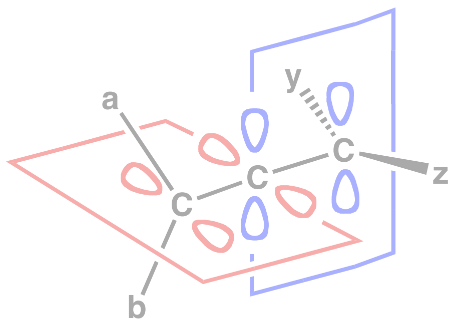
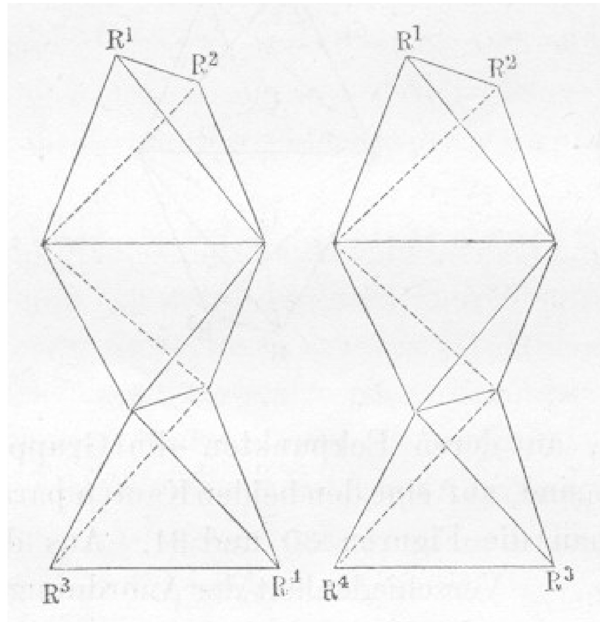
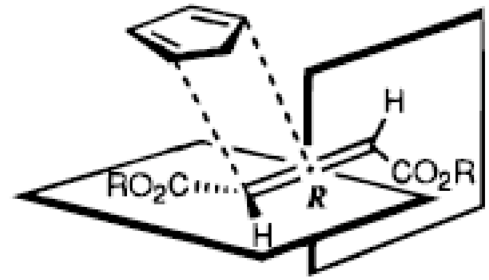
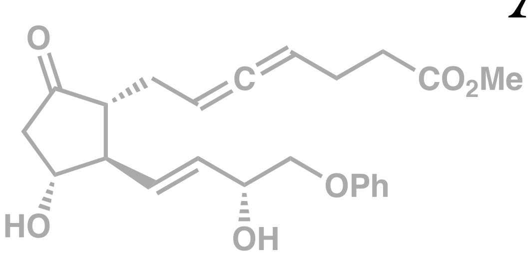


Orthogonal Bonding





Enantioselective Synthesis of Axial Chiral Allenes

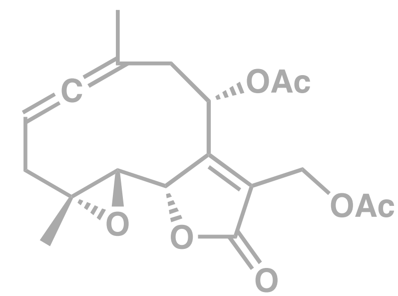


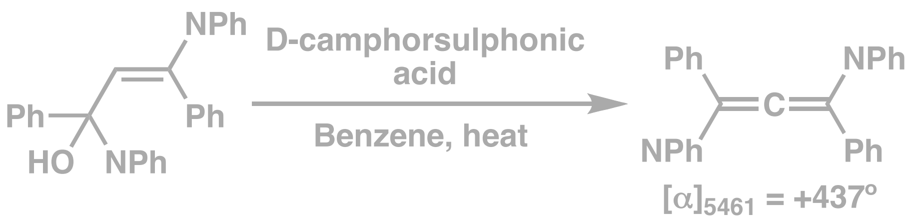
Andrew M. Harned

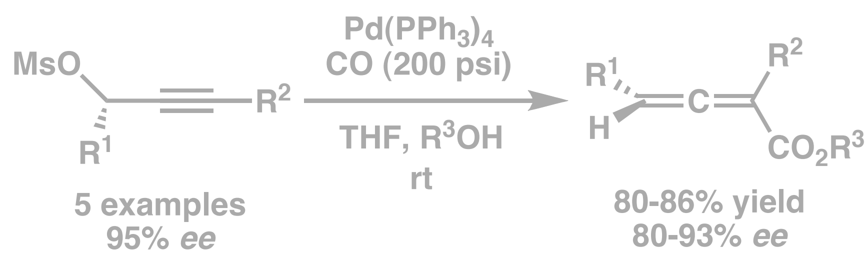
Monday, May 1, 2006

8 pm

147 Noyes







Axial Chiral Allenes: Useful Curiosities

1) The basics of Allenes and Axial Chirality

a) A brief history of allenes
b) Spectroscopy
c) Types of chiral allenes
d) General axial chirality
e) Natural products with axial chiral allenes
f) Allenes as Pharmaceutical Agents

2) Methods of Synthesizing Axially Chiral Allenes

a) Propargyl alcohol derivatives
b) Elimination from allylic compounds
c) Stiochiometric chiral reagents
c) Kinetic resolution
d) Catalytic methods

3) Conclusions

General Allene Reviews:

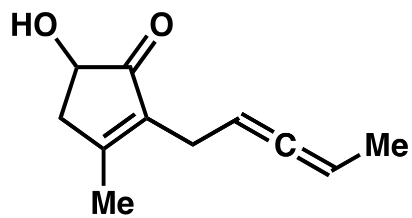
(General reviews) Taylor, D. R. *Chem. Rev.* **1967**, *67*, 317-359. Pasto, D. J. *Tetrahedron* **1984**, *40*, 2805-2827.
(Electrophilic additions to allenes) Smadja, W. *Chem. Rev.* **1983**, *83*, 263-320.
(Synthesis with organometallics) Krause, N.; Hoffmann-Röder, A. *Tetrahedron* **2004**, *60*, 11671-11694.
(Synthesis of allenic esters) Miesch, M. *Synthesis* **2004**, 746-752.
(Pd reactions of allenes) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Hkan, F. A. *Chem. Rev.* **2000**, *100*, 3067-3125.
(Selective reactions with transition metals) Hashmi, A. S. K. *Angew. Chem. Int. Ed.* **2000**, *39*, 3590-3593.
Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley & Sons: New York, 1984.
The Chemistry of the Allenes; Landor, S. R., Ed.; Academic Press: New York, 1982.
The Chemistry of Ketenes, Allenes and Related Compounds; Patai, S., Ed.; The Chemistry of Functional Groups; Wiley & Sons: New York, 1980.
Modern Allene Chemistry; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004.
Bruneau, C.; Renaud, J.-L. Allenes and cumulenes. In *Comprehensive Organic Functional Group Transformations II*; Katritzky, A. R., Taylor, R. J. K., Eds.; Elsevier: Oxford, 2005.

A Brief History of Allenes

1874-1875: Jacobus H. van't Hoff predicts the correct structures of alenes and cumulenes as well as their axial chirality (*La Chemie dans l'Espace*, Bazendijk: Rotterdam, 1875).

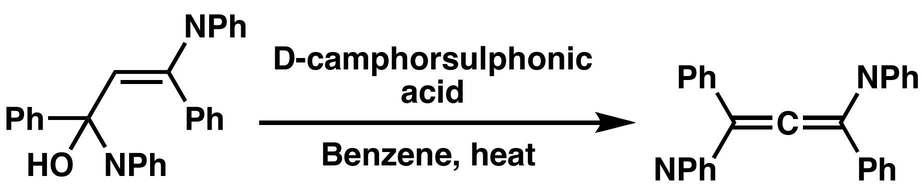
1887: In an attempt to prove the *nonexistence* of these compounds, **B. S. Burton** and **H. von Pechmann** report the first synthesis of an allene (*Ber. Dtsch. Chem. Ges.* **1887**, *20*, 145-149). The paucity of analytical techniques make it very difficult to distinguish from the corresponding alkynes, and the structure is not proven (E. R. H. Jones, G. H. Mansfield, M. L. H. Whiting *J. Chem. Soc.* **1954**, 3208-3212) for almost 70 years!

1924: First naturally occuring allene, pyrethrolone, characterized by **H. Staudinger** and **L. Ruzicka** (*Helv. Chim. Acta* **1924**, *7*, 177).



Pyrethrolone

1935: First axially chiral allene synthesized by **P. Maitland** and **W. H. Mills** (*Nature* **1935**, *135*, 994; *J. Chem. Soc.* **1936**, 987-998).



$[\alpha]_{5461} = +437^o$

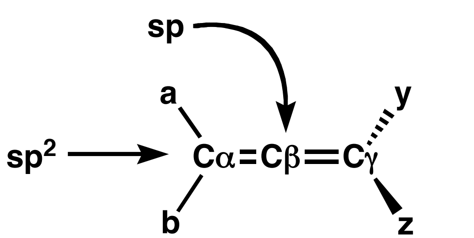
1952?: First cyclic allenes synthesized by **A. T. Blomquist, R. E. Burge, Jr.** and **A. C. Sucsy** (*J. Am. Chem. Soc.* **1952**, *74*, 3636-3642; *J. Am. Chem. Soc.* **1952**, *74*, 3643-47). Ring sizes above nine can be isolated. 1,2-Cyclooctadiene can be detected in small amounts at low temperatures. Ring sizes of seven or below cannot be isolated or detected. Their intermediacy has been determined through trapping/degradation studies. **M. Regitz** and coworkers have described a stable six membered cyclic allene, but is not a hydrocarbon (*Angew. Chem. Int. Ed.* **2000**, *39*, 1261-1263).

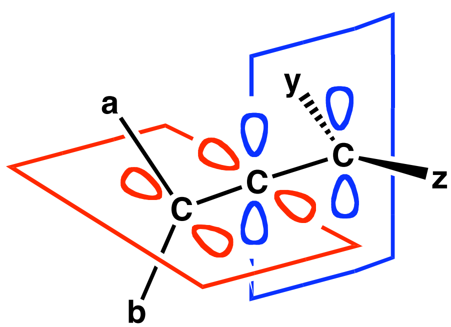
Structure and Spectroscopy of Allenes

IR Spectroscopy: The diagnostic stretch can be found at 2000-1900 cm^{-1} (C=C=C asymm. stretch) and is usually strong.
For comparison, alkynes are at 2260-2100 cm^{-1} and olefins are at 1690-1635 cm^{-1}.
Only other functional groups near this range are: diazo, cyanates, isocyanates, thiocyanates, isothiocyanates, and ketenes; but are typically at slightly higher wavenumbers.

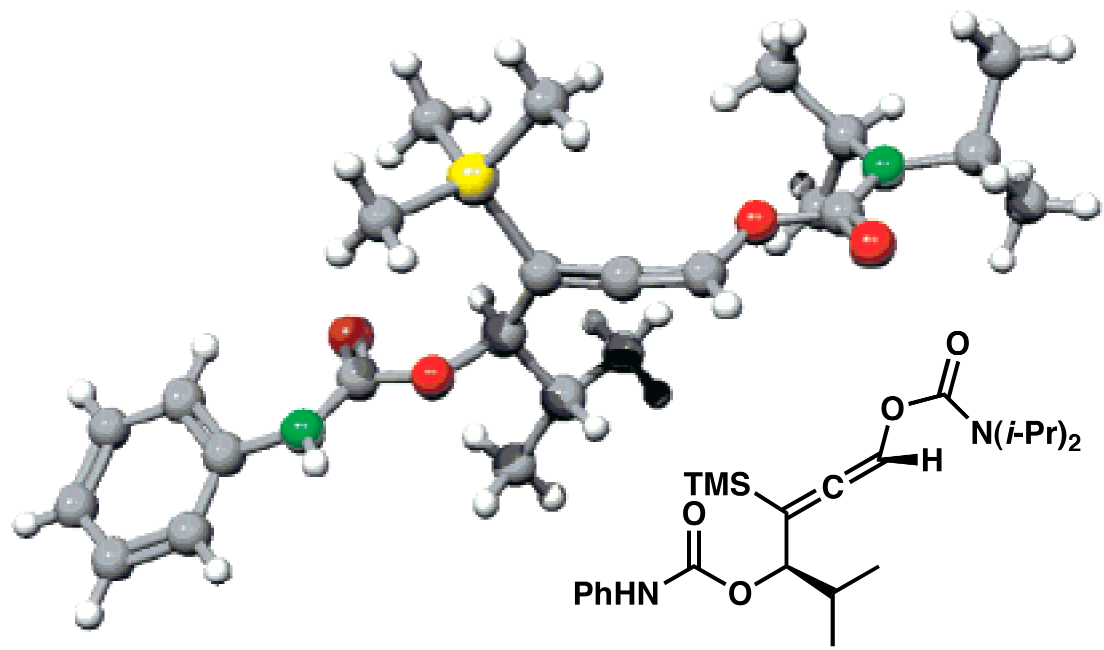
^{1}H NMR Spectroscopy: Typically in the same area as olefinic protons, but slightly upfield (~4.4 - 4.9 ppm).

^{13}C NMR Spectroscopy: Cα and Cγ are more upfield than typical olefin (~73 - 120 ppm).
Cβ is actually slightly more downfield than a ketone! (200-220 ppm)





Orthogonal Bonding



Schultz-Fademrecht, C.; Wibbeling, B.; Fröhlich, R.; Hoppe, D. *Org. Lett.* **2001**, *3*, 1221-1224.

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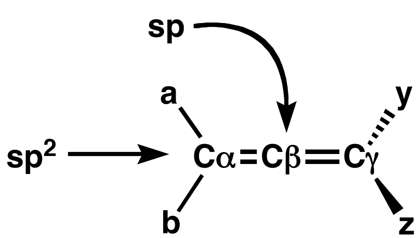
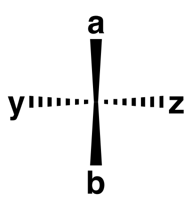
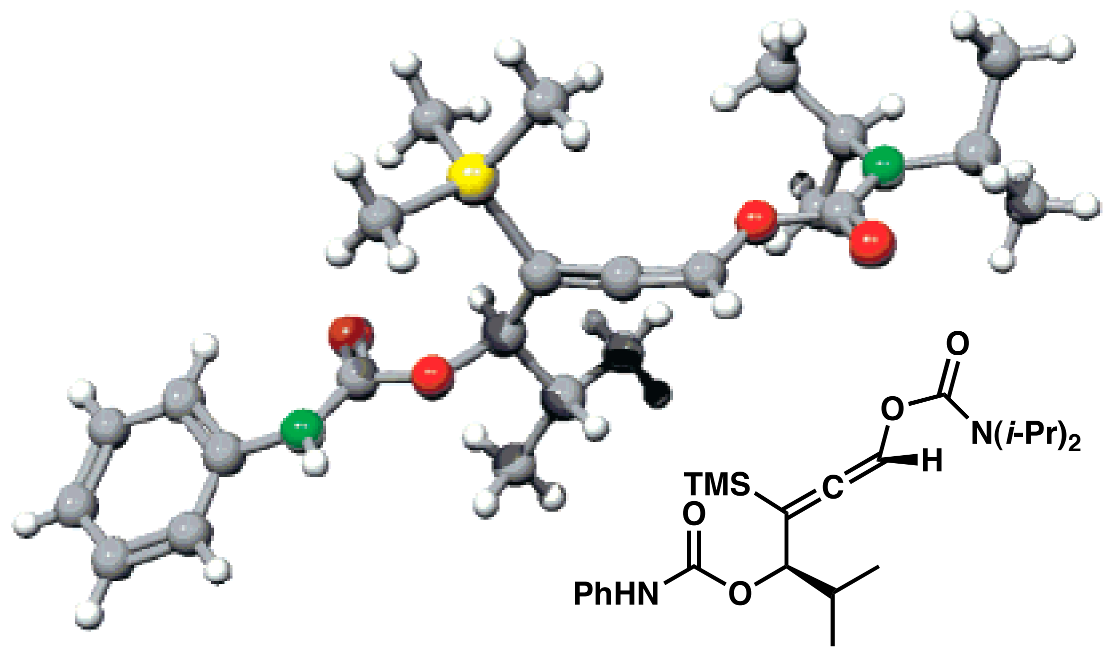




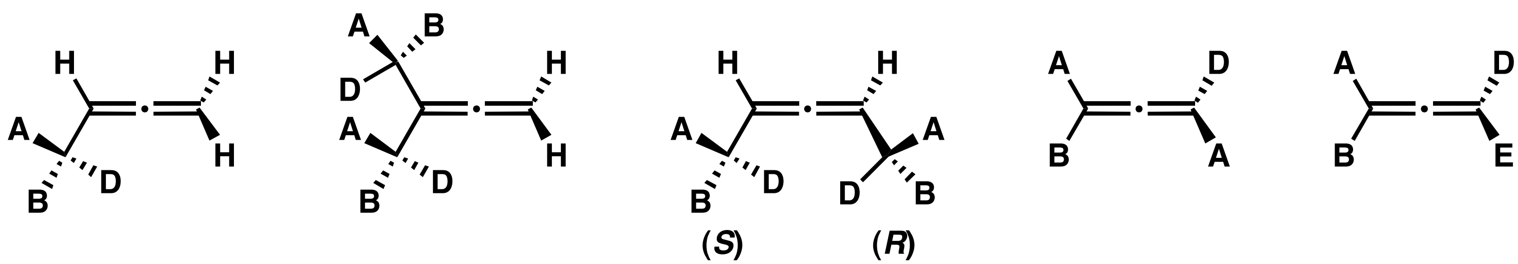
Orthogonal Bonding



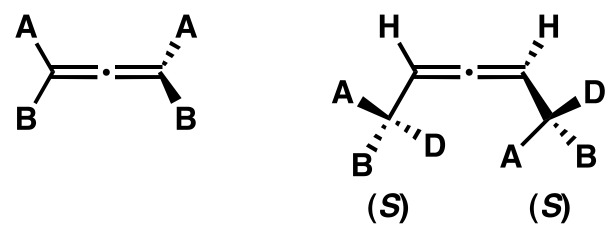
Schultz-Fademrecht, C.; Wibbeling, B.; Fröhlich, R.; Hoppe, D. *Org. Lett.* **2001**, *3*, 1221-1224.

Types of Chiral Allenes

Asymmetric allenes
(no element of symmetry)



Dissymmetric allene
(C_2 proper axis of rotation)



Chiral Allene Reviews: Rossi, R.; Diversi, P. *Synthesis* **1973**, 25-36. Runge, W. Stereochemistry of Allenes. In *The Chemistry of Allenes*; Landor, S. R., Ed.; Academic Press: New York, 1982; 580-678. Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley & Sons: New York, 1984, 1-8. Hoffmann-Röder, A.; Krause, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 2933-2935. Ohno, H.; Nagaoka, Y.; Tomioka, K. Enantioselective synthesis of Allenes. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; 141-181.

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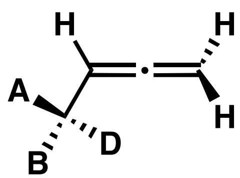
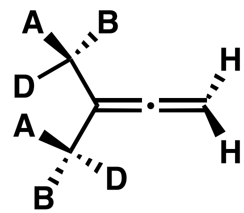
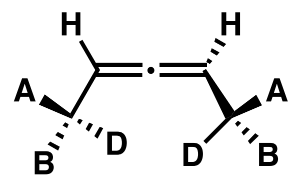
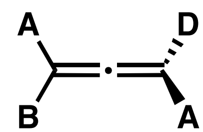


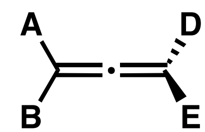


Not covered
Allene is not stereogenic

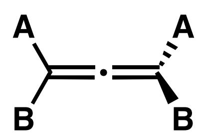


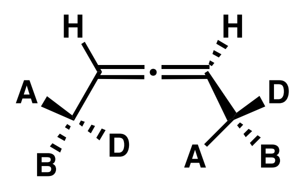
(*S*) (*R*)





Dissymmetric allene
(C_2 proper axis of rotation)





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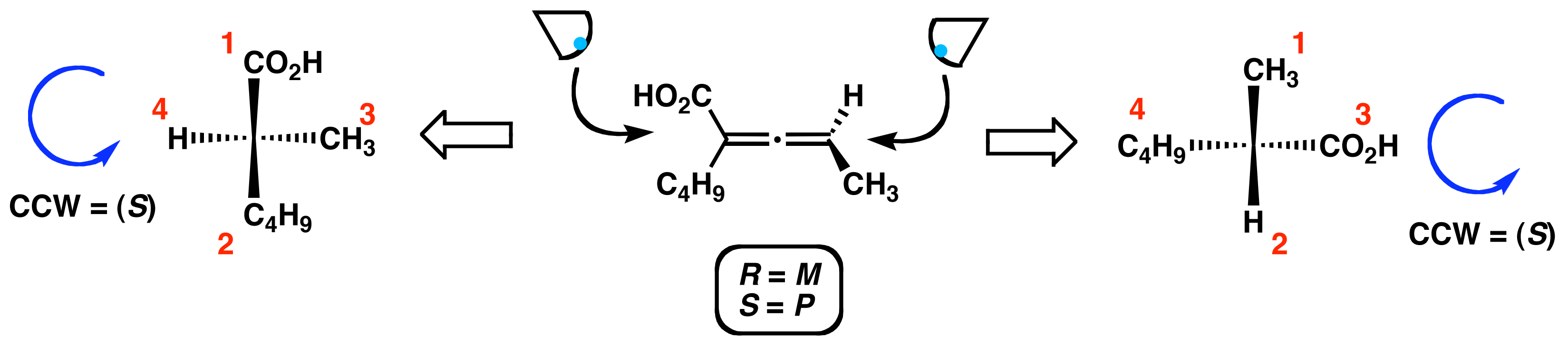
General Axial Chirality

Determining configuration



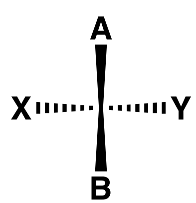
Predicting absolution configuration and magnitude of rotation (Lowe-Brewster Rule)

J. H. Brewster (*Topics in Stereochemistry*, 1967, *2*, 1-72):

Through mathematical models, the actual optical rotation of optically pure chiral allenes can be calculated. At one time this was a very common method to determine approximate optical purity (i.e. % ee). Not very amenable to more complicated systems, and has now been supplanted by GC, HPLC, and NMR methods.

G. Lowe (*J. Chem. Soc., Chem. Commun.*, 1965, 411-413):

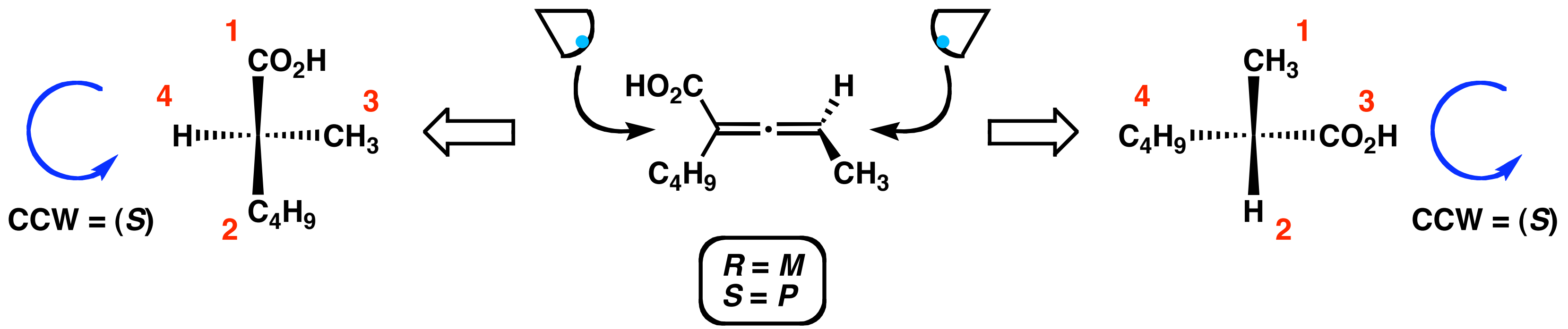
The absolute configuration can be assigned based on the sign (+ or -) of rotation. From this, you can then assign *S* or *R*.



Most polarizable group **A** is placed at the top. If **Y** is more polarizable than **X**, the allene will be dextrorotatory (+). If **X** is more polarizable than **Y**, the allene will be levorotatory (-).

General Axial Chirality

Determining configuration



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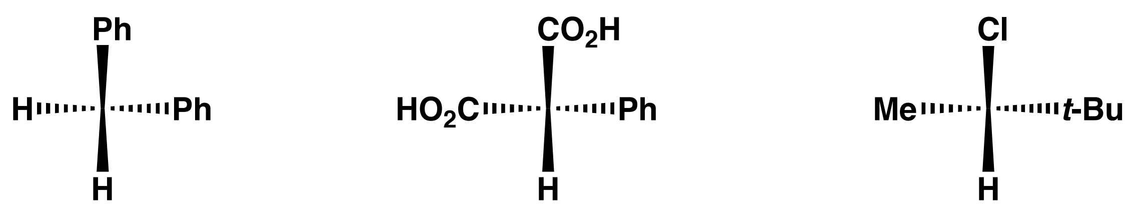
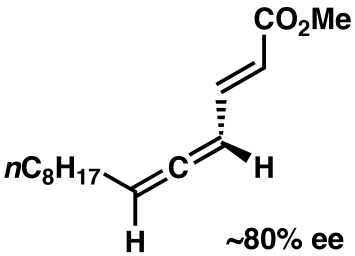
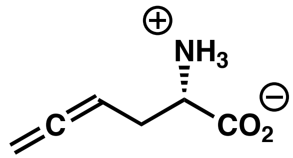


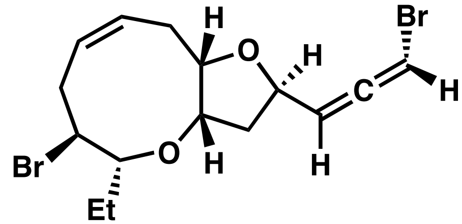
Allenes as Natural Products

Not just curiosities anymore

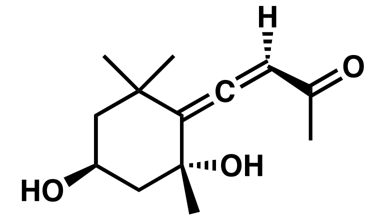


Insect Pheromone

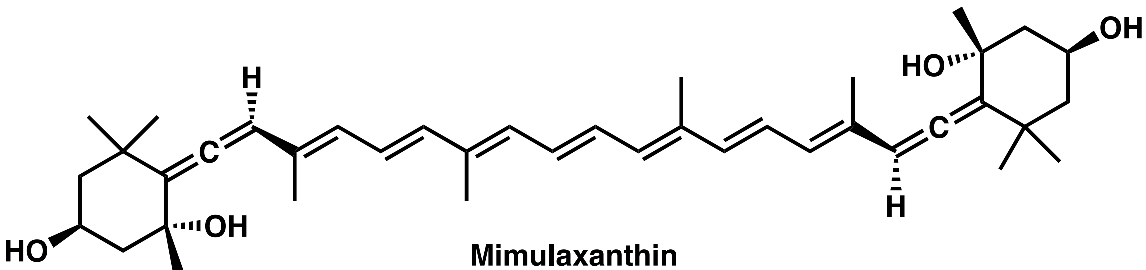




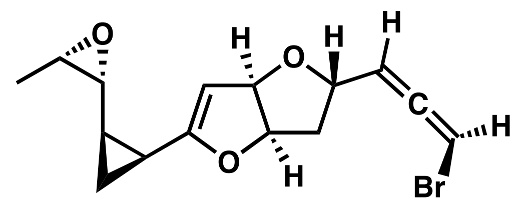
Isolaurallene



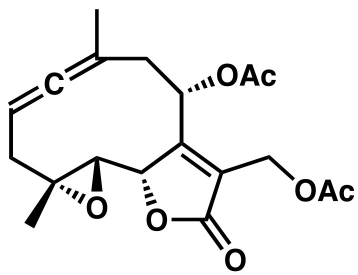
"Grasshopper Ketone"

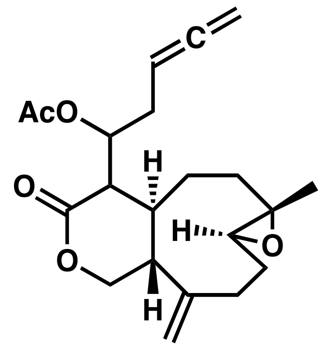


Mimulaxanthin



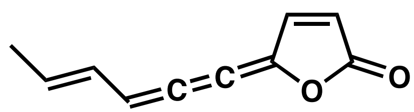
Okamurallene

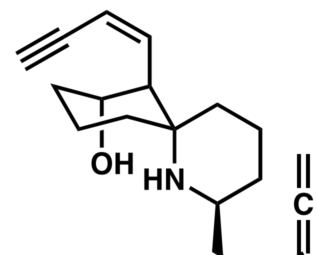




Acalycixeniolide E

Anti-angiogenic





Isodihydrohistrionicotixin

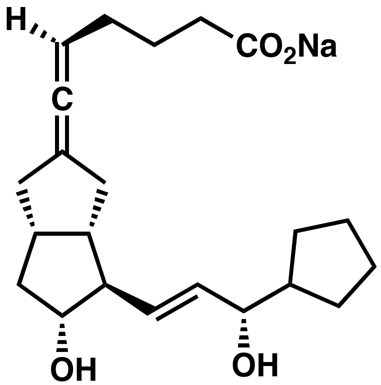
Nicotine acetylcholine receptor active

About 150 Natural Allenes are known. Most are chiral but not necessarily enantiopure.

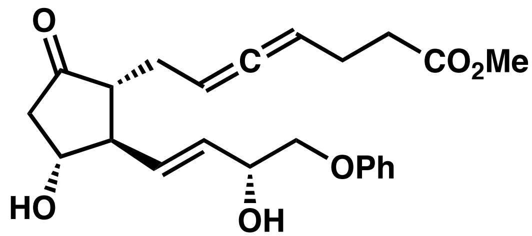
Krause, N.; Hoffmann-Röder, A. Allenic Natural Products and Pharmaceuticals. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; 997-1039.

Allenes as Pharmaceutical Agents

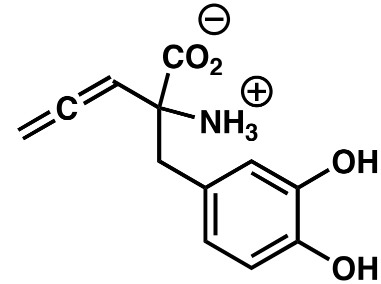
Not just curiosities anymore



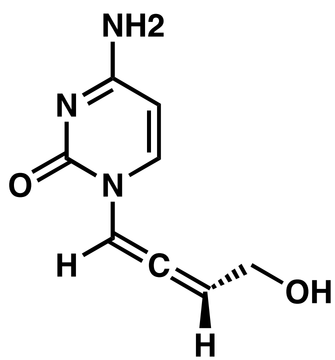
Anti-thrombotic agent



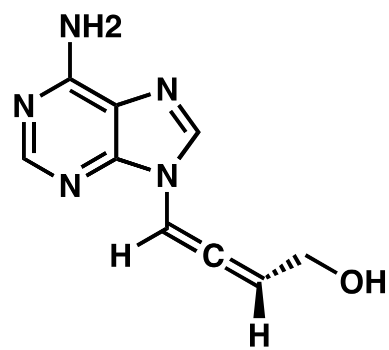
Enprostil
Gastric acid inhibitor



Vitamin B_6-dependent decarboxylase inhibitor (suicide substrate)

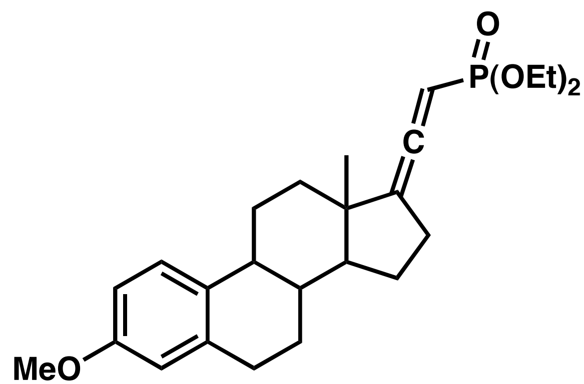


(*R*)-Cytallene



(*R*)-Adenallene

Inhibitors of HIV and Hepatitis B replication



Sterol biosynthesis inhibitor
(AIDS-related pathogen)

Krause, N.; Hoffmann-Röder, A. Allenic Natural Products and Pharmaceuticals. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; 997-1039.

Chirality Transfer from Propargylic Alcohols

A) Copper-Mediated Methods

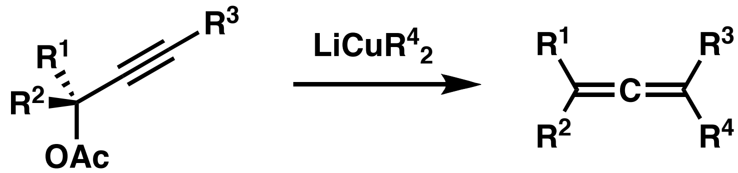
Alkylation
Halogenation

B) Rearrangements

D) S_N2' reactions

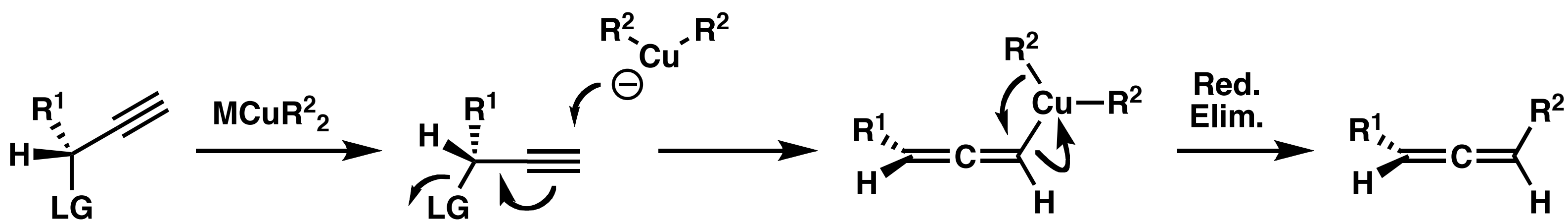
C) Palladium (0)-Mediated Methods

The Beginnings



Rona, P.; Crabbé, P. *J. Am. Chem. Soc.* **1969**, *91*, 3289-3292.

***anti*-elimination**

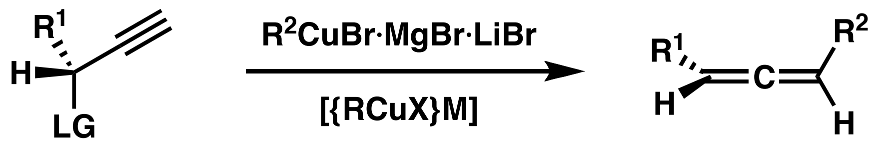


Luche, J.-L.; Barreiro, E.; Dollat, J.-M.; Crabbé, P. *Tetrahedron Lett.* **1975**, 4615.
Dollat, J.-M.; Luche, J.-L.; Crabbé, P. *J. Chem. Soc., Chem. Comm.* **1977**, 761-762.

Many studies with steriodal stystems. Complications due to racemization of product by dialkyl cuprates.

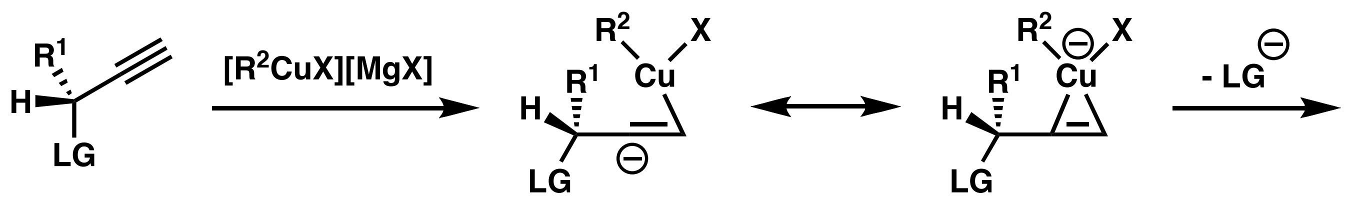
Proparglyic Esters

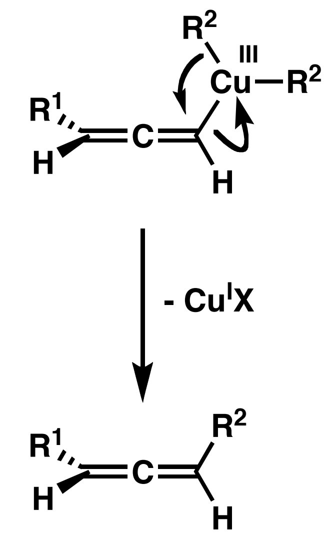
nonsteriodal, acyclic allenes

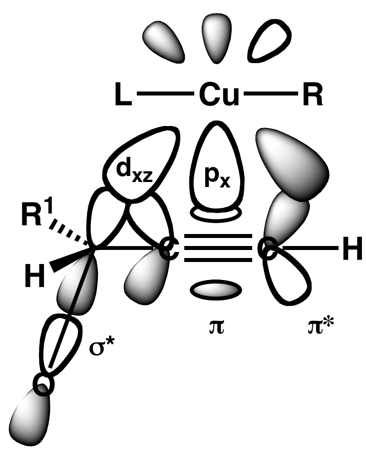


R^1 = Ph, *t*-Bu, octyl, Me
LG = OS(O)Me or OSO_2Me

70-96% yield
>98% *anti*-selectivity



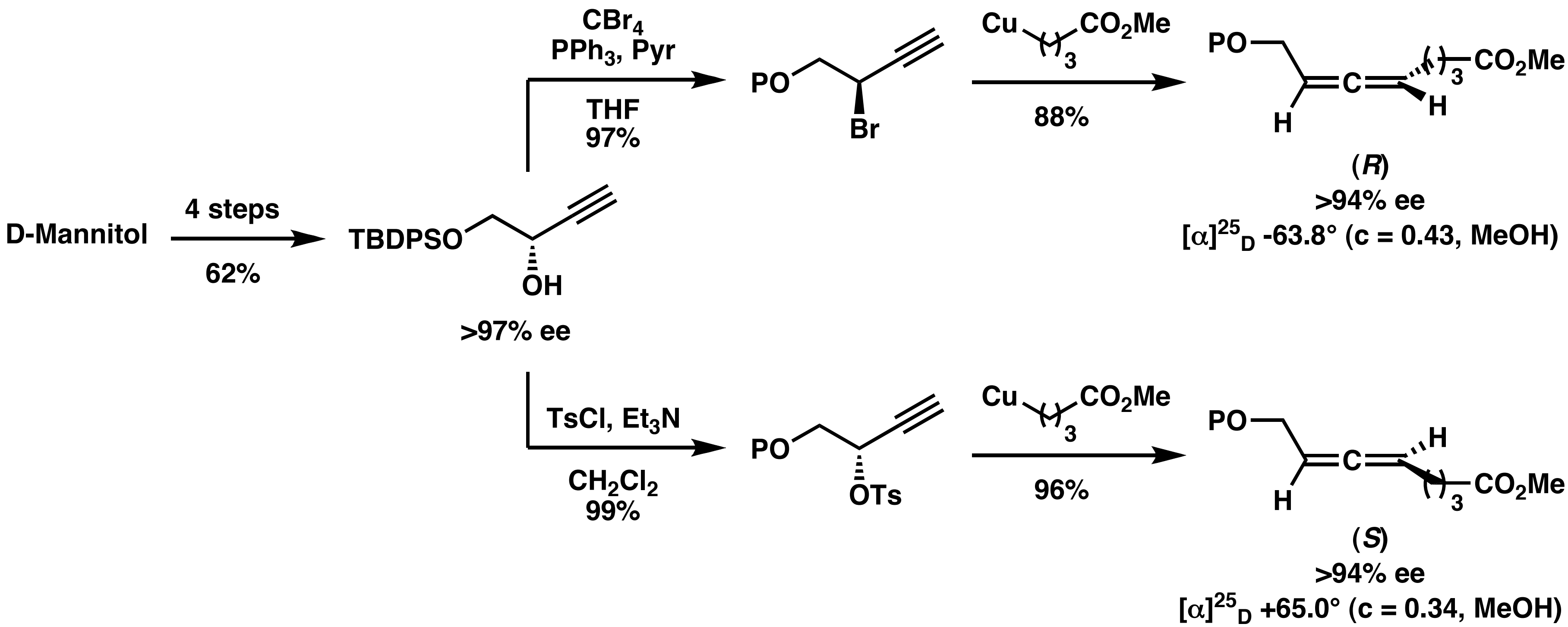


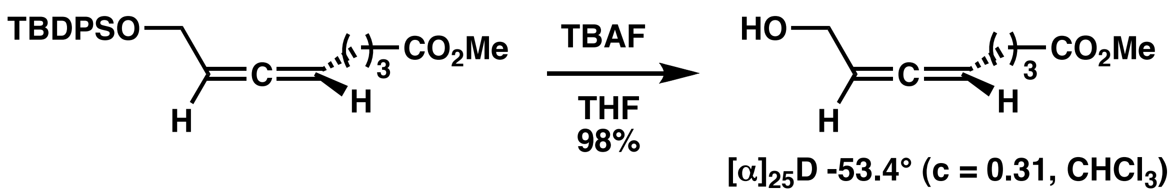


Corey *Tetrahedron Lett.* **1984**, *25*, 3063-3066

Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1989**, *54*, 3726-3730.

Proparglyic Esters

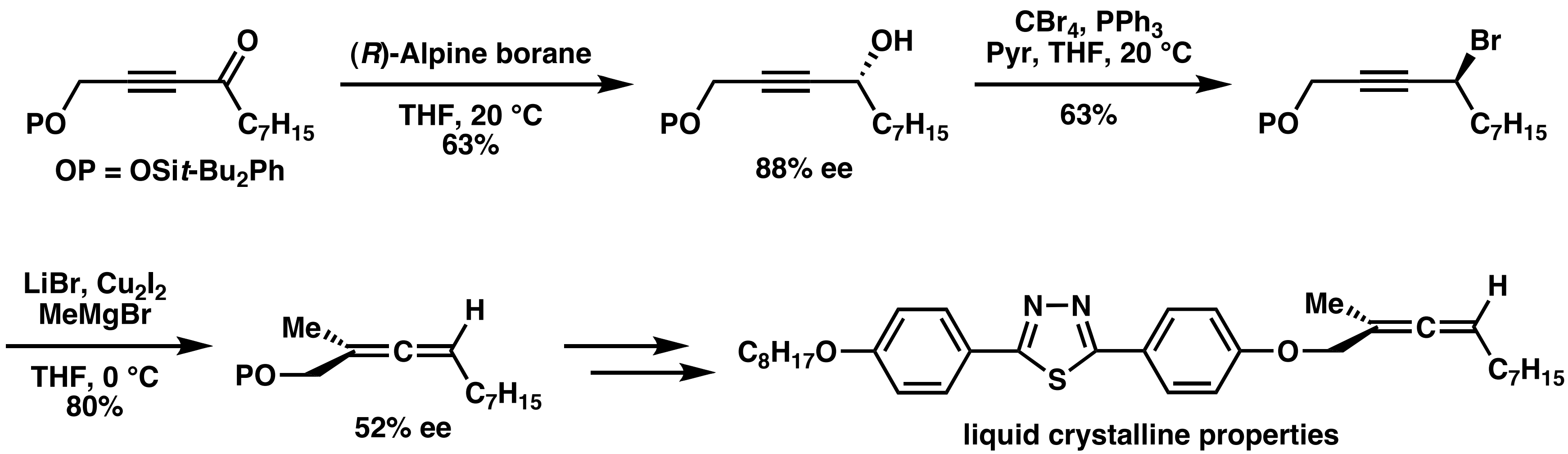




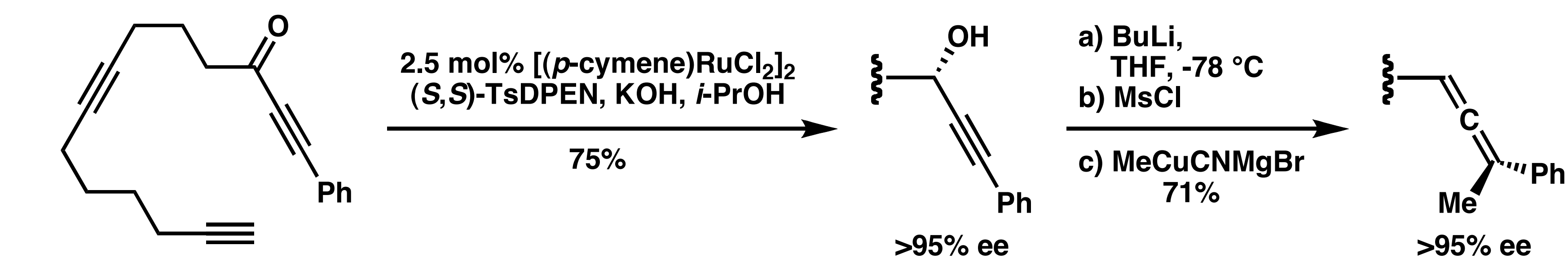
Antifungal constituent from
Sapium japonicum
lit. [α]$_{12}$D -51.3° (c 0.94, $CHCl_3$)

Gooding, O. W.; Beard, C. C.; Jackson, D. Y.; Wren, D. L.; Cooper, G. F. *J. Org. Chem.* **1991**, *56*, 1083-1088.

Enantioenriched Propargyl Alcohols

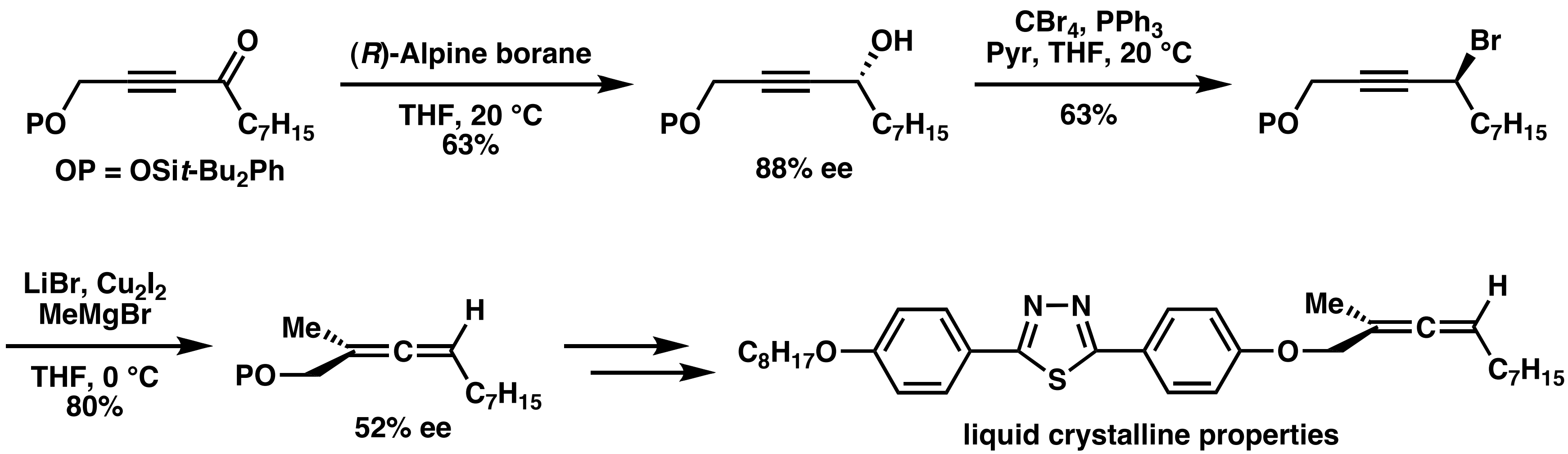


Zab, K.; Kruth, H.; Tschierske, C. *J. Chem. Soc., Chem. Comm.* **1996**, 977-978.

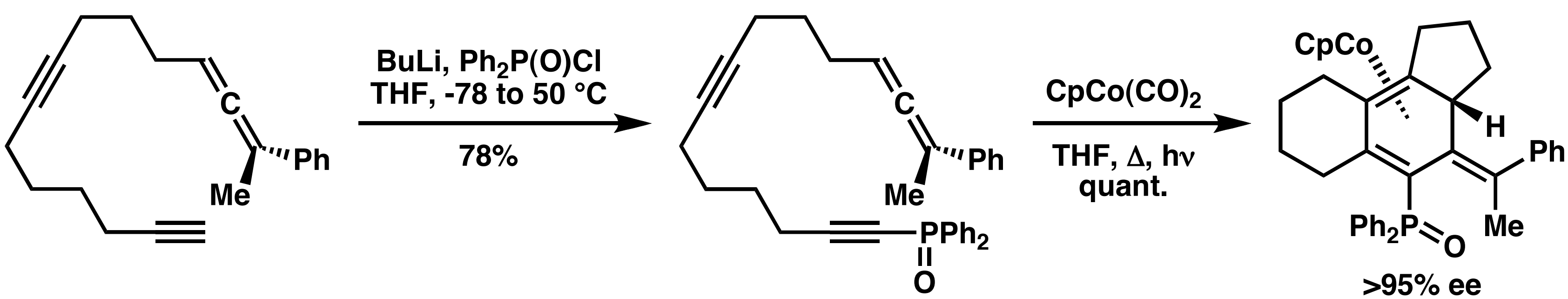


Buisine, O.; Aubert, C.; Malacria, M. *Synthesis* **2000**, 985-989.

Enantioenriched Propargyl Alcohols

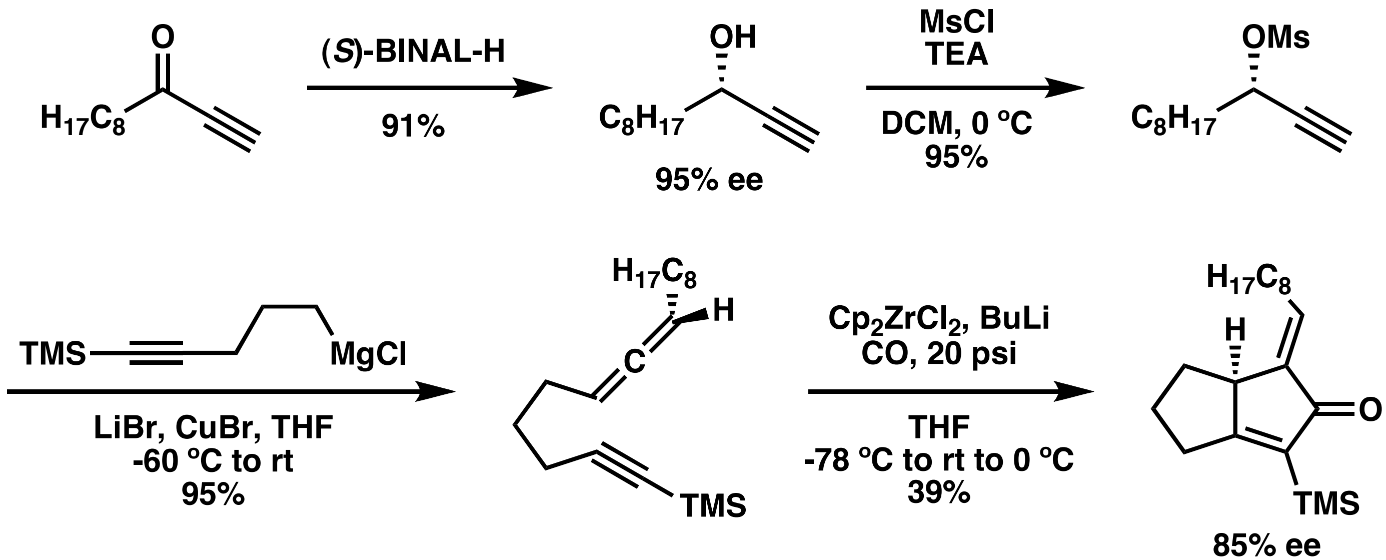


Zab, K.; Kruth, H.; Tschierske, C. *J. Chem. Soc., Chem. Comm.* **1996**, 977-978.

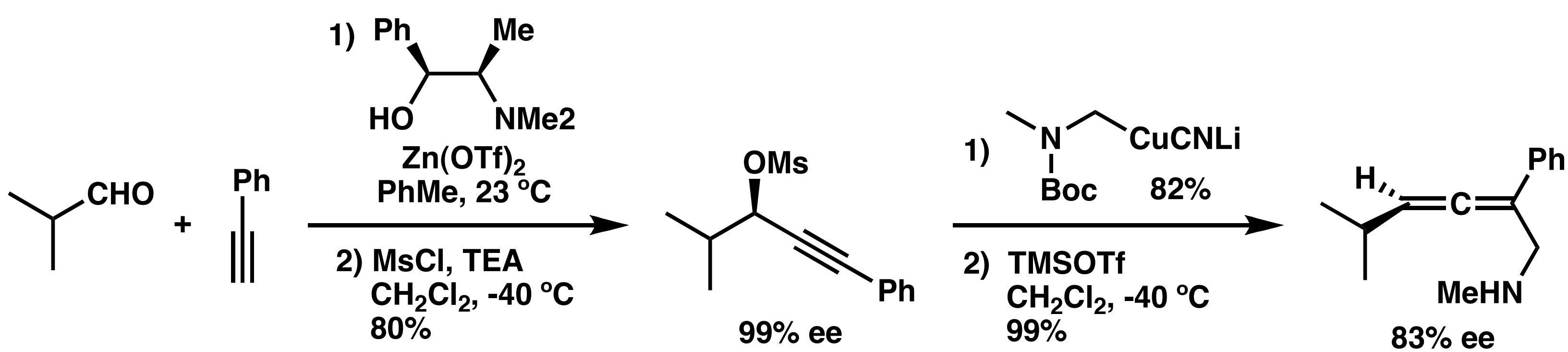


Buisine, O.; Aubert, C.; Malacria, M. *Synthesis* **2000**, 985-989.

Enantioenriched Propargyl Alcohols

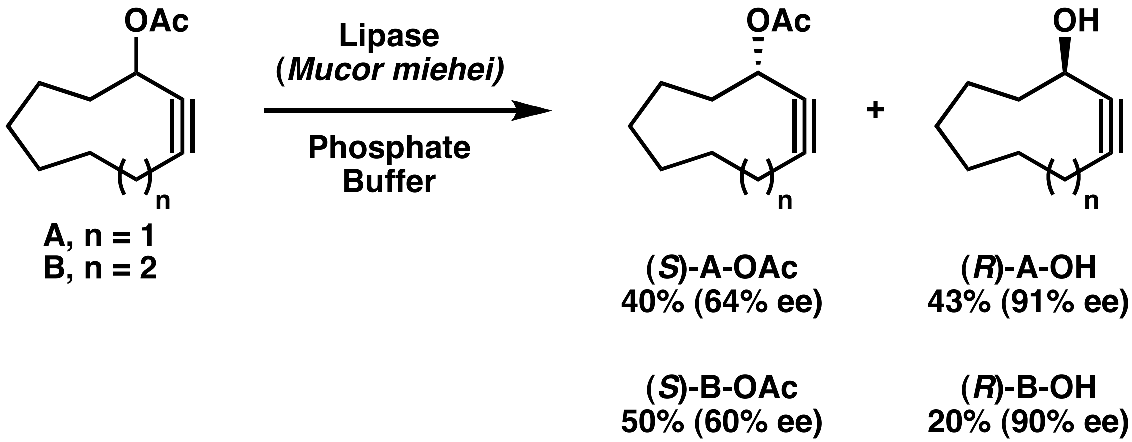


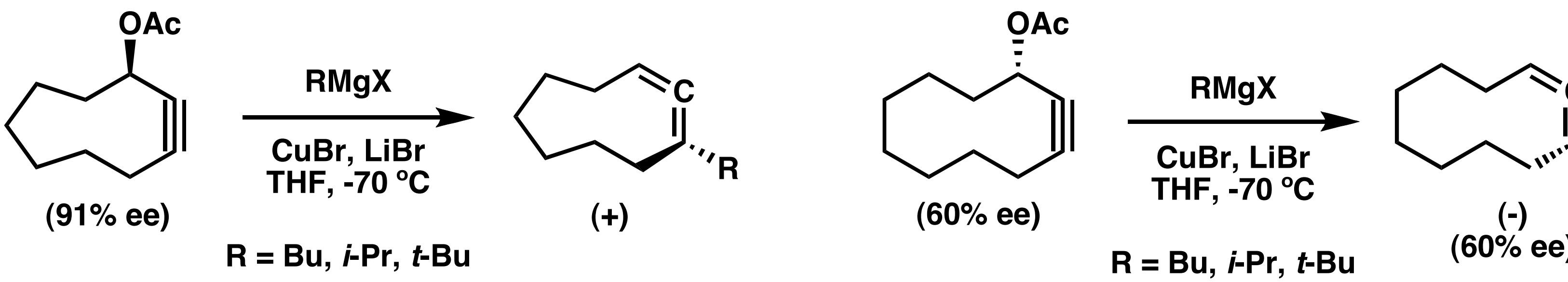
Brummond, K. M.; Kerekes, A. D.; Wan, H. *J. Org. Chem.* **2002**, *67*, 5156-5163.



Dieter, R. K.; Yu, H. *Org. Lett.* **2001**, *3*, 3855-3858.

Enantioenriched Cyclic Allenes

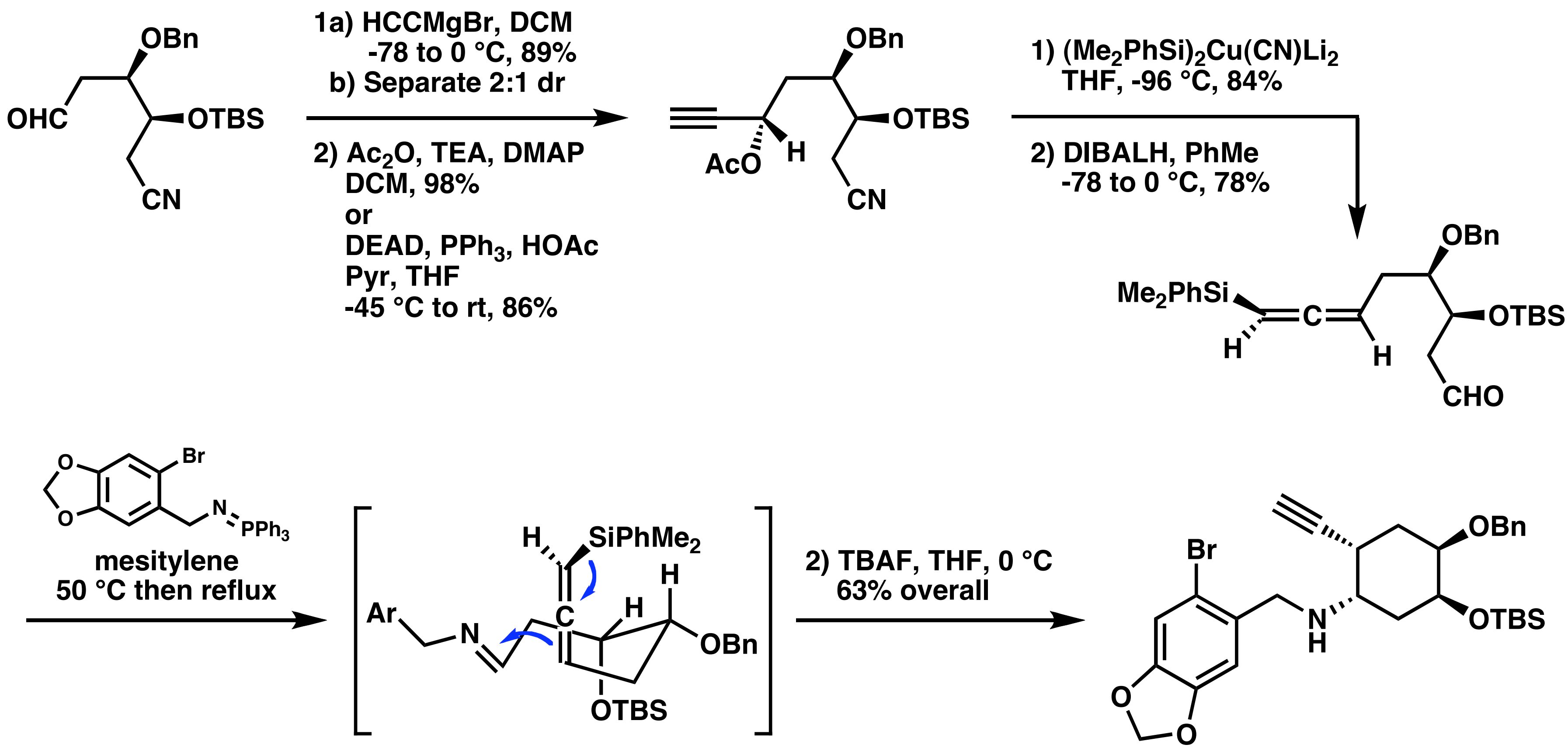


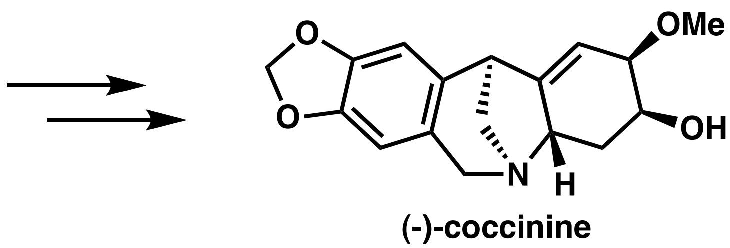


% ee determined for R = Bu, *t*-Bu by GC,
Enantioseparation not achieved for others

Zelder, C.; Krause, N. *Eur. J. Org. Chem.* **2004**, 3968-3971.

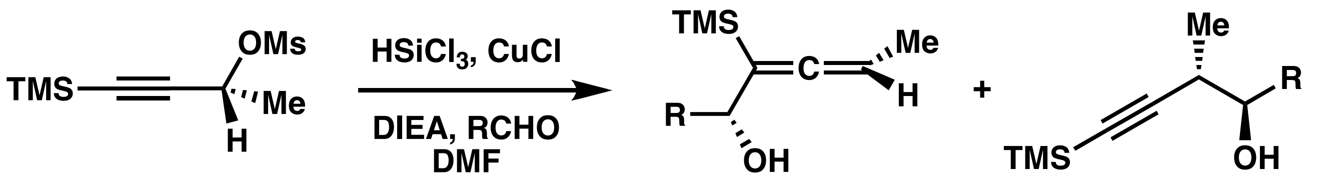
Silyl Cuprates





Jin, J.; Weinreb, S. M. *J. Am. Chem. Soc.* **1997**, *119*, 2050-2051.
For an alternative approach to allenyl silanes, see: Guintchin, B. K.; Bienz, S. *Organometallics* **2004**, *23*, 4944-4951.

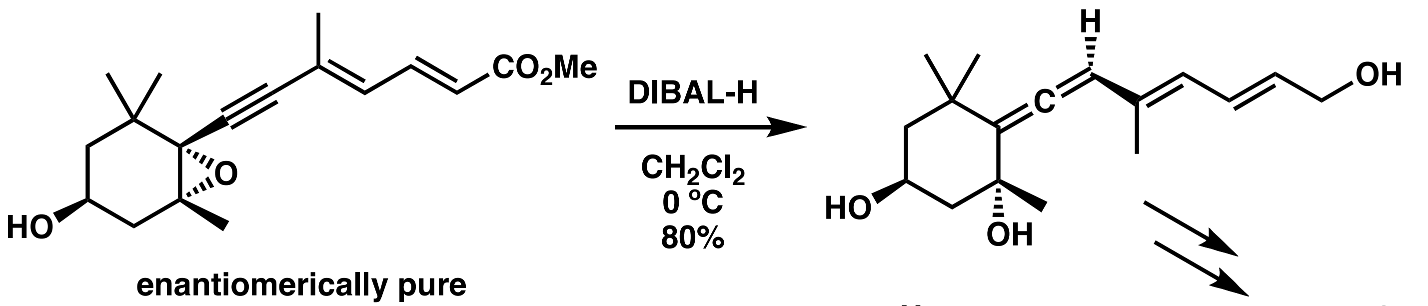
Propargylic Silanes

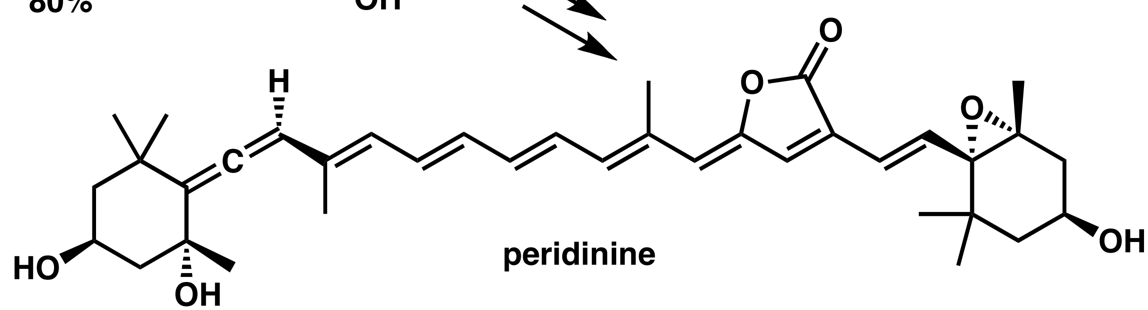


55-92% yield
89:11 to 98:2
>95% chirality transfer

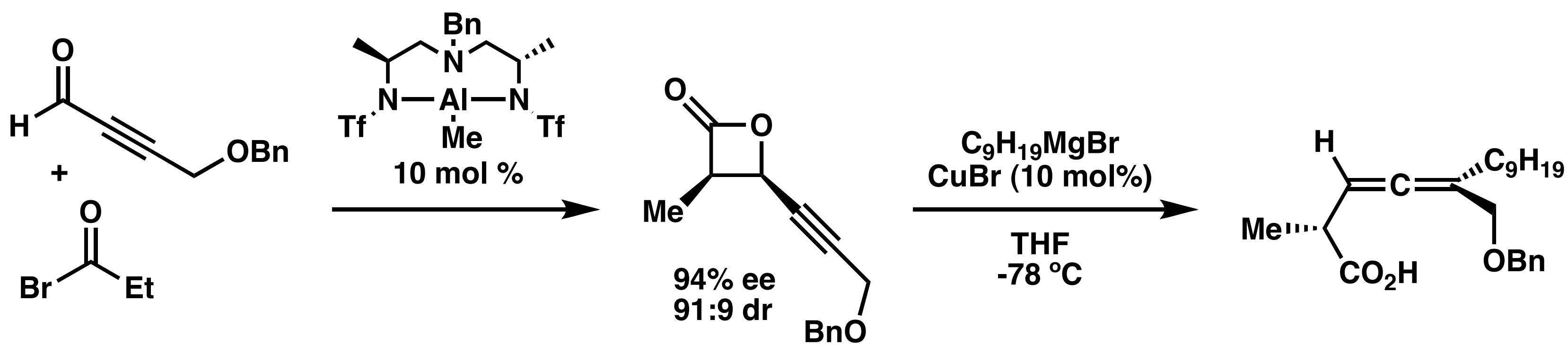
This Work: Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1997**, *62*, 8976-8977.
For similar chemistry with stannanes, see: Marshall, J. A.; Yu, R. H.; Perkins, J. F. *J. Org. Chem.* **1995**, *60*, 5550-5555.

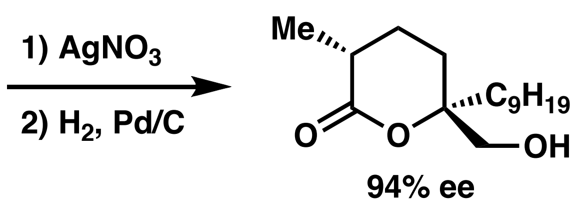
S_N2' reaction





Furuichi, N.; Hara, H.; Osaki, T.; Mori, H.; Katsumura, S. *Angew. Chem. Int. Ed.* **2002**, *41*, 1023-1026.



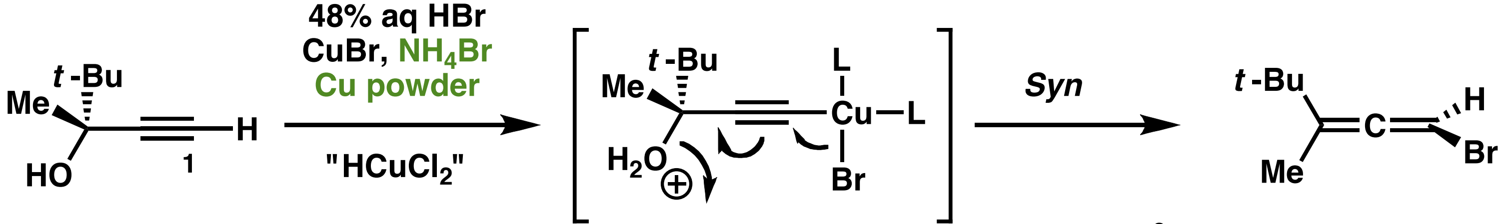


(-)-malyngolide
antibiotic

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

Halogenations

***Syn*-halogenation**



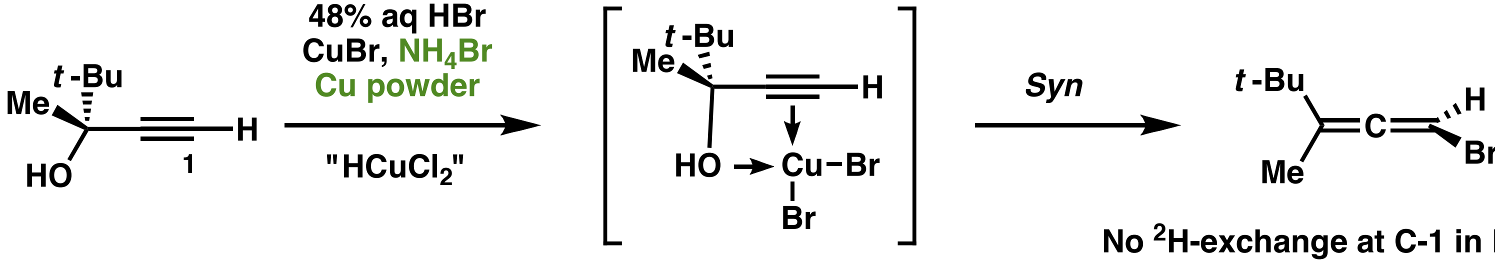
Original proposed mechanism

No ^{2}H-exchange at C-1 in D_2O/DBr, or in H_2O/HBr with 1-*d* alcohol

Landor, S. R.; Demetriou, B.; Evans, R. J.; Grzeskowiak, R.; Davey, P. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1995-1998.

Halogenations

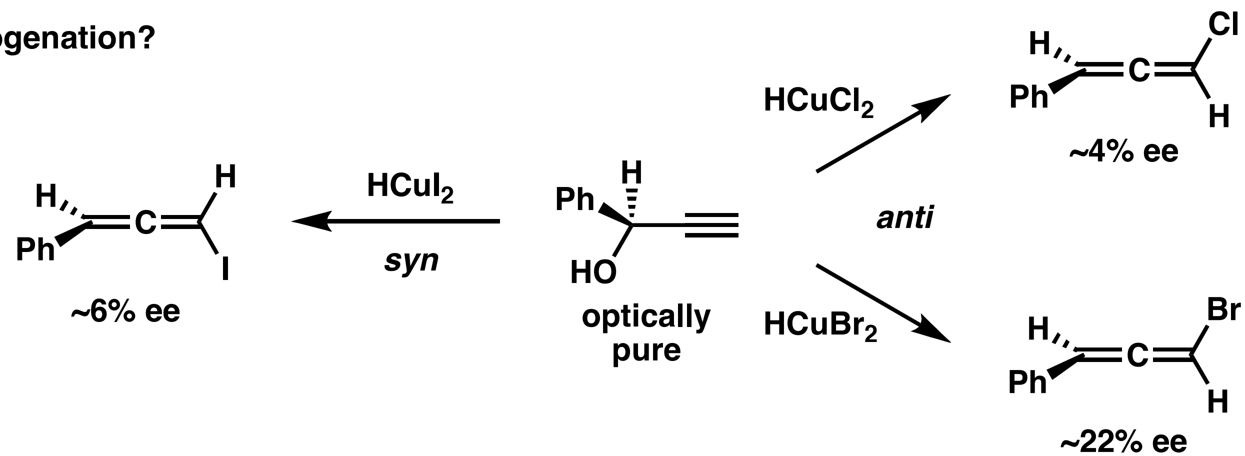
***Syn*-halogenation**



No ^{2}H-exchange at C-1 in D_2O/DBr, or in H_2O/HBr with 1-*d* alcohol

Landor, S. R.; Demetriou, B.; Evans, R. J.; Grzeskowiak, R.; Davey, P. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1995-1998.

***Syn* or *Anti*-halogenation?**

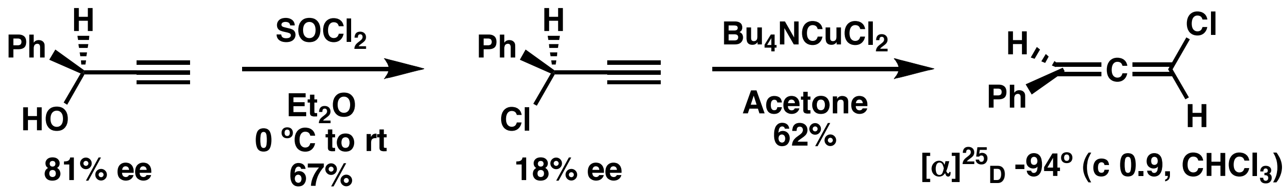


Authors conclude *syn*-elimination is not general for $HCuX_2$.
Substituting for sulfinate ester gave better *anti* selectivity for X = Cl (24% ee) and X = Br (52% ee). X = I also gave *anti*, but low selectivity (~6% ee).

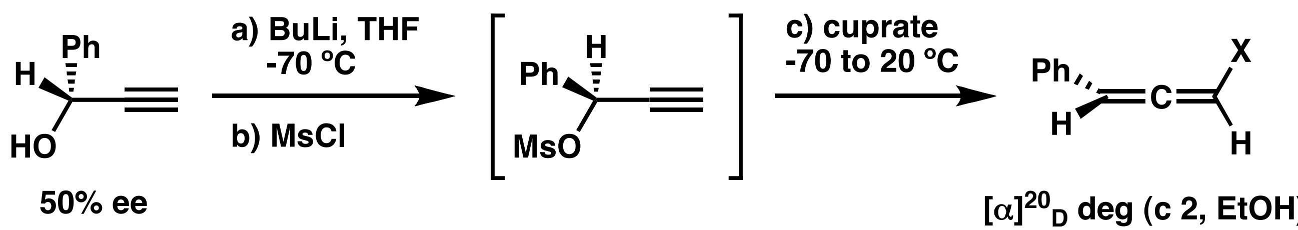
Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1984**, *49*, 1649-1650.

Halogenations

***Anti*-halogenation**



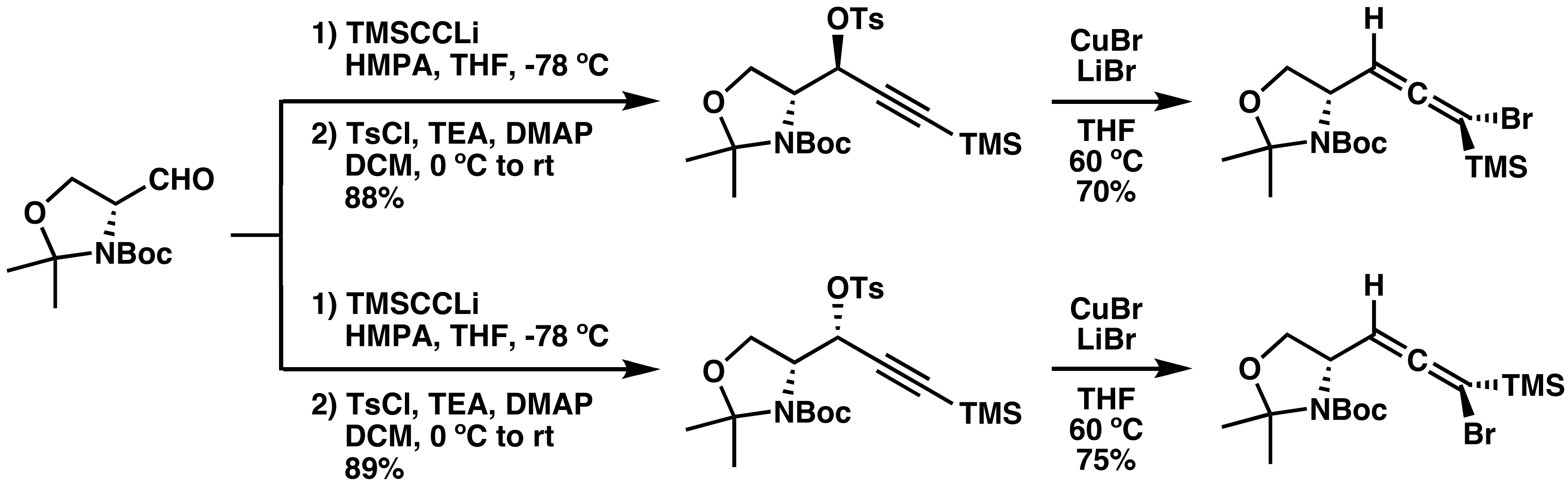
Muscio, O. J.; Jun, Y. M.; Philip, Jr., J. B. *Tetrahedron Lett.* **1978**, 2379-2382.



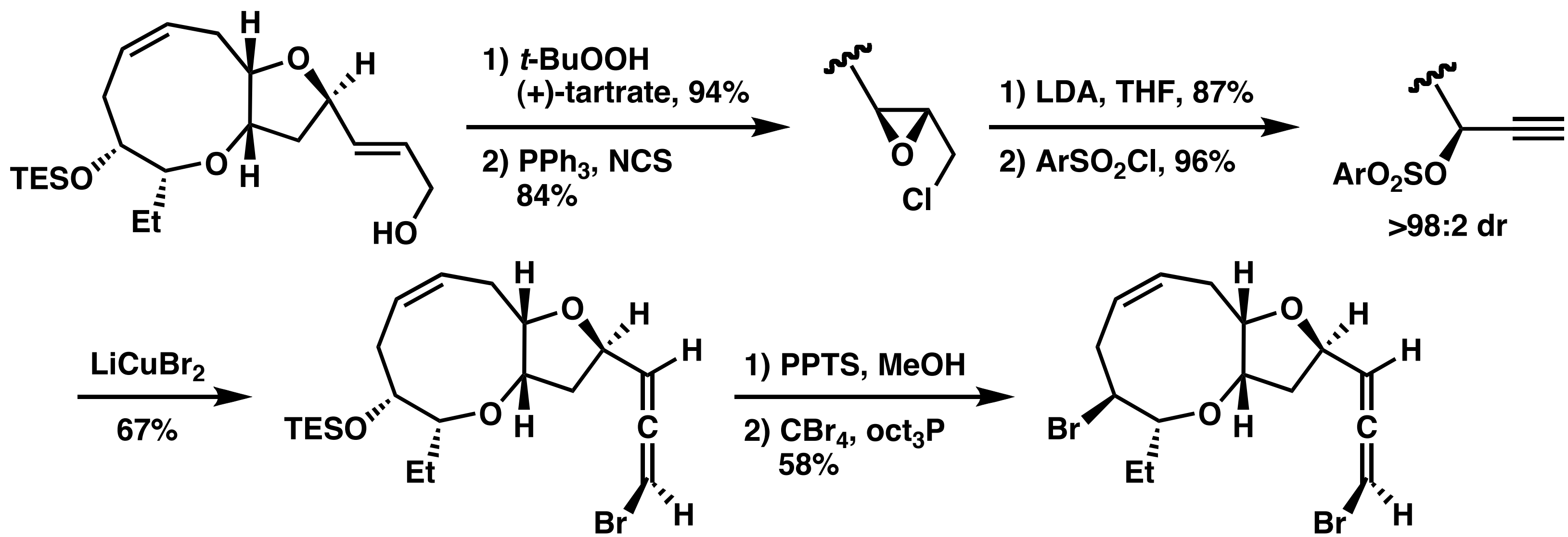
		$[\alpha]^{20}_D$ deg (c 2, EtOH)		
cuprate	equiv.	X = Cl	X = Br	X = I
$LiCuX_2$	1.2	530	920	1220
$LiCu_2X_3$	0.6	600	1040	1350
$LiCu_2X_3$	1.2	610	1235	1550

Elsevier, C. J.; Meijer, J.; Tadema, G.; Stehouwer, P. M.; Bos, H. J. T.; Vermeer, P. *J. Org. Chem.* **1982**, *47*, 2194-2196.

Halogenations



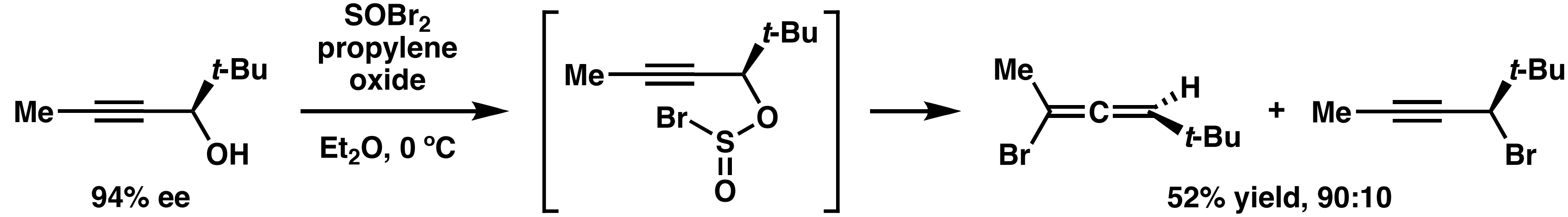
D'Aniello, F.; Schoenfelder, A.; Mann, A.; Taddei, M. *J. Org. Chem.* **1996**, *61*, 9631-9636.



(-)-isolaurallene

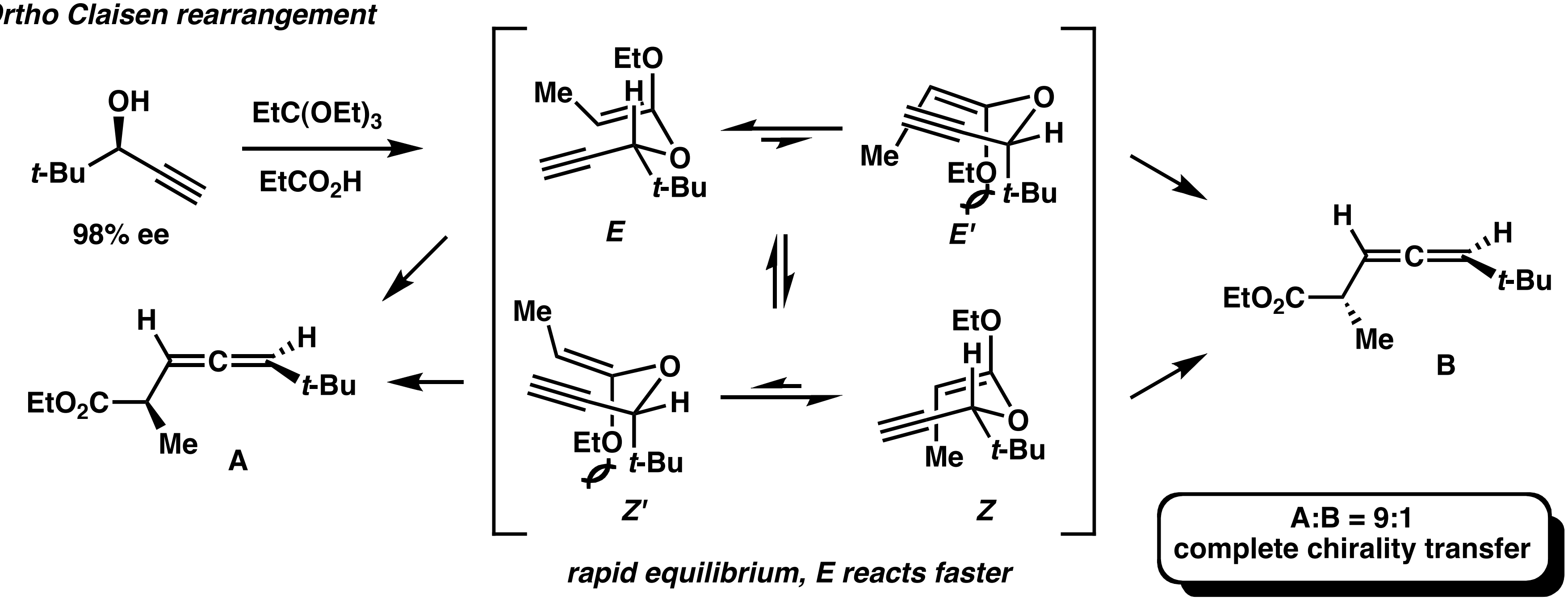
Crimmins, M. T.; Emmitte, K. A. *J. Am. Chem. Soc.* **2001**, *123*, 1533-1534

Rearrangements



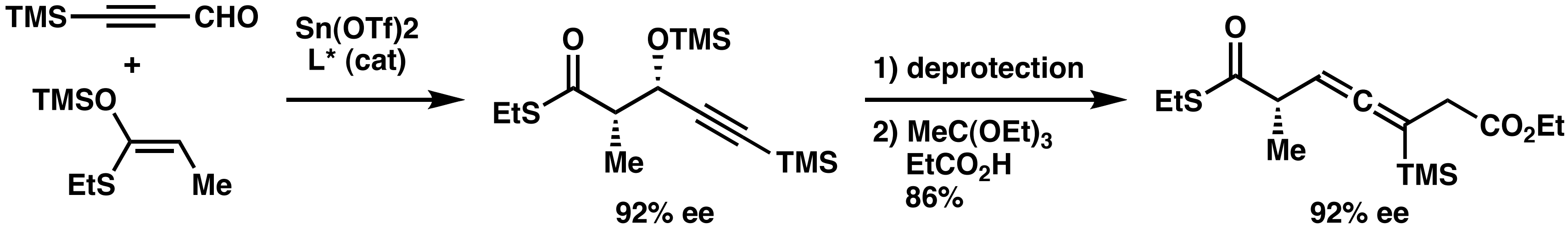
Coery, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3055-3058.
Initial studies: Evans, R. J. D.; Landor, S. R.; Smith, R. T. *J. Chem. Soc.* **1963**, 1506-1511.
Evans, R. J. D.; Landor, S. R. *J. Chem. Soc.* **1965**, 2553-2559.

Ortho Claisen rearrangement

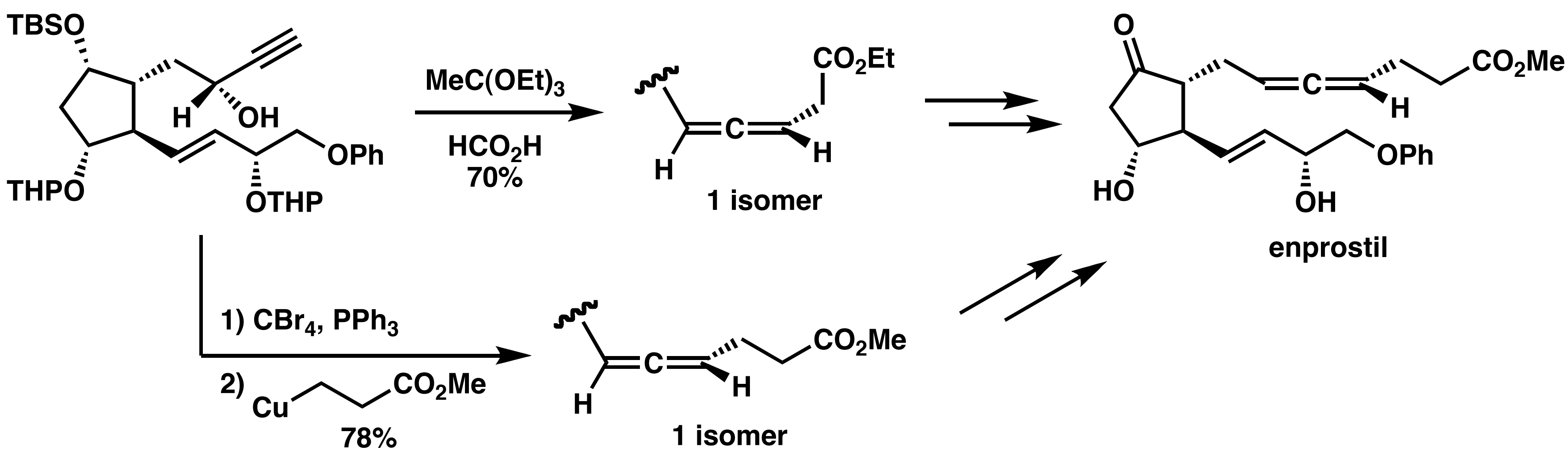


Henderson, M. A.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 4736-4745.

Rearrangements

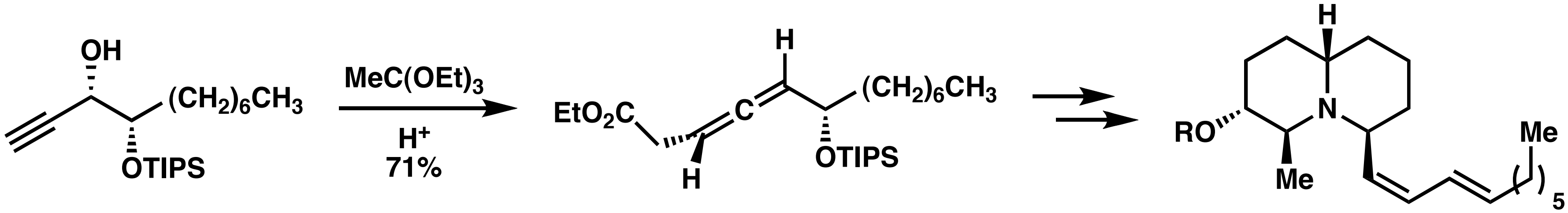


Mukaiyama, T.; Furuya, M.; Ohtsubo, A.; Kobayashi, S. *Chem. Lett.* **1991**, 989-992.



Cooper, G. F.; Wren, D. L.; Jackson, D. Y.; Beard, C. C.; Galeazzi, E.; Van Horn, A. R.; Li, T. T. *J. Org. Chem.* **1993**, *58,* 4280-4286.

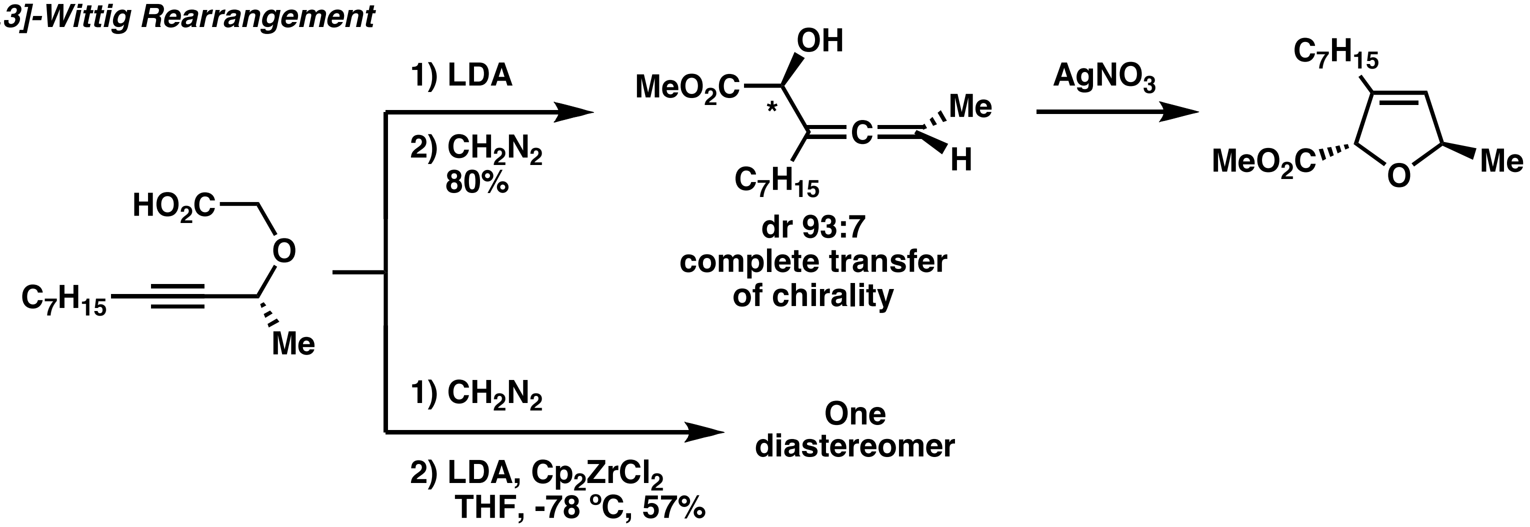
Rearrangements



Ha, J. D.; Lee, D.; Cha, J. K. *J. Org. Chem.* **1997**, *62*, 4550-4551.
Ha, J. D.; Cha, J. K. *J. Am. Chem. Soc.* **1999**, *121*, 10012-10020.

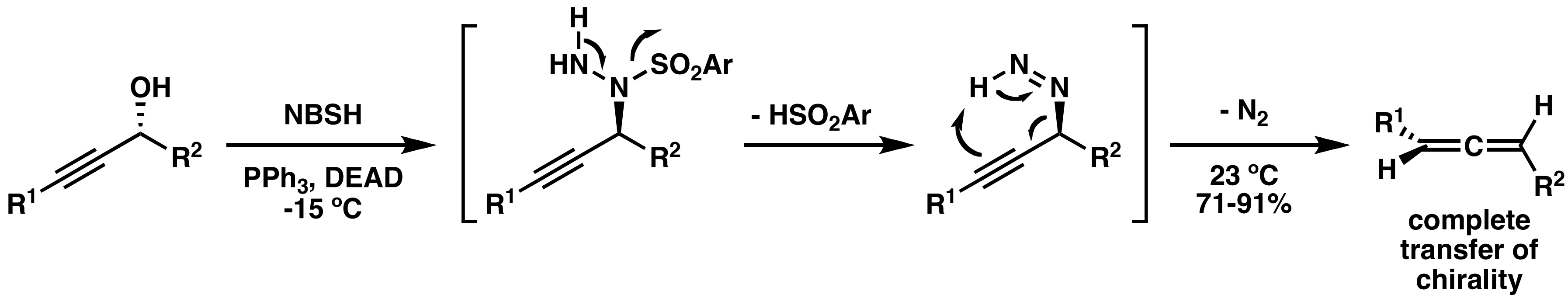
clavepictine A, R = Ac
clavepictine B, R = H

[2,3]-Wittig Rearrangement

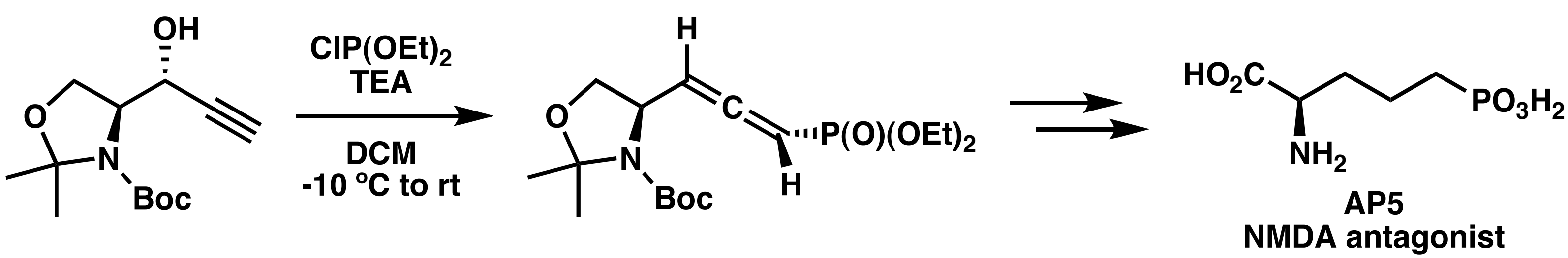


Marshall, J. A.; Robinson, E. D.; Zapata, A. *J. Org. Chem.* **1989**, *54*, 5854-5855.
Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1990**, *55*, 2995-2996.
Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1990**, *56*, 4913-4918.

Rearrangements



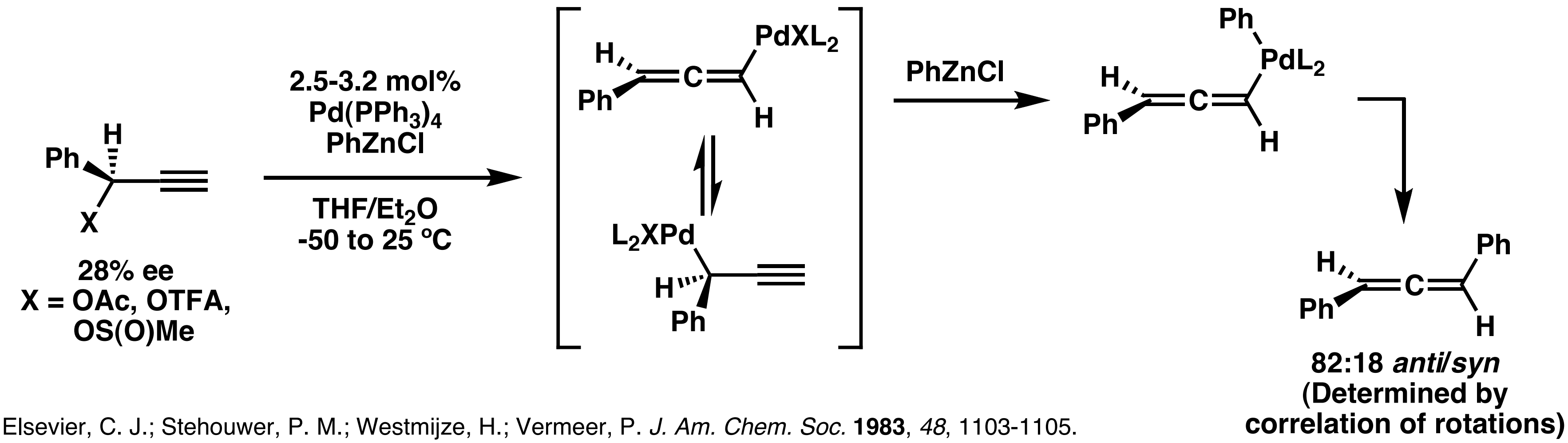
Meyers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492-4493.
For a synthetic application of this, see: Shepard, M. S.Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 2597-2605.



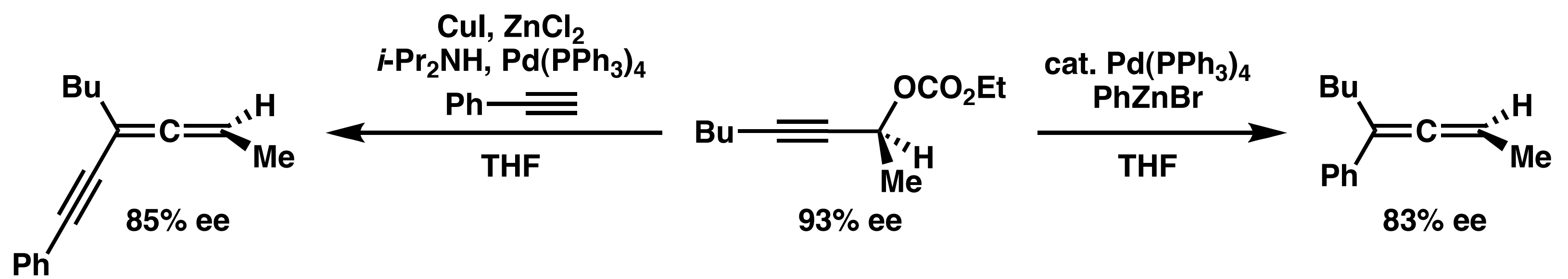
Muller, M.; Mann, A.; Taddei, M. *Tetrahedron Lett.* **1993**, *34*, 3289-3290.

Palladium Catalysis

transmetallation



Elsevier, C. J.; Stehouwer, P. M.; Westmijze, H.; Vermeer, P. *J. Am. Chem. Soc.* **1983**, *48*, 1103-1105.

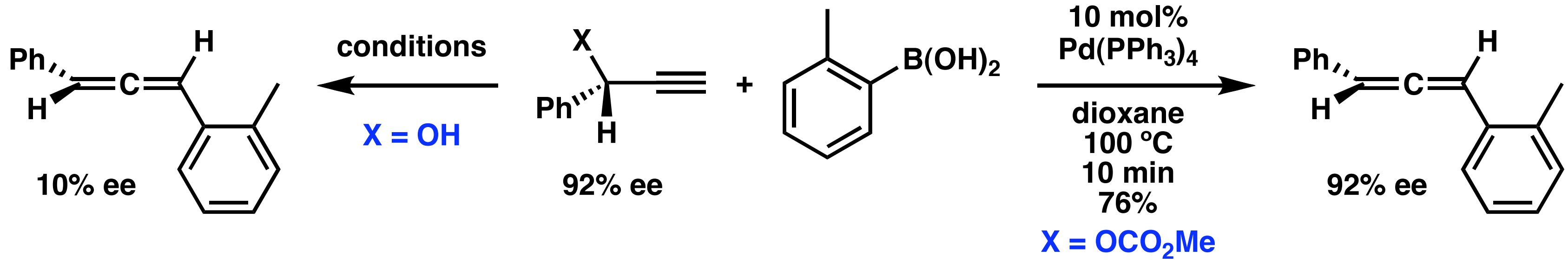


Substituting Ph at alkyne terminus resulting in lower stereoselectivity

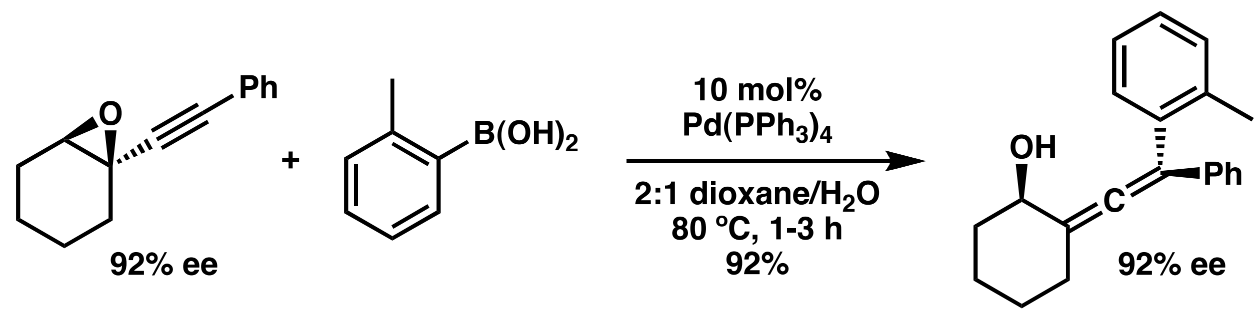
Dixneuf, P. H.; Guyot, T.; Ness, M. D.; Roberts, S. M. *J. Chem. Soc., Chem. Comm.* **1997**, 2083-2084.

Palladium Catalysis

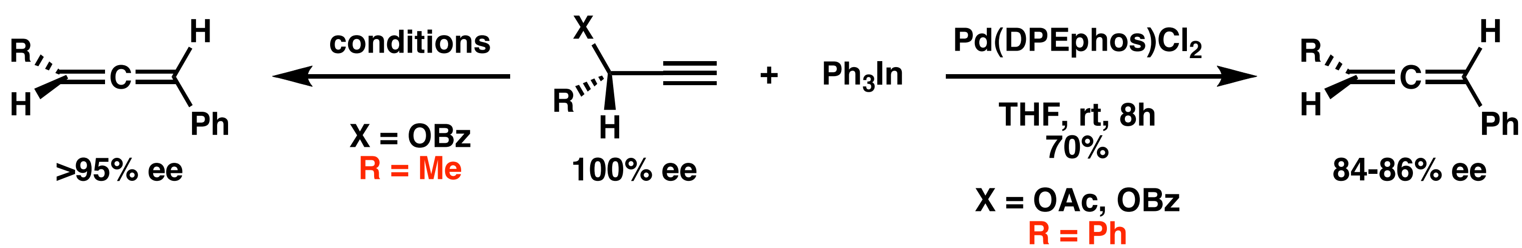
transmetallation



Yoshida, M.; Gotou, T.; Ihara, M. *Tetrahedron Lett.* **2004**, *45*, 5573-5575.



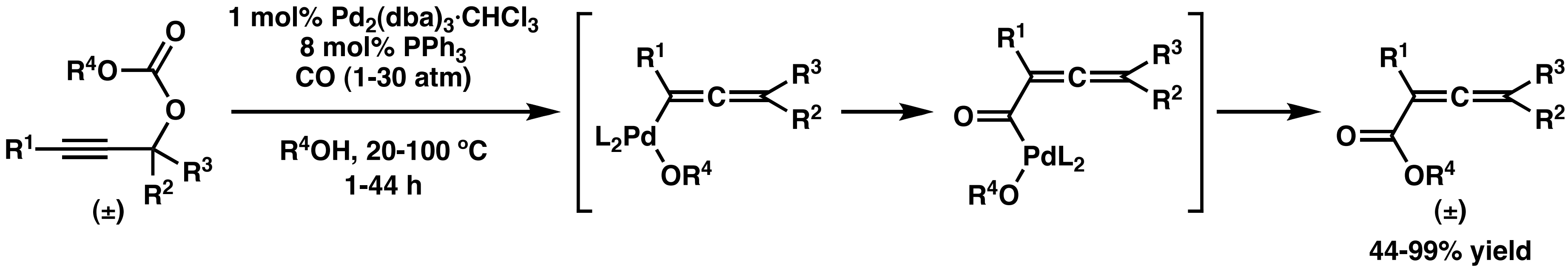
Yoshida, M.; Ueda, H.; Ihara, M. *Tetrahedron Lett.* **2005**, *46*, 6705-6708.



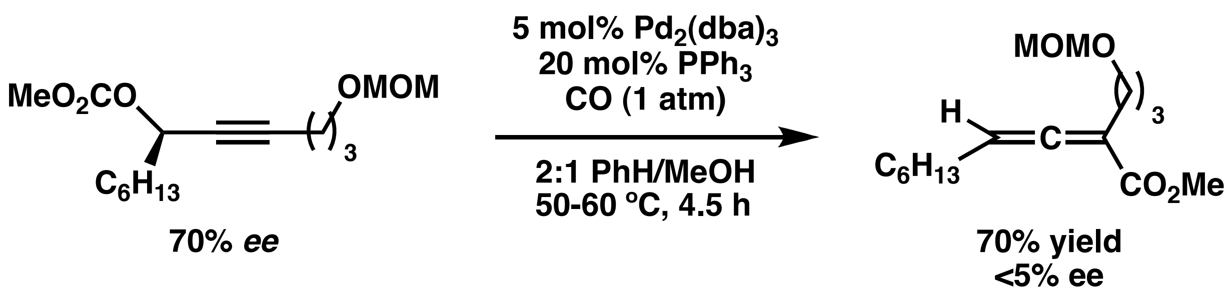
Riveiros, R.; Rodriguez, D.; Sestelo, J. P.; Sarandeses, L. A. *Org. Lett.* **2006**, *8*, 1403-1406.

Palladium Catalysis

Carbonylation



Tsuji, J.; Sugiura, T.; Minami, I. *Tetrahedron Lett.* **1986**, *27*, 731-734.

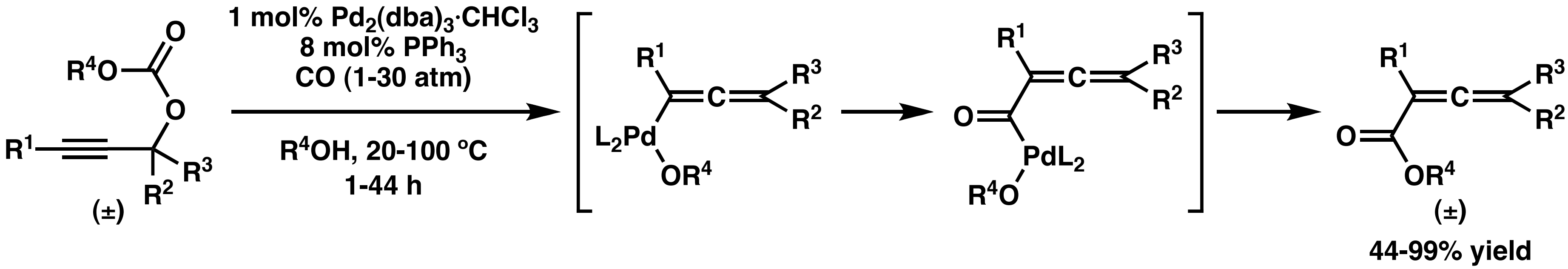


Possible racemization by PPh_3

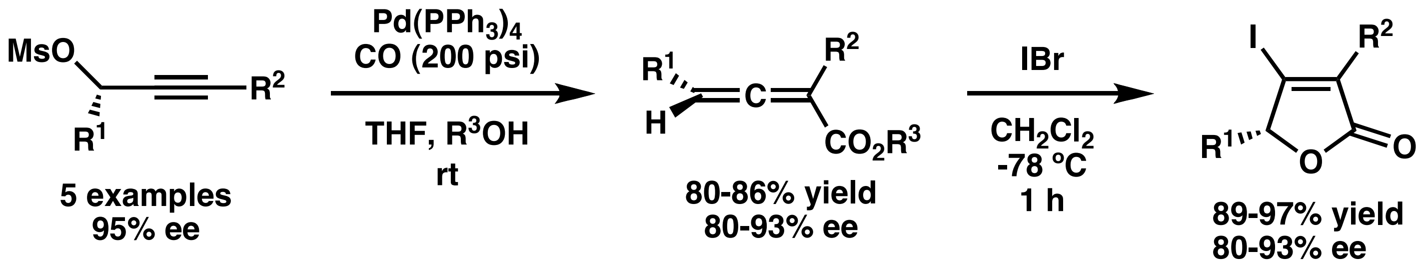
Marshall, J. A.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 3238-3239.
Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367-371.

Palladium Catalysis

Carbonylation



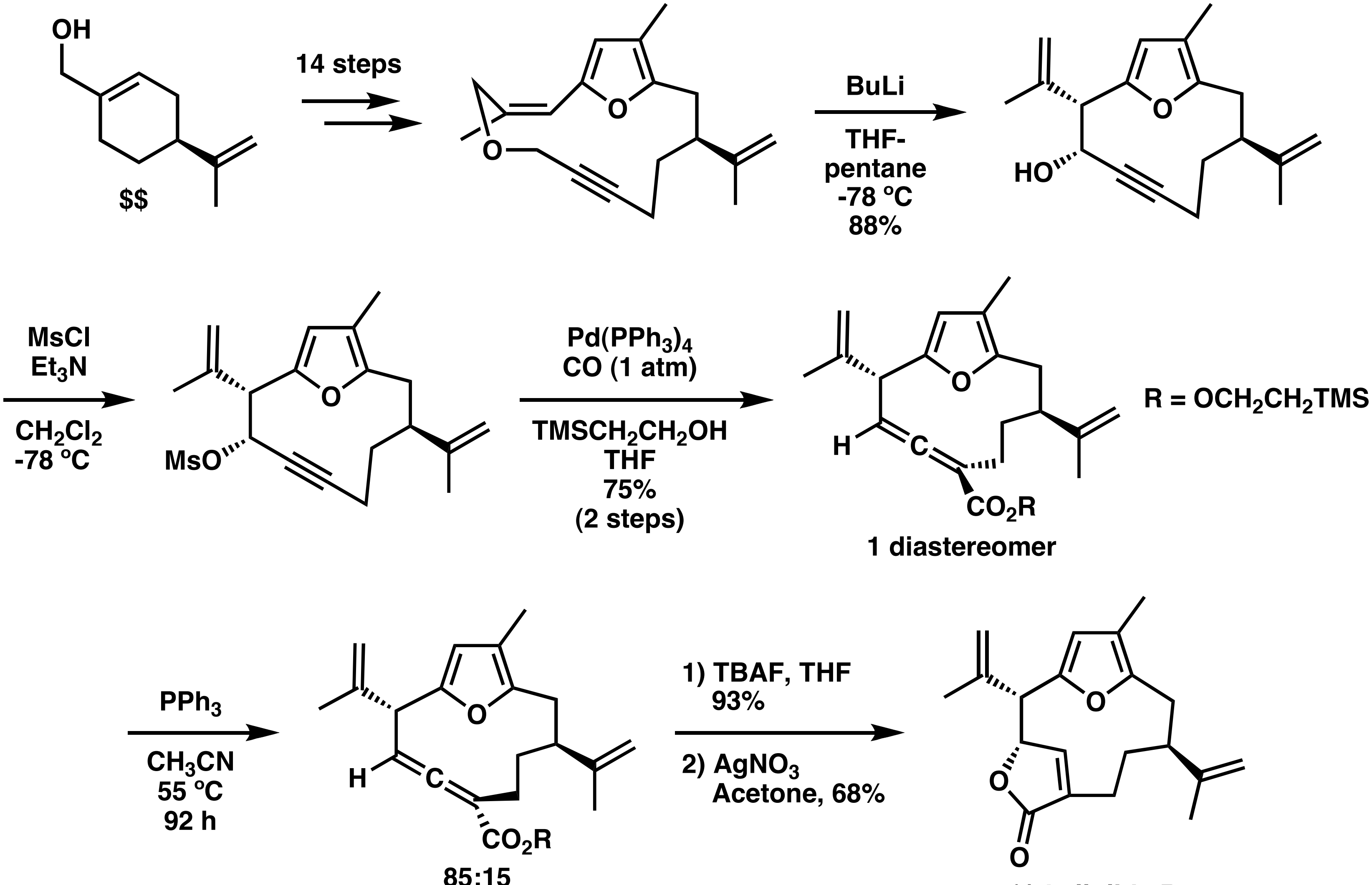
Tsuji, J.; Sugiura, T.; Minami, I. *Tetrahedron Lett.* **1986**, *27*, 731-734.



Marshall, J. A.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 3238-3239.
Marshall, J. A.; Wolf, M. A.; Wallace, E. M. *J. Org. Chem.* **1997**, *62*, 367-371.
Pd-catalyzed formation of butenolides from allenic acids with high chirality transfer: Ma, S.; Shi, Z. *J. Chem. Soc., Chem. Commun.* **2002**, 540-541.

Palladium Catalysis

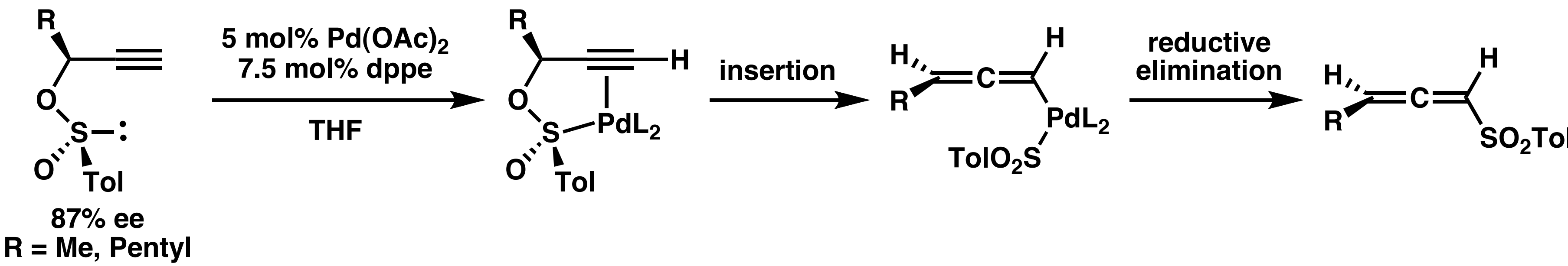
Carbonylation



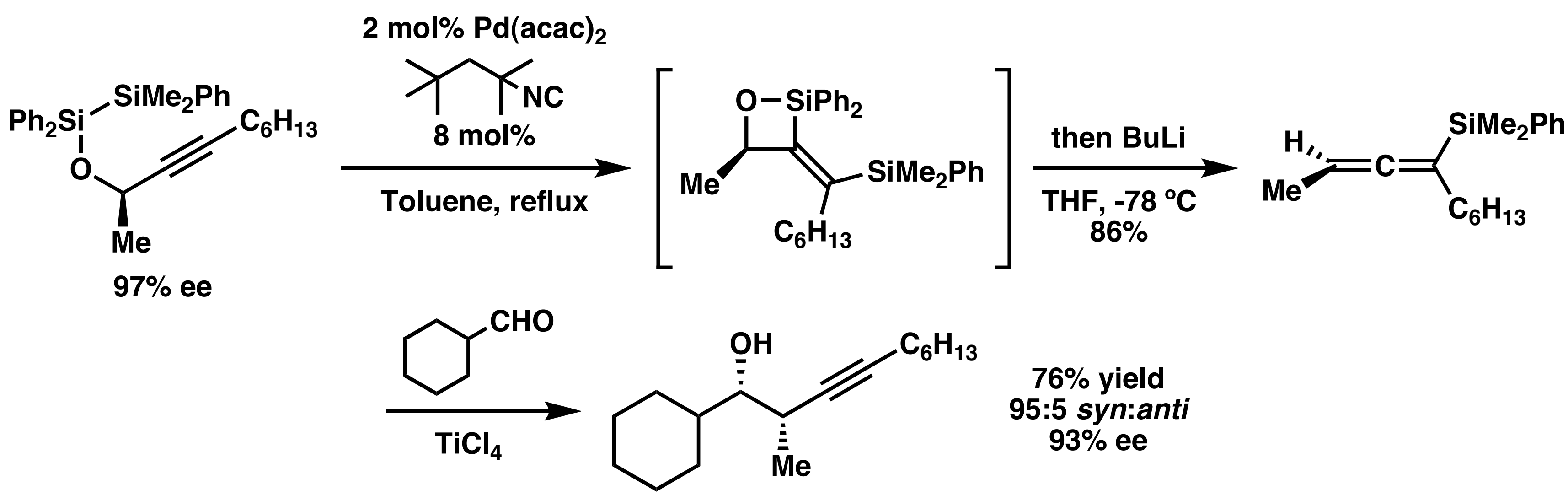
(-)-kallolide B
(unnatural)

Marshall, J. A.; Wallace, E. M.; Coan, P. S. *J. Org. Chem.* **1995**, *60*, 796-797.
Marshall, J. A.; Bartley, G. S.; Wallace, E. M. *J. Org. Chem.* **1996**, *61*, 5729-5735.

Palladium Catalysis

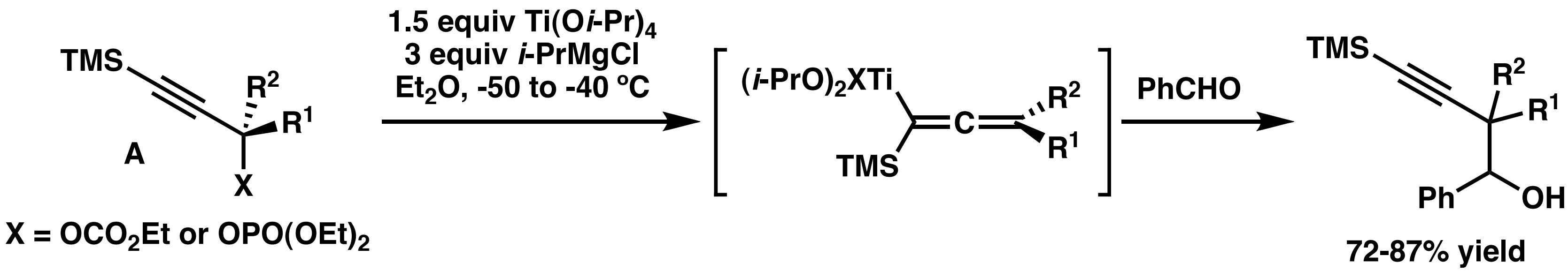


Hiroi, K.; Kato, F. *Tetrahedron* **2001**, *57*, 1543-1550.



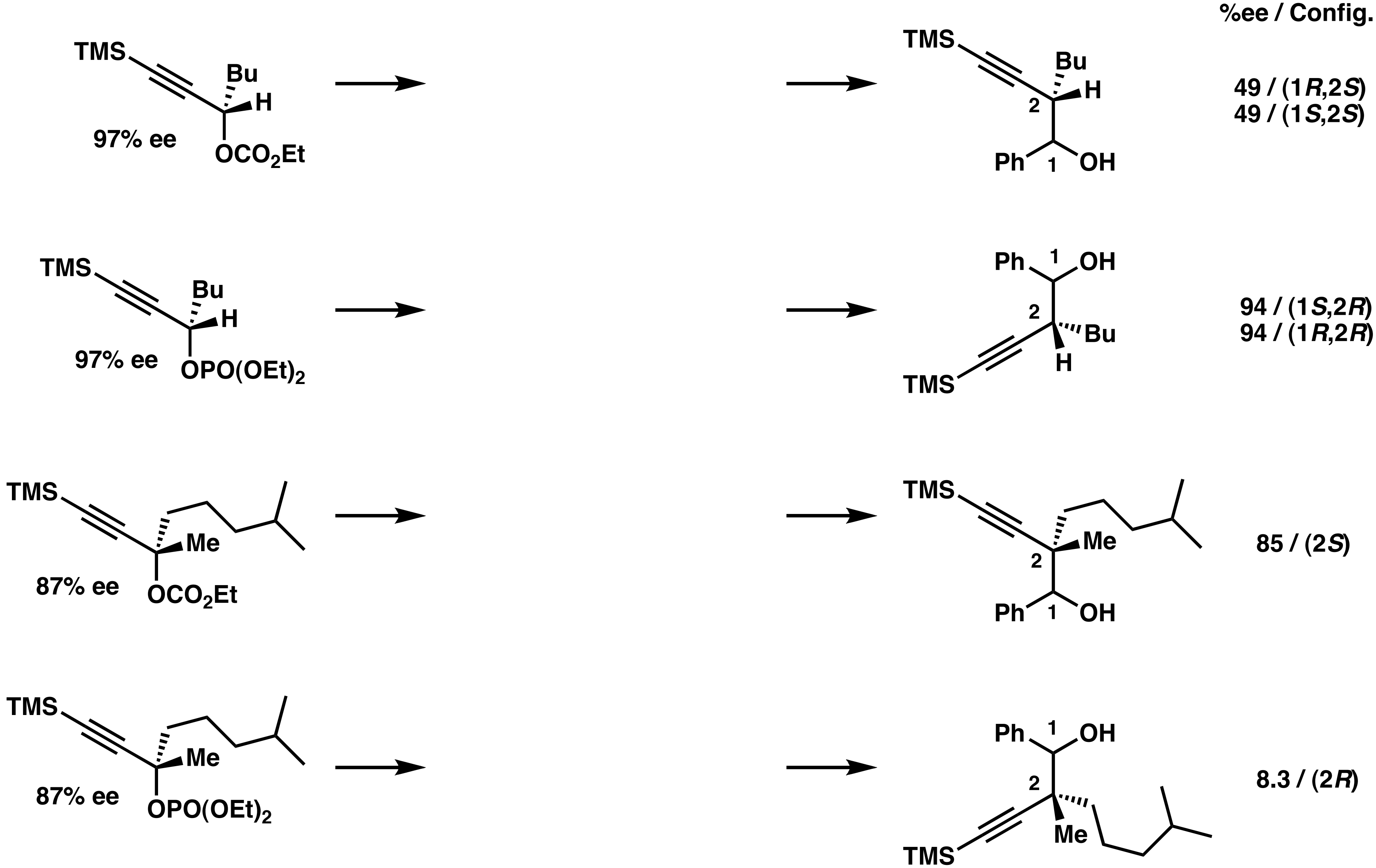
Suginome, M.; Matsumoto, A.; Ito, Y. *J. Org. Chem.* **1996**, *61*, 4884-4885.

Allenylmetal Compounds



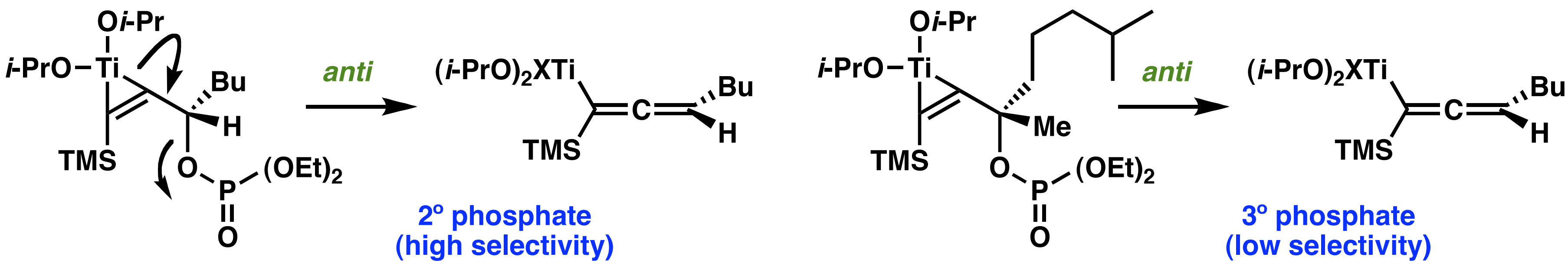
Okamoto, S.; An, D. K.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 4551-4554.
(Mechanism) Nakagawa, T.; Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3207-3210.

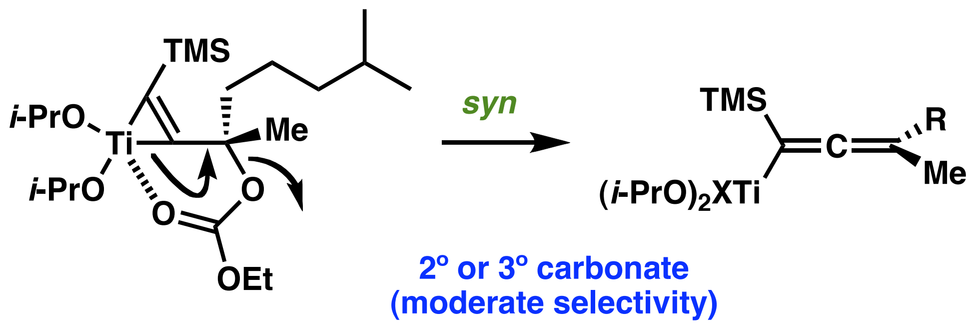
Allenylmetal Compounds

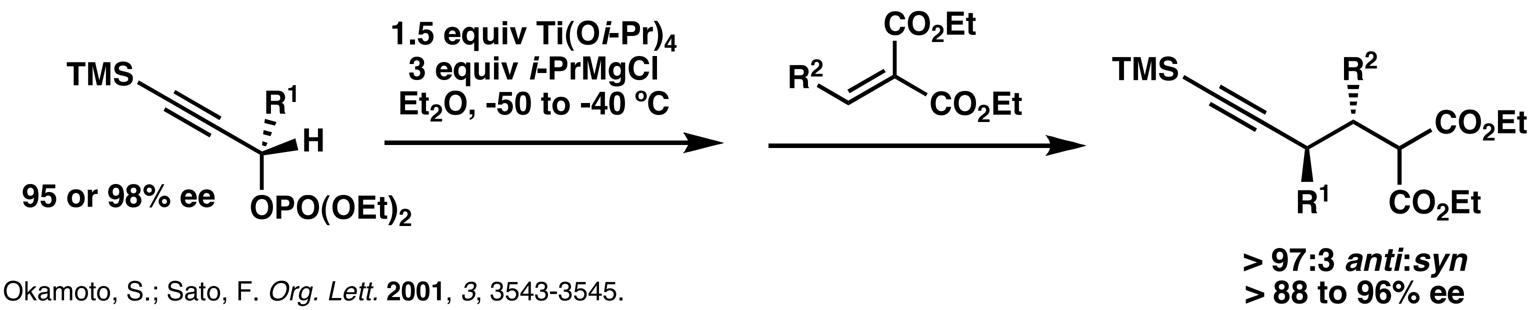


Okamoto, S.; An, D. K.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 4551-4554.
(Mechanism) Nakagawa, T.; Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3207-3210.

Allenylmetal Compounds





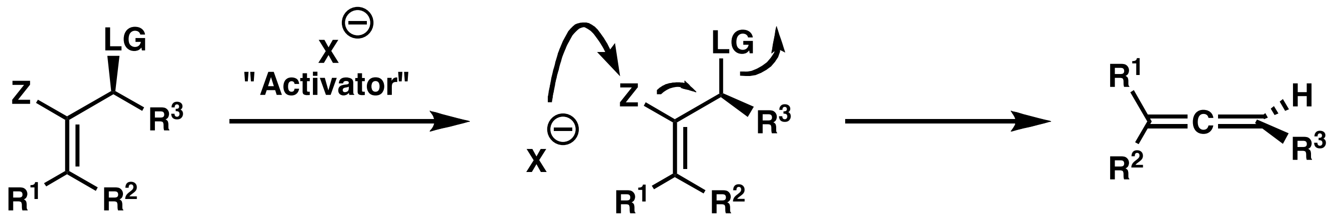


Song, Y.; Okamoto, S.; Sato, F. *Org. Lett.* **2001**, *3*, 3543-3545.

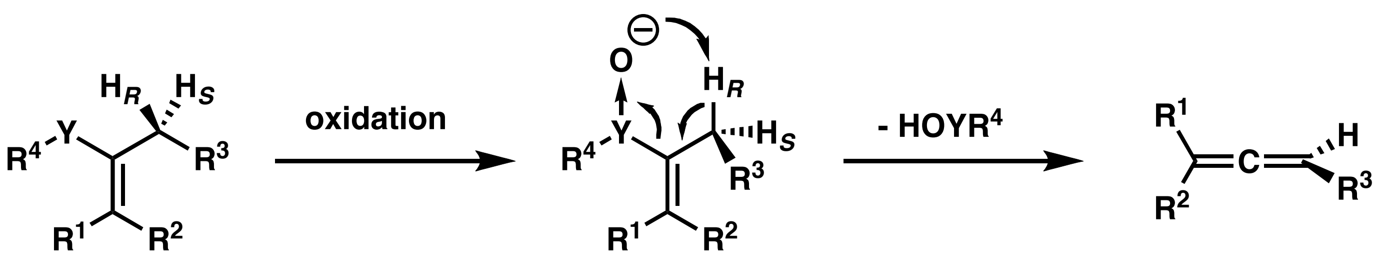
For reviews of the synthesis and reactivity of allenylmetal compounds, see: Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31-47. Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163-3185. Marshall, J. A.; Gung, B. W.; Grachan, M. L. Synthesis and reactions of allenylmetal compounds. In *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004; 493-592.

Allylic Elimination (β-elimination)

A) Chirality transfer from allylic position



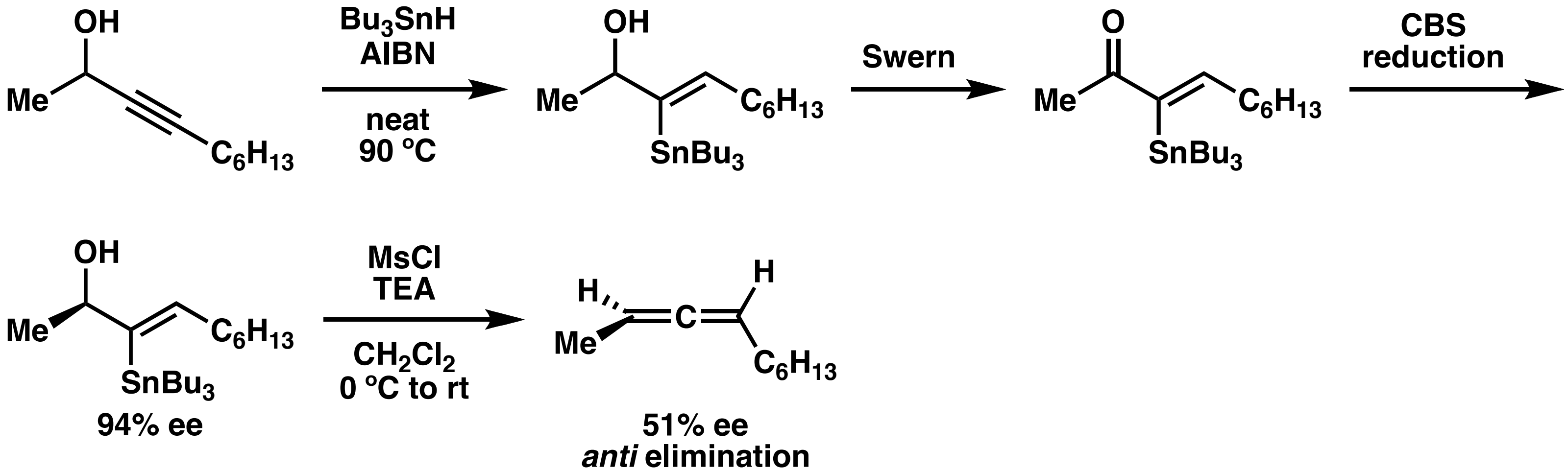
B) Chiral leaving groups



Y = S, Se

Allylic Elimination (β-elimination)

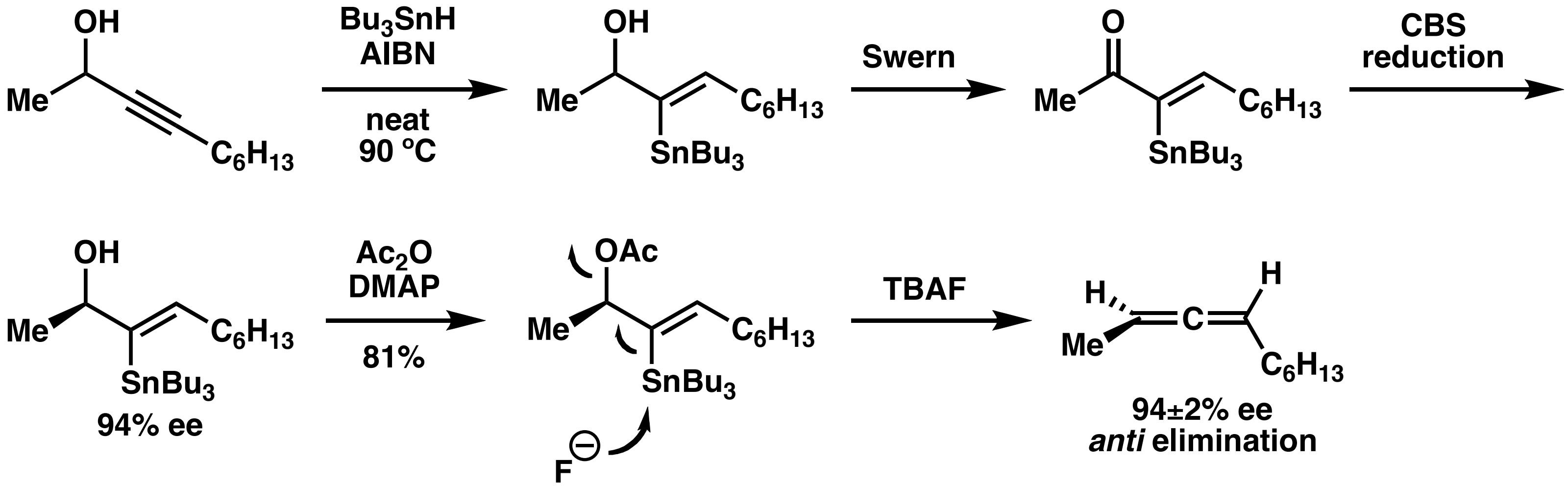
Chirality at allylic position



Konoike, T.; Araki, Y. *Tetrahedron Lett.* **1992**, *33*, 5093-5096.

Allylic Elimination (β-elimination)

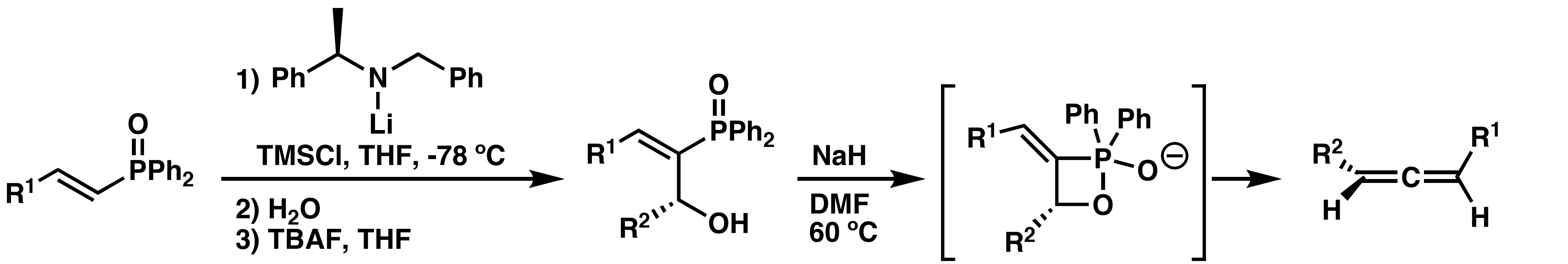
Chirality at allylic position



Konoike, T.; Araki, Y. *Tetrahedron Lett.* **1992**, *33*, 5093-5096.

Allylic Elimination (β-elimination)

Chirality at allylic position



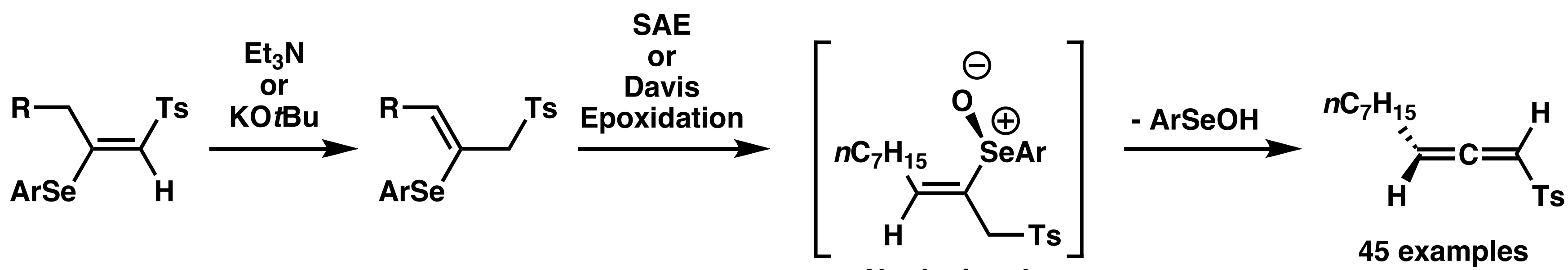
R^1=Ph, R^2=*t*-Bu, 87%, 28% ee
R^1=*t*-Bu, R^2=*t*-Bu, 58%, 51% ee

R^1=Ph, R^2=*t*-Bu, 89%, ~12% ee
R^1=*t*-Bu, R^2=*t*-Bu, 74%, ~23% ee

This work: Fox, D. J.; Medlock, J. A.; Vosser, R.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2240-2249.
For related achiral systems, see: Nagaoka, Y.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 6428-6429. Inoue, H.; Tsubouchi, H.; Nagaoka, Y.; Tomioka, K. *Tetrahedron* **2002**, *58*, 83-90.

Allylic Elimination (β-elimination)

Chiral leaving groups



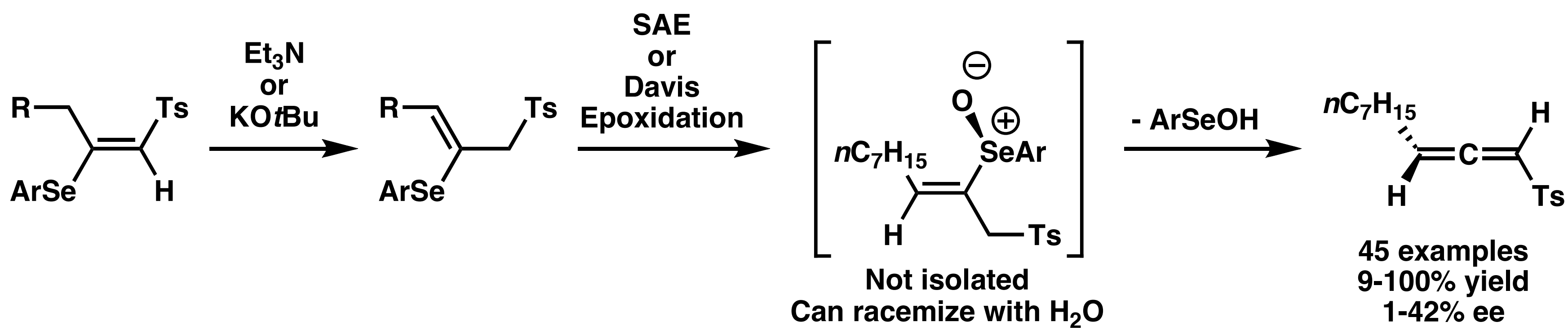
Not isolated
Can racemize with H_2O

45 examples
9-100% yield
1-42% ee

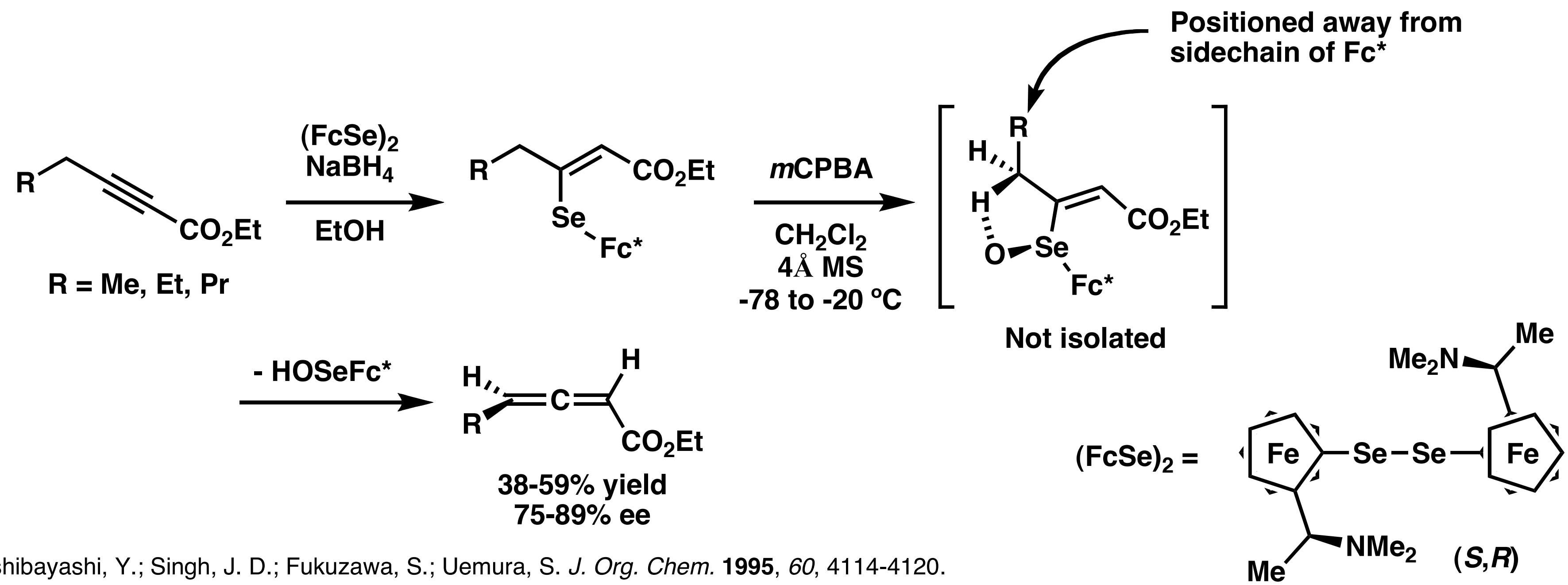
Komatsu, N.; Murakami, T.; Nishibayashi, Y.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 3697-3702.

Allylic Elimination (β-elimination)

Chiral leaving groups



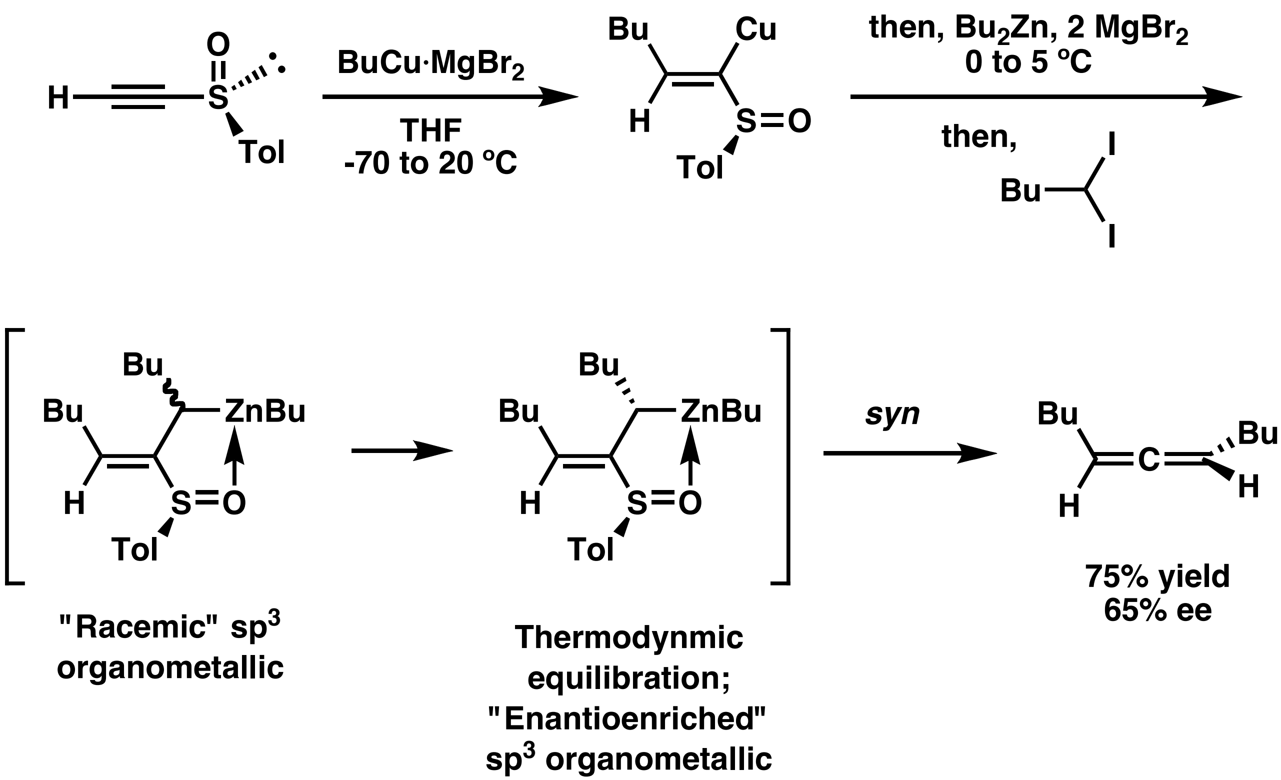
Komatsu, N.; Murakami, T.; Nishibayashi, Y.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 3697-3702.



Hishibayashi, Y.; Singh, J. D.; Fukuzawa, S.; Uemura, S. *J. Org. Chem.* **1995**, *60*, 4114-4120.

Allylic Elimination (β-elimination)

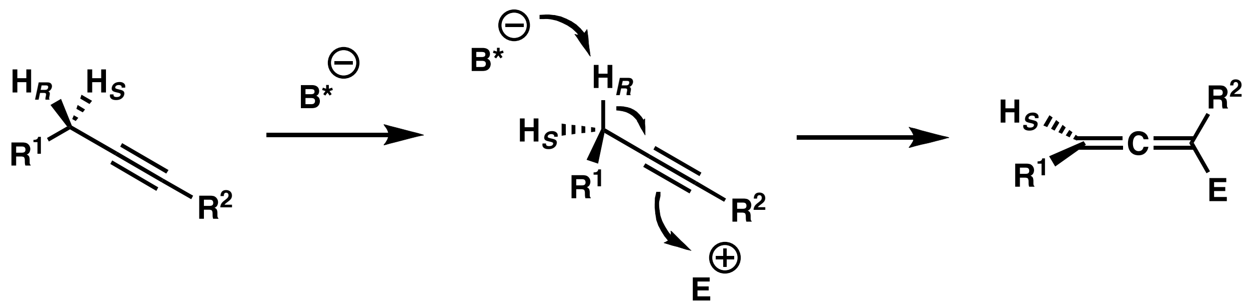
Equilibration of allylic metal center



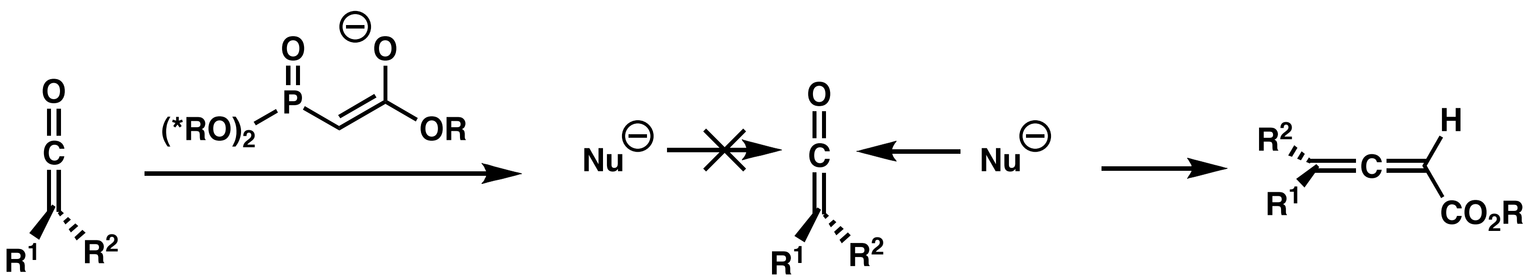
Varghese, J. P.; Zouev, I.; Aufauvre, L.; Knochel, P.; Marek, I. *Eur. J. Org. Chem.* **2002**, 4151-4158.

Stoichiometric Chiral Reagents and Auxilliaries

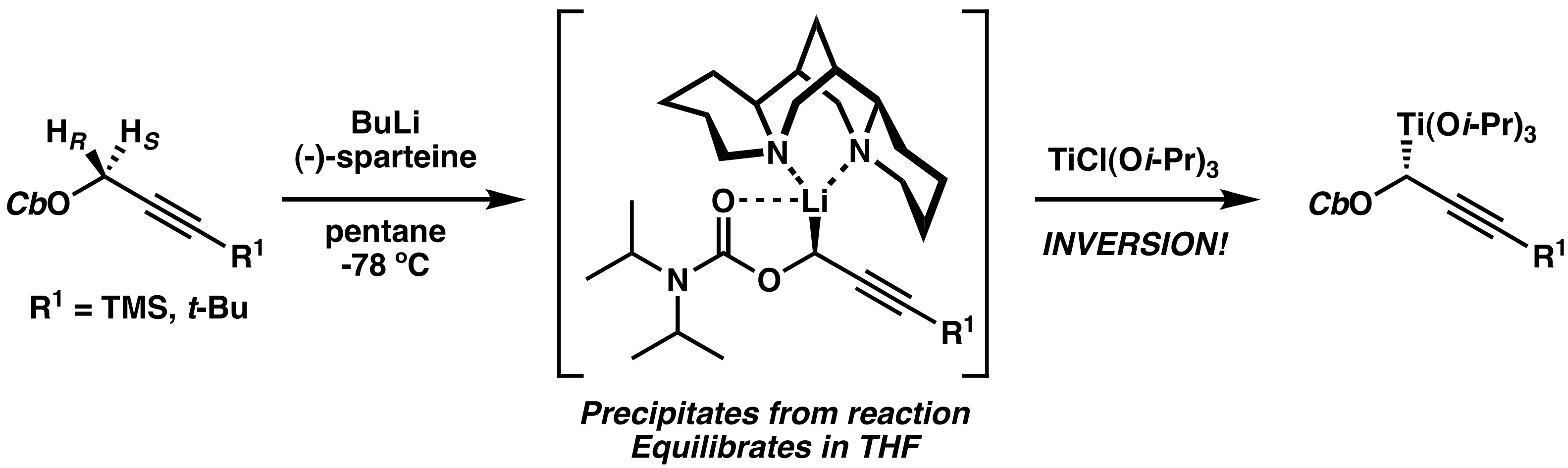
A) Asymmetric Deprotonation-Protonation

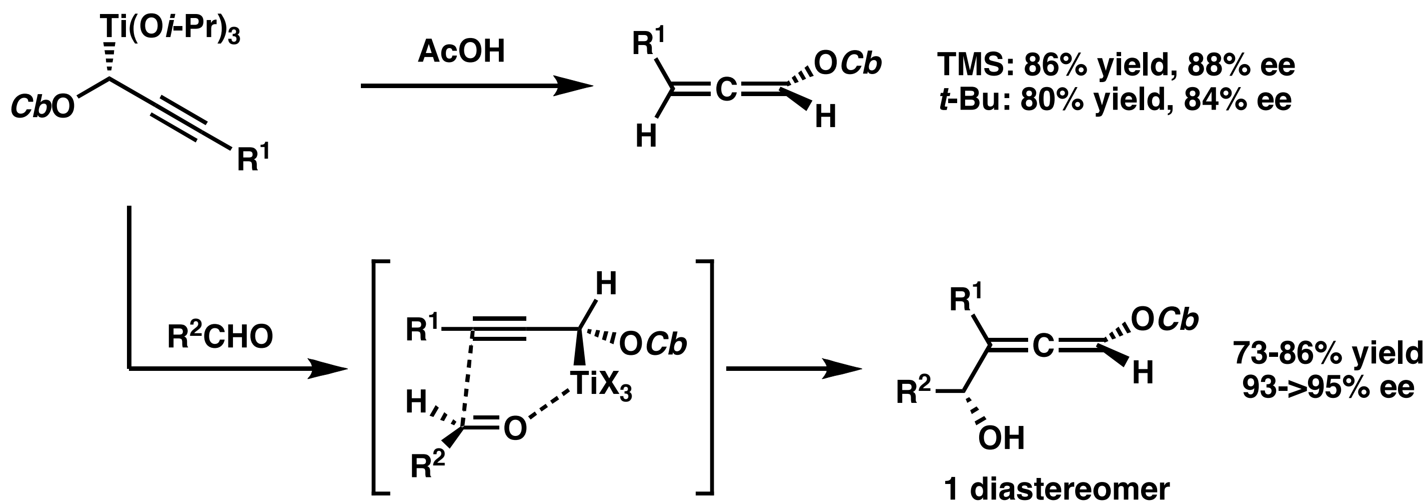


B) Asymmetric Horner-Wadsworth-Emmons



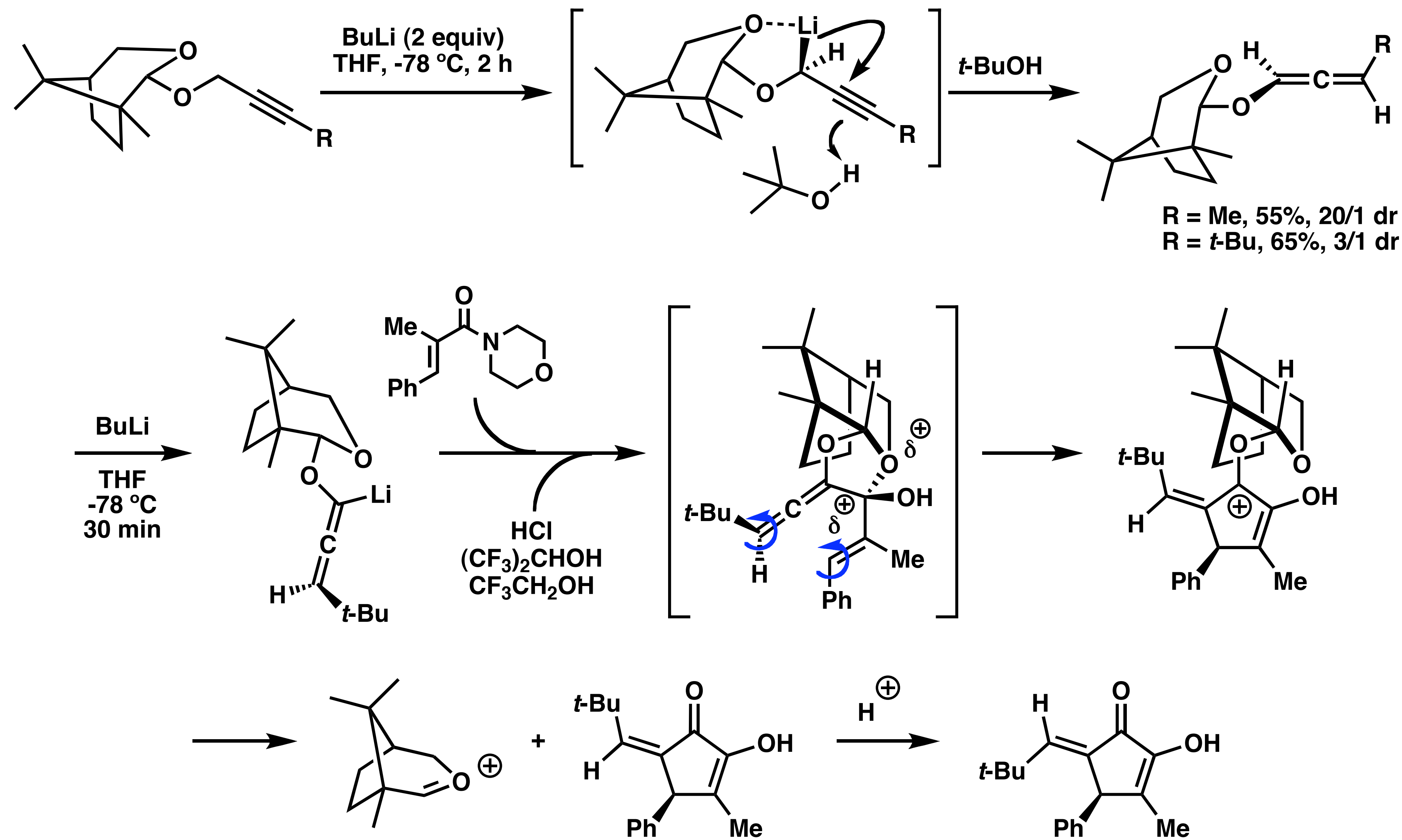
Asymmetric Deprotonation





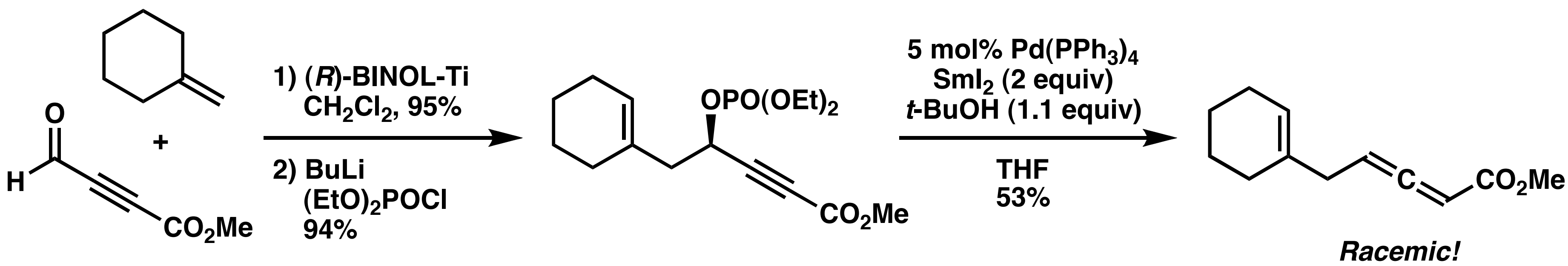
This Work: Schultz-Fademrecht, C.; Wibbeling, B.; Fröhlich, R.; Hoppe, D. *Org. Lett.* **2001**, *3*, 1221-1224.
For inversion in Li-Ti exchange with allyl species, see: Paulsen, H.; Graeve, C.; Hoppe, D. *Synthesis*, **1996**, 141-144.

Asymmetric Deprotonation



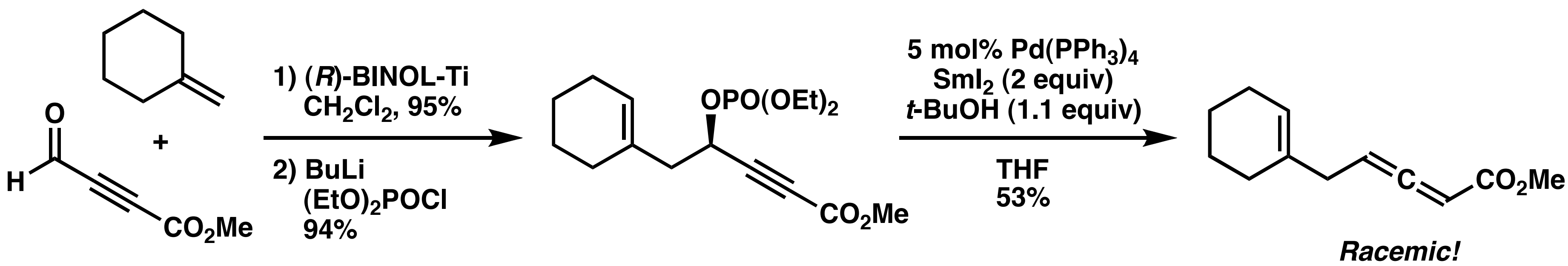
This Work: Harrington, P. E.; Murai, T.; Chu, C.; Tius, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 10091-10100.
For examples with a fructose-derived auxilliary, see: Hausherr, A.; Orschel, B.; Scherer, S.; Reissig, H.-U. *Synthesis* **2001**, 1377-1385.

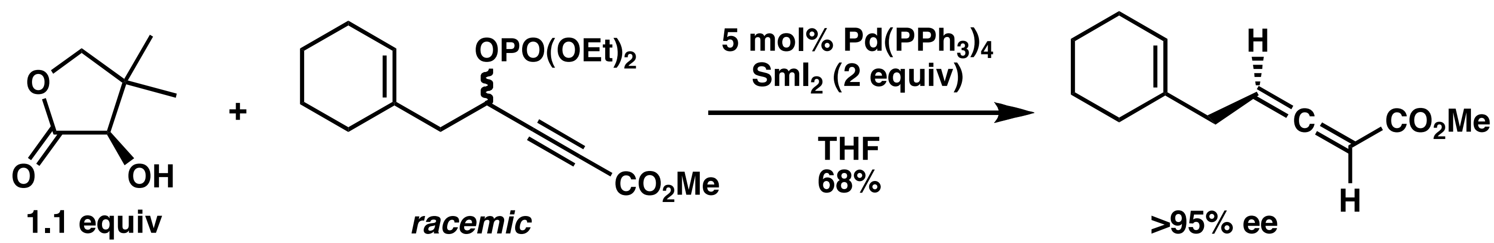
Asymmetric Protonation

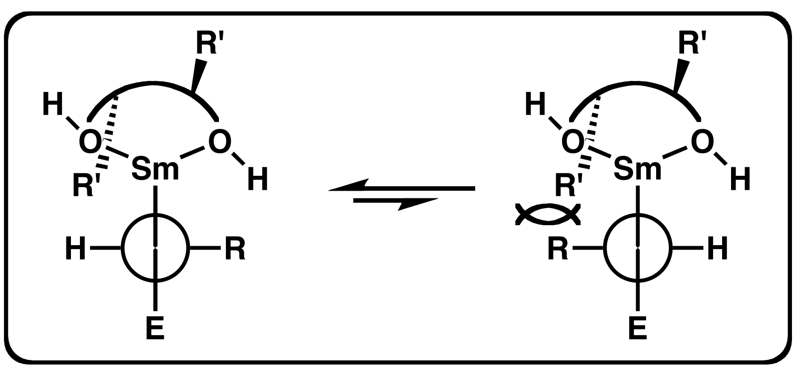


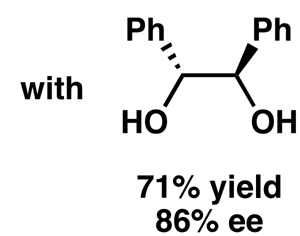
Mikami, K.; Yoshida, A. *Angew. Chem. Int. Ed.* **1997**, *36*, 858-860.
Mikami, K.; Yoshida, A. *Tetrahedron* **2001**, *57*, 889-898.

Asymmetric Protonation



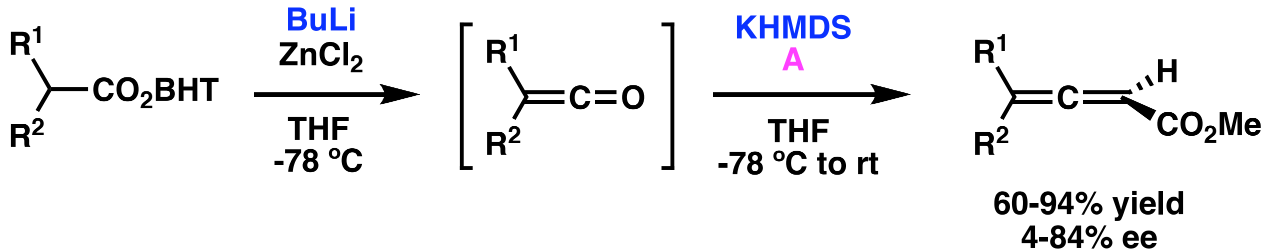


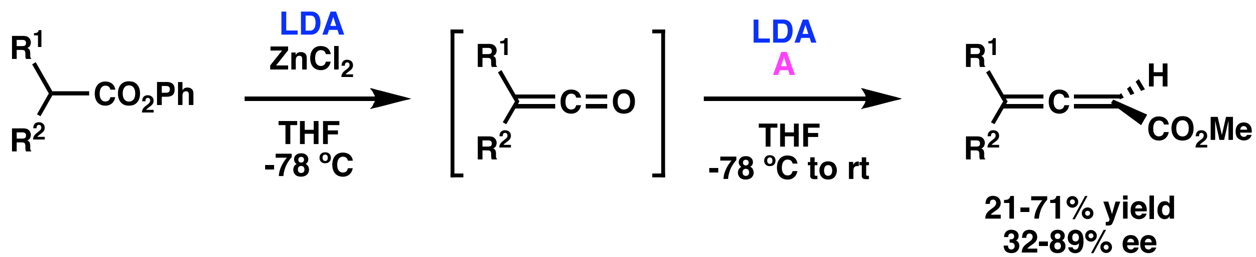


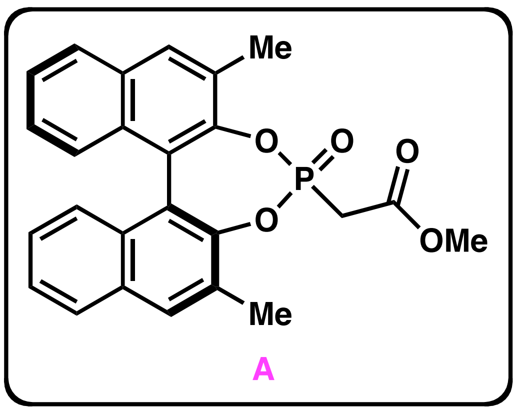


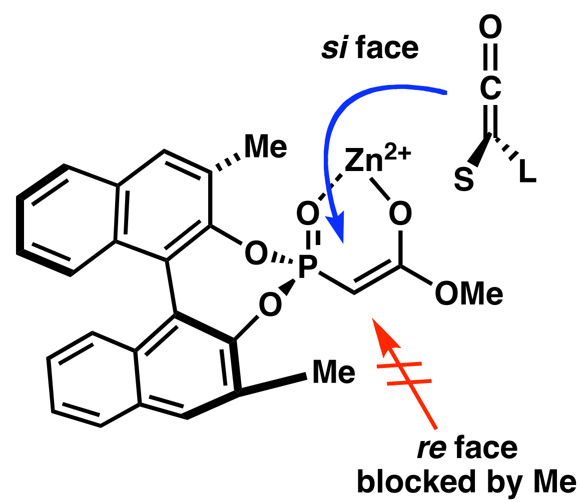
Mikami, K.; Yoshida, A. *Angew. Chem. Int. Ed.* **1997**, *36*, 858-860.
Mikami, K.; Yoshida, A. *Tetrahedron* **2001**, *57*, 889-898.

Asymmetric HWE





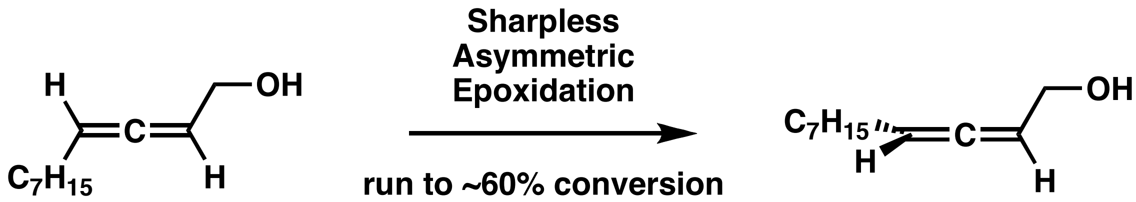




This work: Tanaka, K.; Otsubo, K.; Fuji, K. *Tetrahedron Lett.* **1996**, *37*, 3735-3738. Yamazaki, J.; Watanabe, T.; Tanaka, K. *Tetrahedron: Asymmetry* **2001**, *12*, 669-675.
For examples of Wittig-type olefinations of ketenes, see: Lang, R. W.; Hansen, H. J. *Helv. Chim. Acta* **1980**, *63*, 438-55. Tanaka, K.; Otsubo, K.; Fuji, K. *Synlett* **1995**, 933-934. Tanaka, K.; Otsubo, K.; Fuji, K. *Tetrahedron Lett.* **1995**, *36*, 9513-9514.

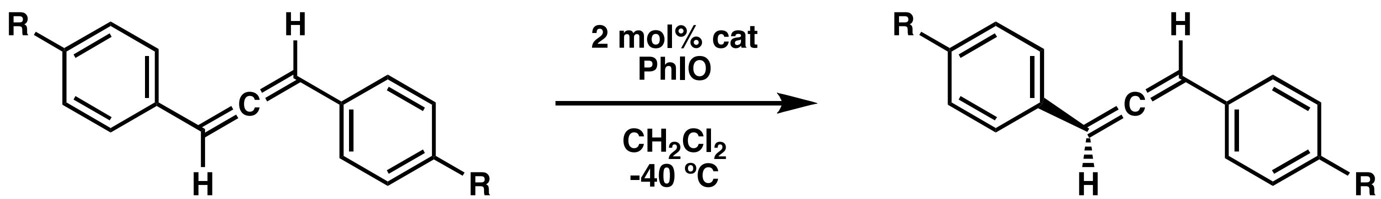
Chiral Catalysis and Kinetic resolution

Kinetic Resolution



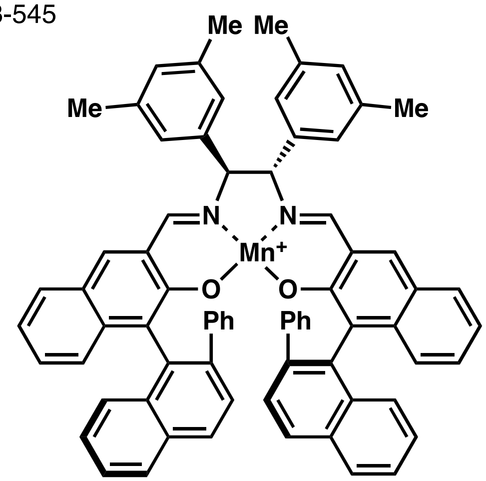
40% ee

Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Viti, S. M.; Walker, F. J.; Woodard, S. S. *Pure Appl. Chem.* **1983**, *55*, 589-604.

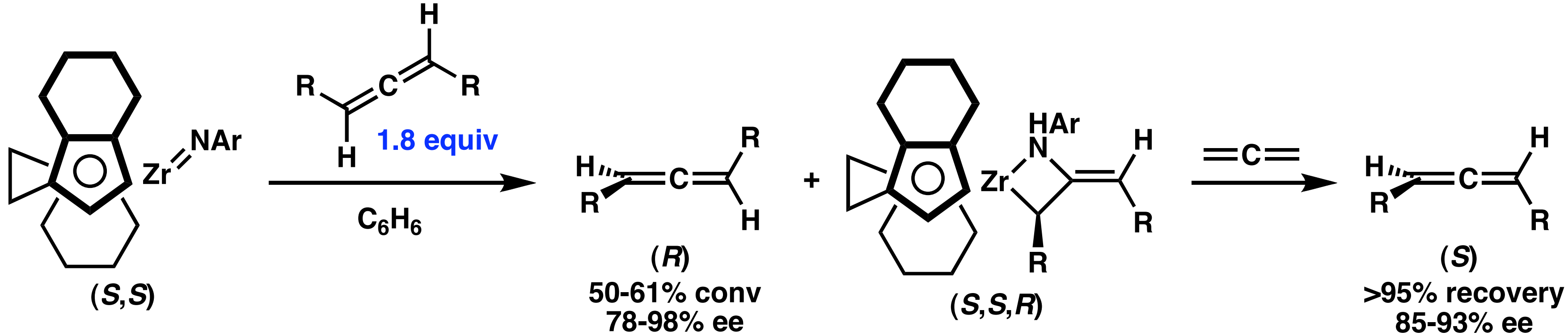


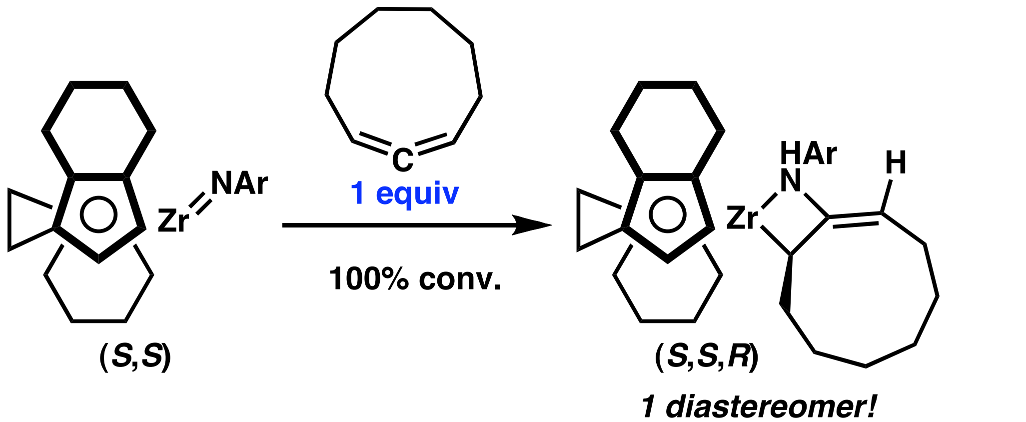
61-98% ee
57-83% conversion

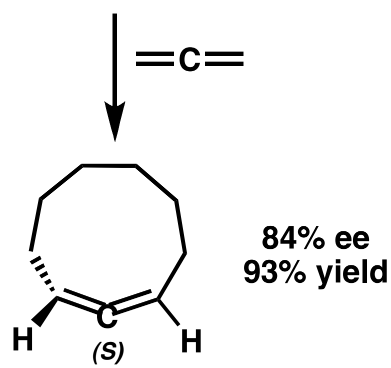
Noguchi, Y.; Takiyama, H.; Katsuki, T. *Synlett* **1998**, 543-545



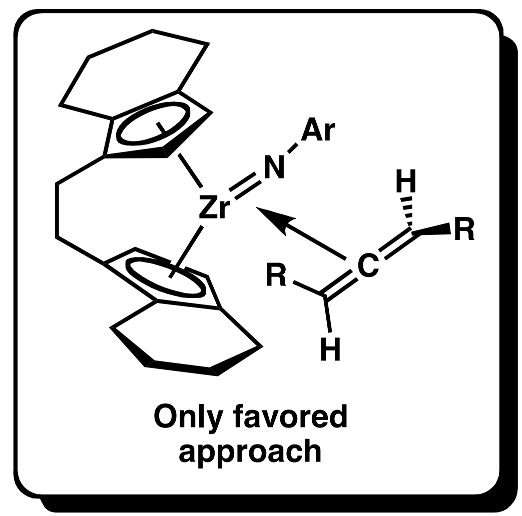
Kinetic Resolution







Thought to involve stepwise mechanism; therefore highly stereoselective, not stereospecific

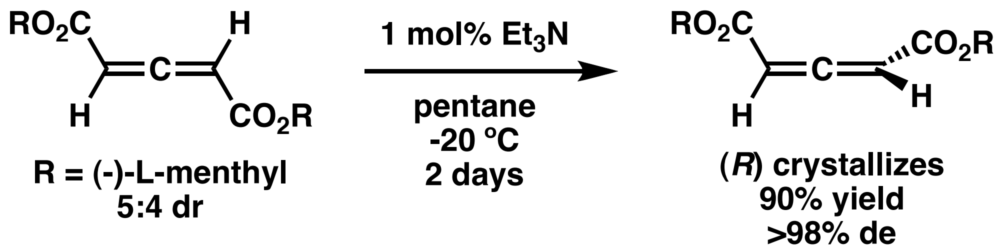


Only favored approach

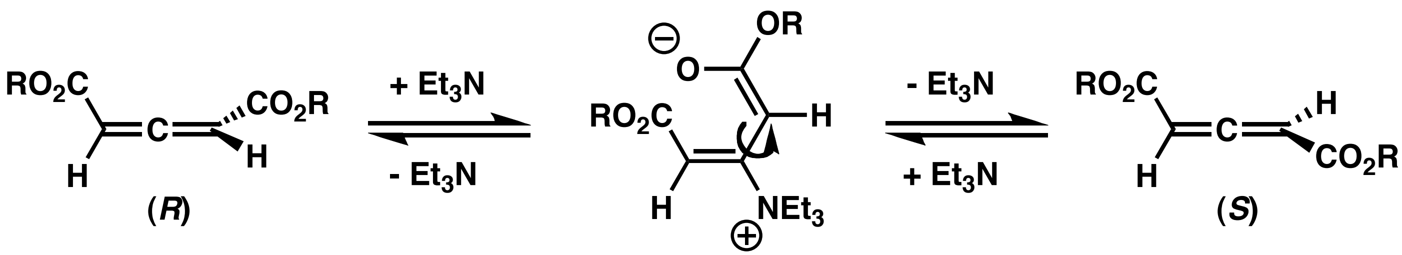
Sweeney, Z. K.; Salsman, J. L.; Anderson, R. A.; Bergman, R. G. *Angew. Chem. Int. Ed.* **2000**, *39*, 2339-2343.

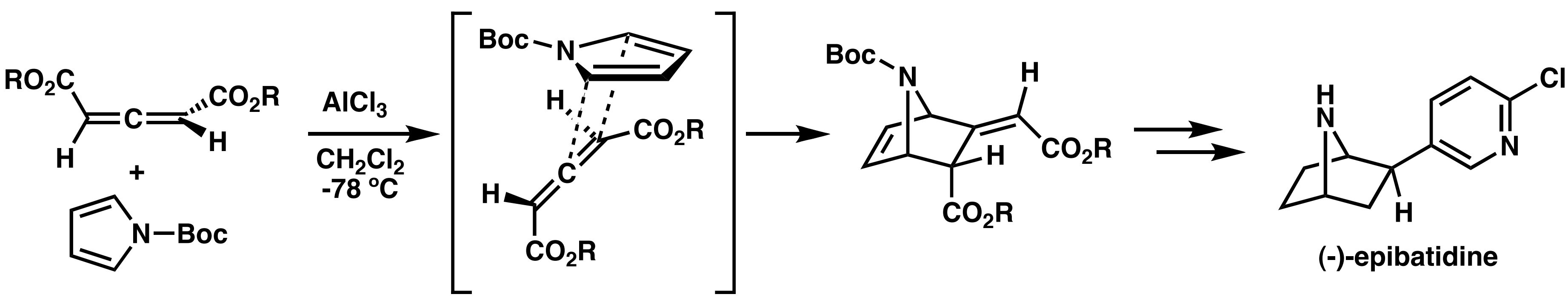
Kinetic Resolution

deracemization



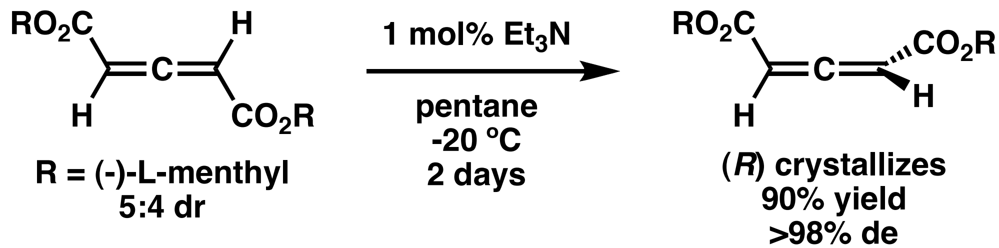
Node, M.; Nishide, K.; Fujiwara, T.; Ichihashi, S. *J. Chem. Soc., Chem. Commun.* **1998**, 2363-2364.



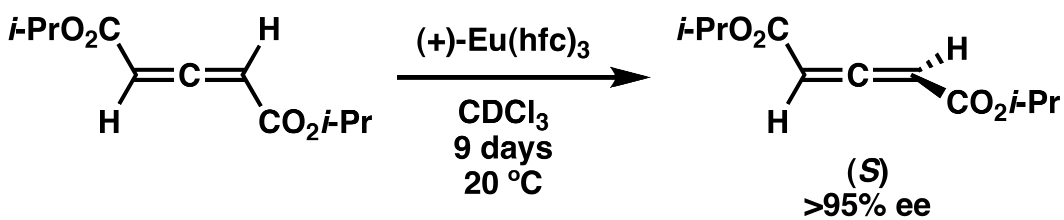


Kinetic Resolution

deracemization



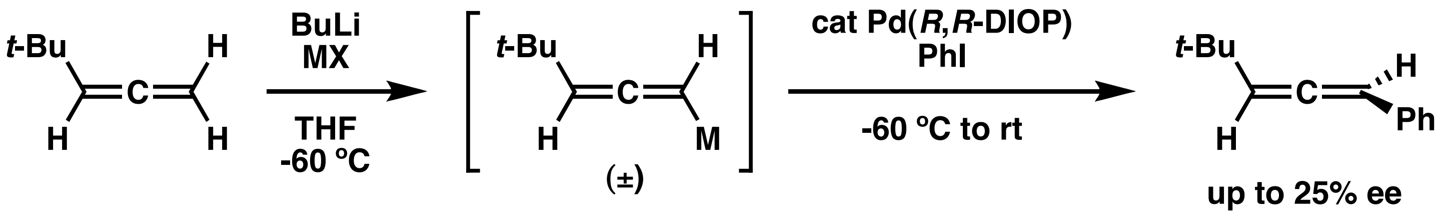
Node, M.; Nishide, K.; Fujiwara, T.; Ichihashi, S. *J. Chem. Soc., Chem. Commun.***1998**, 2363-2364.



Naruse, Y.; Watanabe, H.; Ishiyama, Y.; Yoshida, T. *J. Org. Chem.* **1997**, *62*, 3862-3866

Chiral Catalysis

The Beginning



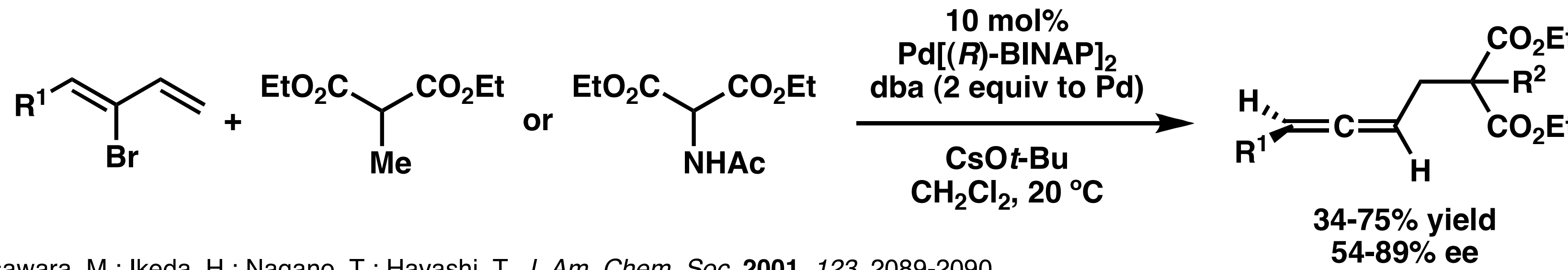
MX = ZnCl, MgCl, CuBr/LiBr

up to 25% ee
changing MX altered sense of induction

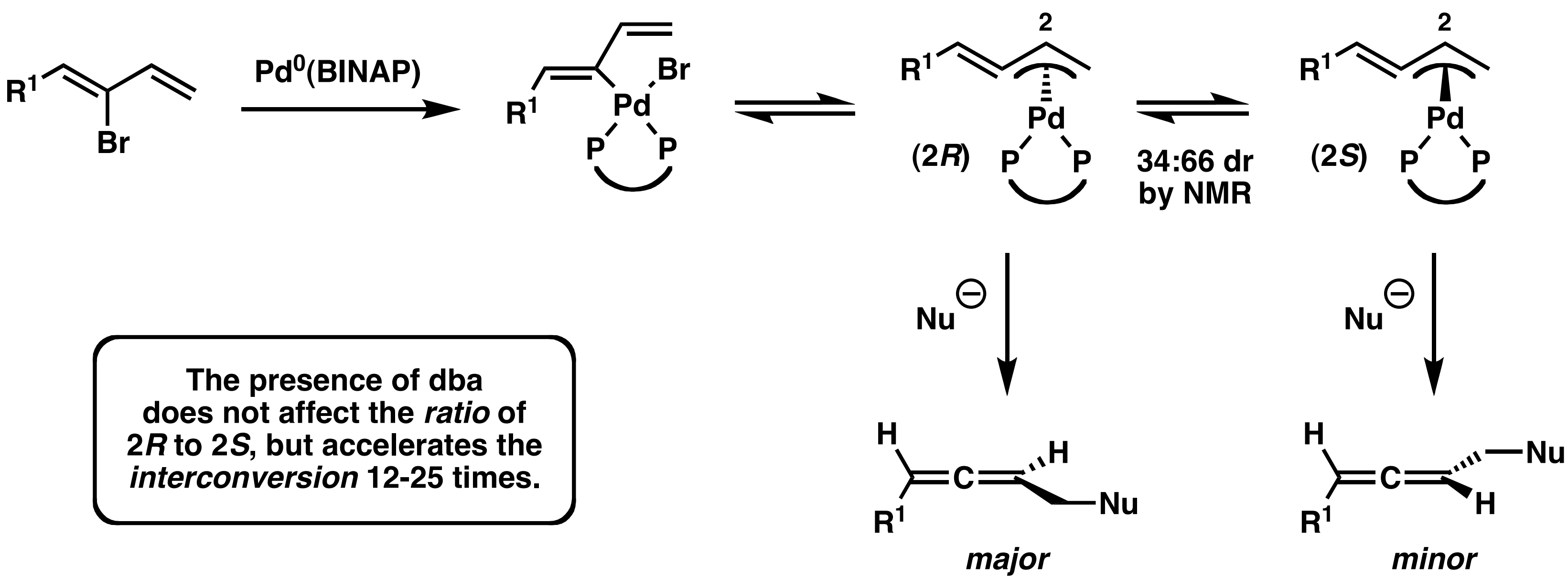
Warning!
Speculation by AMH

de Graaf, W.; Boersma, J.; van Koten, G.; Elsevier, C. J. *J. Organometallic Chem.* **1989**, *378*, 115-124.

Chiral Catalysis

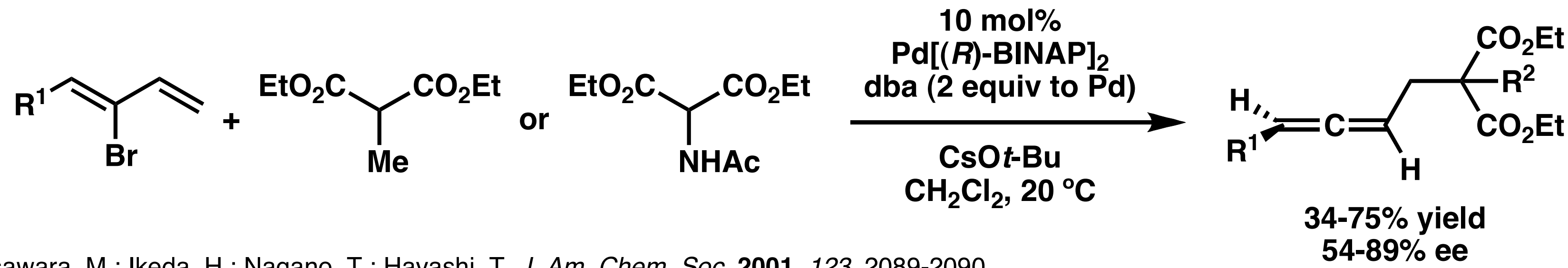


Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089-2090.
Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 5764-5767.

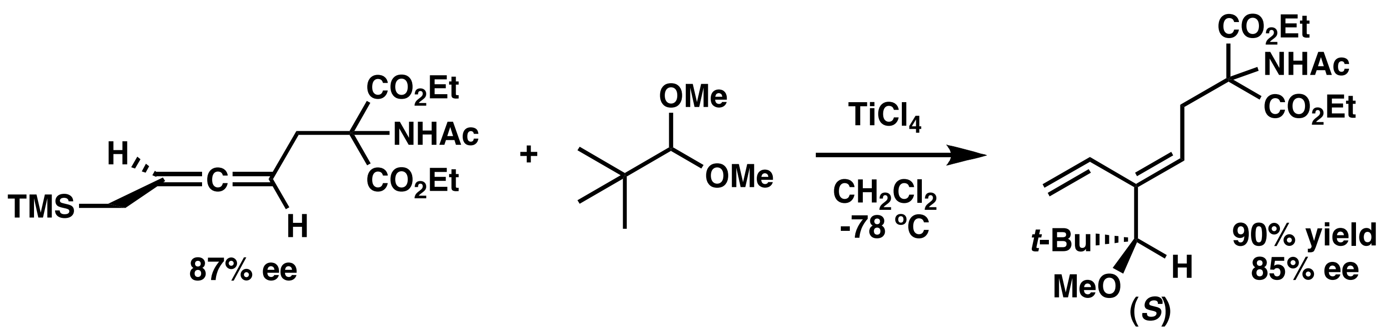


The presence of dba does not affect the *ratio* of 2*R* to 2*S*, but accelerates the *interconversion* 12-25 times.

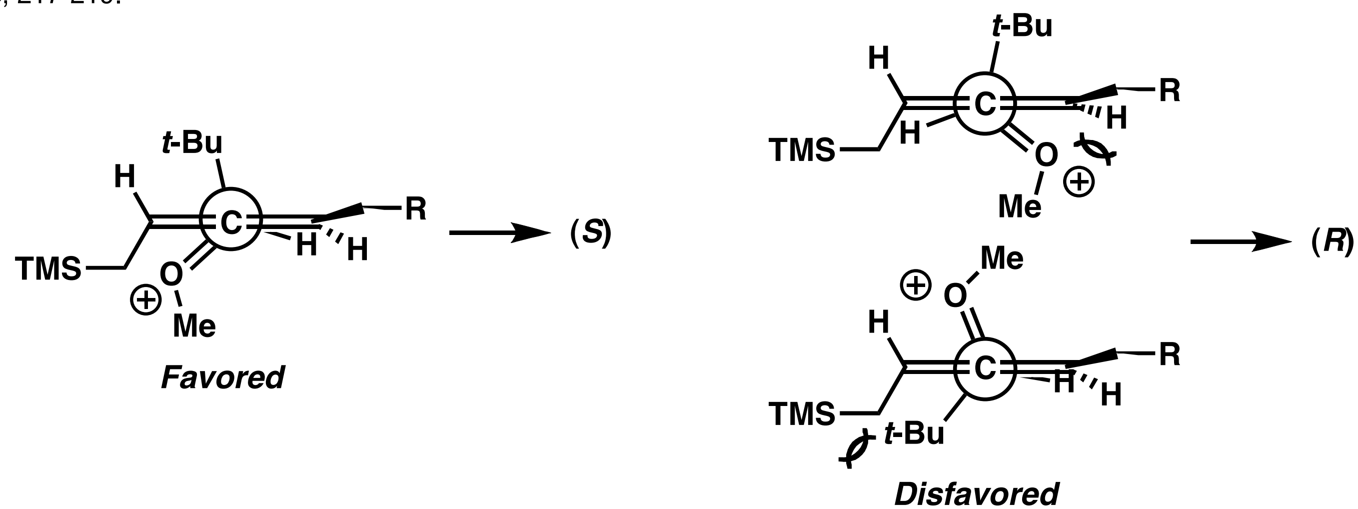
Chiral Catalysis



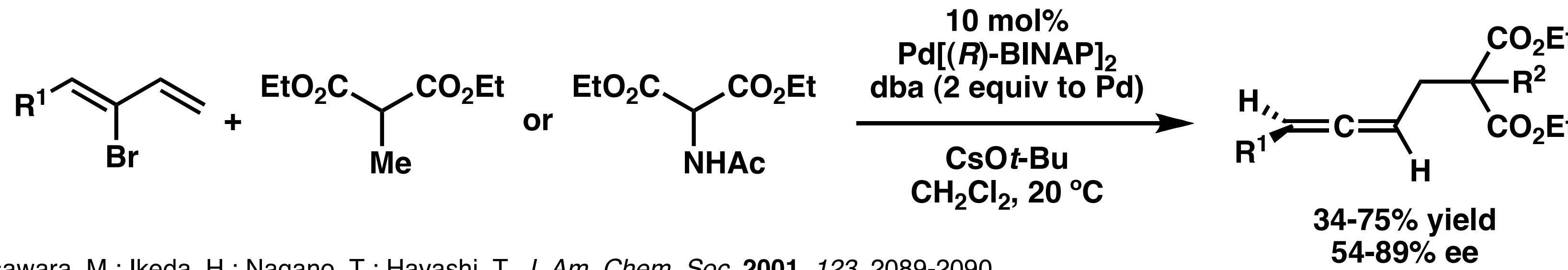
Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089-2090.
Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 5764-5767.



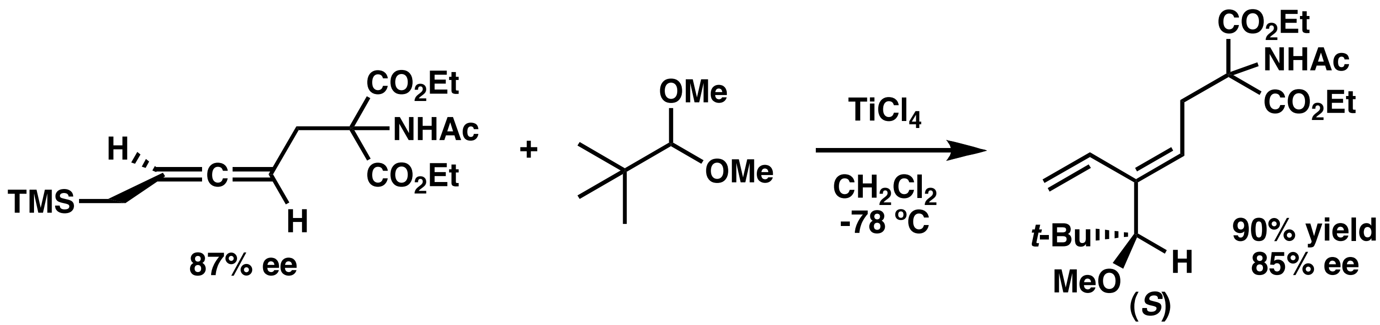
Ogasawara, M.; Ueyama, K.; Nagano, T.; Mizuhata, Y.; Hayashi, T.
Org. Lett. **2003**, *5*, 217-219.



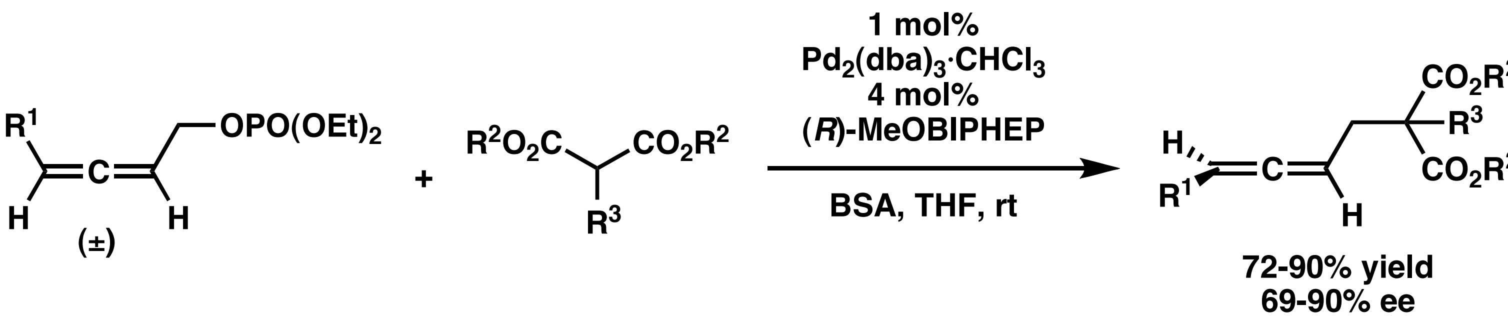
Chiral Catalysis



Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089-2090.
Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 5764-5767.

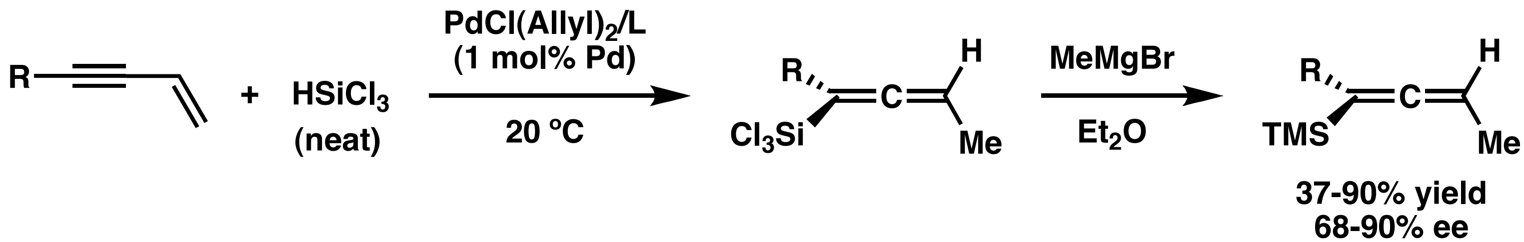


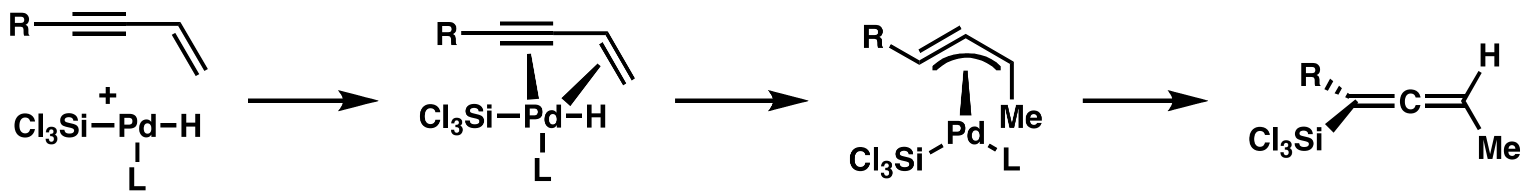
Ogasawara, M.; Ueyama, K.; Nagano, T.; Mizuhata, Y.; Hayashi, T.
Org. Lett. **2003**, *5*, 217-219.

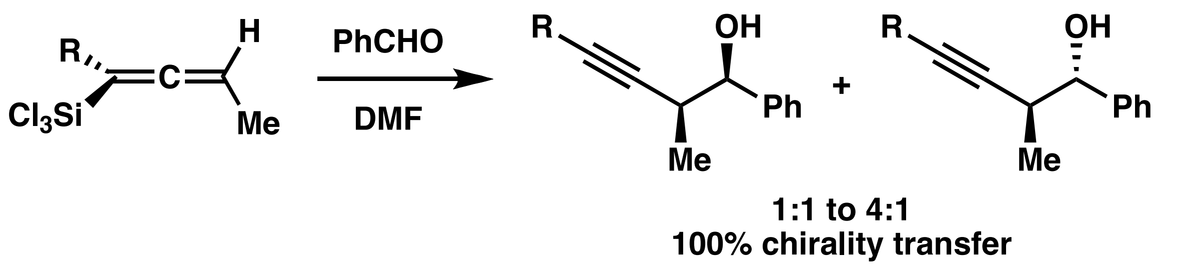


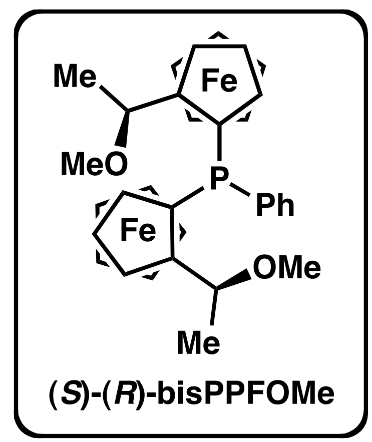
Imada, Y.; Ueno, K.; Kutsuwa, K.; Murahashi, S.-I. *Chem. Lett.* **2002**, *5*, 140-141.

Chiral Catalysis



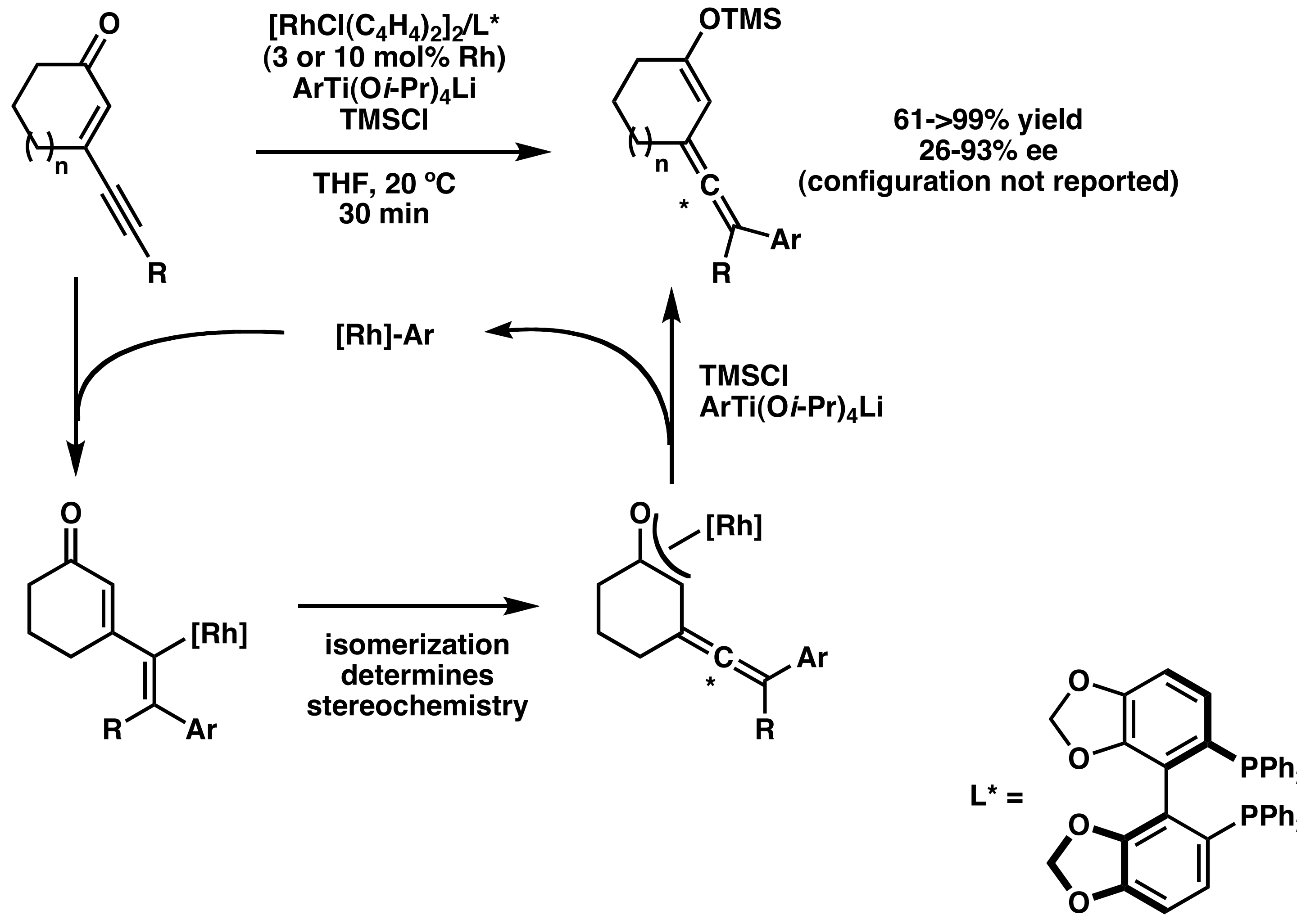






Han, J. W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 12915-12916.
For hydrosilylation of butadiynes with low selectivity, see: Tillack, A., Koy, C.; Michalix, D.; Fischer, C. *J. Organometallic Chem.* **2000**, *603*, 116-121.
For hydroboration of ene-ynes with low selectivity, see: Matsumoto, Y.; Naito, M.; Uozumi, Y.; Hayashi, T. *J. Chem. Soc., Chem. Commun.* **1993**, 1468-1469.

Chiral Catalysis



(*R*)-segphos

Hayashi, T.; Tokunaga, N.; Inoue, K. *Org. Lett.* **2004**, *6*, 305-307.

Conclusions

Presented a flavor of the methods known to construct axial chiral allenes in an enantioselective manner, as well as a few reactions these products are useful for.

Many reliable methods for chirality transfer from pre-generated stereocenters with stiochiometric reagents.

There is still a deficiency in catalytic asymmetric methods. The selectivities of these processes are not as reliable, and scope has yet to be defined.

Allenes are not just theoretical curiosities and can be useful synthons for asymmetric synthesis as well as potentially useful final targets for biologically relavant molecules.

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