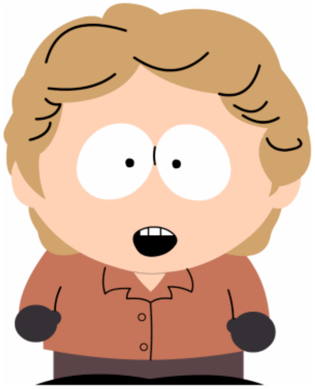
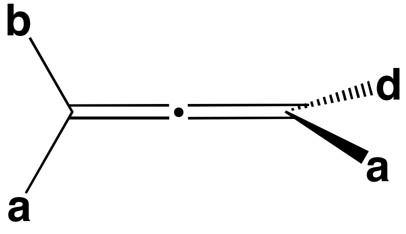


Axially Chiral Allenes: Not a Laboratory Curiosity Any More!

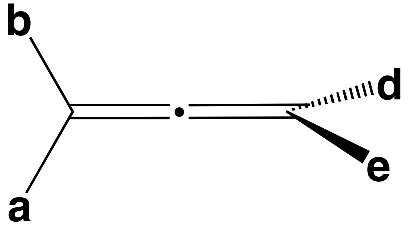
Alexander V. Predeus

Michigan State University, 2004

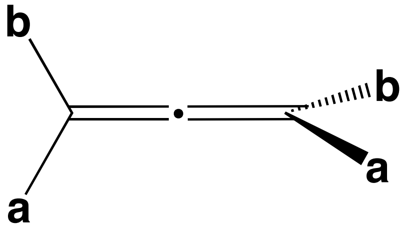
Chiral Allenes: General Information



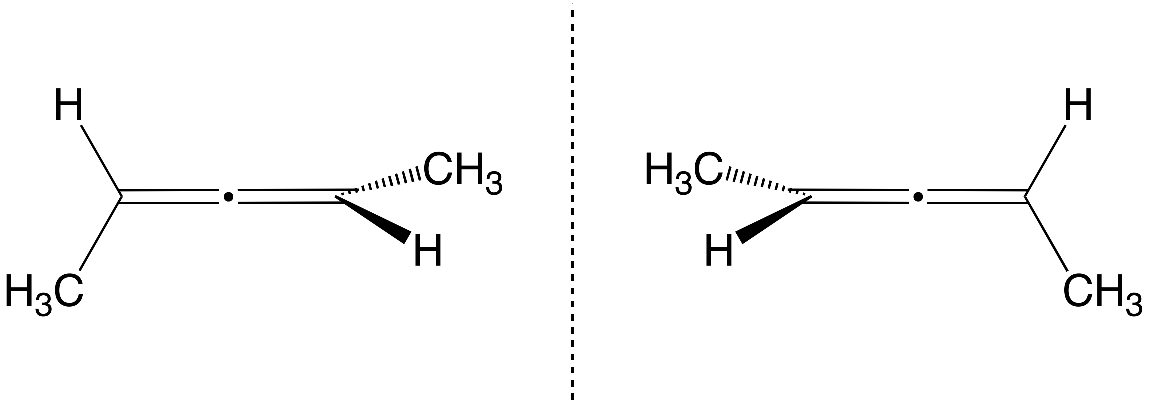
asymmetric



asymmetric



dissymmetric

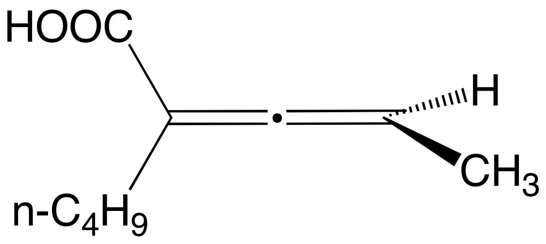


propadiene-2,3

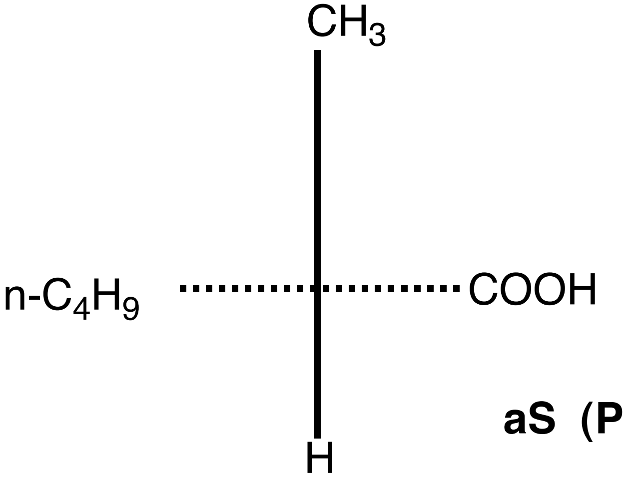
FW = 68.12 (C_5H_8)

bp = 48°C $[\alpha]_D$ +,-80°

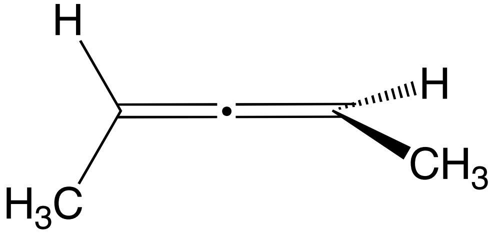
Axially Chiral Allenes: Nomenclature



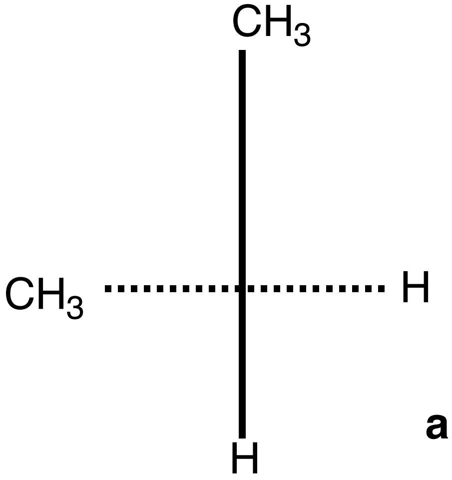
$CH_3 > H > COOH > n\text{-}C_4H_9$



aS (P)



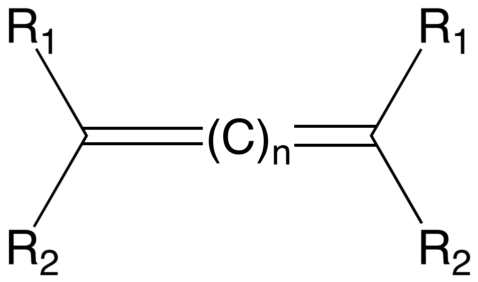
$CH_3 > H > CH_3 > H$



aR (M)

Some Facts About Chiral Allenes

- The rotation barrier to stereoisomerization of chiral allenes amounts to 195 kJ/mol for 1,3-dialkylallenes and to > 125 kJ/mol for 1,3-diarylallenes, while the threshold for isolation of stereoisomers at 20°C is 83 kJ/mol.
- Higher cumulenes - pentatetraenes and heptahexaenes - have lower rotation barrier. Thus, only few enantioenriched pentatetraenes and no heptahexaenes are known.
- Cumulated double bonds in allenes are strained. Upon undergoing any addition reaction it experiences a relief in strain of about 40 kJ/mol.



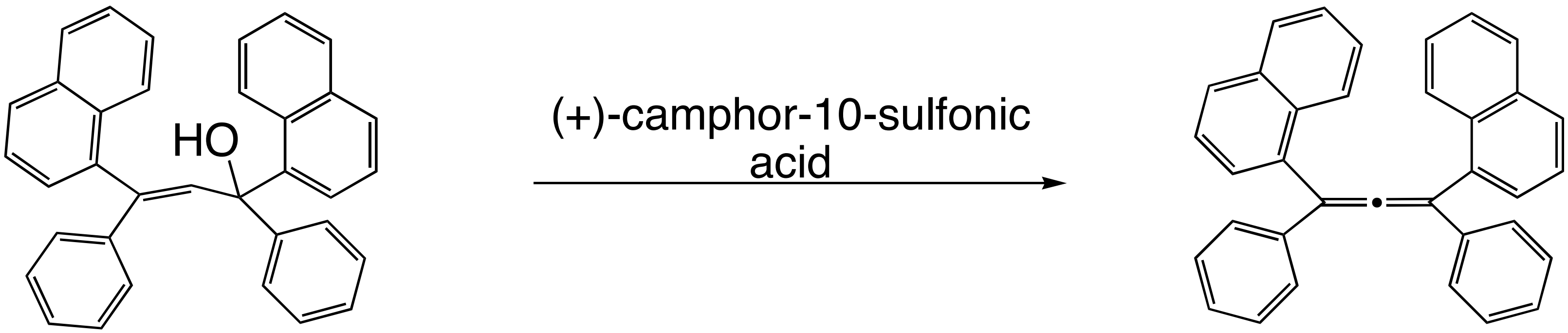
n = 0,2,4,6...
flat molecule
Z/E isomerism

n = 1,3,5,7...
chiral molecule
optical isomerism

Elsevier, C.J. In *Houben-Weyl, series Methods of Organic Chemistry;* Helmchen, G., Hoffmann, R.W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1995; Vol. E21a, p 537

Chiral Allenes: Historical Insight

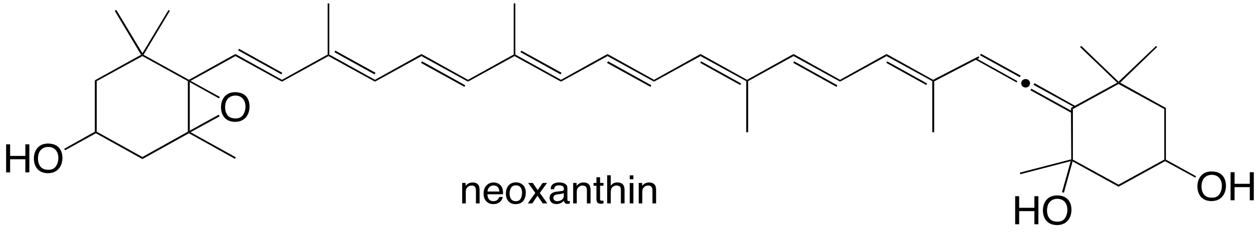
- 1875, Jacob van't Hoff - Prediction of the existence of two enantiomeric forms for an asymmetrically substituted allene
- 1935, Maitland and Mills - First experimental confirmation of van't Hoff's hypothesis. Formation of slightly dextrorotatory sample of allene by dehydration of allylic alcohol with (+)-camphor-10-sulfonic acid.
- 1952, Celmer and Solomons - The discovery of mycomycin, the first optically active allene found in nature.



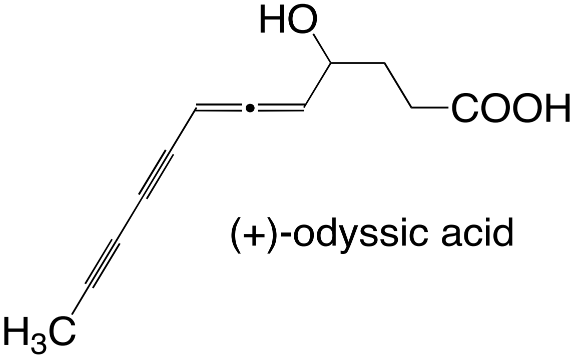
$[\alpha]_D$ +437^o (benzene), after several crystallizations

Rossi, R; Diversi, P. *Synthesis*, **1973**, 25

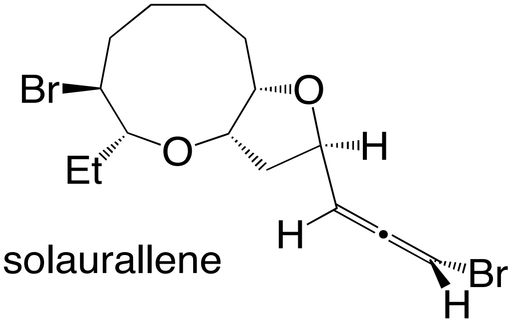
Some Naturally Occurring Chiral Allenes



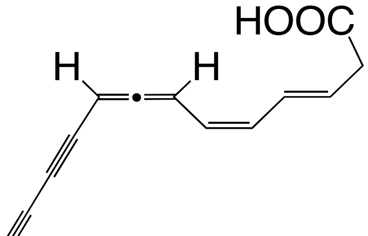
neoxanthin



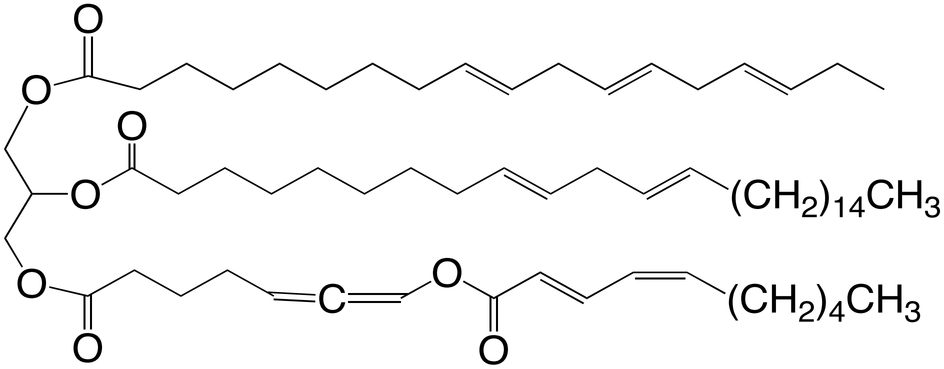
(+)-odyssic acid



(-)-isolaurallene

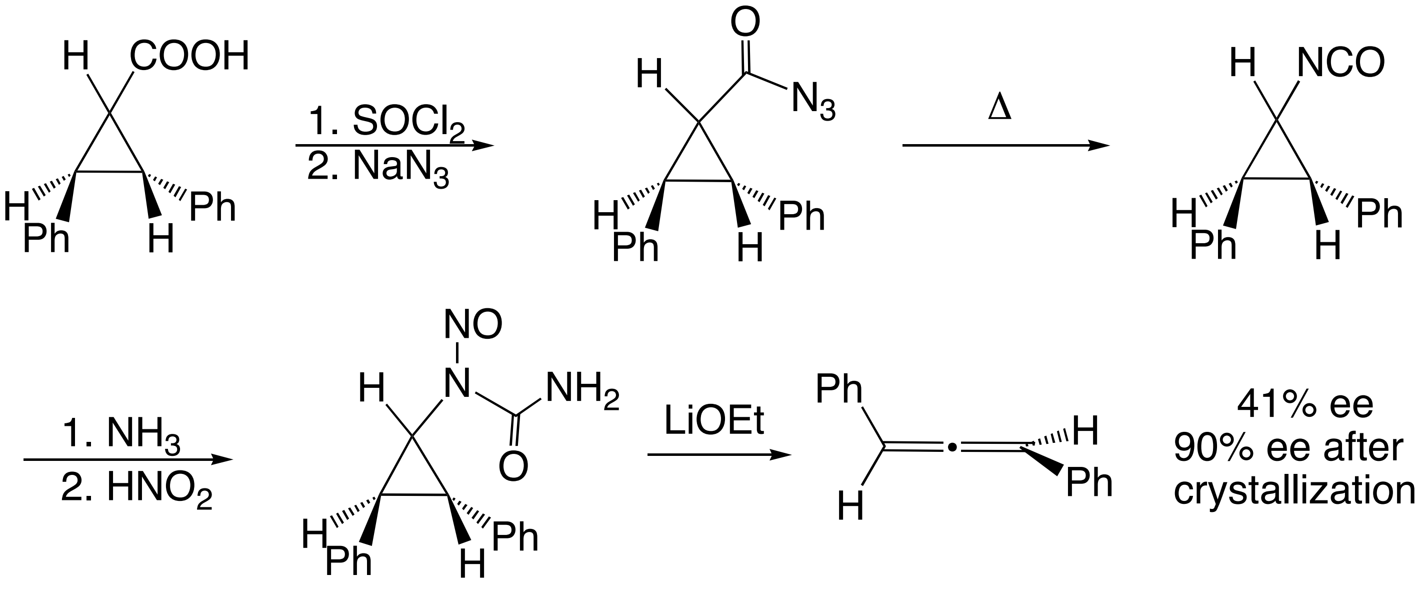


(-)-mycomycin

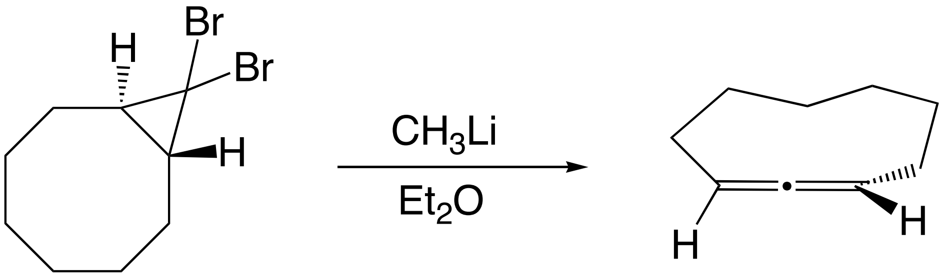


Rossi, R; Diversi, P. *Synthesis*, **1973**, 25;
Hoffmann-Roder, A.; Krause, N.; *Angew. Chem. Int. Ed*. **2002**, *41, No. 16*, 2933 - 2935

Ring Opening of Cyclopropanes



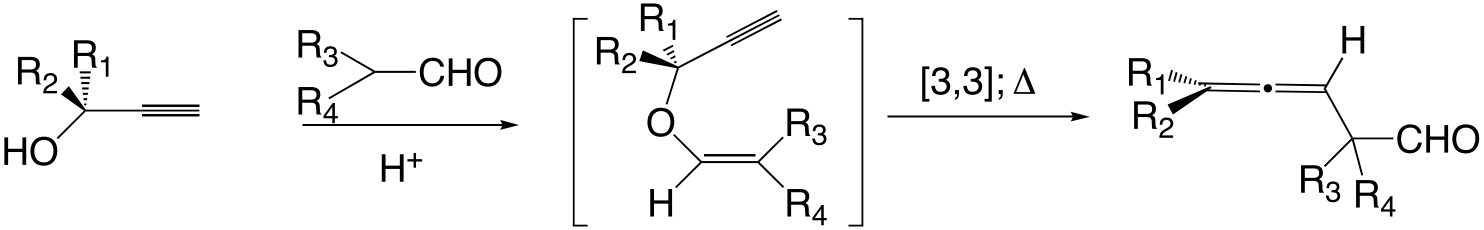
41% ee
90% ee after 3
crystallizations

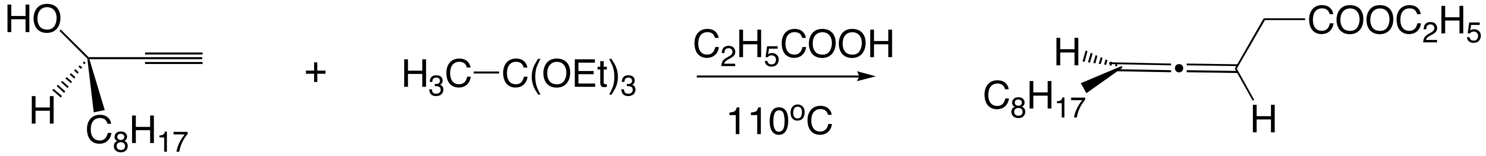


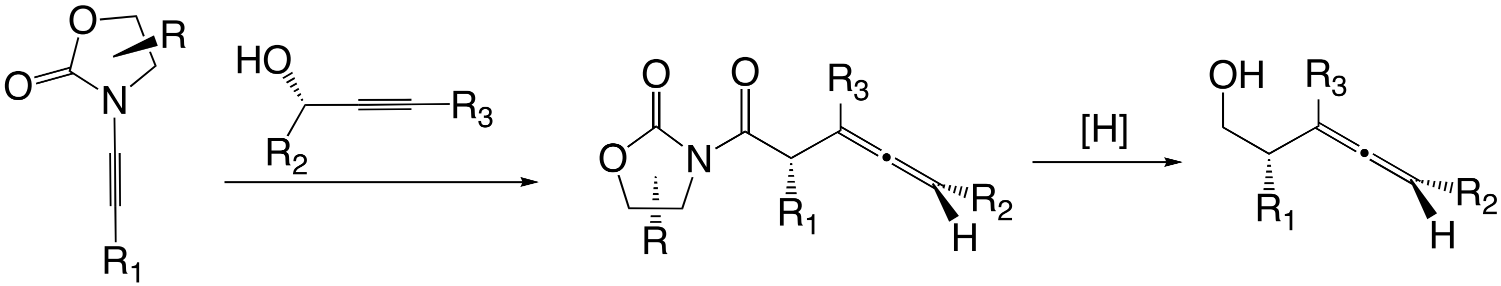
89% yield, 88% ee

Walbrick, J.M.; Wilson, J.W., Jr.; Jones, W. M. *J. Am. Chem. Soc.* **1968**, *90*, 2895
Cope, A.C.; Moore, W.R.; Bach, R.D.; Winkler, H.J.S. *J. Am. Chem. Soc.* **1970**, *92*, 1243

Synthesis of Chiral Allenes: [3,3]-Rearrangements

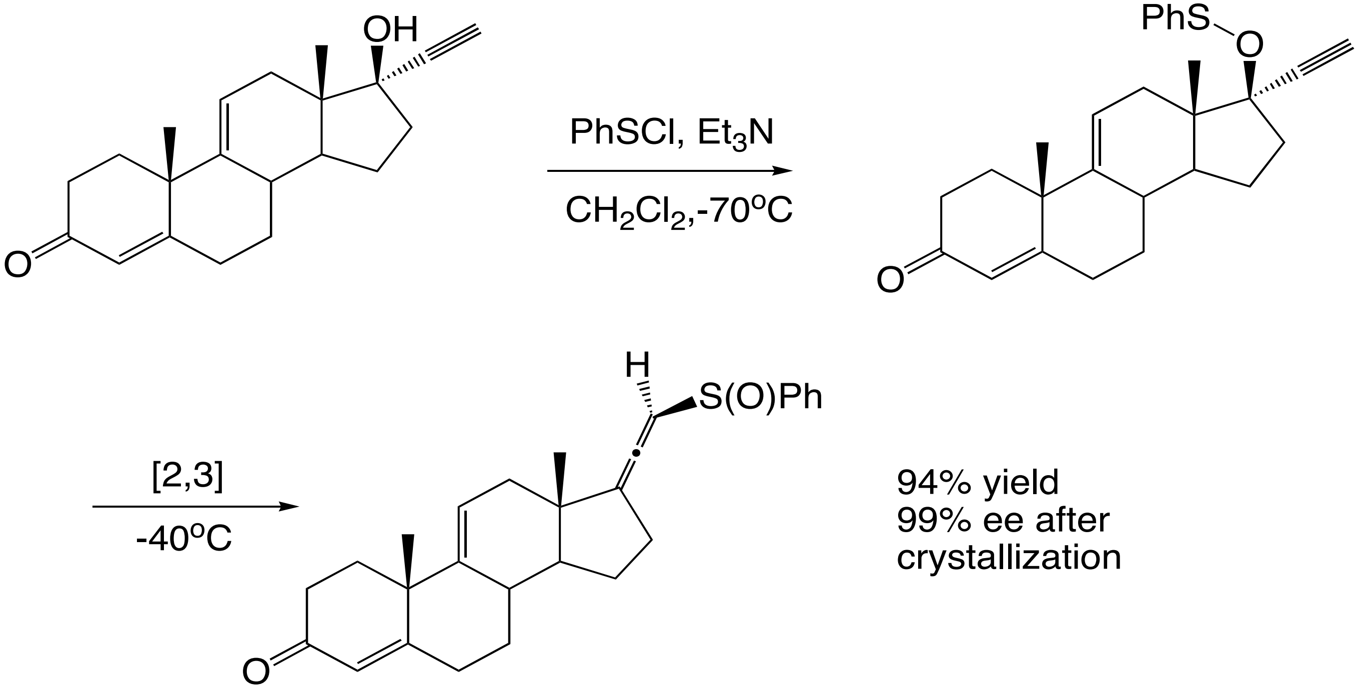




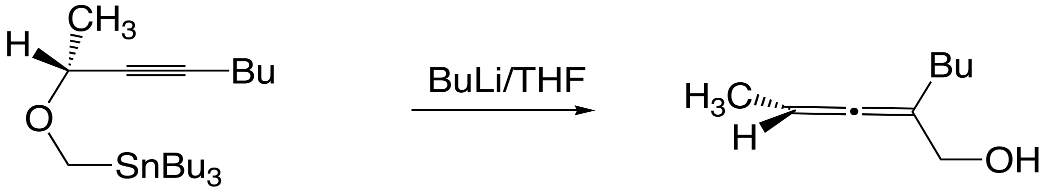


Jones, E.R.H.; Loder, L.D.; Whiting, M.C. *Proc. Chem. Soc*. **1960**, 180;
Mori, K.; Nukada, T.; Ebata, T. *Tetrahedron* **1981**, *37*, 1343;
Frederick, M.O.; Hsung, R.P.; Lambeth, R.H.; Mulder, J.A.; Tracey, M.R. *Org. Lett.* **2003**, *5*, 2663

Synthesis of Chiral Allenes: [2,3]-Rearrangements



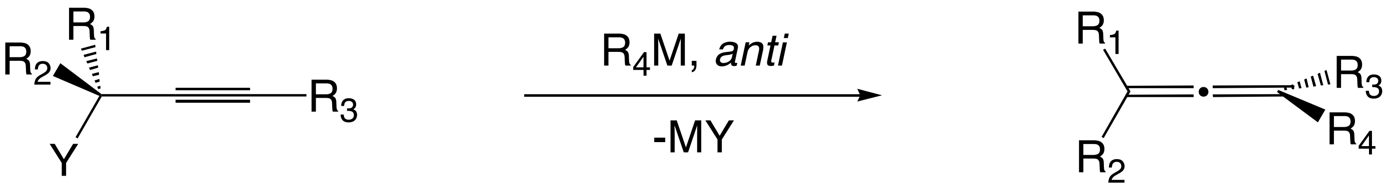
94% yield
99% ee after
crystallization



71%, 93% ee

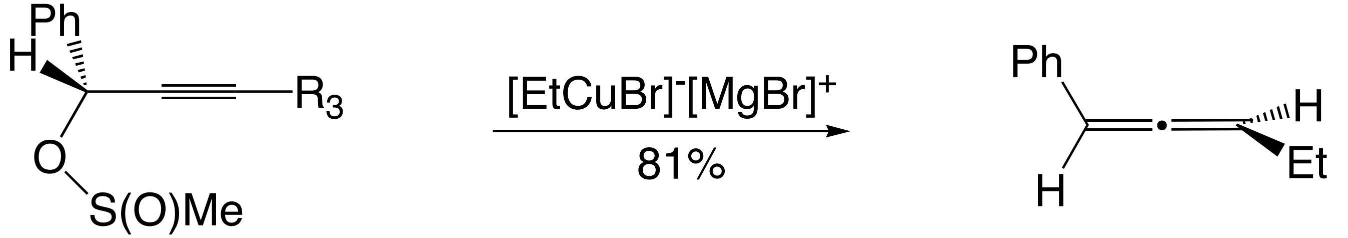
Smith, G.; Stirling, C.J.M. *J. Chem. Soc. C* **1971**, 1530
Marshall, J.A.; Robinson, E.D.; Zapata, A. *J. Org. Chem.* **1989**, *54*, 5854

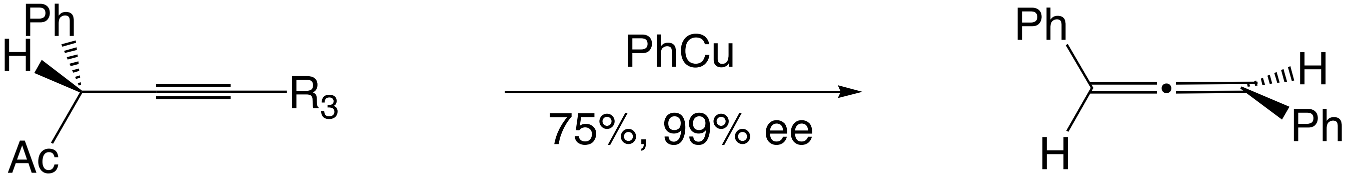
Copper-Mediated S_N2' Substitution



R_1, R_2, R_3 - alkyl, aryl, H
R_4M - mixed lithium and magnesium cuprates
R_4 - Me, Et, i-Pr, t-Bu, Cy, Ph, allyl
Y - PhCOO, Ac, OSO_2R, OSOR, Br

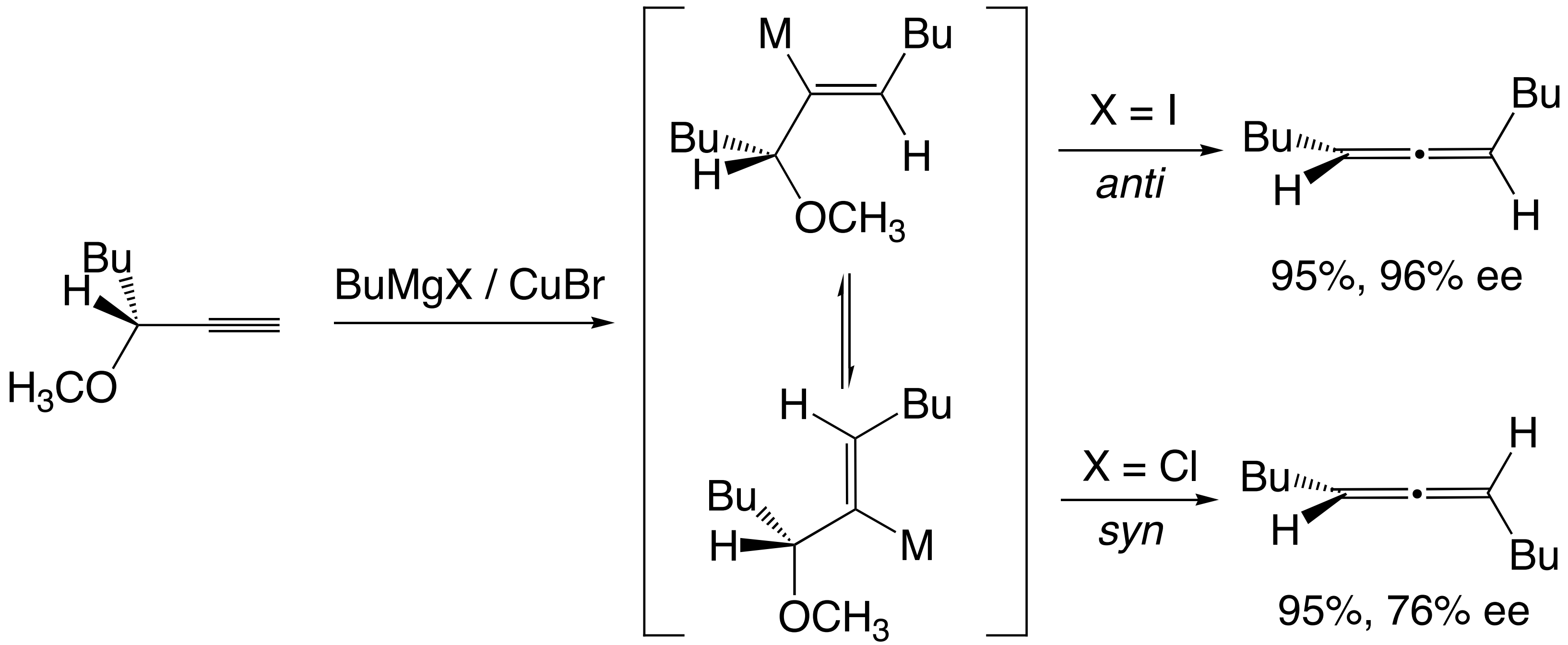
70 - 98% yield
> 95% chirality
transfer





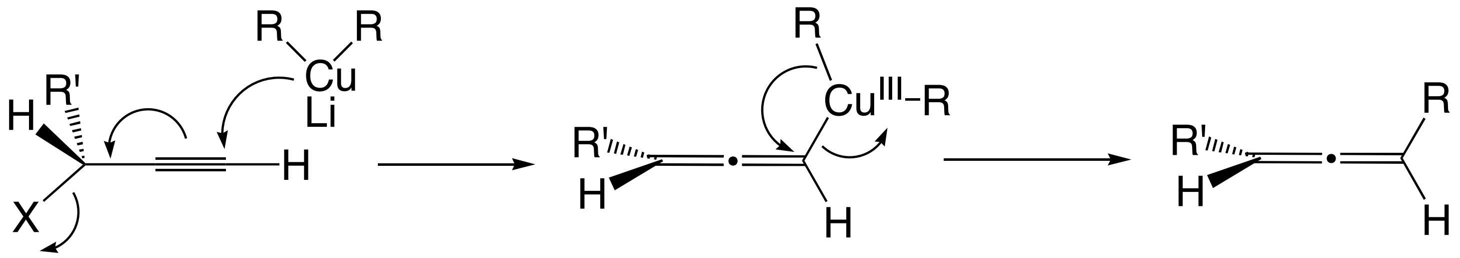
Elsevier, C.J.; Vermeer, P. *J. Org. Chem.* **1989**, *54*, 3726

Halogen Effect in Copper-Mediated Substitution

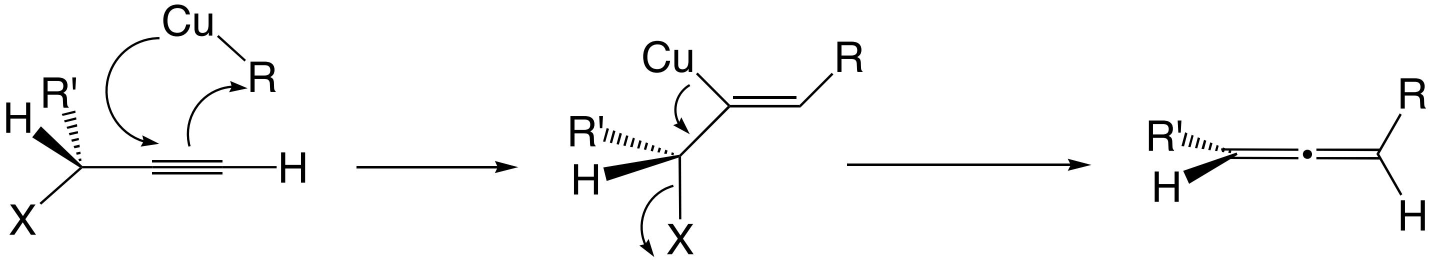


Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J.F. *J. Am. Chem. Soc.* **1990**, *112*, 8042 - 8047

Two Possible Mechanisms of Copper-Mediated Substitution



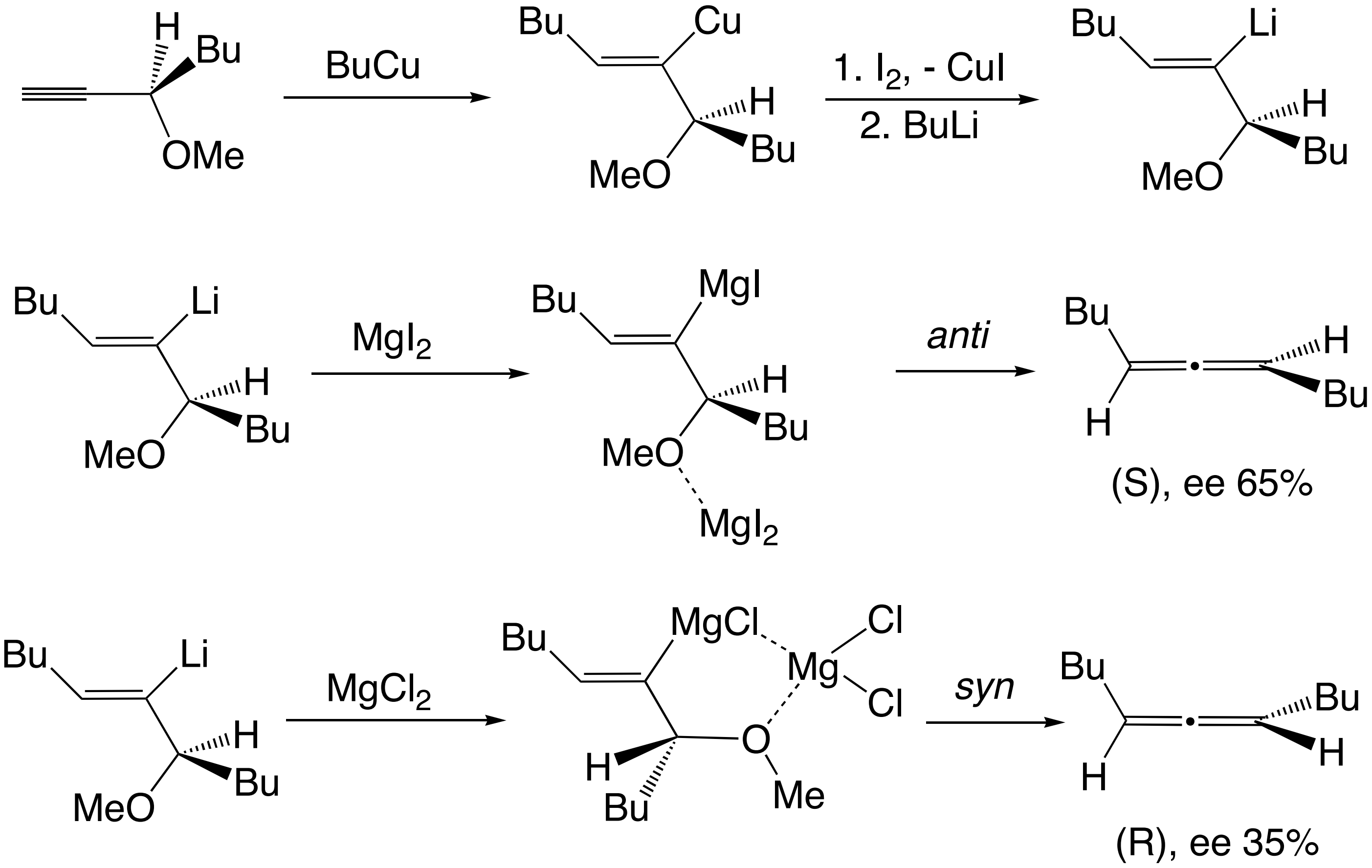
when X is a good leaving group, as OSO_2R, OAc, etc.



when X is poor leaving group, as OMe

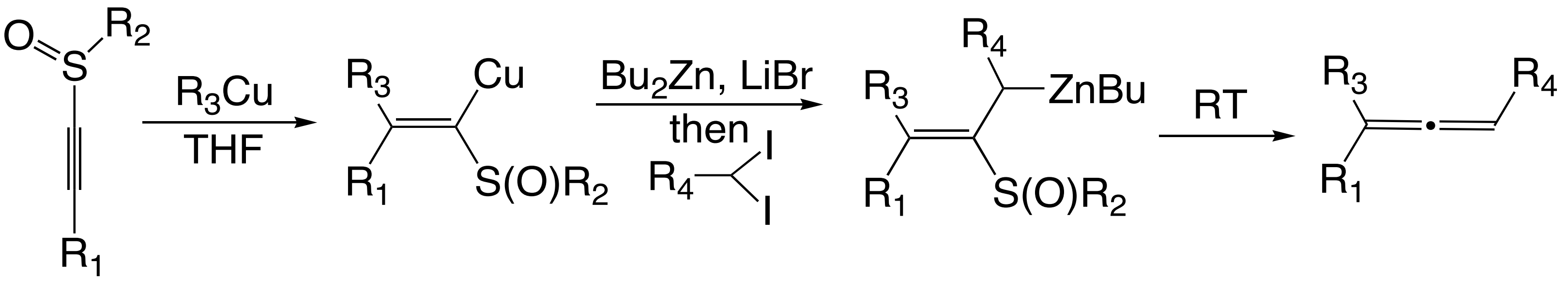
Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J.F. *J. Am. Chem. Soc.* **1990**, *112*, 8042 - 8047

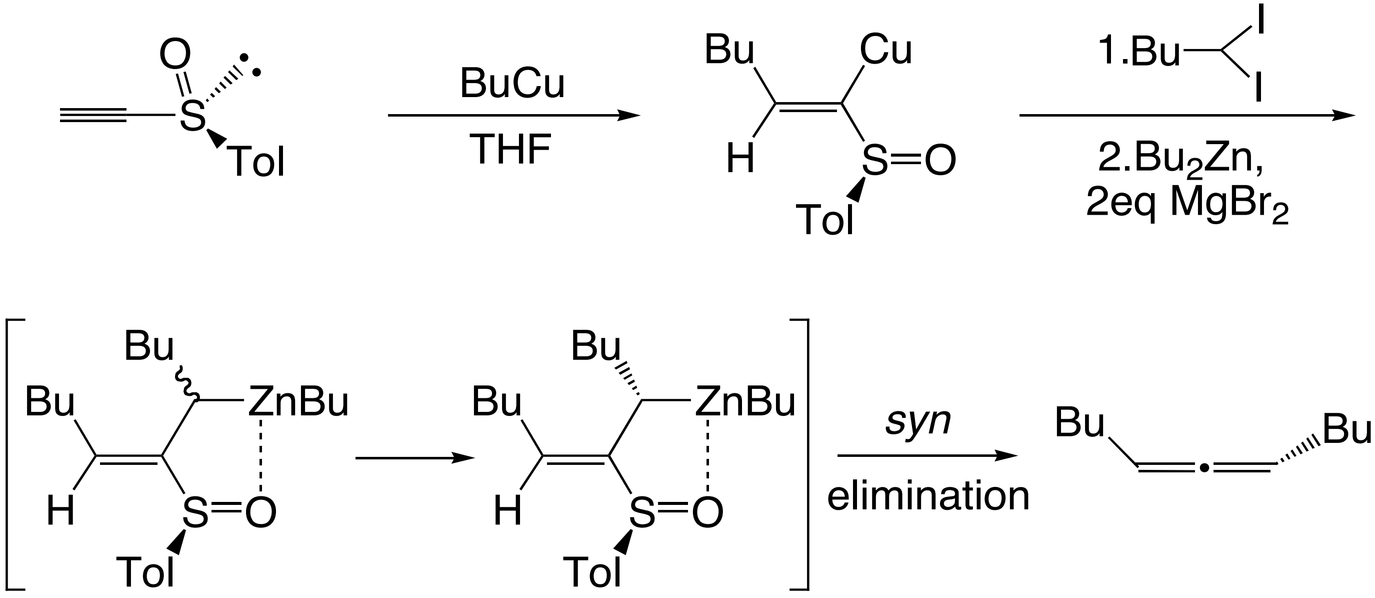
Studies on the Nature of Halogen Effect



Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J.F. *J. Am. Chem. Soc.* **1990**, *112*, 8042 - 8047

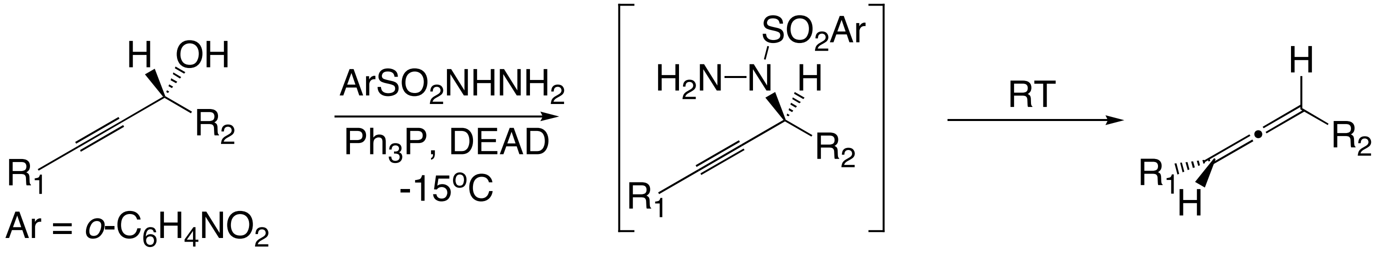
Synthesis of Chiral Allenes Using Organozinc Reagents

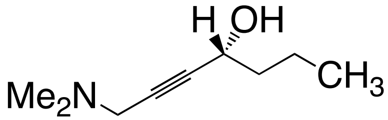
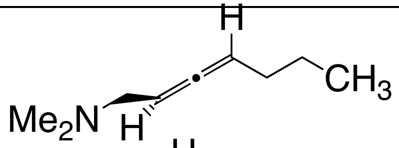
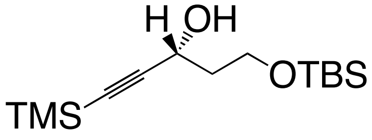
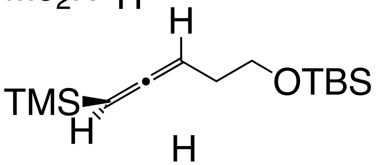
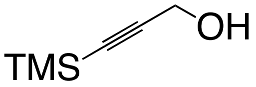
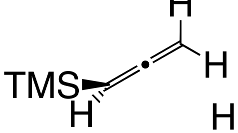
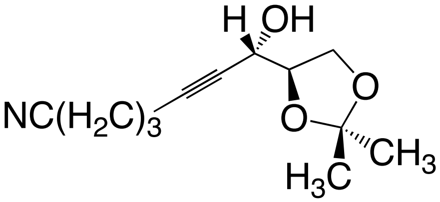
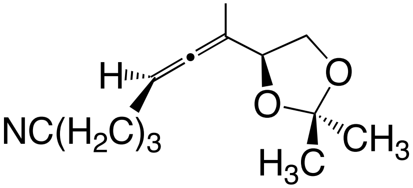




Varghese, J.P.; Zouev, I.; Aufauvre, L.; Knochel, P.; Marek, I. *Eur. J. Org. Chem*. **2002**, 4151 - 4158

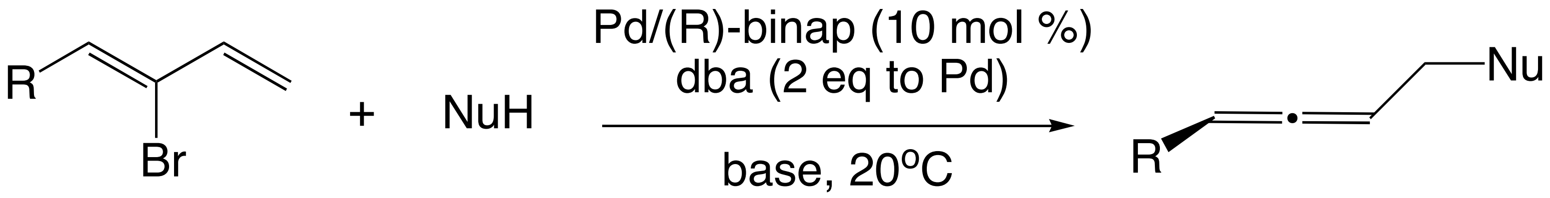
Approach based on Mitsunobu reaction



Substrate	Product	Yield, %
		83
		91
		53 (88)
		70

Myers, A.G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492-4493

First successful catalytic synthesis of chiral allene

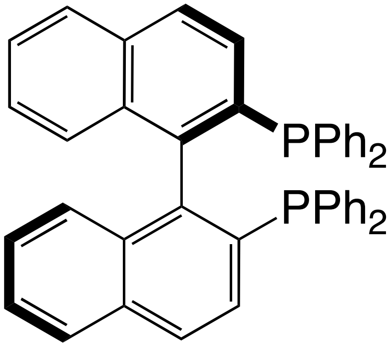


R = Ph, ferrocenyl, t-Bu, n-C_8H_{17}

base - CsO*t*-Bu

Nu = C(NHAc)$(COOEt)_2$, CMe$(COOMe)_2$

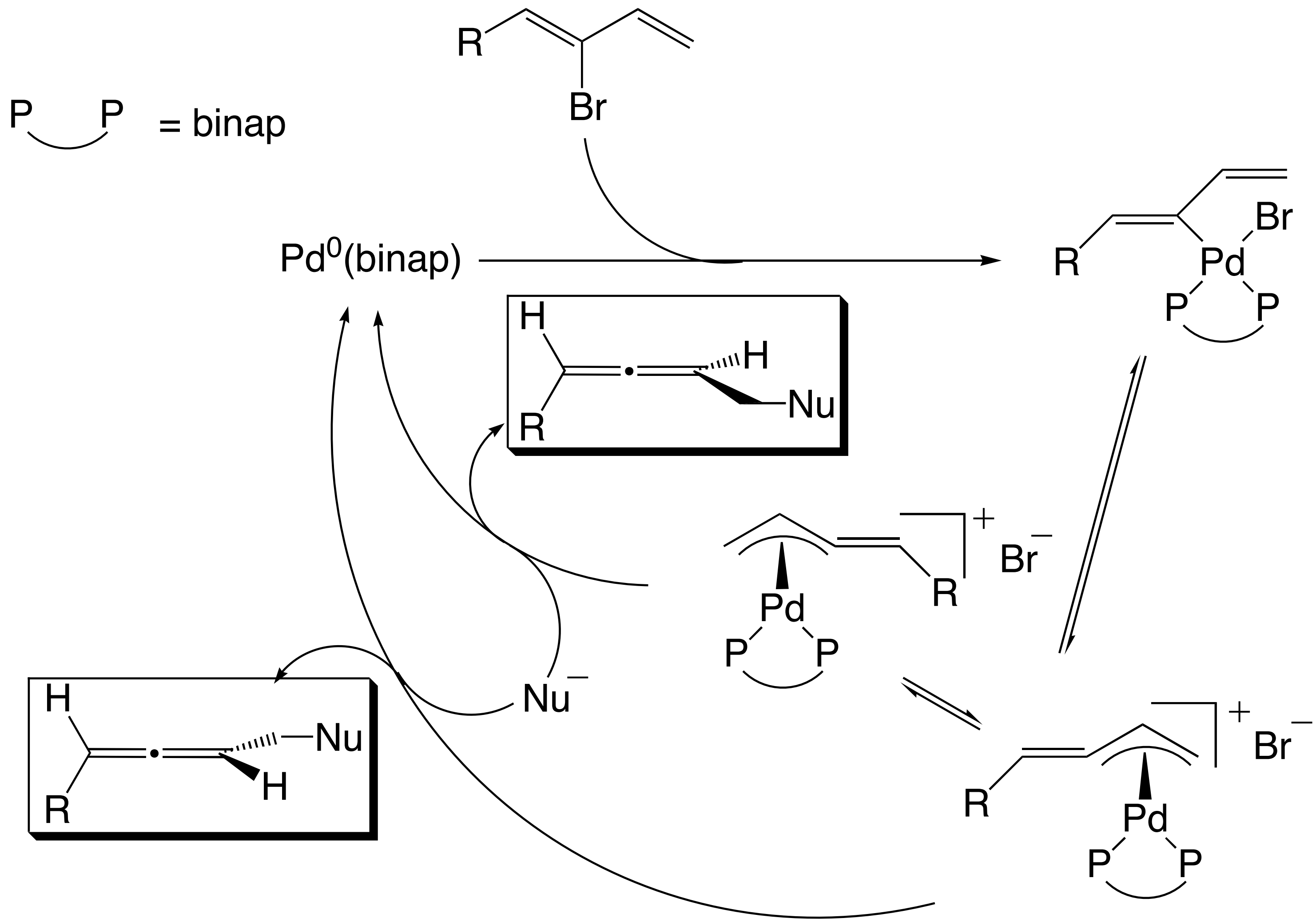
52 - 89% ee, 34-98% yield



(R)-binap

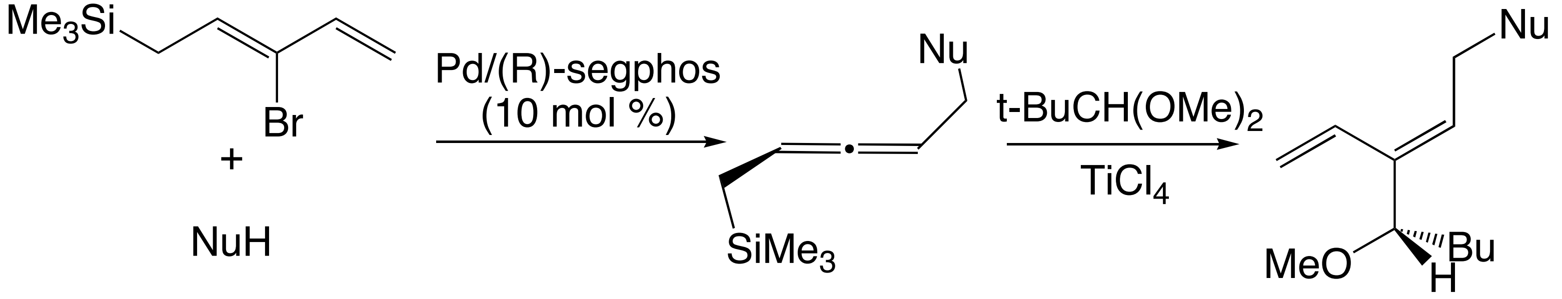
Osagawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089 - 2090

Scheme of Suggested Mechanism of Catalytic Reaction



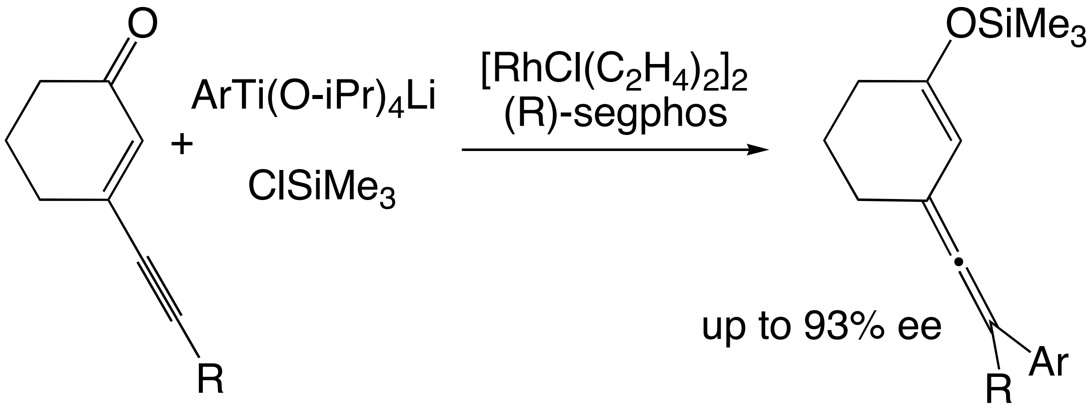
Osagawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089 - 2090

Other Catalytic Syntheses of Chiral Allenes



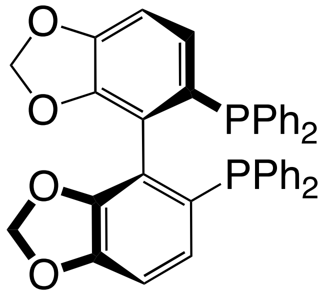
87% ee
axially chiral

74%ee
centrally chiral



up to 93% ee

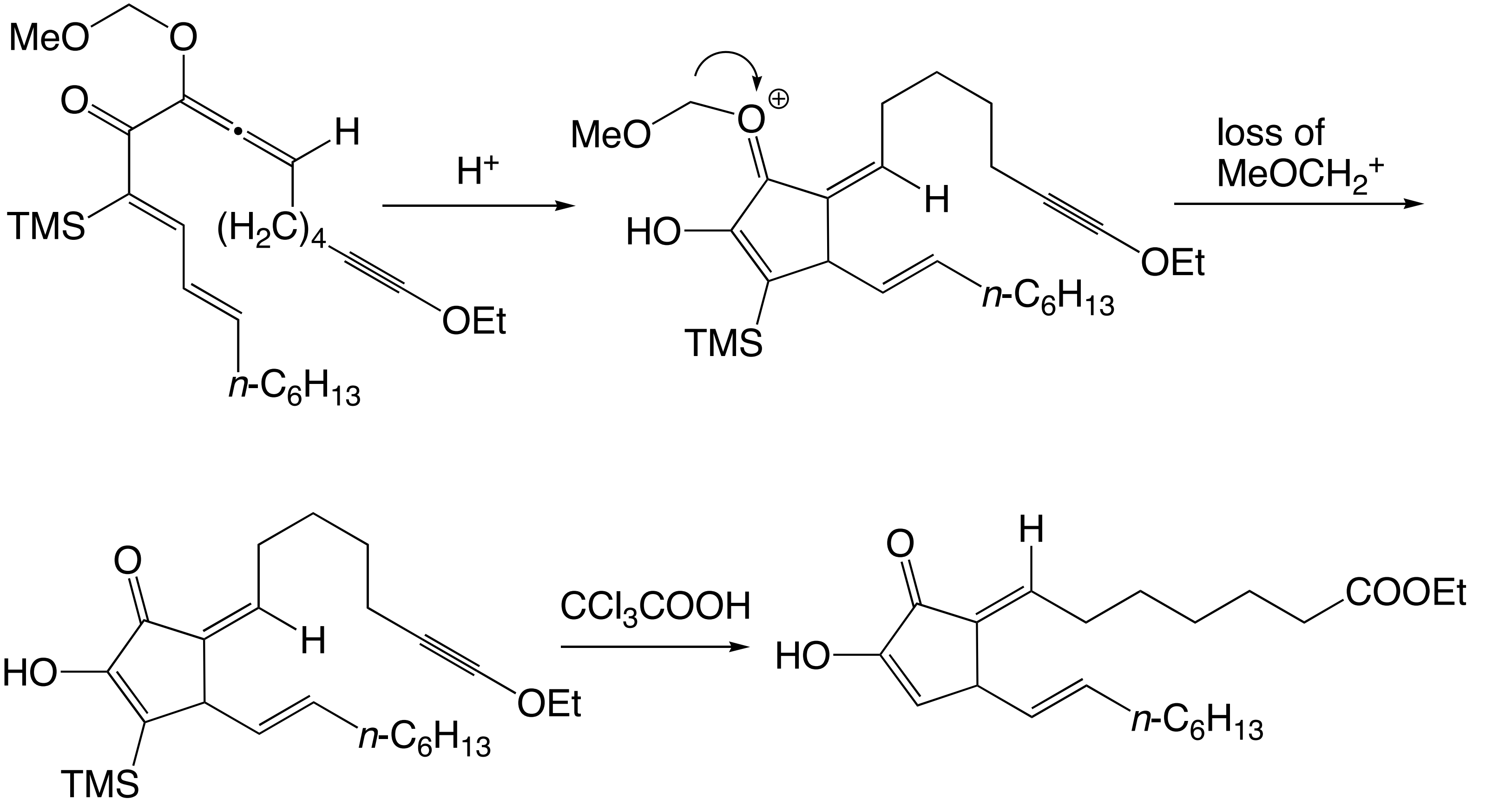
R = n-Bu, Cy, 4-MeOC$_6$H$_4$
Ar = Ph, 4-FC$_6$H$_4$, 4-MeOC$_6$H$_4$



(R)-segphos

Osagawara, M.; Ueyama, K.; Nagano, T.; Mizuhata, Y.; Hayashi, T. *Org. Lett.* **2002**, *123*, 2089 - 2090; Hayashi, T.; Tokunaga, N.; Inoue, K. *Org. Lett.* **2003**, *123*, 2089 - 2090

Nazarov Cyclization of Allenyl Ketones

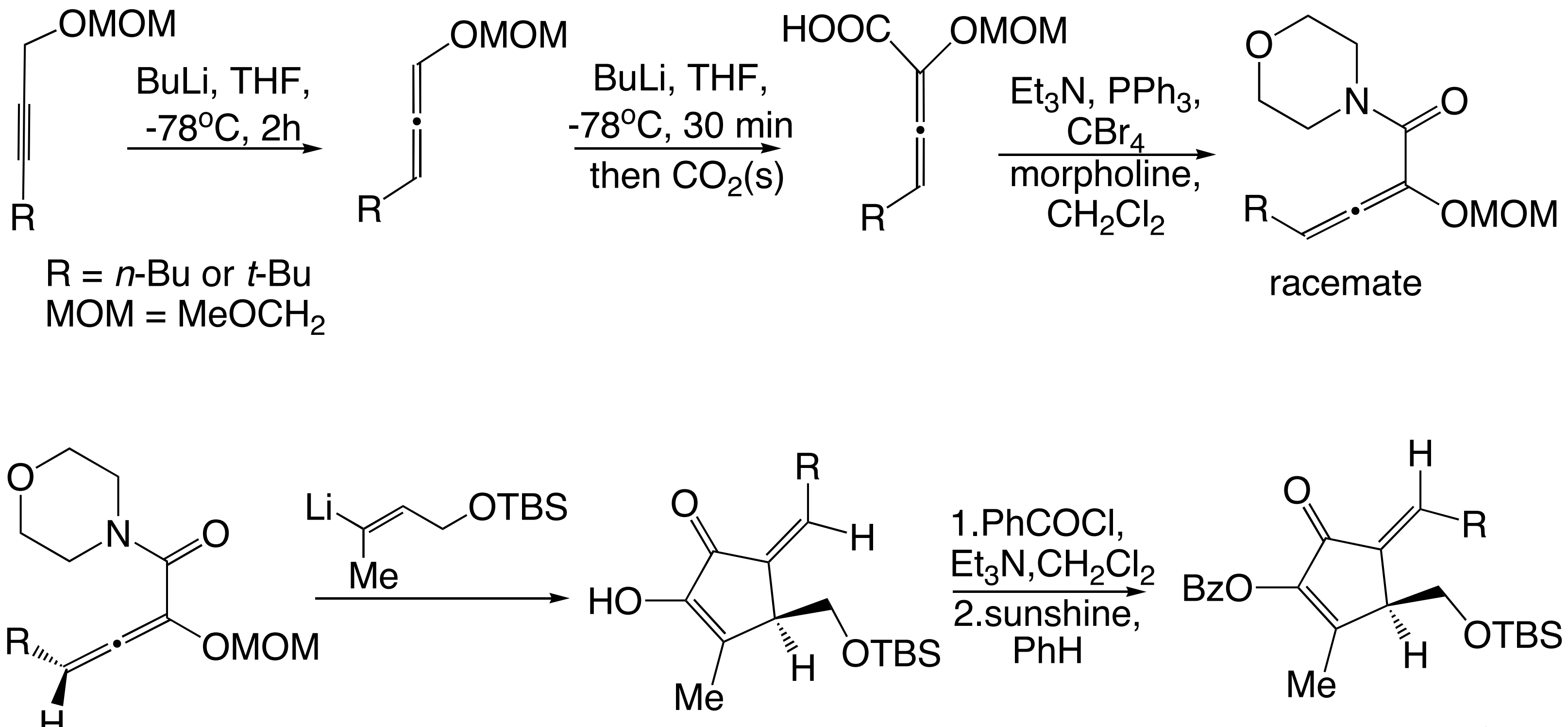


Hu, H.; Smith, D.; Cramer, R.E.; Tius, M.A. *J. Am. Chem. Soc*. **1999**, *121*, 9895-9896

Proposed Mechanism for Allenyl Ketone Cyclization

Hu, H.; Smith, D.; Cramer, R.E.; Tius, M.A. *J. Am. Chem. Soc*. **1999**, *121*, 9895-9896

Chiral Modification of Allene Nazarov Reaction



R = *n*-Bu or *t*-Bu
MOM = MeOCH$_2$

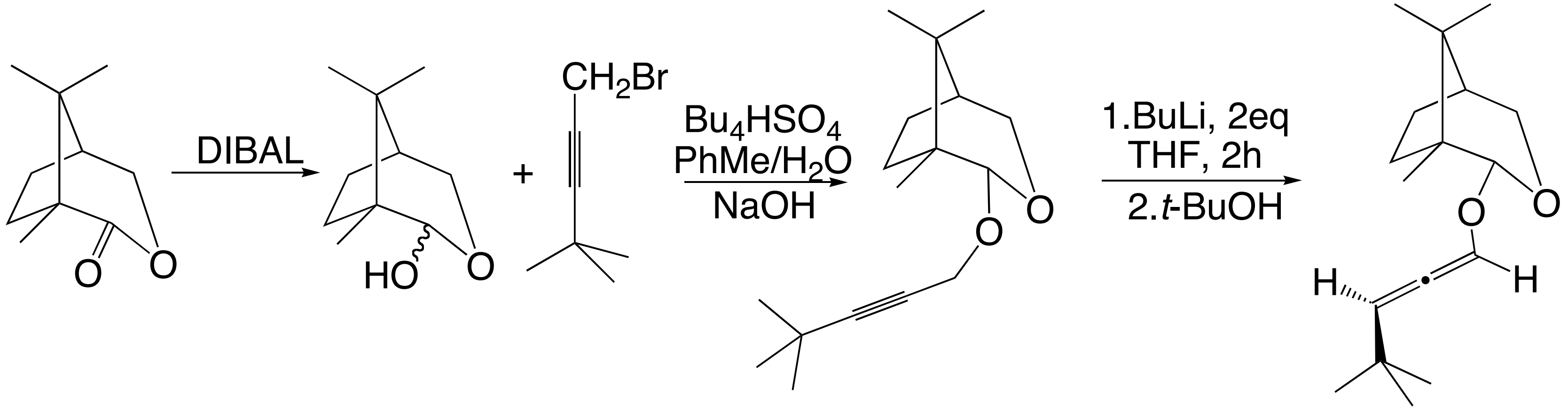
racemate

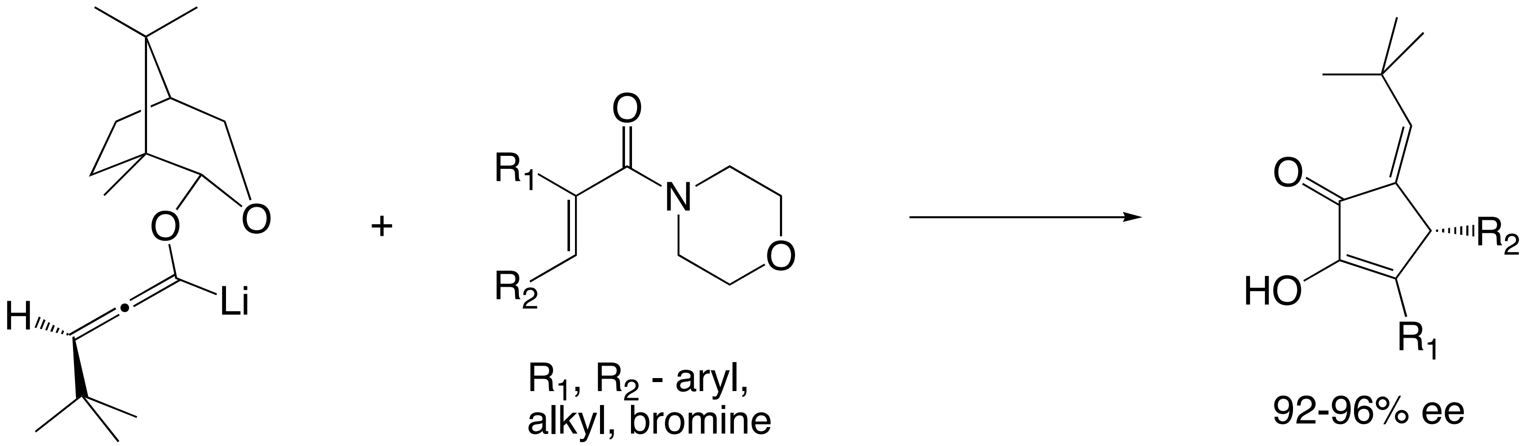
(+) after
separation

chirality transfer:
84% for *n*-Bu
>95% for *t*-Bu

Harrington, P.E.; Tius, M.A. *Org. Lett.* **2000**, *Vol. 2, No. 16*, 2447-2450

Camphor-Derived Auxiliary for Asymmetric Cyclopentannelation



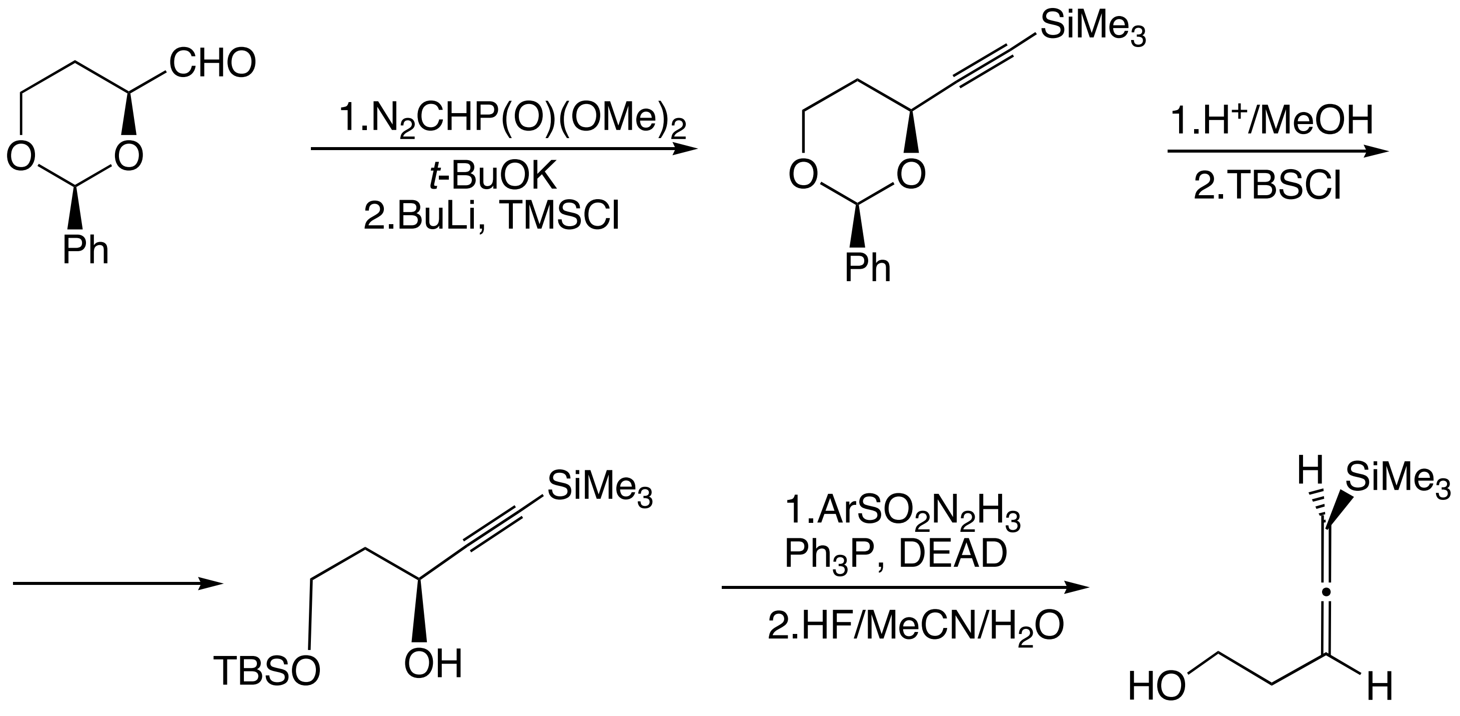


R_1, R_2 - aryl,
alkyl, bromine

92-96% ee

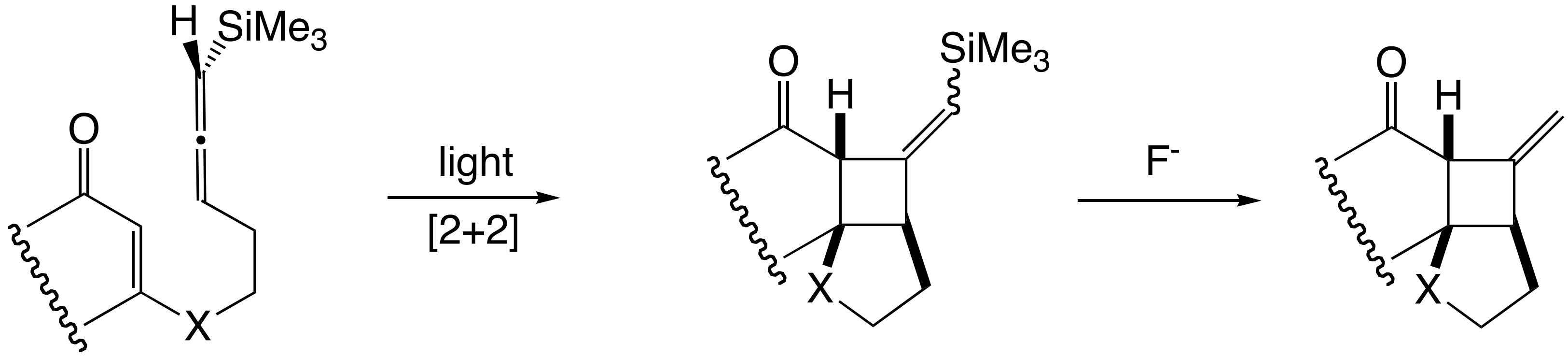
Harrington, P.E.; Murai, T.; Chu, C.; Tius, M.A. *J. Am. Chem. Soc*. **2002**, *124*, 10091-10100

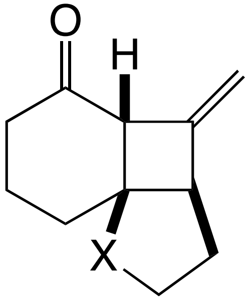
Preparation of Optically Active Allenylsilane



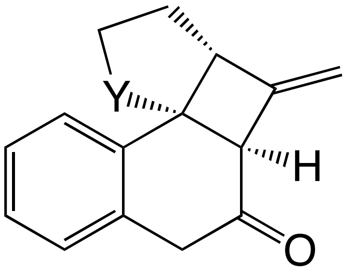
Shepard, M.S.; Carreira, E.M. *J. Am. Chem. Soc.* **1997**, *119*, 2597 - 2605

Asymmetric Photocycloaddition with an Optically Active Allenylsilane





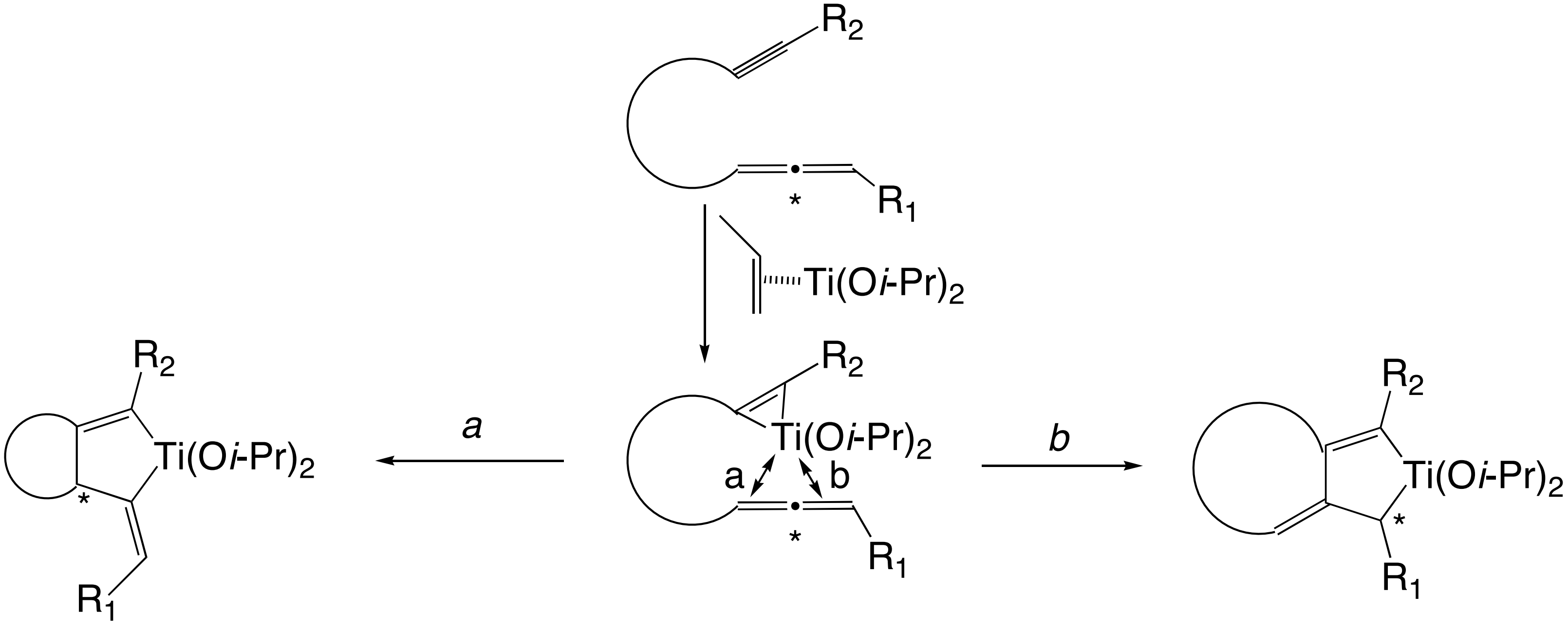
X = O, NBoc
85-92% ee

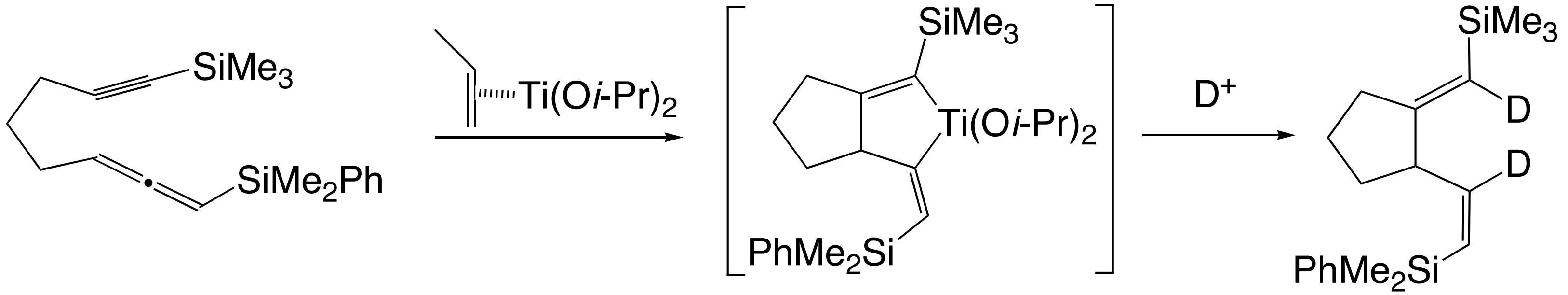


Y = O, S
89-100%ee

Shepard, M.S.; Carreira, E.M. *J. Am. Chem. Soc.* **1997**, *119*, 2597 - 2605

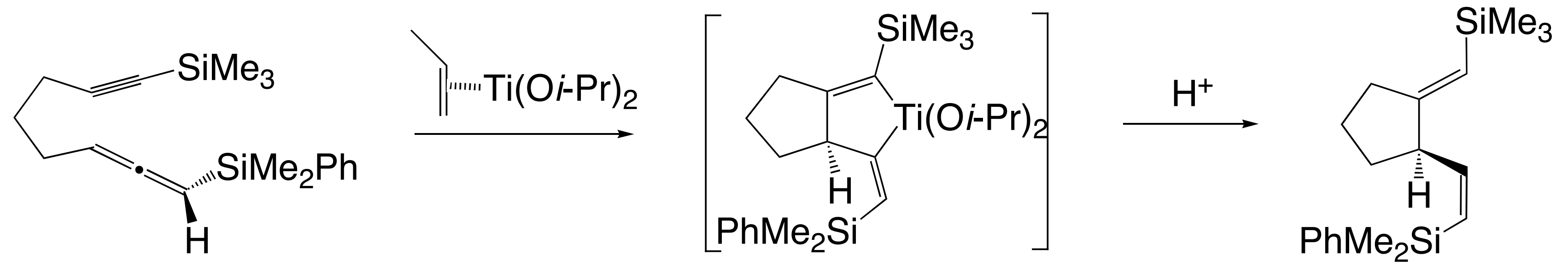
Ti(II)-mediated Asymmetric Allenyne Cyclization

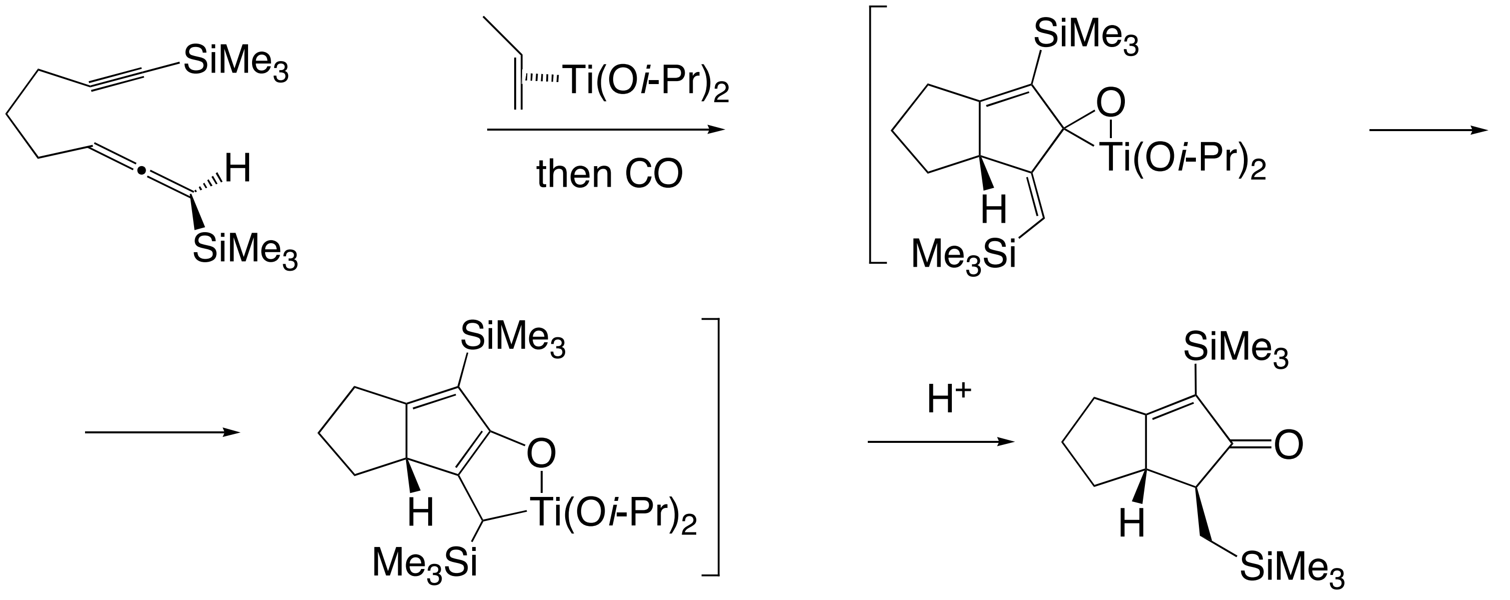




Urabe, H.; Takeda, T.; Hideura, D.; Sato, F. *J. Am. Chem. Soc*. **1997**, *119*, 11295-11305

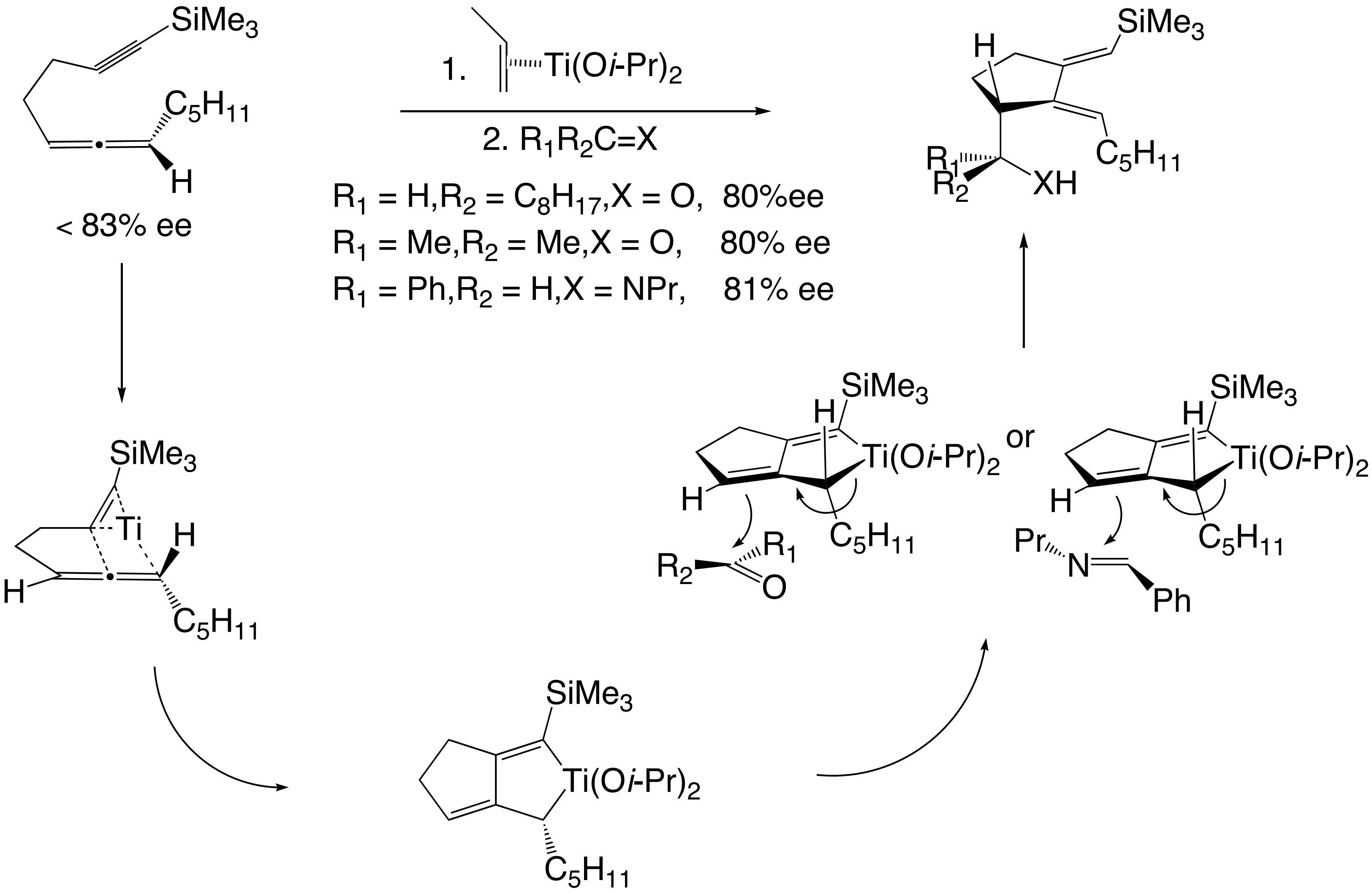
Cyclization of 1,2-Dien-7-ynes





Urabe, H.; Takeda, T.; Hideura, D.; Sato, F. *J. Am. Chem. Soc*. **1997**, *119*, 11295-11305

Cyclization of 1,2-Dien-6-ynes



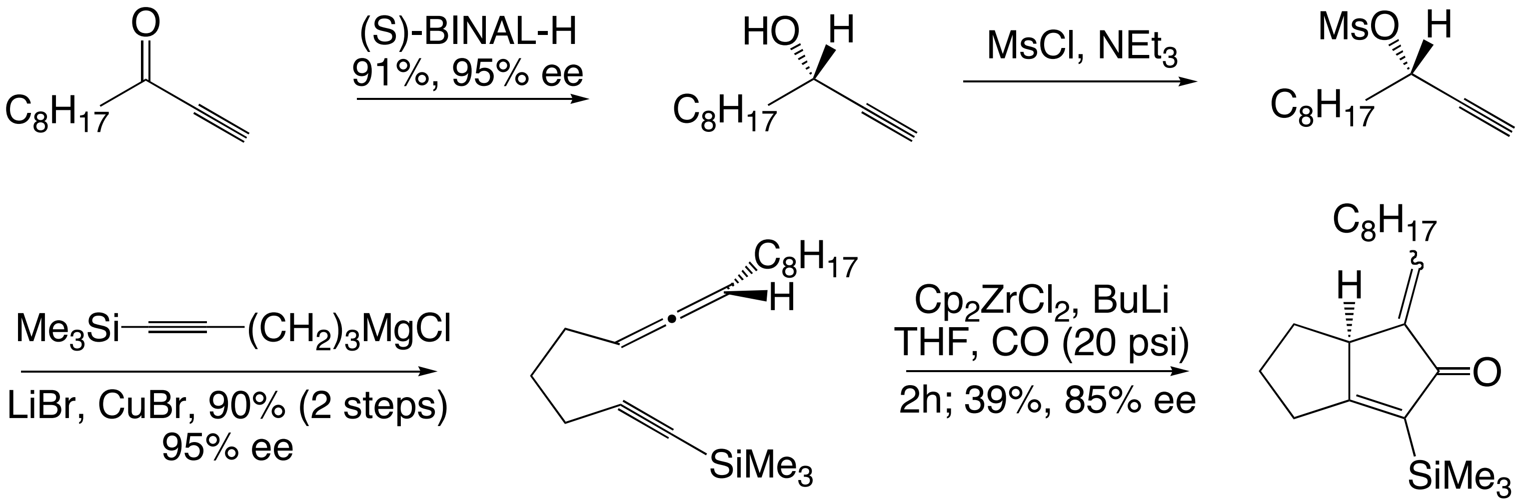
R_1 = H, R_2 = C_8H_{17}, X = O, 80%ee

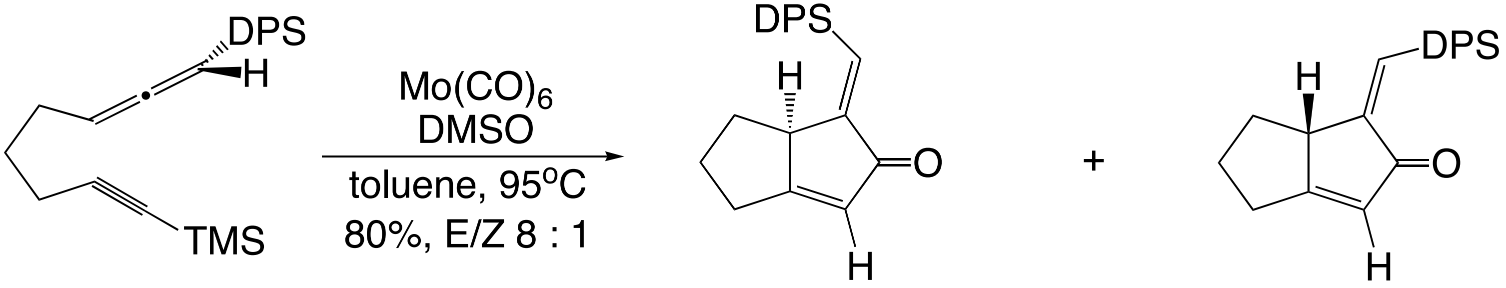
R_1 = Me, R_2 = Me, X = O, 80% ee

R_1 = Ph, R_2 = H, X = NPr, 81% ee

Urabe, H.; Takeda, T.; Hideura, D.; Sato, F. *J. Am. Chem. Soc*. **1997**, *119*, 11295-11305

Allenic Pauson-Khand Type Cycloaddition





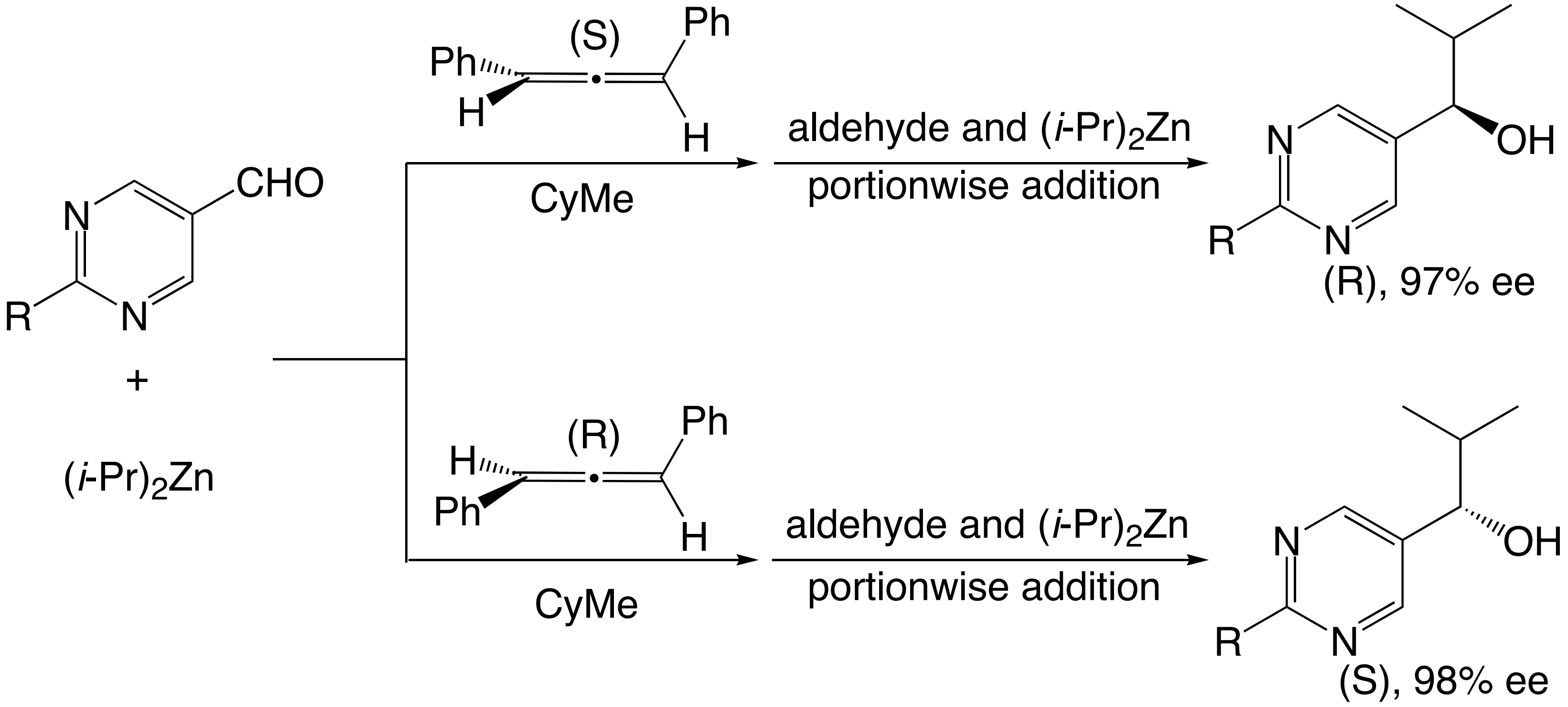
DPS = Me_2PhSi

95% ee

63% ee

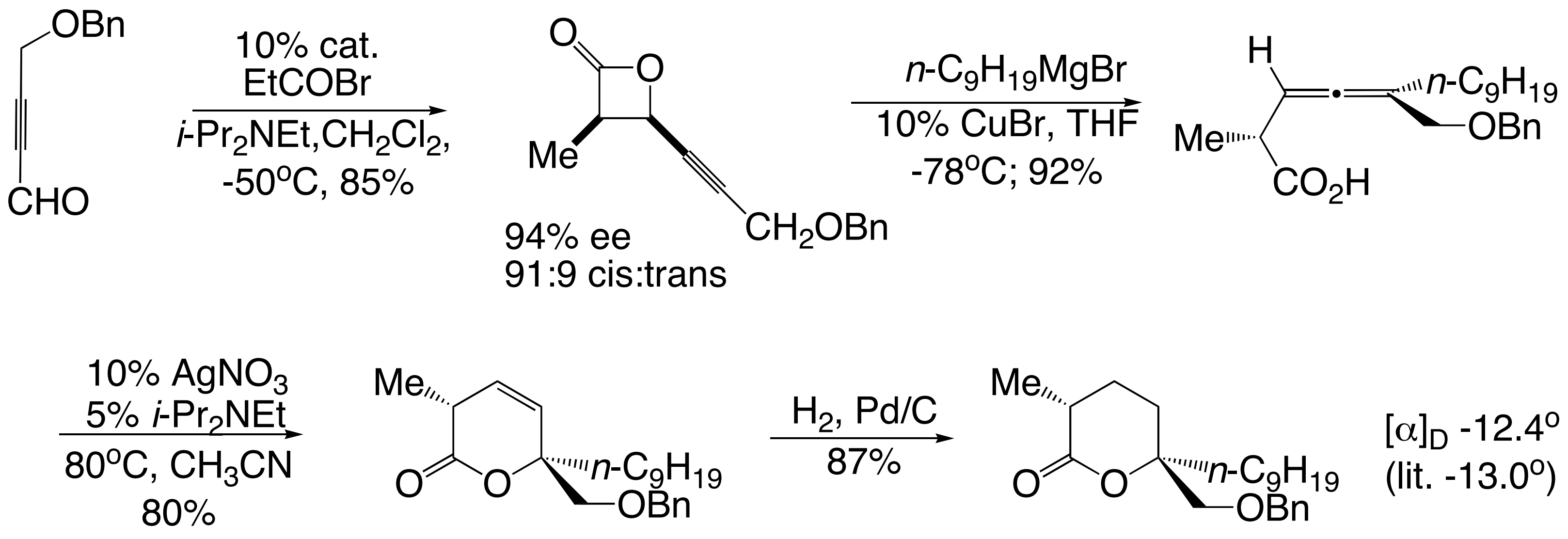
Brummond, K.M.; Kerekes, A.D.; Wan, H. *J. Org. Chem.* **2002**, *67*, 5156-5163

The Use of Chiral Allenes as Ligands for Catalysis



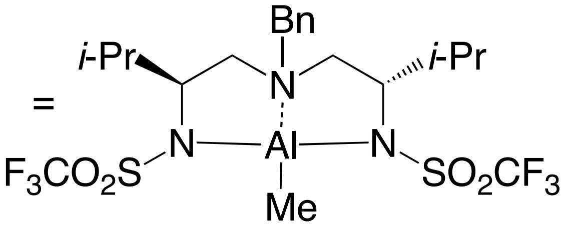
Sato, I.; Matsueda, Y.; Kadowaki, K.; Yonekubo, S.; Shibata, T.; Soai, K. *Helv. Chim. Acta*, **2002**, *85*, 3383 - 3387.

Synthesis of (-)-Malyngolide Using Chiral Allene



$[\alpha]_D$ -12.4°
(lit. -13.0°)

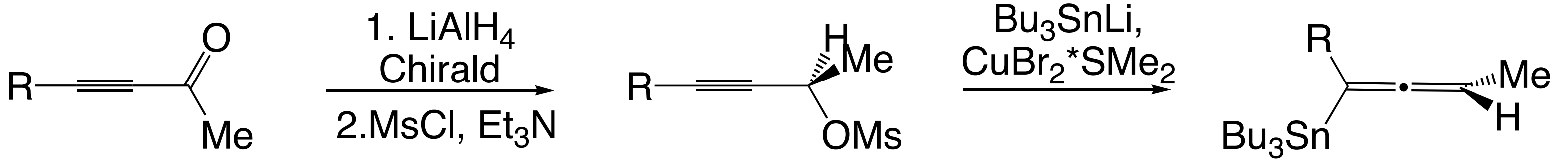
Catalyst =

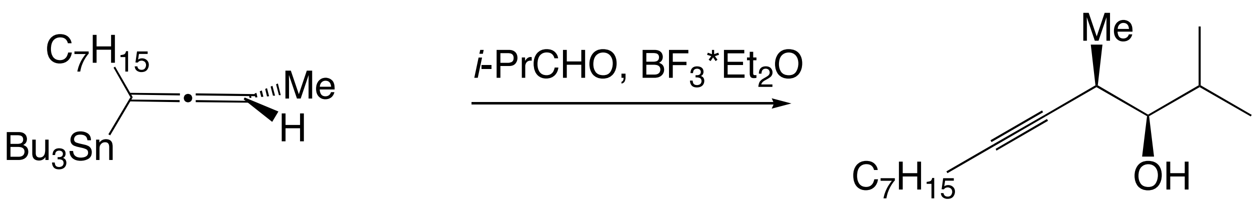


(-)-malyngolide
naturally occuring
antibiotic
94% ee, 100% de
54% overall yield

Wan, Z.; Nelson, S.G. *J. Am. Chem. Soc*. **2000**, *122*, 10470-10471

Chiral Allenic Stannanes: Preparation

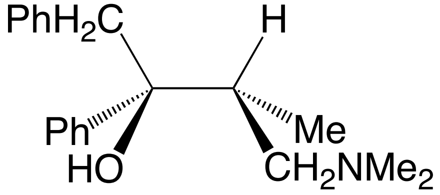




> 99% syn

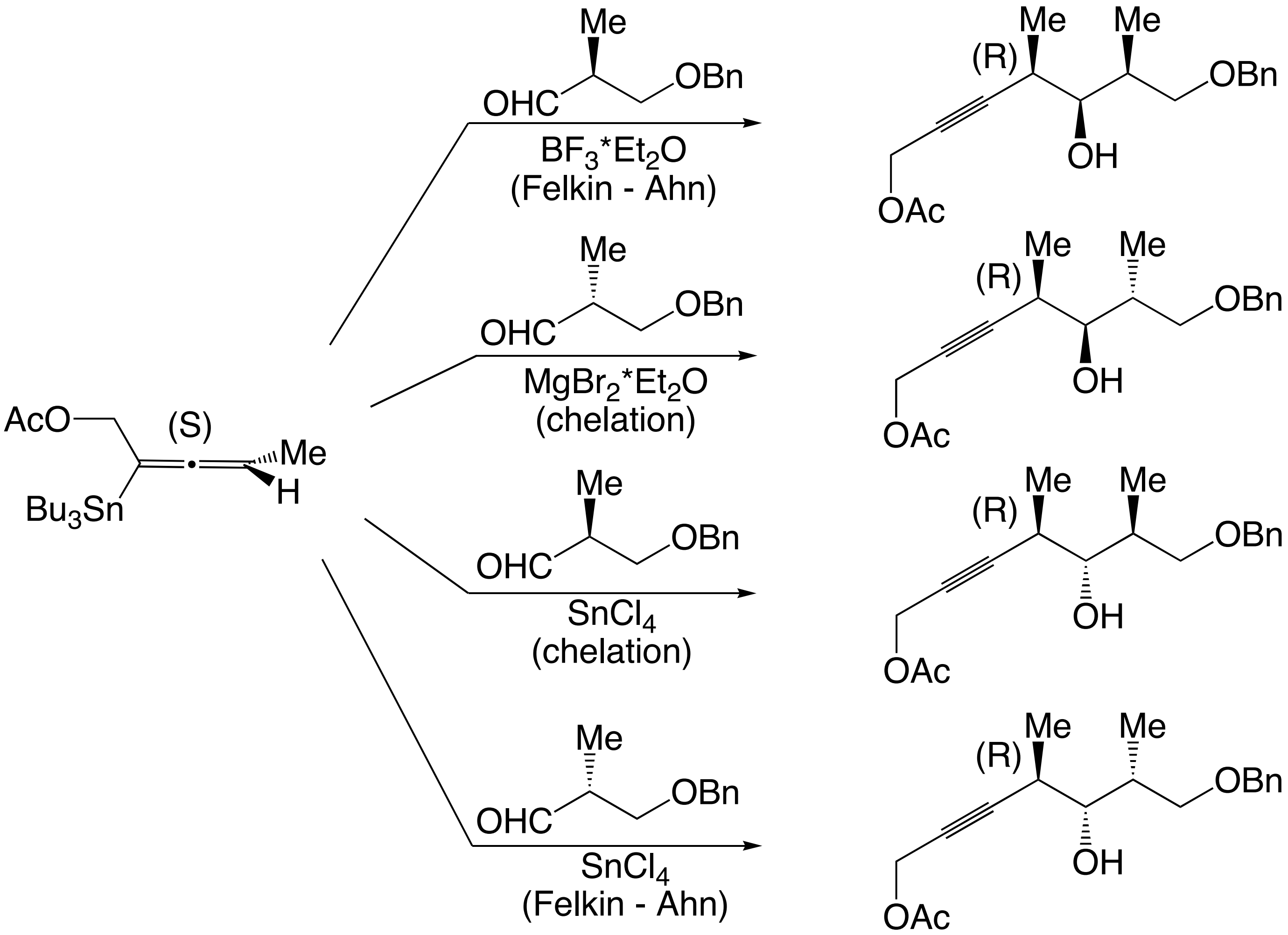
Chirald aka
Darvon alcohol

=



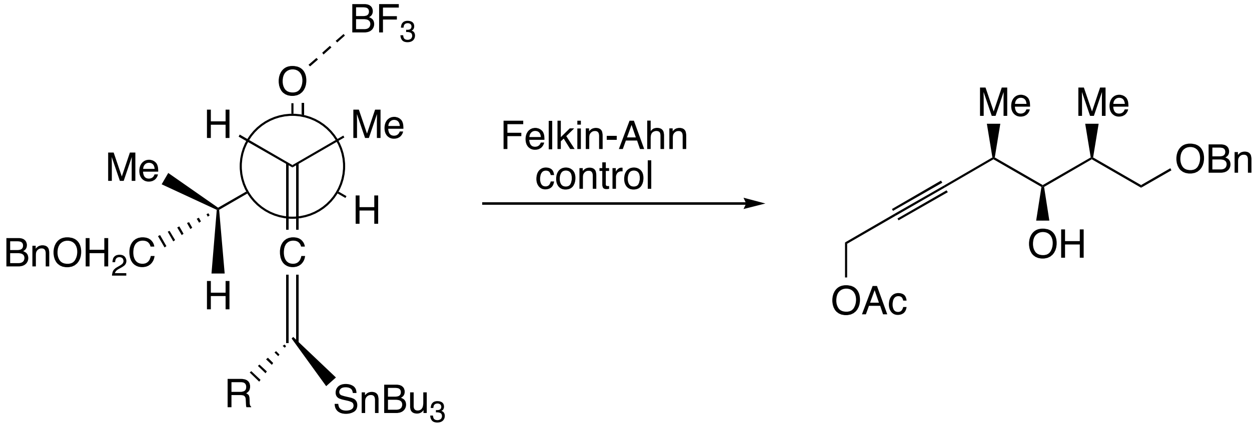
Marshall, J.A.; Wang, X.-j.; *J. Org. Chem.* **1991**, *56*, 3211

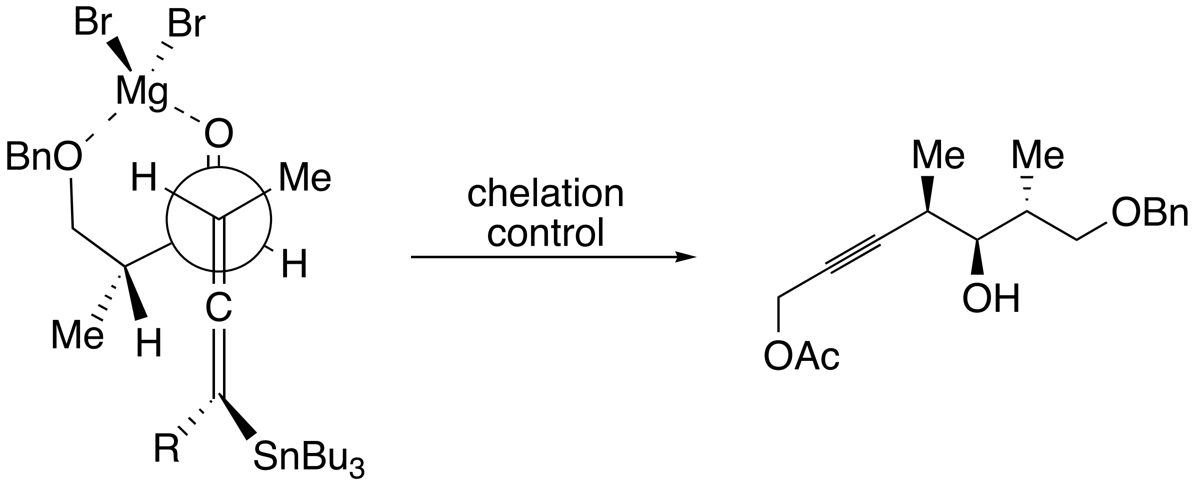
Chiral Allenic Stannanes: Preparation of Four Possible Naturally Occurring Chiral Triads



Marshall, J.A.; Perkins, J.F.; Wolf, M.A. *J. Org. Chem.* **1995**, *60*, 5556

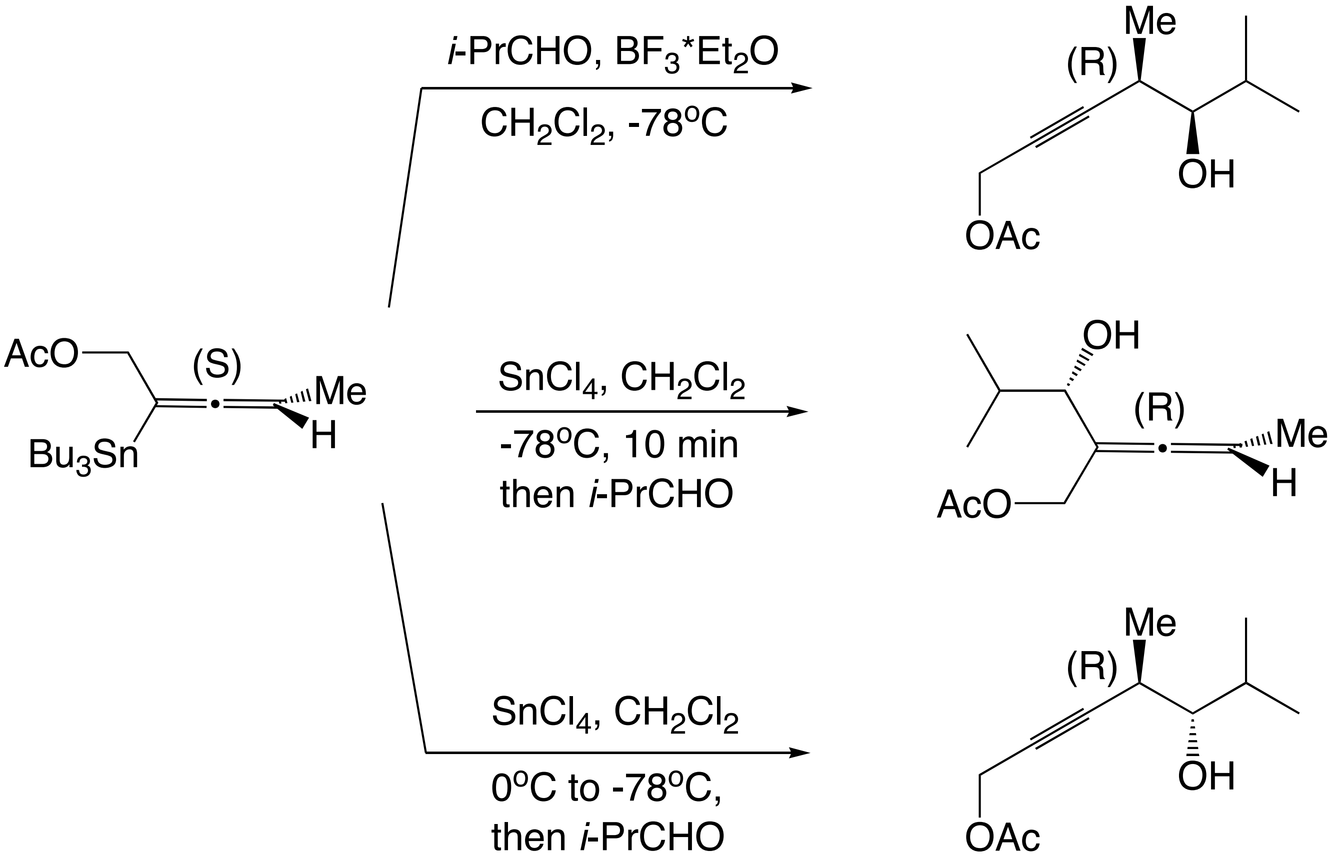
Mechanism for *syn,syn*- and *syn,anti*- Products Formation





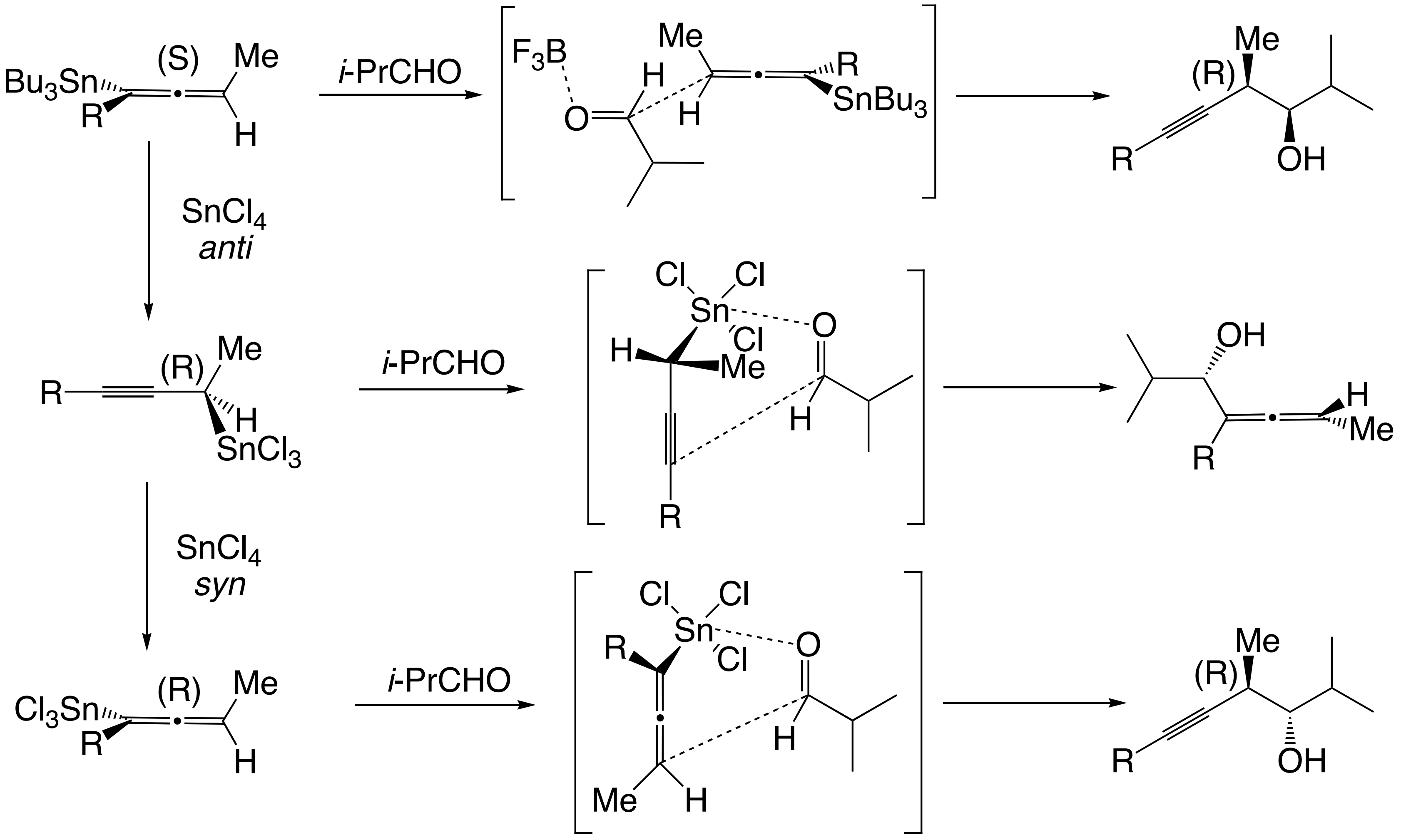
Marshall, J.A.; Wang, X.-j.; *J. Org. Chem.* **1992**, *57*, 1242

Transmetallations with $SnCl_4$



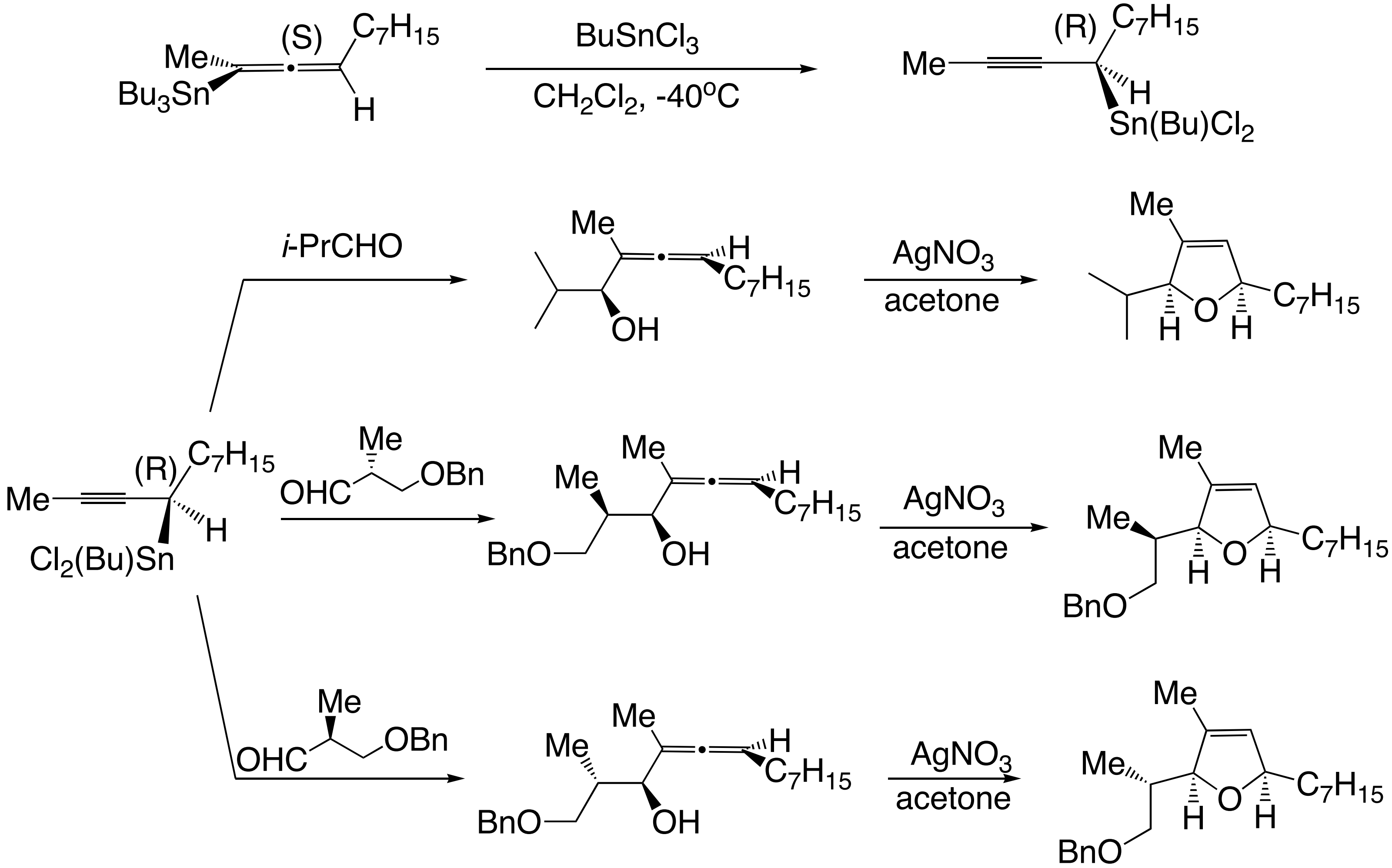
Marshall, J.A.; Perkins, J.F. *J. Org. Chem.* **1994**, *59*, 3509

Mechanism for $SnCl_4$ Reactions



Marshall, J.A.; Perkins, J.F. *J. Org. Chem.* **1994**, *59*, 3509

The Use of Propargylic Stannanes



Marshall, J.A.; Yu, R.H.; Perkins, J.F. *J. Org. Chem.* **1995**, *60*, 5550

Conclusions

- Axially chiral allenes are very diverse and interesting synthetically useful class of compounds. Numerous chiral allenes can be found in nature.
- There are many effective methods of nonracemic chiral allene preparation. Only a few effective asymmetric catalytic reactions are known.
- Allenes are successfully used in many synthetic transformations, but rarely exploited as ligands for catalytic asymmetric reactions. They have been extensively used in natural product synthesis. Naturally occurring chiral allenes also have been synthesized.

Acknowledgements

My sincere and warm gratitude to:

- Prof. William D. Wulff
- Prof. Babak Borhan
- Laboratory coworkers, especially Victor Prutyanov, Vijay Gopalsamuthiram, and Keith Korthals
- Banibrata Ghosh (Bani)