



# Recent Utilization of Allenes in Multiple Bond-Forming Reactions

Timothy Martin

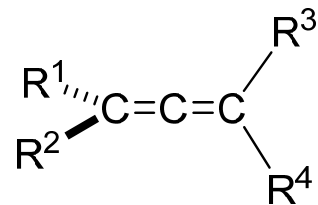
UNC

April 3<sup>rd</sup> 2008

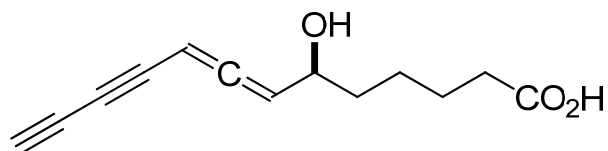
# Presentation Scope

- Background
- Formation of C-C and C-M Bonds
  - Allyl Silanes
  - Allyl Germanes
  - Allyl Boronates
- Formation of C-C bonds
  - Alkenes and Dienes
  - Homoallylic Alcohols
  - Homoallylic Amines
  - Allylic Alcohols
- Conclusions

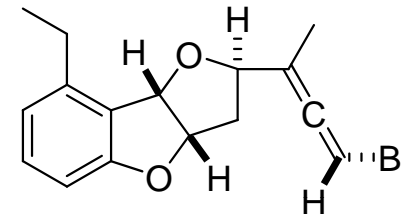
# Allenes



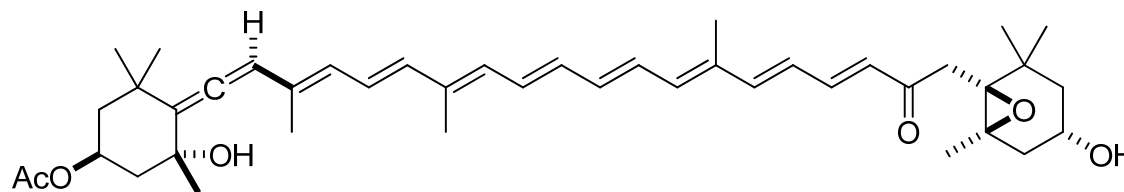
- 1,2-diene
- First allene derivative was prepared in 1887
- Originally thought to be unstable
- Discovered in naturally occurring molecules by Staudinger and Ruzicka in 1924



**07F275**  
linear allene



**panacene**  
bromoallene

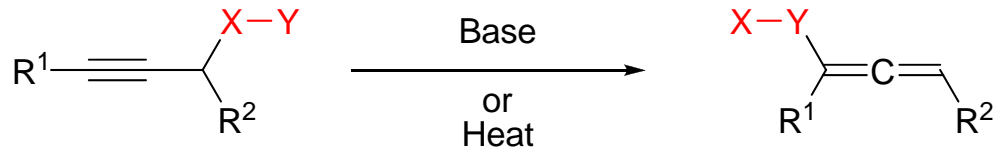
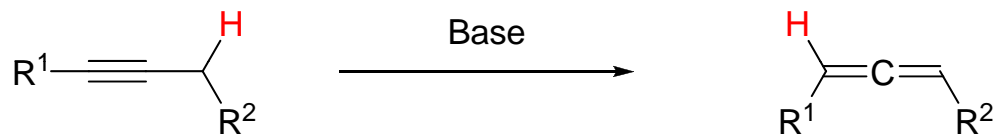


**fucoxanthin**  
allenic carotenoid

Modern Allene Chemistry; Krause, N.; Hashmi, A. S. K. Eds.; Wiley-VCH: Weinheim, Germany, 2004; Vols. 1-2.  
Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2000**, *39*, 3590-3593.  
Zimmer, R.; Dinesh, C. U.; Nandan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067-3125.

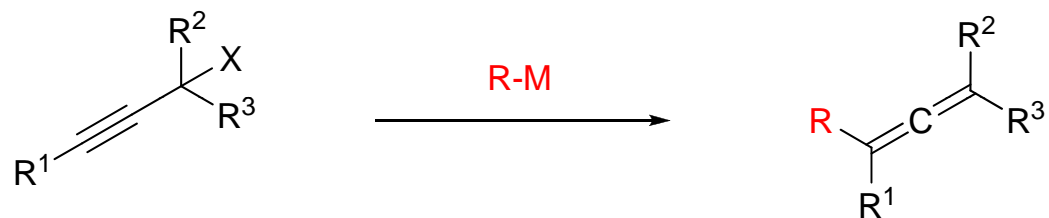
# Synthesis of Allenes

Isomerization Reactions:



Prototropic Rearrangement  
Sigmatropic Rearrangement

Metal Mediated Reactions

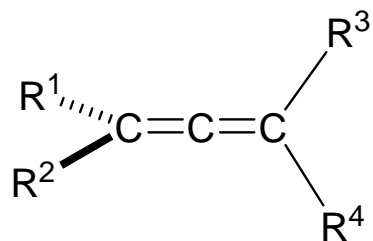


$\text{S}_{\text{N}}2'$ -Substitution  
1,6-Addition



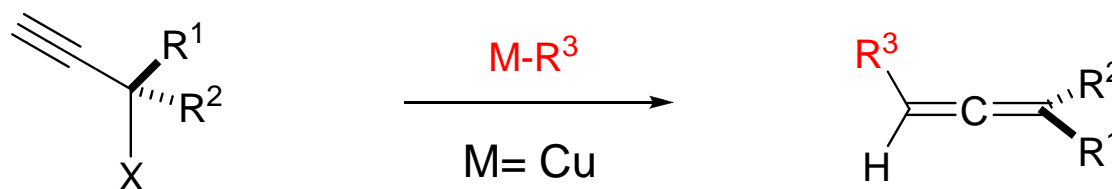
R= Cu, Mg, Li, Ti, In

# Enantioselective Synthesis of Allenes

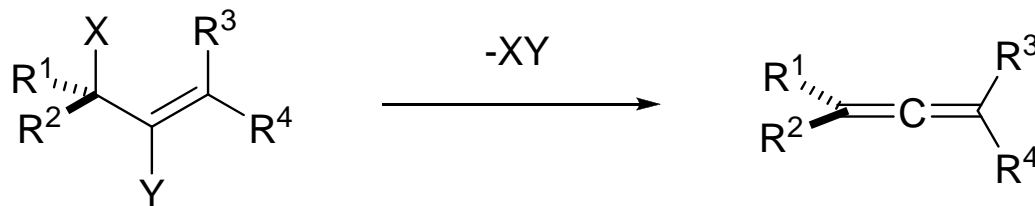


Axial Chirality is an important feature of allenes.

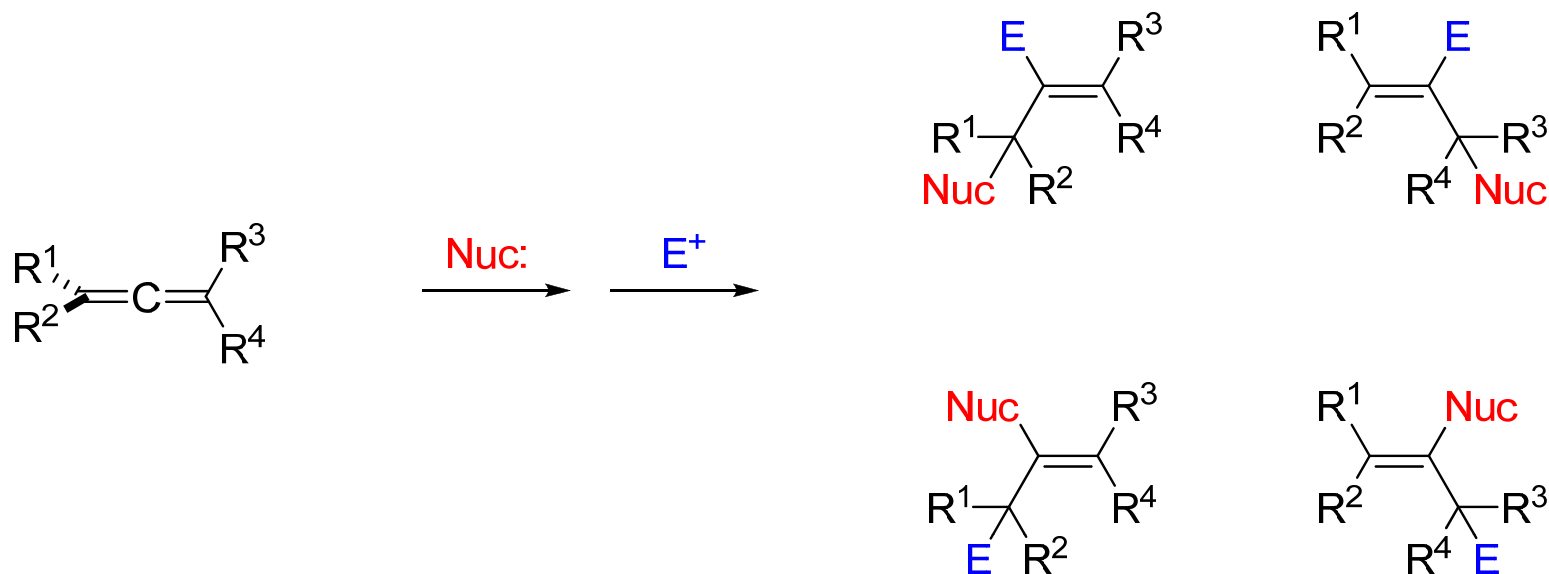
Addition of Cuprates to Enantiopure Propargylic Compounds:



Elimination of Chiral Allylic Compounds:



# Allenes in Multicomponent Coupling Reactions



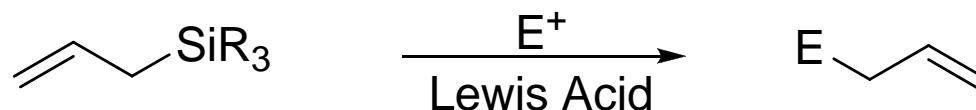
- Allenes can serve as useful substrates in multiple component coupling reactions
- Coupling of multiple organic compounds to form multiple bonds in a single reaction.
- Need to suppress direct coupling of the nucleophile and the electrophile.
- Issues of selectivity also arise.

# Presentation Scope

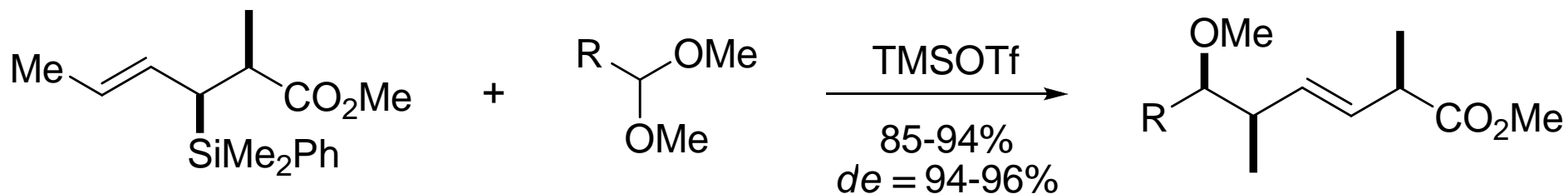
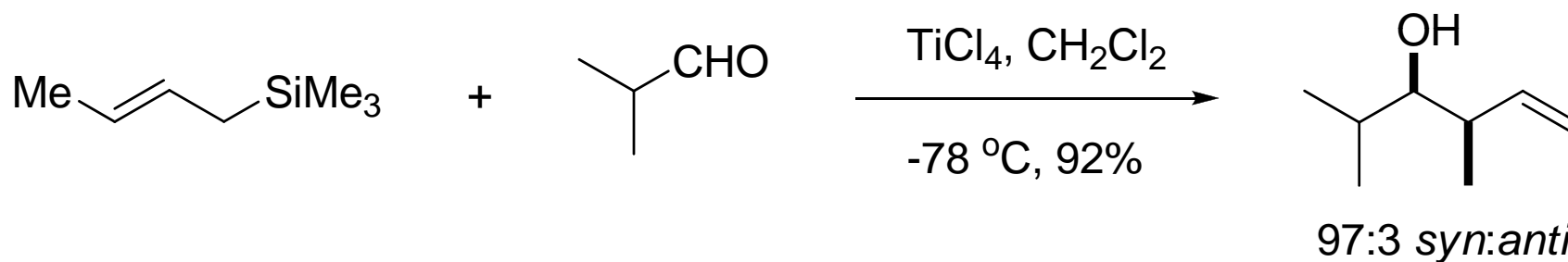
- Background
- Formation of C-C and C-M Bonds
  - Allyl Silanes
  - Allyl Germanes
  - Allyl Boronates
- Formation of C-C bonds
- Conclusions

# Allyl Silanes

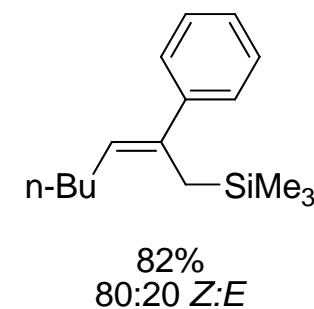
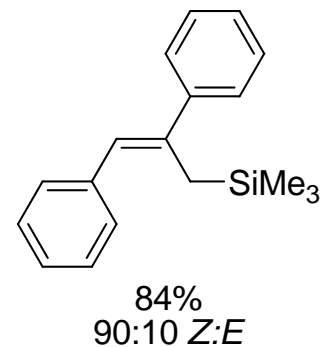
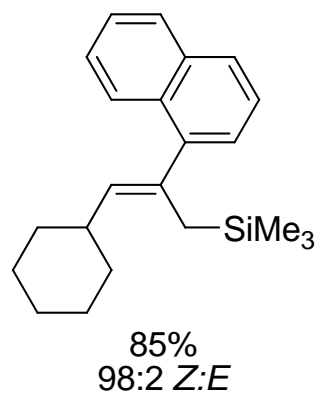
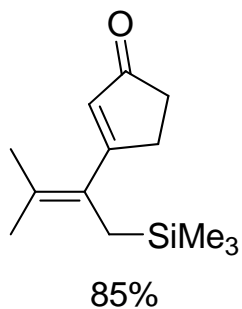
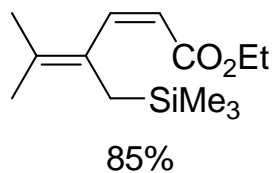
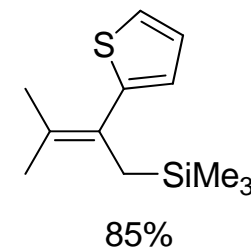
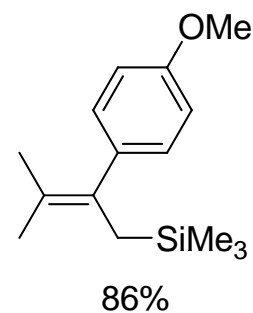
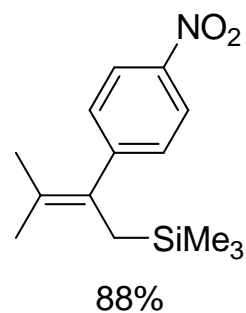
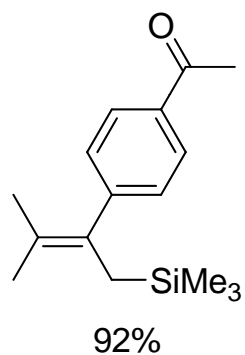
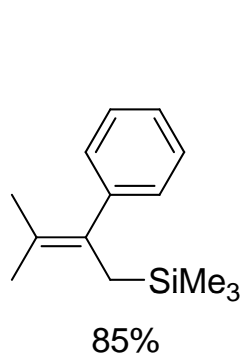
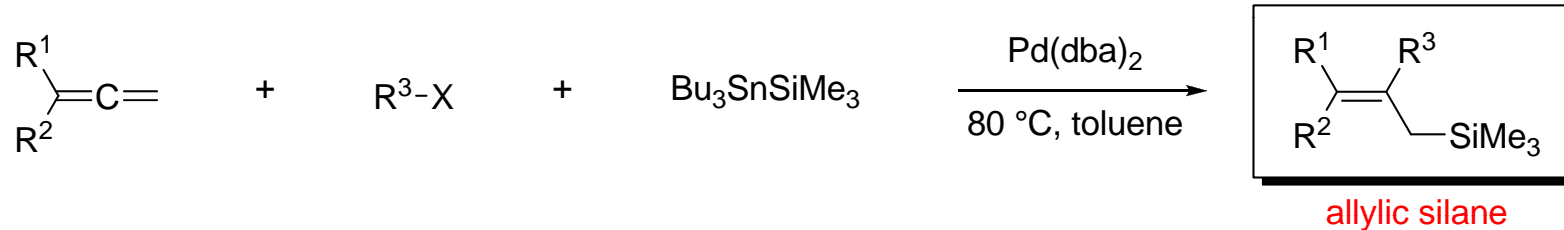
- Useful for selective C-C bond formation
- Stable and storeable



$\text{E}^+$  = carbonyls, imines, electrophilic alkenes

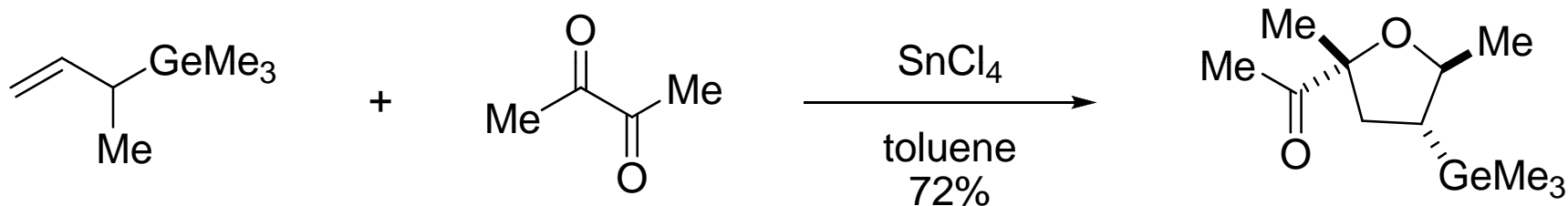


# Cheng – Synthesis of Allylsilanes

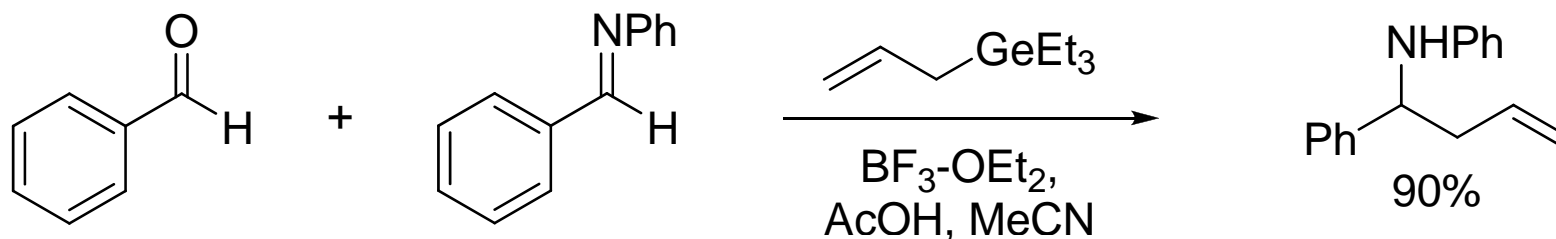


# Allyl Germanes

- Low toxicity
- Undergo [3+2] cycloadditions
- Selective addition to imines

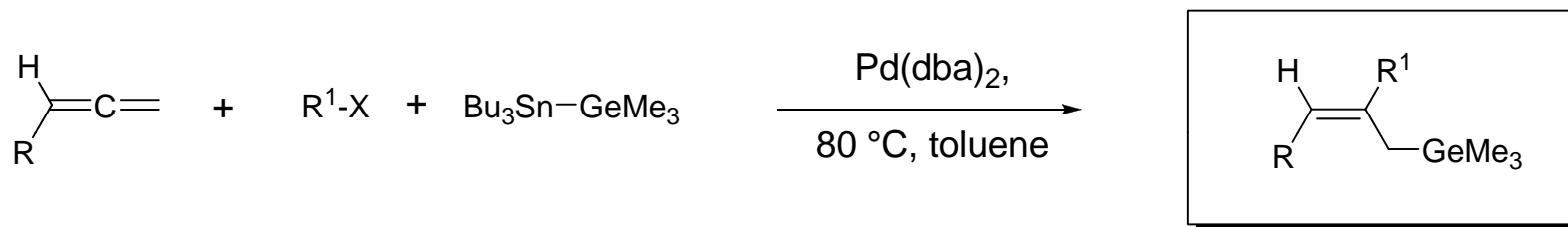


Akiyama, T.; Suzuki, M. *Chem. Commun.* **1997**, 2357-2358

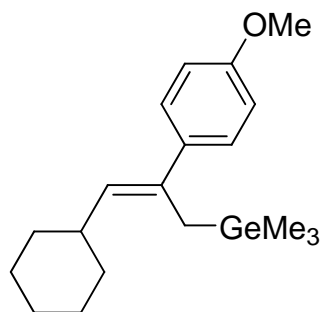


Akiyama, T.; Iwai, J.; Onuma, Y.; Kagoshima, H. *Chem. Commun.* **1999**, 2191-2192

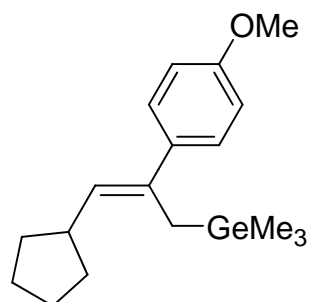
# Cheng – Synthesis of Allylgermanes



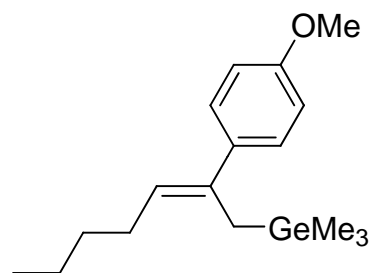
allylic germane



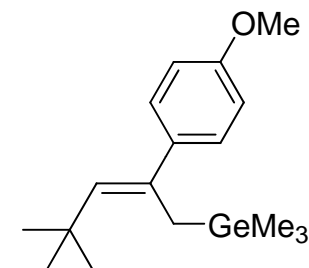
88%,  
99:1 Z:E



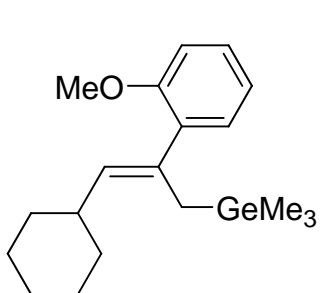
88%,  
98:2 Z:E



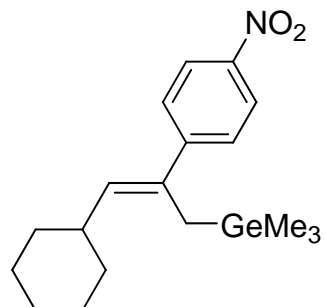
84%,  
94:6 Z:E



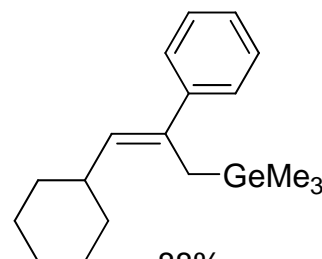
82%,  
99:1 Z:E



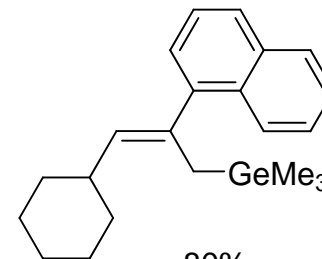
82%,  
99:1 Z:E



89%,  
99:1 Z:E

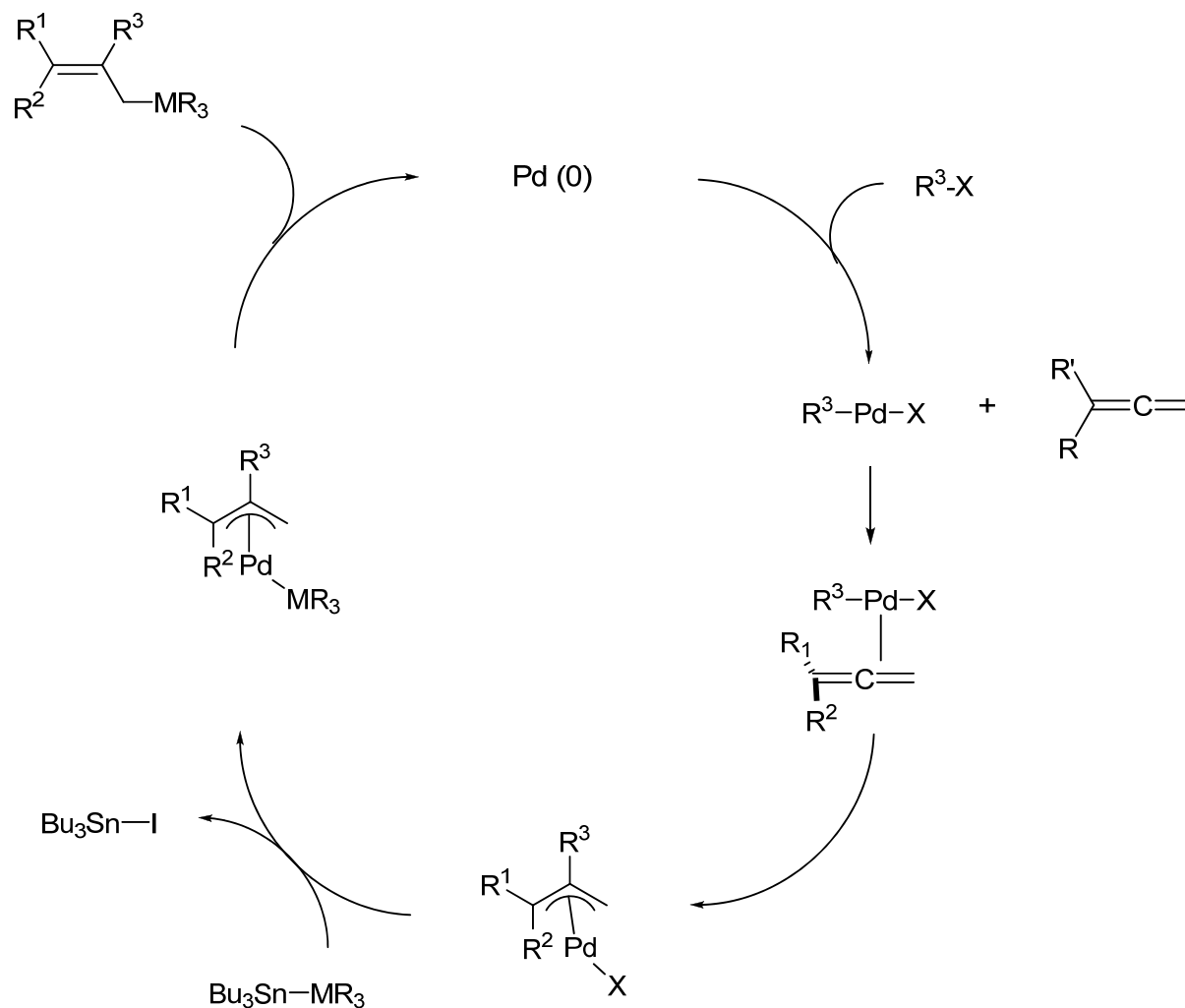
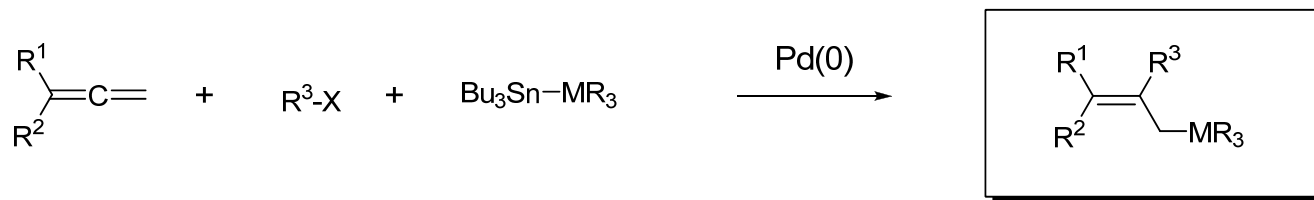


88%,  
98:2 Z:E



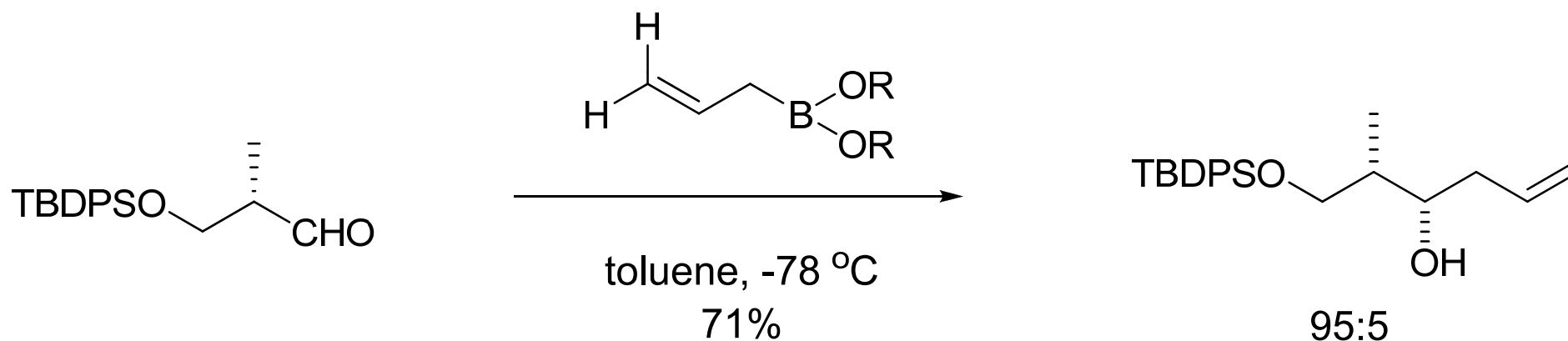
80%,  
98:2 Z:E

# Mechanism of Allylmetalation

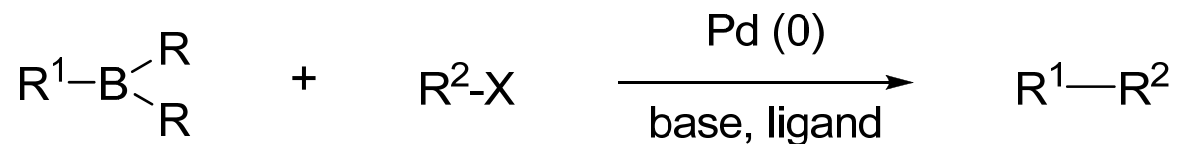


# Allyl Boronates

- Selective Addition to Carbonyls
- Suzuki couplings

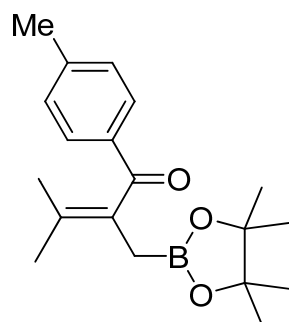
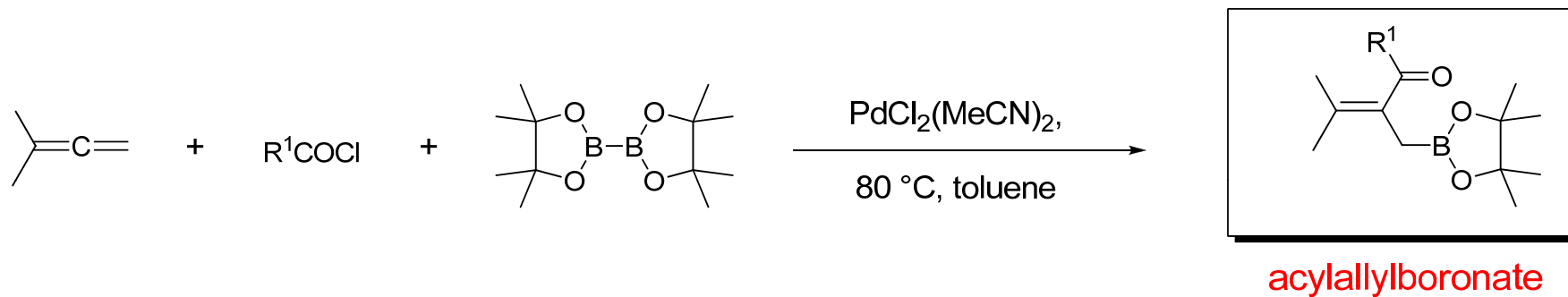


Roush, W.R.; Grover, P.T. *J. Org. Chem.* **1995**, *60*, 3806-3813

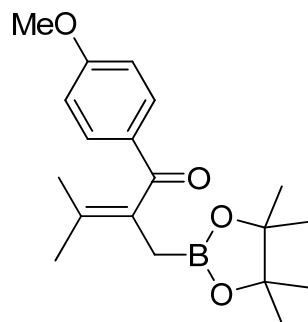


Miyaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Commun.* **1979**, 866-867

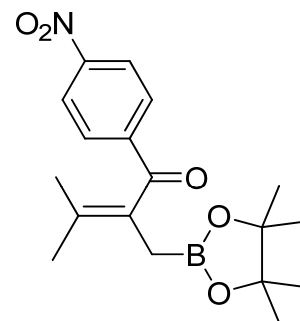
# Cheng - Synthesis of Acylallylboronates



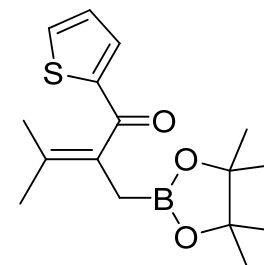
72%



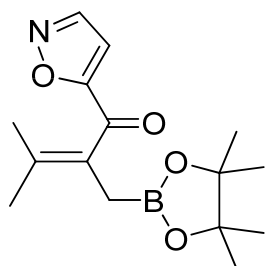
61%



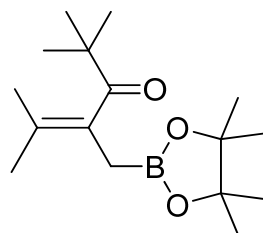
77%



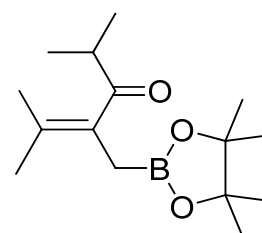
71%



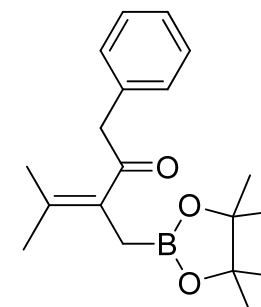
62%



80%

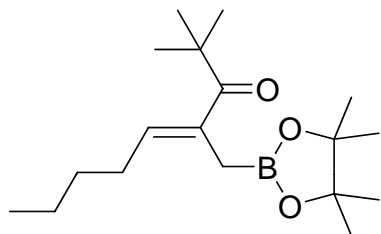
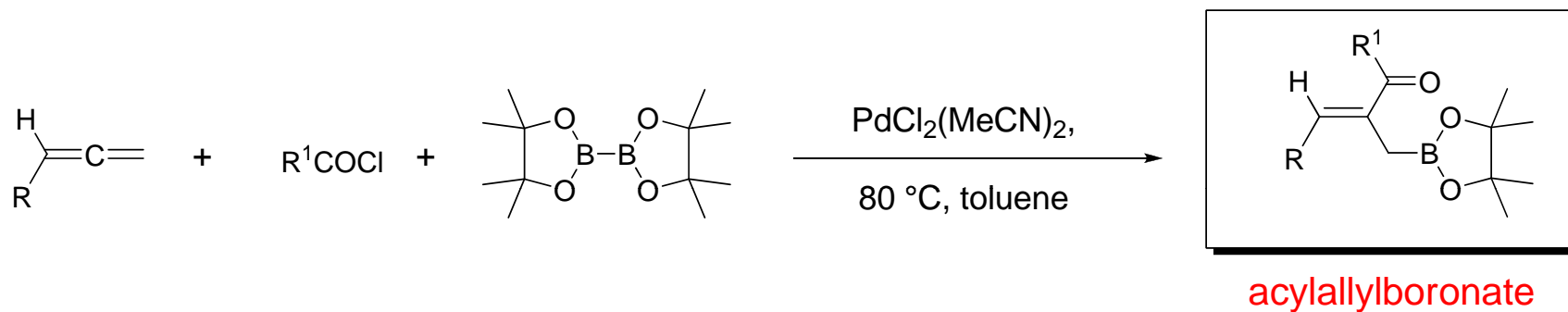


63%

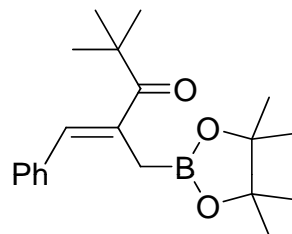


57%

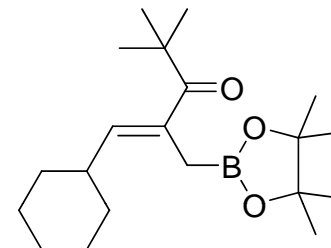
# Monosubstituted Allenes



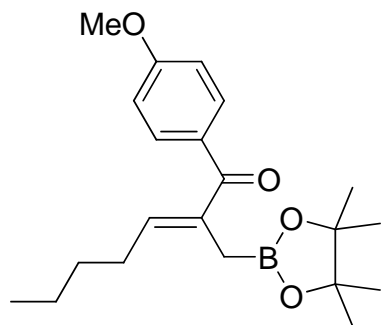
91%, 99:1 E:Z



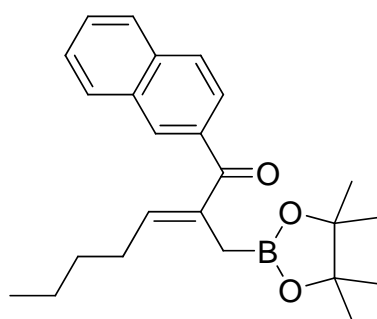
77%, 93:7 E:Z



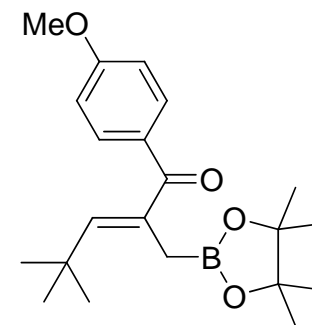
88%, 93:7 E:Z



70%, 98:2 E:Z

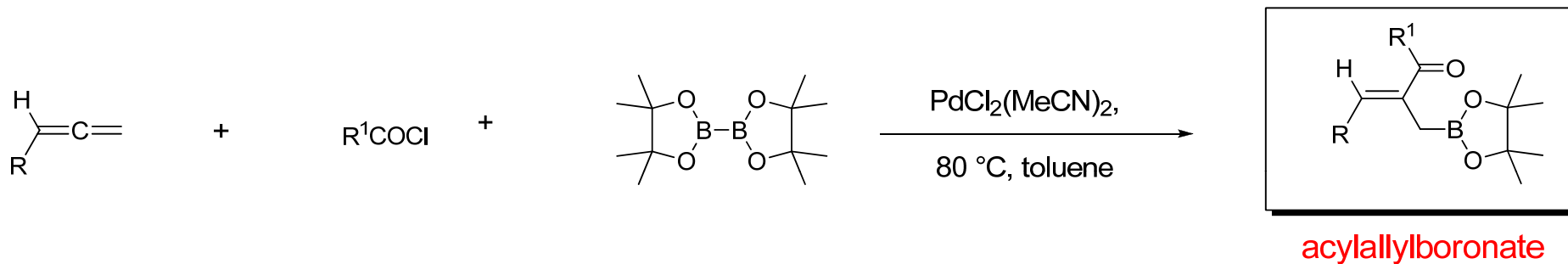


71%, 99:1 E:Z

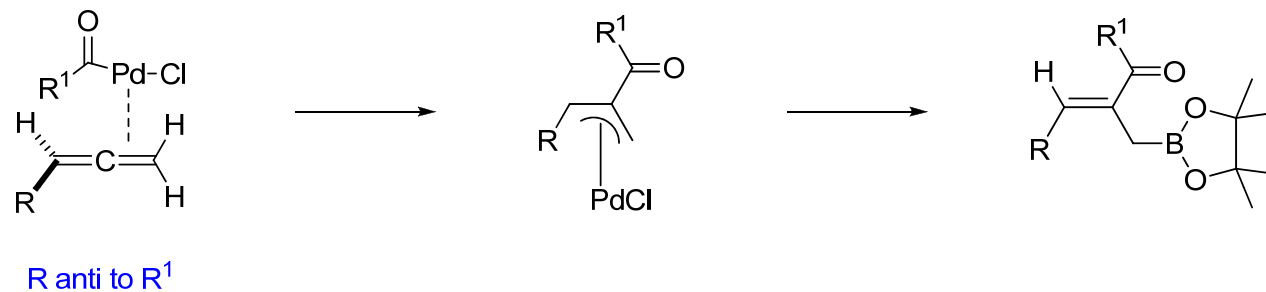


50%, 98:2 E:Z

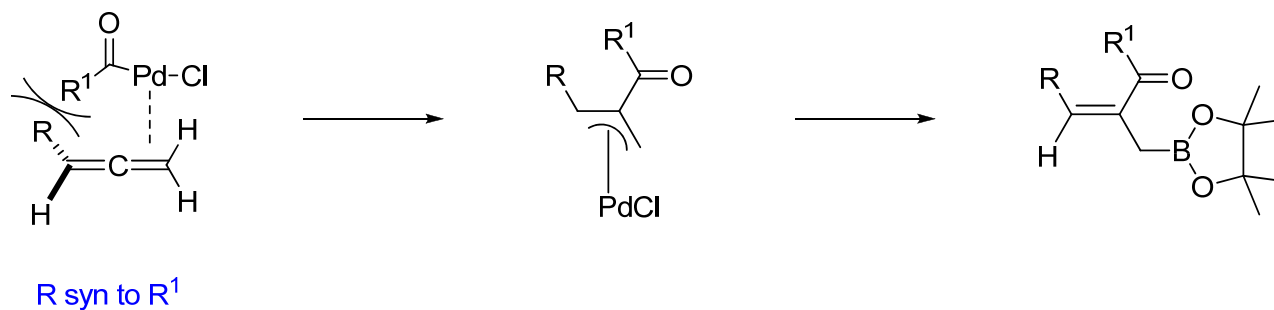
# Explanation of *E* selectivity



*E* Isomer



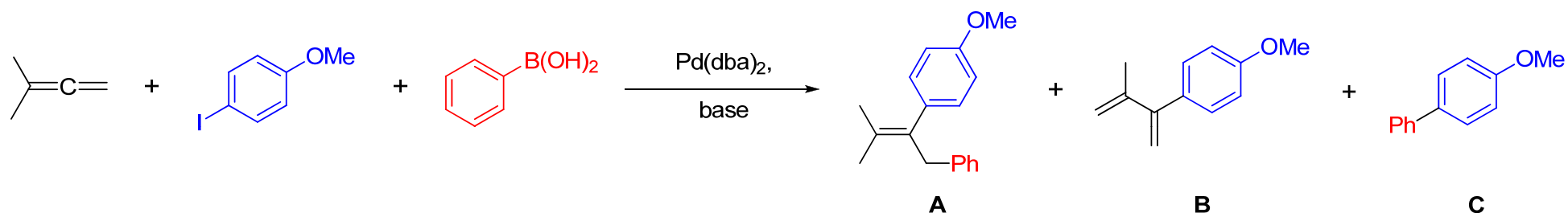
*Z* Isomer



# Presentation Scope

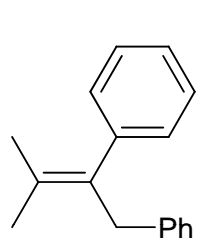
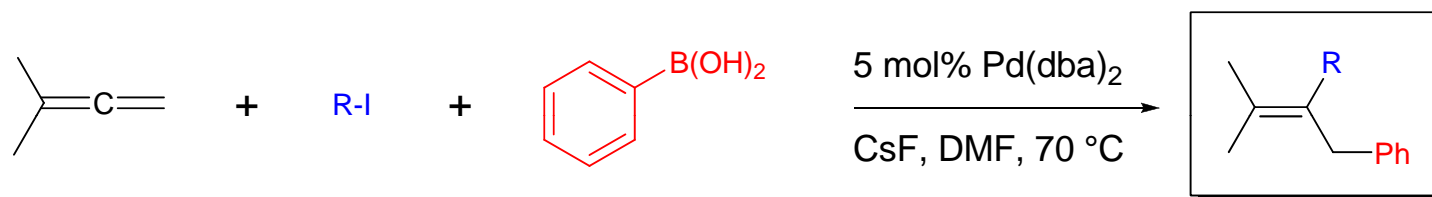
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  - Homoallylic Amines
  - Allylic Alcohols
- Conclusions

# Suzuki Type Multicomponent Coupling

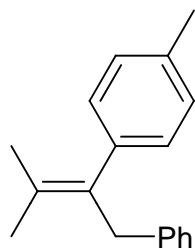


Base, solvent	Temp (°C) / time (h)	Yield (%) A:B:C
None / DMF	70 / 48	No Rxn
NaOH / DMF	70 / 7	0 : 12 : 63
$\text{K}_2\text{CO}_3$ / DMF	70 / 12	51 : 14 : 10
CsF / $\text{CH}_3\text{CN}$	70 / 24	12 : 0 : 23
CsF / THF	Reflux / 24	20 : 0 : 32
<b>CsF / DMF</b>	<b>70 / 7</b>	<b>88 : 0 : 0</b>

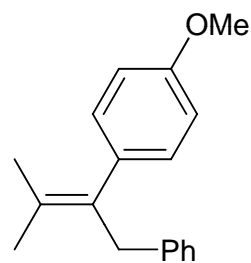
# Disubstituted Allenes and Various Organic Halides



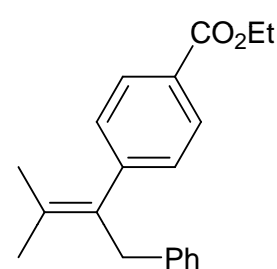
89%



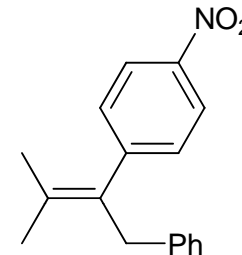
88%



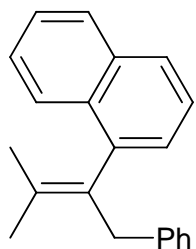
81%



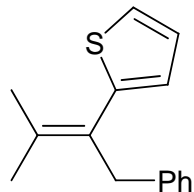
70%



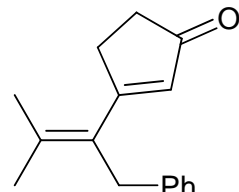
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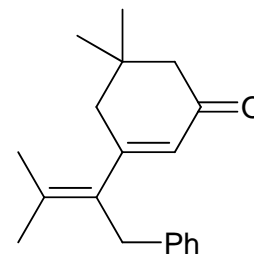
51%



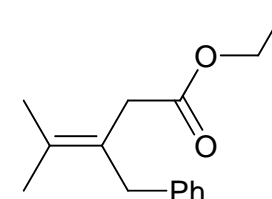
91%



68%

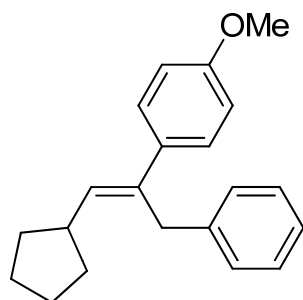
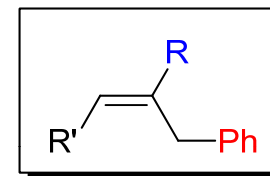
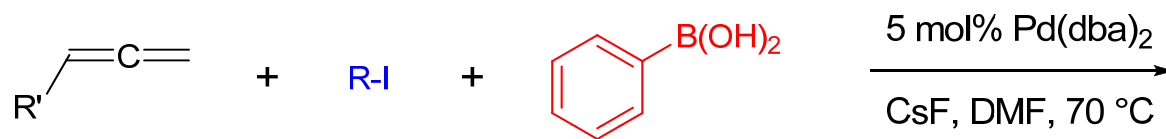


62%

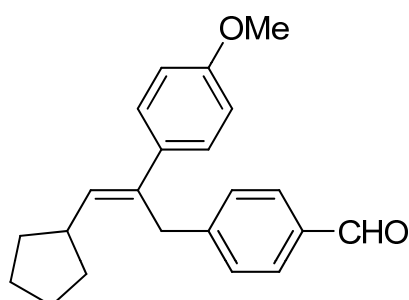


42%

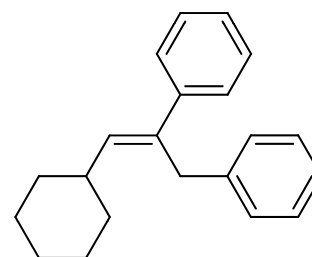
# Monosubstituted Allenes



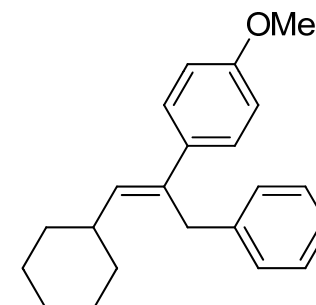
78%, 78:22 E:Z



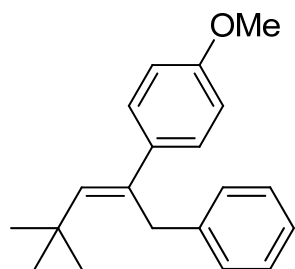
75%, 73:27 E:Z



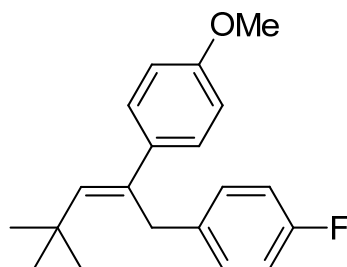
85%, 75:25 E:Z



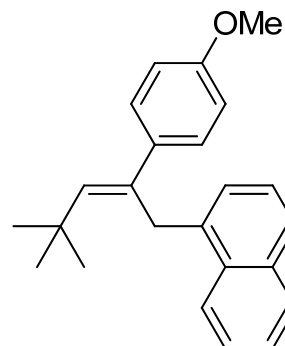
80%, 88:12 E:Z



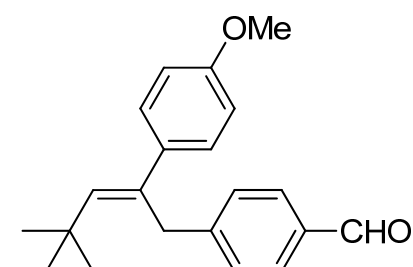
82%, 96:4 E:Z



78%, 97:3 E:Z

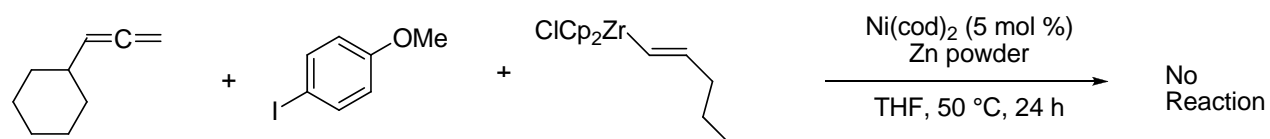
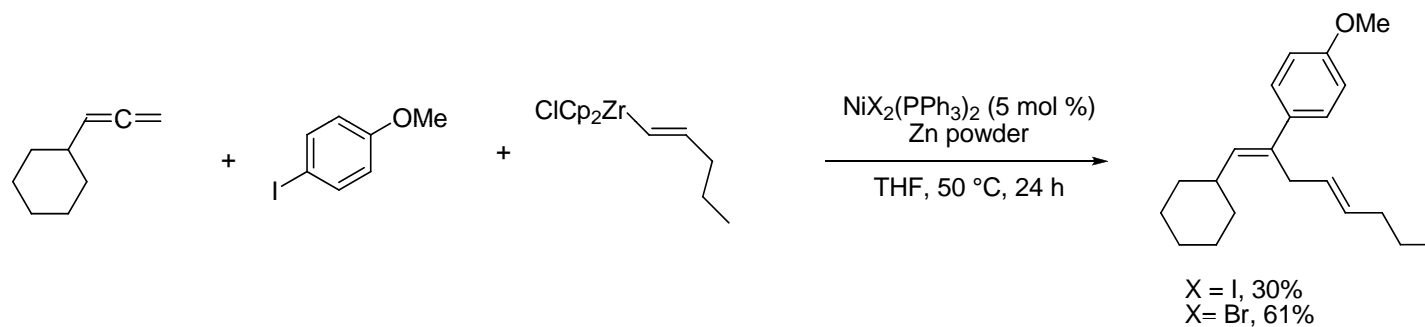
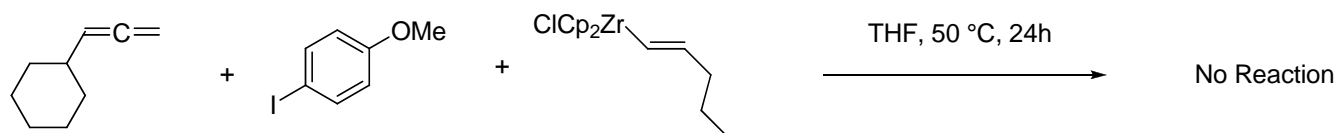
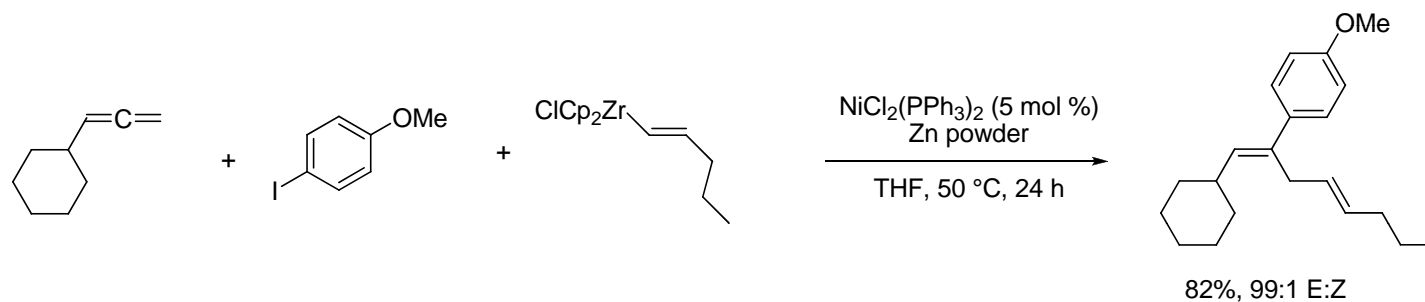


69%, 92:8 E:Z

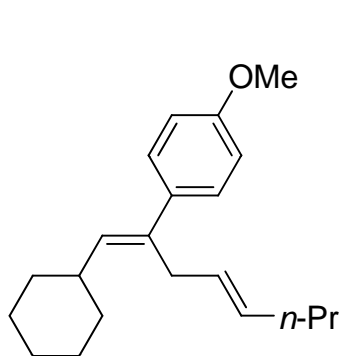
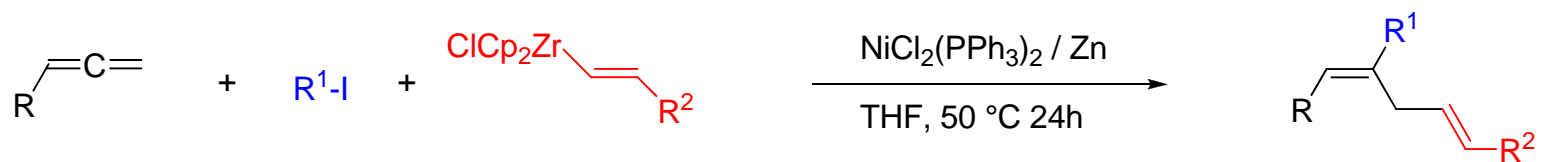


81%, 91:9 E:Z

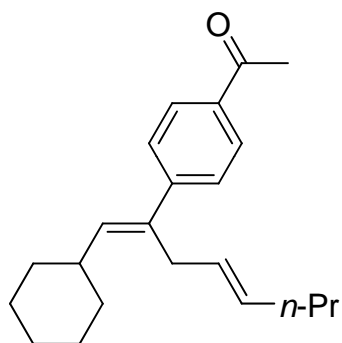
# Cheng - Nickel Catalyzed Coupling



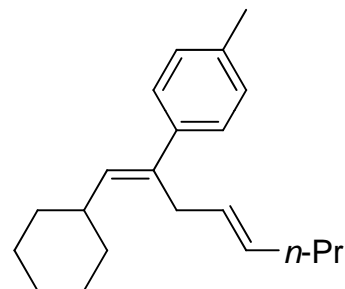
# Substrate Scope



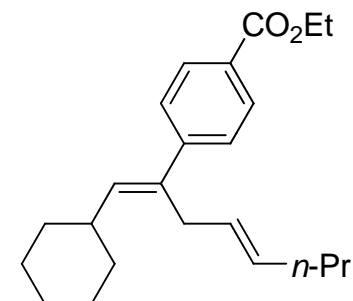
82%, 99:1 E:Z



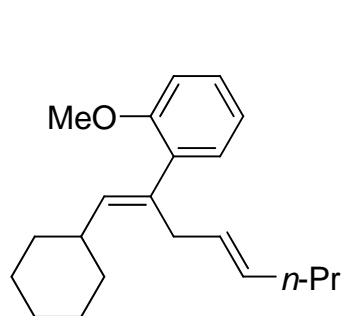
81%, 98:2 E:Z



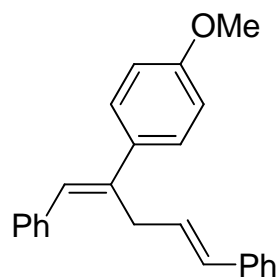
85%, 98:2 E:Z



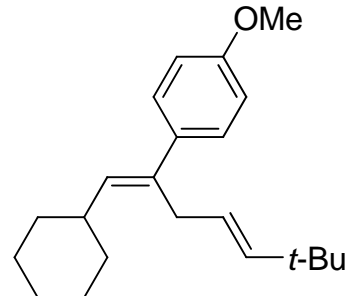
81%, 99:1 E:Z



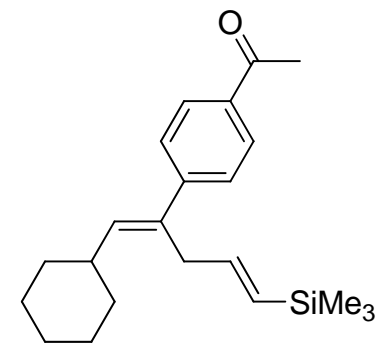
37%, 99:1 E:Z



65%, 98:2 E:Z

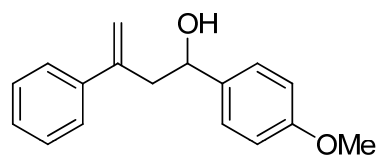
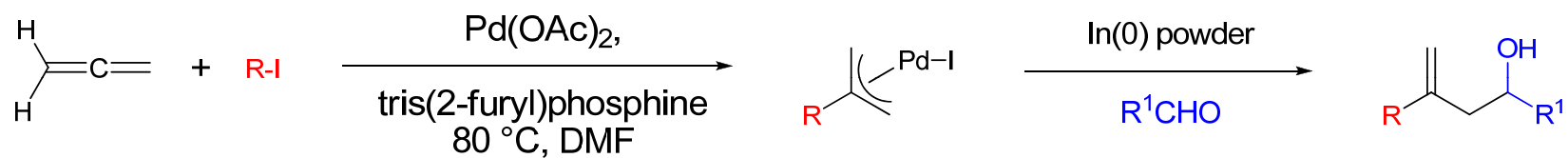


73%, 99:1 E:Z

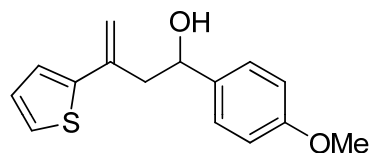


61%, 99:1 E:Z

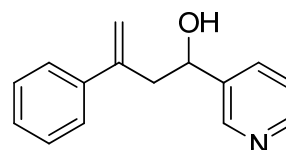
# Grigg – Allylation of Aldehydes



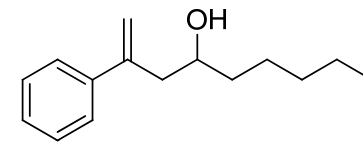
64%



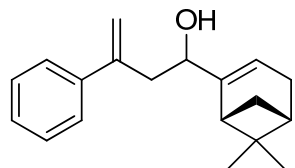
66%



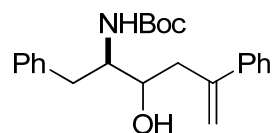
65%



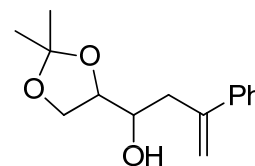
65%



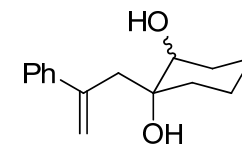
47%  
1:1 *syn:anti*



75%  
1:1 *syn:anti*

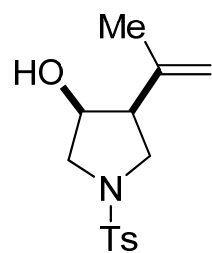
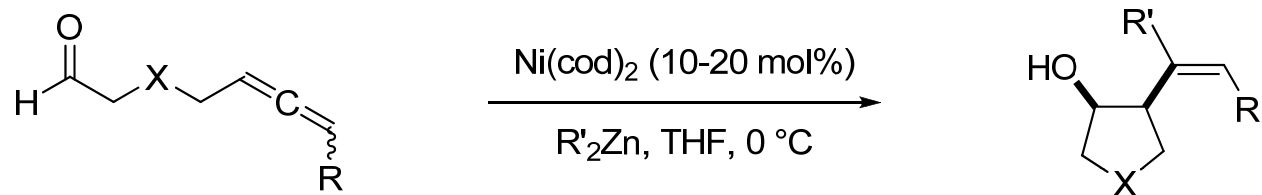


55%  
5:1 *syn:anti*

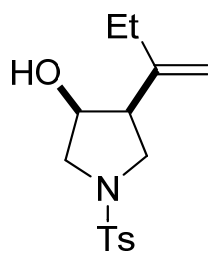


67%  
96:4 *syn:anti*

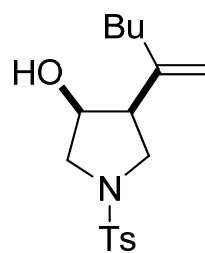
# Montgomery – Intramolecular Coupling



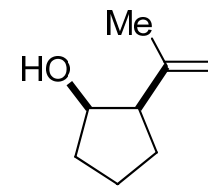
70%  
dr > 97:3



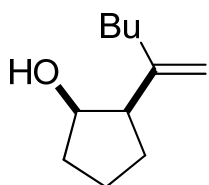
64%  
dr > 97:3



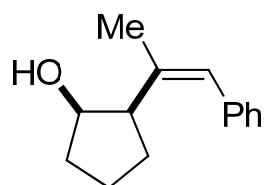
52%  
dr 75:25



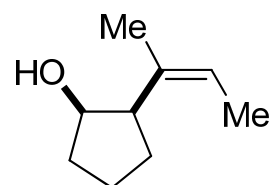
69%  
dr > 97:3



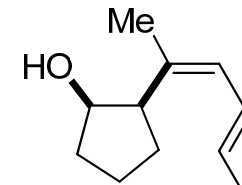
69%  
dr > 91:9



71%  
dr > 97:3  
Z:E > 97:3

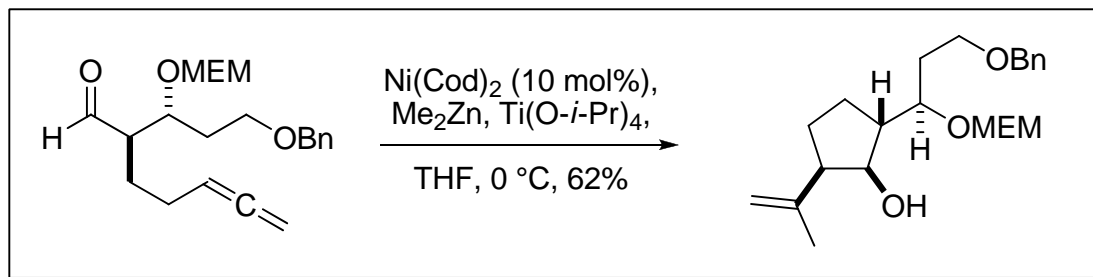
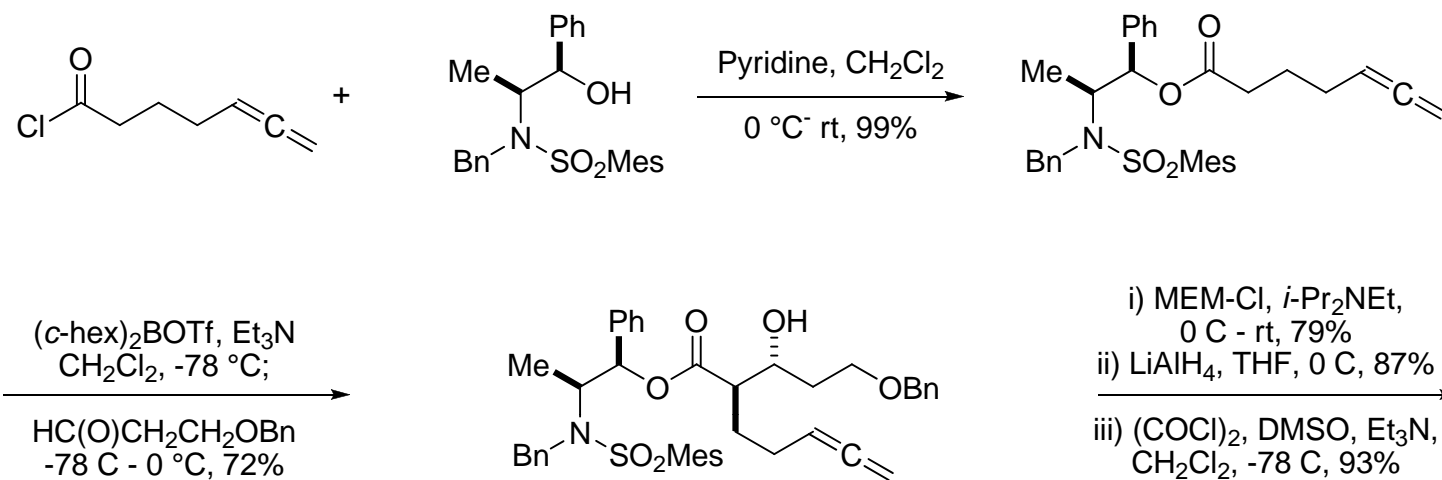
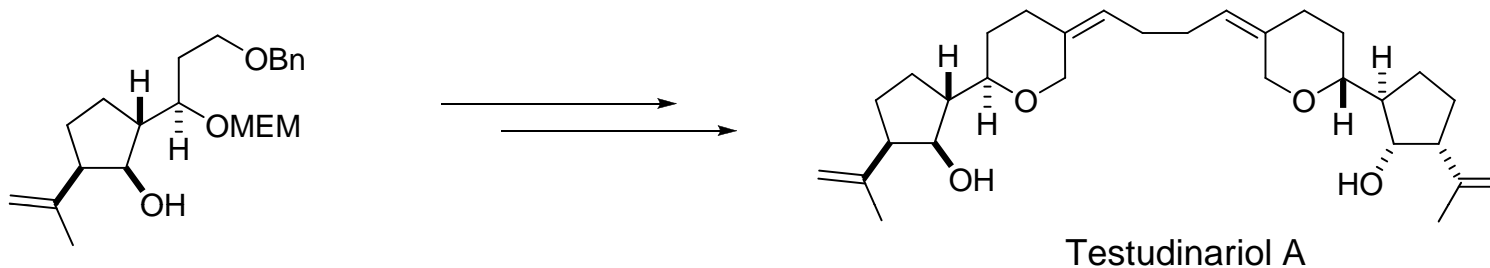


77%  
dr > 97:3  
Z:E = 80:20

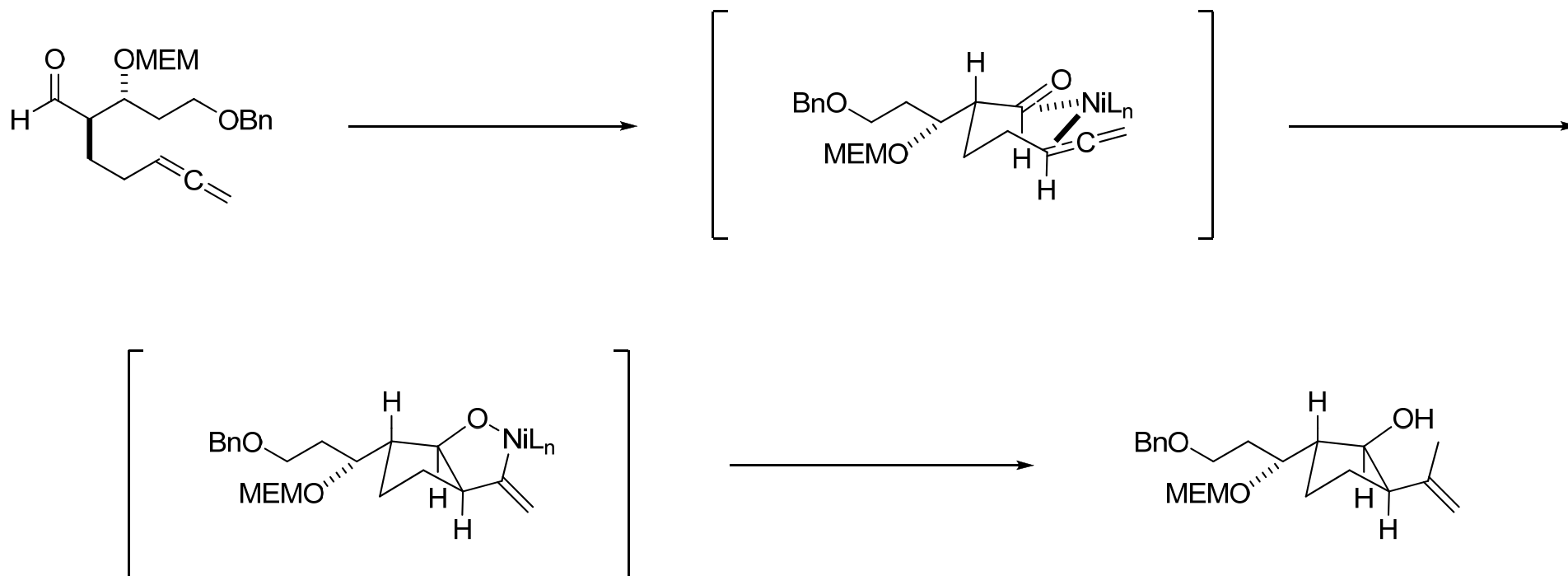


68%  
dr > 97:3  
Z:E = 84:16

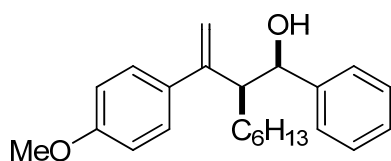
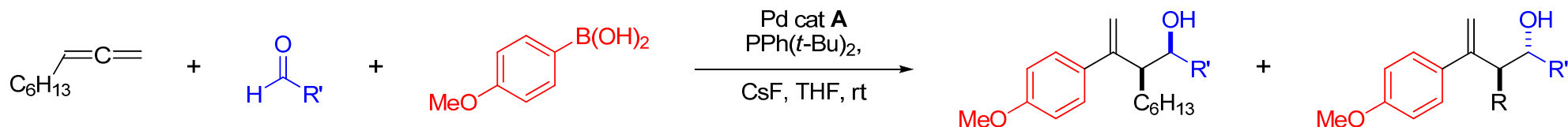
# Total Synthesis of (+)-Testudinariol A



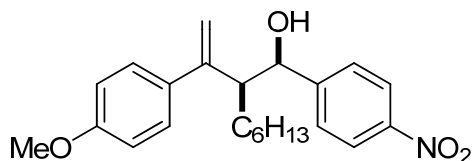
# Intramolecular Coupling Mechanism



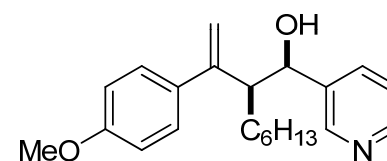
# Malinakova – Intermolecular Coupling



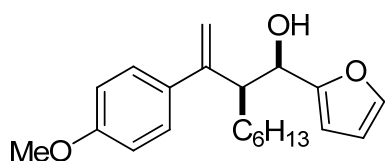
76%,  
5.3:1 *syn* : *anti*



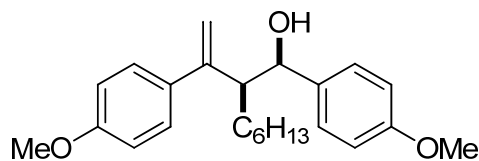
85%,  
1.9:1 *syn* : *anti*



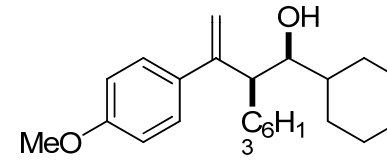
71%,  
8.1:1 *syn* : *anti*



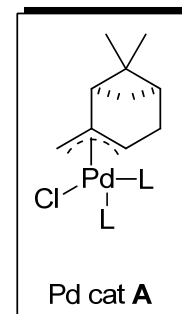
76%,  
4.4:1 *syn* : *anti*



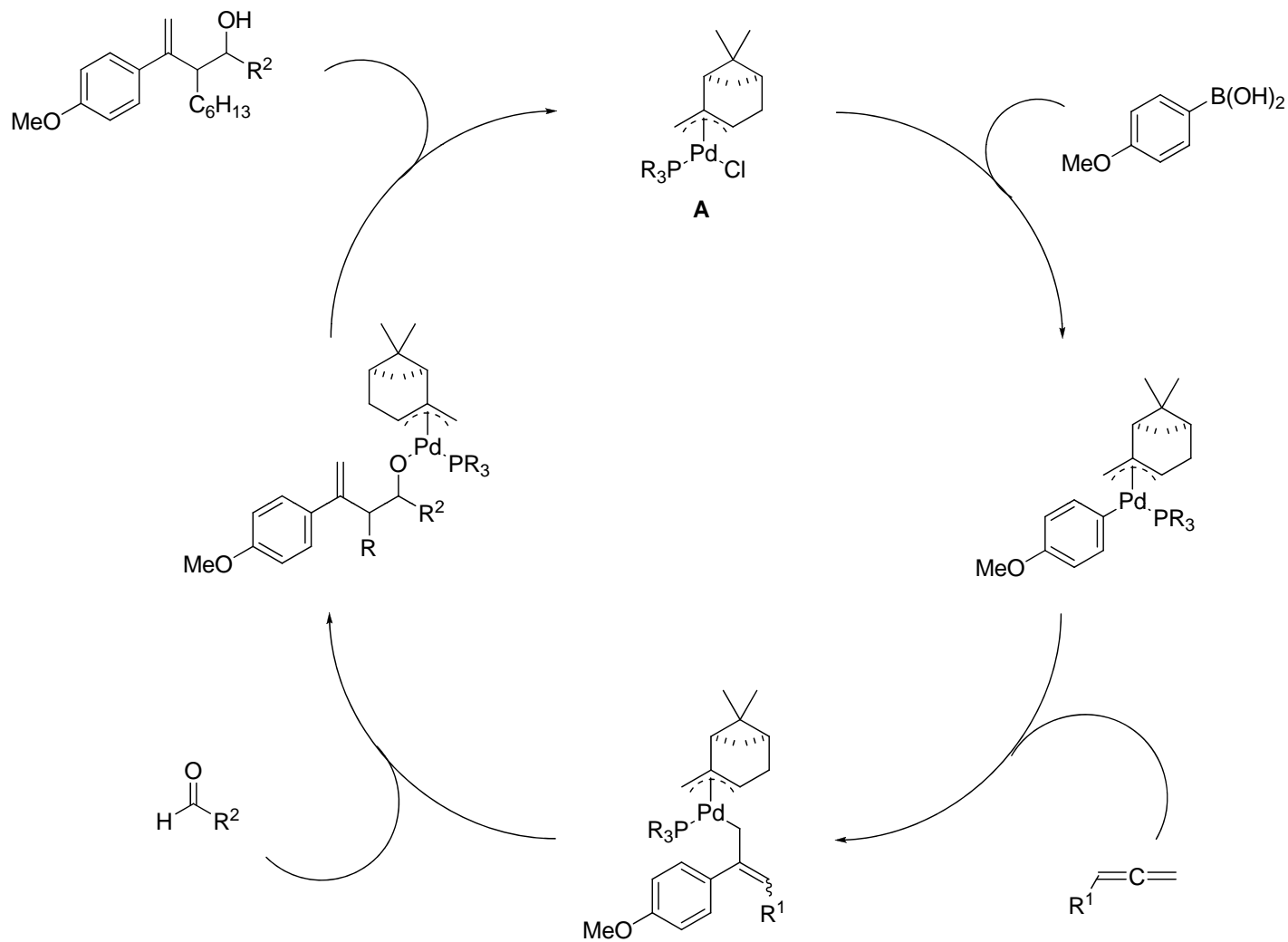
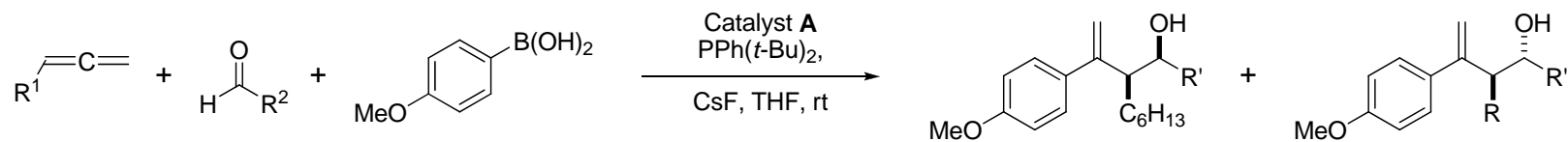
54%,  
32:1 *syn* : *anti*



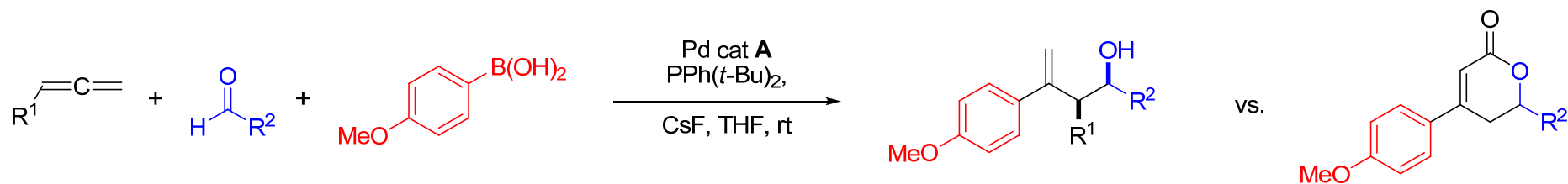
46%,  
3.0:1 *syn* : *anti*



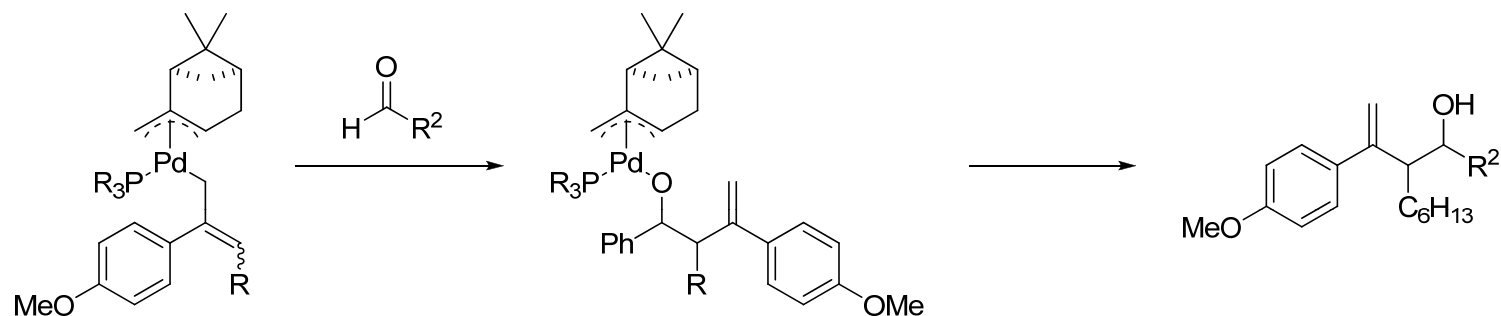
# Mechanism



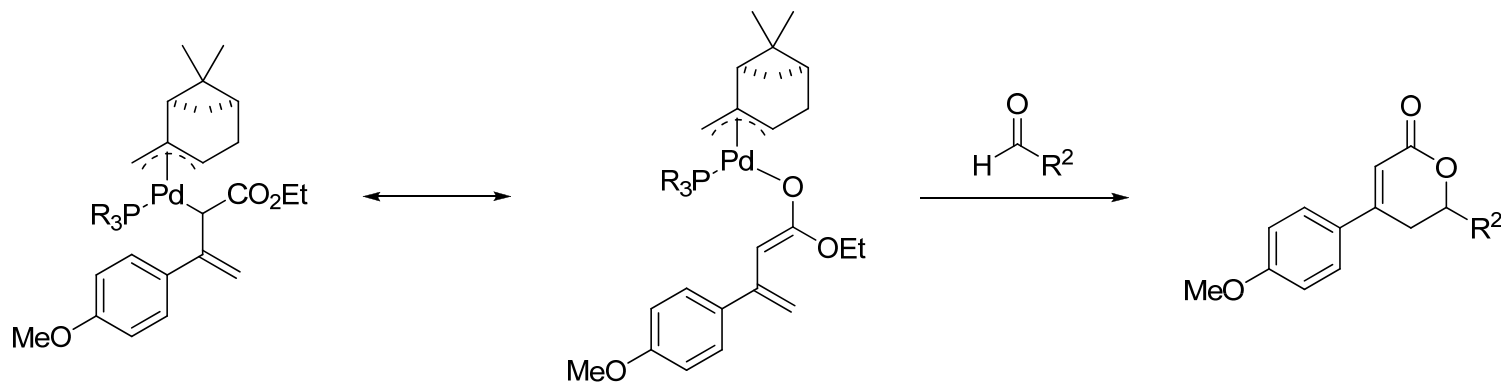
# Explanation of Regiochemistry



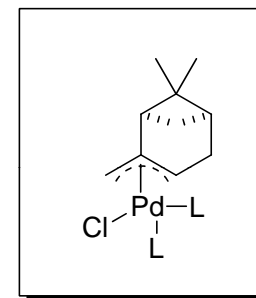
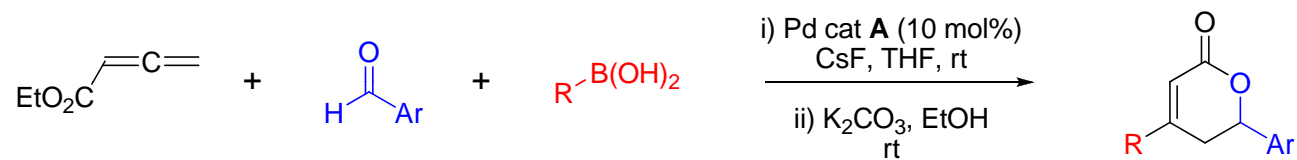
When  $R = C_6H_{13}$ :



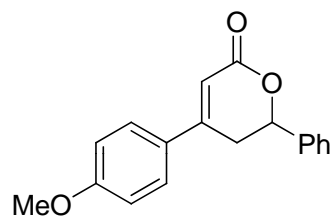
When  $R = CO_2Et$ :



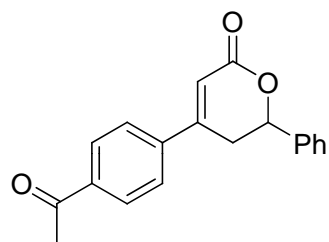
# Reaction Scope



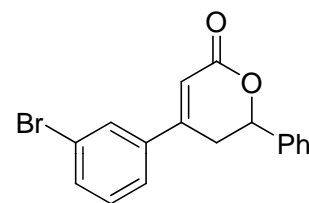
Pd cat **A**



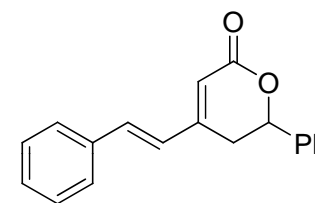
75%



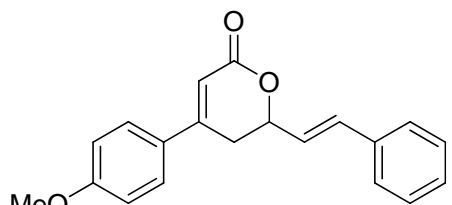
59%



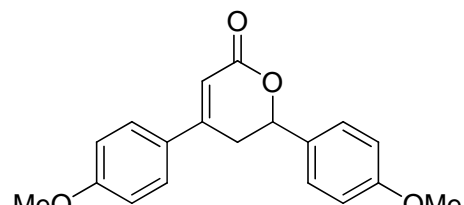
58%



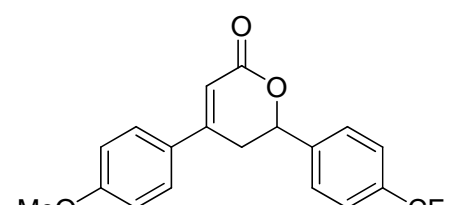
78%



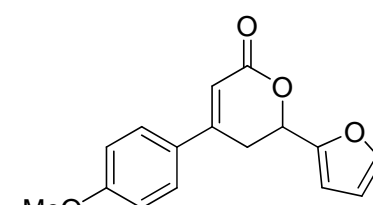
51%



58%

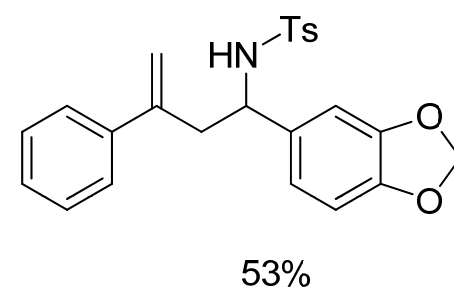
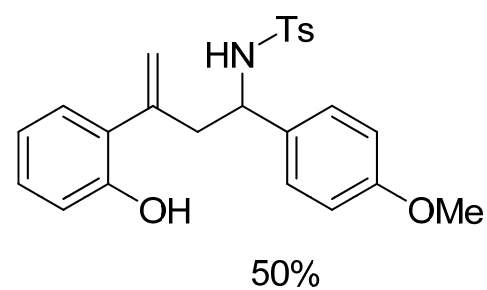
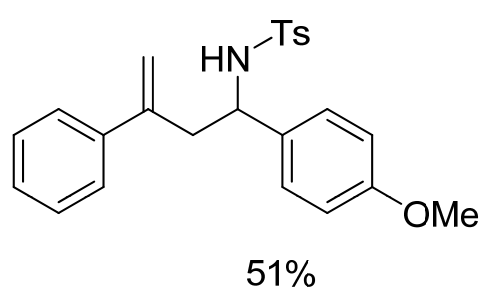
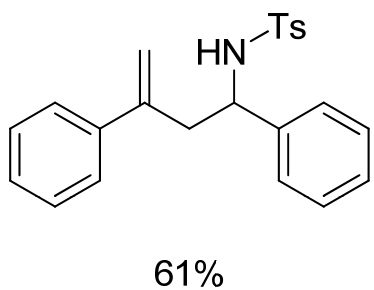
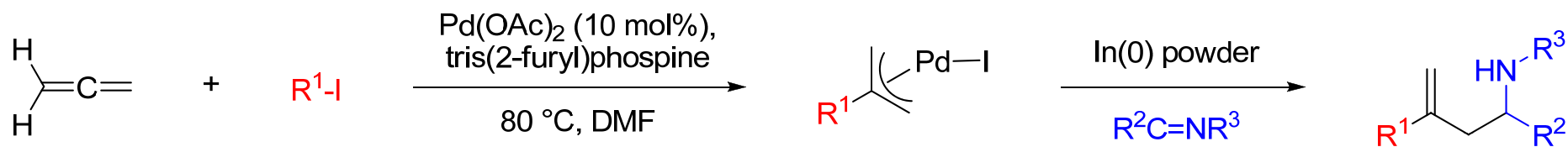


51%

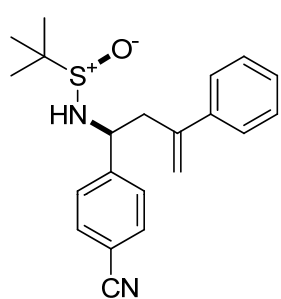
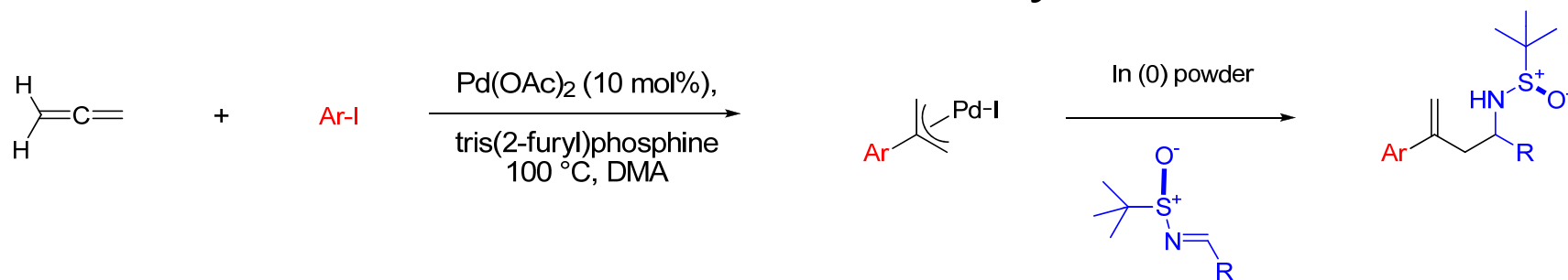


51%

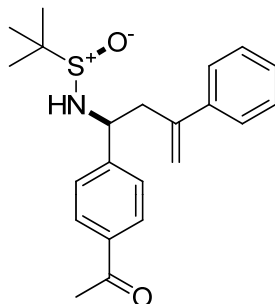
# Grigg – Allylation of Imines



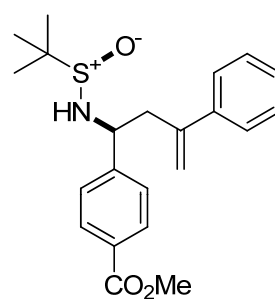
# Diastereoselective Allylation



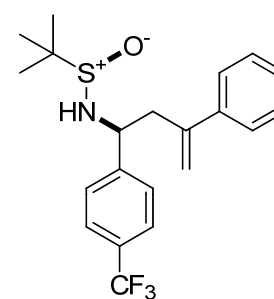
52%



45%

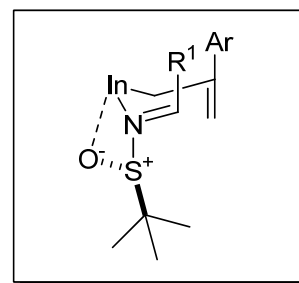


56%

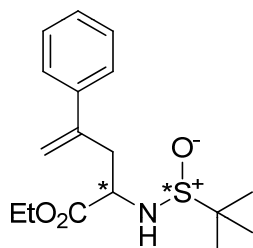
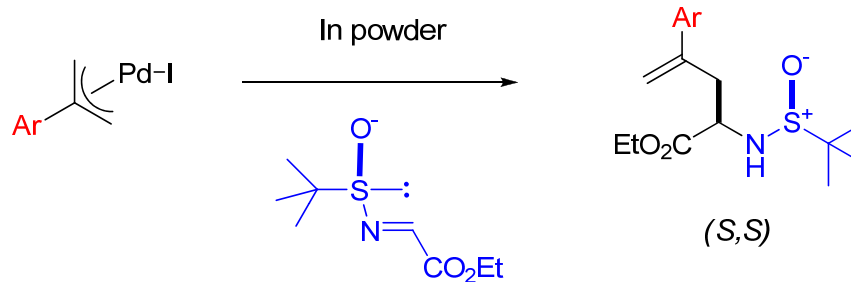
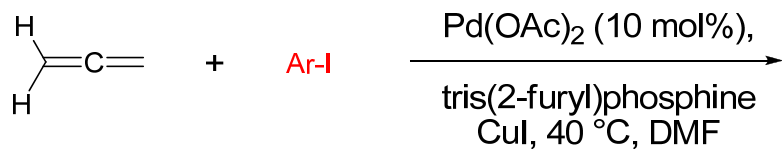


56%

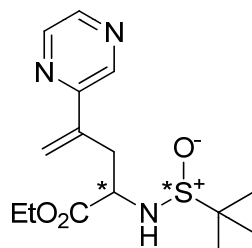
Selectivity based on chelation:



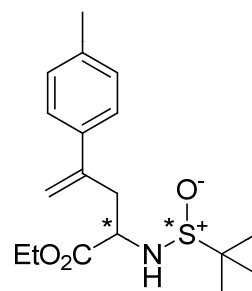
# Synthesis of Unnatural Amino Acids



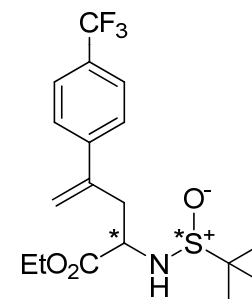
S,S - 92%  
R,R - 80%



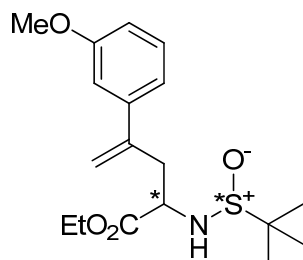
S,S - 69%  
R,R - 55%



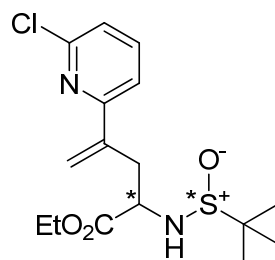
S,S - 68%  
R,R - 68%



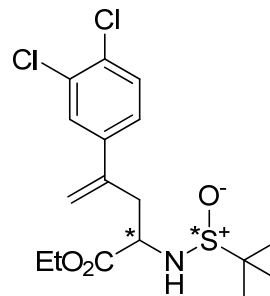
S,S - 54%  
R,R - 49%



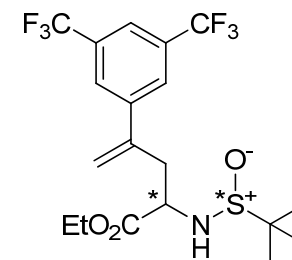
S,S - 72%  
R,R - 67%



S,S - 52%  
R,R - 69%

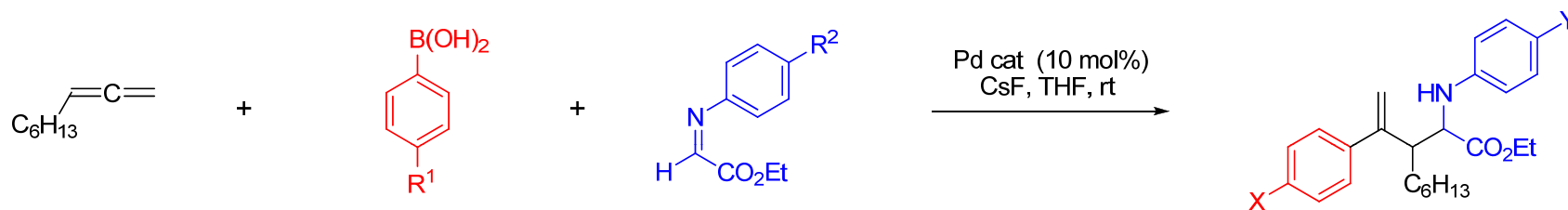


S,S - 73%  
R,R - 74%

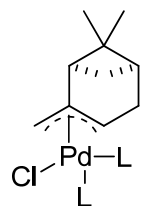


S,S - 69%  
R,R - 76%

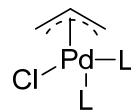
# Malinakova - Synthesis of Homoallylic Amines



Catalyst	Ligand	R <sup>1</sup> =	R <sup>2</sup> =	Yield (%)	dr
<b>A</b>	-	OMe	H	35	8:1
<b>A</b>	P( <i>o</i> -Tol) <sub>3</sub>	OMe	H	61	7:1
<b>B</b>	P( <i>o</i> -Tol) <sub>3</sub>	OMe	H	51	8:1
<b>C</b>	-	OMe	H	41	6:1
<b>A</b>	P( <i>t</i> -Bu) <sub>3</sub>	CO <sub>2</sub> Me	H	70	18:1
<b>A</b>	P( <i>t</i> -Bu) <sub>3</sub>	CO <sub>2</sub> Me	OMe	62	13:1
<b>C</b>	P( <i>t</i> -Bu) <sub>3</sub>	CO <sub>2</sub> Me	OMe	74	12:1



Pd cat **A**

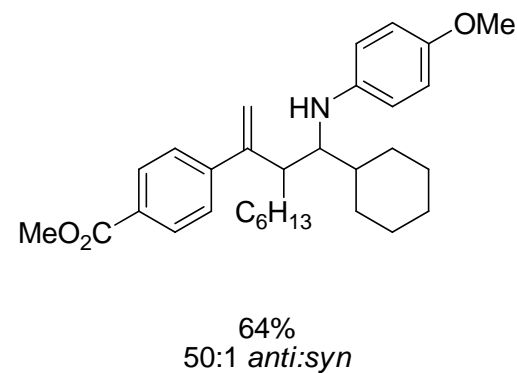
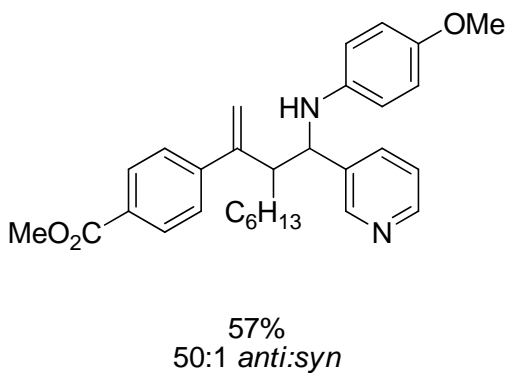
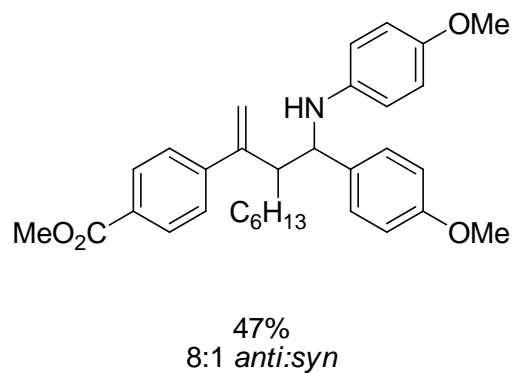
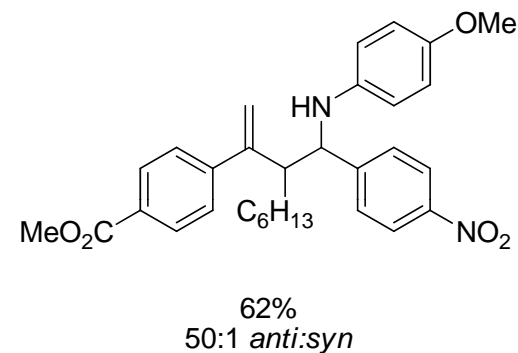
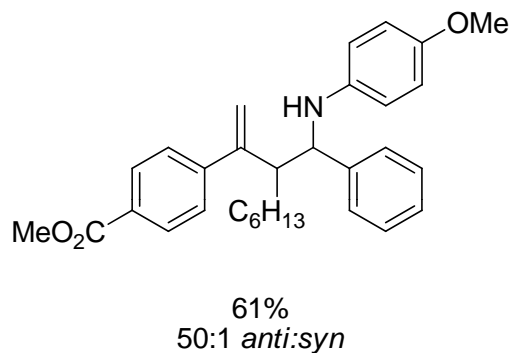
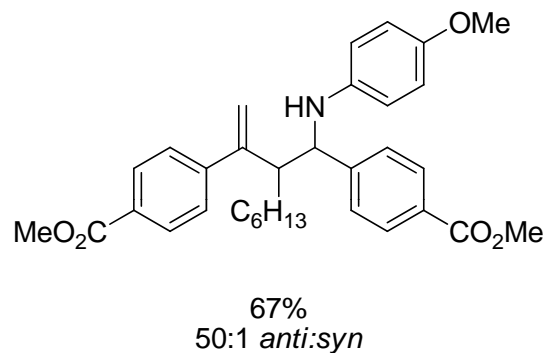
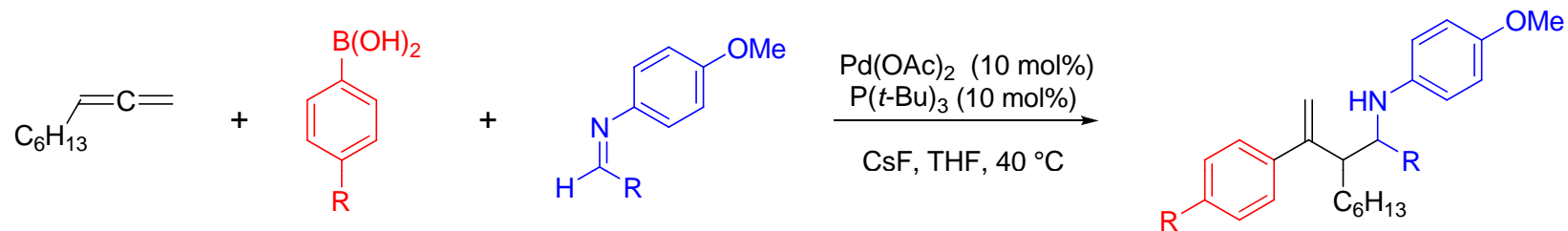


Pd cat **B**

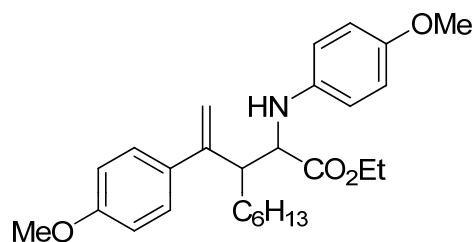
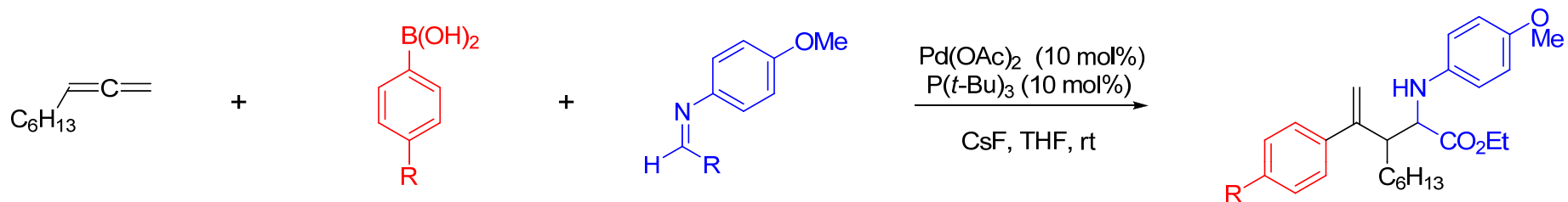


Pd cat **C**

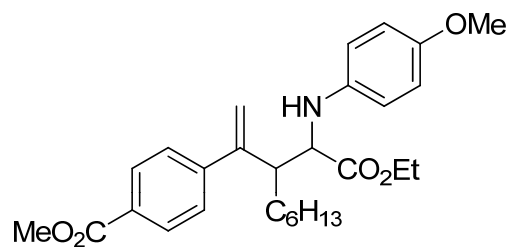
# Unactivated Imines



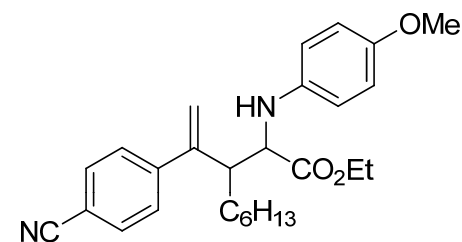
# Synthesis of Amino Esters



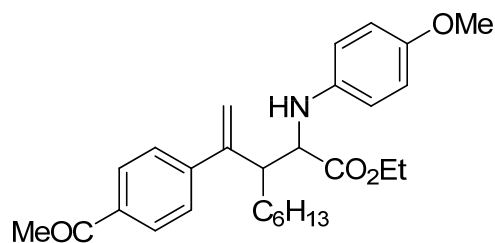
54%  
10:1 *anti:syn*



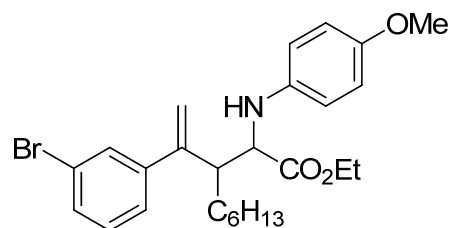
74%  
21:1 *anti:syn*



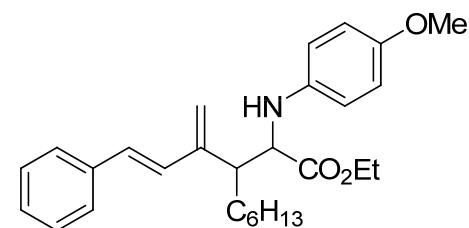
63%  
14:1 *anti:syn*



72%  
8:1 *anti:syn*

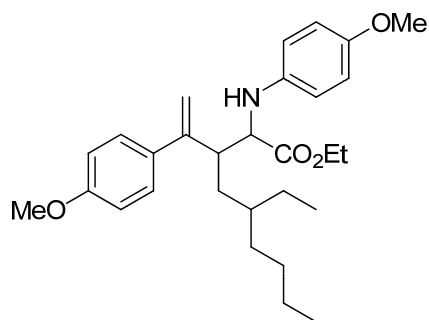
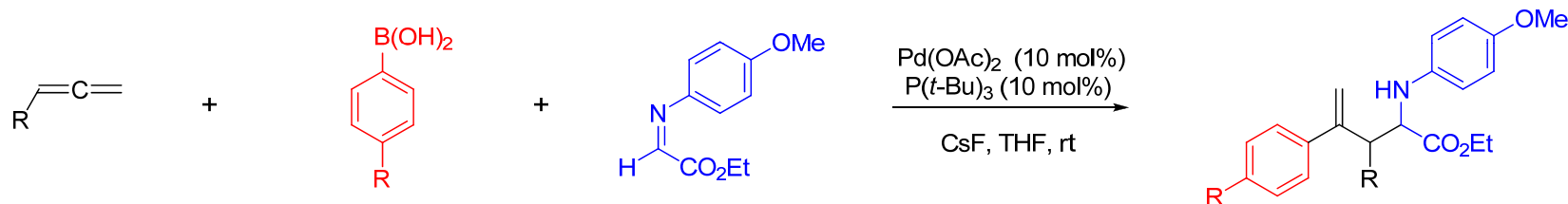


82%  
5:1 *anti:syn*

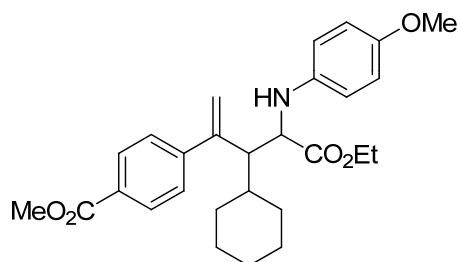


65%  
4:1 *anti:syn*

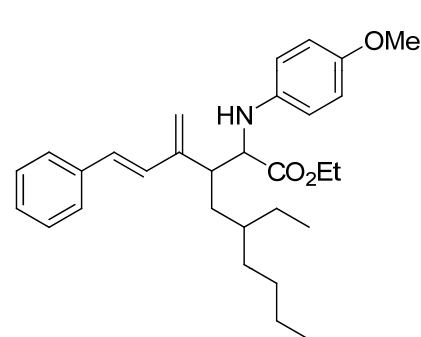
# Other Allenes



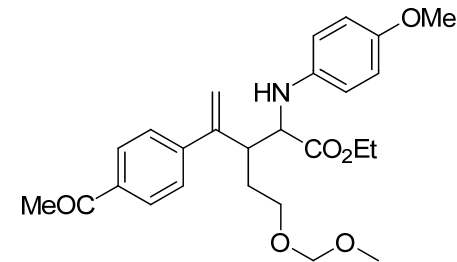
81%  
25:1 *anti:syn*



69%  
25:1 *anti:syn*



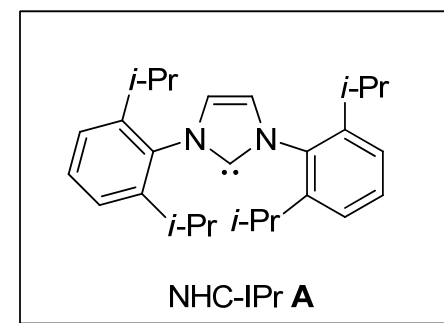
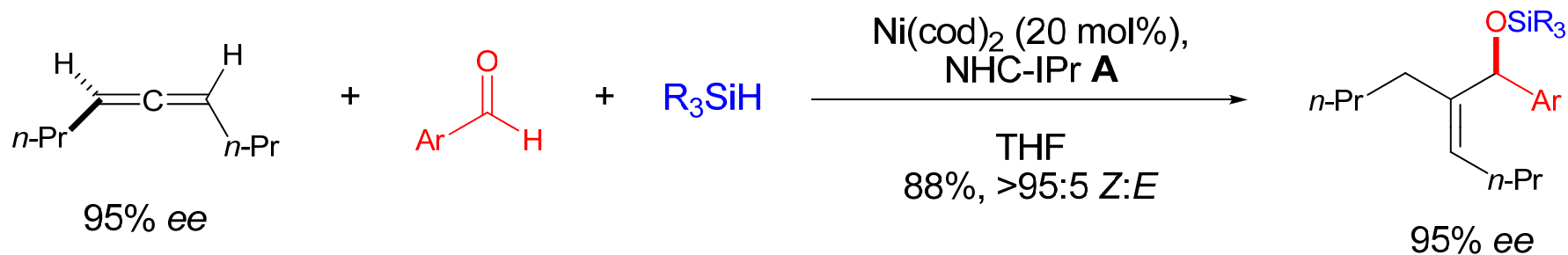
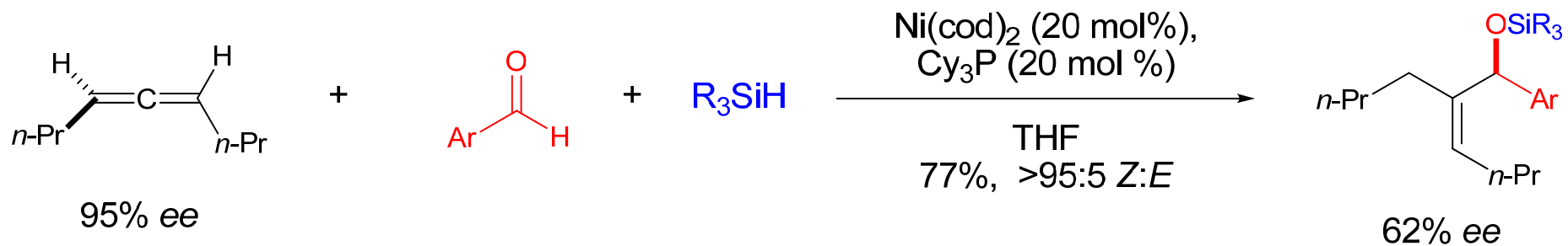
76%  
7:1 *anti:syn*



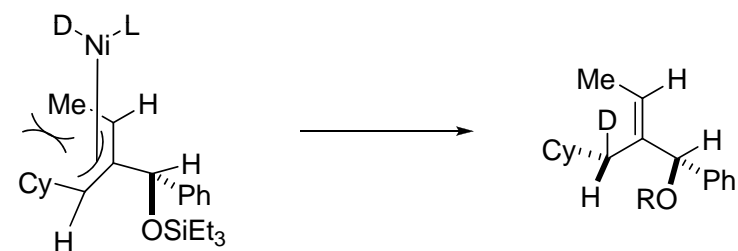
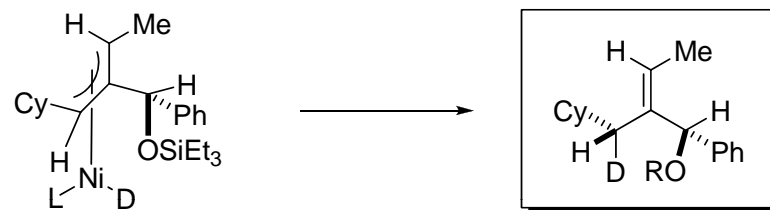
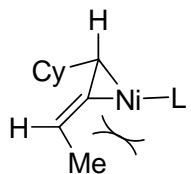
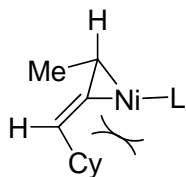
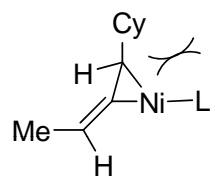
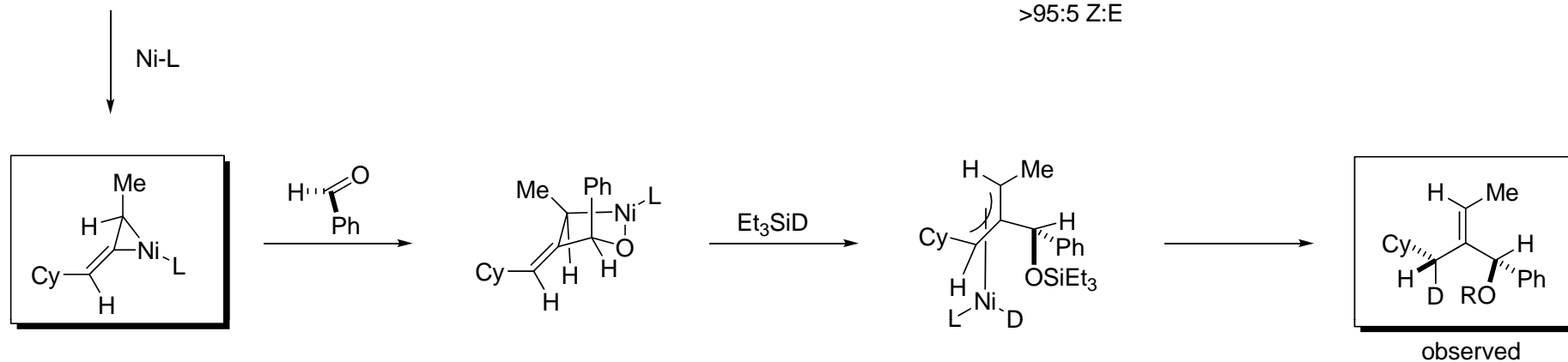
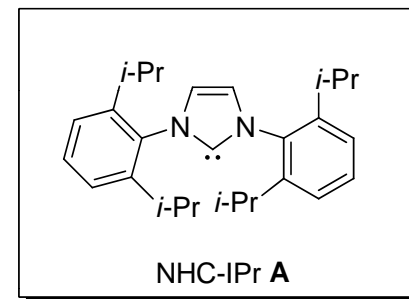
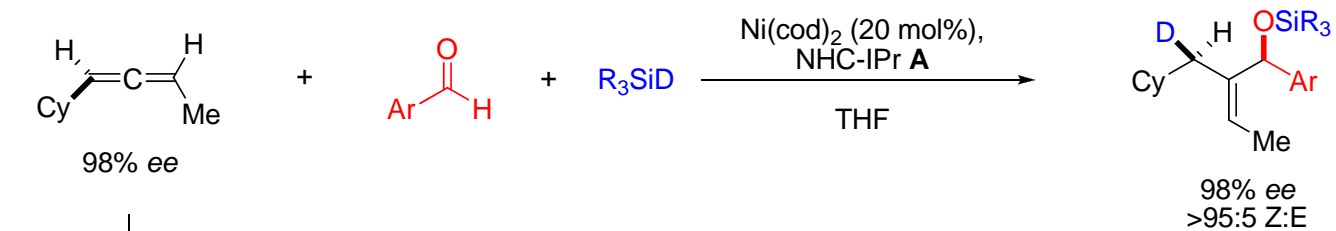
51%  
7:1 *anti:syn*

Hopkins, C.D.; Malinakova, H. C. *Synthesis*. **2007**, 22, 3558-2566.

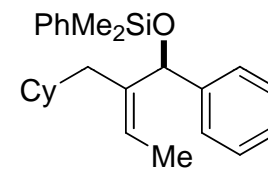
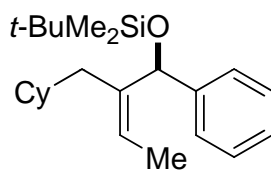
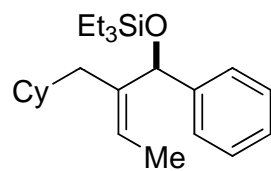
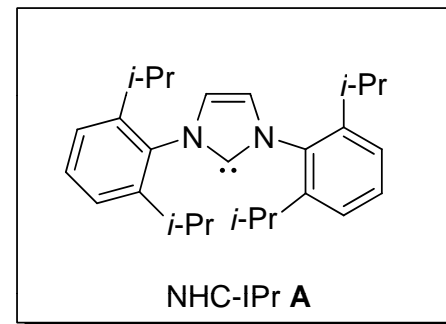
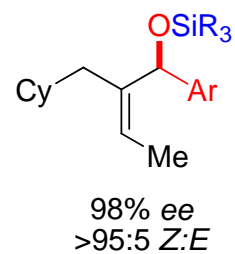
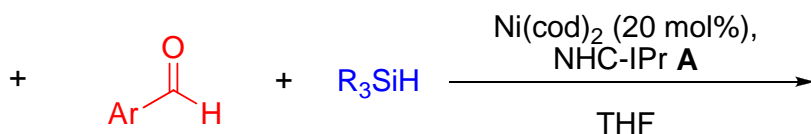
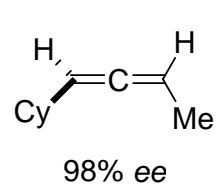
# Jamison – Enantioselective Coupling



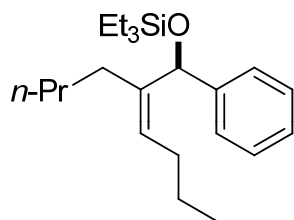
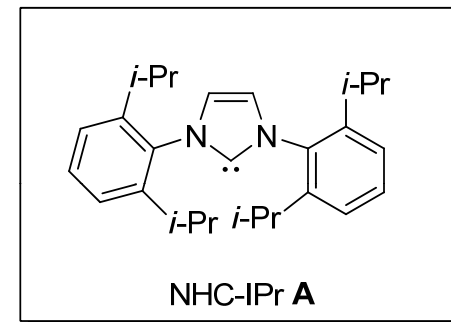
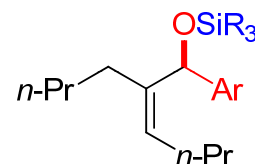
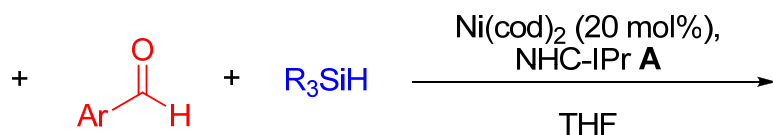
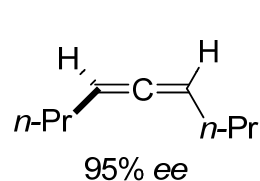
# Mechanism



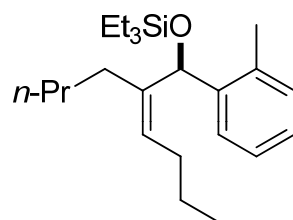
# Site Selectivity



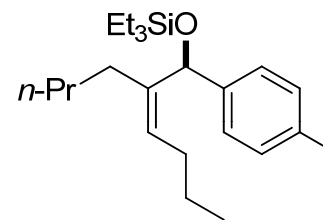
# Jamison – Aldehyde Scope



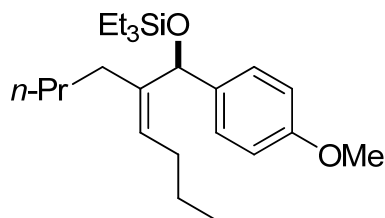
94:6 allylic:homoallylic  
80%, >95:5 Z:E, 95% ee



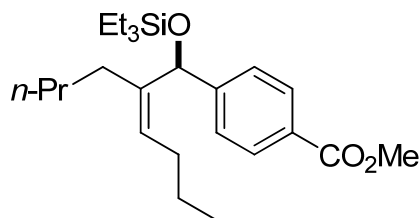
90:10 allylic:homoallylic  
70%, >95:5 Z:E, 95% ee



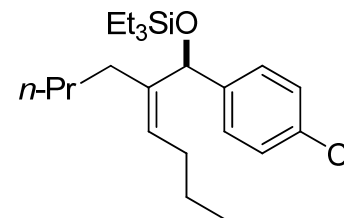
95:5 allylic:homoallylic  
74%, >95:5 Z:E, 95% ee



93:7 allylic:homoallylic  
75%, >95:5 Z:E, 95% ee



90:10 allylic:homoallylic  
56%, >95:5 Z:E, 95% ee



90:10 allylic:homoallylic  
66%, >95:5 Z:E, 95% ee

# Conclusions

- Allenes are versatile substrates for multiple component coupling reactions
- Useful for the synthesis of a variety important compounds
- Can participate in reactions catalyzed by rhodium, nickel, and palladium
- Improvements to be made:
  - Expanded substrate scope
  - Improved diastereoselectivities
  - Utilization of axial chirality



# Acknowledgements

Prof. Michael T. Crimmins



## Crimmins Group Members

Dr. Anita Mattson  
Dr. Christie Stauffer  
Adam Azman  
Anne-Marie Dechert

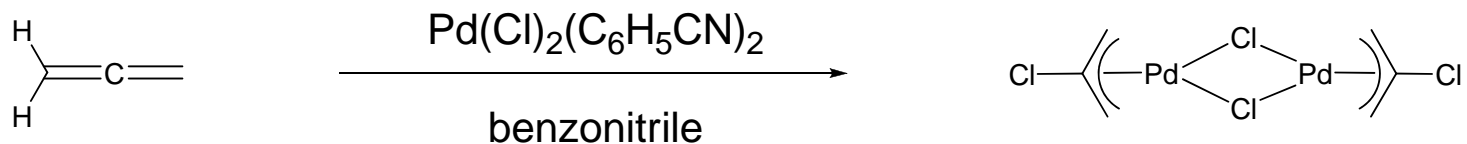
Matt Haley  
Colin Hughes  
Dee Jacobs  
Mark Mans

Lizzie O'Bryan  
Mariam Shamszad  
Jason Stevens  
Philip Williams

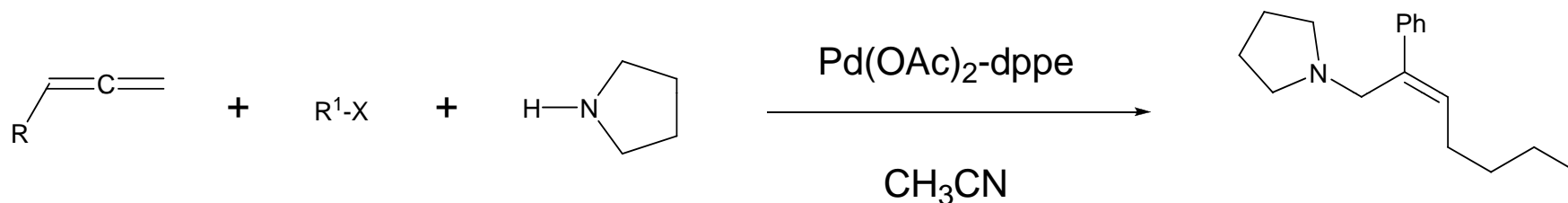




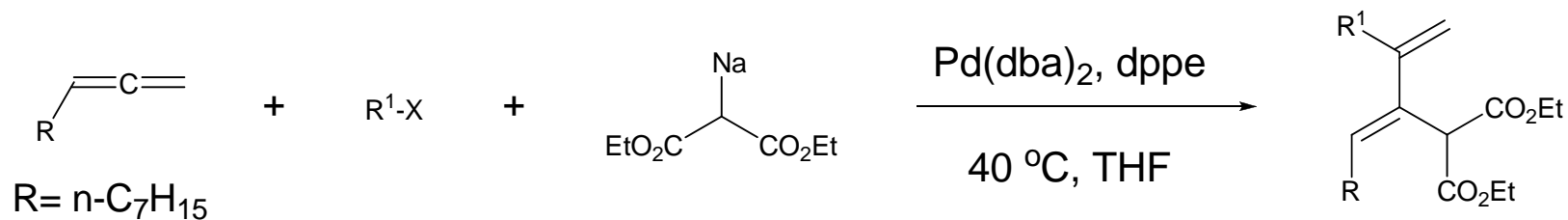
# Early Work with Allenes



Schultz, R.G. *Tetrahedron*. **1964**, 20, 2809-2813

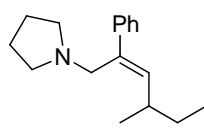
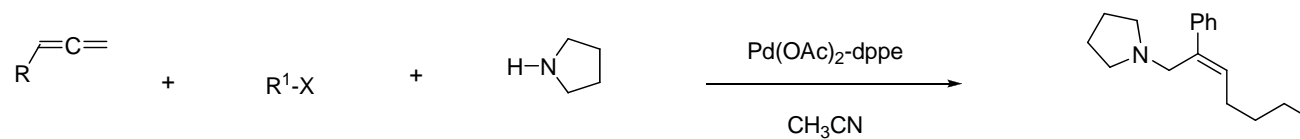


Shimizu, I.; Tsuji, J. *Chem Lett*. **1984**, 233-236.

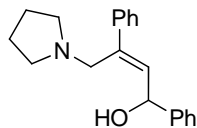


Ahmar, M.; Barieux, J. J.; Cazes, B.; Gore, J. *Tetrahedron* **1987**, 43, 513-526.

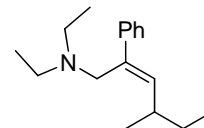
# Tsuji – Early Work



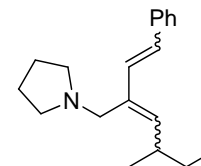
82%, 3:1 Z:E



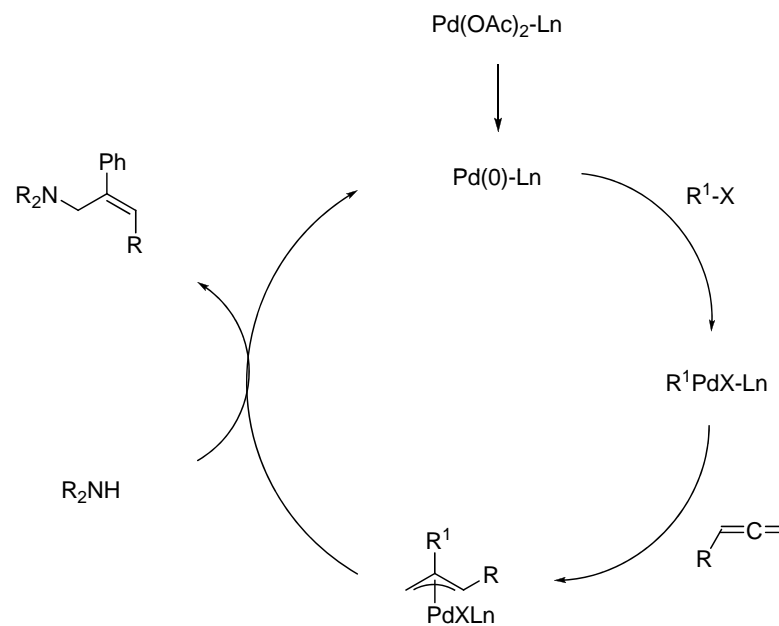
84%, 9:1 Z:E



8%, 2.5:1 Z:E

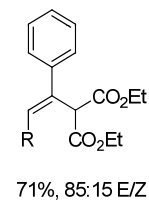
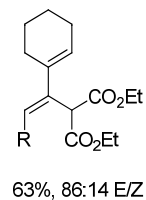
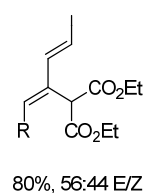
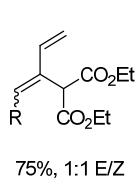
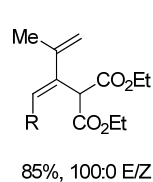
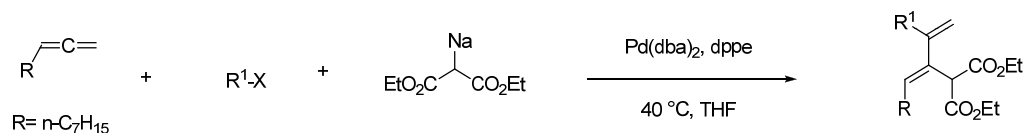


79%, 1:1 Z:E

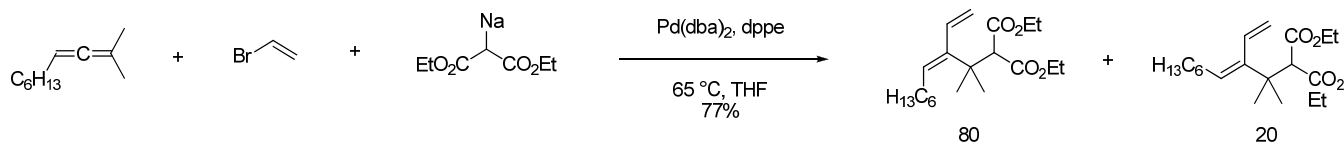
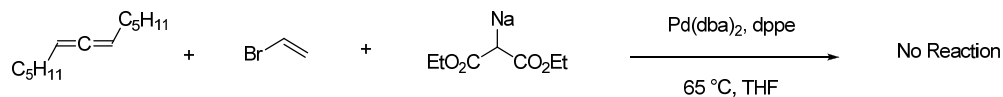
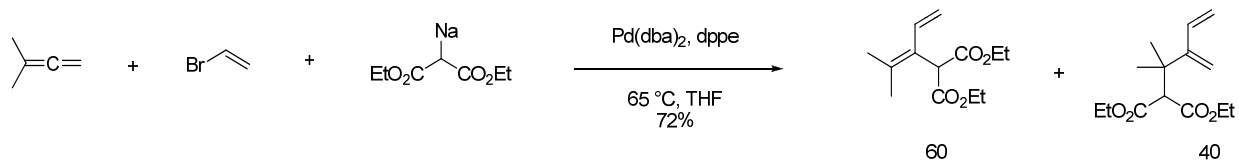


Shimizu, I.; Tsuji, J. *Chem Lett.* **1984**, 233-236.

# Gore - Early Work

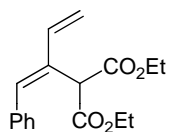
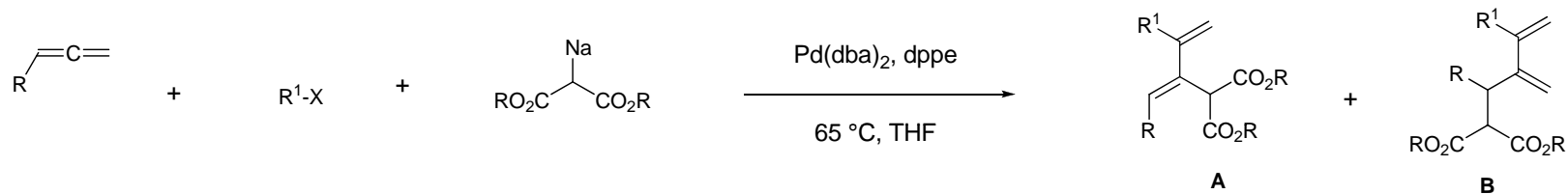


Postulated that the stereoselectivity is dependent upon relative stabilities of syn or anti  $\pi$ -allyl complexes.

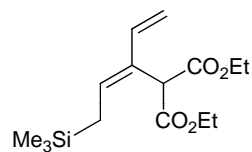


Reaction is slowed by steric hinderance of the intermediate  $\pi$ -allyl complex.

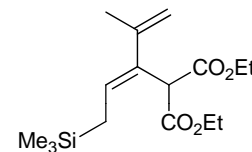
# Gore - Substituent Effects



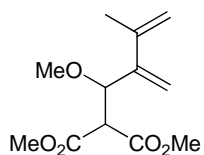
69%  
A:B 91/9  
E/Z 35/65



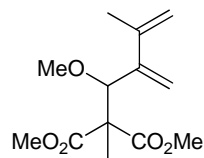
47%  
A:B 100/0  
E/Z 35/65



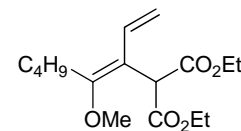
21%  
A:B 100/0  
E/Z 100/0



94%  
A:B 0/100

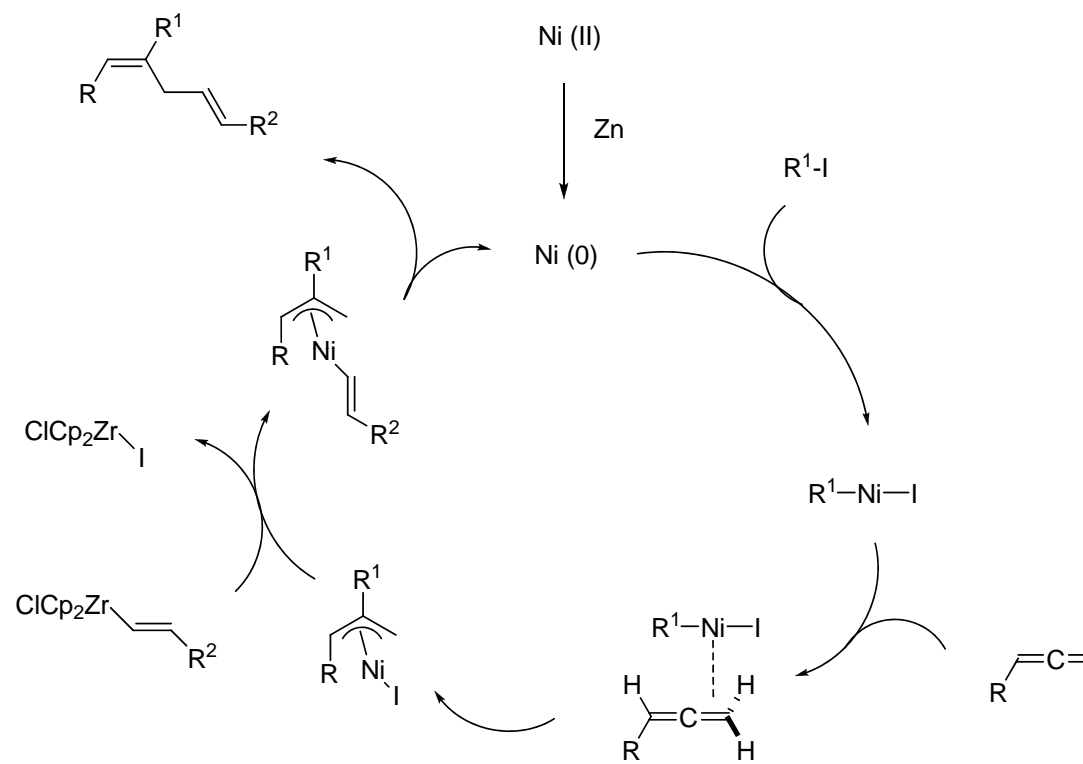
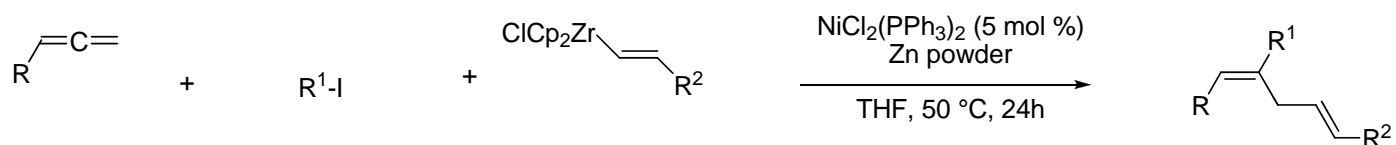


62%  
A:B 8/92  
E/Z 67/33

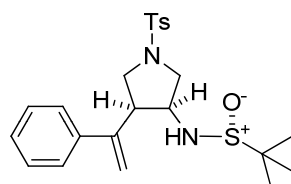
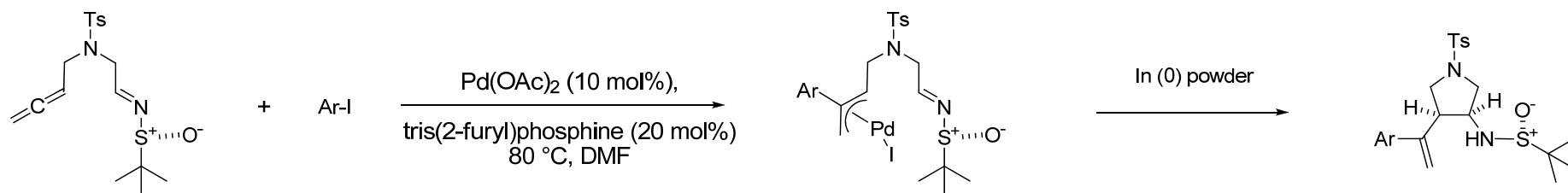


41%  
A:B 90/10

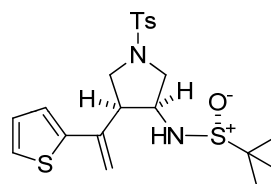
# Cheng- Ni Catalyzed Mechanism



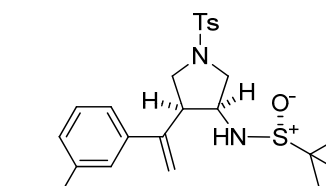
# Intramolecular Diastereoselective Allylation



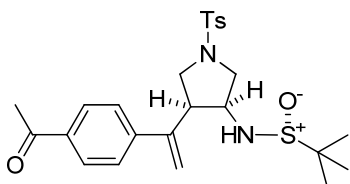
60%, 87:13



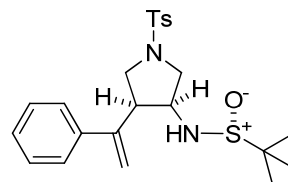
37%, 77:23



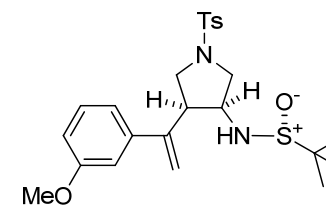
58%, 89:11



56%, 85:15

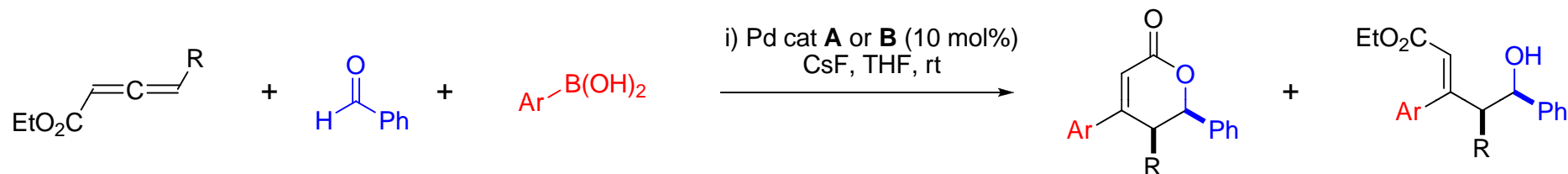


61%, 91:9

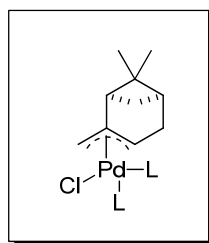


55%, 91:9

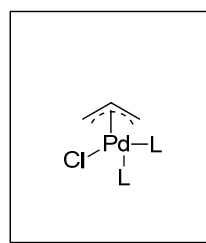
# Allenyl Esters as Lactone Precursors



Catalyst	Ligand (mol%)	Boronic Acid (Eq)	Allene (Eq)	Aldehyde (Eq)	Yield (%)
<b>A (10 mol%)</b>	None	2	5	1	75
<b>A (5 mol%)</b>	None	2	5	1	41
<b>A (5 mol%)</b>	None	1	2.5	4	63
<b>A (5 mol%)</b>	None	1	1.5	2	69
<b>A (5 mol%)</b>	None	1	1.5	1	57
<b>B</b>	None	2	5	1	33
Pd(OAc) <sub>2</sub>	PCy <sub>3</sub> (10)	2	5	1	39
Pd <sub>2</sub> (dba) <sub>3</sub>	PCy <sub>3</sub> (10)	2	5	1	23

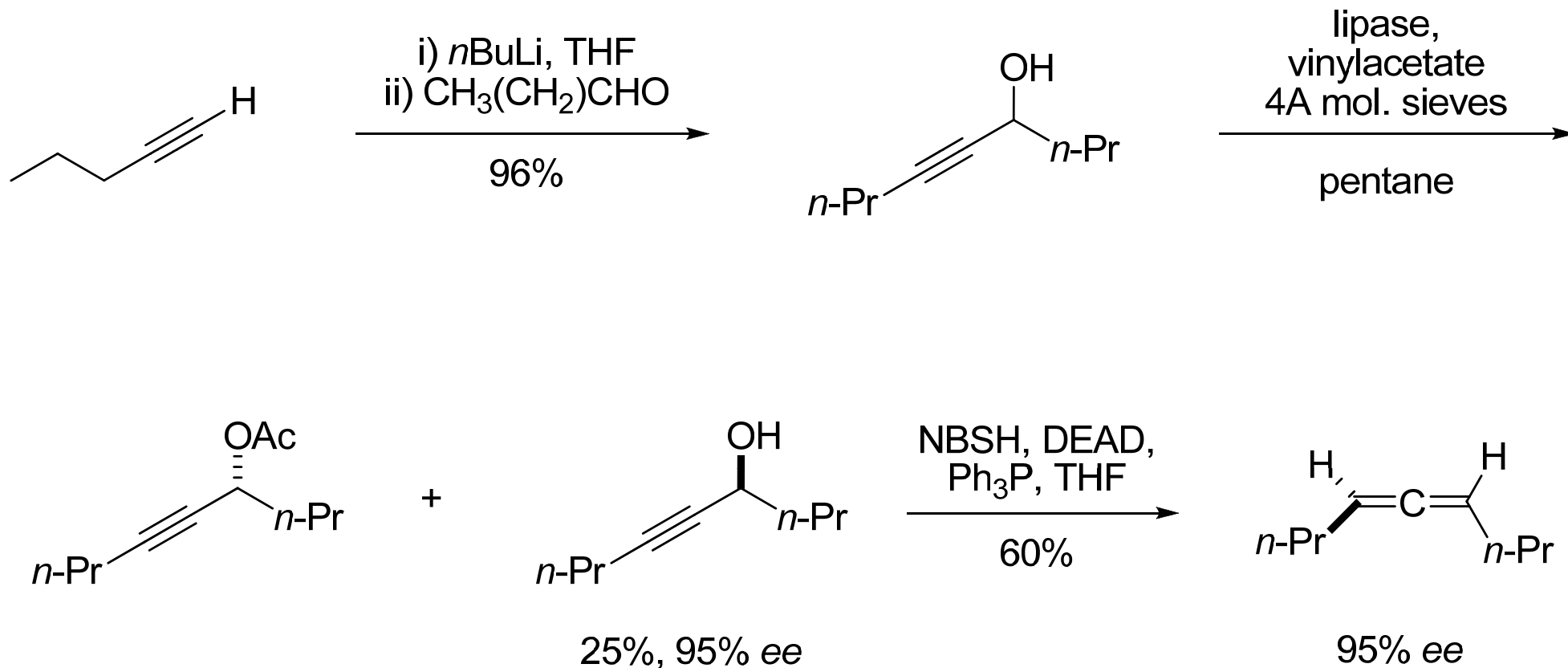


Catalyst A



Catalyst B

# Jamison- Synthesis of the Chiral Allene



NBSH =  $\alpha$ -nitrobenzenesulfonylhydrazine