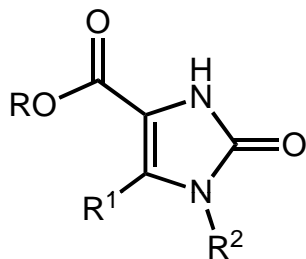


N-H Insertions: Rhodium vs. Copper

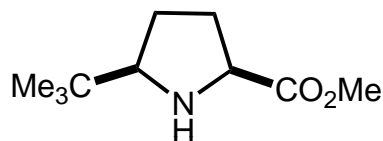
Mark Mans
Literature Seminar
March 20, 2008

Importance of N-H Insertions

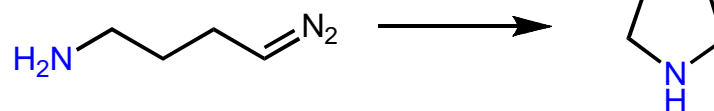
Synthesis of nitrogen-containing heterocycles



imidazolones

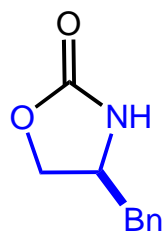


pyrrolidines

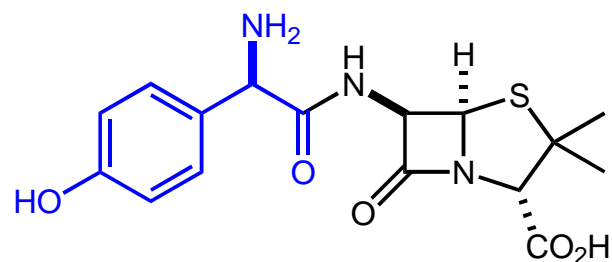


Synthesis of enantioenriched α -amino acids

- Chiral starting materials, auxiliaries, and catalysts
- Aryl glycines are building blocks for pharmaceuticals (vancomycin, amoxicillin, cephalosporins)



oxazolidinone



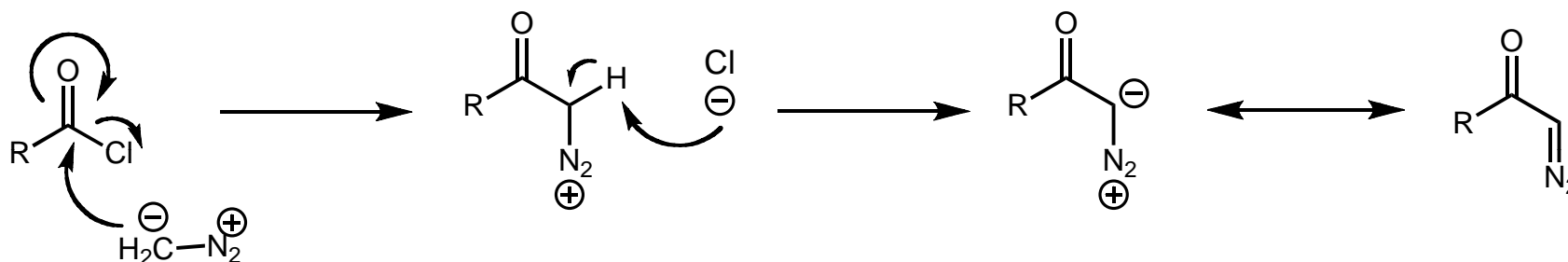
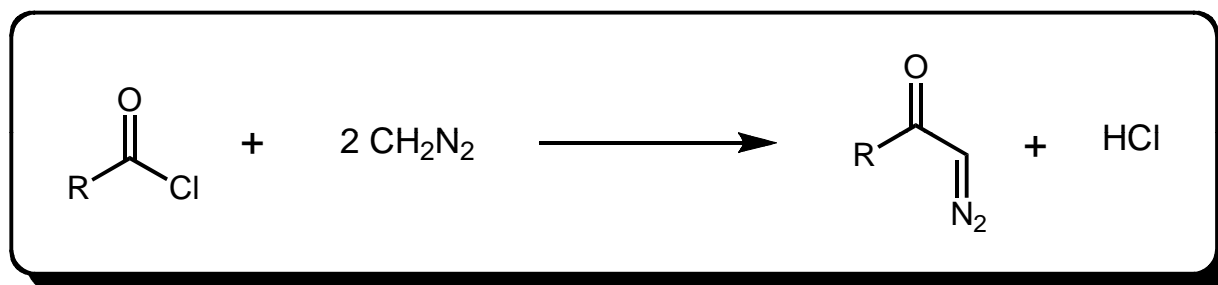
amoxicillin

Outline

- **Background**
- **Intramolecular N-H insertions**
 - 4, 5, and 6-membered aza rings
 - Synthesis of fully substituted azetidines
- **Intermolecular N-H insertions**
 - Asymmetric reactions with rhodium
 - Asymmetric reactions with copper
- **Conclusions**

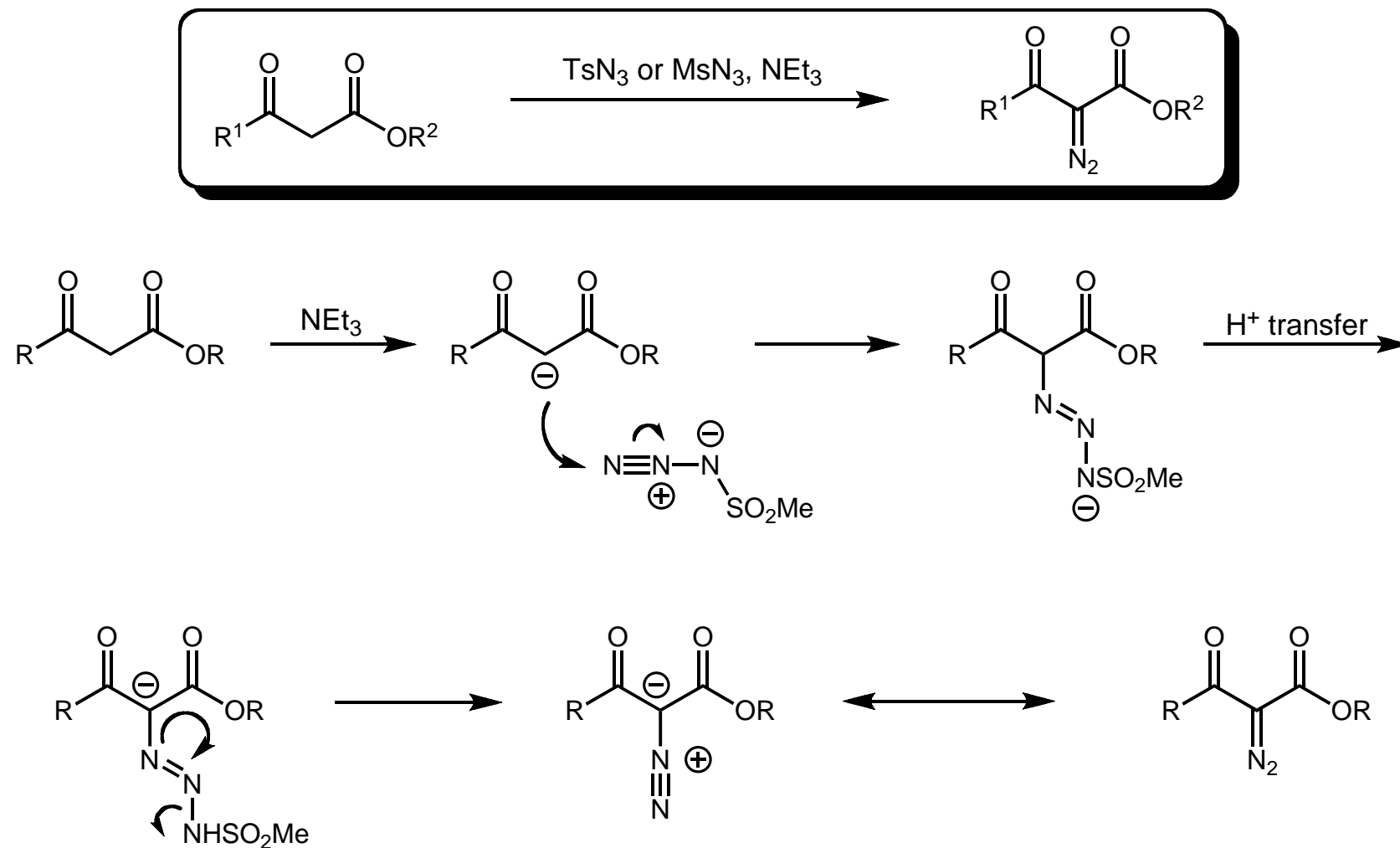
Synthesis of Diazo Compounds

Acyclic Terminal α -Diazo Ketones



Synthesis of Diazo Compounds

Diazo Transfer

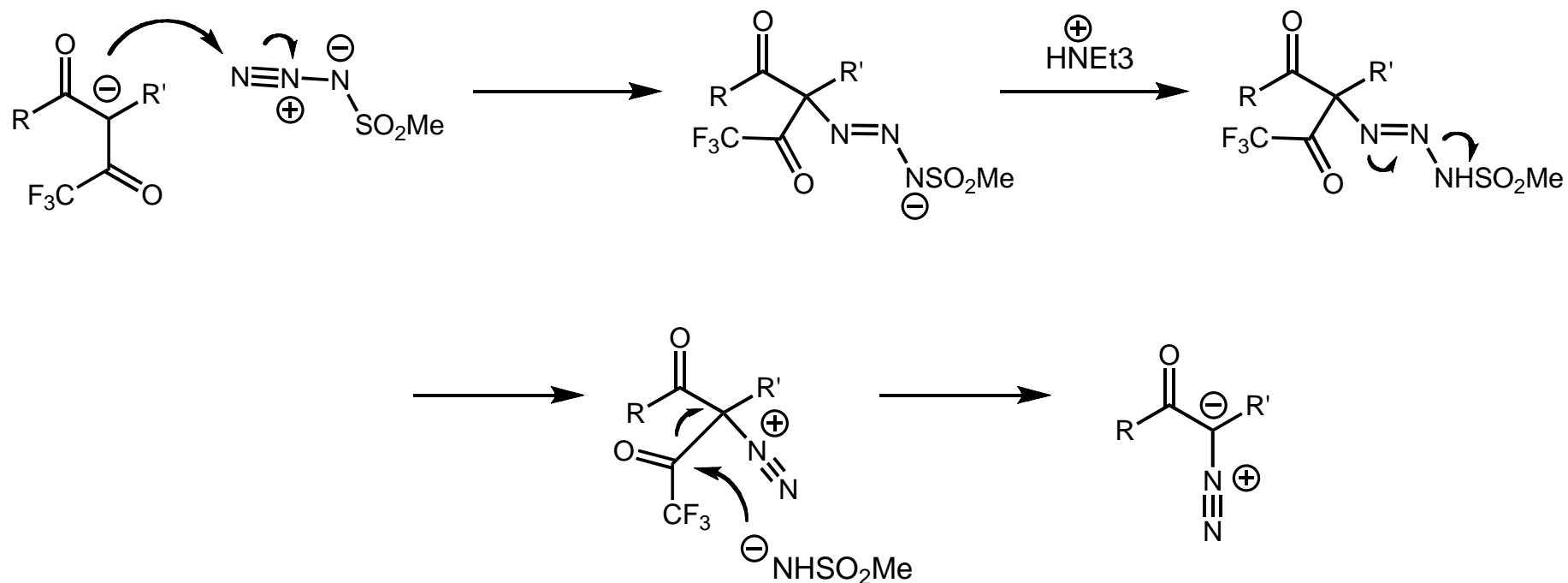
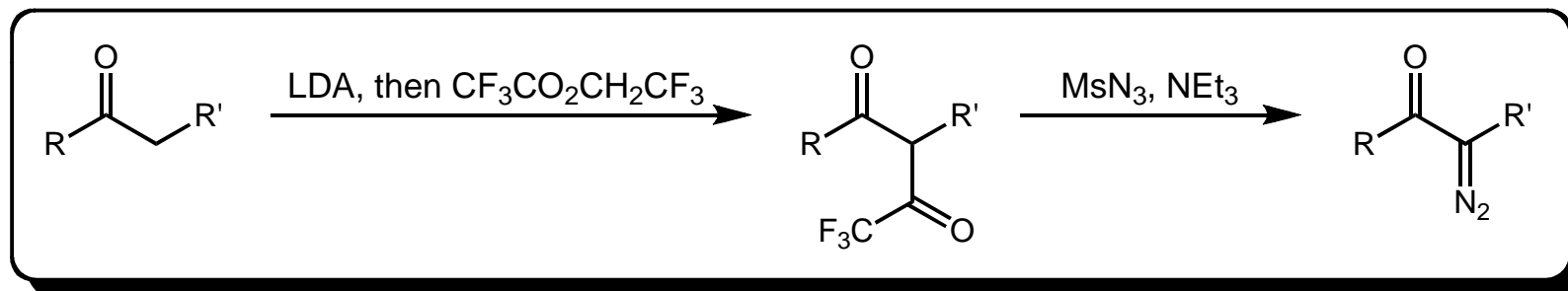


Regitz, M. *Synthesis*, **1972**, 351.

Taber, D.; Ruckle, R.; Hennessy, M. *J. Org. Chem.* **1986**, 51, 4077-4078.

Synthesis of Diazo Compounds

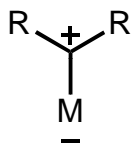
Modified Diazo Transfer



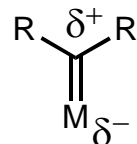
Carbenes



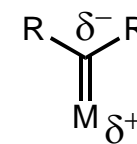
free carbene
very reactive



carbene complexes,
Rh, Cu, Pd, Pt



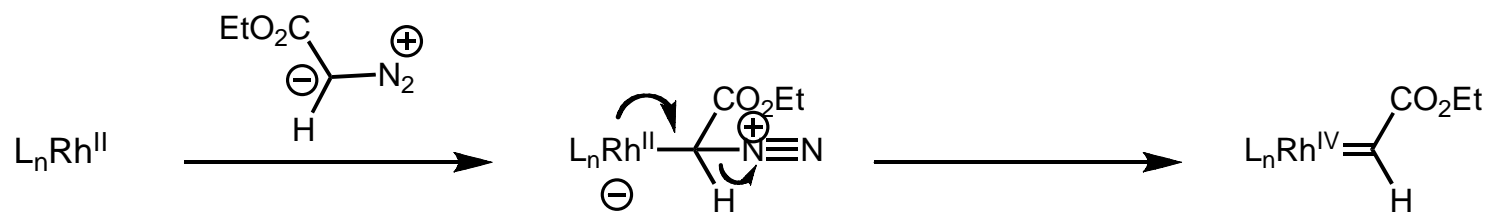
Fischer-type



Schrock-type

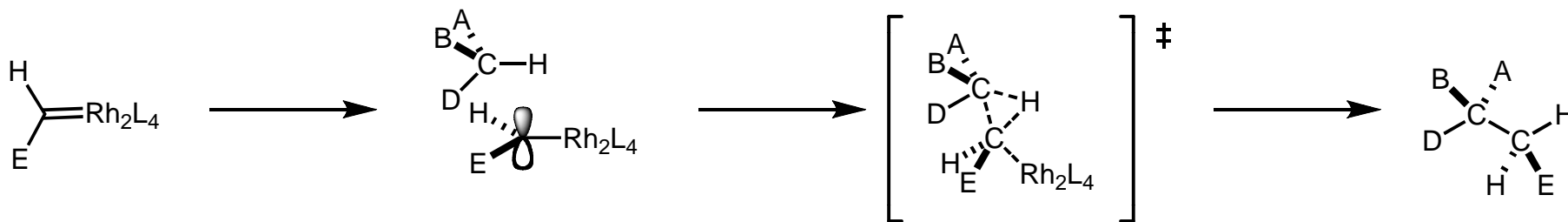
pi back-donation from metal to carbon increases

nucleophilicity of carbene carbon increases

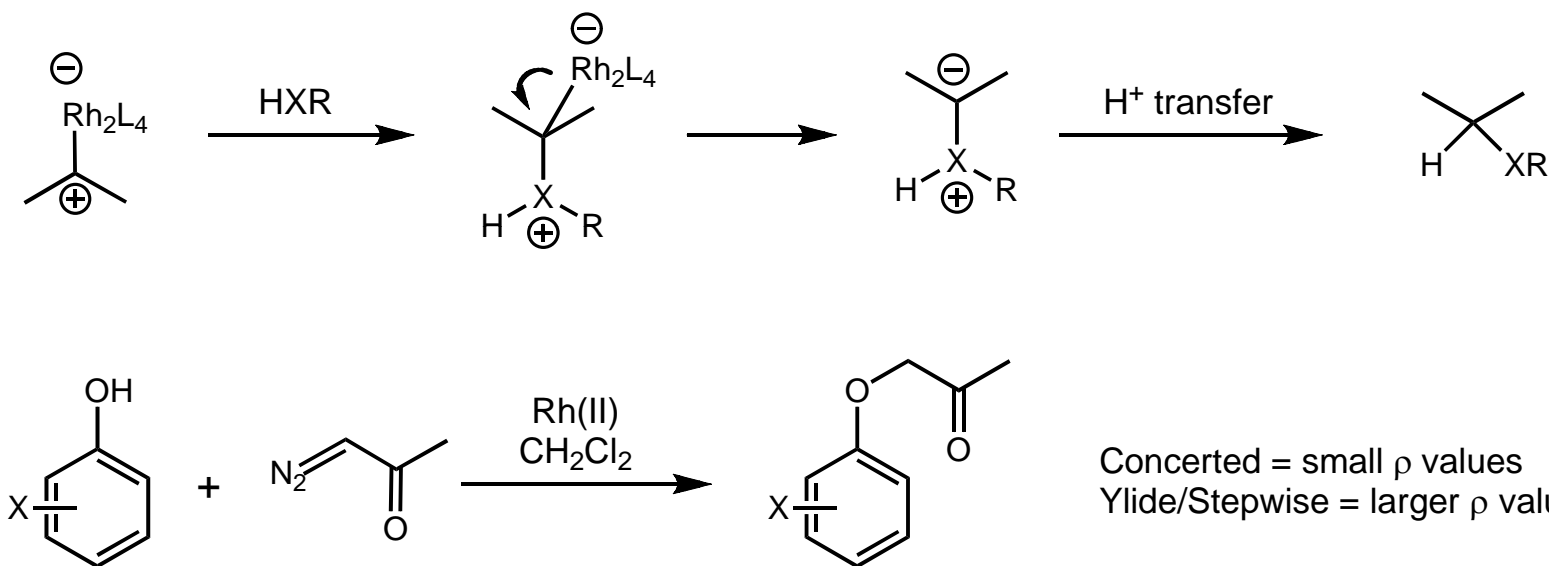


Insertion Mechanisms

Concerted proposed for nonpolar bonds (C-H, Si-H)



Ylide proposed for polar bonds (O-H, N-H)

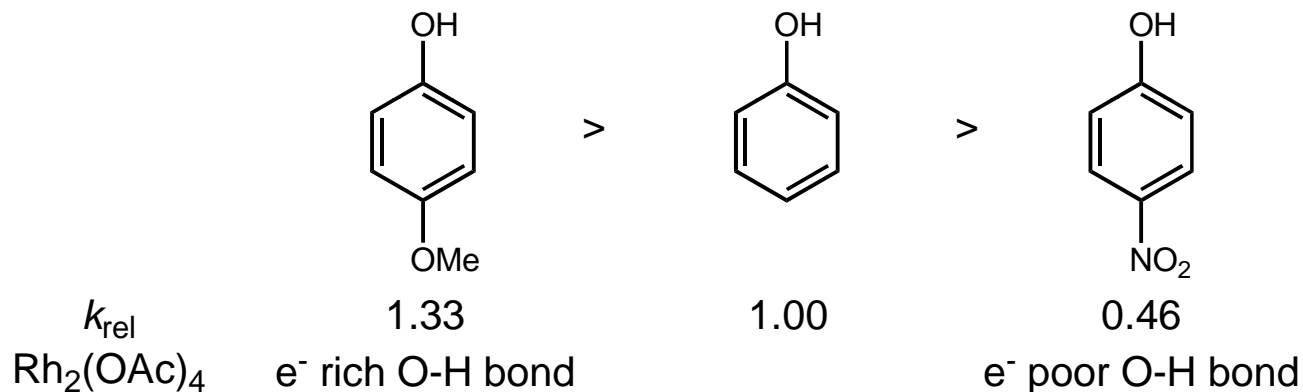


M. P. Doyle, M. A. McKervey and T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley-Interscience, New York, 1998.
Qu, Z.; Shi, W.; Wang, J. *J. Org. Chem.* **2004**, 69, 217-219.

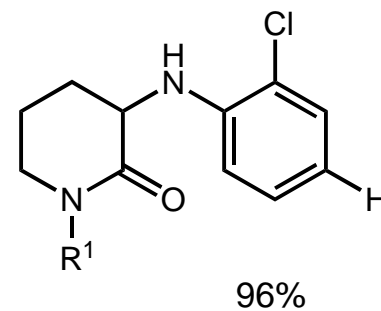
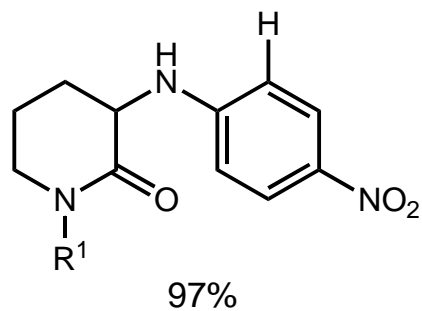
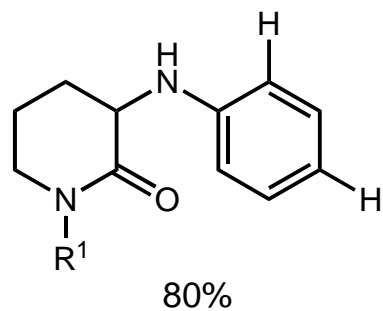
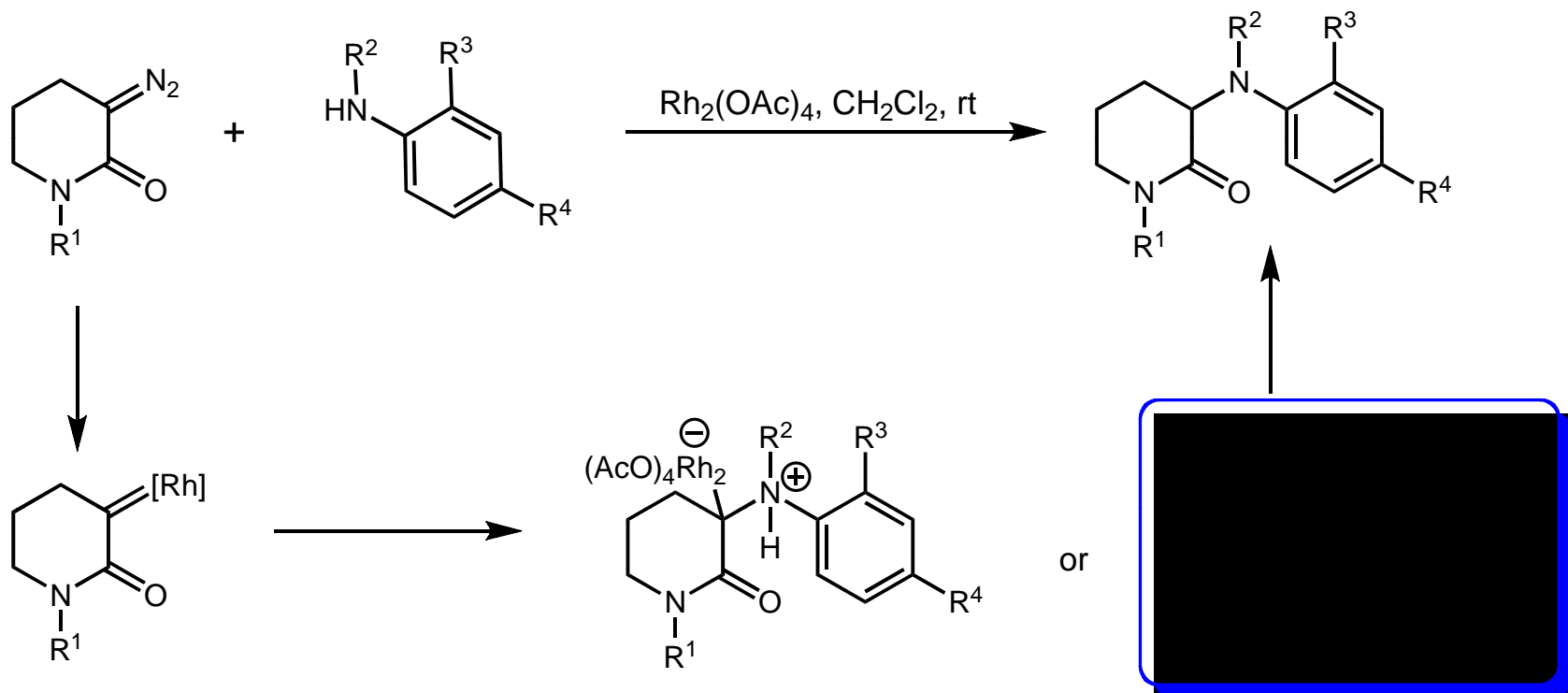
Concerted or Stepwise

substituent constant	ρ (r)		
	$\text{Rh}_2(\text{OAc})_4$	$\text{Rh}_2(\text{OOct})_4$	$\text{Rh}_2(\text{tfa})_4$
σ^+	-0.25 (-0.91)	-0.28 (-0.93)	-0.09 (-0.70)
σ	-0.32 (-0.88)	-0.35 (-0.86)	-0.13 (-0.74)
σ^-	-0.25 (-0.89)	-0.26 (-0.82)	-0.11 (-0.83)

\Rightarrow ρ values smaller than expected for ylide mechanism implies concerted rxn

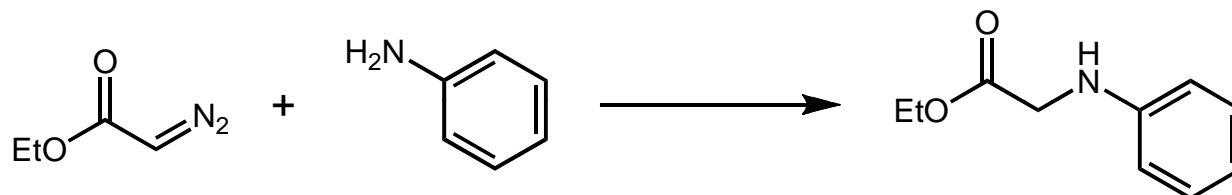


Concerted or Stepwise

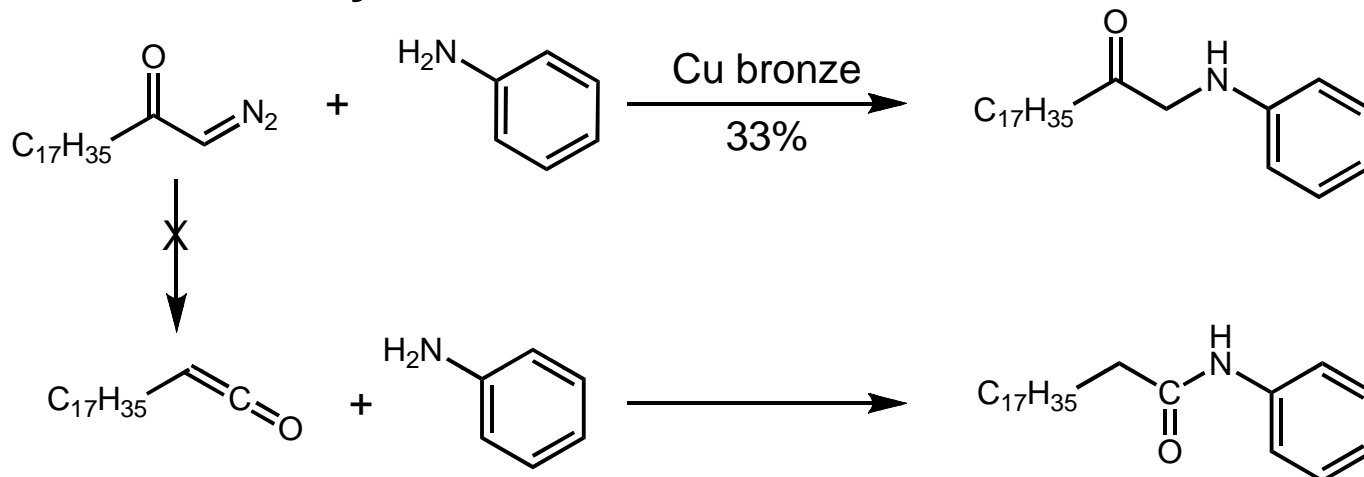


Discovery of N-H Insertions

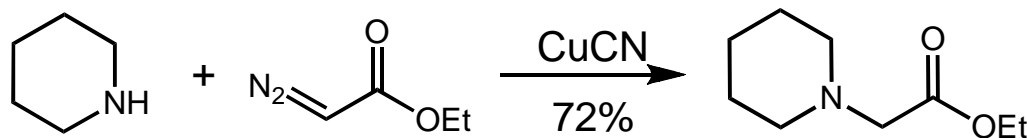
Curtius, 1888



Yates, 1952, first catalytic insertion



Saegusa, 1966, expands upon the work of Yates

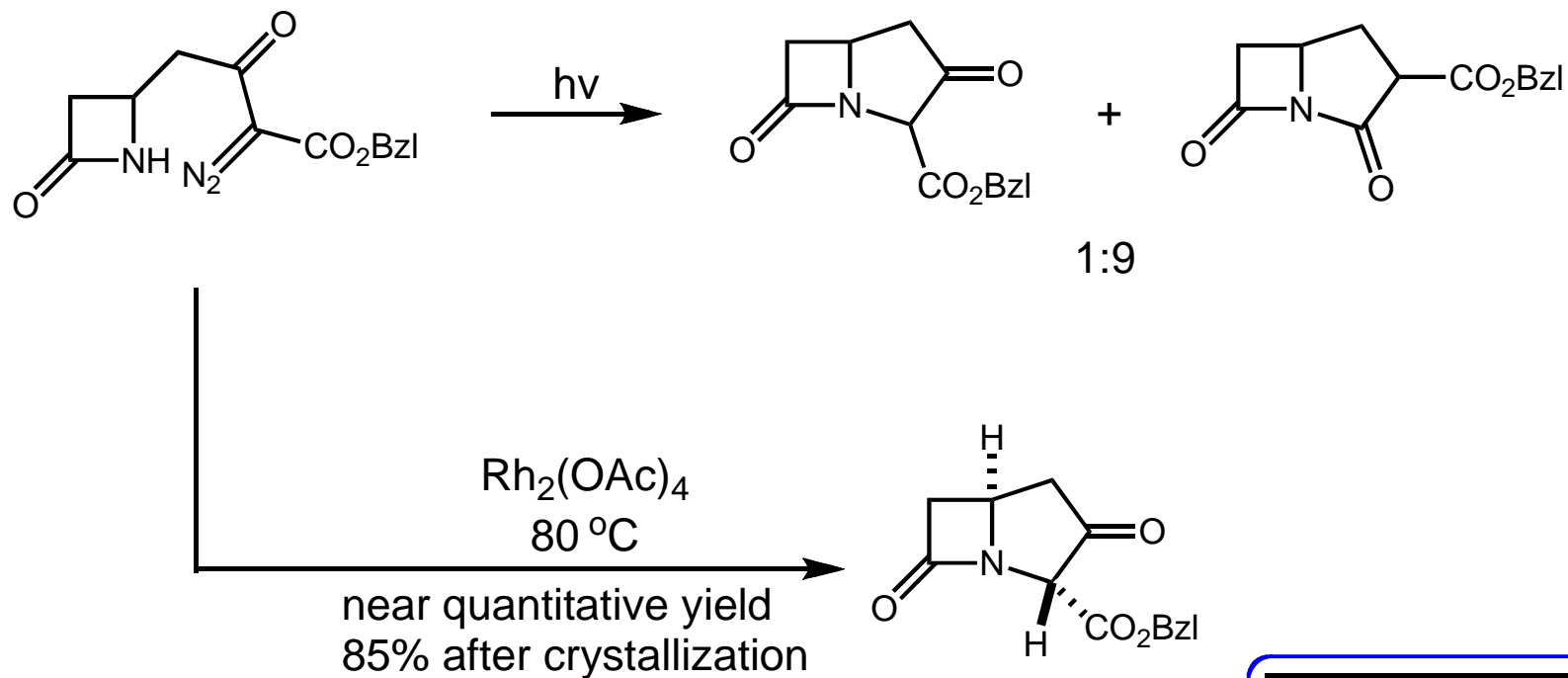


Curtius, T. *J. Prakt. Chem.* **1888**, 38, 396.

Yates, P. *J. Am. Chem. Soc.* **1952**, 74, 5376-5381.

Saegusa, T.; Ito, Y.; Kobayashi, S.; Hirota, K.; Shimizu, T. *Tetrahedron Lett.* **1966**, 49, 6131-6134.

Merck Synthesis of Thienamycin

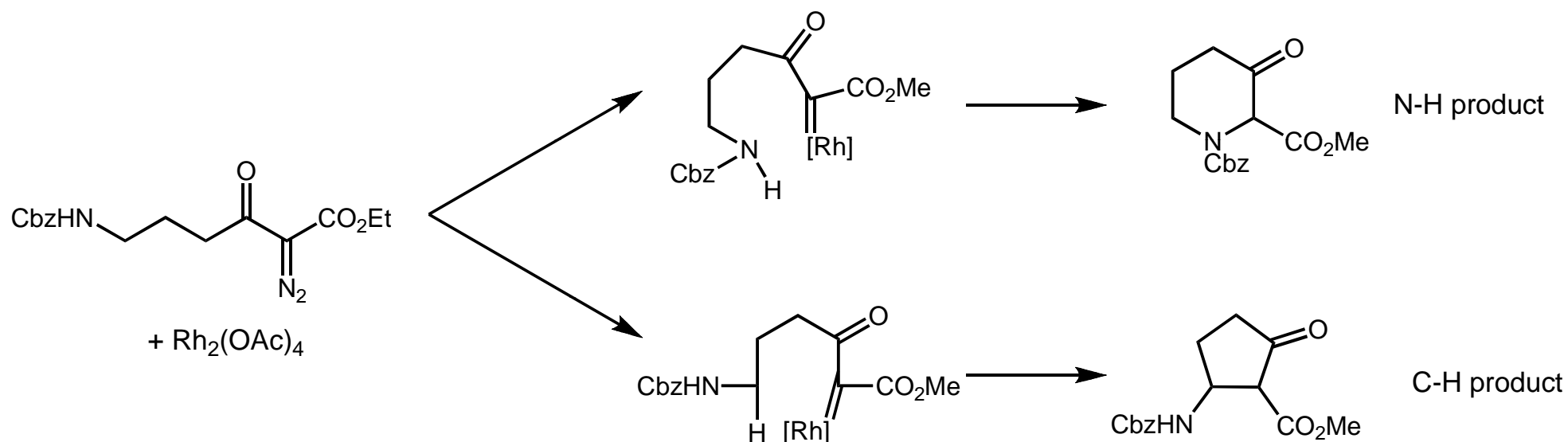


Copper started the field of N-H insertions
Rhodium very effective for β -lactams and very popular
Recent work shows copper also very effective

Outline

- **Background**
- **Intramolecular N-H insertions**
 - 4, 5, and 6-membered aza rings
 - **Synthesis of fully substituted azetidines**
- **Intermolecular N-H insertions**
 - **Asymmetric reactions with rhodium**
 - **Asymmetric reactions with copper**
- **Conclusions**

Why Not Rhodium?



Benzene, 80 °C, 1.5 mol % cat.

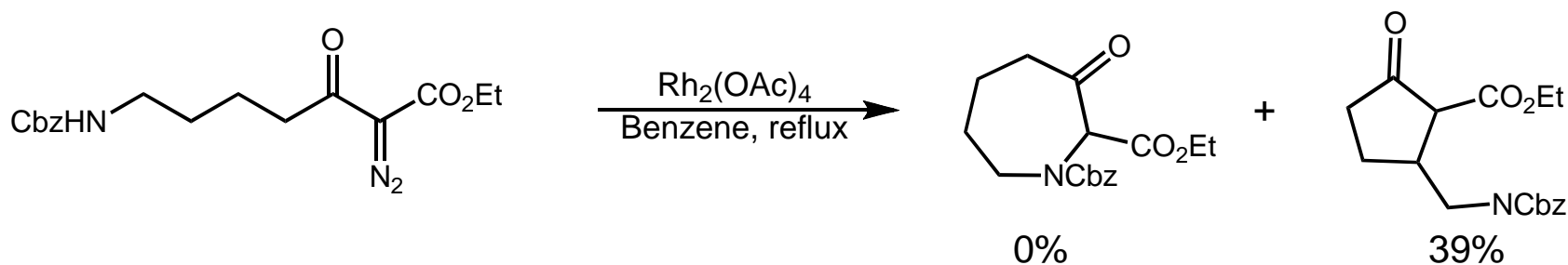
44% N-H

10% C-H

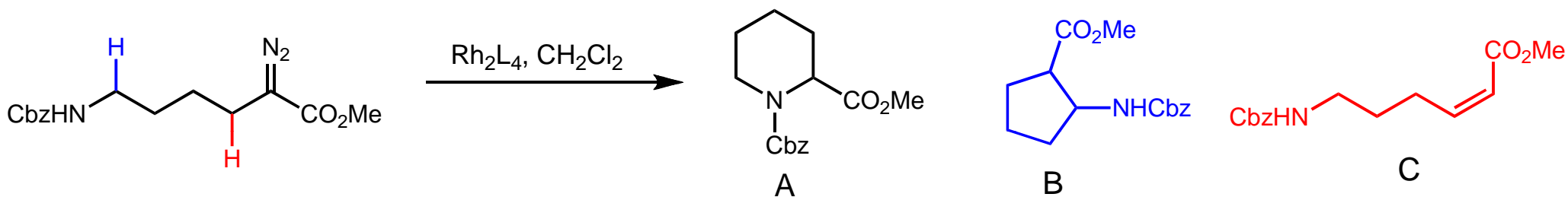
Toluene, 111 °C, 1.5 mol % cat.

56% N-H

7% C-H



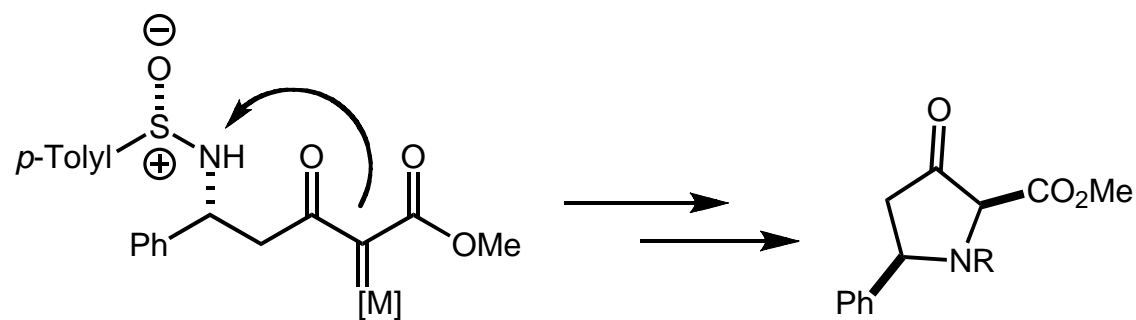
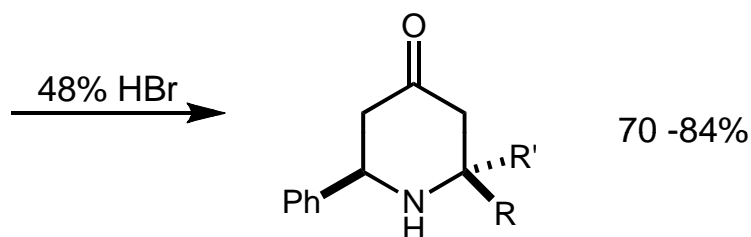
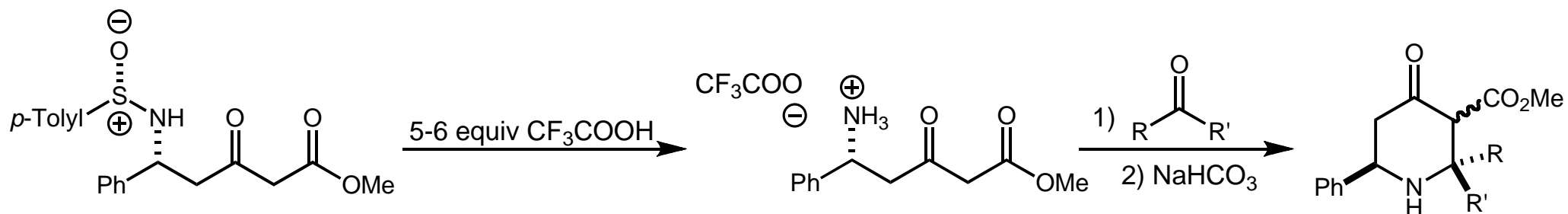
Why Not Rhodium?



Entry	Ligand	Temperature	Product Ratio		
			A	B	C
1		reflux	0	4	1
		room temp.	2.4	1	2.4
2		room temp.	3.2	1	1.9
3		reflux	5	1.2	1
		room temp.	2.5	1	1.8
4		reflux	7	2.6	1
		room temp.	9	3	1
		0 °C	2.6	1	1.3

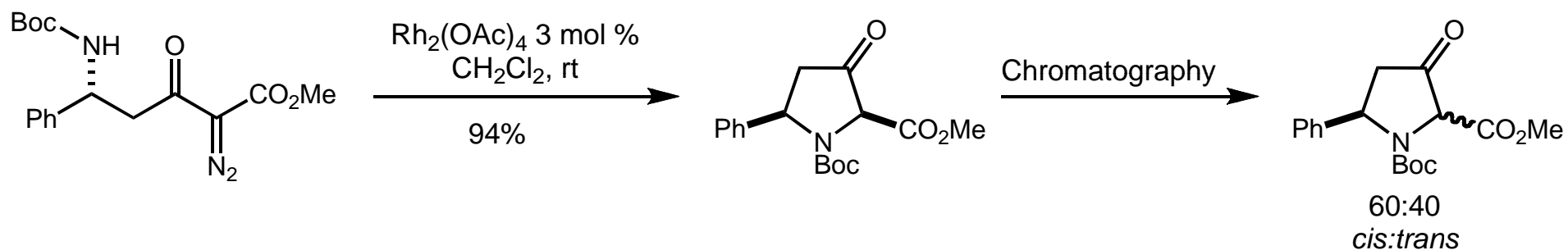
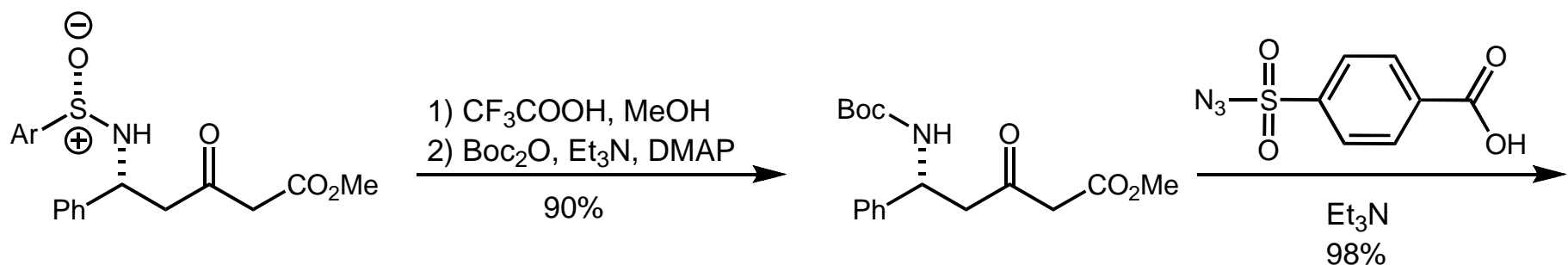
Problems = competitive
C-H insertion and β -elimination

Pyrrolidines from Rhodium

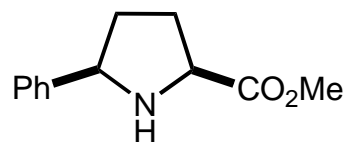
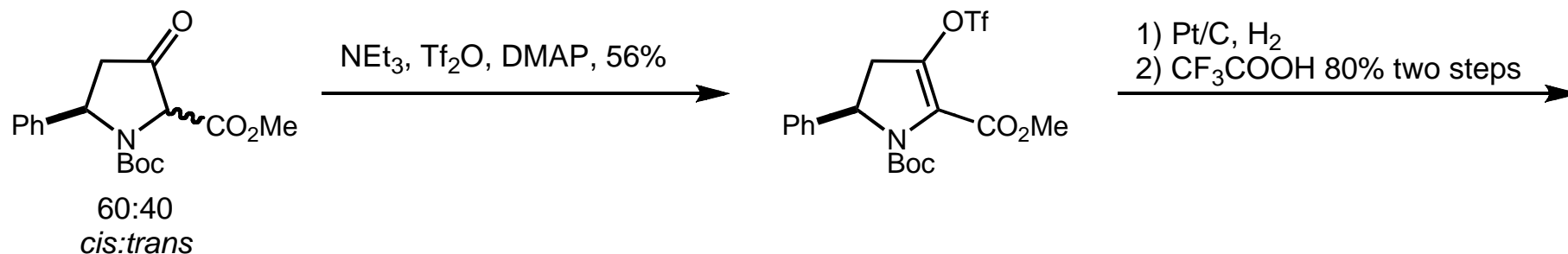


Davis, F.; Chao, B.; Rao, A. *Org. Lett.* **2001**, 3, 3169-3171.
Davis, F.; Fang, T.; Goswami, R. *Org. Lett.* **2002**, 4, 1599-1602.

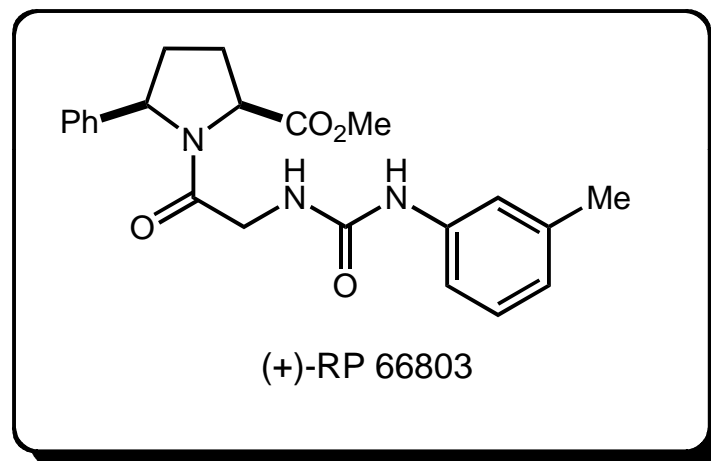
Pyrrolidines from Rhodium



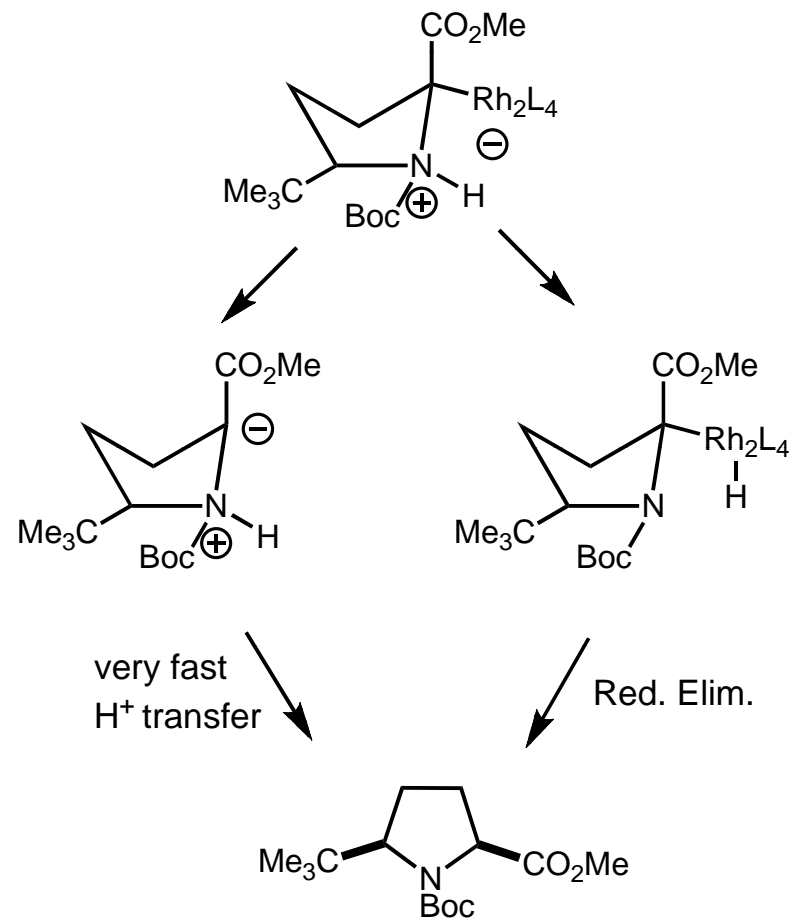
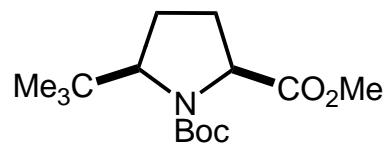
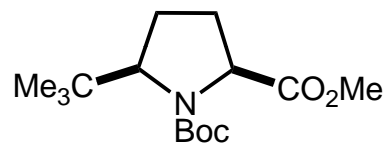
Removal of 3-Oxo Group



Previous synthesis -13 steps
New - 7 from chiral building block

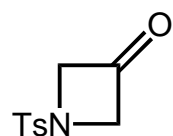
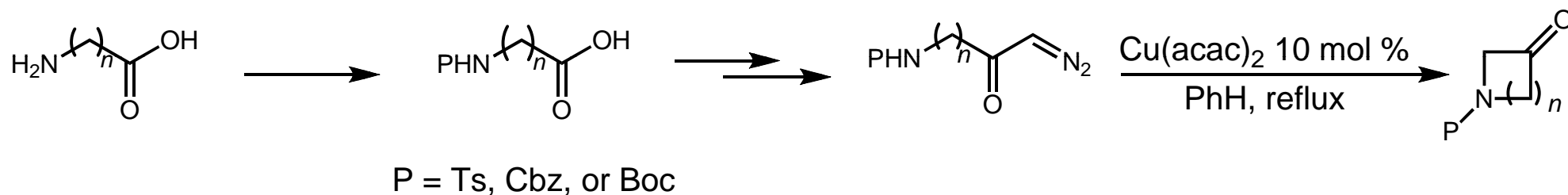


Pyrrolidines from Rhodium

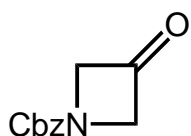


Copper Catalyzed Reactions

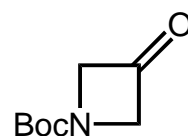
Synthesis of 4, 5, and 6-membered aza rings



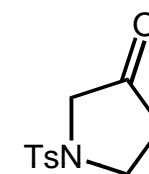
54%



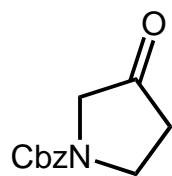
32%



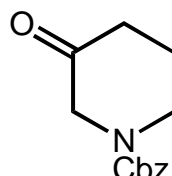
complex mixture



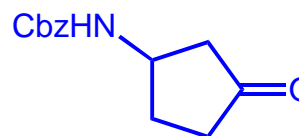
55%



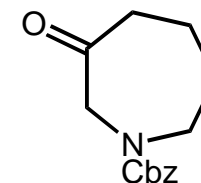
62%



76%

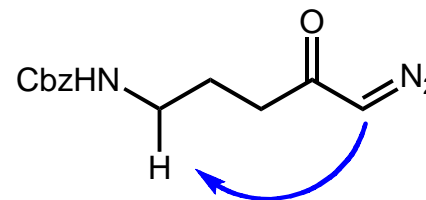


not observed

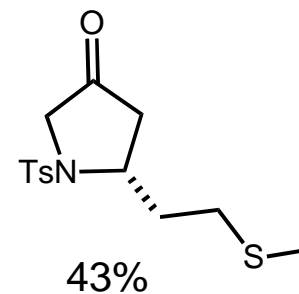
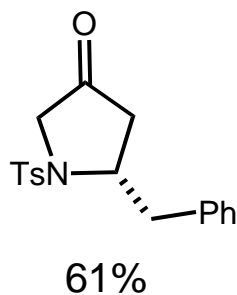
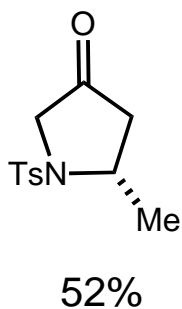
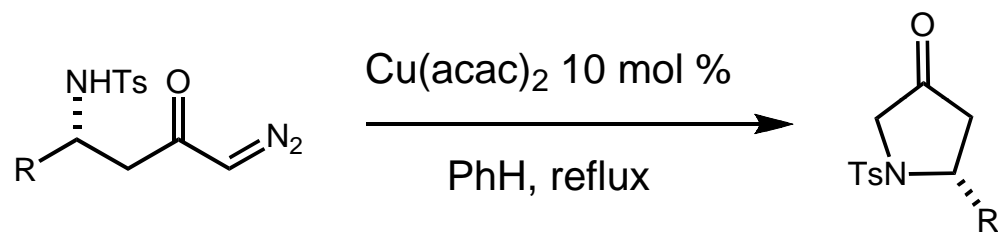
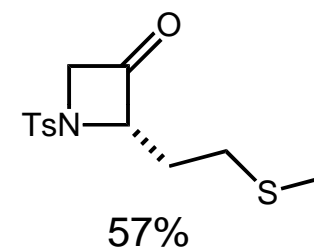
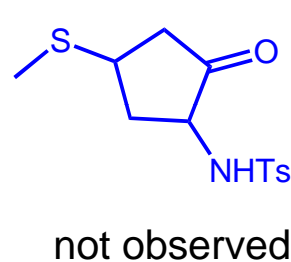
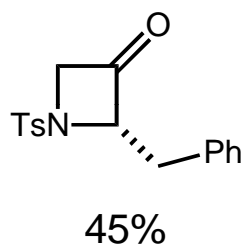
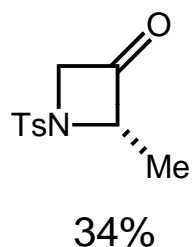
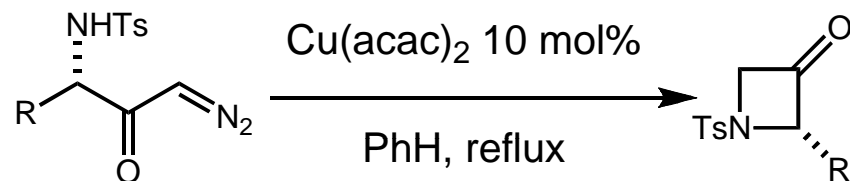


complex mixture

Cu selective for N-H over C-H

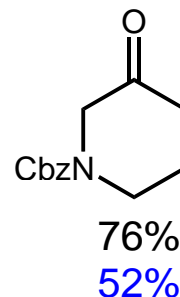
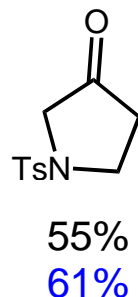
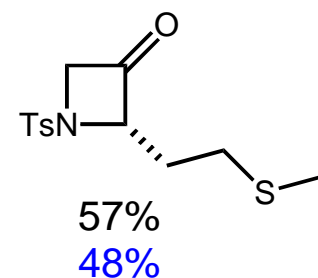
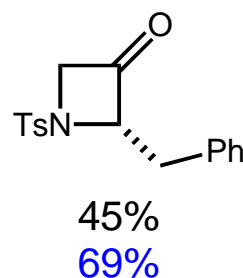
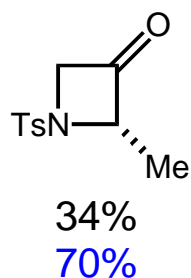
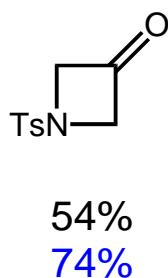
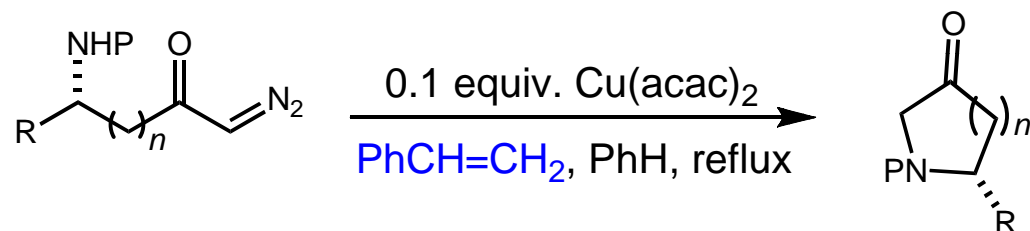


Aza Rings with Functionality



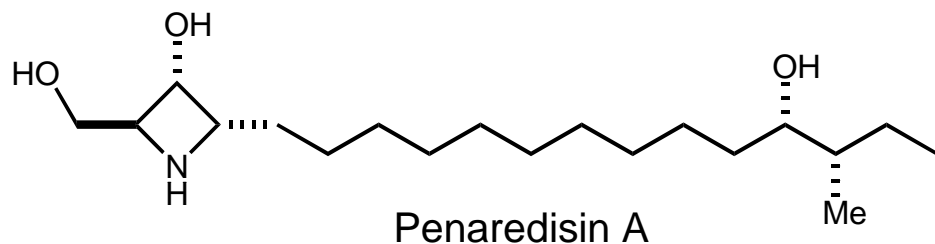
Styrene Additive

$\text{Cu}(\text{acac})_2$ normally used in cyclopropanations

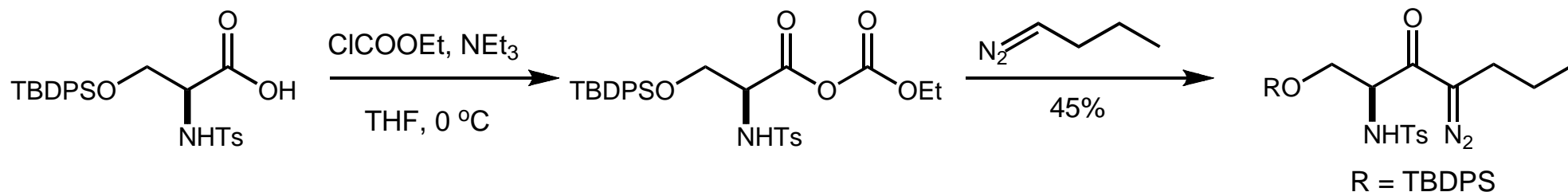
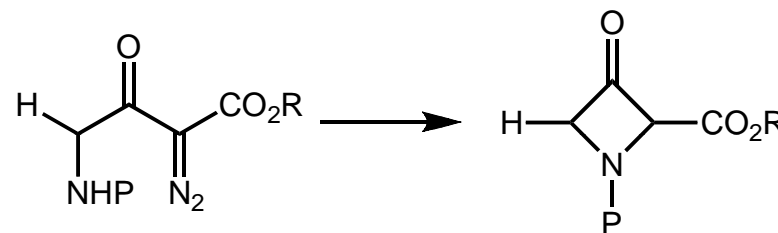
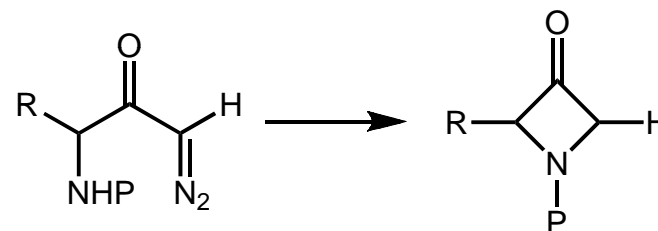


Sigma - $\text{Rh}_2(\text{OAc})_4$ \$244/g, $\text{Cu}(\text{acac})_2$ \$0.33/g

Fully Substituted Azetidines



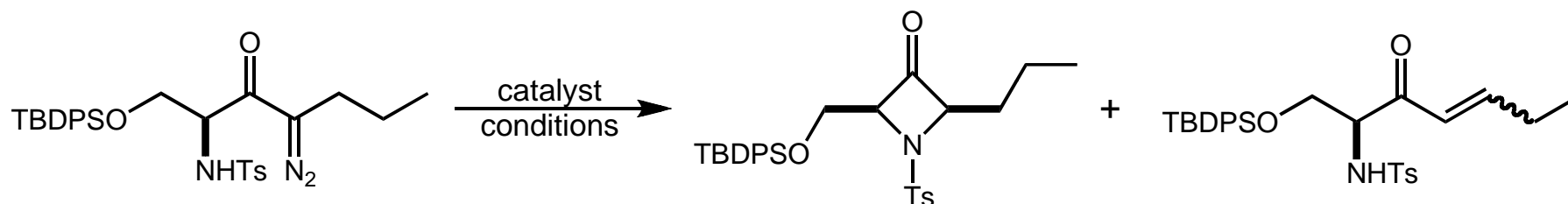
2-substituted azetidin-3-ones



Burtoloso, A.; Correia, C. *Tetrahedron Lett.* **2004**, *45*, 3355-3358.
Burtoloso, A.; Correia, C. *J. Organomet. Chem.* **2005**, *690*, 5636-5646.

Fully Substituted Azetidines

Catalyst Screen



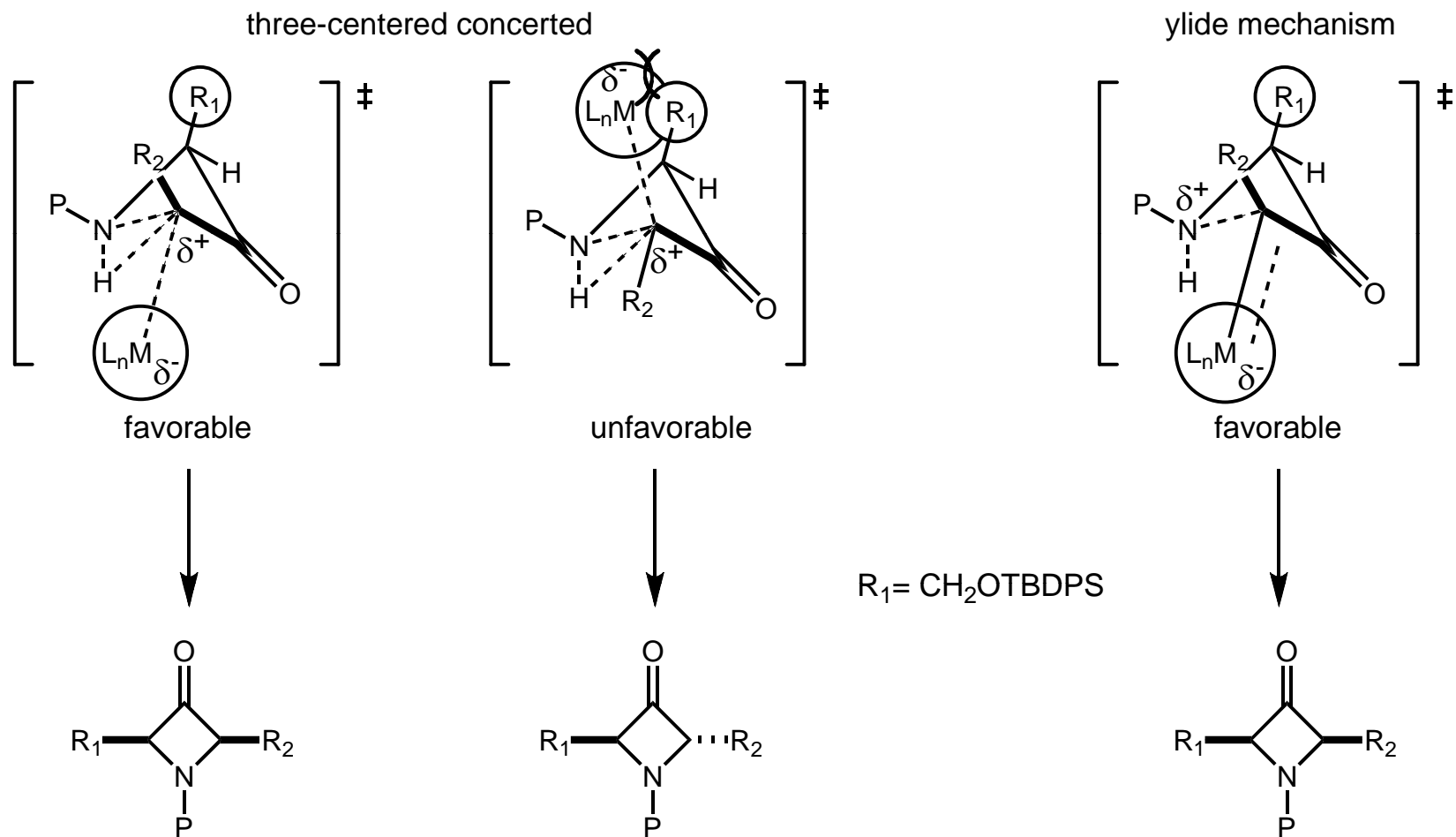
Catalyst	Conditions	Azetidine-3-one Yield	Olefin Yield
Rh ₂ (OAc) ₄	CH ₂ Cl ₂ , 0 °C, 1 h	~35	not determined
Rh ₂ (OAc) ₄	CH ₂ Cl ₂ , rt, 15 min	0	89
Rh ₂ (OAc) ₄	C ₆ H ₆ , rt, 45 min	0	63
Rh ₂ (OAc) ₄	C ₆ H ₆ , reflux 1 min	0	81
Cu(acac) ₂	CH ₂ Cl ₂ , rt, 24 h	no reaction	no reaction
Cu(acac) ₂	C ₆ H ₆ , rt, 24 h	0	67
Cu(acac) ₂	C ₆ H ₆ , 60 °C, 45 min	41	35
Cu(acac) ₂	C ₆ H ₆ , reflux, 1 min	67	22
Cu(OAc) ₂ *H ₂ O	C ₆ H ₆ , reflux, 1 min	77	17

Burtoloso, A.; Correia, C. *Tetrahedron Lett.* **2004**, 45, 3355-3358.

Burtoloso, A.; Correia, C. *J. Organo-metallic Chem.* **2005**, 690, 5636-5646.

Fully Substituted Azetidines

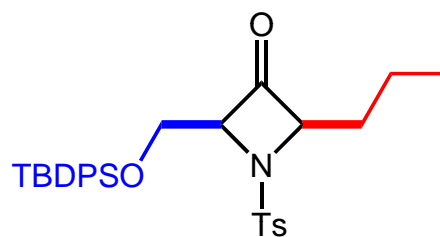
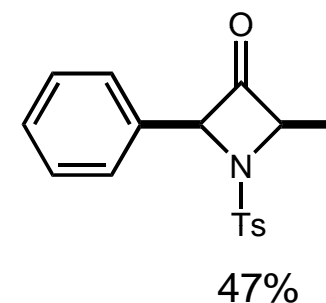
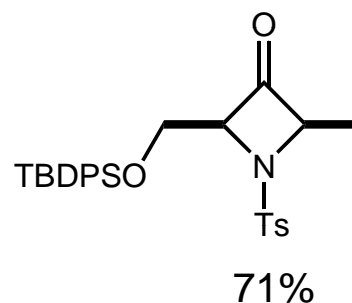
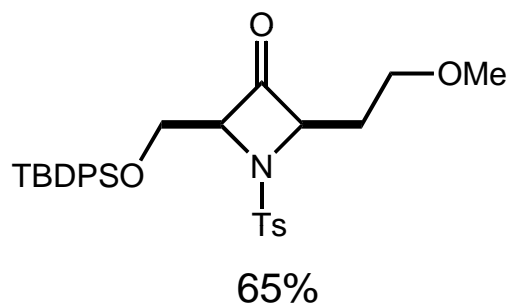
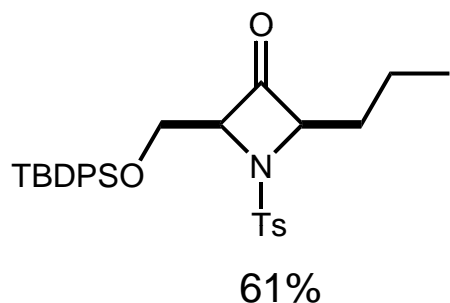
Transition State Models



Burtoloso, A.; Correia, C. *Tetrahedron Lett.* **2004**, 45, 3355-3358.
Burtoloso, A.; Correia, C. *J. Organometallic Chem.* **2005**, 690, 5636-5646.

Fully Substituted Azetidines

Substrates



serine, alanine, phenylalanine,
valine, etc.

diazobutane, diazomethane, etc.

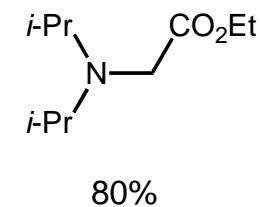
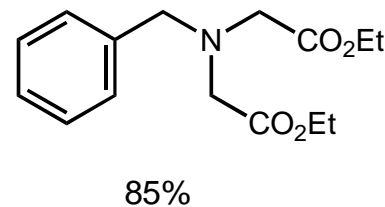
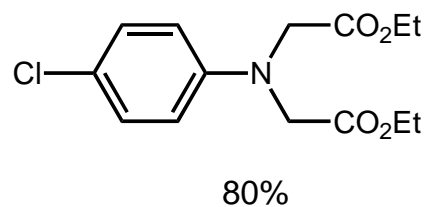
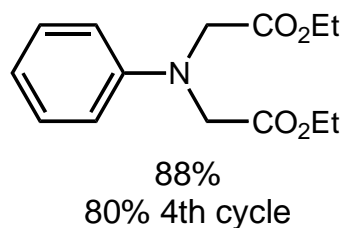
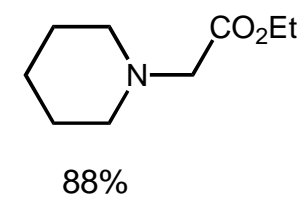
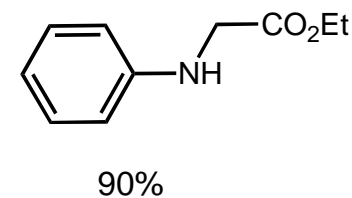
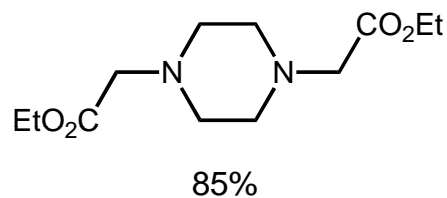
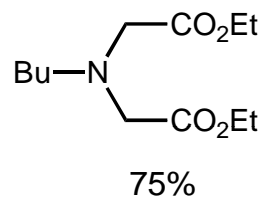
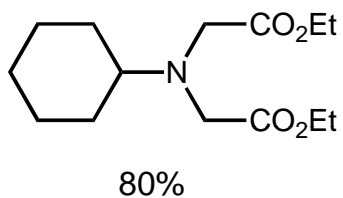
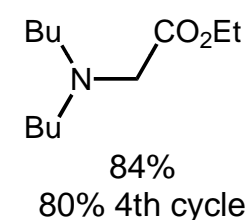
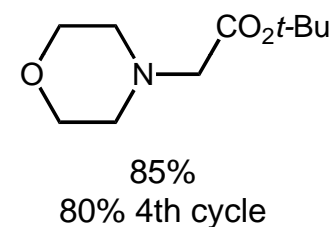
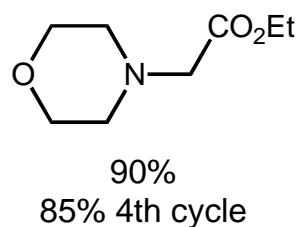
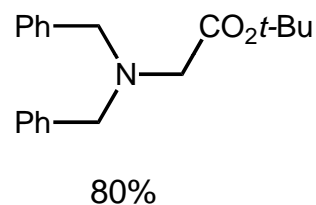
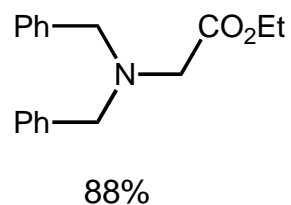
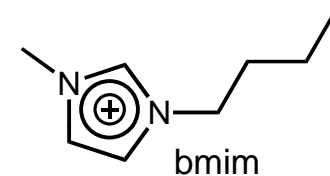
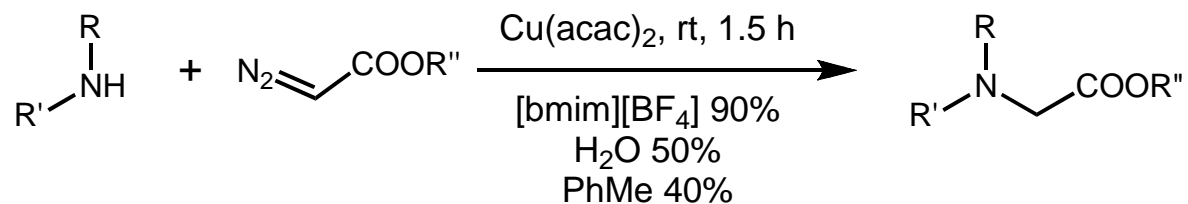
Amino acid stereochemistry determines other stereocenters

Burtoloso, A.; Correia, C. *Tetrahedron Lett.* **2004**, *45*, 3355-3358.
Burtoloso, A.; Correia, C. *J. Organomet. Chem.* **2005**, *690*, 5636-5646.

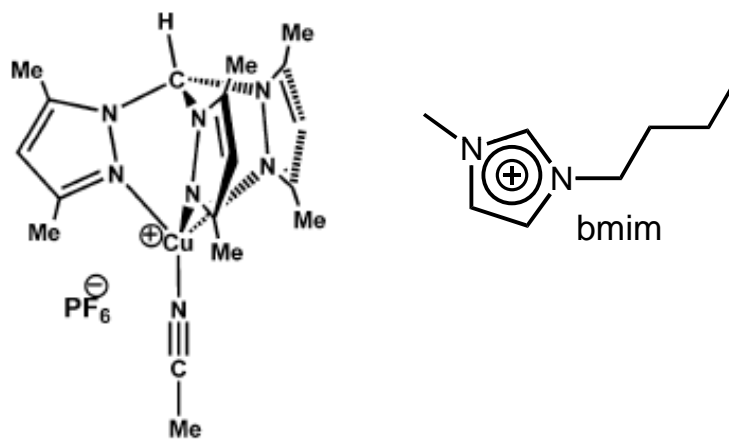
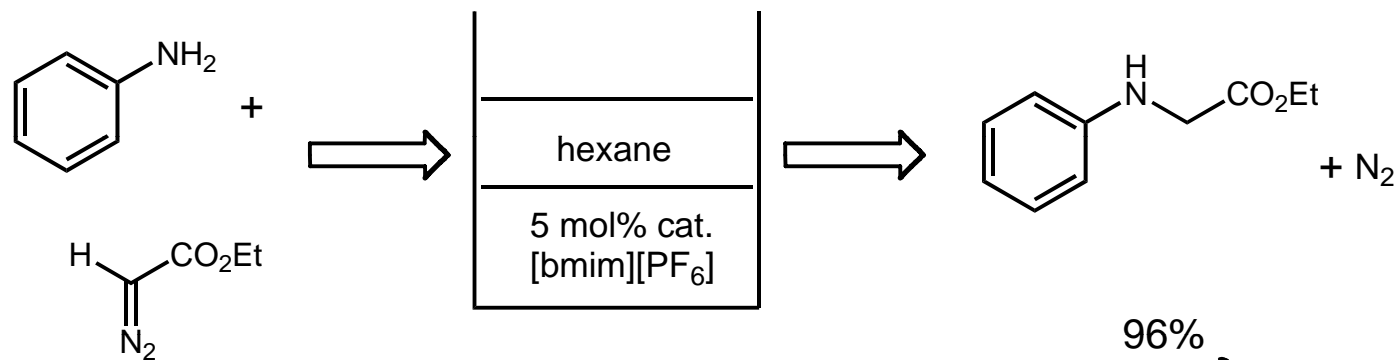
Outline

- **Background**
- **Intramolecular N-H insertions**
 - 4, 5, and 6-membered aza rings
 - **Synthesis of fully substituted azetidines**
- **Intermolecular N-H insertions**
 - **Asymmetric reactions with rhodium**
 - **Asymmetric reactions with copper**
- **Conclusions**

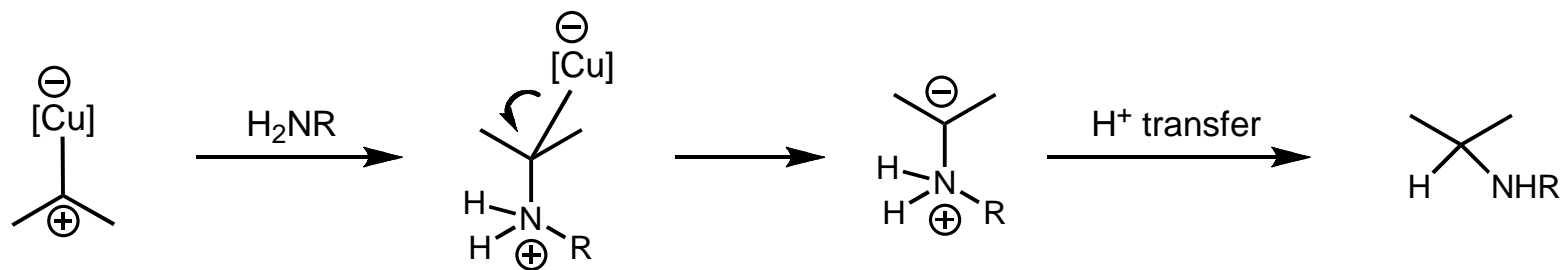
Copper in Ionic Liquids



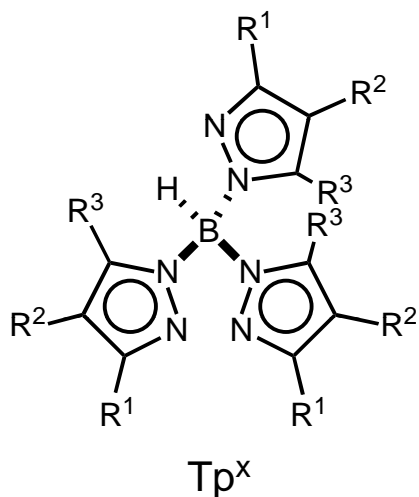
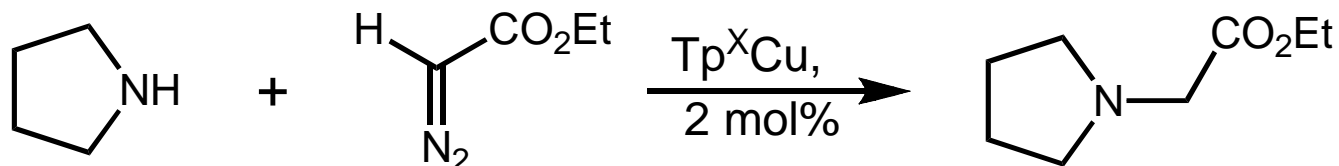
Ionic Liquids



96%
93%
94%
95%
95% } recycle ionic liquid layer



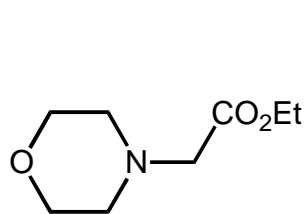
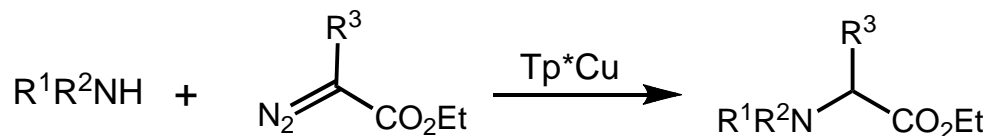
Insertions with Homoscorpionate Ligands



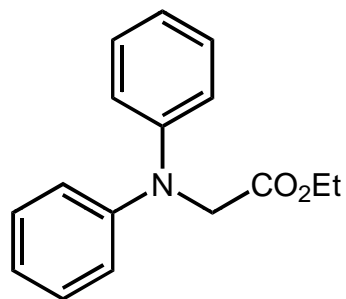
Tp^X	R^1	R^2	R^3	Time (min)	Yield (%)
Tp^*	Me	H	Me	20	> 95
Tp^{Cy}	Cy	H	H	20	> 95
Tp^{Ph}	Ph	H	H	120	> 95
Tp^{Ms}	Ms	H	H	240	> 95

$\text{Cu}(\text{OTf})$ and $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ gave between 70-80%

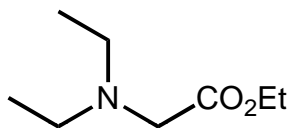
Substrate Scope



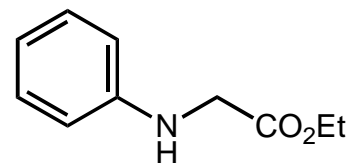
> 95%



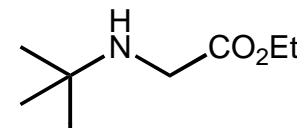
90%



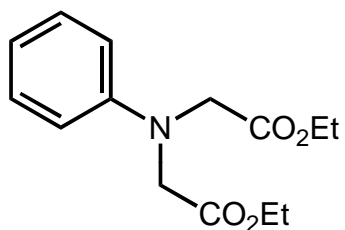
> 95%



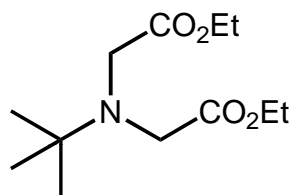
> 95%



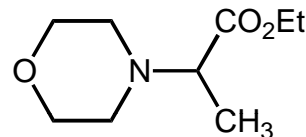
> 95%



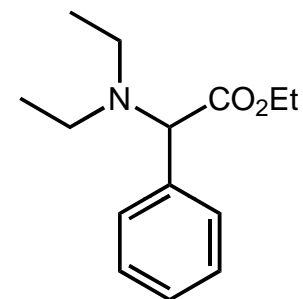
> 95%
2 equiv. EDA



> 95%
2 equiv. EDA

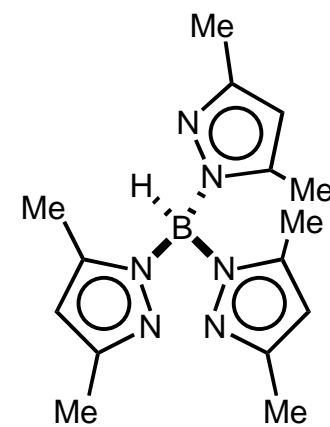


quantitative



80%

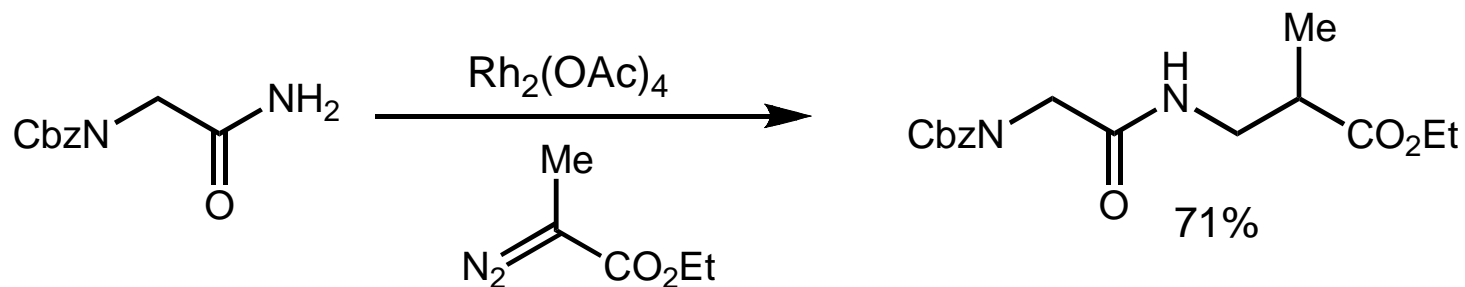
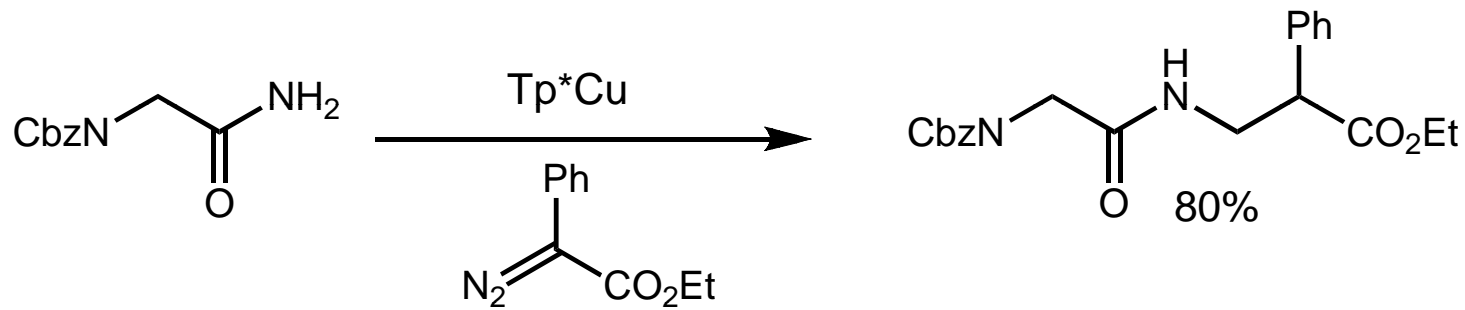
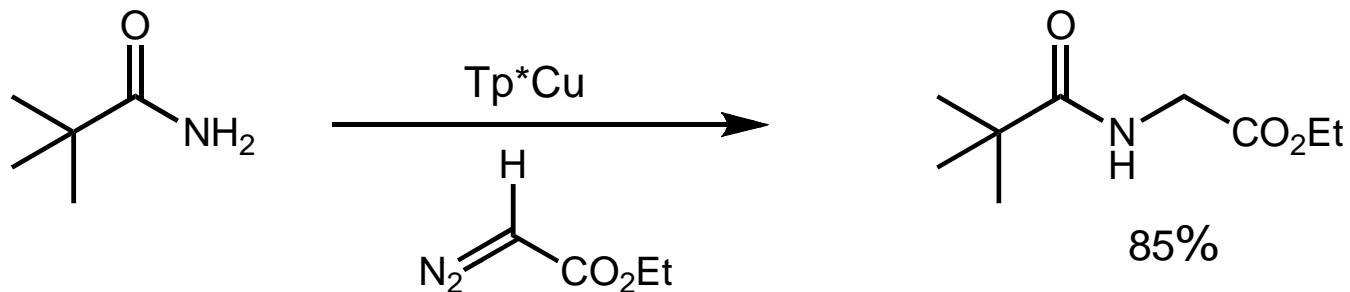
No excess amine required
Room temp. reactions
Unprecedented yields



Tp*

Peptide Bonds

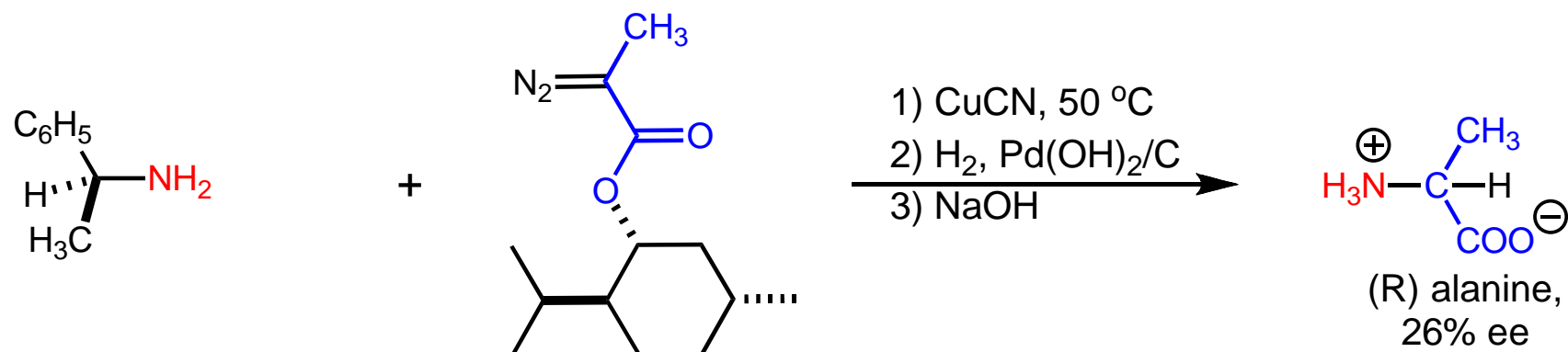
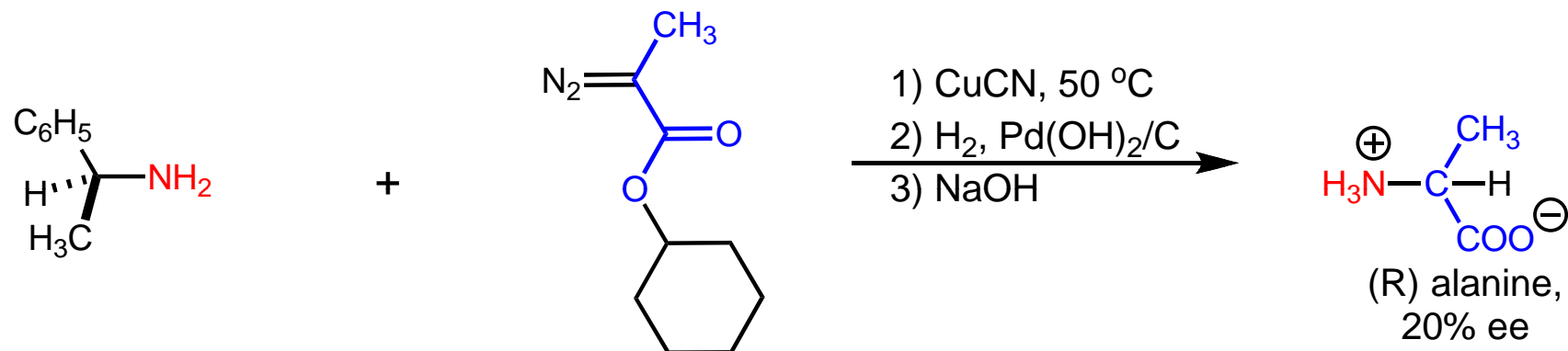
Competitive with Rhodium Chemistry



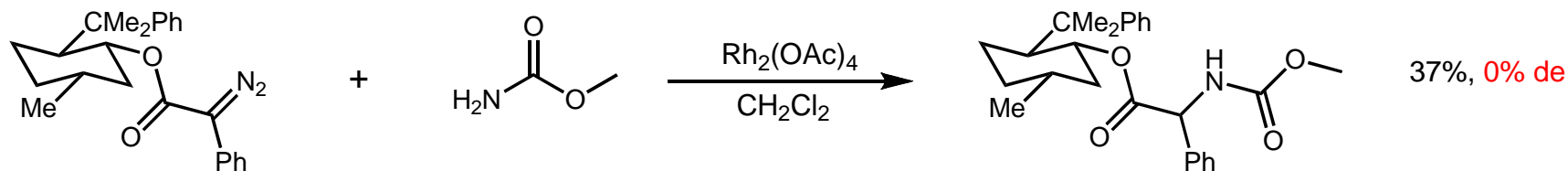
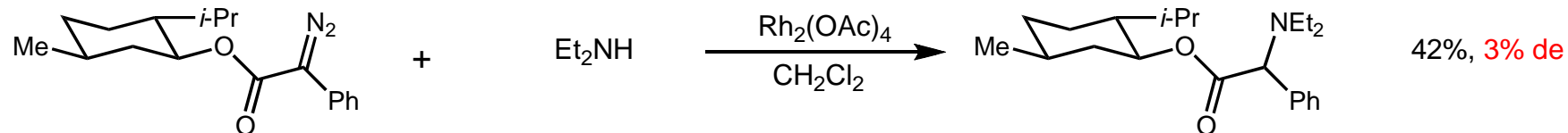
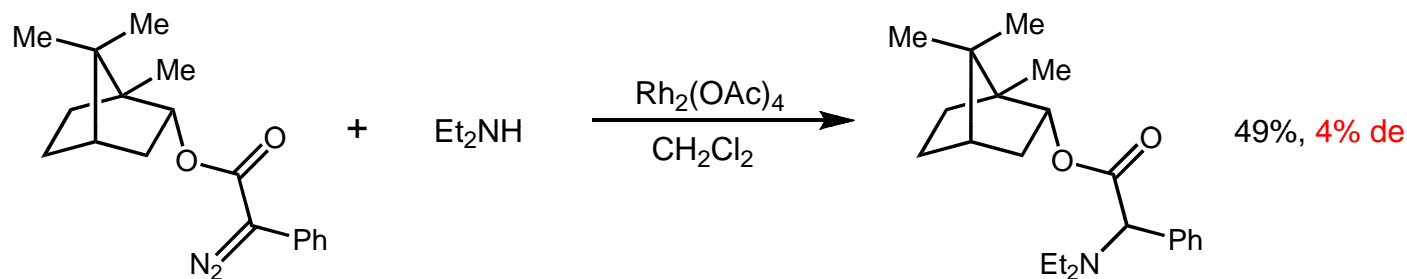
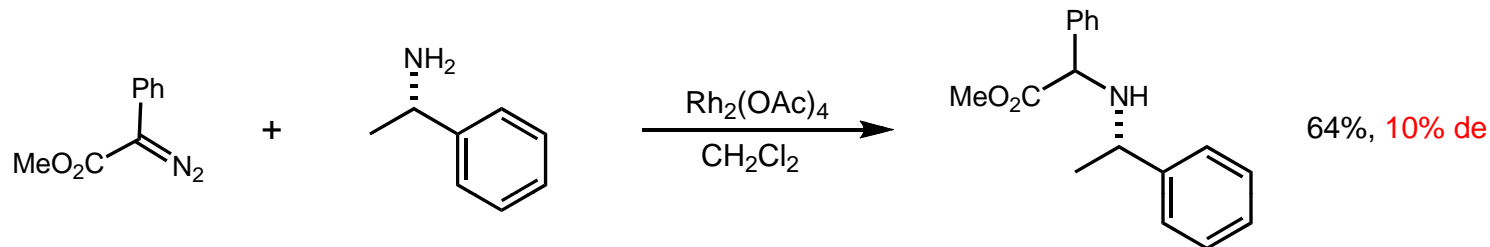
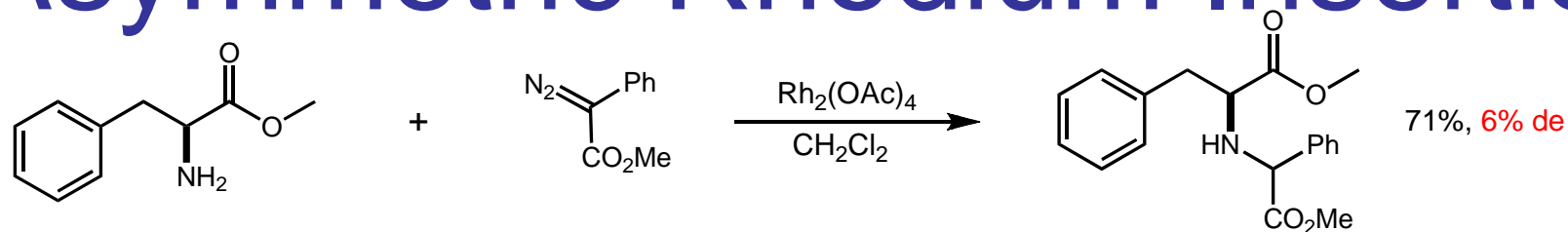
Morilla, M.; Diaz-Requejo, M.; Belderrain, T.; Nicasio, M.; Trofimenko, S.; Perez, P.
Chem. Commun. **2002**, 2998-2999.

Bagley, M.; Buck, R.; Hind, S.; Moody, C. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 591-5960.

Seminal Asymmetric N-H Insertions



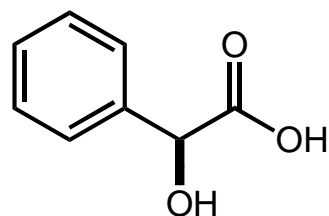
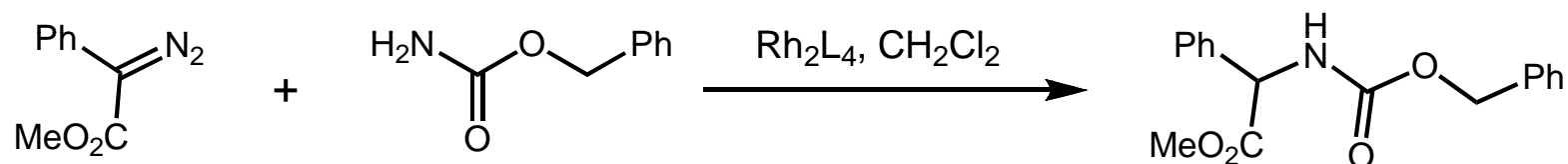
Asymmetric Rhodium Insertions



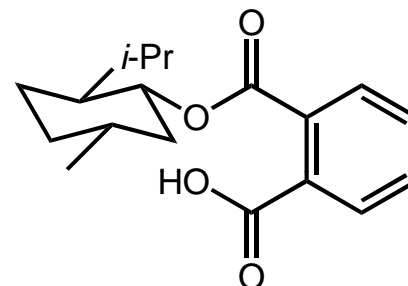
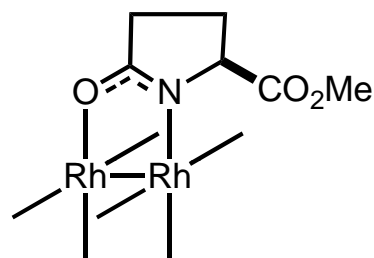
Aller, E.; Buck, R.; Drysdale, M.; Ferris, L.; Haigh, D.; Moody, C.; Pearson, N.; Sanghera, J.
J. Chem. Soc., Perkin Trans. 1. **1996**, 2879-2884.

Asymmetric Rhodium Insertions

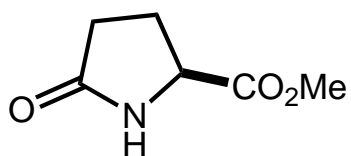
Chiral Catalysts



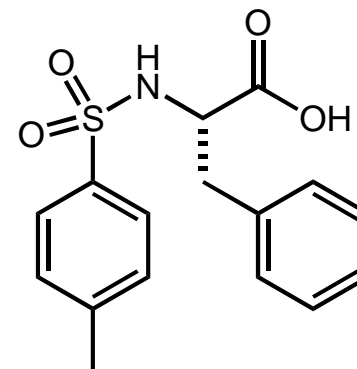
92%, 2% ee



80%, 4% ee



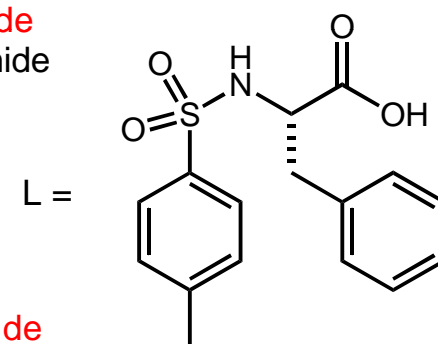
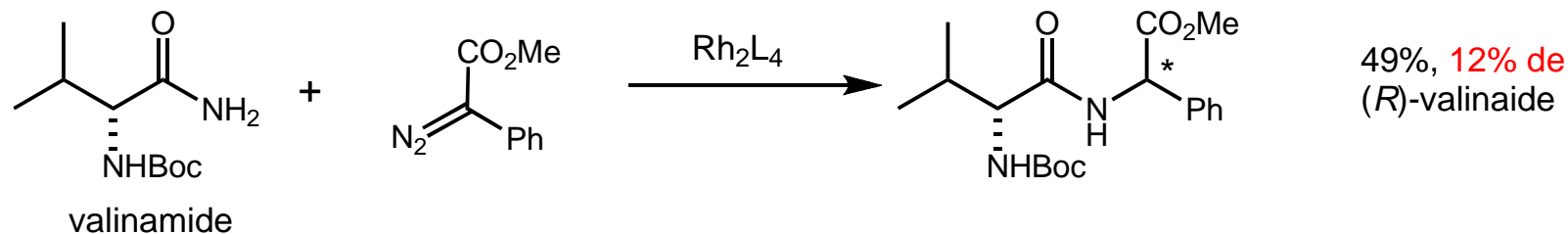
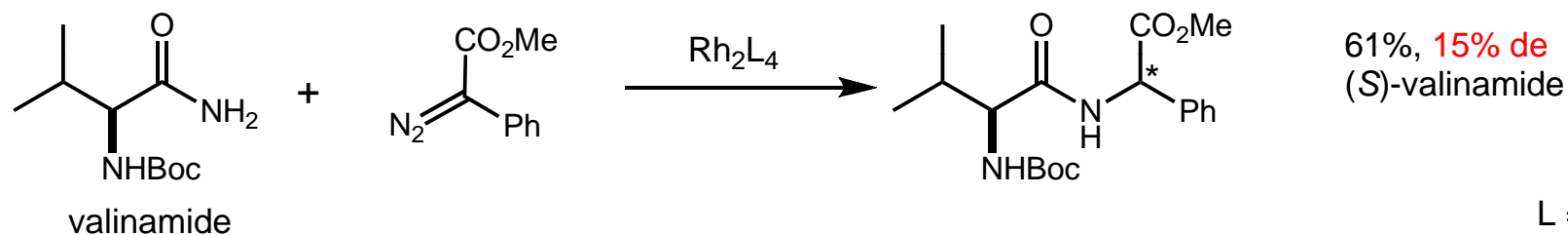
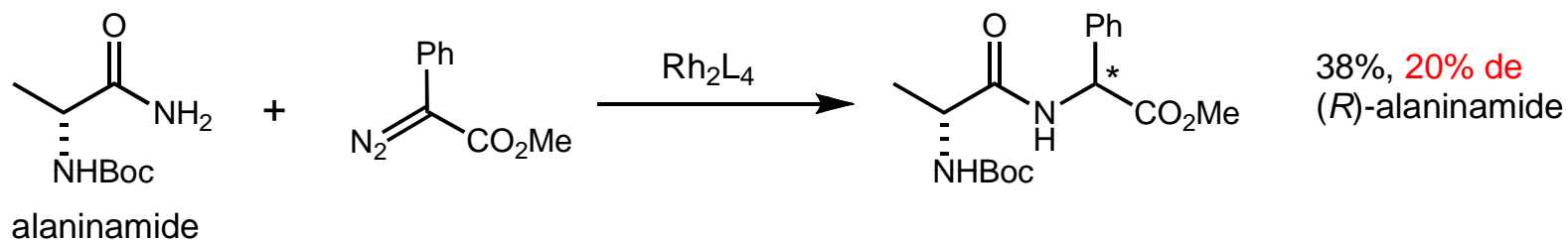
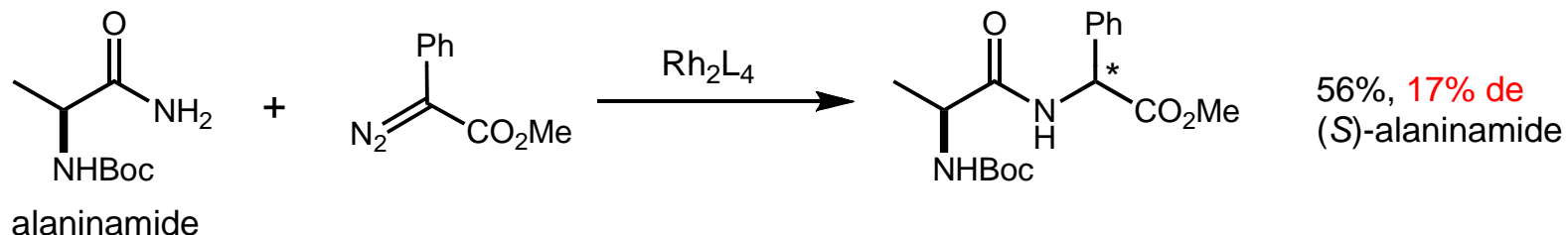
62%, 0% ee



69%, 4% ee

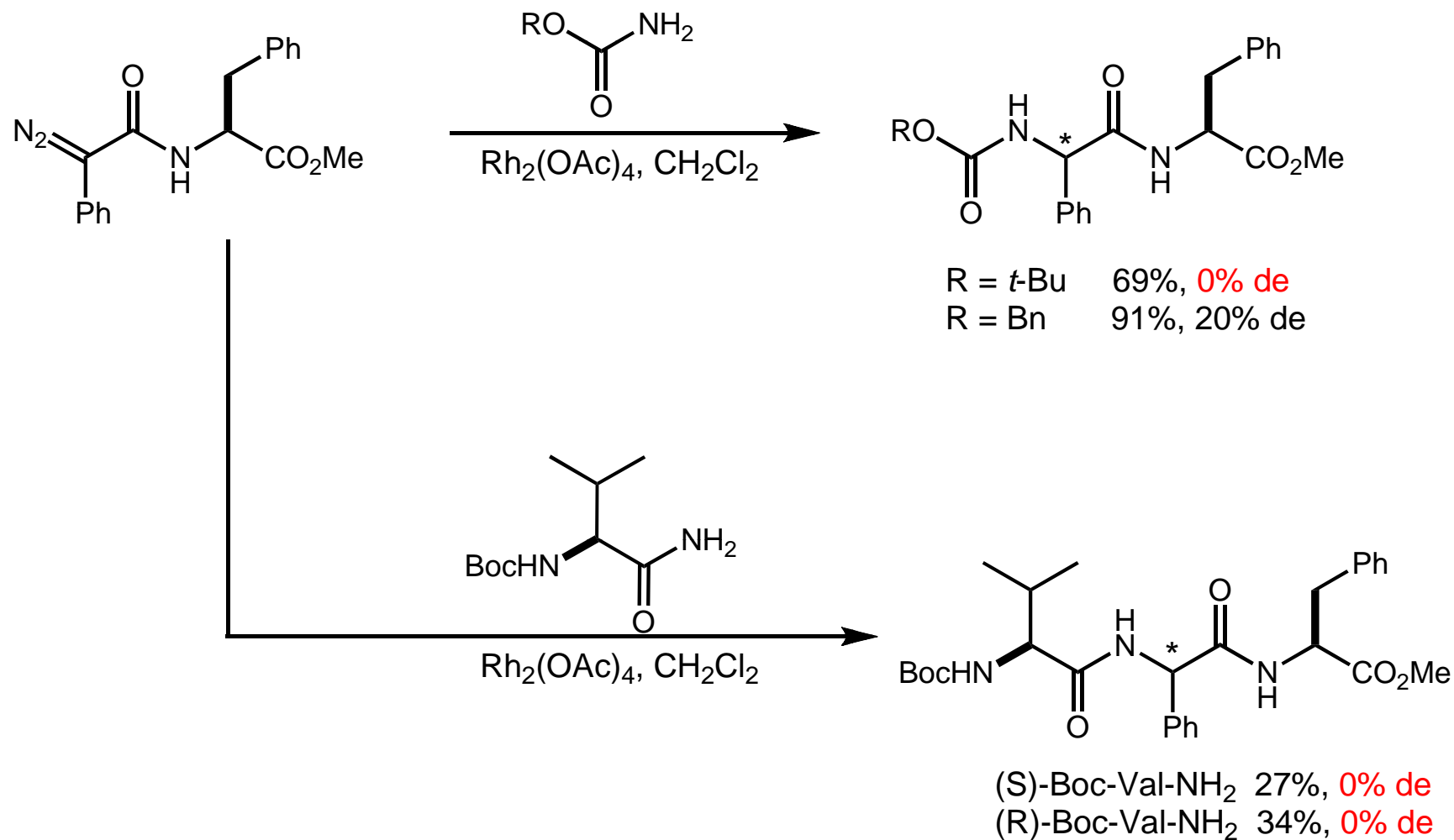
Asymmetric Rhodium Insertions

N-H Bond from Chiral Amides

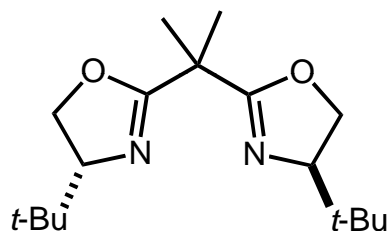
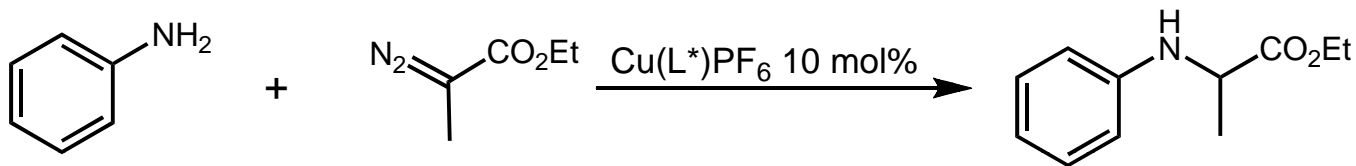


Asymmetric Rhodium Insertions

Chiral Diazo Compounds

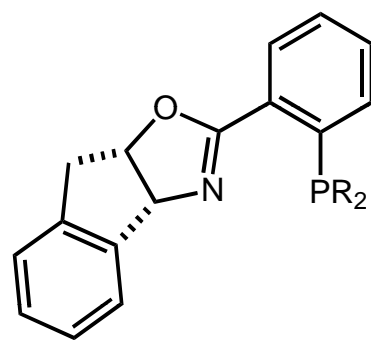


Copper Shows Promise



CuPF_6 , CH_2Cl_2 ,
54%, 28% ee

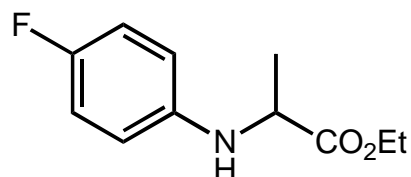
CuOTf , CH_2Cl_2 ,
33%, racemic



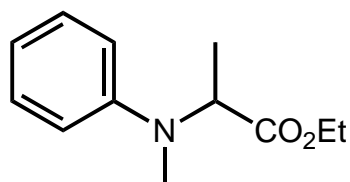
R = tol, CuPF_6 , CH_2Cl_2 ,
95%, 5% ee

R = 2,4-dimethylphenyl, CuPF_6 ,
 CH_2Cl_2 , 75%, 26% ee

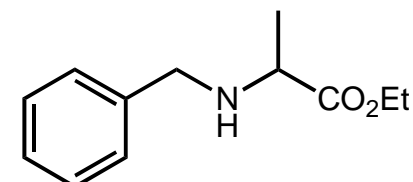
Moody - 20% ee
Nicoud/Kagan - 26% ee



40%, 20% ee

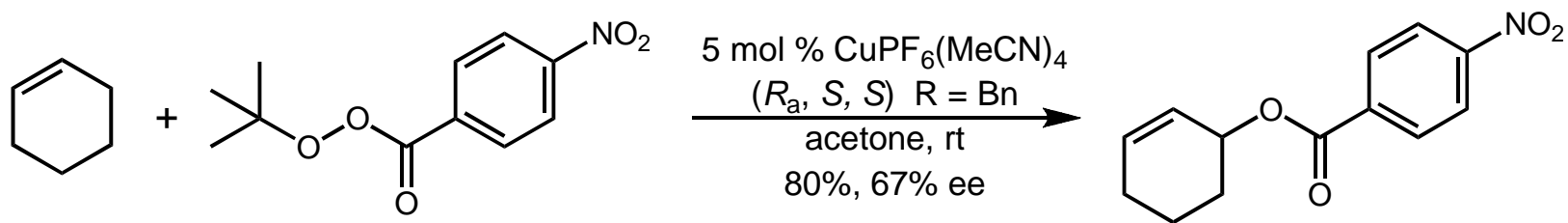
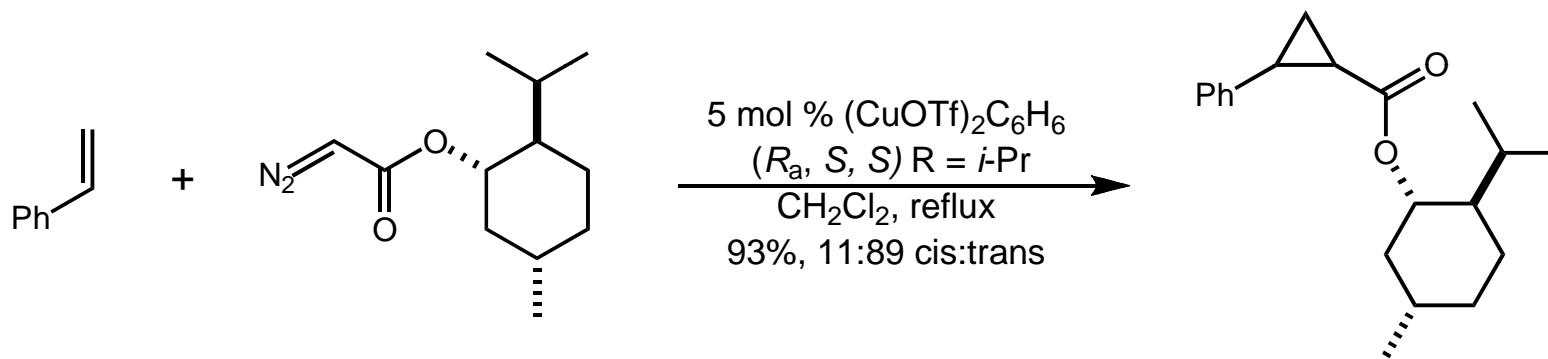
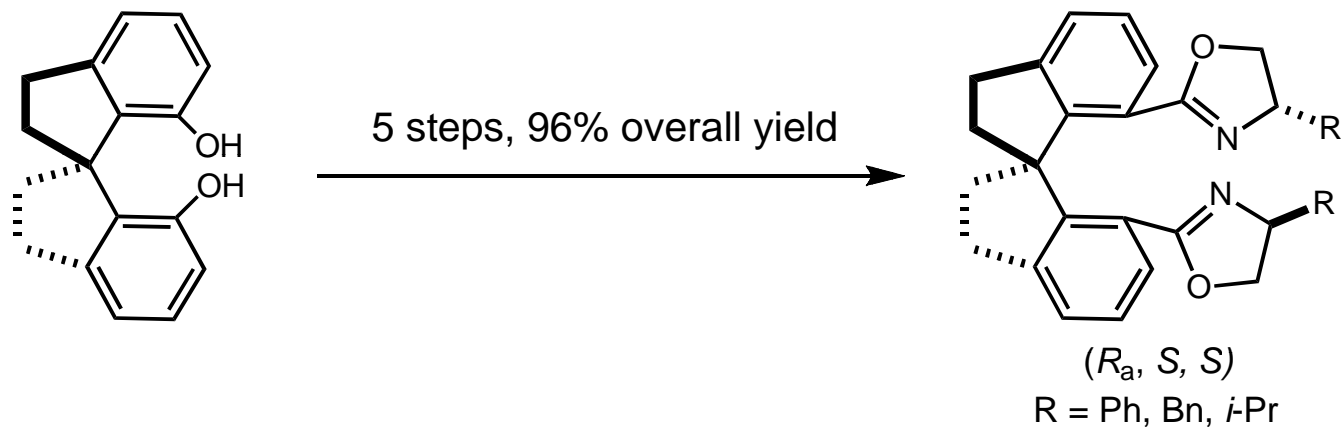


29%, 9% ee

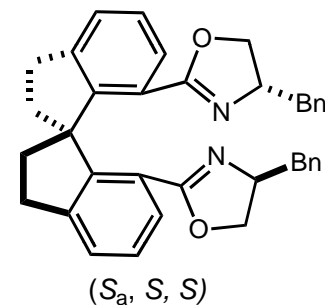


27%, 10% ee
(R)

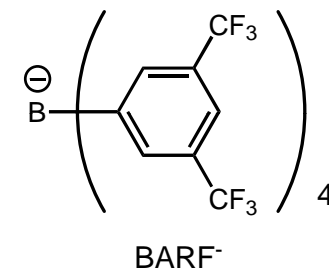
Spiro Bisoxazolines



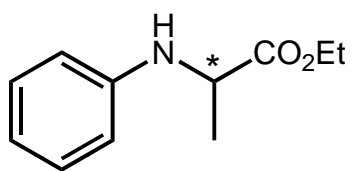
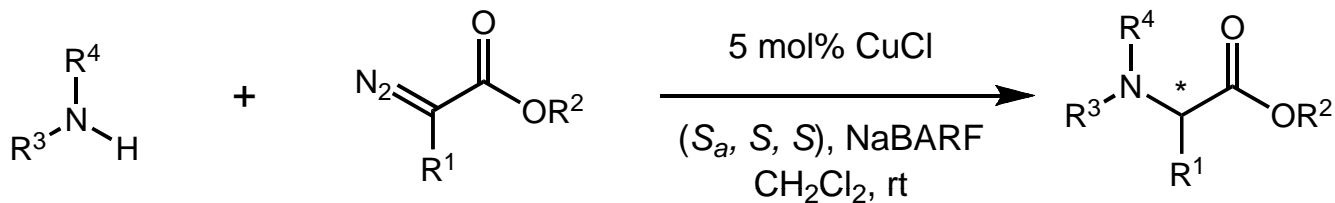
Spiro Bisoxazolines



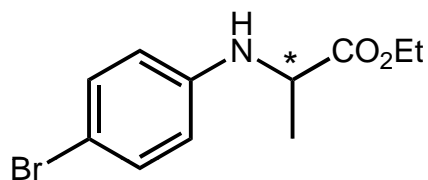
ligand	[Cu]	solvent	time (h)	yield (%)	ee (%)
(S _a , S, S)	CuPF ₆ (MeCN) ₄	CH ₂ Cl ₂	2	78	43
(R _a , S, S)	CuPF ₆ (MeCN) ₄	CH ₂ Cl ₂	2	95	5
(S _a , S, S)	CuOTf(Tol) _{1/2}	CH ₂ Cl ₂	2	83	5
(S _a , S, S)	CuCl	CH ₂ Cl ₂	24	15	rac
(S _a , S, S)	CuCl/NaBARF	CH ₂ Cl ₂	2	94	98
(S _a , S, S)	CuCl ₂ /NaBARF	CH ₂ Cl ₂	2	80	85
(S _a , S, S)	CuCl/NaBARF	CHCl ₃	2	89	98
(S _a , S, S)	CuCl/NaBARF	C ₆ H ₆	6	80	85



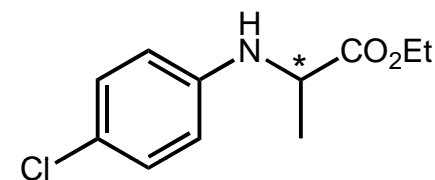
Spiro Bisoxazolines



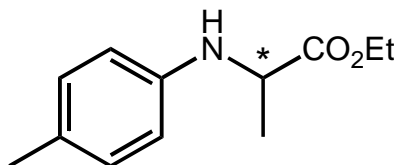
94%, 98% ee



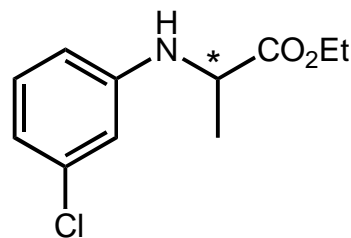
95%, 98% ee



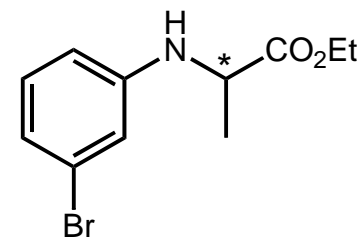
92%, 98% ee



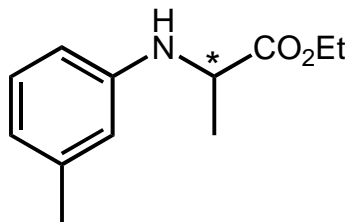
94%, 91% ee



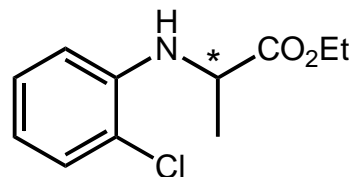
95%, 97% ee



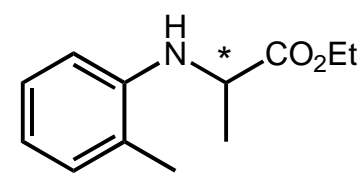
96%, 98% ee



92%, 96% ee

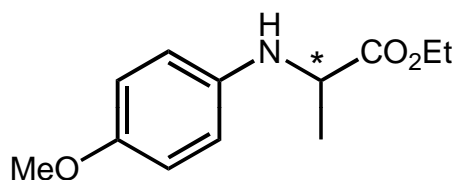
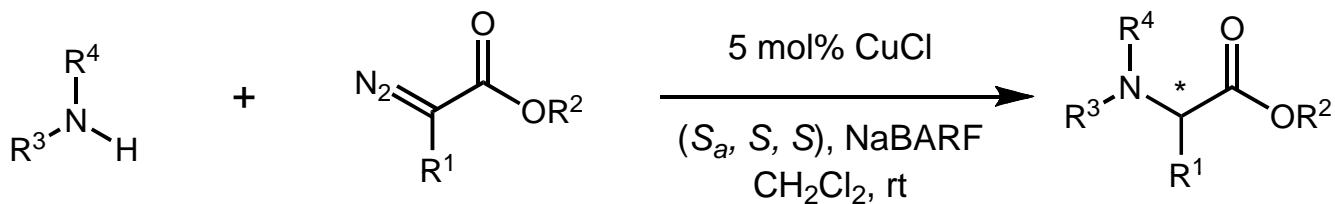


95%, 88% ee

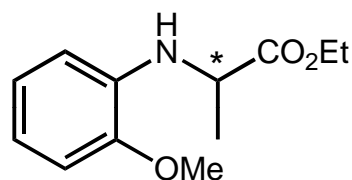


95%, 98% ee

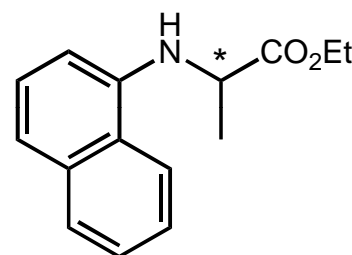
Spiro Bisoxazolines



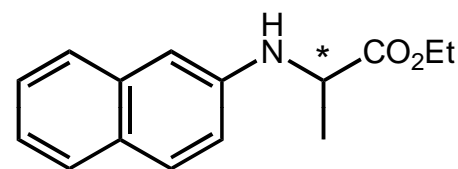
96%, 85% ee



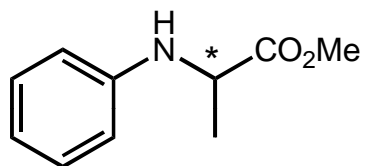
86%, 96% ee



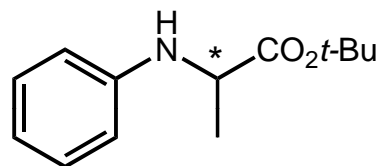
89%, 98% ee



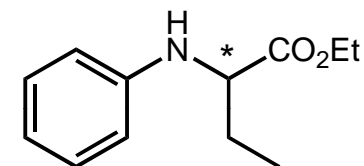
91%, 98% ee



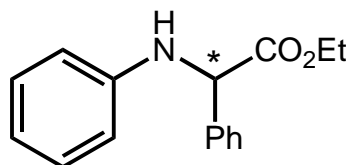
78%, 96% ee



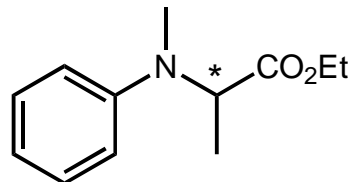
93%, 96% ee



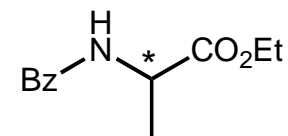
51%, 94% ee



85%, 8% ee



93%, racemic

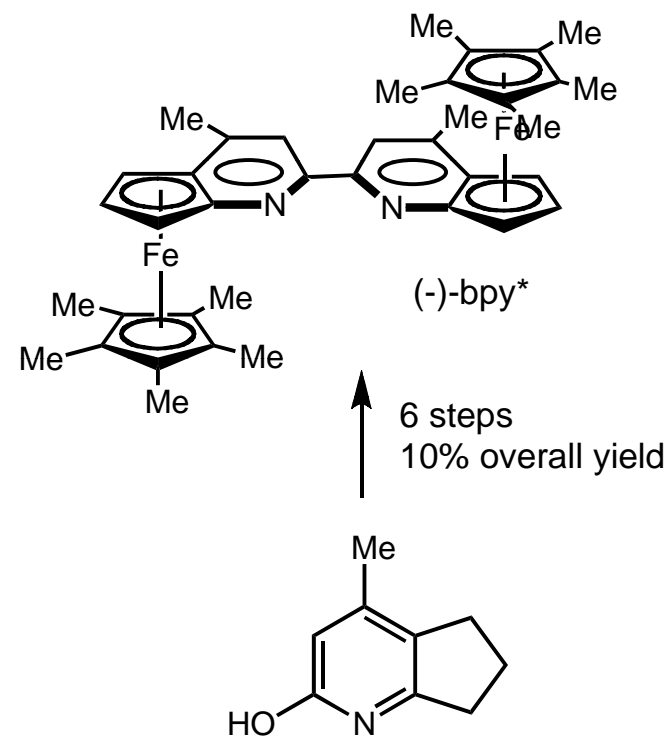


55%, racemic

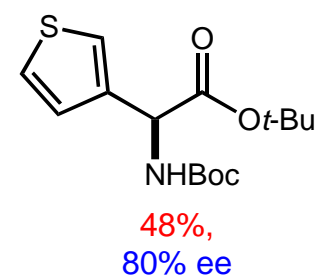
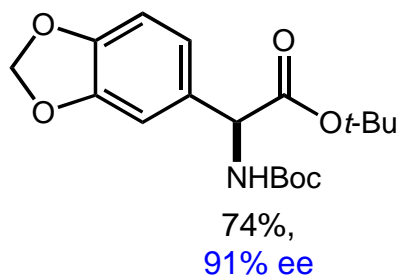
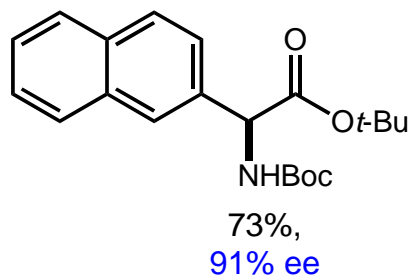
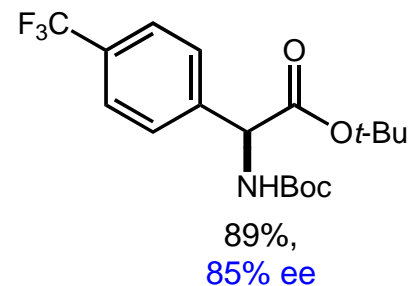
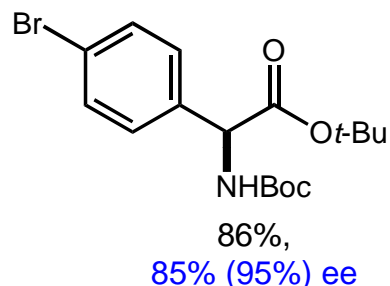
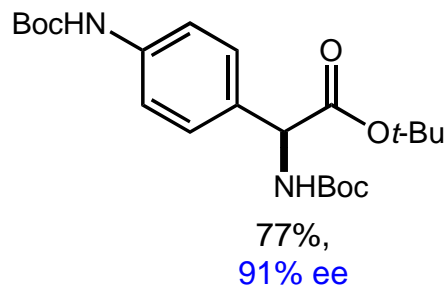
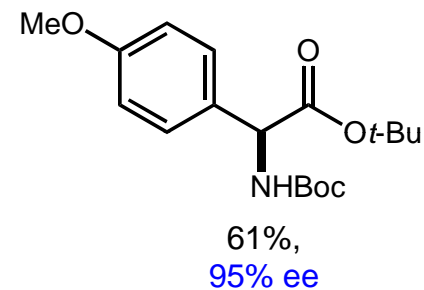
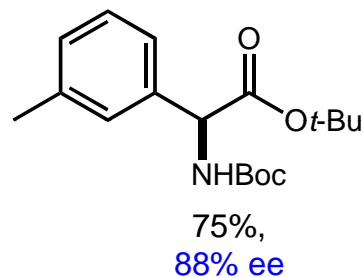
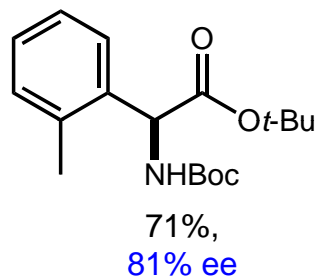
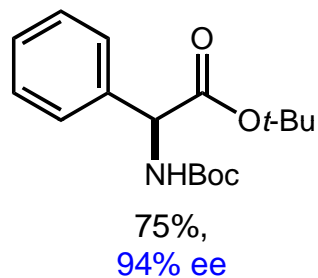
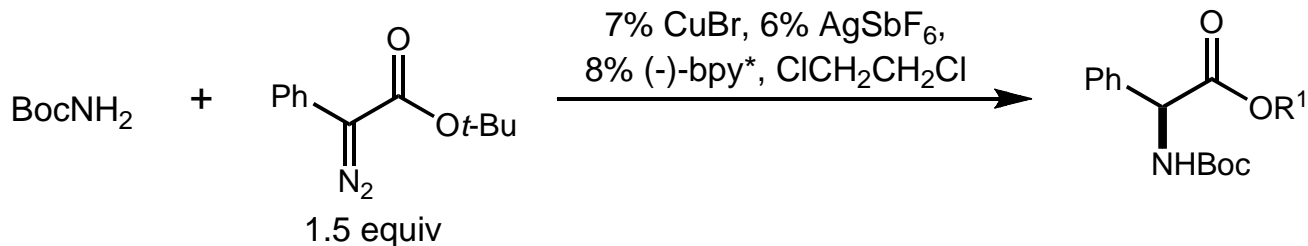
Amino Acid Synthesis



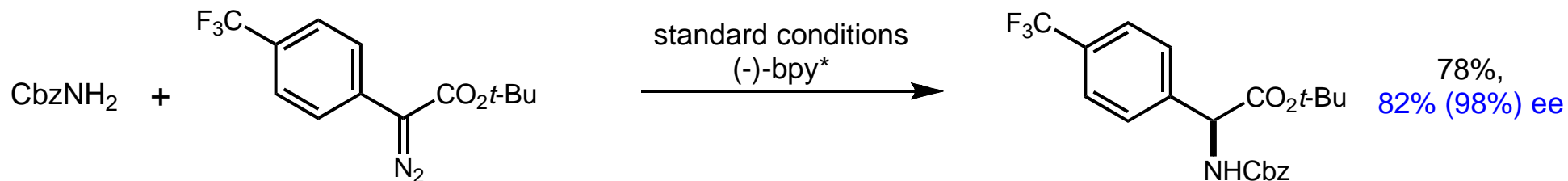
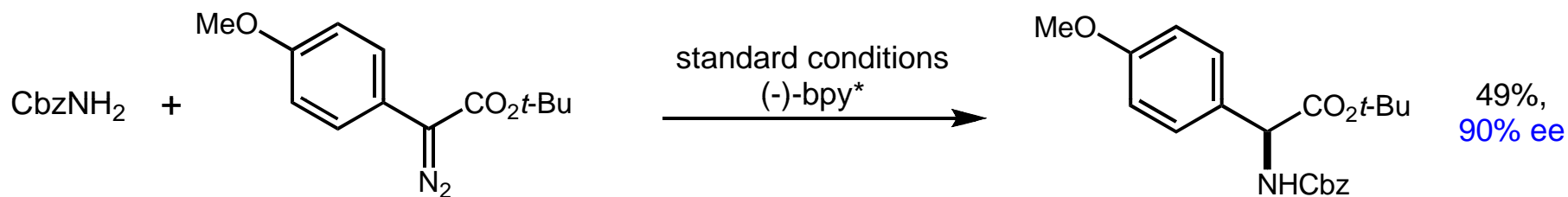
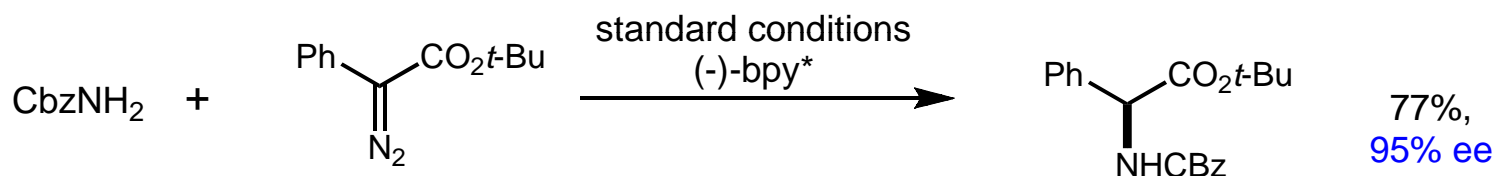
variation	yield (%)	ee (%)
none	74	94
R ¹ = <i>i</i> -Pr	69	84
R ¹ = Bn	81	77
R ¹ = Me	70	70
no AgSbF ₆	<2	-
no bpy*	80	0
12% bpy* instead of 8%	77	92
8% bis(oxazoline) instead of bpy*	80	<10
CH ₂ Cl ₂	71	88
THF	66	69
Toluene	42	74



Amino Acid Synthesis



Amino Acid Synthesis



Conclusions

- Rh catalysts great for β -lactams and intramolecular cyclizations via N-H insertions
- Rh suffers competitive C-H insertion while Cu does not
- Cu catalysts are much cheaper than Rh catalysts
- Cu catalysts are just as effective as Rh catalysts
- Cu has had success with intermolecular enantioselective reactions
- Lots of progress still to be made

Acknowledgments

Prof. Michael T. Crimmins

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

Crimmins Group Members

Dr. Anita Mattson

Anne-Marie Dechert

Timothy Martin

Dr. Christie Stauffer

Matthew Haley

Elizabeth O'Bryan

Adam Azman

Colin Hughes

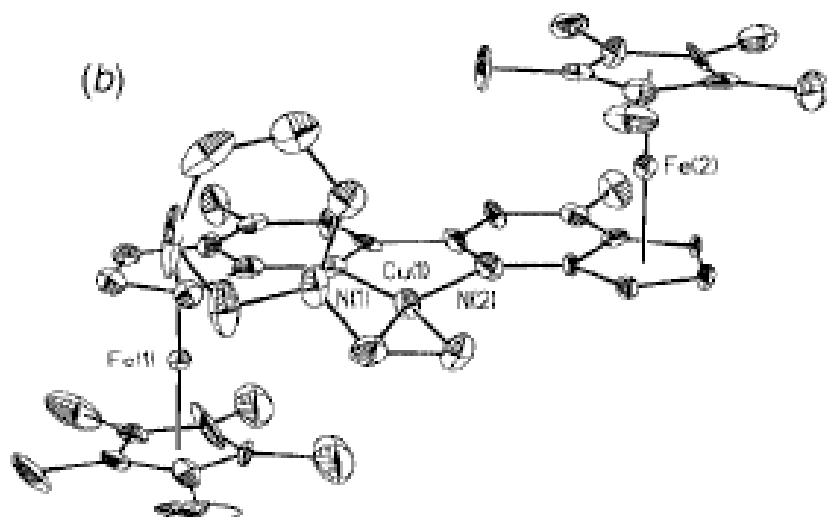
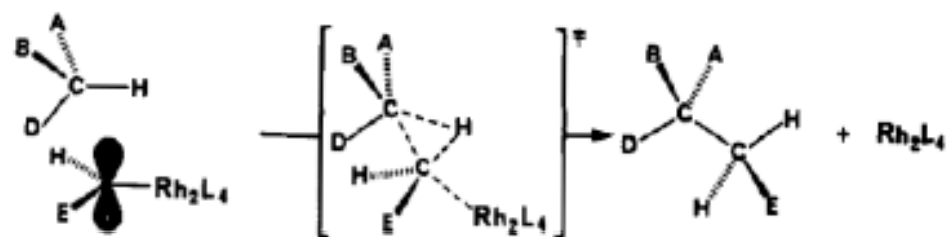
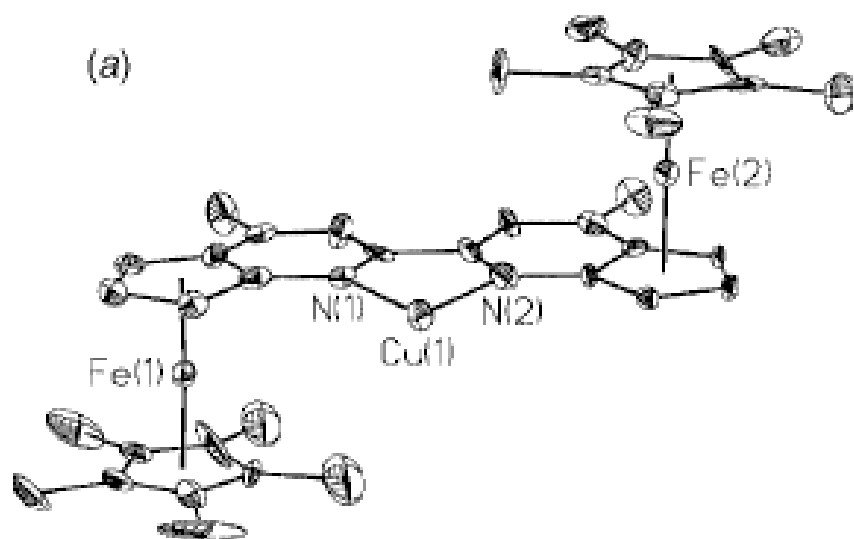
Jason Stevens

Danielle Jacobs

Philip Williams

Mariam Shamszad

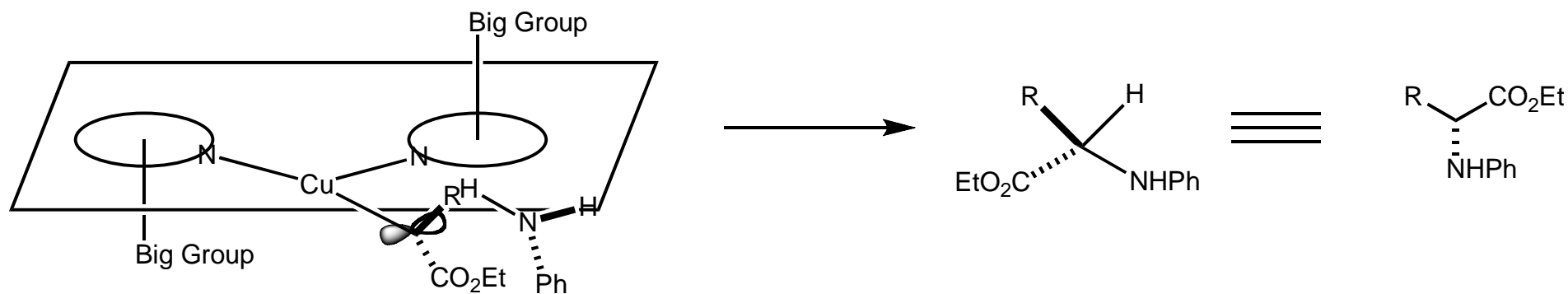
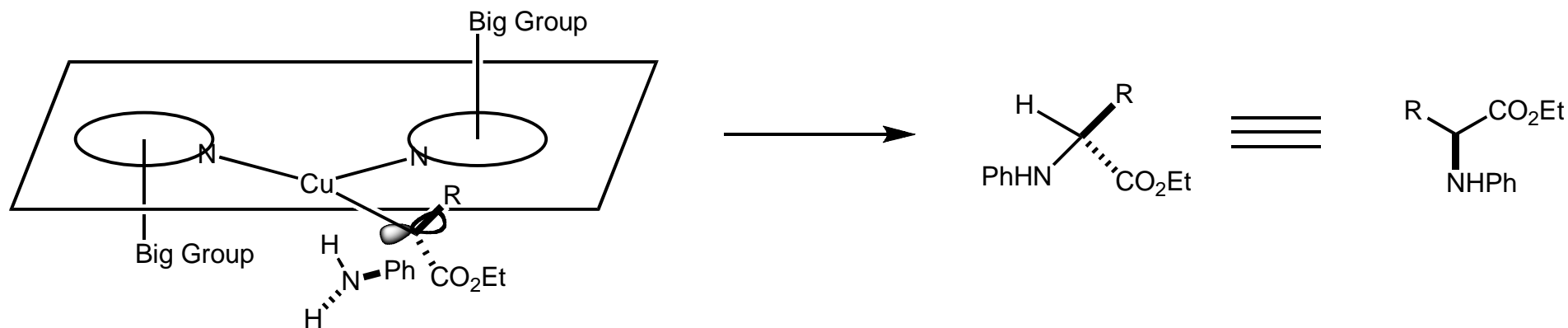
Possible Transition States



Doyle et. al. JACS 1993, 958.

Fu et al. Chem Comm. 2000, 377-378.

Possible Transition States



N-Cu-N plane is 90° to Cu-C-RR plane
J. Molecular Structure **2006**, 765, 13-20.