



Recent Advances in Organocopper Chemistry

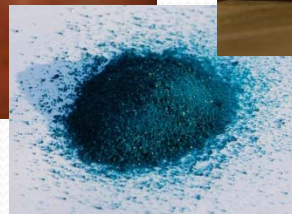
V. A. Schmidt

8 April 2010

Alexanian Group

Copper

- Group 11 coinage metal
- Building materials, pipes, jewelry, etc.
- High electrical conductivity and ductility make it ideal for wires





Overview

- Scope
- Synthetically Useful Organocopper Nucleophiles
 - Cuprates in Conjugate Addition
 - Allylic Substitutions
- Synthetically Useful Cu-mediated Couplings
 - C-C forming couplings
 - C-O forming couplings
 - C-N forming couplings

Organocopper Nucleophiles



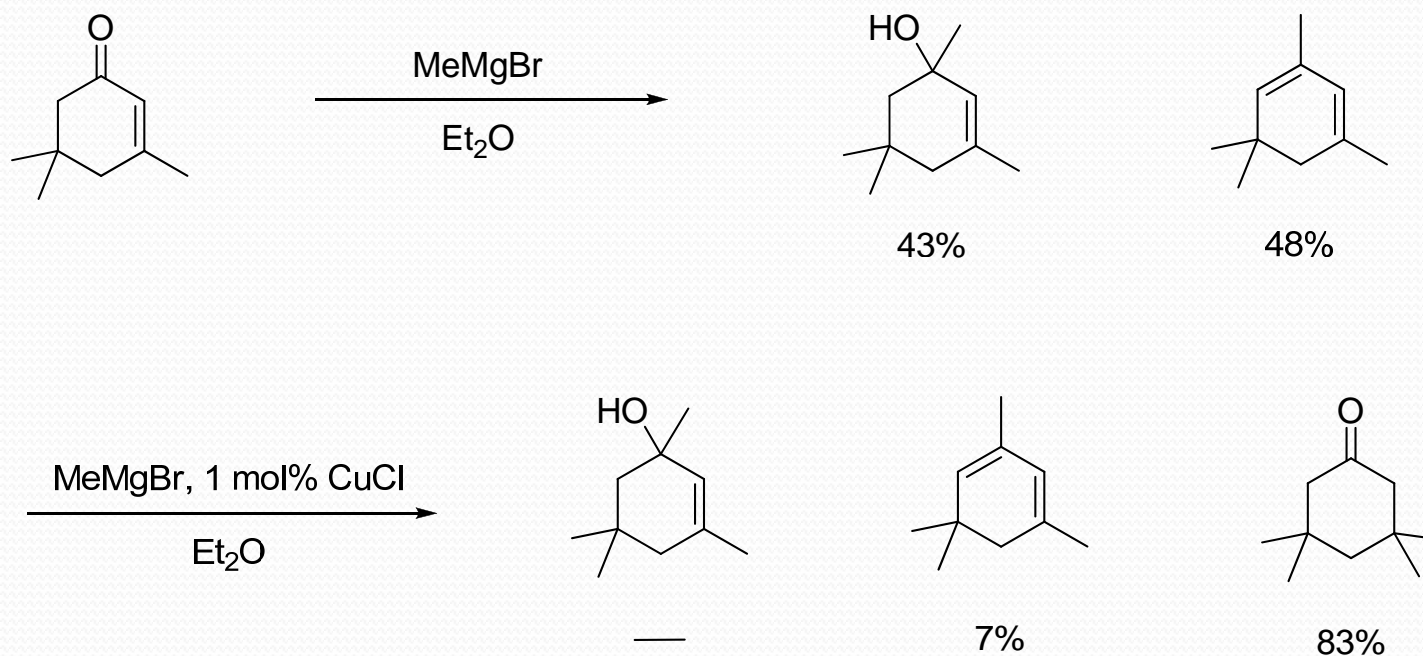
Common Cu sources : CuI , CuCN , $\text{CuBr}\cdot\text{Me}_2\text{S}$



Henry Gilman

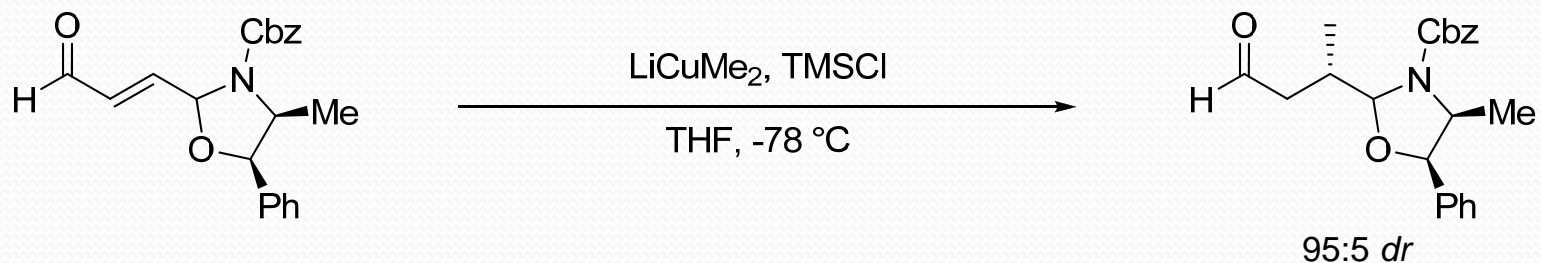
Mono-organocoppers	RCu	- thermally unstable
Homocuprates	LiCuR_2	- Gilman Cuprates
Heterocuprates	$\text{LiCuR}(\text{OR}')$	- alkoxy cuprates
	$\text{LiCuR}(\text{SR}')$	- thiolato cuprates
	$\text{LiCuR}(\text{2-Th})$	- thienyl cuprates
Cyanocuprates	$\text{LiCuR}(\text{CN})$	- "lower order" cuprates
	$\text{Li}_2\text{CuR}_2(\text{CN})$	- "higher order" cuprates

Transmetalation from Grignards



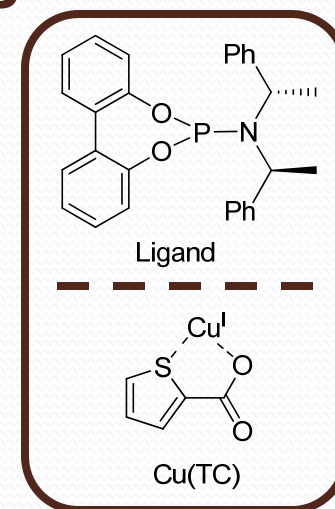
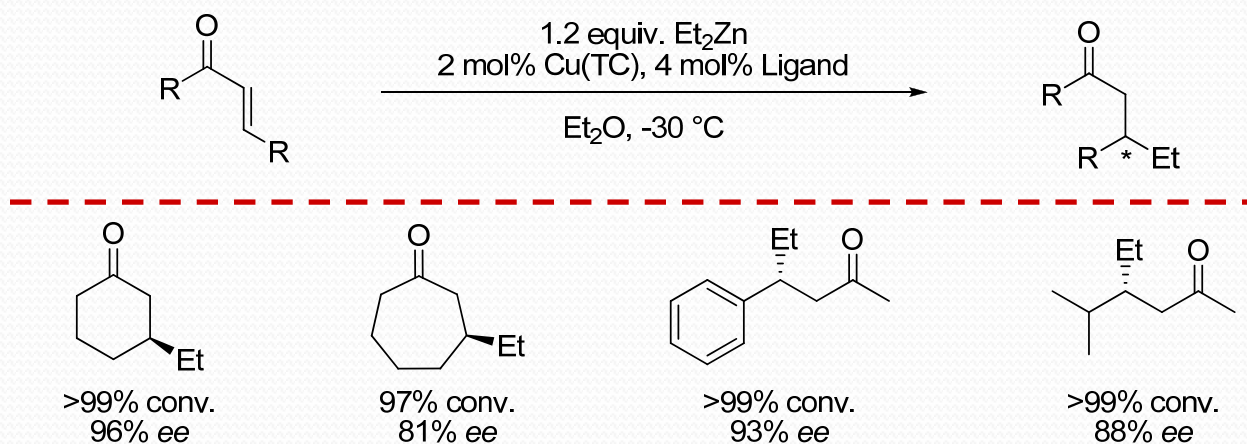
FeCl_3 , NiCl_2 , CoCl_2 , AgCl , PbCl_2 , CrCl_3 , VCl_2 , MnCl_2 were also screened but none gave any significant amount of 1,4-addition product.

Stereoselective Conjugate Additions

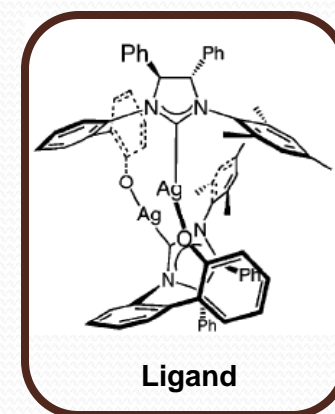
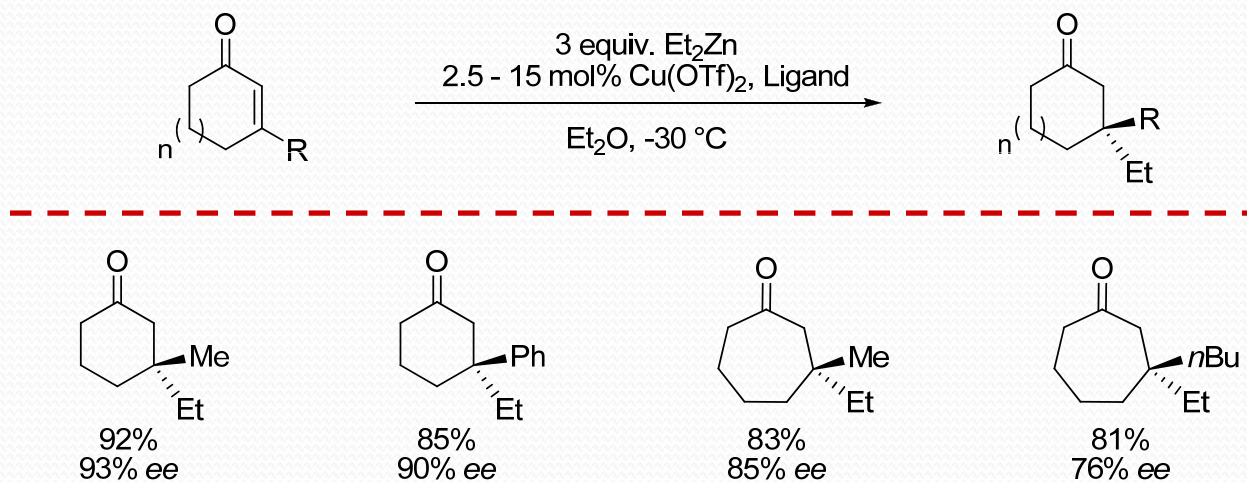


The development of catalytic asymmetric reactions has grown exponentially since 1941.

Catalytic Asymmetric Conjugate Additions

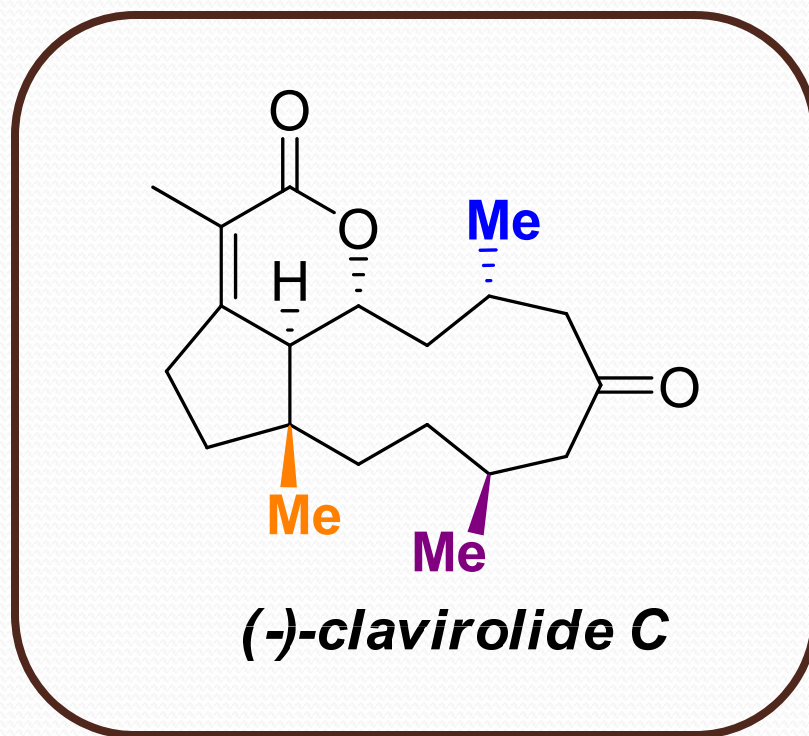


Alexakis, A.; Polet, D.; Rosset, S.; March, S. *J. Org. Chem.* **2004**, *69*, 5660.

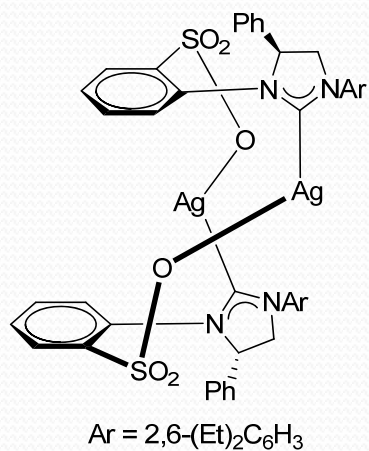
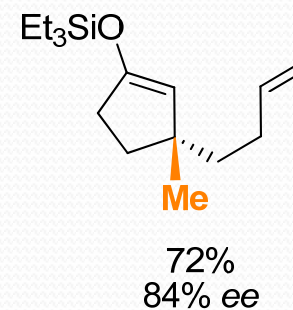
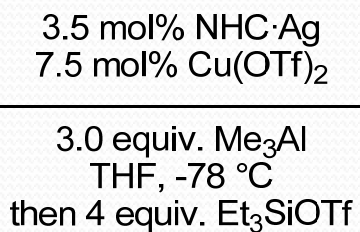
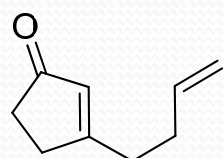
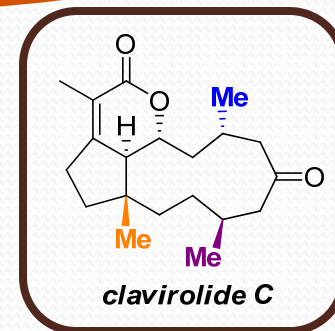


Lee, K.; Brown, M.K.; Hird, A.W.; Hoveyda, A.H. *J. Am. Chem. Soc.* **2006**, *128*, 7182.

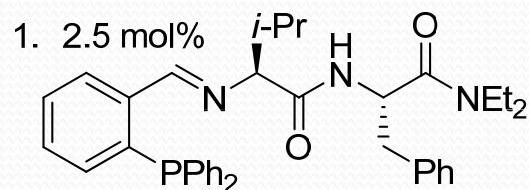
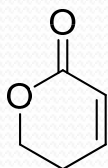
Cuprates in Synthesis – (-)-Clavirolide C



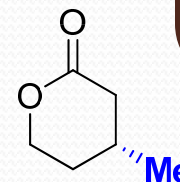
Synthesis of Clavirolide C



Synthesis of Clavirolide C

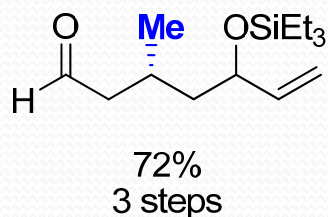
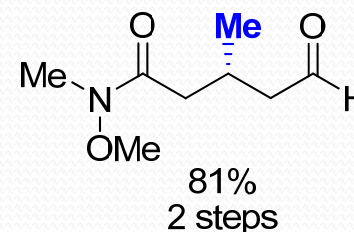


1 mol% (CuOTf)₂·toluene
 3 equiv. Me₂Zn, PhCHO
 toluene, -15 °C
 2. K₂CO₃, toluene, 120 °C



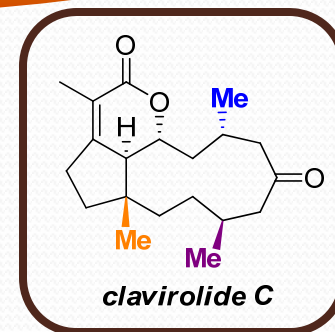
86%
 2 steps
 99% ee

1. Me(OMe)NH·HCl
i-PrMgCl, THF, 0 °C
 2. (COCl)₂, DMSO
 CH₂Cl₂, -78 °C
 then NEt₃ -78 °C to rt

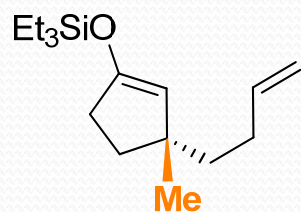


1. MgBr
 THF, 0 °C

2. Et₃SiCl, imidazole
 CH₂Cl₂, rt
 3. DIBAL, THF, -78 °C

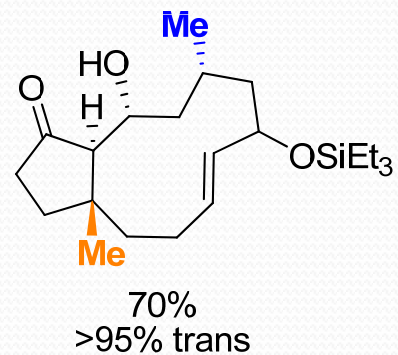
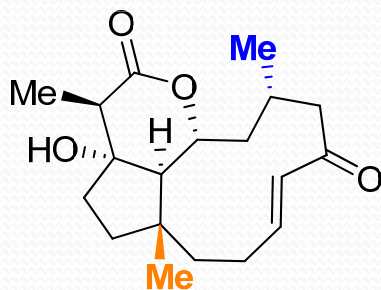
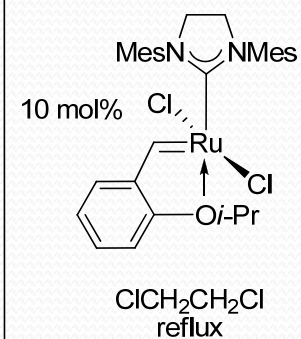
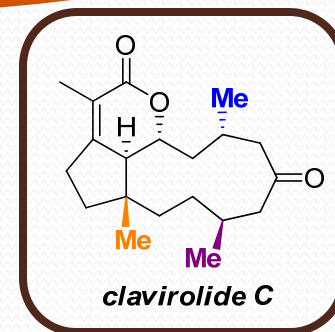
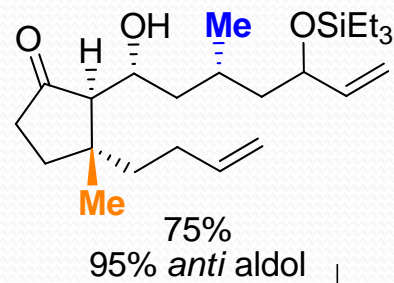
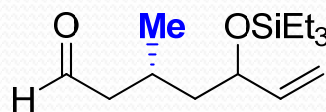


Synthesis of Clavirolide C



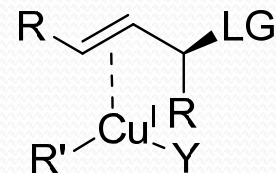
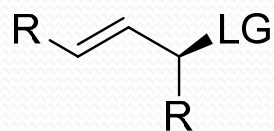
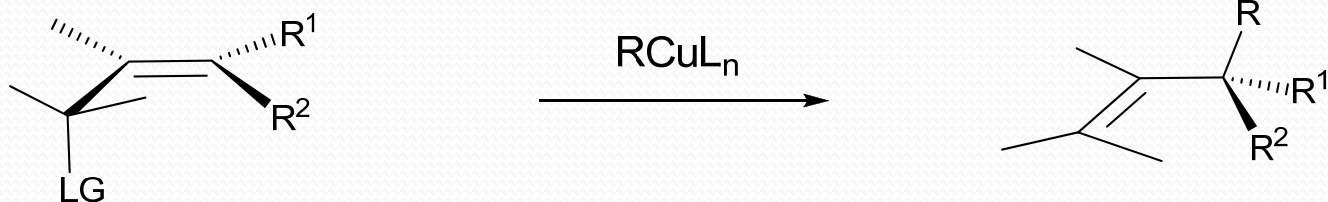
$n\text{BuLi}$, THF, rt

3 equiv. BEt_3 , $-78\text{ }^\circ\text{C}$

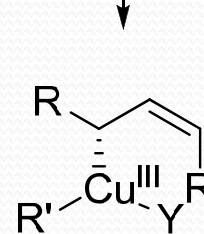


Allylic Substitutions

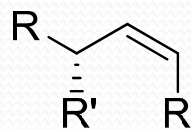
General Form



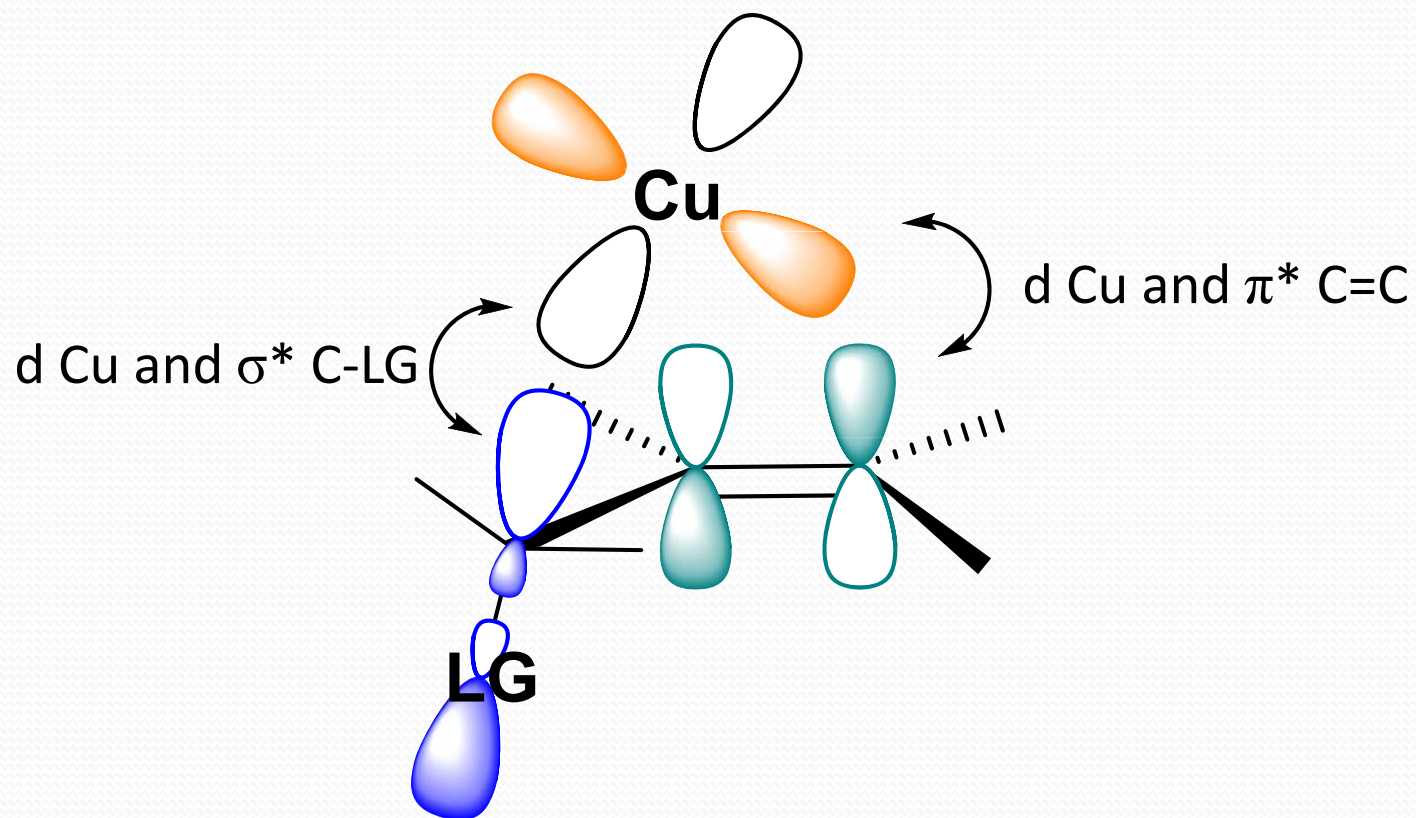
oxidative addition



reductive elimination

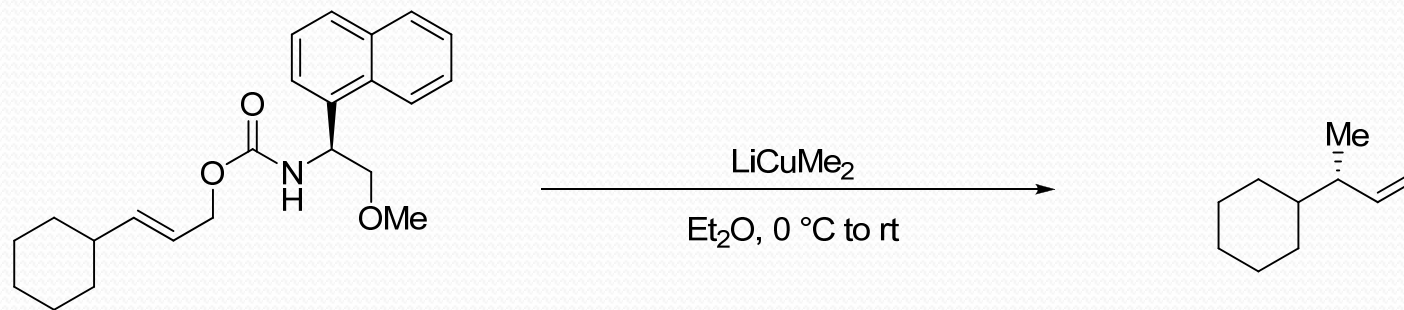


FMO Analysis



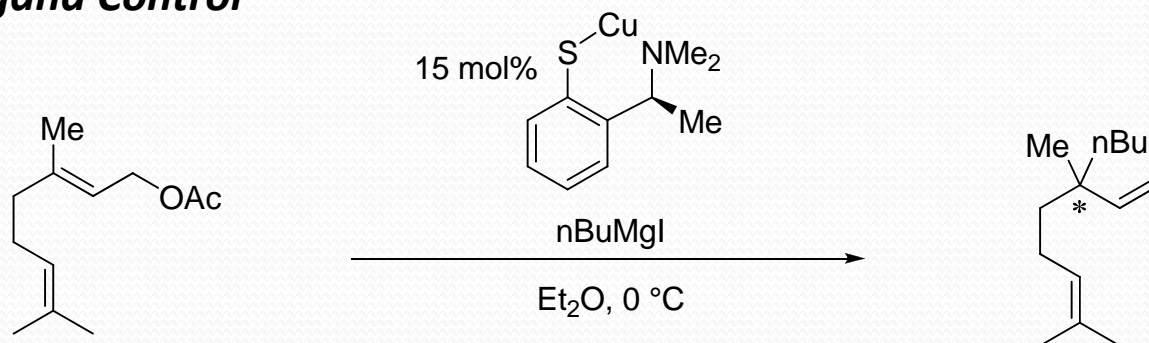
Early Examples of Stereocontrol

Chiral Leaving Group Control



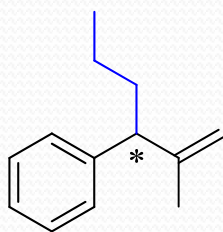
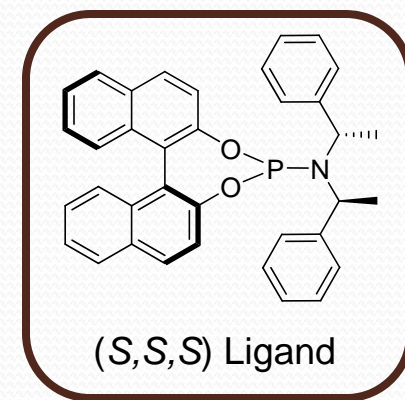
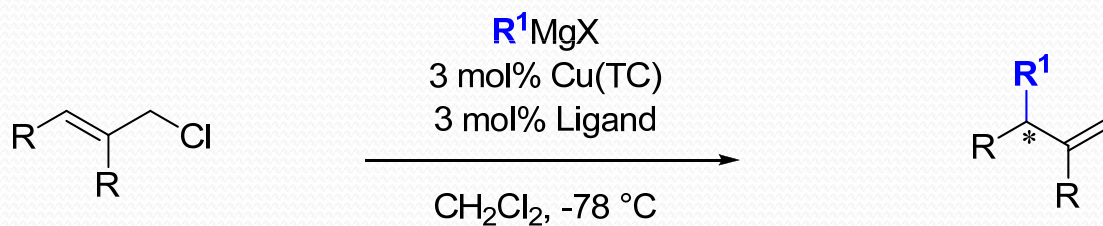
Denmark, S.E.; Marble, L.K. *J. Org. Chem.* **1990**, 55, 1984.

Chiral Ligand Control

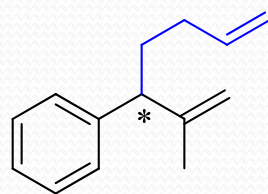


Backvall, J.E.; van Koten, G. *et. al. Tetrahedron Lett.* **1995**, 36, 3059.

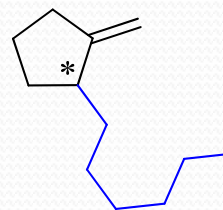
Asymmetric Allylic Alkylations (AAA)



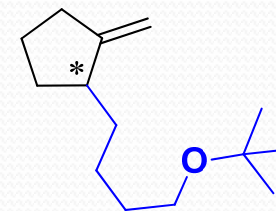
85%
84:16 $\gamma:\alpha$
97% ee



84%
89:11 $\gamma:\alpha$
97% ee

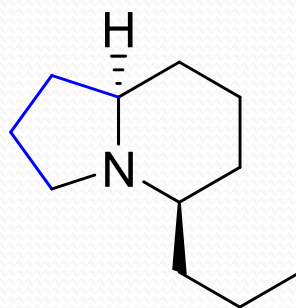


91%
98:2 $\gamma:\alpha$
98% ee



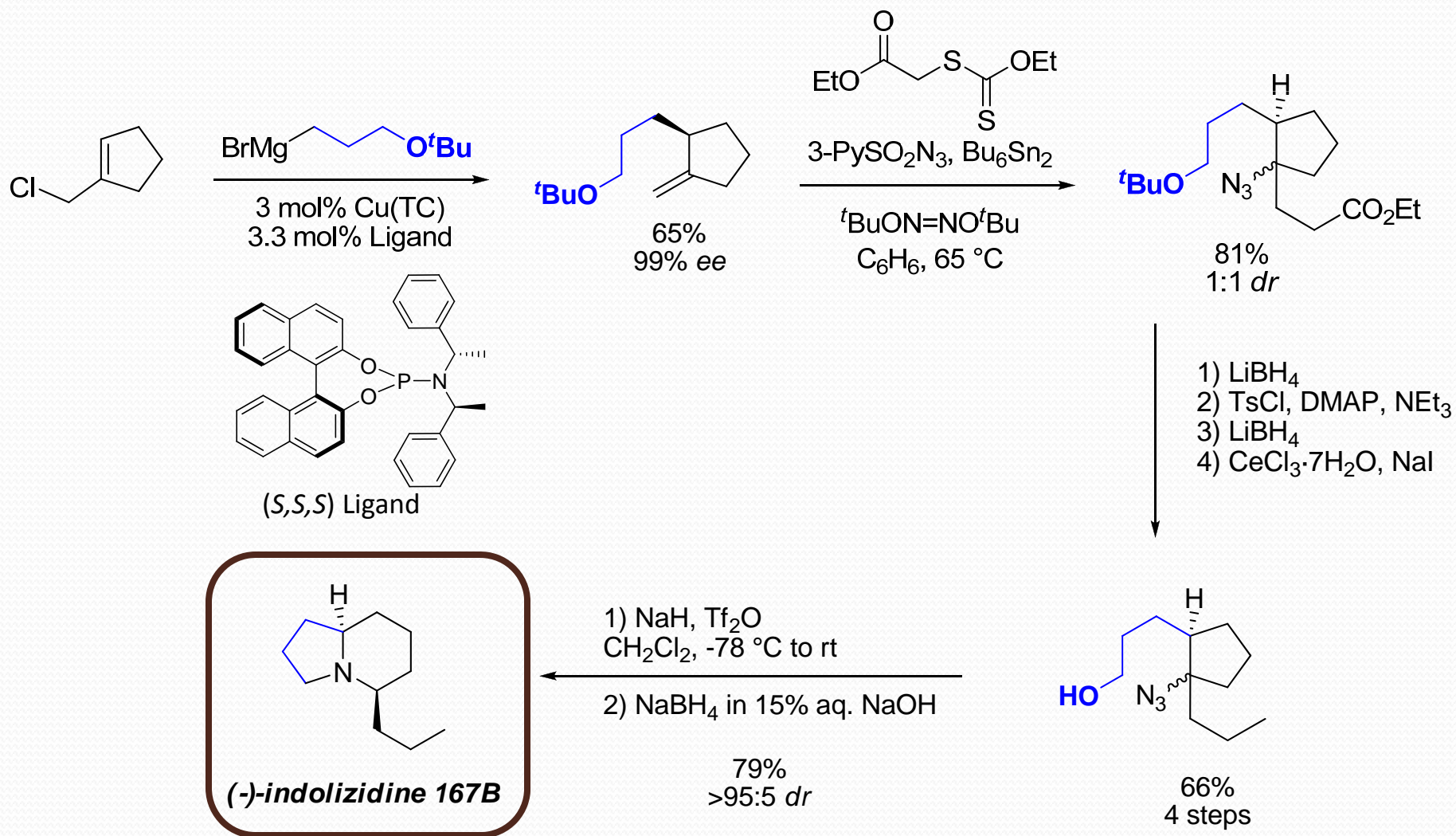
60%
98:2 $\gamma:\alpha$
98% ee

AAA in Synthesis - (-)-Indolizidine 167B



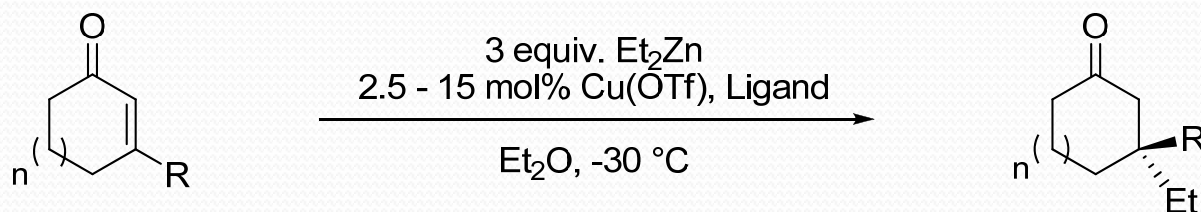
(-)-indolizidine 167B

Synthesis of (-)-Indolizidine 167B

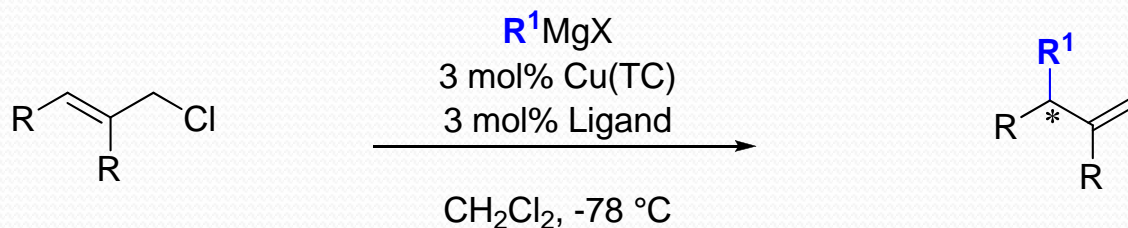


Organocopper Nucleophiles Summary

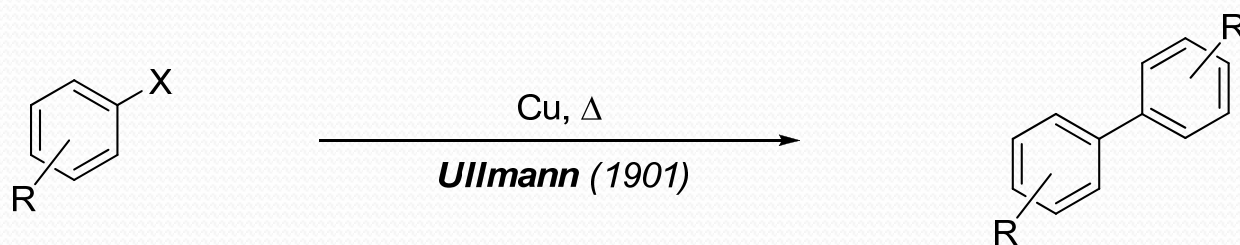
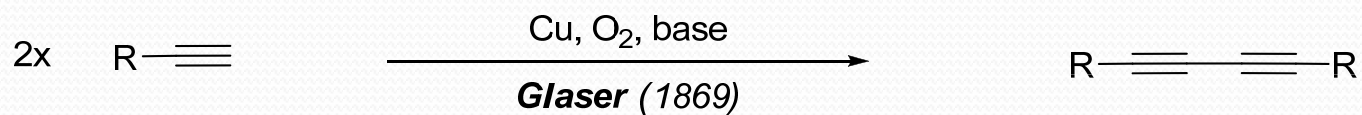
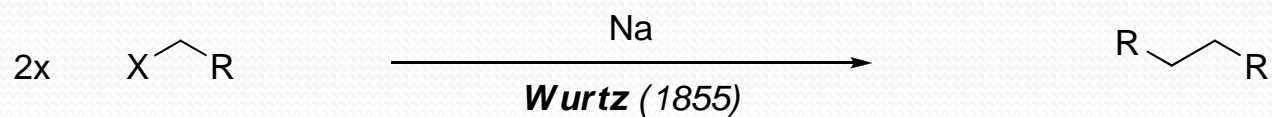
- Catalytic asymmetric conjugate additions
 - Using organozinc and organoaluminum reagents



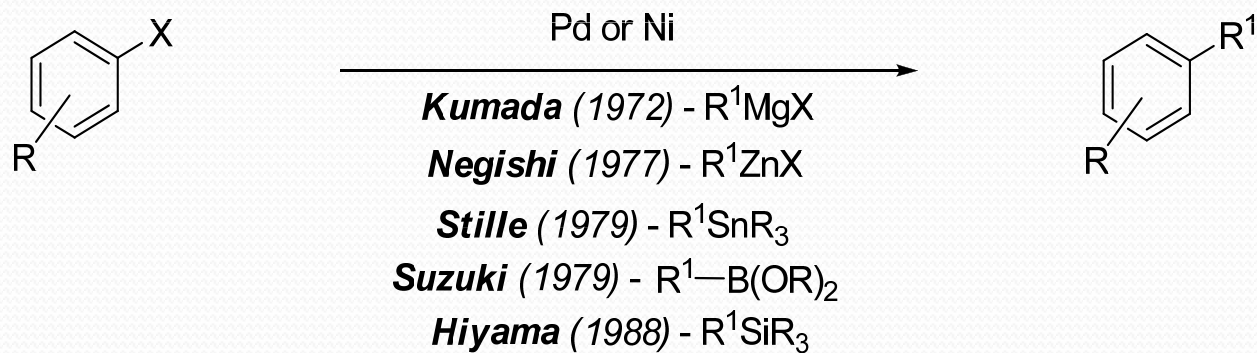
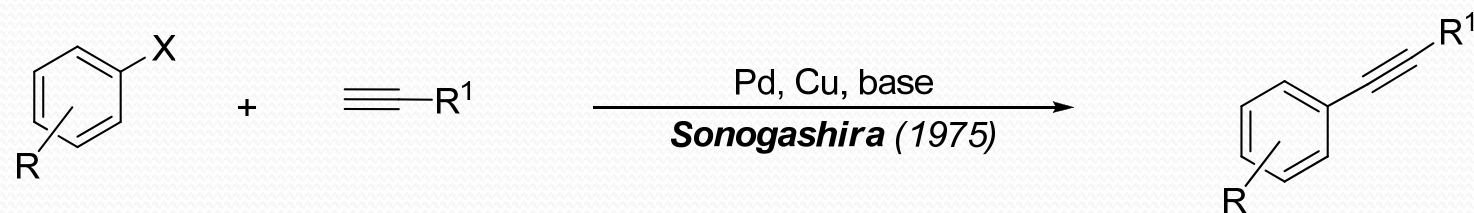
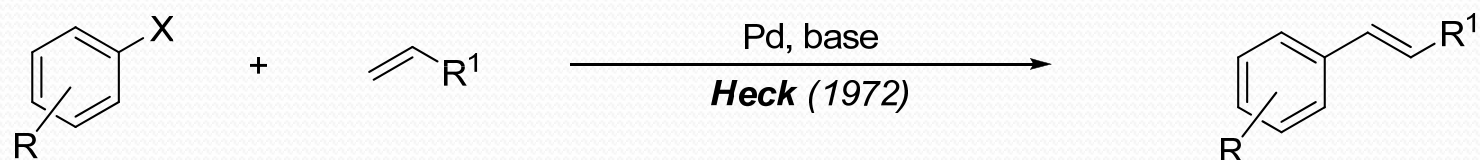
- Catalytic asymmetric allylic alkylations
 - Using Grignard reagents



Overview of Coupling Reactions

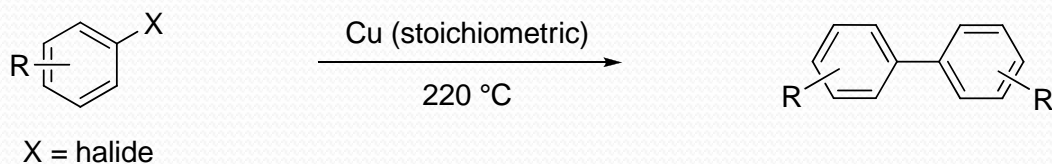


Overview of Coupling Reactions

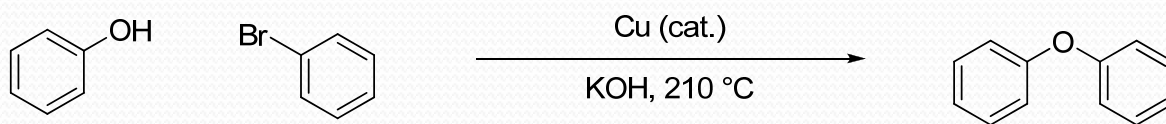


Ullmann and Goldberg

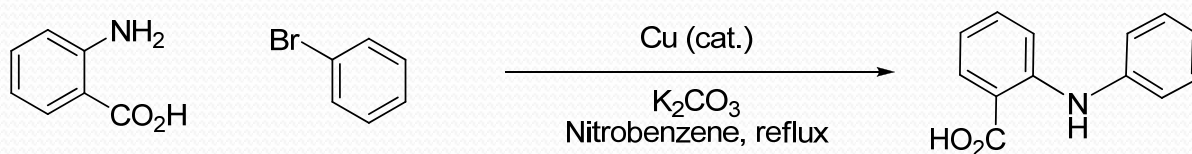
Ullmann (1901) - *Biaryls*



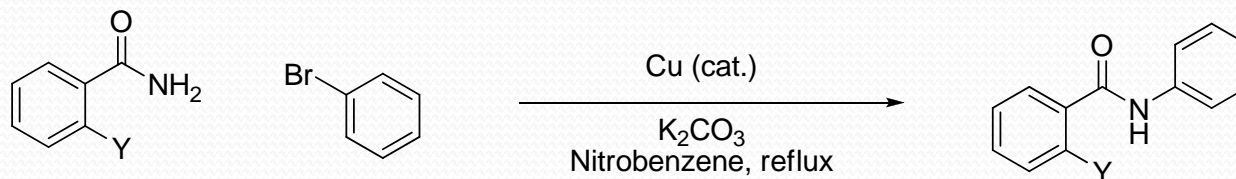
Ullmann (1905) - *Diarylethers*



Goldberg (1906) - *Diarylamines*

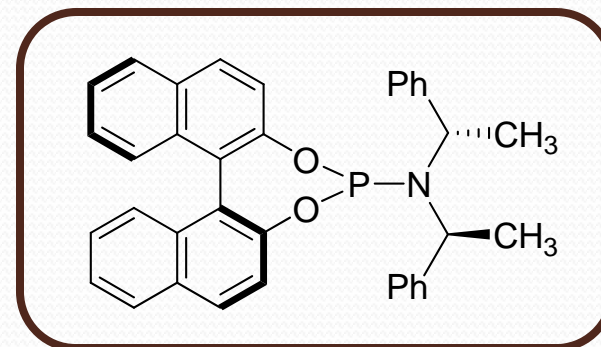
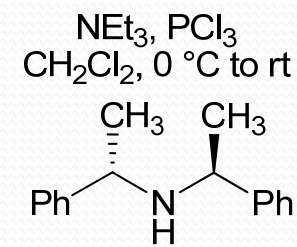
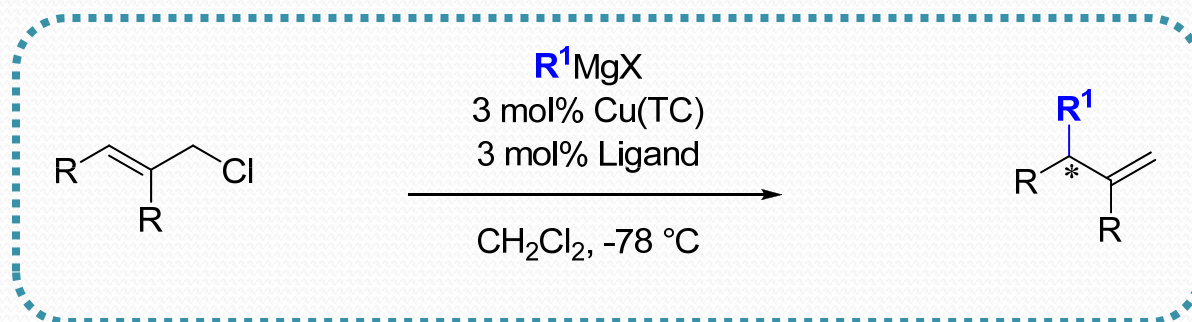
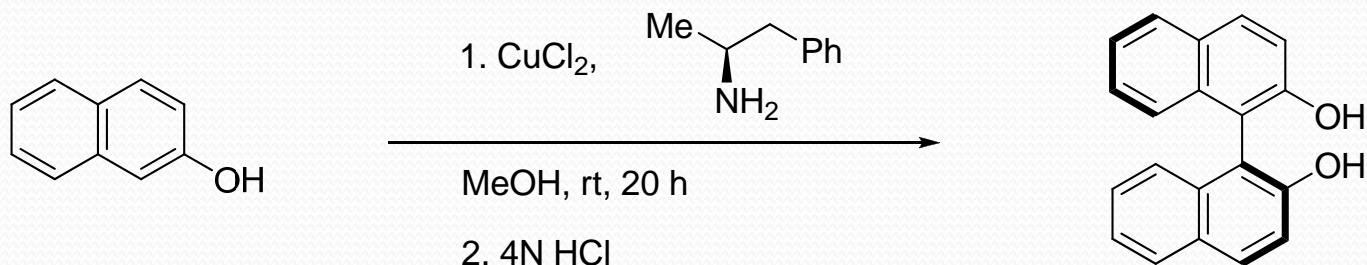


Goldberg (1906) - *Arylamides*



Fritz Ullmann

C-C Couplings – Synthesis of Phosphoramidites

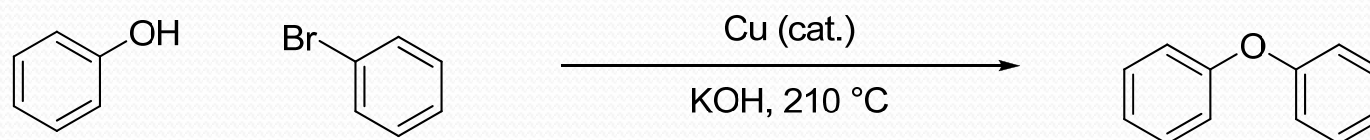


Brussee, J.; Groenendijk, J.L.G.; te Koppele, J.M.; Jansen, A.C.A. *Tetrahedron* **1985**, *41*, 3313.

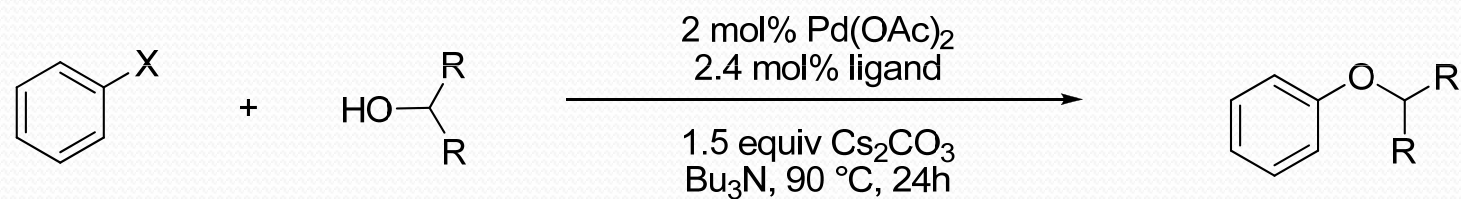
Falciola, C.A.; Tissot-Croset, K.; Alexakis, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 5995.

Synthesis of Aryl Ethers

Ullmann (1905)

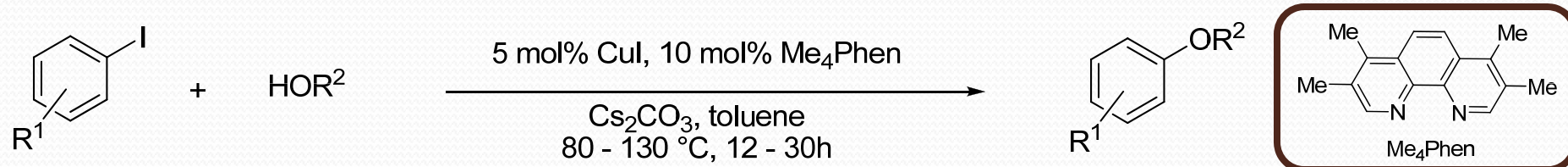


Buchwald (2001 1° alcohols; 2005 2° alcohols)

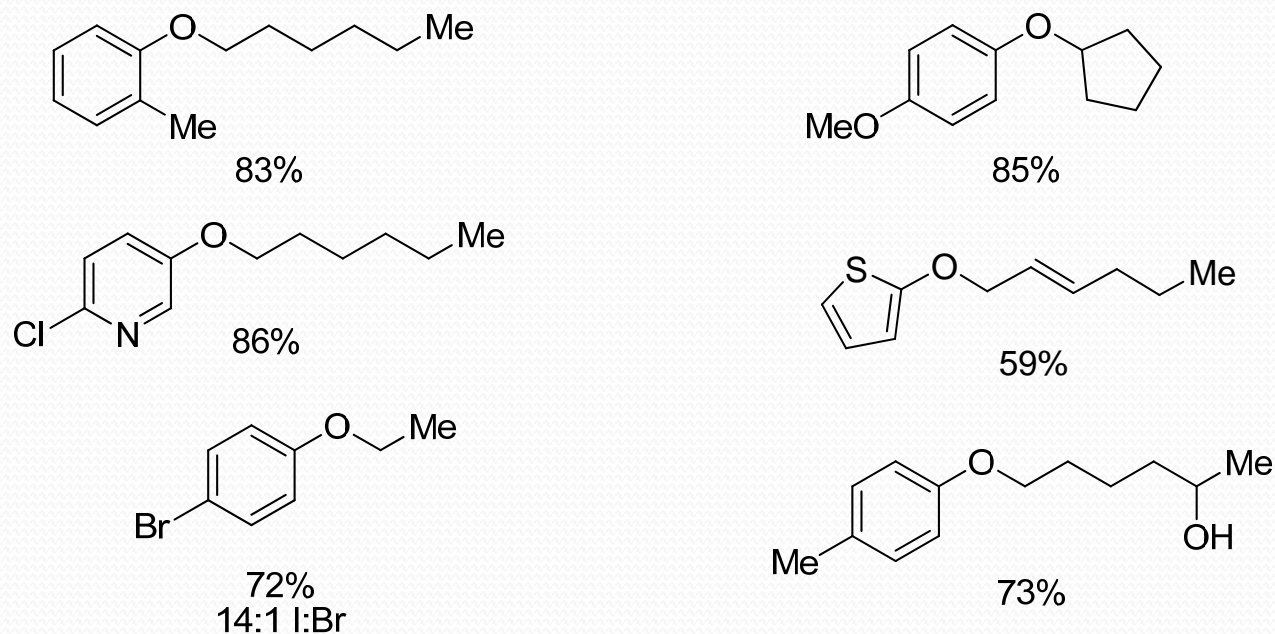


Torraca, K.E.; Huang, X.; Parrish, C.; Buchwald, S.L. *J. Am. Chem. Soc.* **2001**, *123*, 10770.
Vorogushin, A.V.; Huang, X.; Buchwald, S.L. *J. Am. Chem. Soc.* **2005**, *127*, 8146.

Cu Catalyzed Etherifications



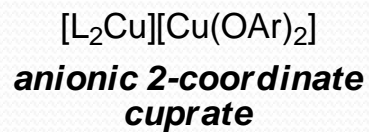
Complimentary Pd catalyzed reactions suffer from slow reductive elimination to form C-O bonds relative to β -hydride elimination



Mechanistic Studies

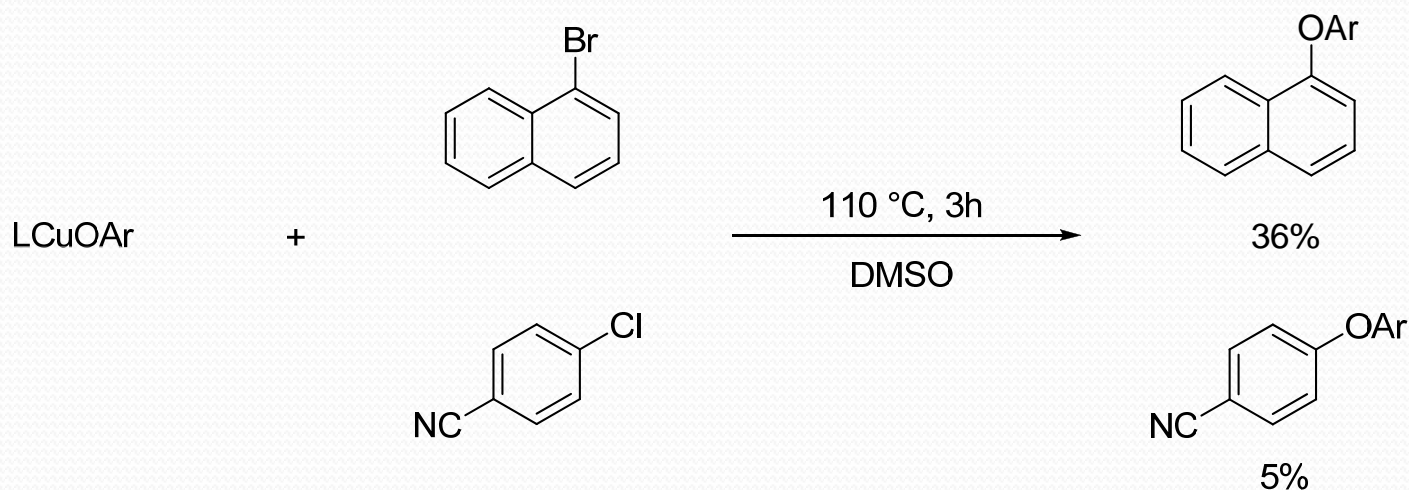
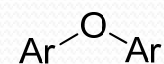


OR



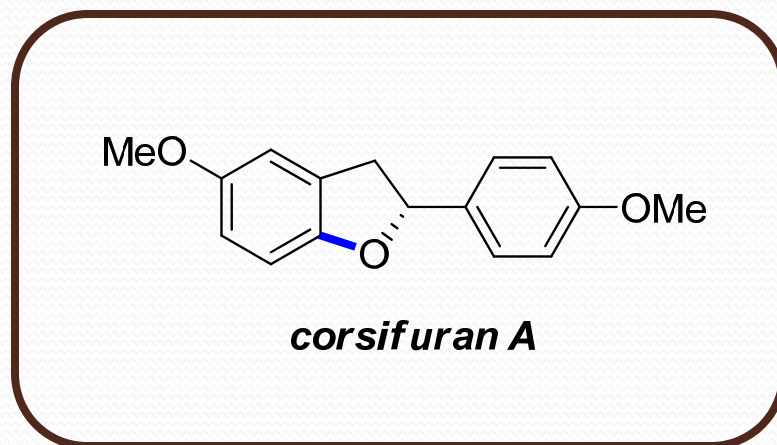
Excess ligand did not result in a significant reduction in rate; supporting a mechanism with a ligated copper alkoxide.

Ar-X

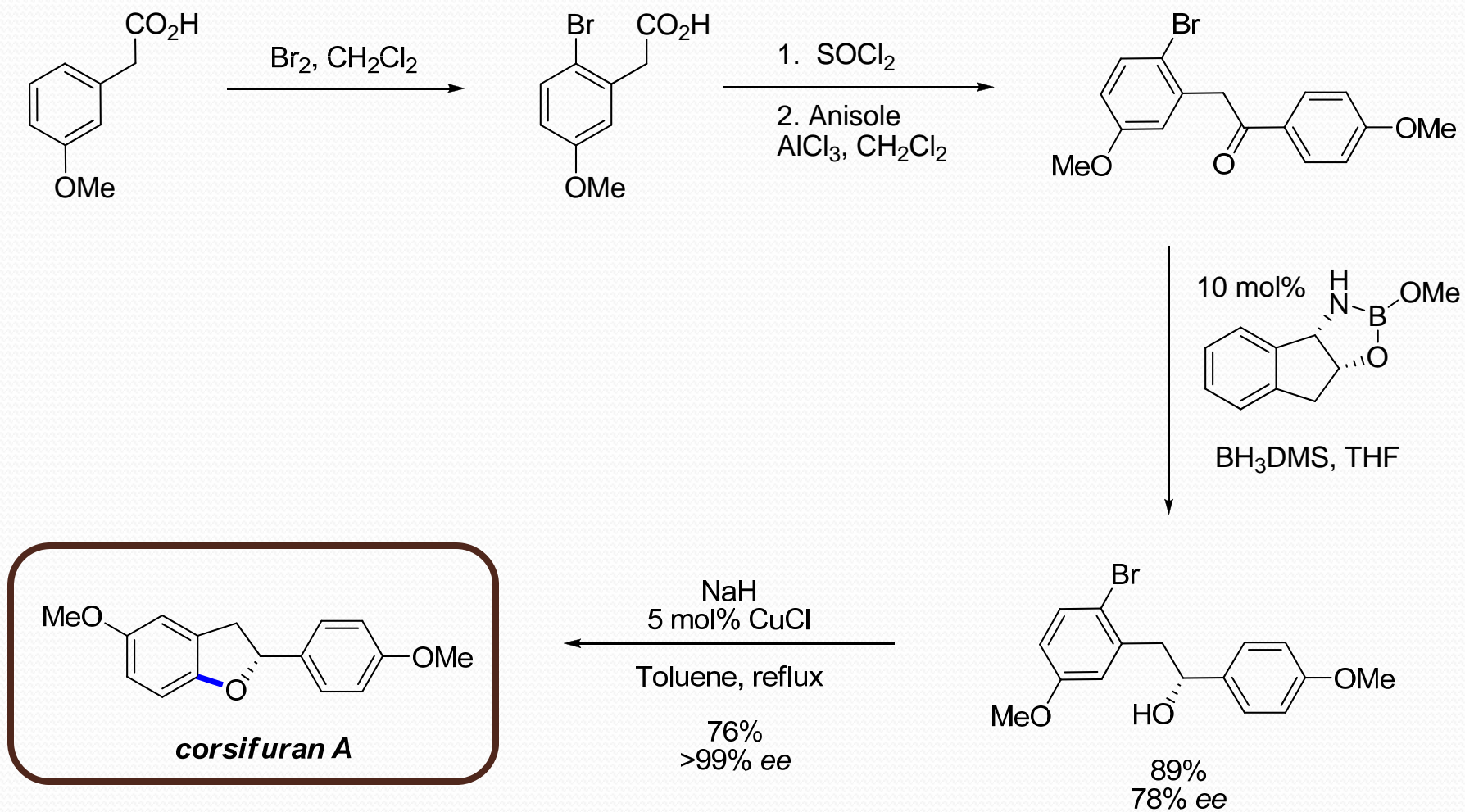


- Higher yield for Br coupling argues against an outer-sphere electron transfer

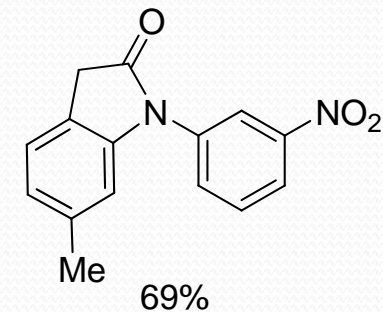
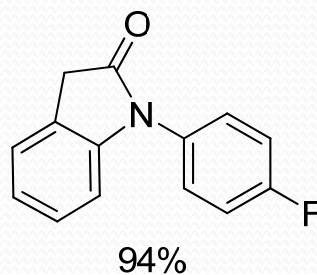
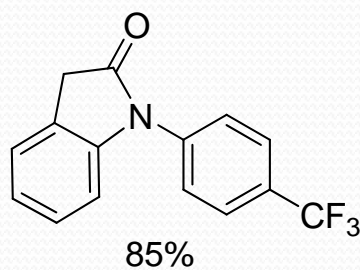
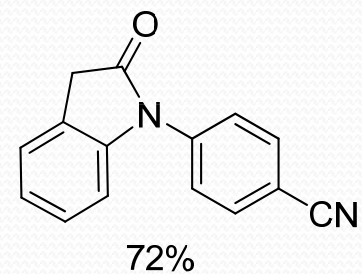
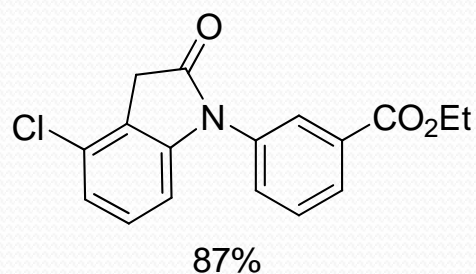
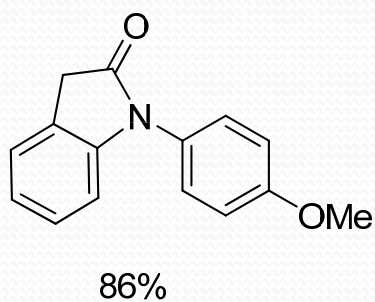
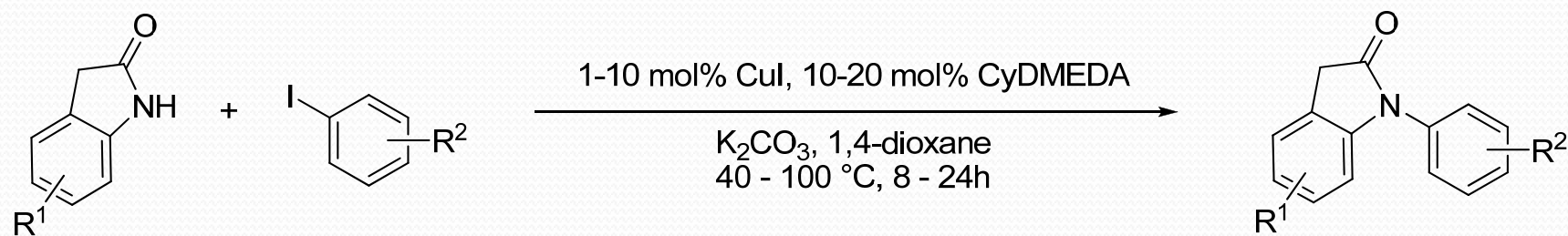
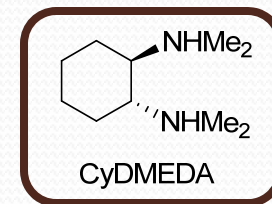
Etherification in Synthesis – Corsifuran A



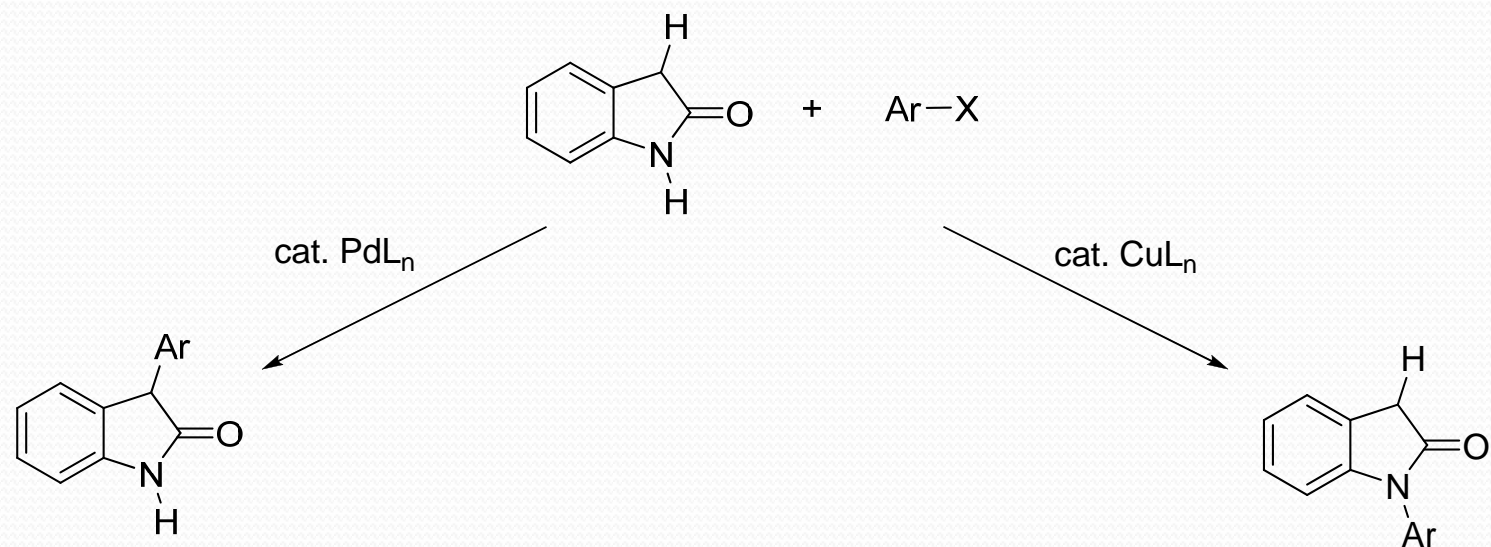
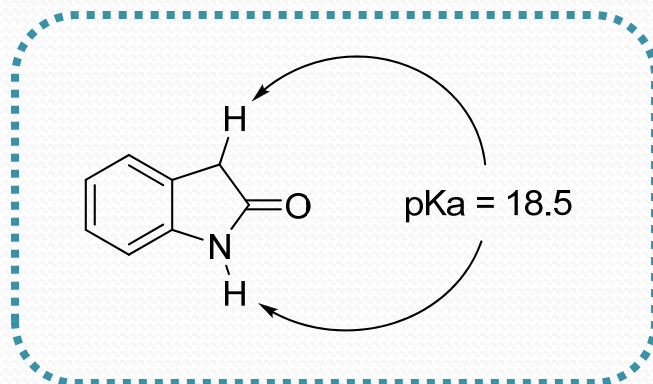
Synthesis of Corsifuran A



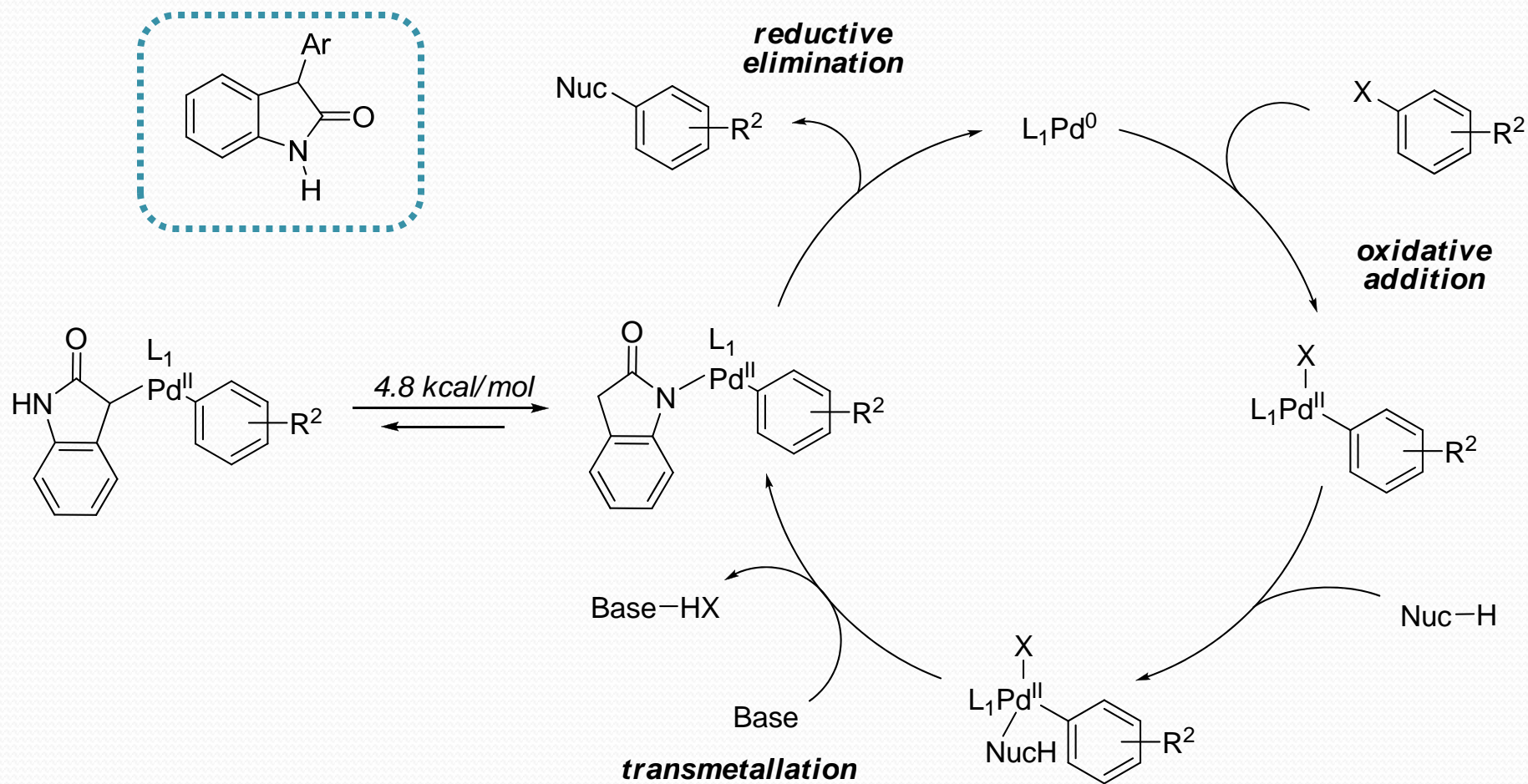
N-Arylation of Oxindoles



Opposing Reactivity of Oxindoles

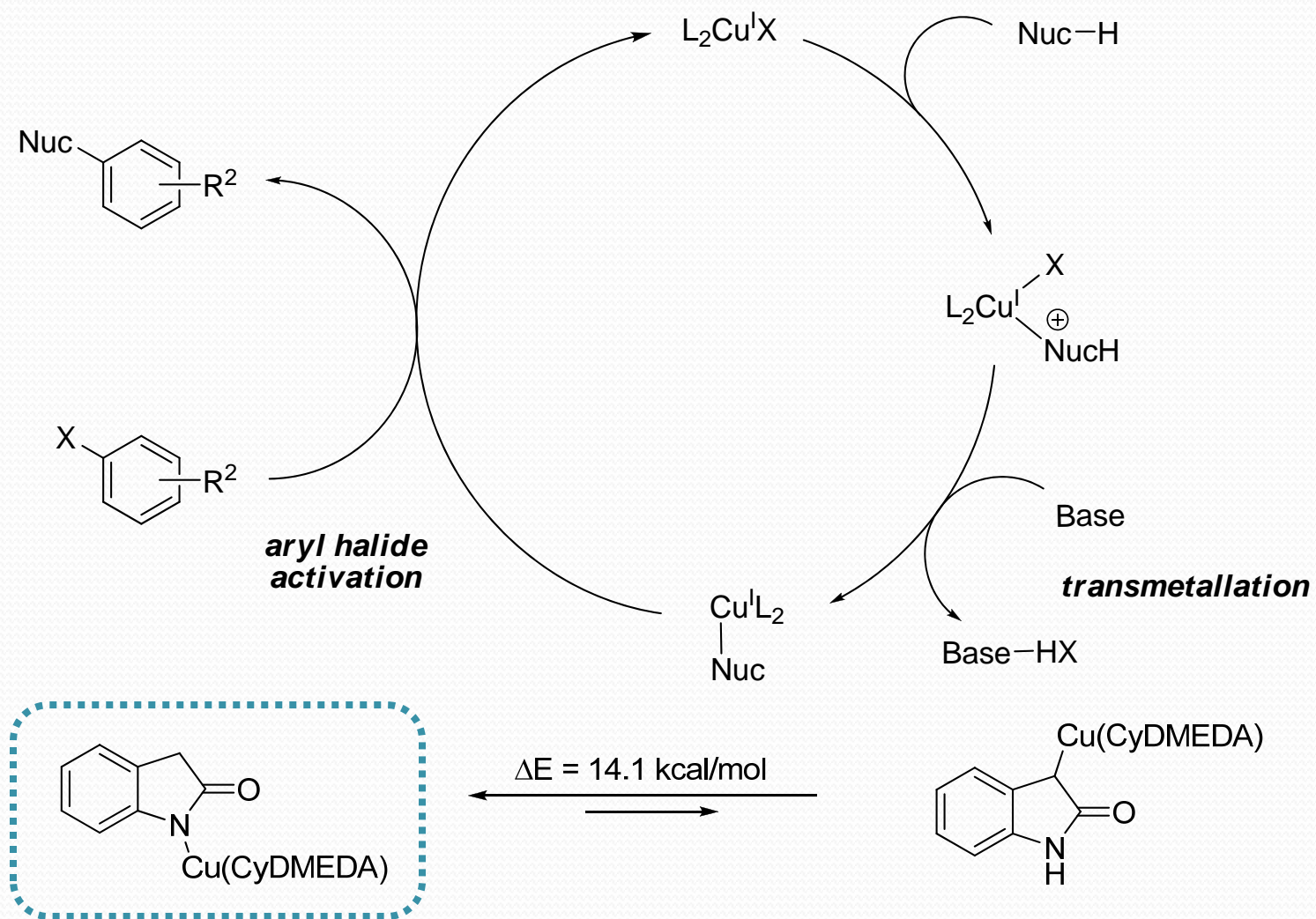


Pd Catalyzed Mechanism

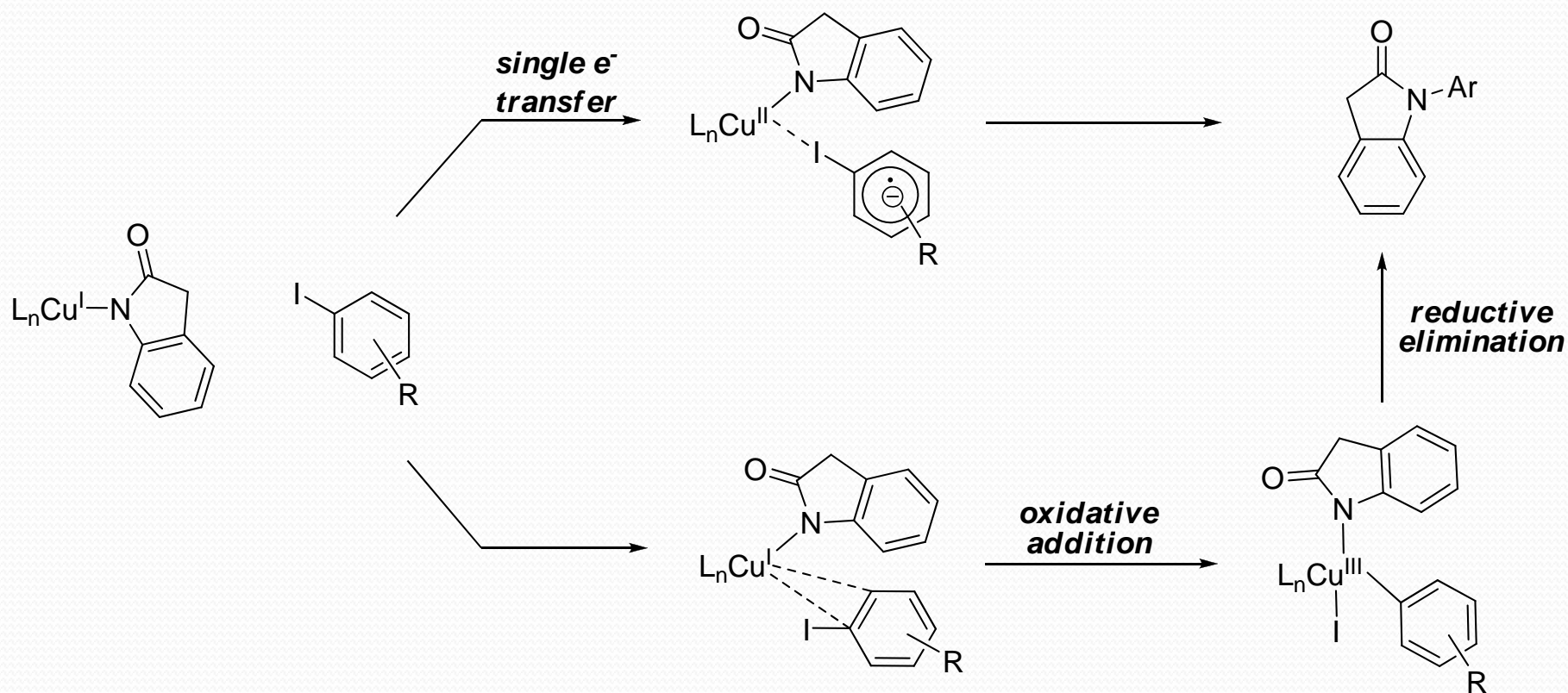


Reductive elimination occurs rapidly from the higher energy C bound Pd-enolate.

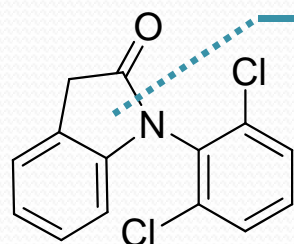
Cu Catalyzed Mechanism



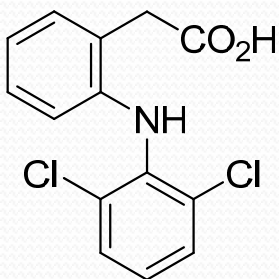
Proposed Routes of Aryl Halide Activation



Pharmaceutical Applications

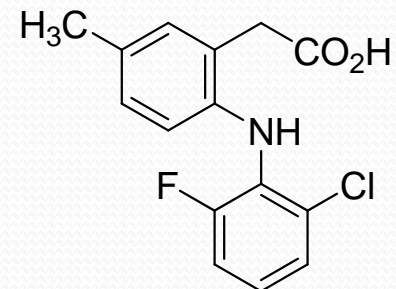


Hydrolytic Amide
Bond Cleavage



Diclofenac
generic

NSAID pain relievers



Lumiracoxib
Novartis

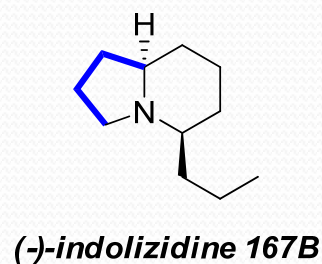
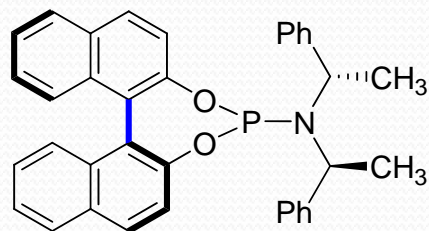
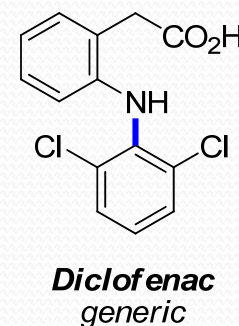
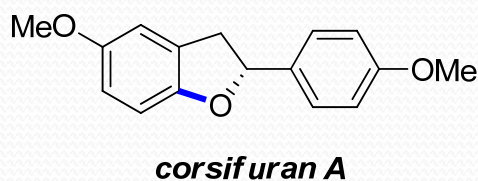
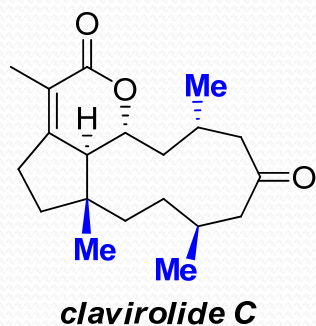
Conclusions

Organocopper reagents are an indispensable part of the Organic Chemist's Toolbox

Can be used to form a wide variety of new bonds

Recent synthetically useful advances include :

- catalytic enantioselective conjugate additions
- catalytic asymmetric allylic alkylations
- catalytic couplings to make C-C, C-N, and C-O bonds



Thank You!

- Professor Erik Alexanian
- Alexanian Group Members
 - Liz Cline
 - Andy Brusoe
 - Kayla Bloome
 - Justin Goodwin
 - Ben Giglio

