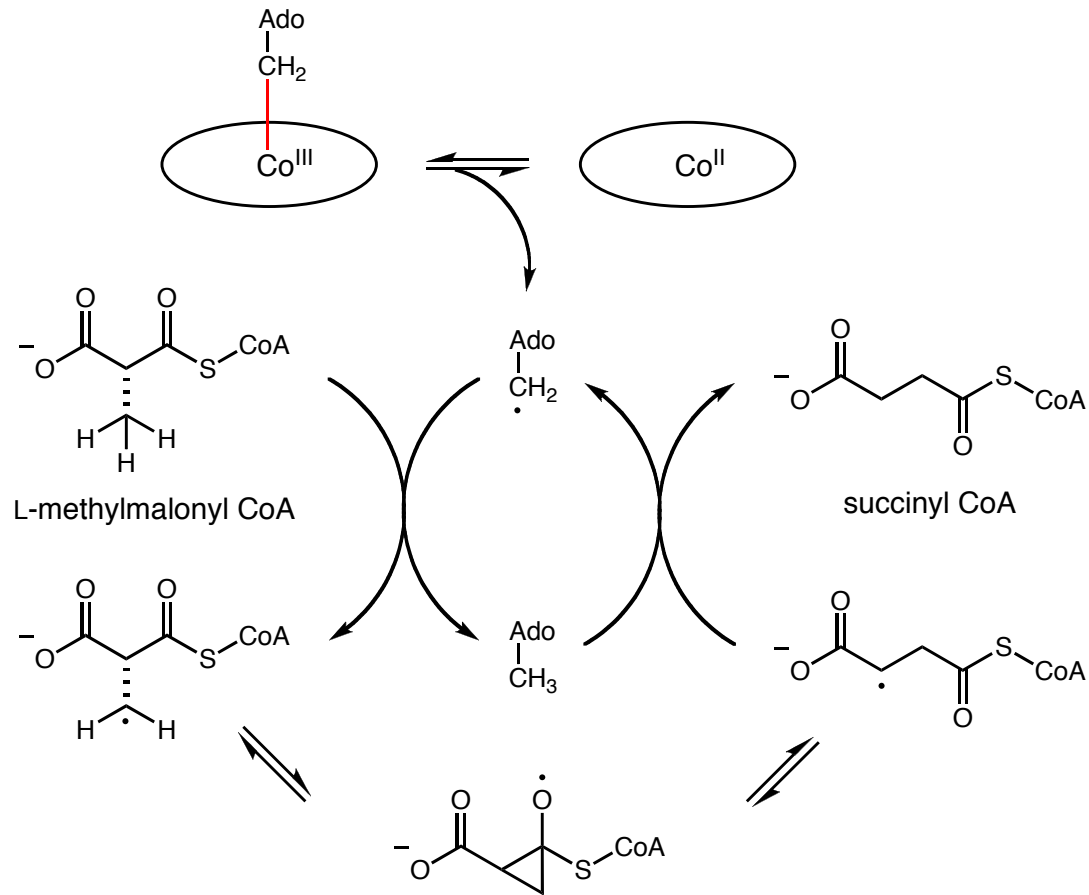
## Catalysis by Coenzyme Vitamin B<sub>12</sub>

- Glutamate mutase converts (S)-glutamate to (2S,3S)-3-methylaspartate



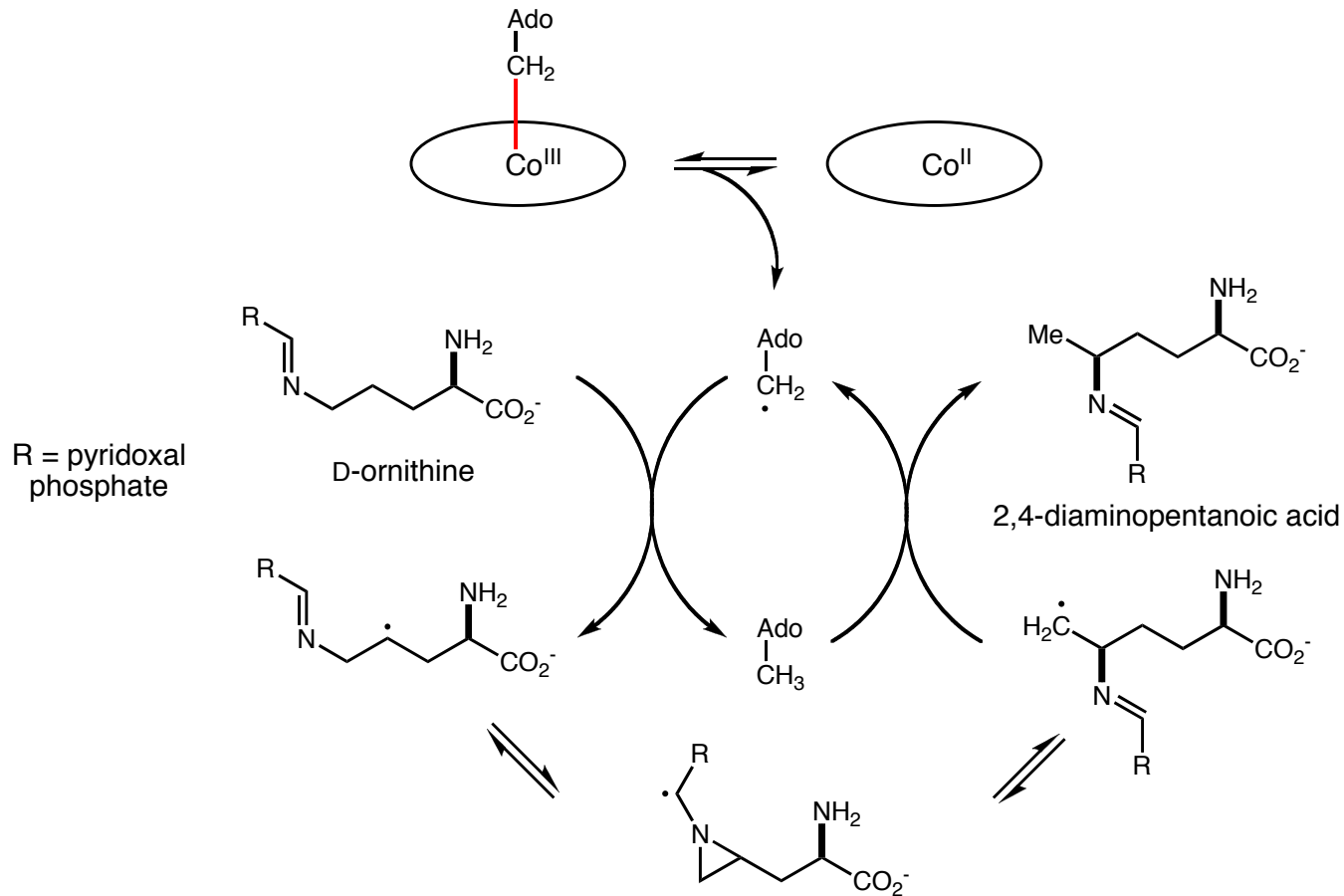
## Catalysis by Coenzyme Vitamin B<sub>12</sub>

- Methylmalonyl CoA mutase converts L-methylmalonyl CoA to succinyl CoA



## Catalysis by Coenzyme Vitamin B<sub>12</sub>

- D-ornithine aminomutase converts D-ornithine to (2R,4S)-2,4-diaminopentanoic acid



Banerjee, R.; Ragsdale, S. W. *Annu. Rev. Biochem.* **2003**, *72*, 209-247.  
 Chen, H.-P.; Wu, S.-H.; Lin, Y.-L.; Chen, C.-M. *J. Biol. Chem.* **2001**, *276*, 44744-44750.

## Interaction of Organic Radicals with Transition Metals

