

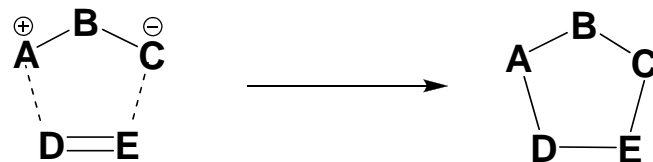
# Cu(I)-Catalyzed 1,3 Dipolar Cycloadditions

Anne-Marie Dechert  
Feb. 7, 2008

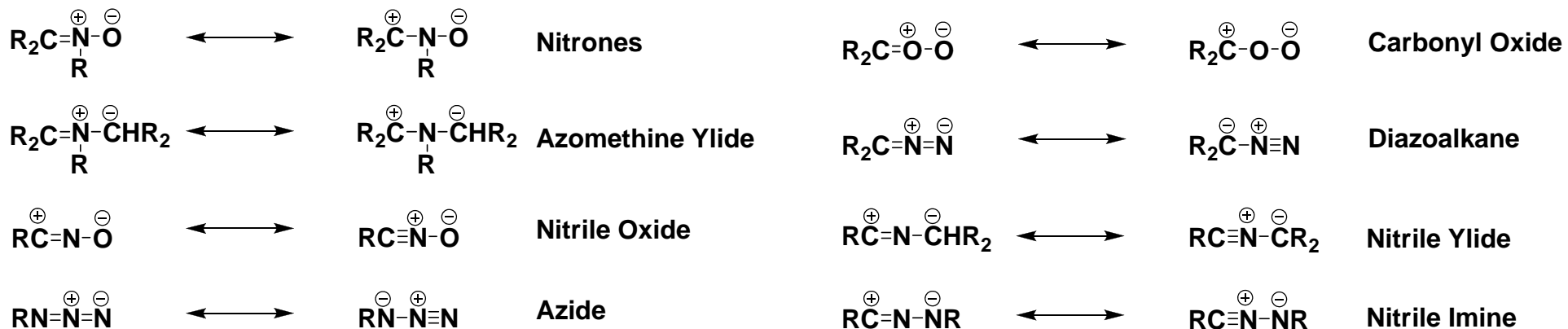
# Outline

- Introduction to 1,3 Dipolar Cycloadditions
- Cu(I)-catalyzed 1,3 Dipolar Cycloaddition Between Azides and Alkynes
  - Cascade Reactions
  - Extension of the Original Methodology
- Synthesis of  $\beta$ -Lactams
  - Kinugasa Reaction
- 1,3 Dipolar Cycloadditions Between Azomethine Ylides and Activated Alkenes

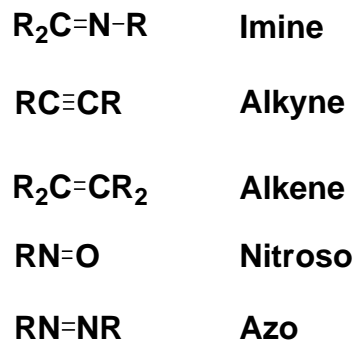
# 1, 3 Dipolar Cycloadditions



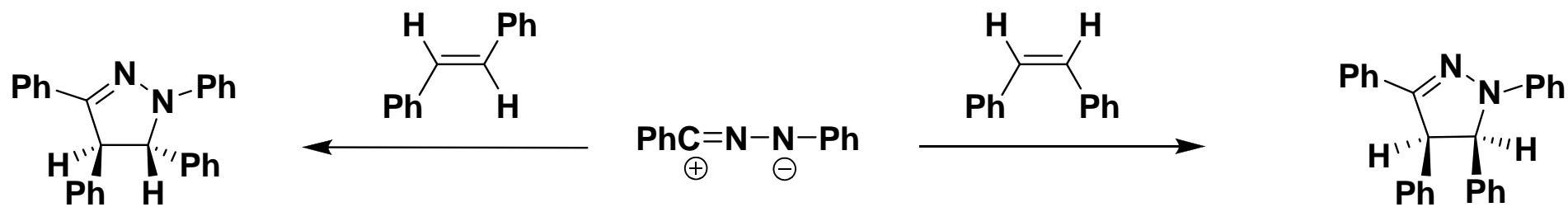
## Typical 1,3 Dipoles



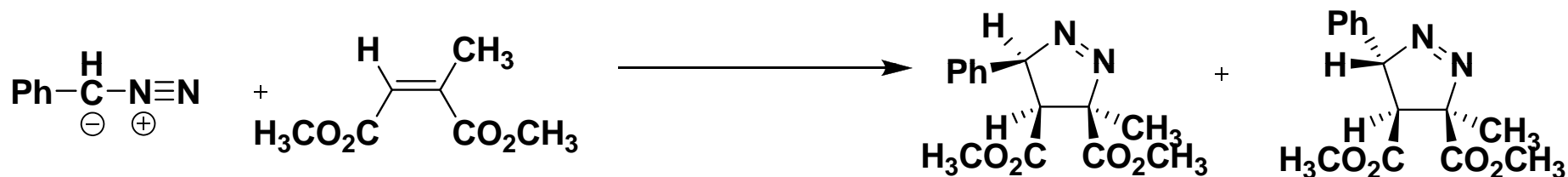
## Typical Dipolarophiles



# Stereospecificity



- Stereospecific *syn* addition with respect to dipolarophile

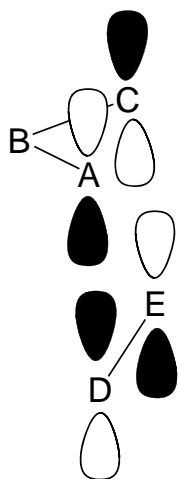


Huisgen, R.; Seidel, G.; Wallibillich, G.; Knupfer, H. *Tetrahedron* **1962**, *17*, 3.

Huisgen, R.; Eberhard, P. *Tetrahedron Lett.* **1971**, 4743.

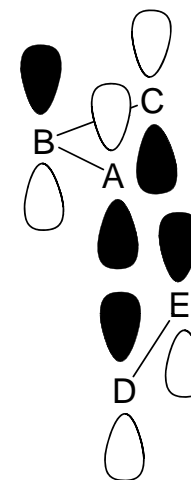
# Regioselectivity

- Dominated by Frontier Molecular Orbital (FMO) interactions
- Sterics can also play a role



**HOMO<sub>dipole</sub> - LUMO<sub>dipolarophile</sub>**

*typical for an electron deficient dipolarophile*

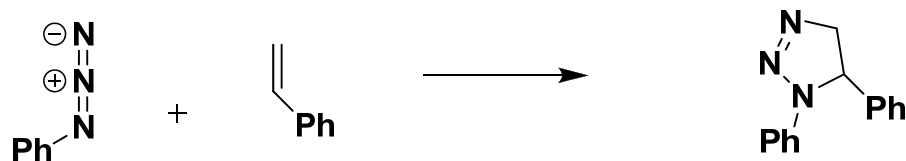


**LUMO<sub>dipole</sub> - HOMO<sub>dipolarophile</sub>**

*typical for an electron rich dipolarophile*

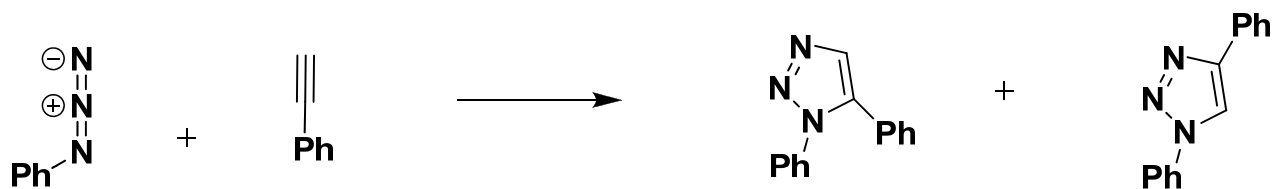
***If the energies of the two interactions are similar, both reactions can occur.***

# 1,3 Dipolar Cycloadditions of Azides and Alkynes



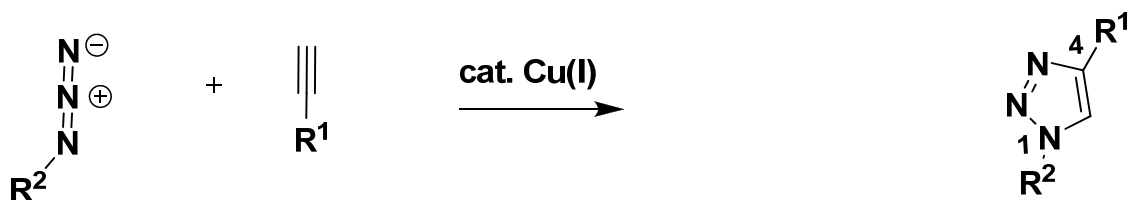
- **LUMO<sub>Dipole</sub>-HOMO<sub>Dipolarophile</sub> interaction**

Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*. Wiley, New York, **1976**, 154-157.



- **HOMO and LUMO lowered by 0.5 eV**

Clarke, D.; Mares, R.; McNab. *J. Chem. Soc., Perkin Trans. 1*. **1997**, 1, 1799.

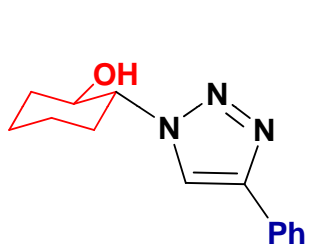


**1, 4 regioisomer obtained exclusively**

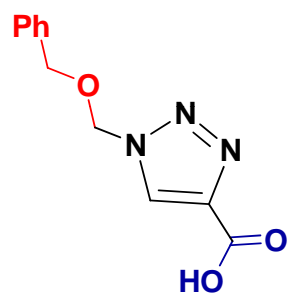
Fokin, V.; Green, L.; Rostovtsev, V.; Sharpless, B. *Angew. Chem. Int. Ed.* **2002**, 41, 2596.

Christensen, C.; Meldal, M.; Tornøe, C. *J. Org. Chem.* **2002**, 67, 3057.

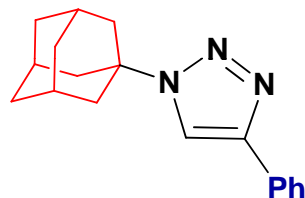
# The Cu(I) Catalyzed 1,3 Dipolar Cycloadditions of Azides and Alkynes



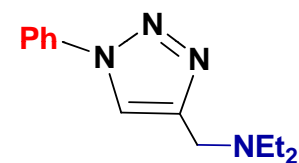
82%



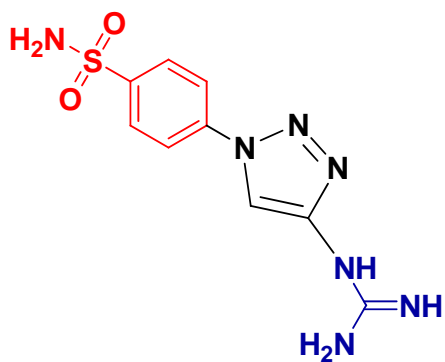
88%



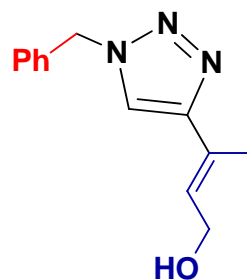
84%



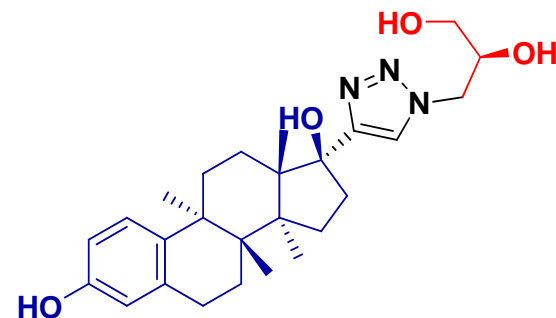
90%



91%



84%

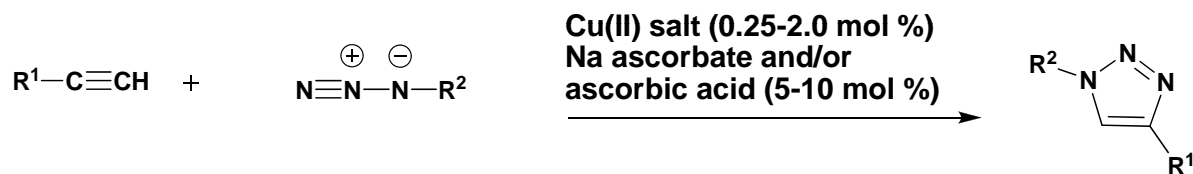
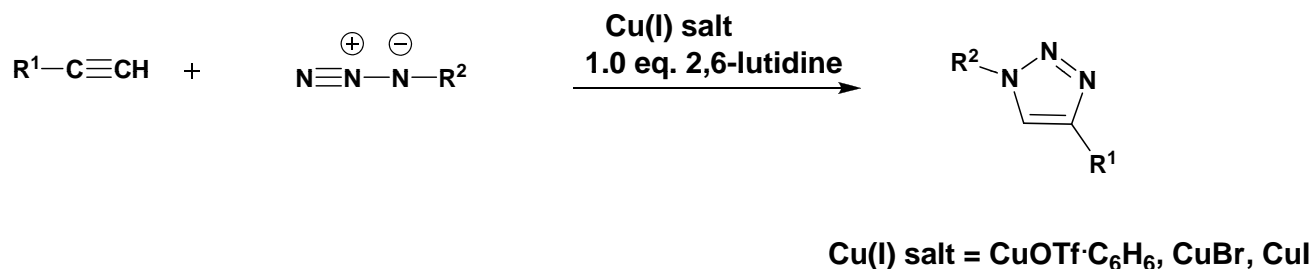


94%

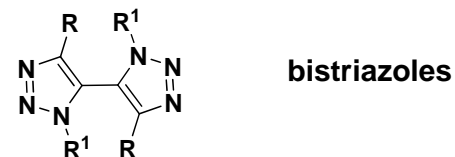
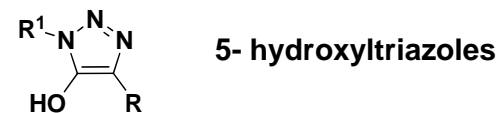
Rostovtsev, V.; Green, L.; Fokin, V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, 41, 2596.

Tornøe, C.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, 67, 3057.

# Generation of The Cu(I) Catalyst



## Formation of Byproducts



## Click Chemistry

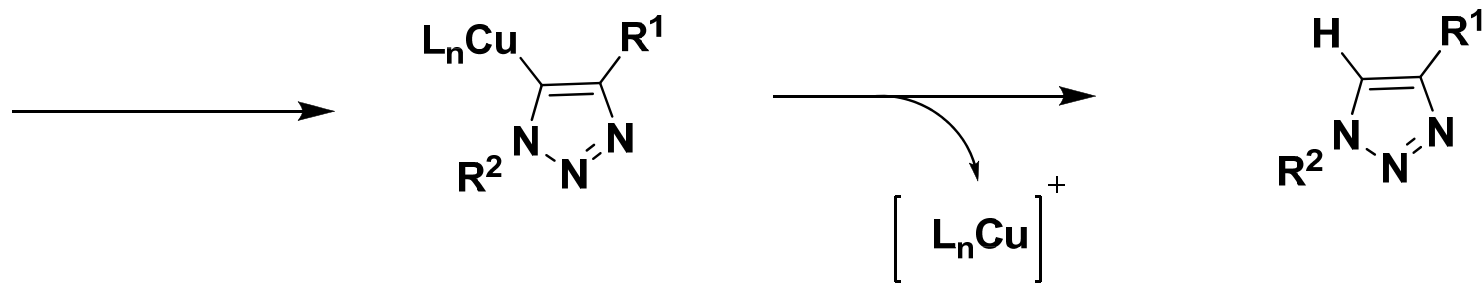
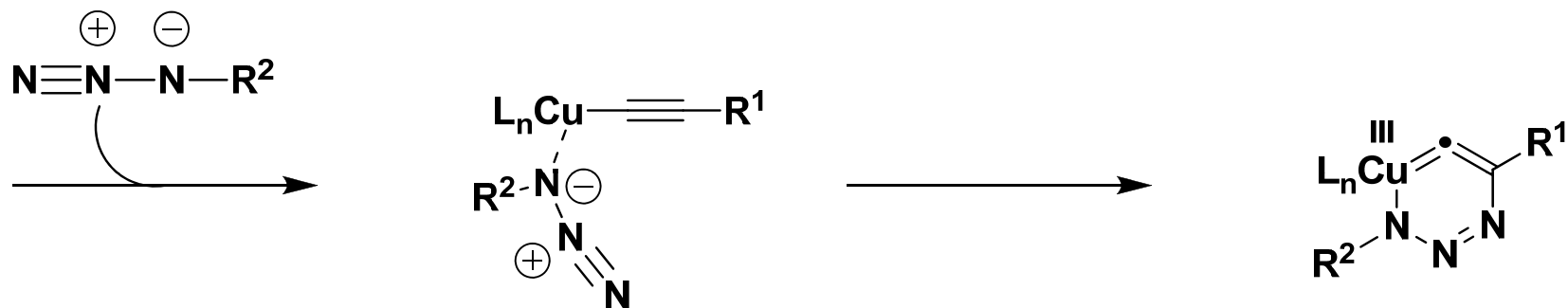
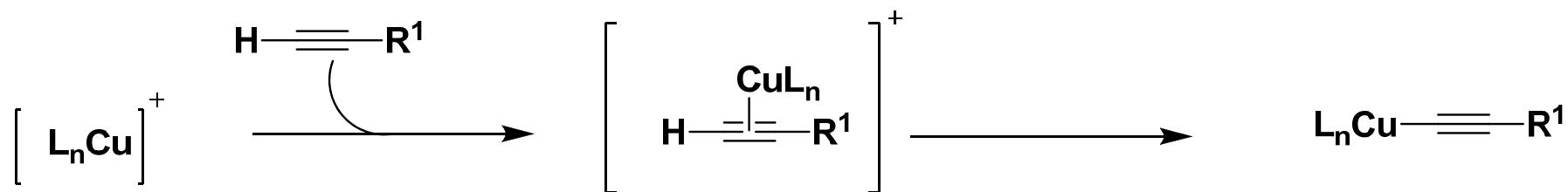
- high yielding
- wide in scope
- stereospecific
- inoffensive byproducts
- simple reaction conditions

Rostovtsev, V.; Green, L.; Fokin, V.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.

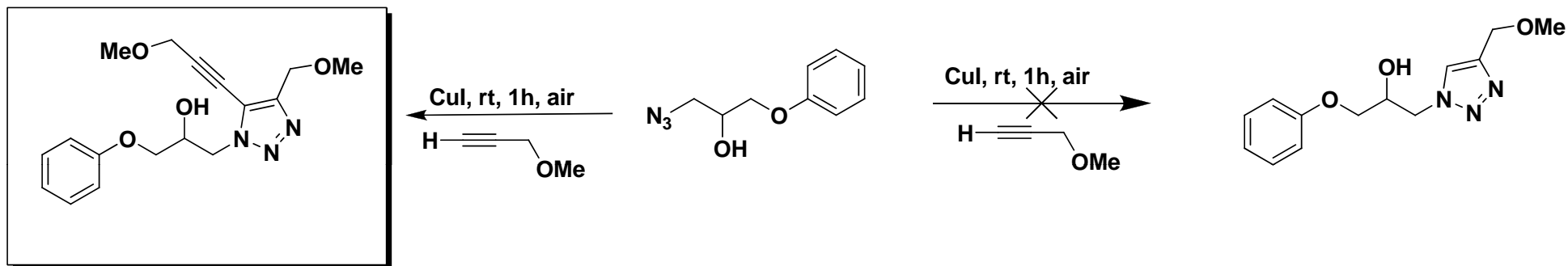
Kolb, H.; Finn, M.; Sharpless, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004.

Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. *J. Am. Chem. Soc.* **2005**, *127*, 210.

## A Stepwise Mechanism is Proposed

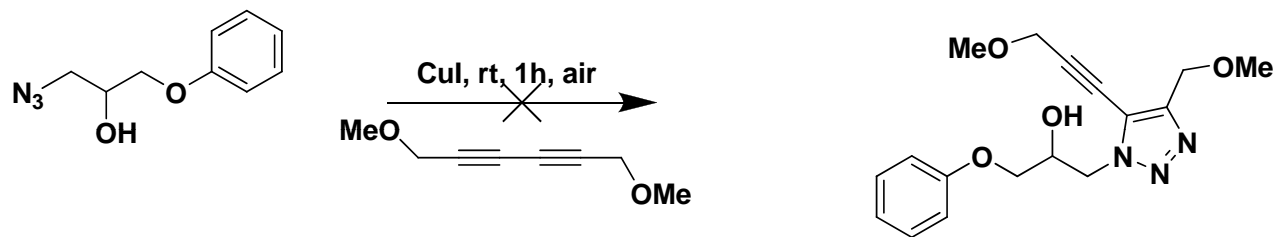


# The Unexpected Formation of Trisubstituted Triazoles

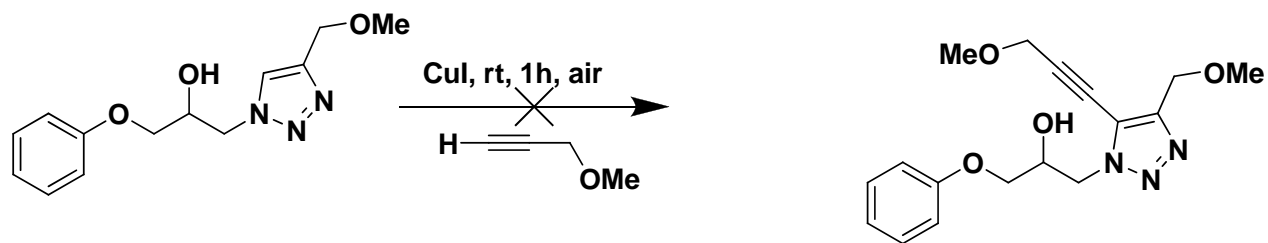


Unexpected Result

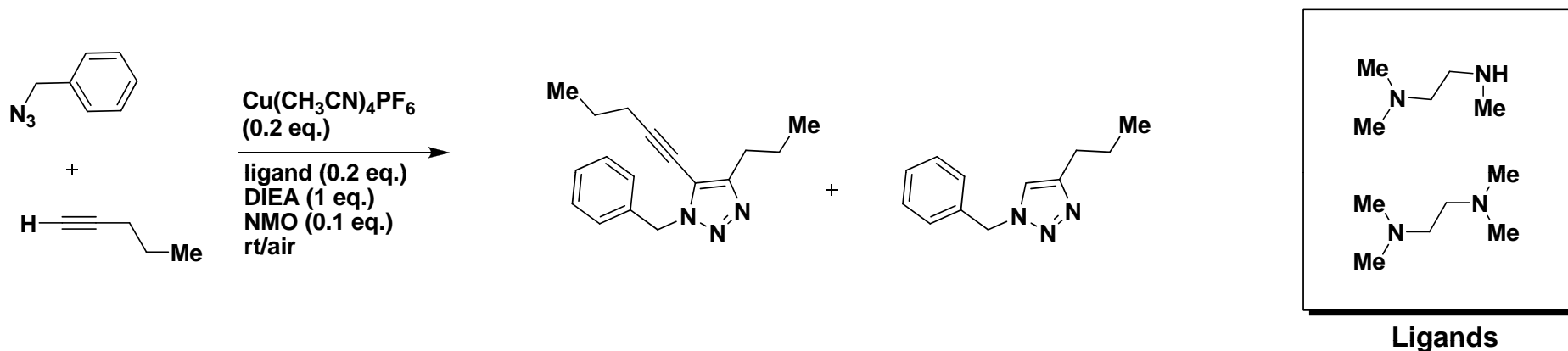
- Perhaps Glaser Coupling:



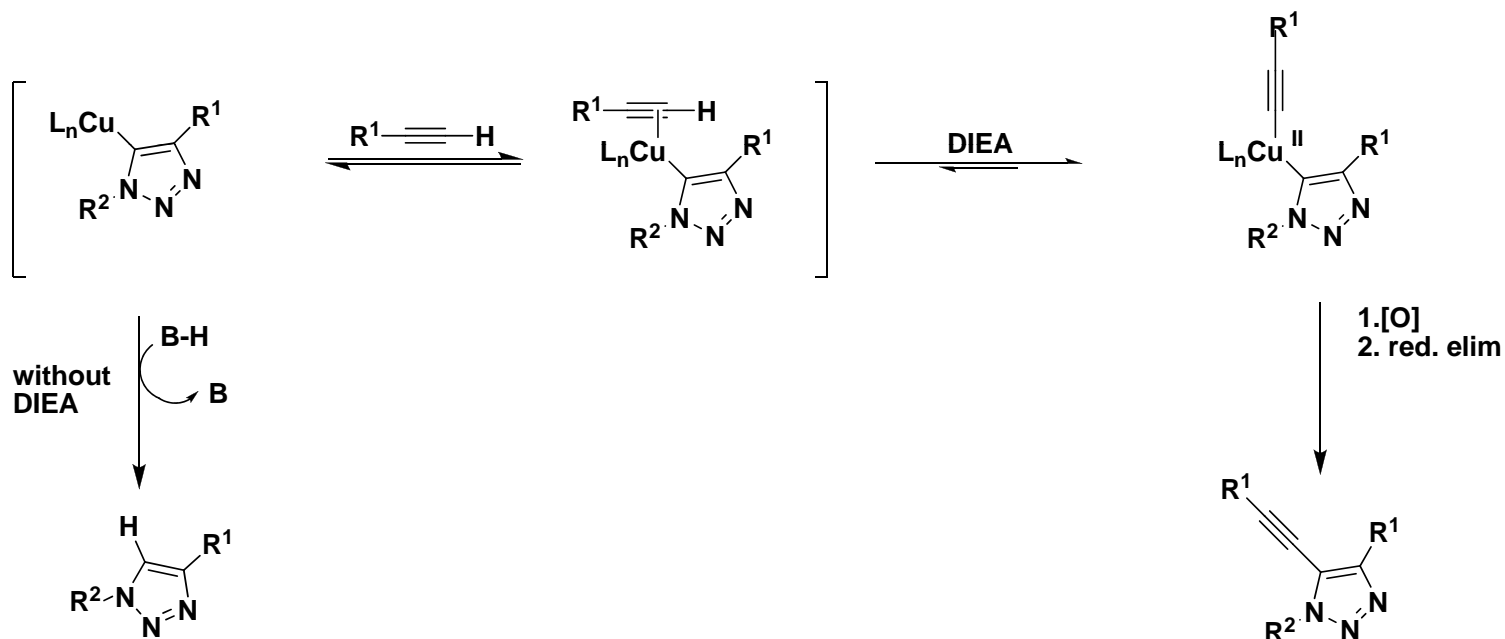
- Alternative Pathway:



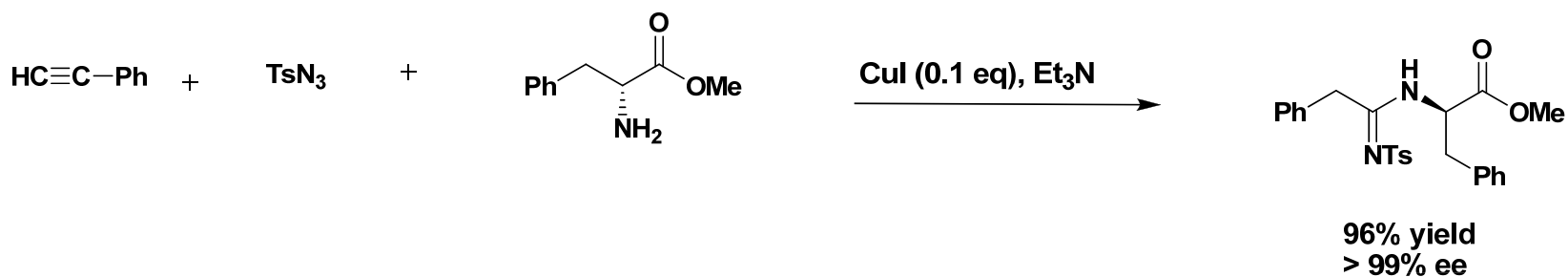
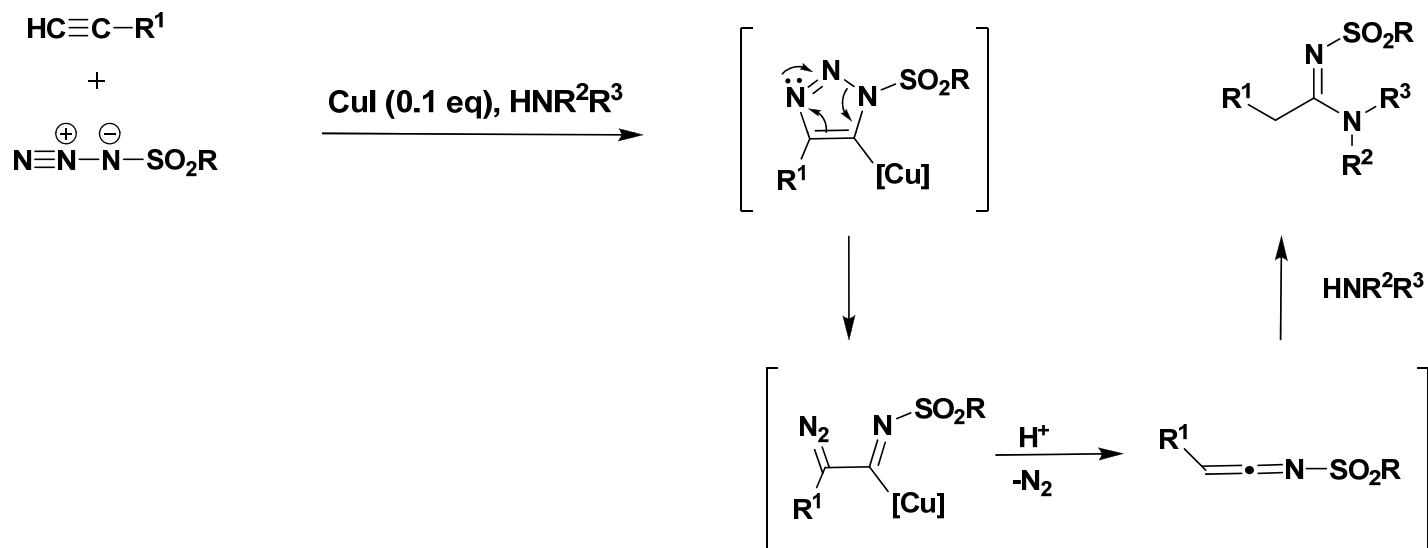
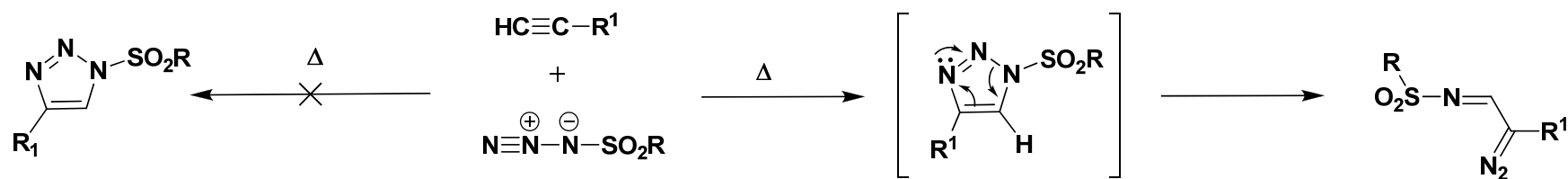
# Mechanistic Rational for the Formation of Trisubstituted Triazoles



## Proposed Mechanism:



# The Use of N-Sulfonyl Azides as 1,3 Dipoles

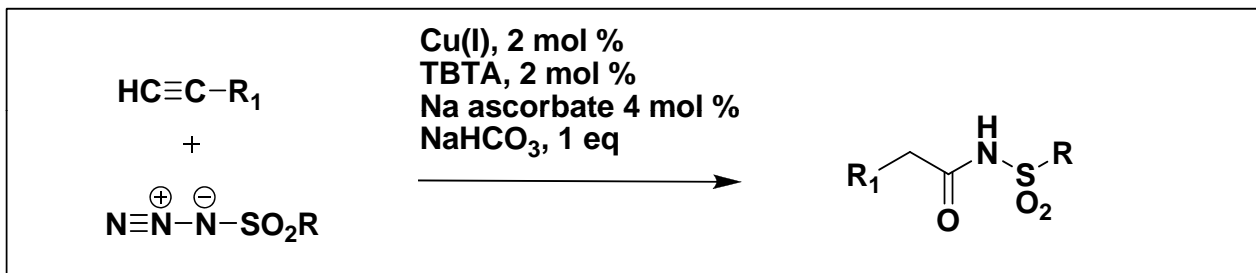


Finzi, P.; Grunanger, P. *Tetrahedron Lett.* **1963**, 4, 1839.

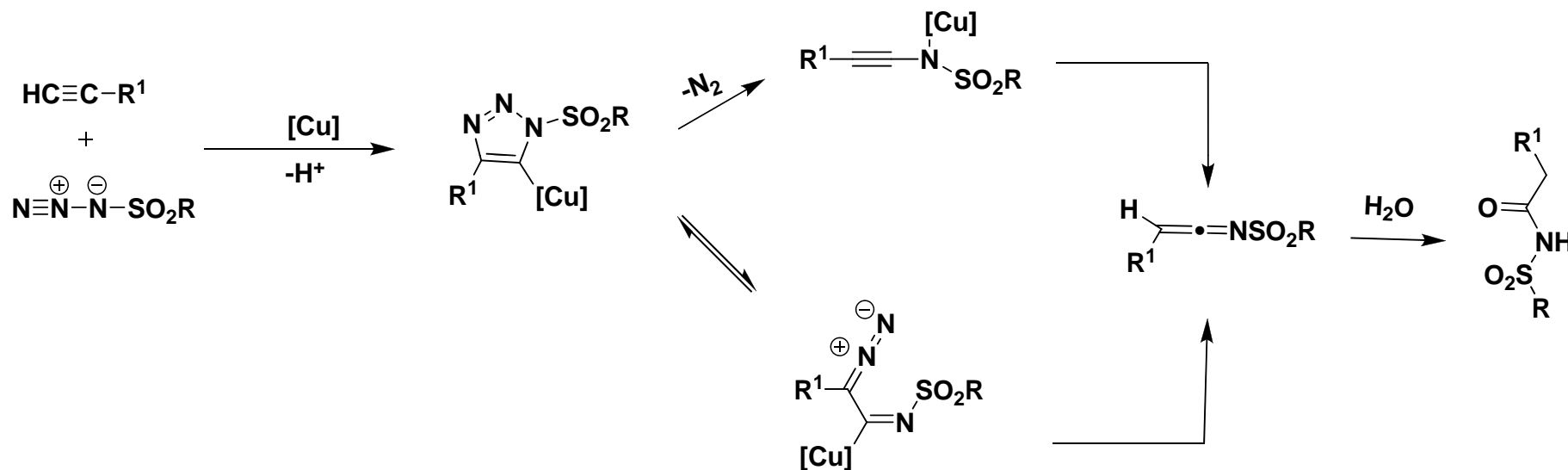
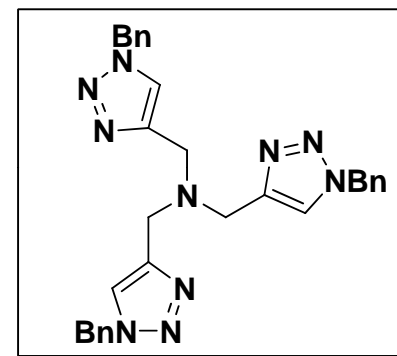
Yoo, E.; Ahlquist, M.; Kim, S.; Bae, I.; Fokin, V.; Sharpless, K. B.; Chang, S. *Angew. Chem. Int. Ed.* **2007**, 46, 1730.

Bae, I.; Han, H.; Chang, S. *J. Am. Chem. Soc.* **2005**, 127, 2038.

# Proposed Route to Sulfonamides



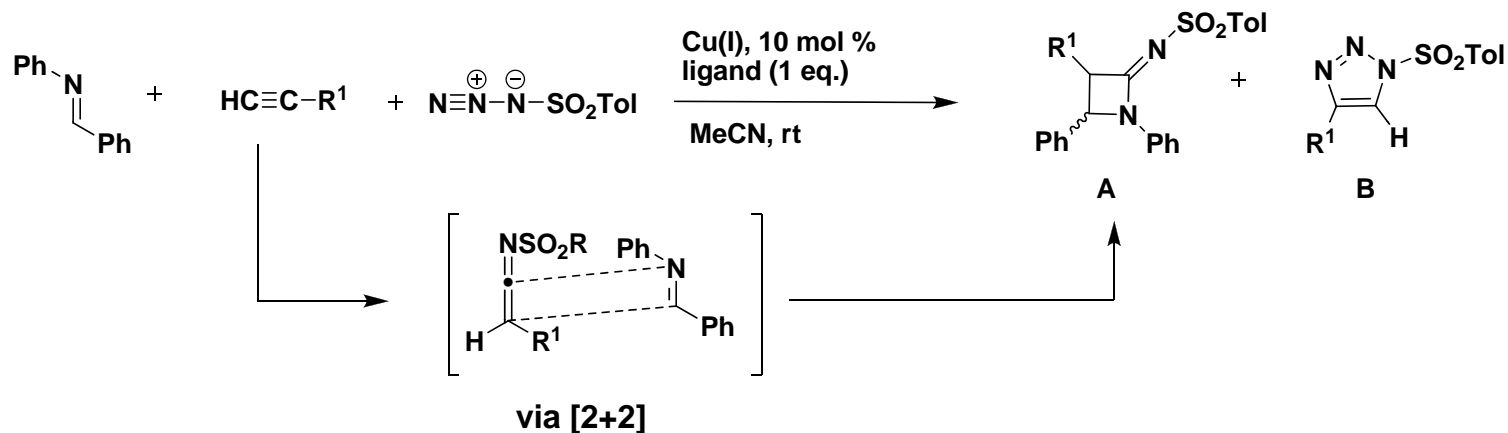
TBTA =



Cassidy, M.; Raushel, V.; Fokin, V. *Angew. Chem. Int. Ed.* **2006**, *118*, 3154.

Cho S.; Yoo, E.; Bae, I.; Chang, S. *J. Am. Chem. Soc.* **2005**, *127*, 16047.

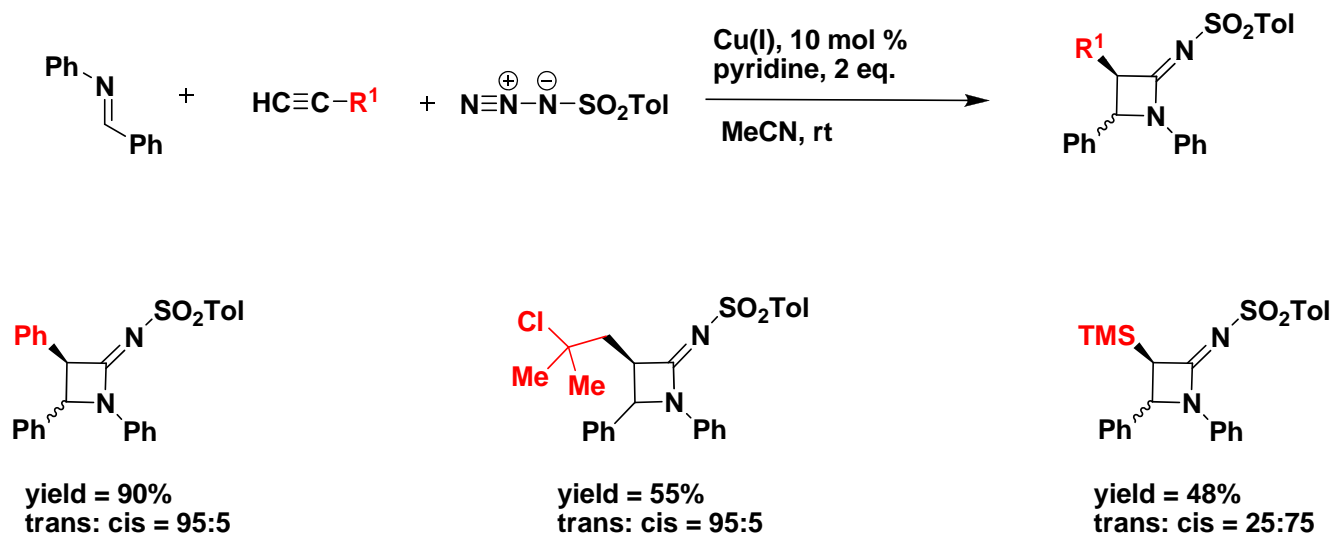
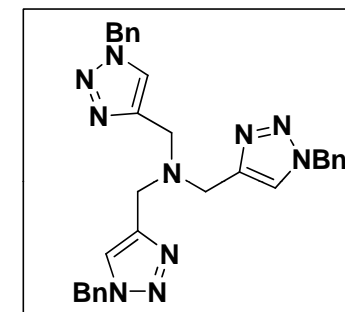
# A Cu(I) Catalyzed Cascade to Form Azetidines



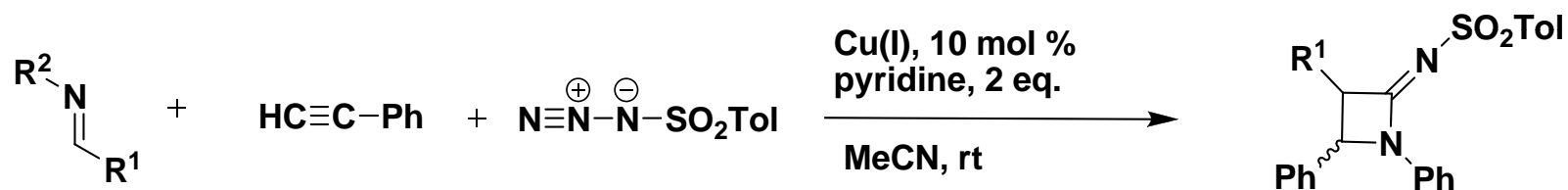
Ligand	t[h]	<i>trans</i> -A: <i>cis</i> -A: B
2,6 lutidine	3	80:13:7
pyridine	3	95:5:0
TBTA	<2	42:58:0

## Alkyne Scope

TBTA =

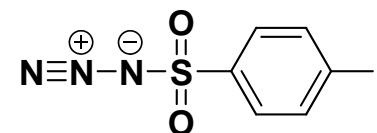
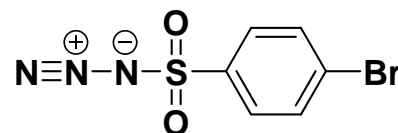
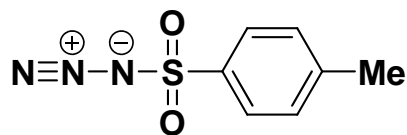
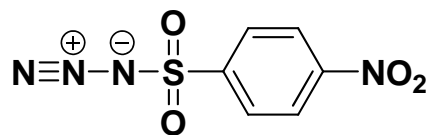


# Reaction Scope: the Imine Component

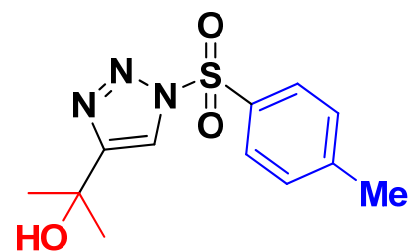
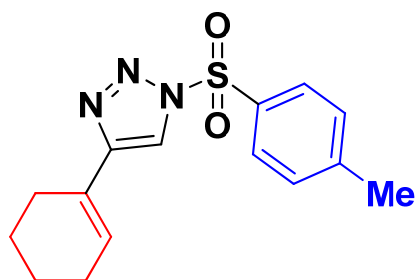
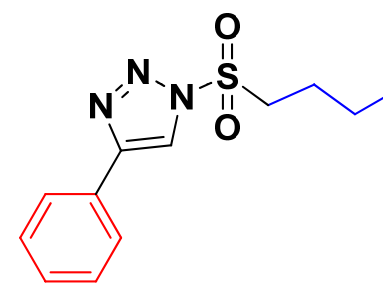
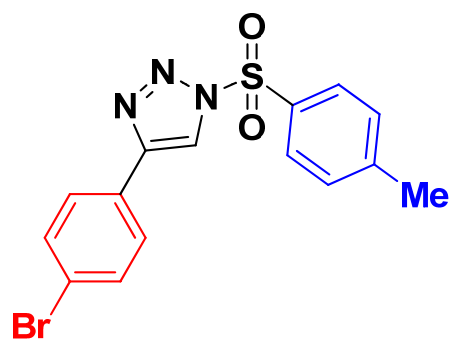
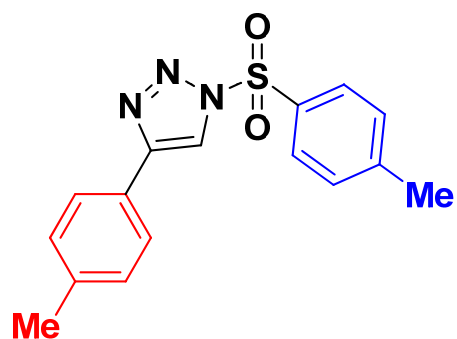
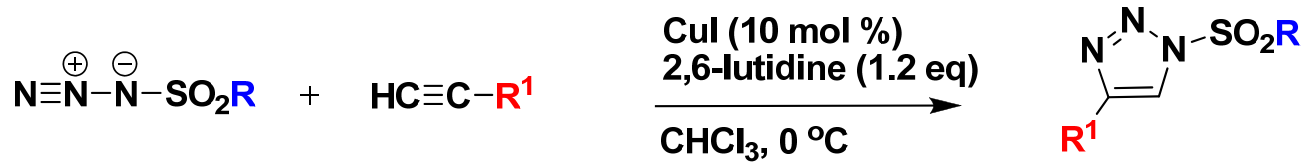


R <sup>1</sup>	R <sup>2</sup>	Yield (%)	<i>trans:cis</i>
4-FC <sub>6</sub> H <sub>4</sub>	Ph	87	95:5
4-(MeO)C <sub>6</sub> H <sub>4</sub>	Ph	79	95:5
Ph	SO <sub>2</sub> Ph	5	NR
CO <sub>2</sub> Et	Ph	53	5:95
CO <sub>2</sub> Et	4-(MeO)C <sub>6</sub> H <sub>4</sub>	63	5:95

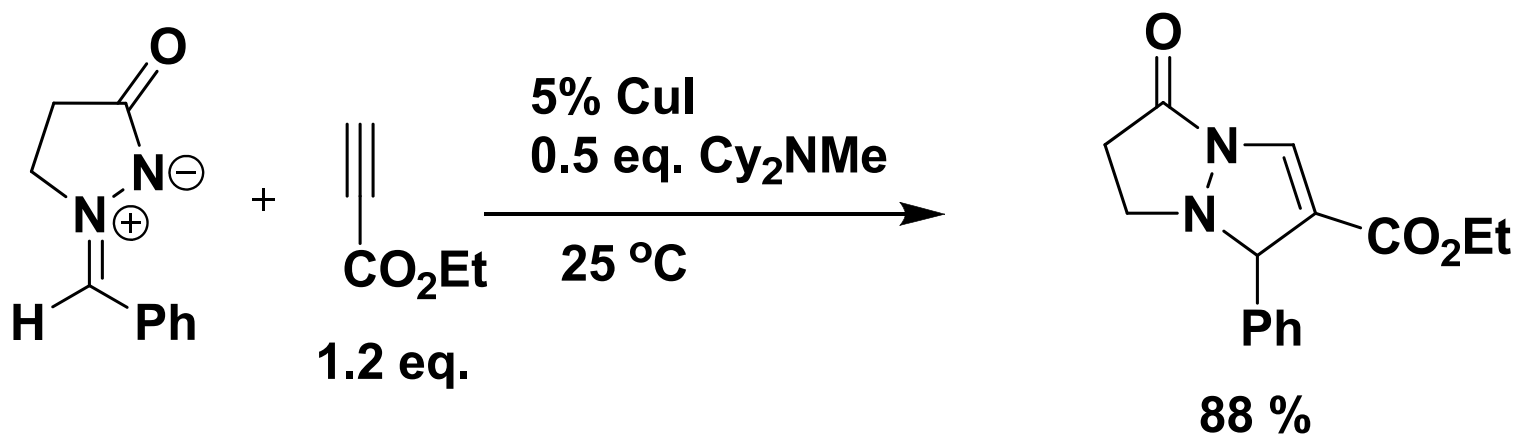
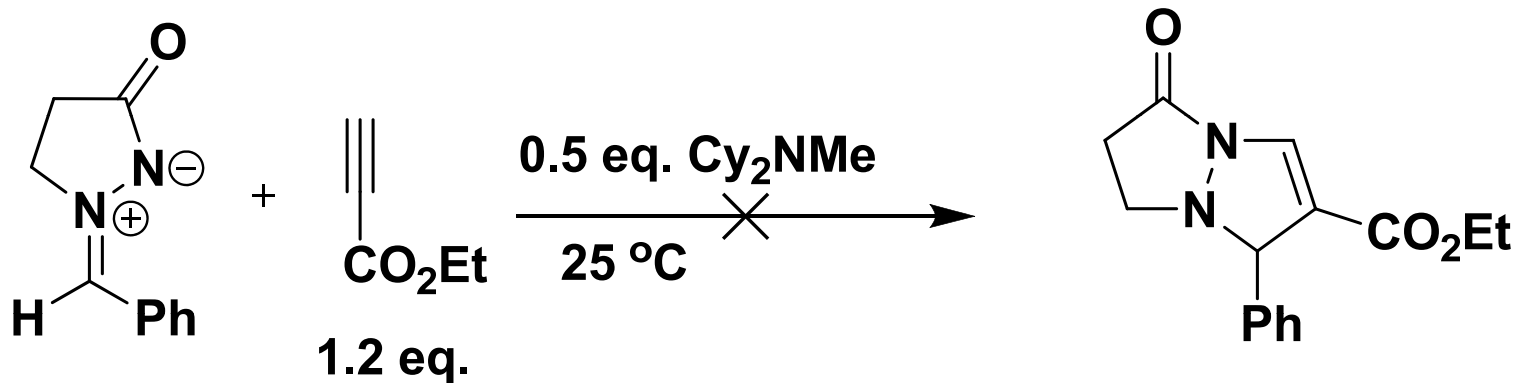
## Sulfonyl Azides



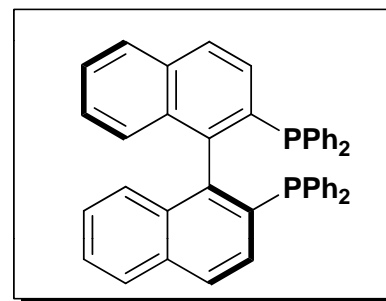
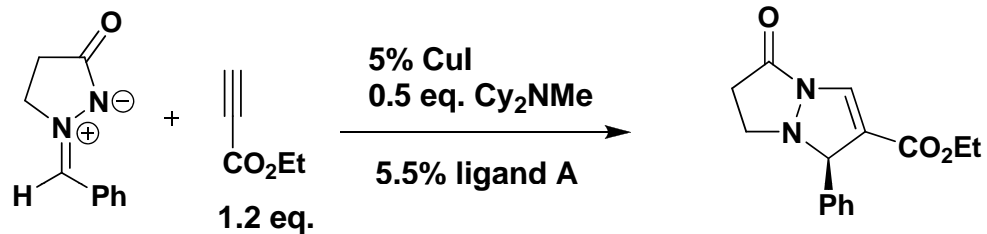
# Synthesis of *N*-Sulfonyl-1,2,3-Triazoles



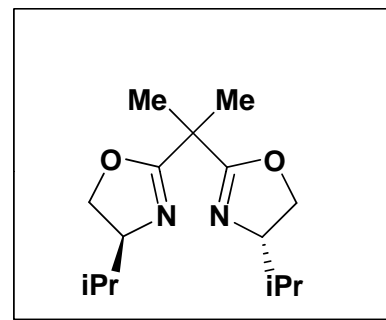
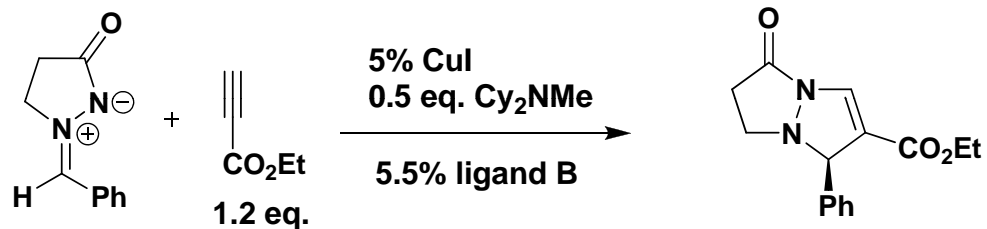
## Fu's Extension to Azomethine Imine Dipoles



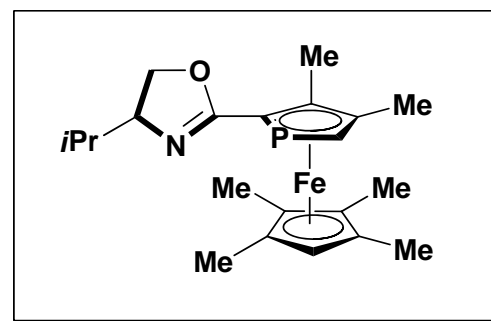
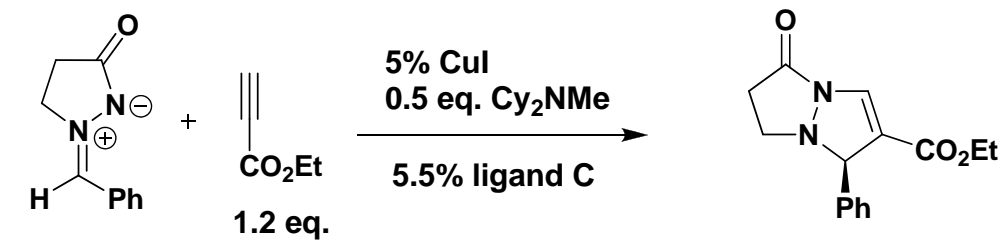
# Asymmetric Extension



= A

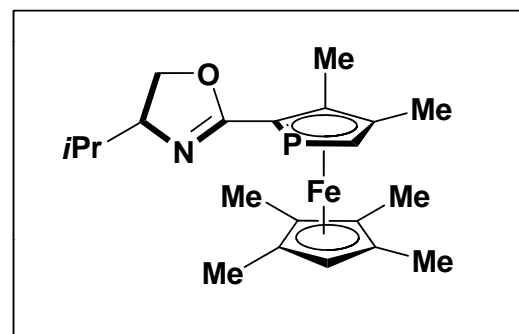
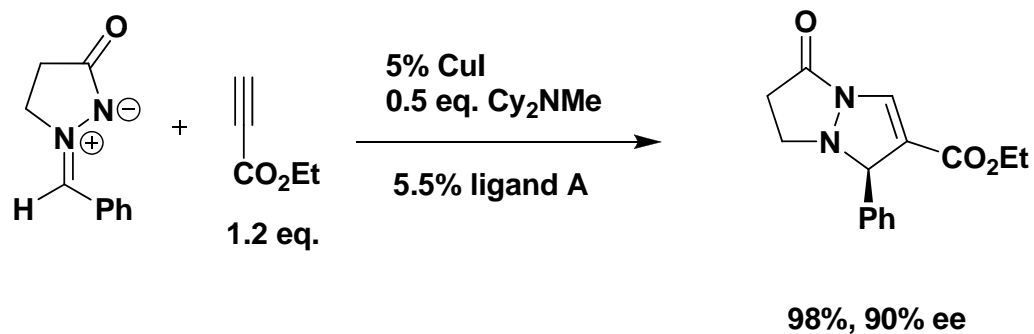


= B

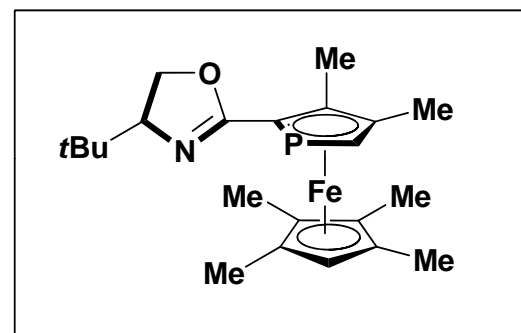
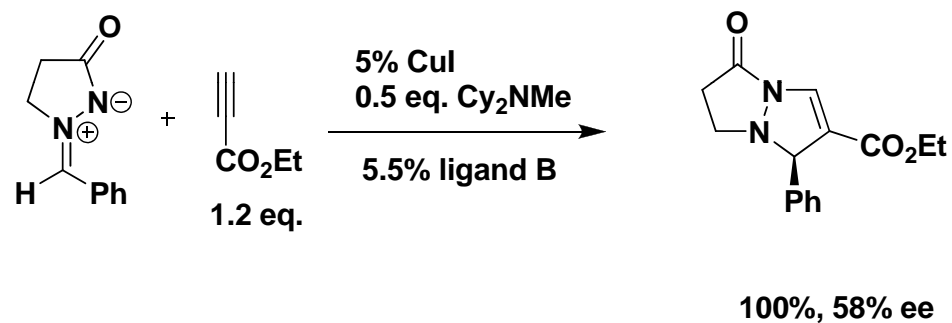


= C

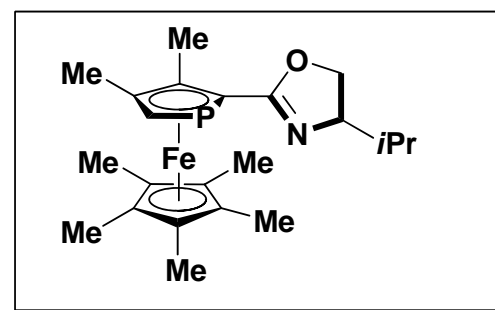
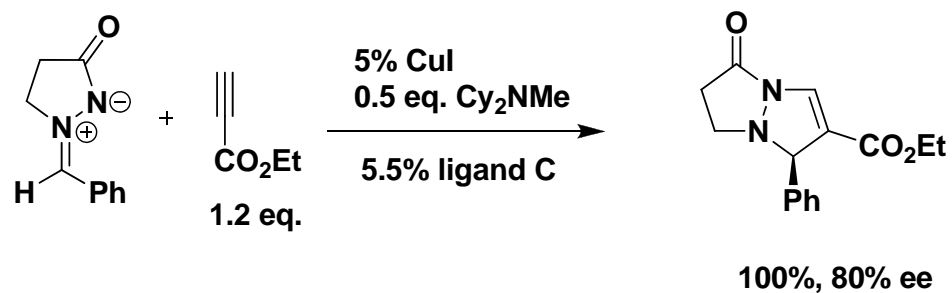
# Asymmetric Extension



= A

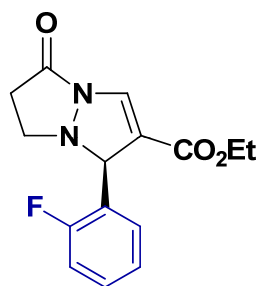
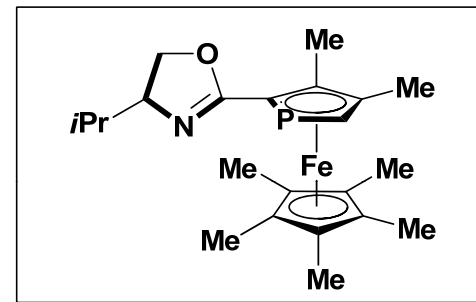
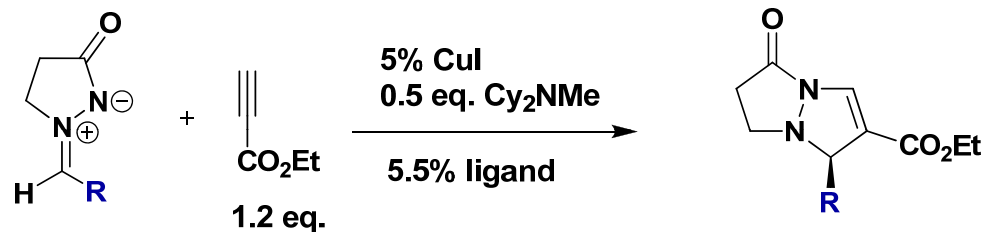


= B

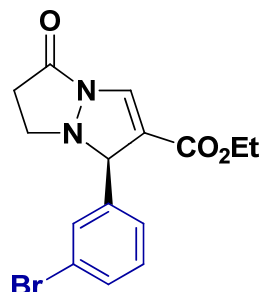


= C

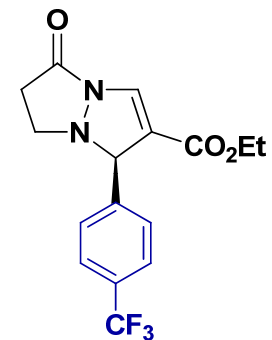
# Reaction Scope: The Azomethine Imine Component



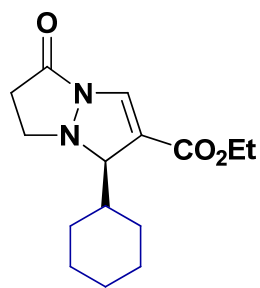
99%, 81% ee



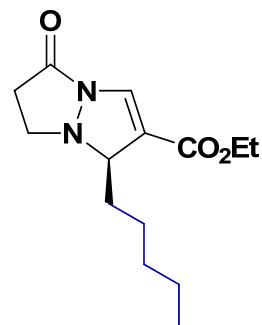
99%, 86% ee



99%, 95% ee

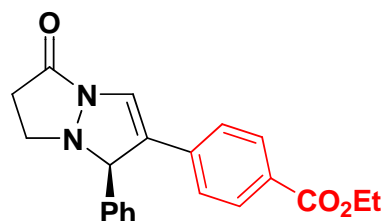
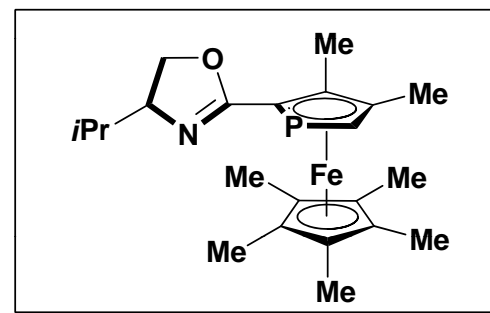
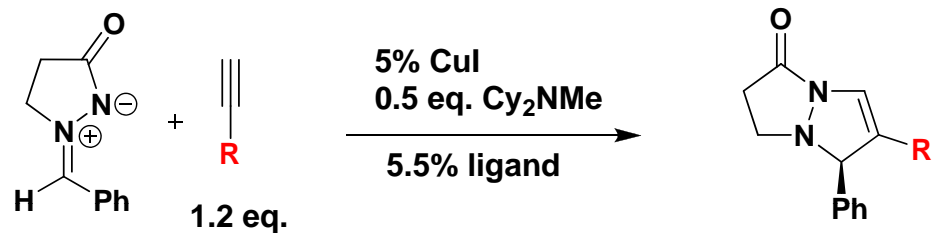


98%, 94% ee

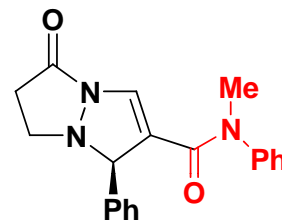


94%, 96% ee

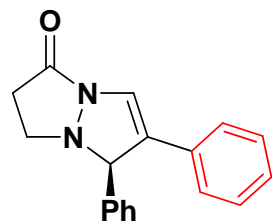
# Reaction Scope: The Alkyne Component



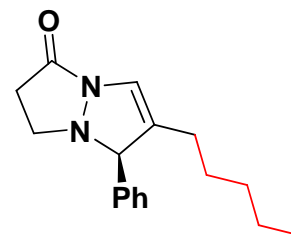
77%, 88% ee



100%, 94% ee



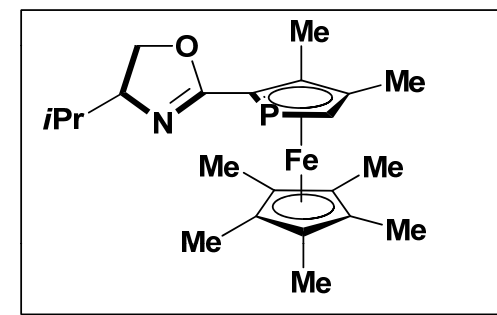
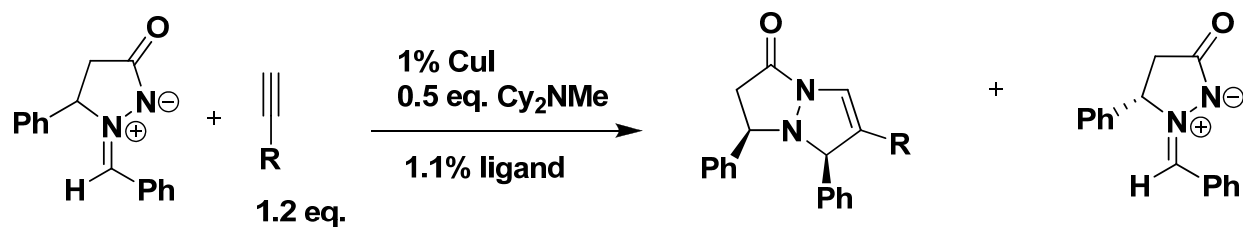
73%, 88% ee



63%, 74% ee

- erosion of regioselectivity observed for electron rich alkynes

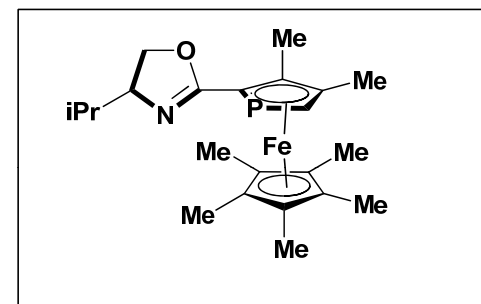
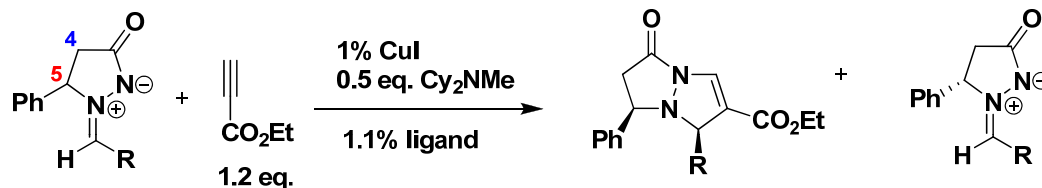
## Application to Kinetic Resolution



selectivity factor =  $\frac{\text{rate of fast-reacting enantiomer}}{\text{rate of slow-reacting enantiomer}}$

R	selectivity factor	ee of dipole (%)	isolated yield (%)
CO <sub>2</sub> Et	53	99	42
CONMePh	30	91	42
4-(trifluoromethyl)phenyl	50	99	39

# Limitations to the Kinetic Resolution of Azomethine Imine Dipoles



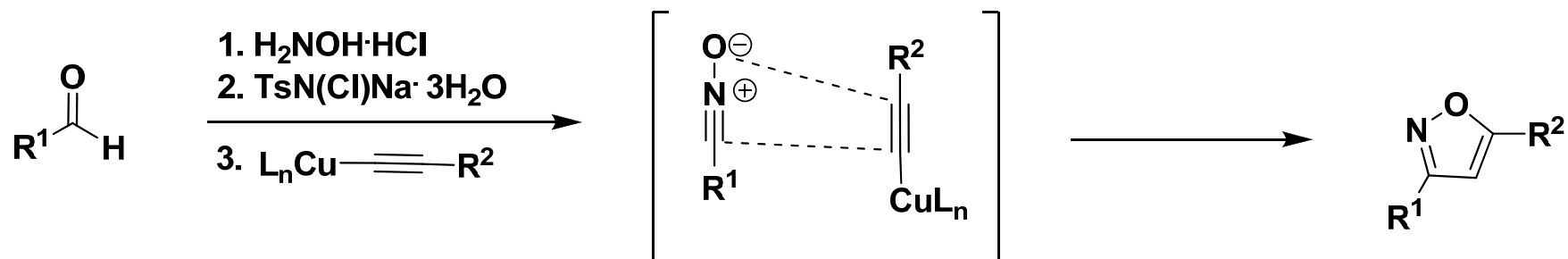
R	selectivity factor	ee of dipole (%)	isolated yield (%)
Ph	53	99	42
	9	95	48
	27	99	31
	35	95	36
Cy	15	91	36

If R is an acyclic alkyl group, the dipole decomposes during cycloaddition.

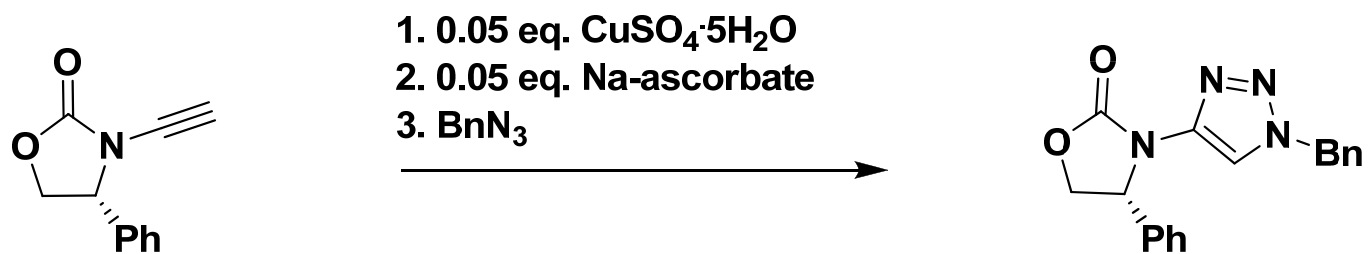
**C4** substituted azomethine imines do not undergo kinetic resolution with useful selectivities.

**C5** can be substituted with aryl, heteroaryl, or branched alkyl.

## Other Cu(I) Catalyzed 1,3 Dipolar Cycloadditions

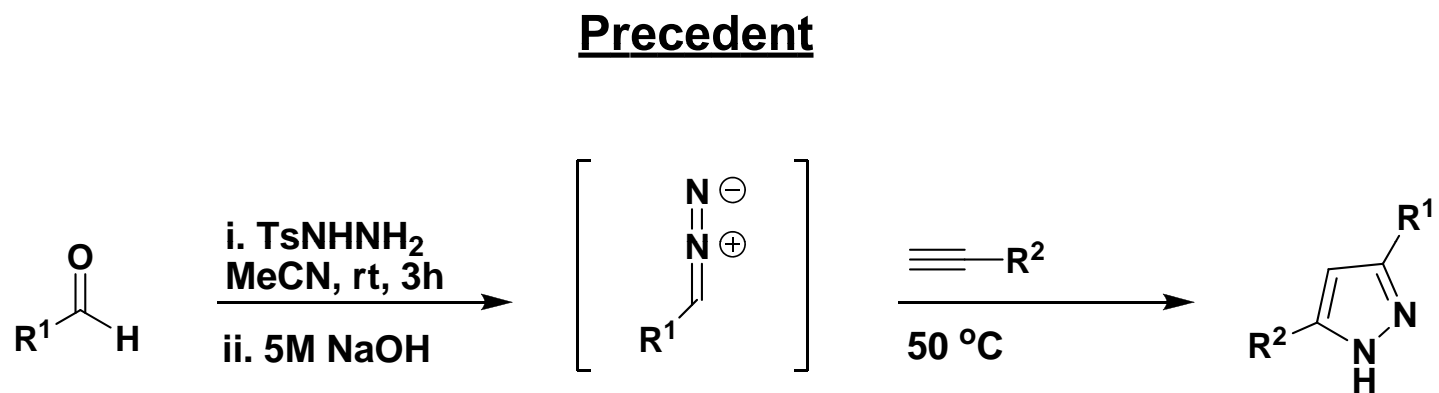


Hansen, T.; Wu, P.; Fokin, V. *J. Org. Chem.* **2005**, *70*, 7761.

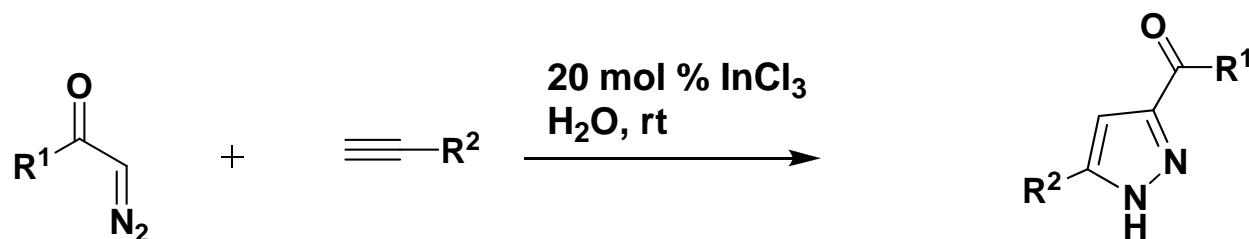


Zhang, X.; Li, H.; You, L.; Tang, Y.; Hsung, R. *Adv. Synth. Catal.* **2006**, *348*, 2437.

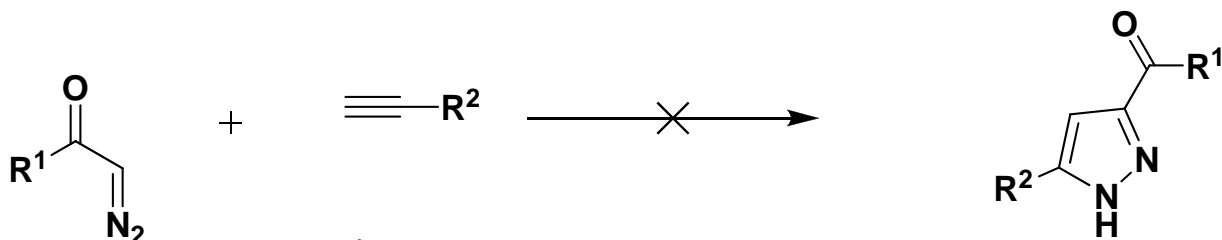
# Synthesis of Pyrazoles: A Direct Approach



$\text{R}^1 = \text{EDG}$   
 $\text{R}^2 = \text{EWG}$



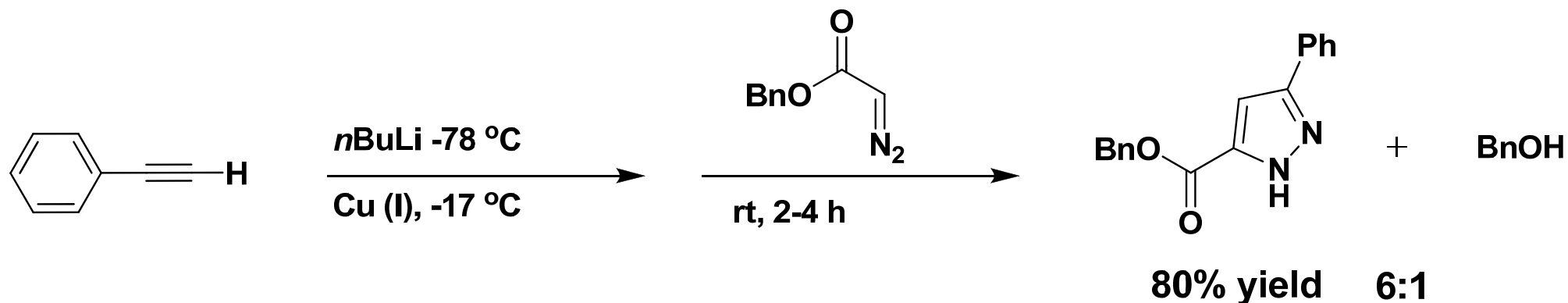
$\text{R}^1 = \text{OEt}$   
 $\text{R}^2 = \text{EWG}$



$\text{R}^1 = \text{OEt}$   
 $\text{R}^2 = \text{aryl, alkyl}$

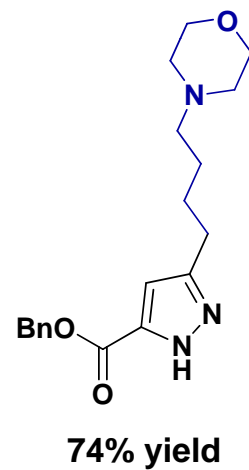
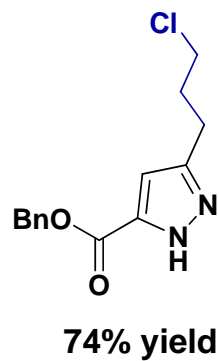
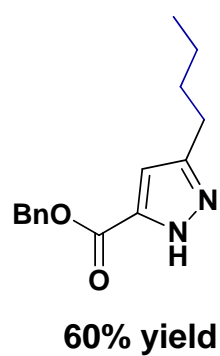
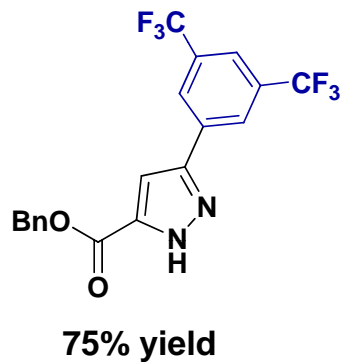
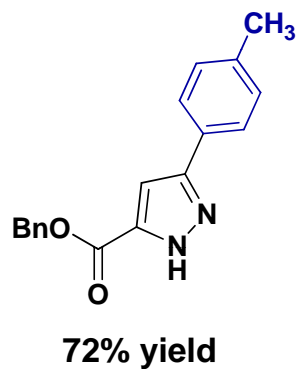
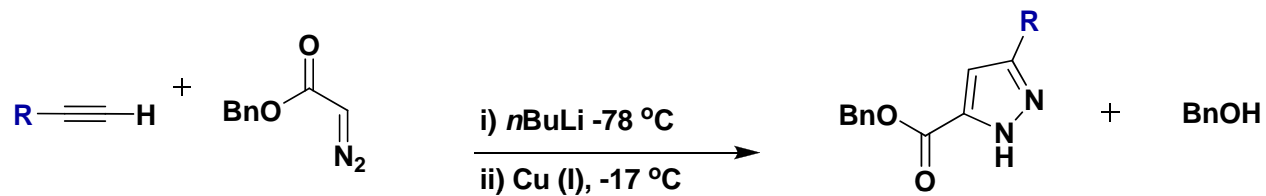
- Aggarwal, V.; Bonnert, R.; Vicente, J. *J. Org. Chem.* **2003**, *68*, 5381.  
Jiang, N.; Li, C. *Chem. Commun.* **2004**, 394.  
Ready, J.; Qi, X. *Angew. Chem. Int. Ed.* **2007**, *46*, 3242.

# Initial Attempts to Form Pyrazoles Using Cu(I) as a Promoter

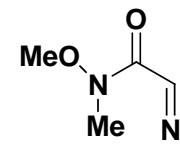
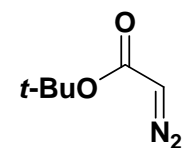
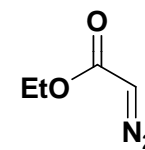
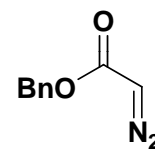


- 1 equivalent  $\text{CuCN}\cdot 6\text{LiCl}$  necessary
- Alkali-metal acetylide required
- Copper required
- Single regioisomer

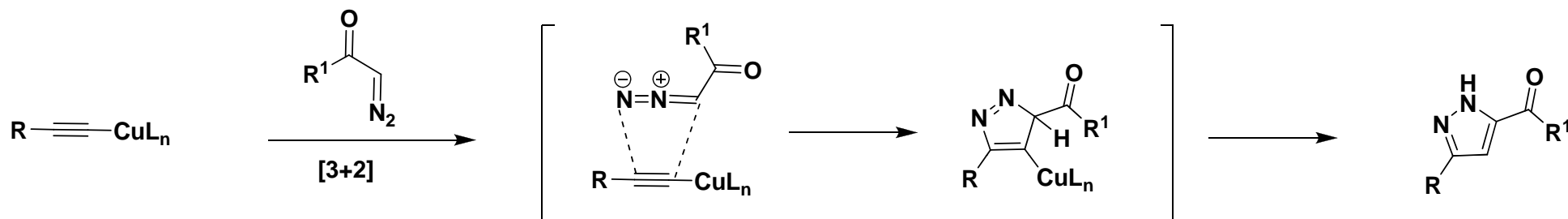
# Reaction Scope: The Alkyne Component



## Diazoacetyl Compounds



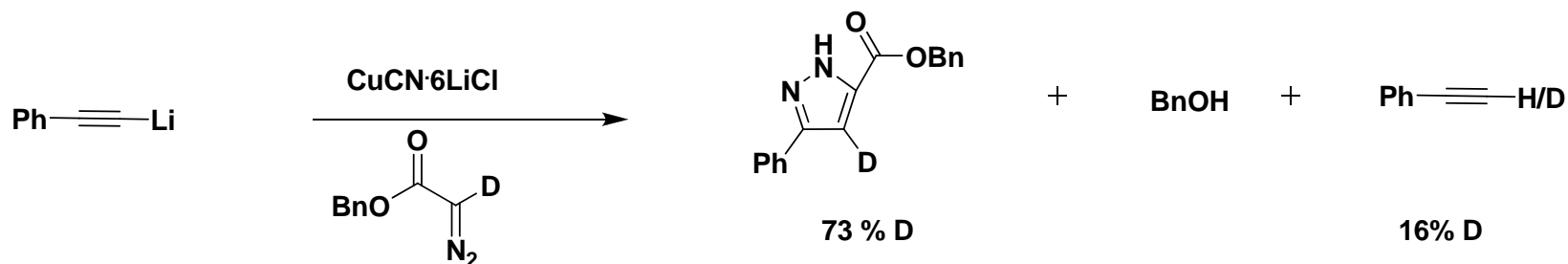
## A Concerted Mechanism



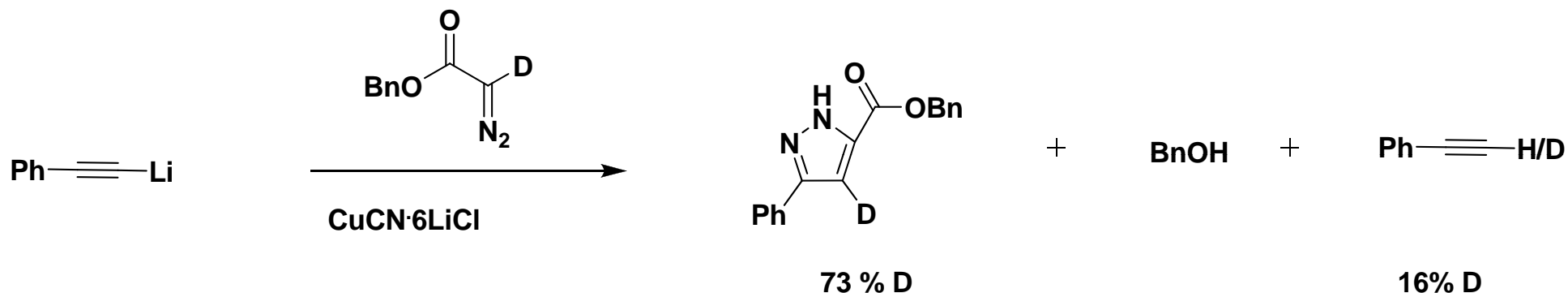
- EWGs slow reaction
- Similar rates in THF, ether, and toluene
- Observed regioselectivity

$\Longrightarrow$  consistent with a concerted mechanism

## Labeling Studies



## An Unexplained Side Product



General base:

$n\text{BuLi}$ , LDA,  $\text{Li}_2\text{Cu}(n\text{-C}_4\text{H}_9)_2\text{CN}$ , lithium phenylacetylide

Mechanisms to be ruled out:

- E2 elimination of the alkoxide
- Direct addition
- Ester hydrolysis

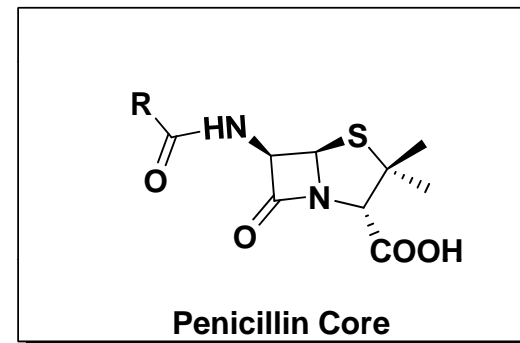
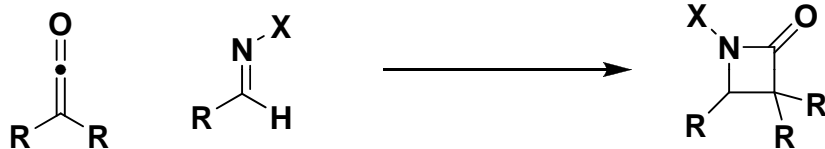
	major product: BnOH
Non-deuterated	6.0:1
Deuterated	6.2:1

# Outline

- Introduction to 1,3 Dipolar Cycloadditions
- Cu(I)-catalyzed 1,3 Dipolar Cycloaddition Between Azides and Alkynes
  - Cascade Reactions
  - Extension of the Original Methodology
- **Synthesis of  $\beta$ -Lactams**
  - **Kinugasa Reaction**
- 1,3 Dipolar Cycloadditions Between Azomethine Ylides and Activated Alkenes

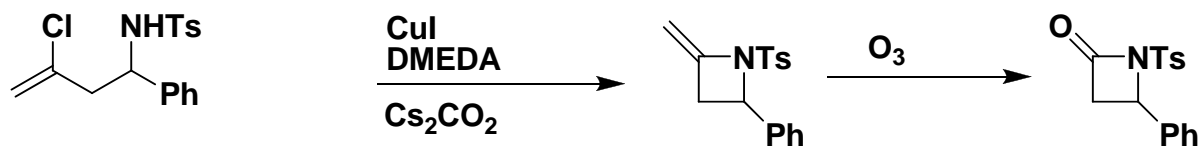
# Synthesis of $\beta$ -Lactams

## The Staudinger Synthesis



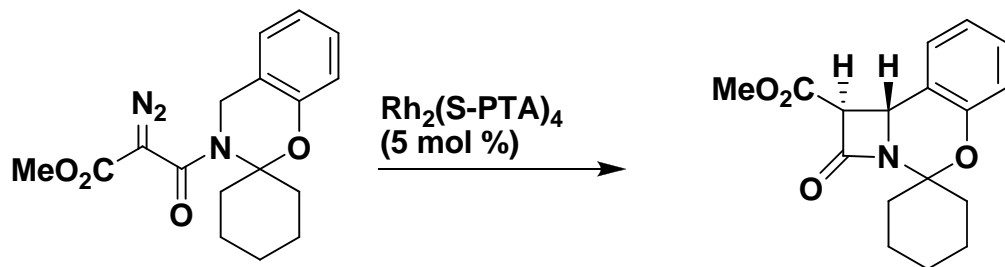
Staudinger, H. *Liebigs. Ann. Chem.* **1908**, 356, 51.

## Ullmann Type Coupling



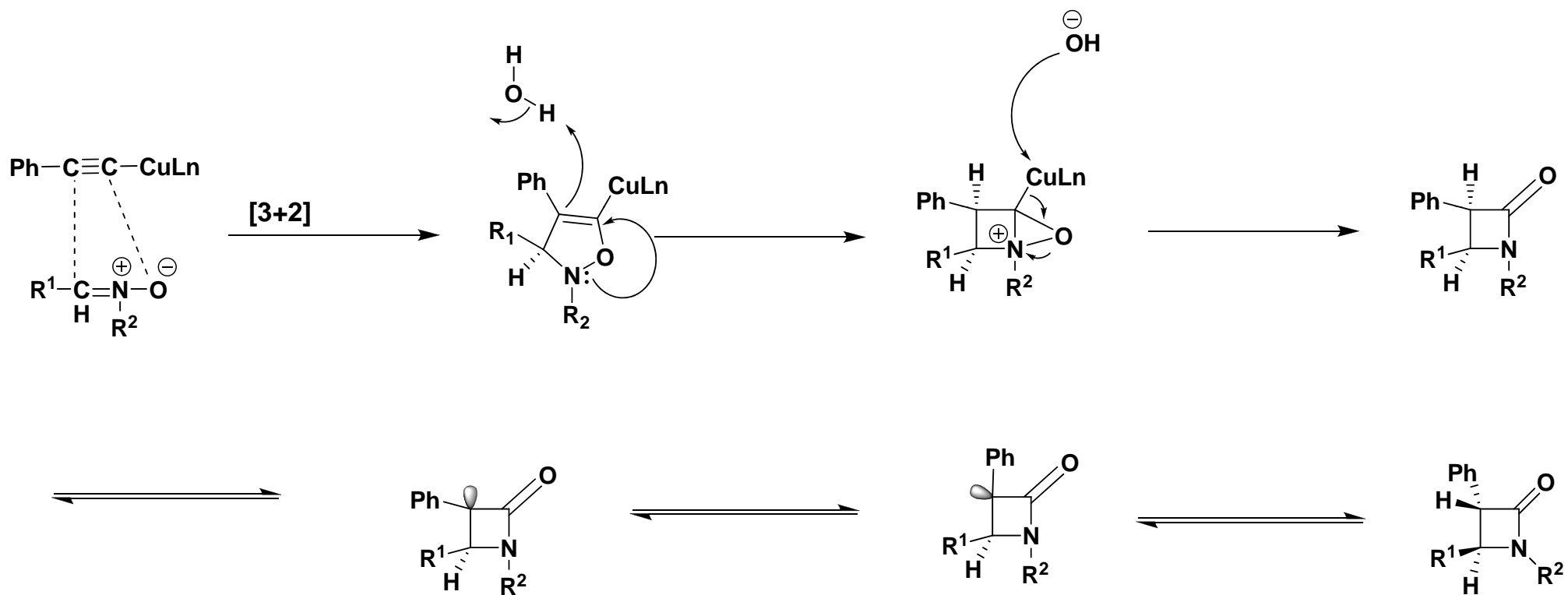
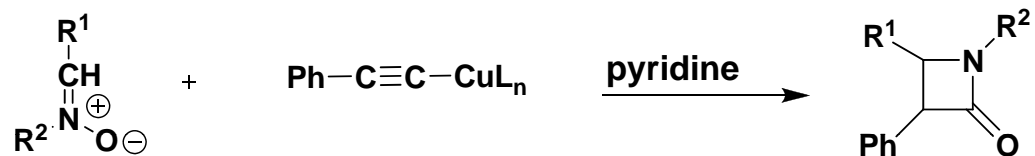
Lu, H.; Li, C. *Org. Lett.* **2006**, 8, 5365.

## Intramolecular C-H insertion



Ananda, M.; Hashimoto, S. *Tetrahedron Lett.* **1998**, 39, 9063.

# The Kinugasa Reaction

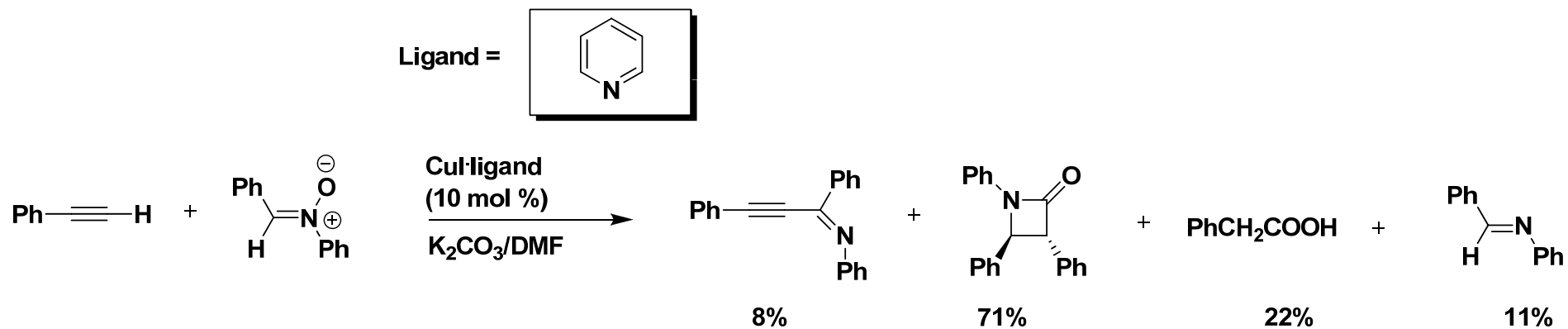
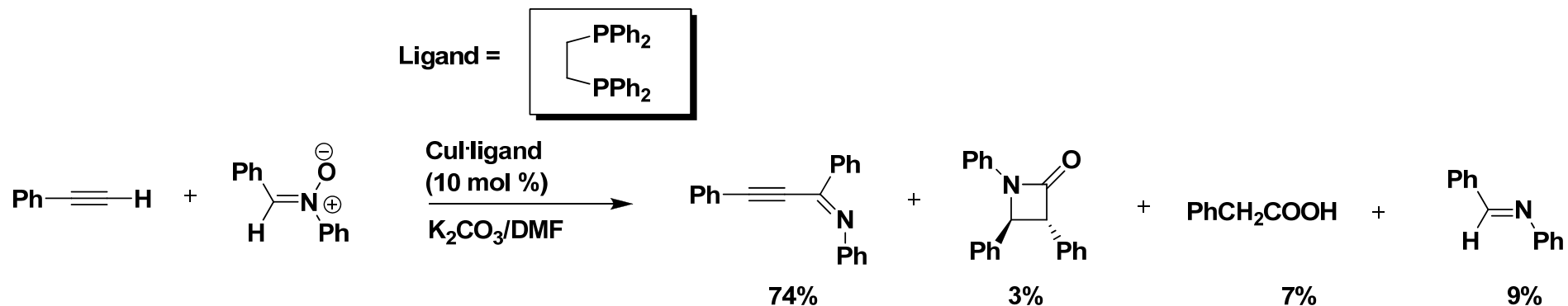
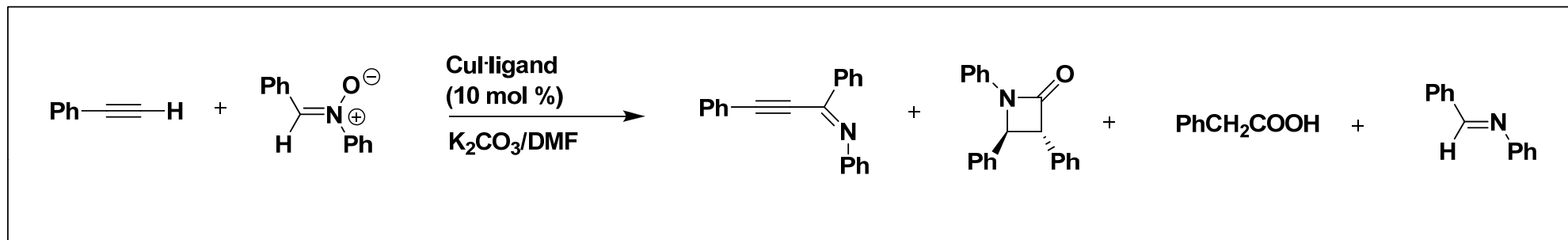


Kinugasa, M.; Hashimoto, S. *J. Chem. Soc. Chem. Commun.* **1972**, 466-467.

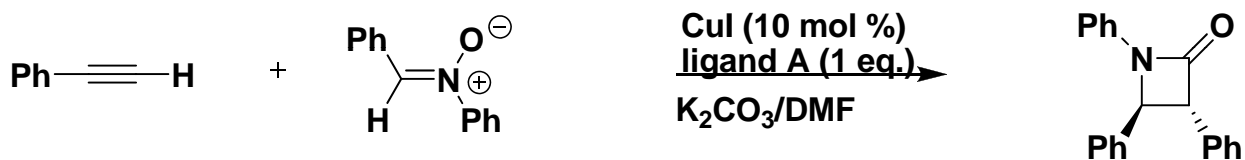
Ding, L.; Irwin, W. *J. Chem. Soc. Perkin Trans. 1.* **1976**, 2382.

Miura, M.; Enna, M.; Okuro, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999.

# Pioneering Efforts by Miura

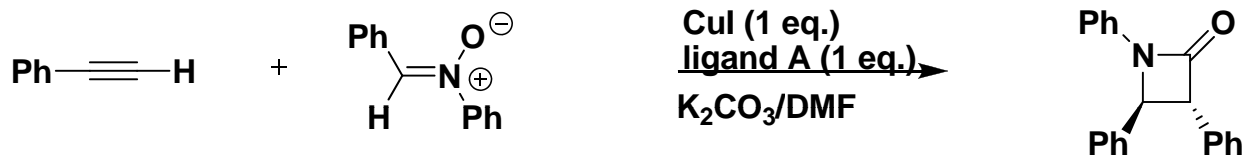
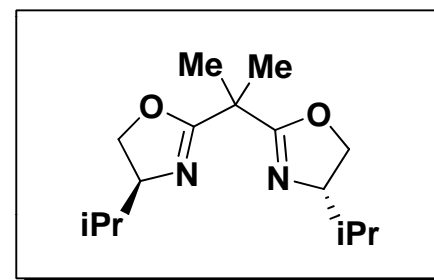


# Attempts at Asymmetric Induction in the Kinugasa Reaction



45% yield  
40% ee

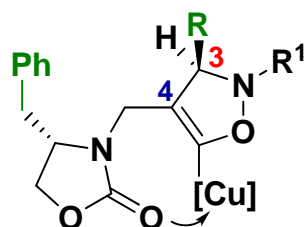
Ligand A =



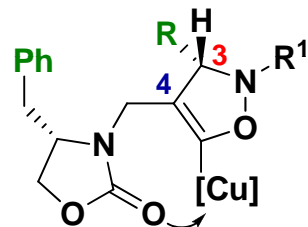
54% yield  
68% ee

# A Chiral Auxiliary Based Approach

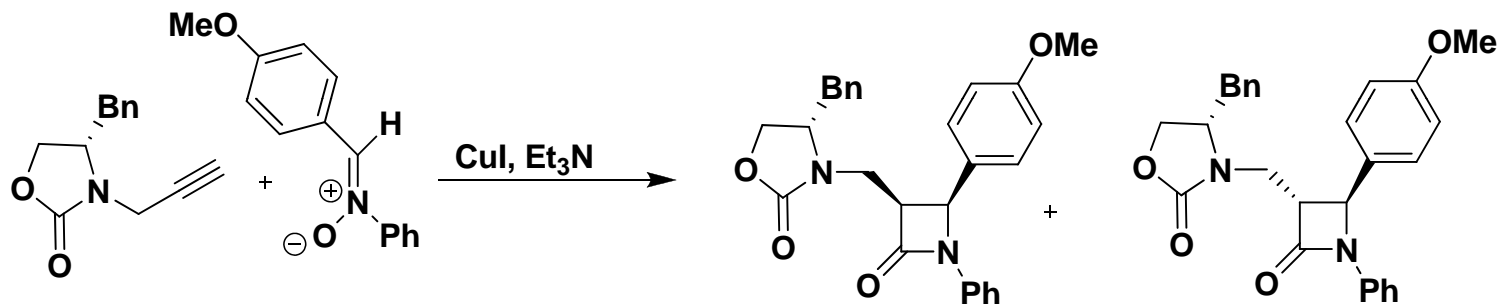
The oxazolidinone side chain controls the approach of the nitron.



lower in energy:  
substituents on opposite faces



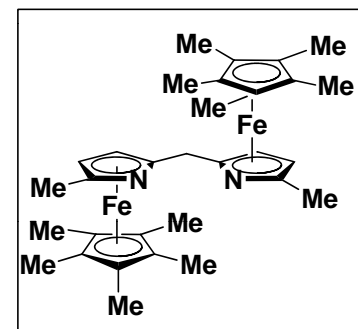
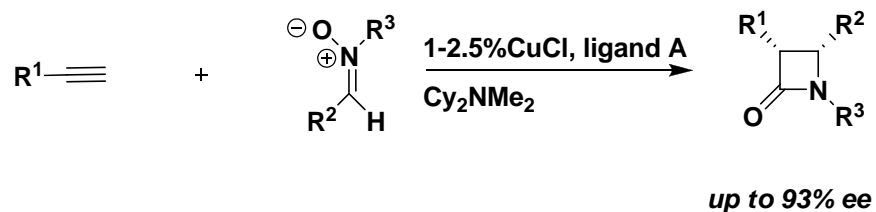
higher in energy:  
substituents on the same face



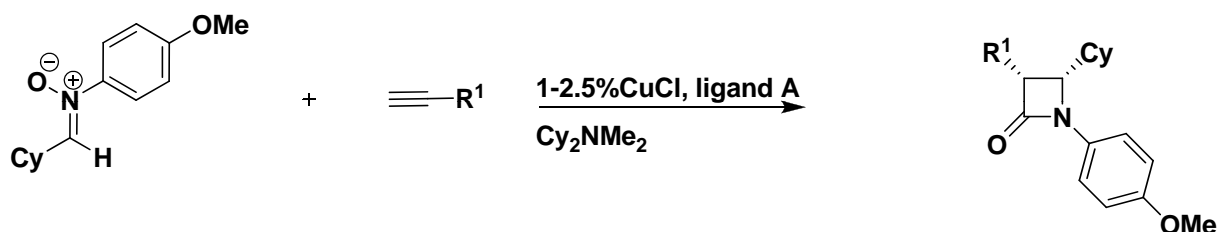
5:3

70% combined yield

# Fu's Use of a Chiral Ligand to Induce Asymmetry



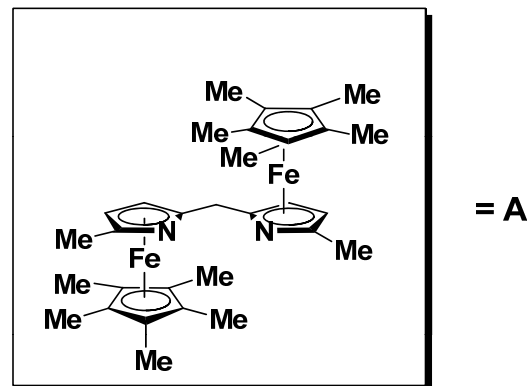
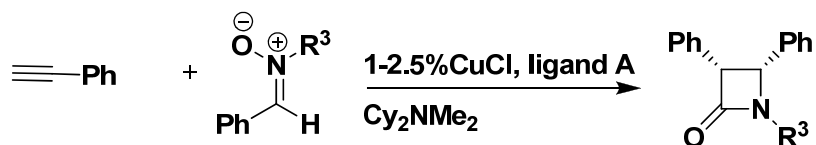
## Alkyne Scope



R <sup>1</sup>	cis:trans	% ee, cis	isolated yield % (cis isomer)
4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub>	>95:5	92	65
4-OMeC <sub>6</sub> H <sub>4</sub>	>95:5	93	57
CH <sub>2</sub> Ph	71:29	73	43
1-cyclohexenyl	90:10	91	45

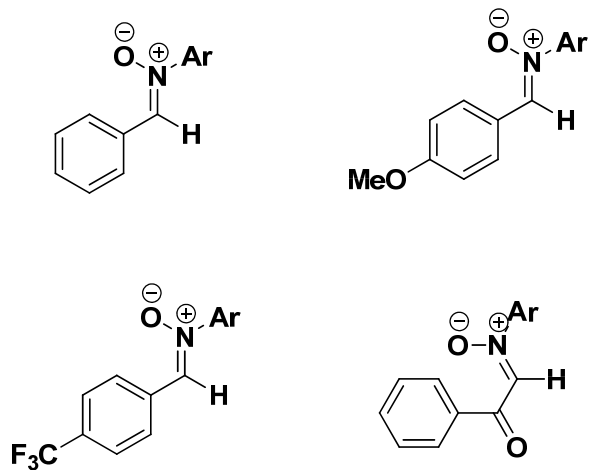
# Variation of the Nitrono Component

## Variation of the N-based substituent

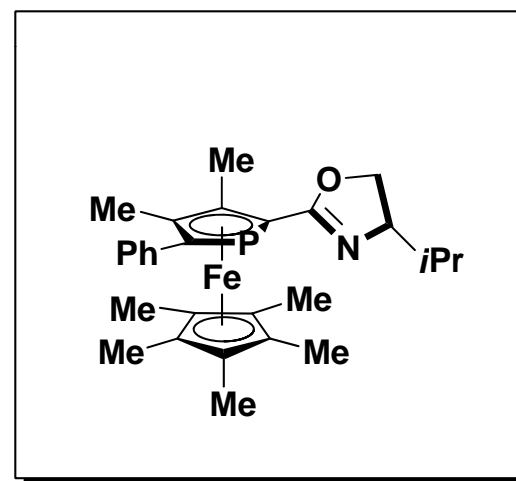
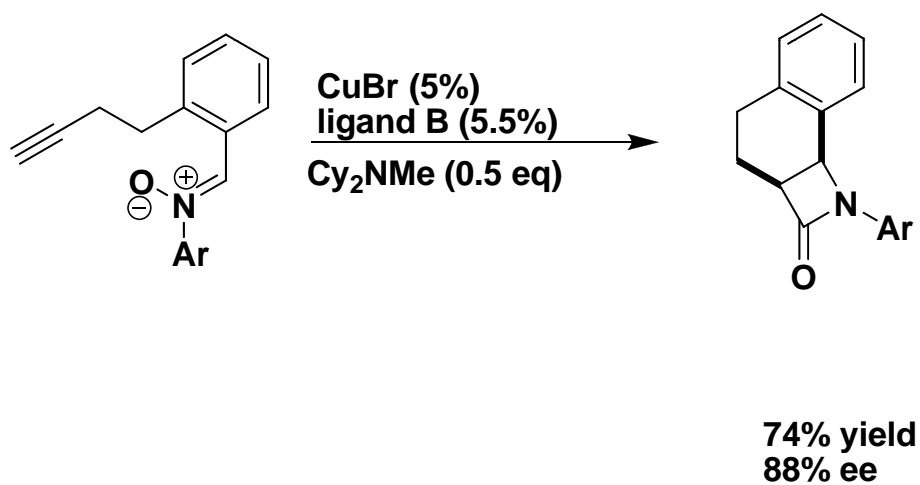
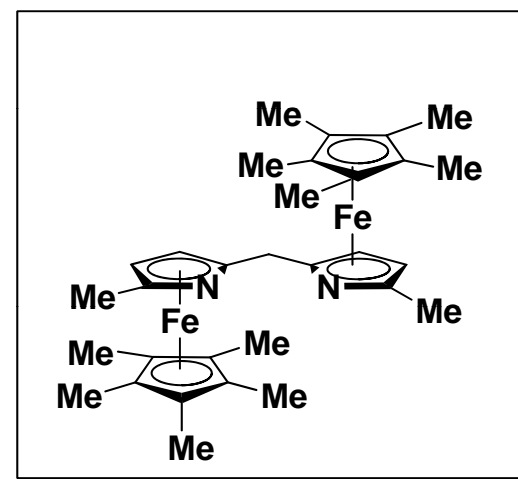
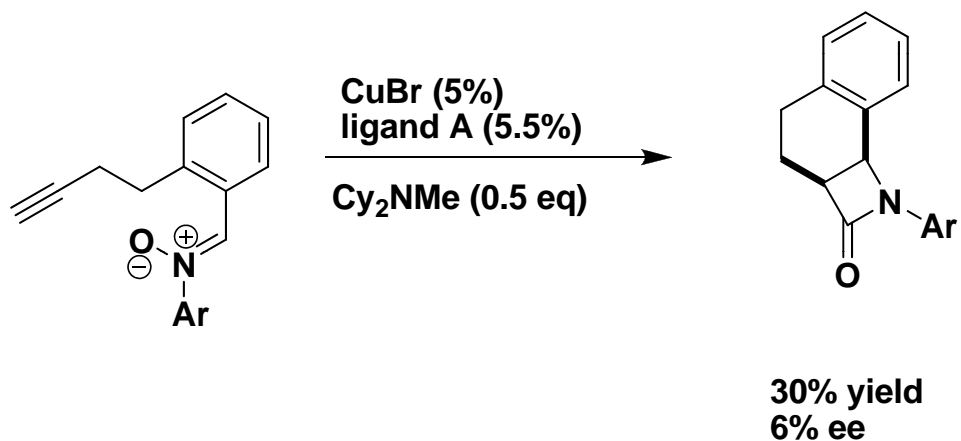


R <sup>3</sup>	<i>cis:trans</i>	% ee (cis)	isolated yield % (cis isomer)
Ph	95:5	77	69
4-OMeC <sub>6</sub> H <sub>4</sub>	95:5	85	53
4-BrC <sub>6</sub> H <sub>4</sub>	94:6	72	74
4-(EtO <sub>2</sub> C)C <sub>6</sub> H <sub>4</sub>	94:6	71	91

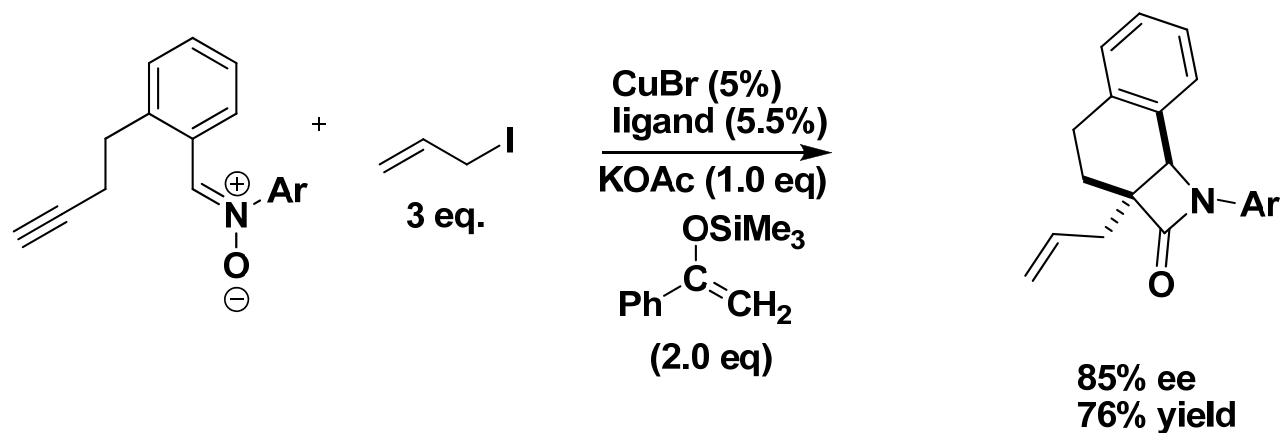
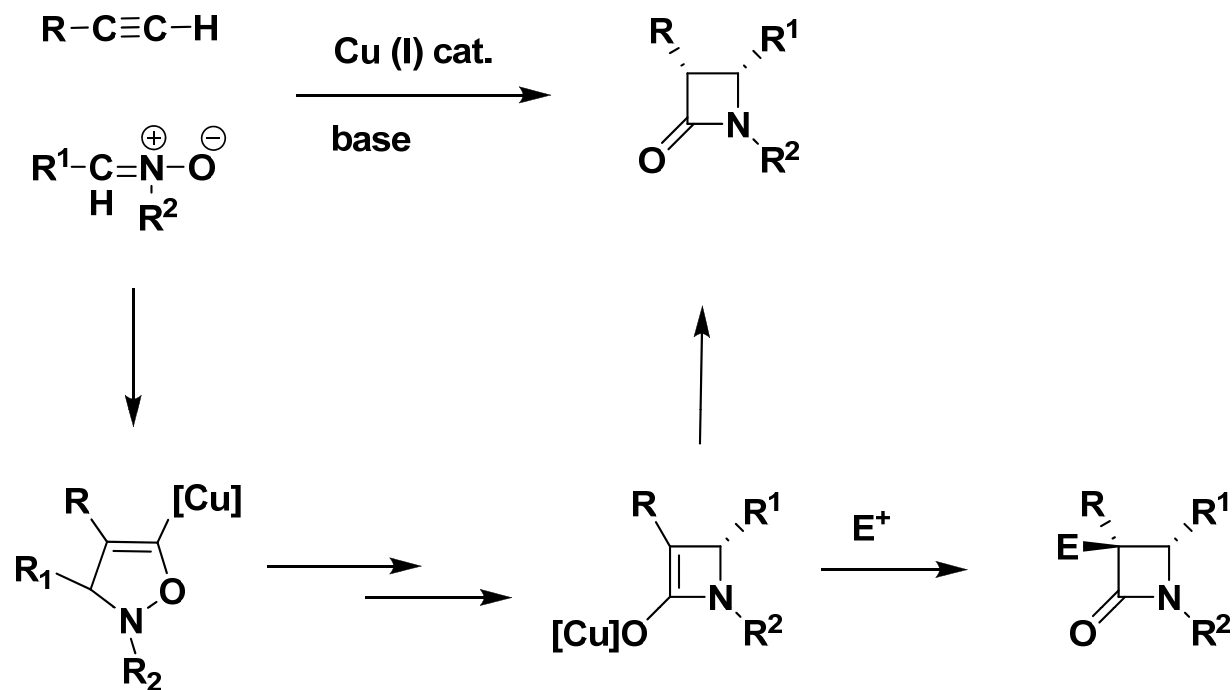
## Variation of the Nitrono Component



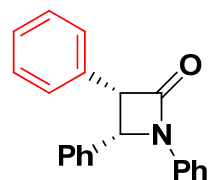
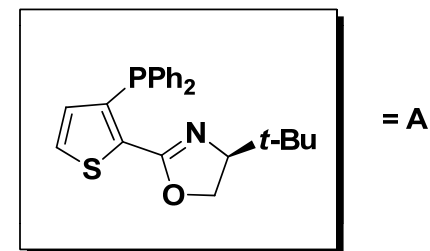
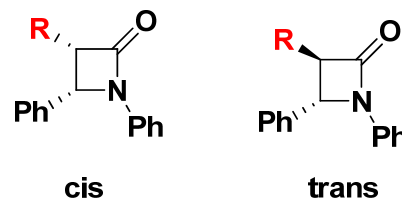
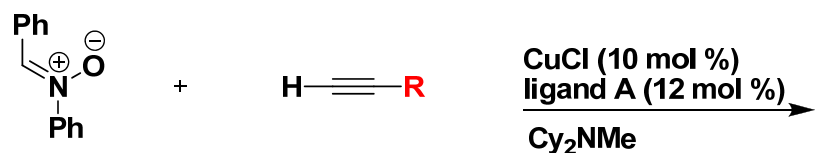
# Intramolecular Attempts With the Kinugasa Reaction



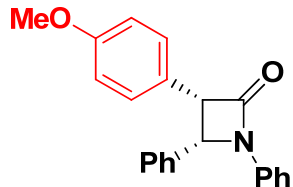
# Intercepted Intermediate



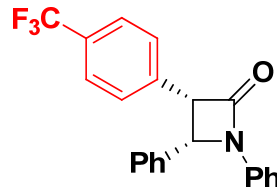
# Other Attempts to Induce Asymmetry in the Kinugasa Reaction



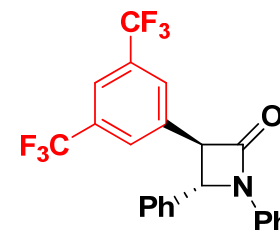
73% conversion  
91:9 cis:trans  
37% ee



22% conversion  
92:8 cis:trans  
10% ee



80% conversion  
76:24 cis:trans  
29% ee

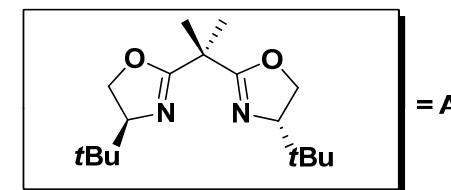
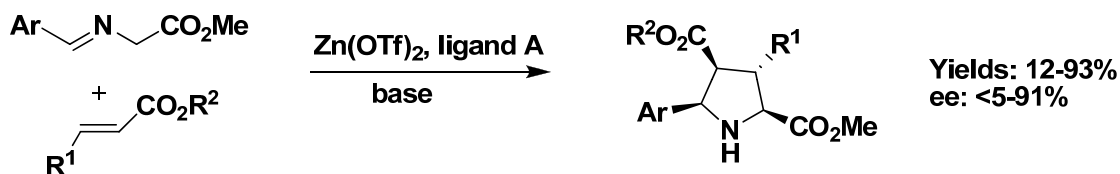


64% conversion  
8:92 cis:trans  
53% ee

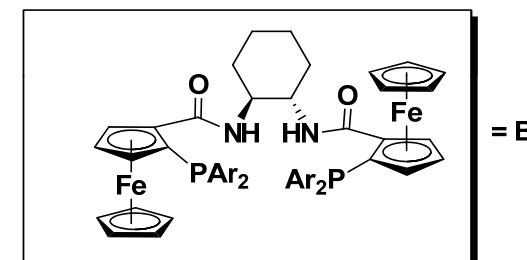
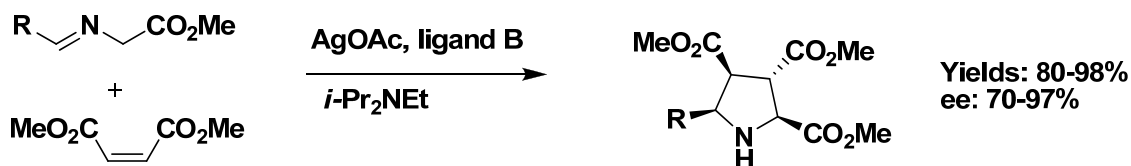
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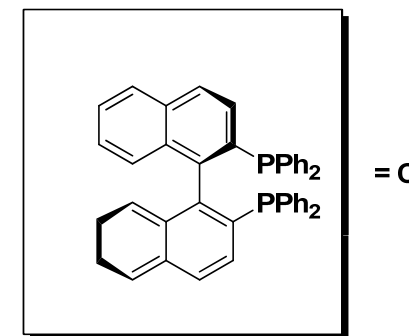
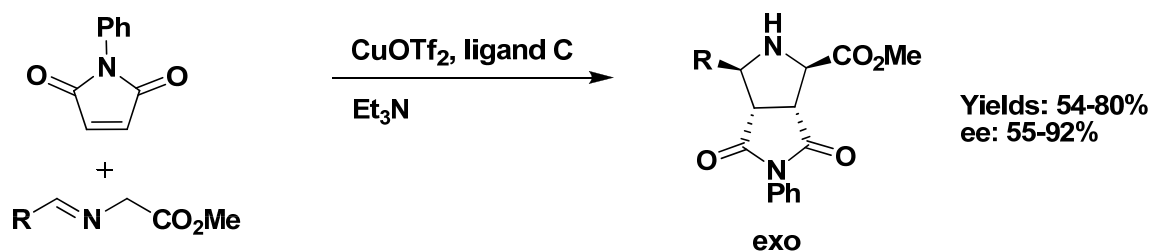
# 1,3 Dipolar Cycloadditions of Azomethine Ylides Catalyzed by Chiral Metal Complexes



Gothelf, A.; Gothelf, K.; Hazell, R.; Jorgensen, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 4236.

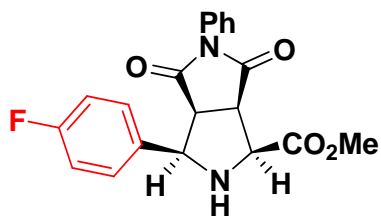
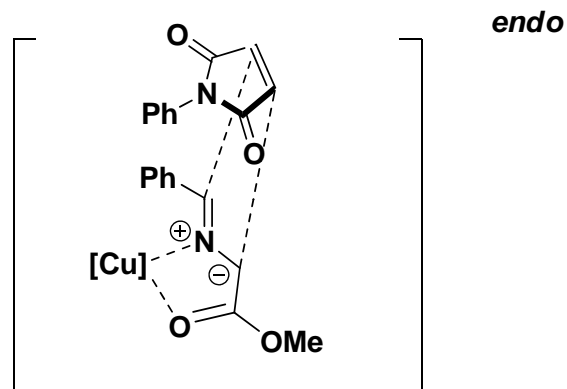
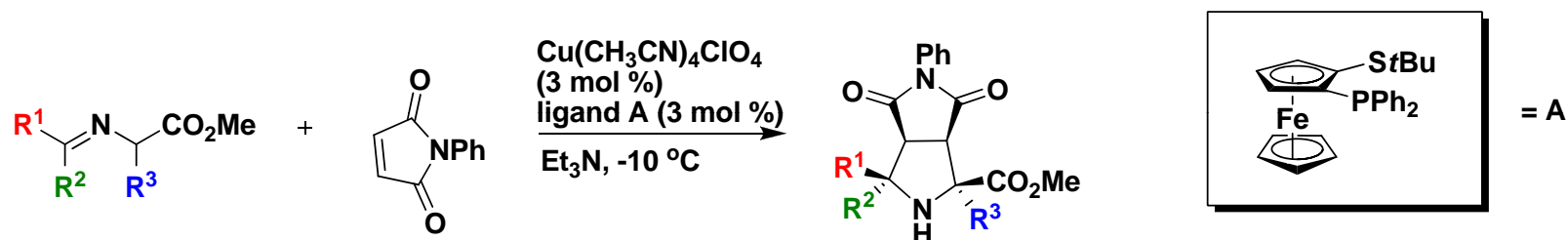


Longmire, J.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400.

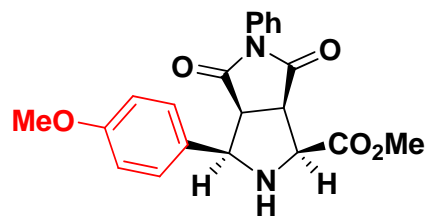


Oderaotshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, *5*, 5043.

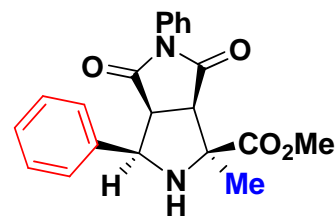
# Highly Endo Selective Cycloadditions of Azomethine Ylides



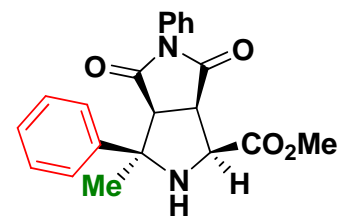
endo:exo = >98:2  
 yield(%) = 82  
 ee(%) = >99



endo:exo = >98:2  
 yield(%) = 81  
 ee(%) = >99

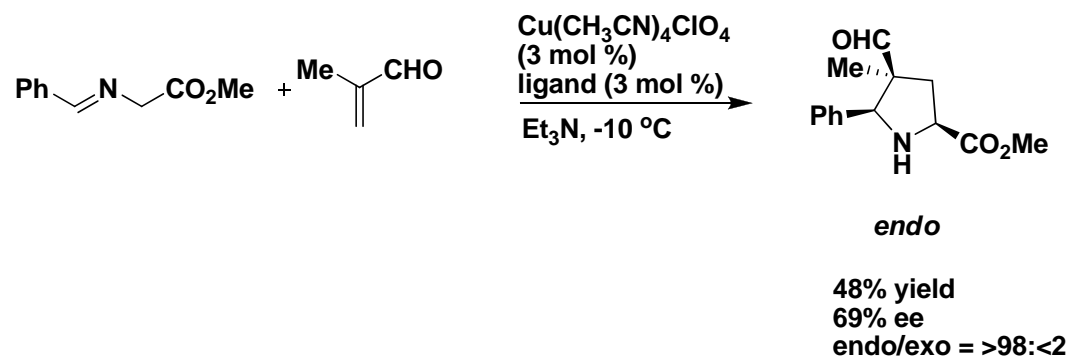
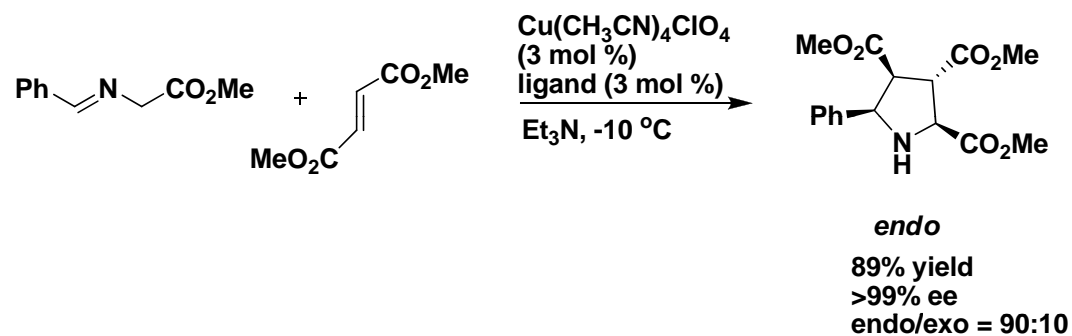
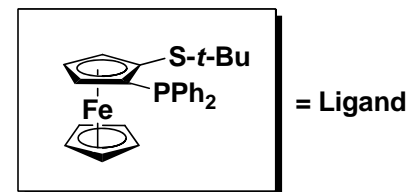
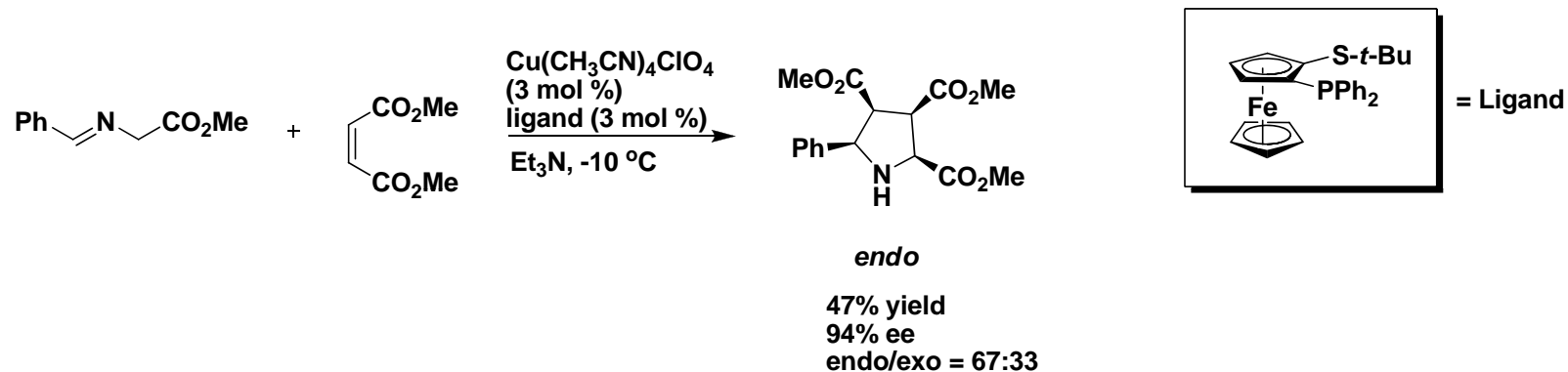


endo:exo = >98:2  
 yield(%) = 50  
 ee(%) = 80

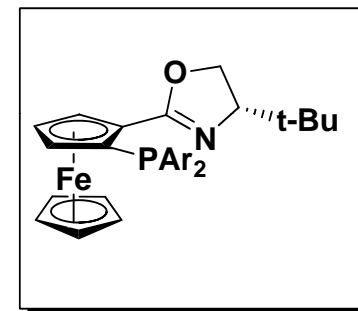
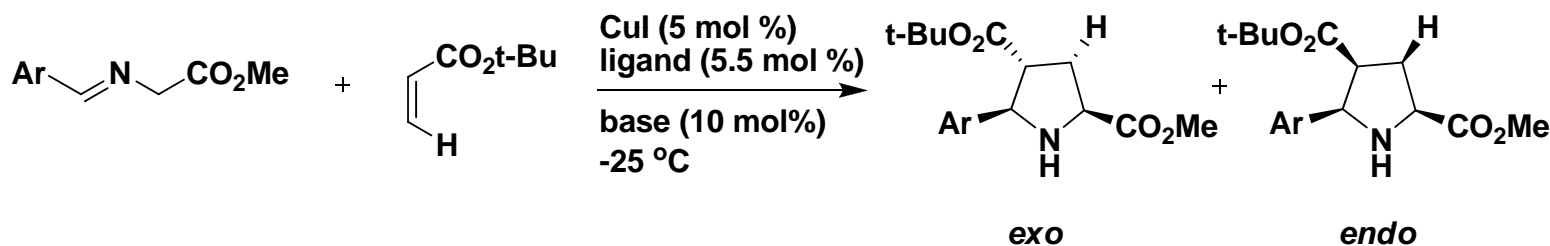


endo:exo = >98:2  
 yield(%) = 78  
 ee(%) = 94

# Endo Selectivity Scope Continued

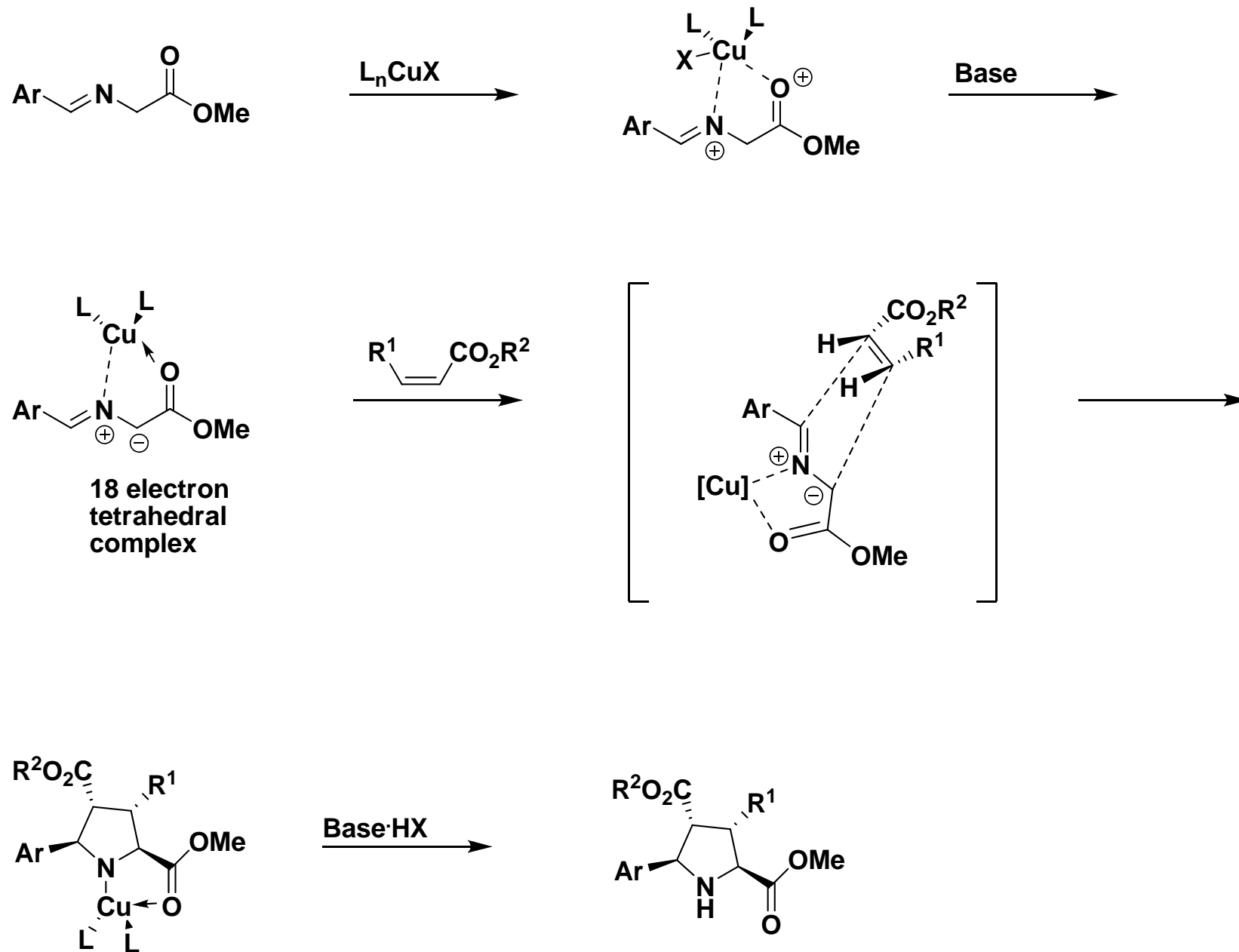


# Highly Exo-selective and Enantioselective Cycloadditions of Azomethine Ylides

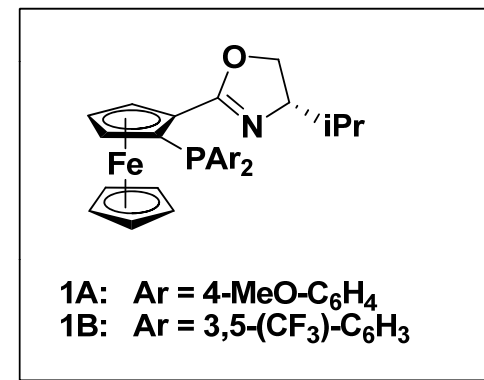
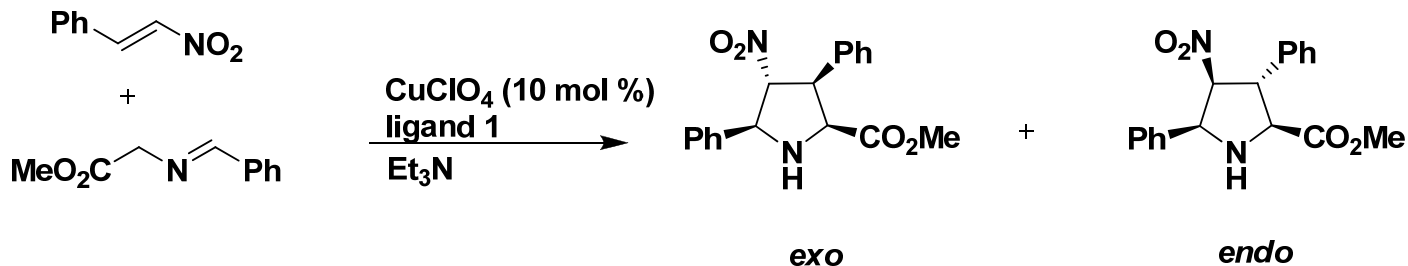


Ar	base	exo/endo	yield (exo, %)	ee of exo
<i>o</i> -ClPh	Et <sub>3</sub> N	76/24	76	98
<i>p</i> -MePh	DBU	97/3	61	89
<i>p</i> -OMePh	DBU	97/3	82	91

# Mechanism

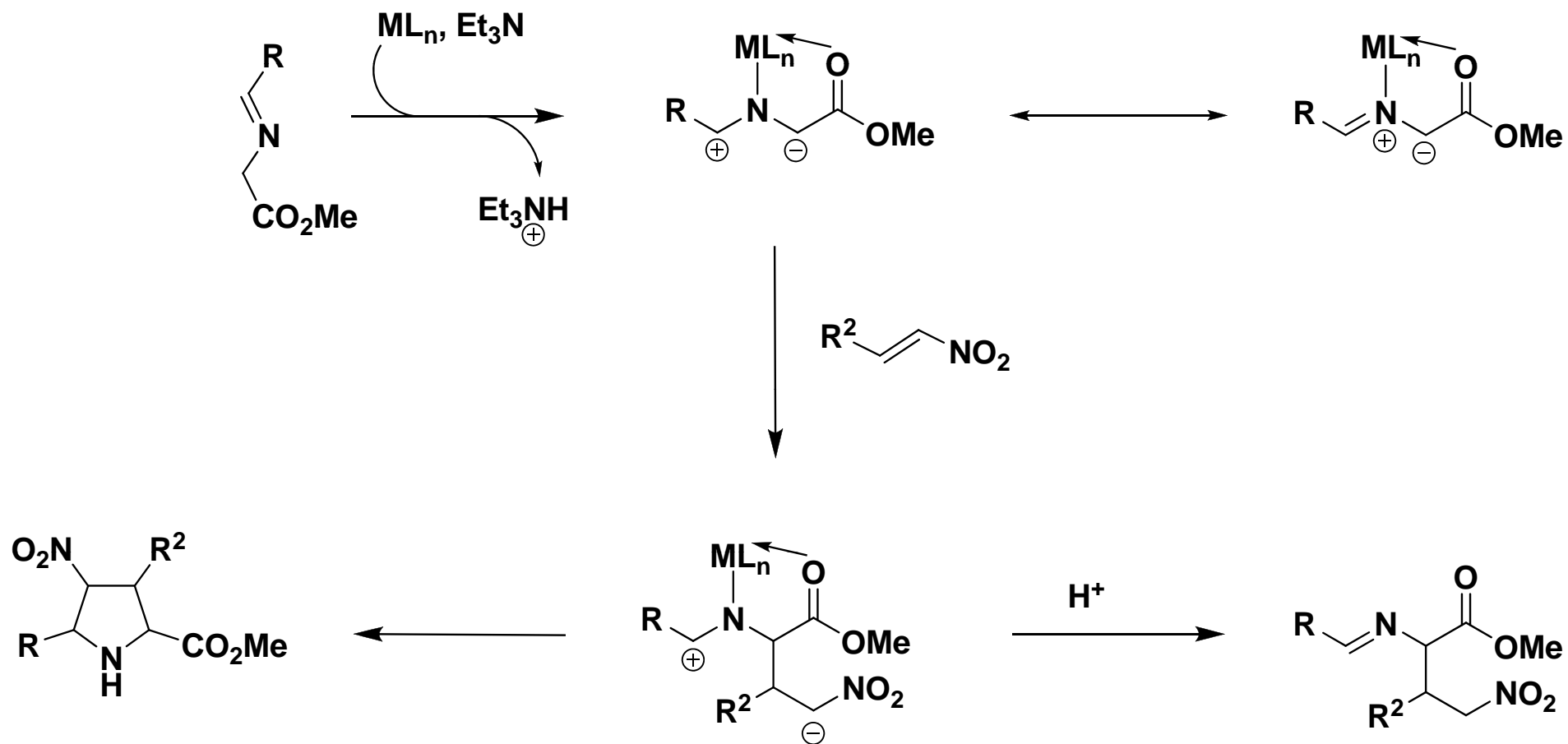


# Varying the Electronic Nature of the Ligand to Change Stereoselectivity



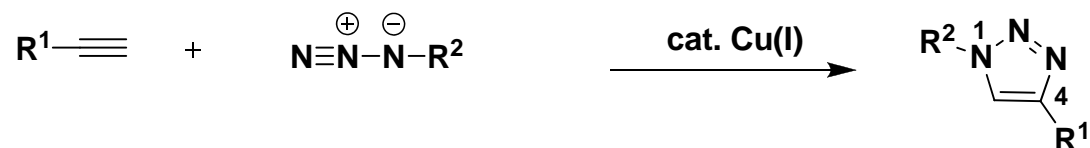
ligand	yield	exo/endo	ee %
1A	65%	only exo	98
1B	62%	18:82	97

# Proposed Mechanism



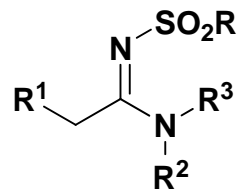
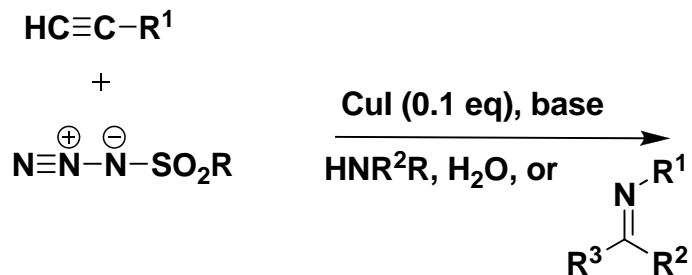
# Summary of Cu(I)-Catalyzed Processes

- Regioselective formation of 1,4 disubstituted triazoles

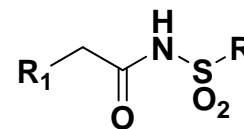


*1, 4 regioisomer obtained exclusively*

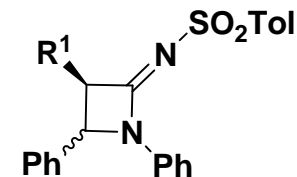
- Cascade reactions



amidines



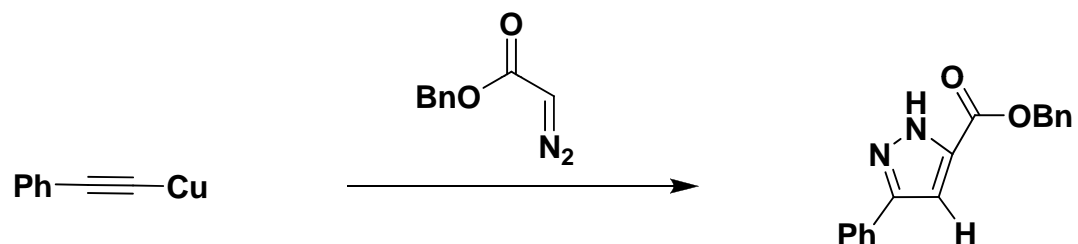
sulfonamides



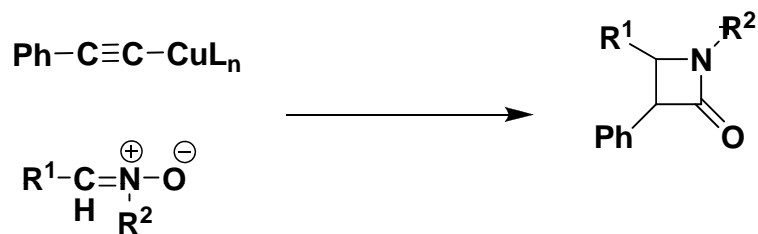
azetidiminines

# Summary of Cu(I)-Catalyzed Processes

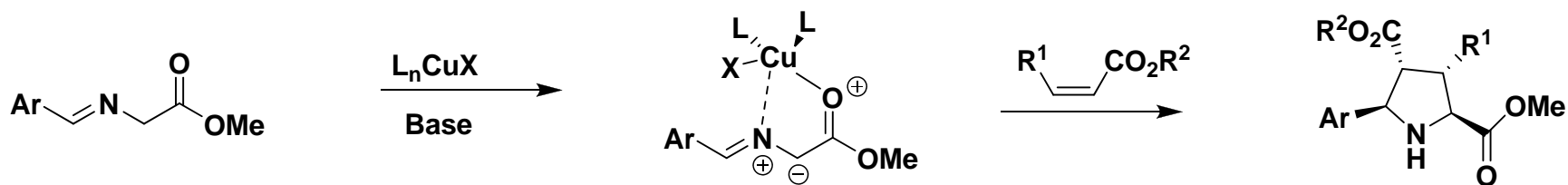
- Reactions of other 1,3 dipoles



- Kinugasa reaction



- Lewis acid activation



## Acknowledgements

**Dr. Michael T. Crimmins**

### The Crimmins' Group

Dr. Anita Mattson

Dee Jacobs

Mariam Shamszad

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Lizzie O'Bryan

Colin Hughes

Mark Mans

Tim Martin

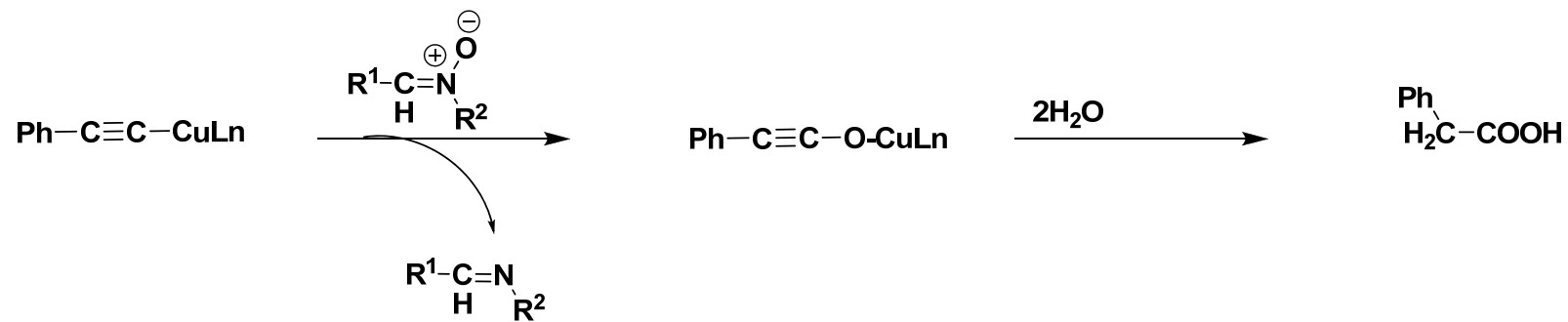
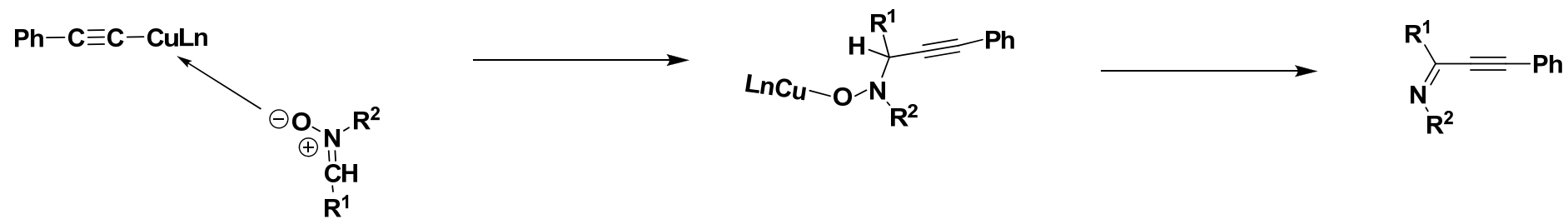
Philip Williams

Dr. Michael Ellis

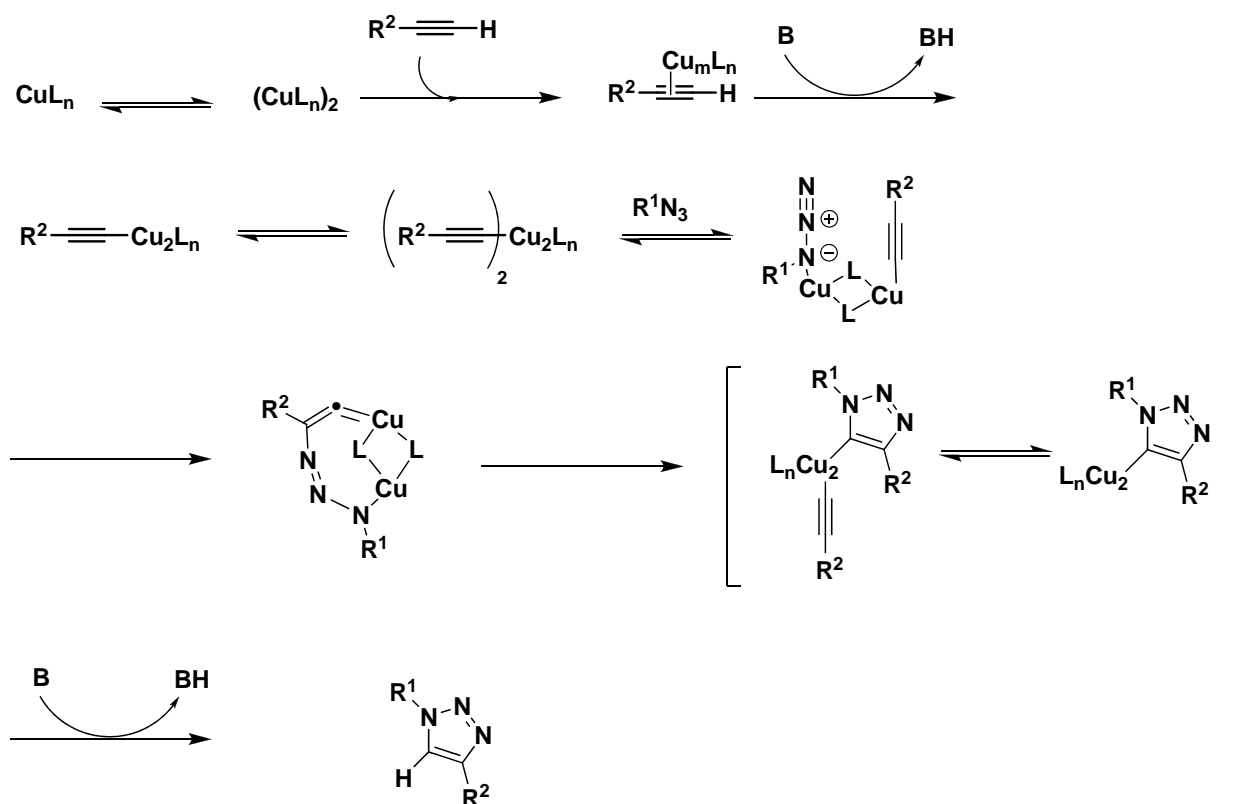




# Byproduct Formation



# Azide-Acetylide Mechanism

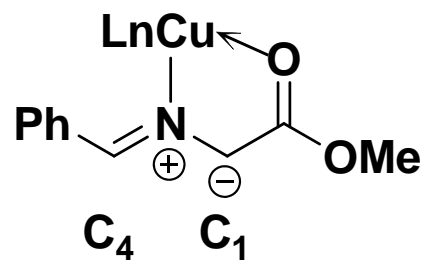
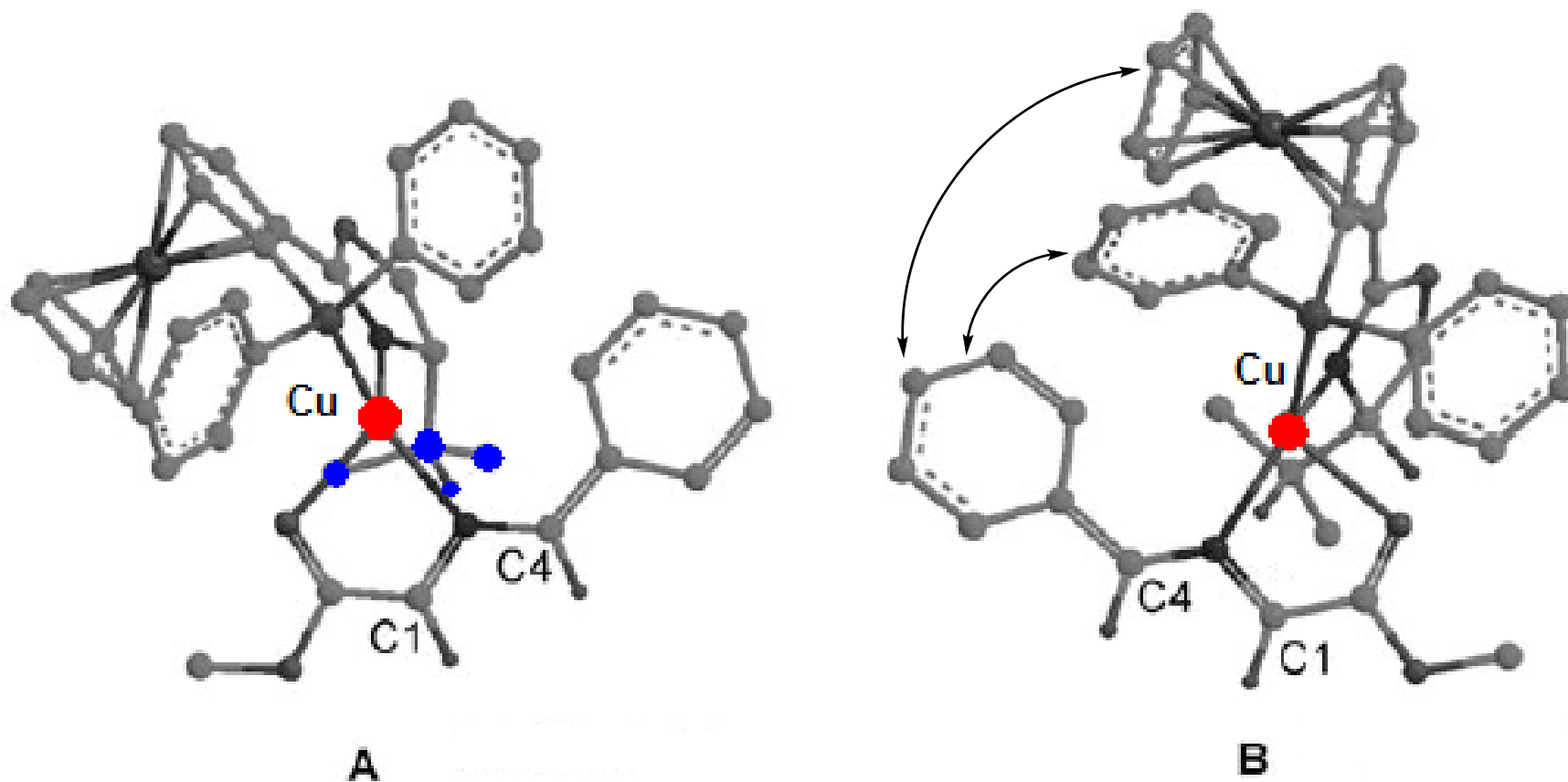


## Kinetic Studies:

- Process is 2nd Order in Cu when process is catalytic in Cu.
- Increasing [Cu] causes less reactive metal aggregates to form -> indicate that  $\text{Cu}^1$  acetylide species is changing in solution.
- $\pi$  complexation may play a role.
- 2nd Cu atom is likely is to activate the azide functionality, or complex with the acetylide (causing a reduction in alkyne electron density, favoring cyclization)

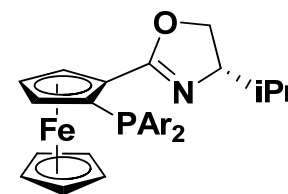
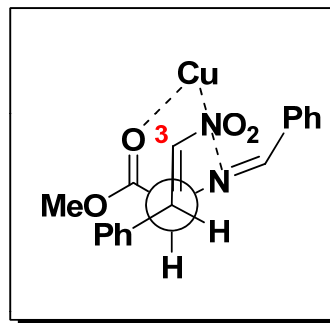
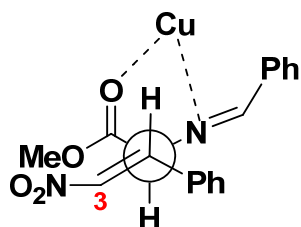
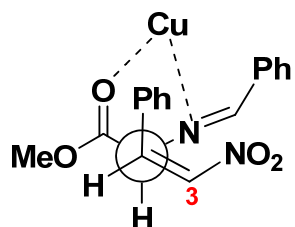
Overall, little is known about the copper acetylide complex.

## An Explanation for the Stereochemical Outcome



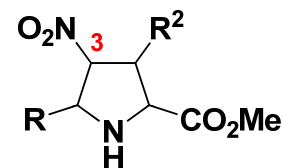
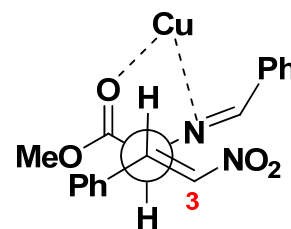
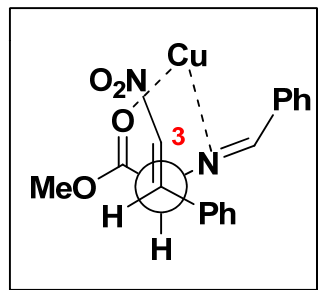
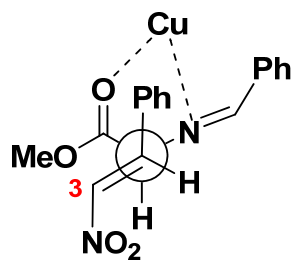
# Stereochemical Explanation Continued

exo

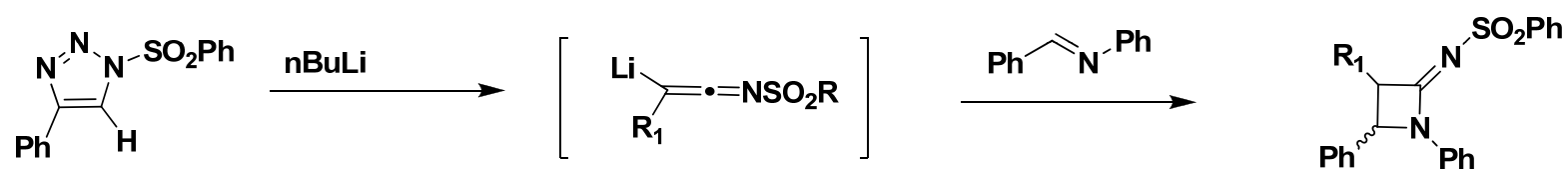


1A: Ar = 4-MeO-C<sub>6</sub>H<sub>4</sub>  
 1B: Ar = 3,5-(CF<sub>3</sub>)-C<sub>6</sub>H<sub>3</sub>

endo



# Mechanism Support



Further support for the mechanism was obtained by conversion of sulfonamide triazole 8 into the corresponding azetidine product. Triazole was stable when subjected to reaction conditions.

When it was metalated with  $n\text{BuLi}$ , resulted in the immediate extrusion of  $\text{N}_2$ . Addition of benzylideneaniline and  $\text{HCl}$  gave rise to the product.