

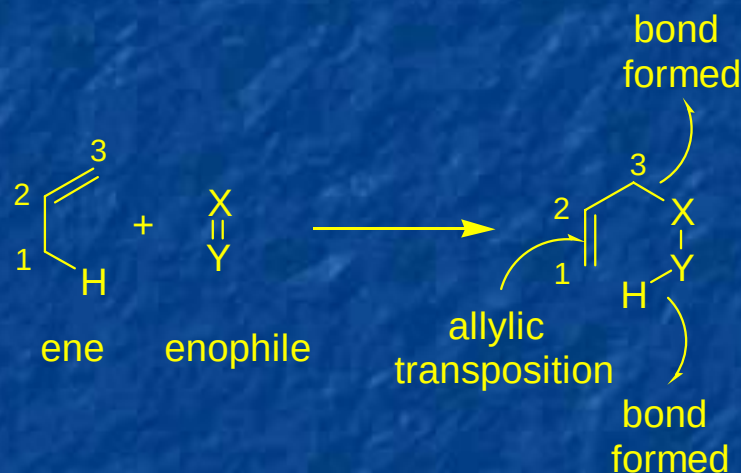
Asymmetric Ene Reactions in Organic Synthesis

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Justus-Liebig University, Giessen
19.05.2006

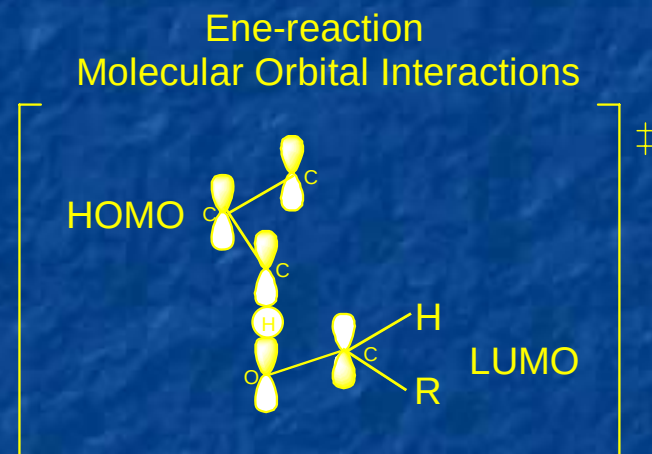
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Introduction



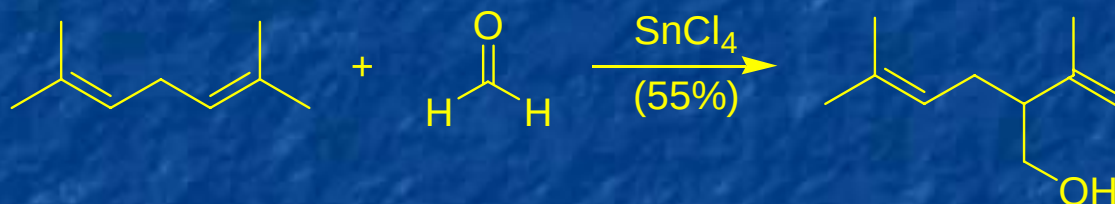
ene: alkene, alkyne, allene, arene, carbon-heteroatom bond
X=Y: C=C, C=N, C=N, C=S, O=O, N=N



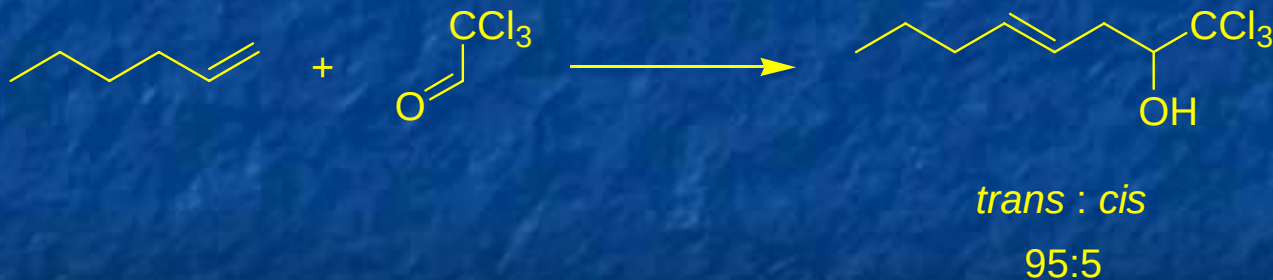
1. Treibs, W.; Schmidt, H. *Ber. Dtsch. Chem. Ges.* **1927**, 60, 2335.
2. Alder, K.; Pascher, F.; Schmitz, A. *Ber. Dtsch. Chem. Ges.* **1943**, 76, 27.
3. Nobel Lectures – Chemistry, 1942-1962; Elsevier: Amsterdam, **1964**; pp. 253-305.
4. Paderes, G.D.; Jorgensen, W.L. *J. Org. Chem.*, **1992**, 57, 1904.

Scope and Limitations: Carbonyl-Ene Reactions

Formaldehyde



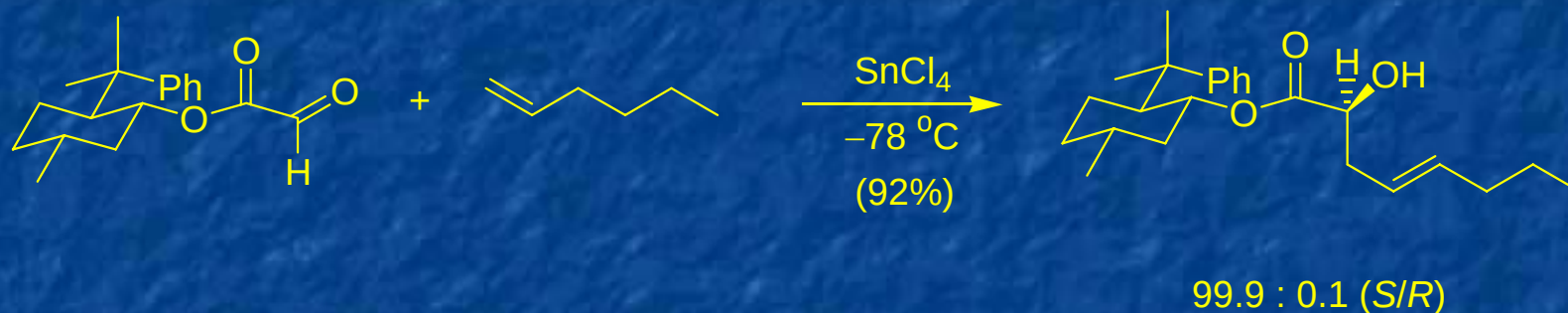
Chloral



1. Cookson, R.C.; Mirza, N.A. *Synth. Commun.* **1981**, 11, 299.
2. Gill, G.B.; Wallace, B. *J. Chem. Soc., Chem. Commun.* **1977**, 380.

Scope and Limitations: Carbonyl-Ene Reactions

Glyoxilates



Aliphatic and Aromatic Aldehydes



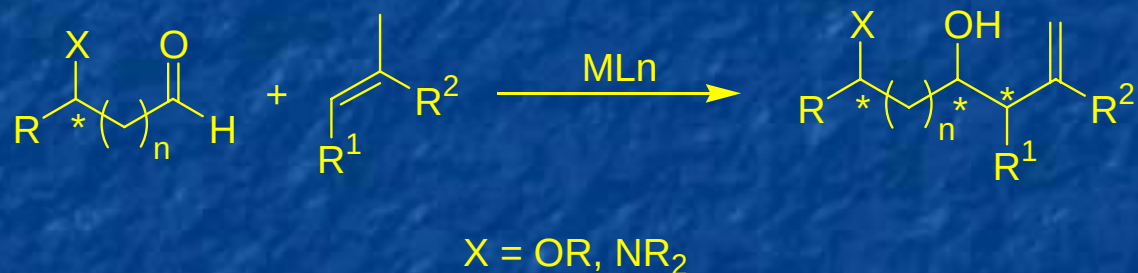
$\text{R} = \text{C}_3\text{H}_7, \text{C}_{11}\text{H}_{23}, (\text{CH}_2)_6\text{COOH}, (\text{CH}_2)_3\text{OCOCH}_3, \text{etc.}$

$\text{R}^1 = \text{H}, \text{CH}_3, \text{C}_6\text{H}_{13}$

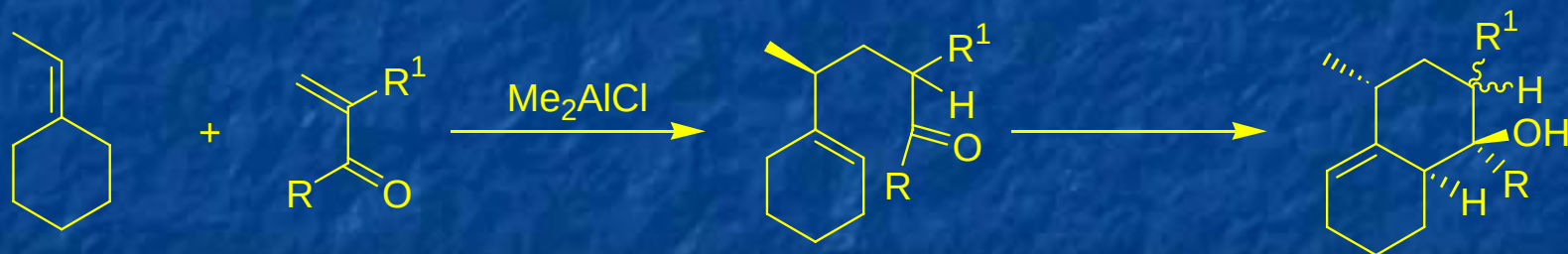
1. Whitesell, J.K. *Acc. Chem. Res.* **1985**, 18, 280.
2. Snider, B.B.; Phillips, G.B. *J. Org. Chem.* **1983**, 48, 464.

Scope and Limitations: Carbonyl-Ene Reactions

Hetero-Substituted Aliphatic Aldehydes



α,β -Unsaturated Aldehydes and Ketones



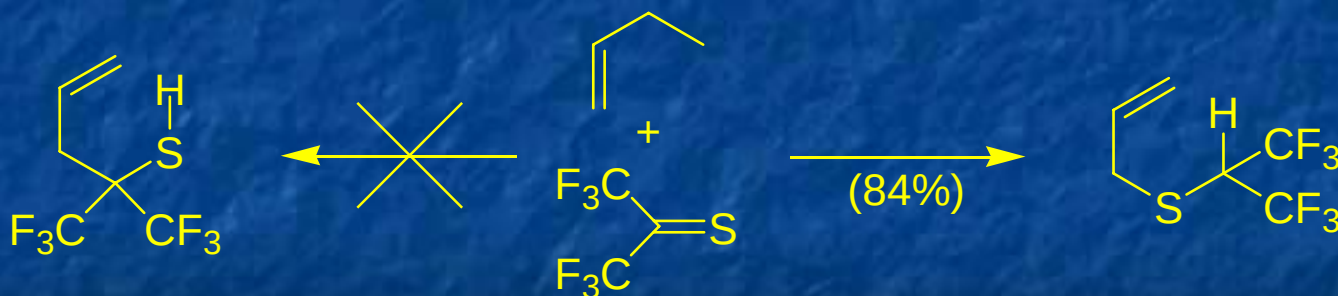
1. Mikami, K.; Loh, T.-P.; Nakai, T. *Tetrahedron: Asymmetry* **1990**, 1, 13.
2. Mikami, K.; Kaneko, M.; Loh, T.-P.; Terada, M.; Nakai, T. *Tetrahedron Lett.* **1990**, 31, 3909.
3. Snider, B.B.; Goldman, B.E. *Tetrahedron* **1986**, 42, 2951.
4. Snider, B.B.; Deutsch, E.A. *J. Org. Chem.* **1982**, 47, 745; **1983**, 48, 1822.

Scope and Limitations: Carbonyl-Ene Reactions

Imine Derivatives



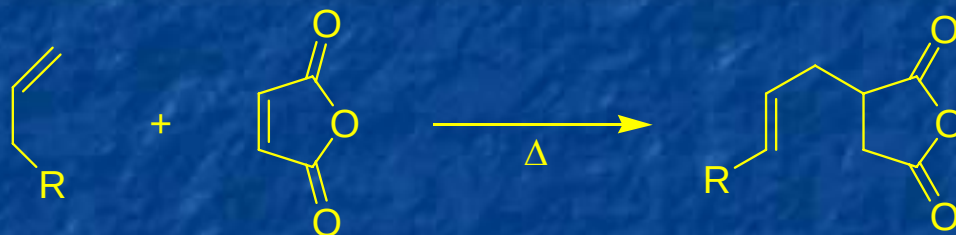
Thiocarbonyl Compounds



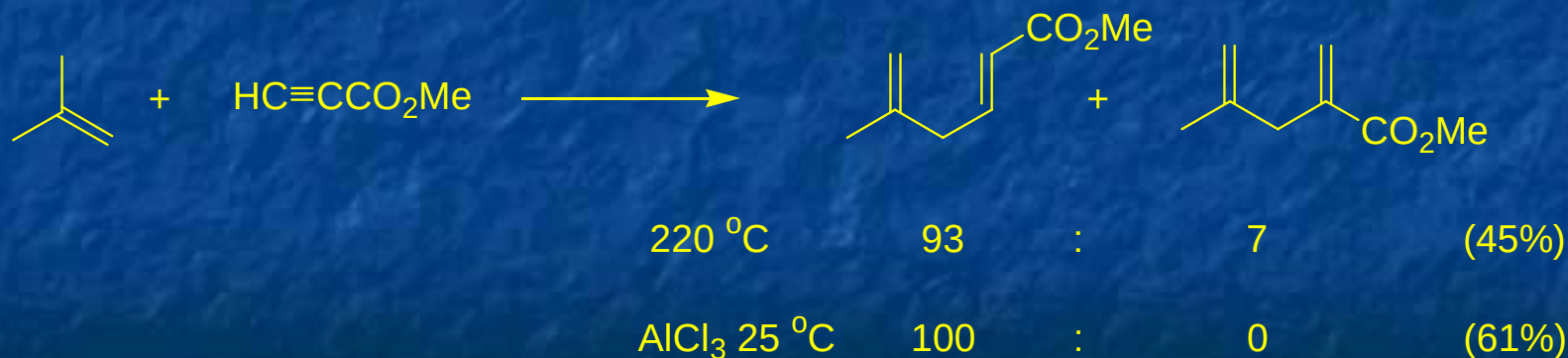
1. Hayashi, Y.; Shibata, T.; Narasaka, K. *Chem. Lett.* **1990**, 1693.
2. Middleton, W.J. *J. Org. Chem.* **1965**, 30, 1395.
3. Middleton, W.J.; Howard, E.G.; Sharkey, W.H. *J. Am. Chem. Soc.* **1961**, 83, 2589.

Scope and Limitations: Olefin-Ene Reactions

Maleic Anhydride



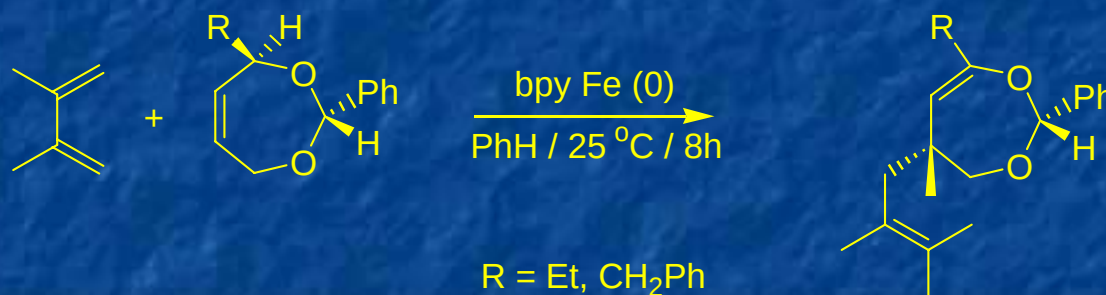
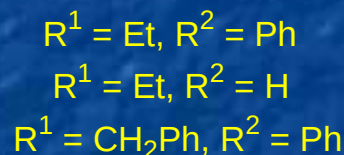
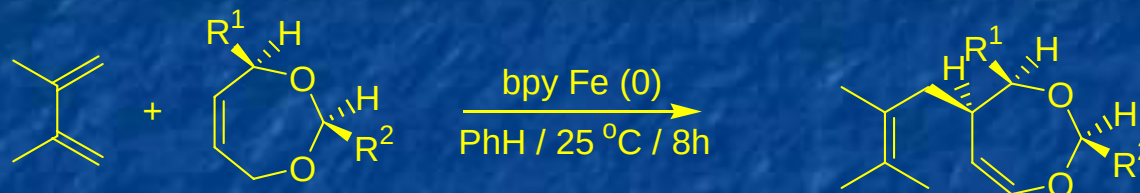
(α -Substituted) Acrylates



1. Rondestvedt, C.S., Jr.; Filbey, A.H. *J. Org. Chem.* **1954**, 19, 548.
2. Alder, K.; von Brachel, H. *Justus Liebigs Ann. Chem.* **1962**, 651, 141.

Scope and Limitations: Olefin-Ene Reactions

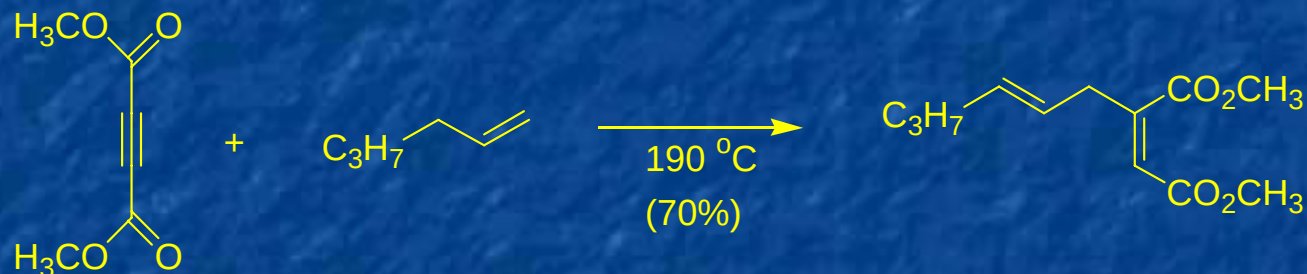
Diene-Iron Complex



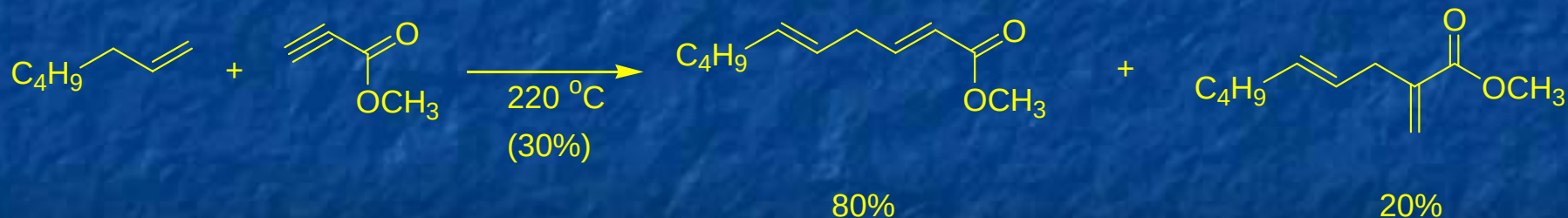
1. Takasc, J.M.; Anderson, L.G.; Madhavan, G.V.B.; Creswell, M.W.; Seely, F.L.; Devroy, W.F. *Organometallics* **1986**, 5, 2395.
2. Takasc, J.M.; Anderson, L.G.; Madhavan, G.V.B.; Seely, F.L. *Angew. Chem., Int. Ed. Engl.* **1987**, 26, 1013.
3. Takasc, J.M.; Anderson, L.G.; Newsome, P.W. *J. Am. Chem. Soc.* **1987**, 109, 2542.
4. Takasc, J.M.; Myoung, Y.C. *Tetrahedron Lett.* **1992**, 33, 317.

Scope and Limitations: Acetylene-Ene Reactions

Acetylene Dicarboxylates

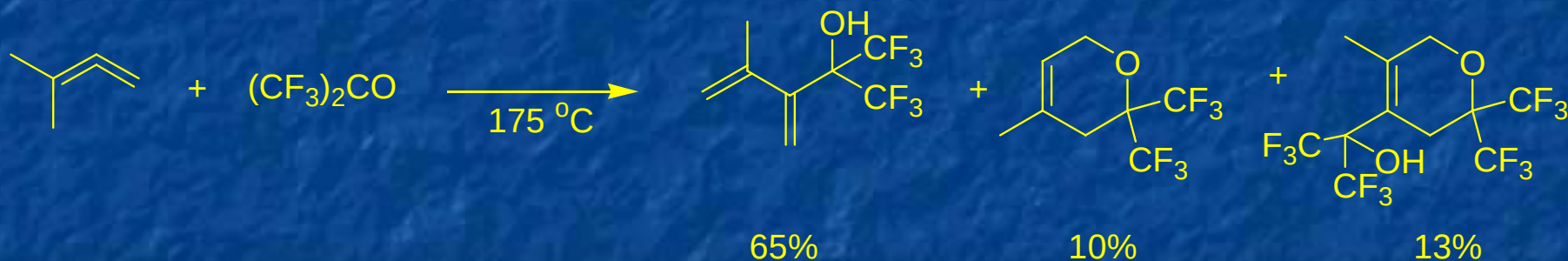
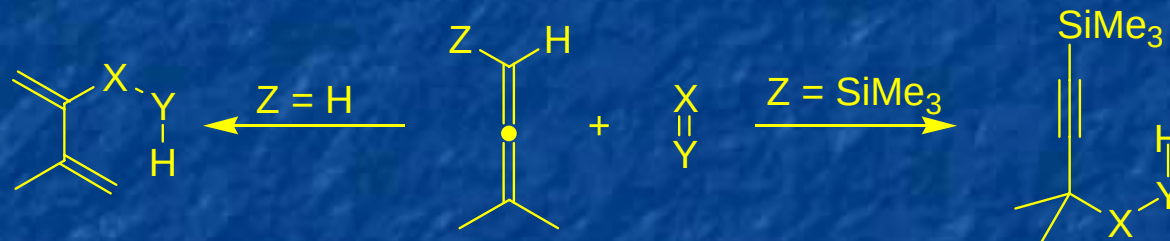


Propiolates



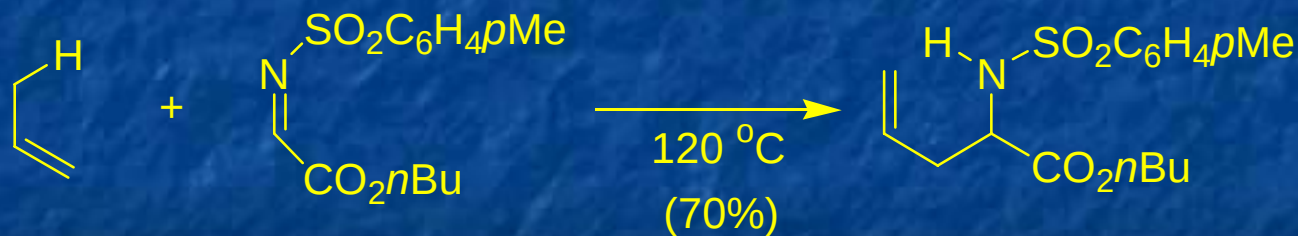
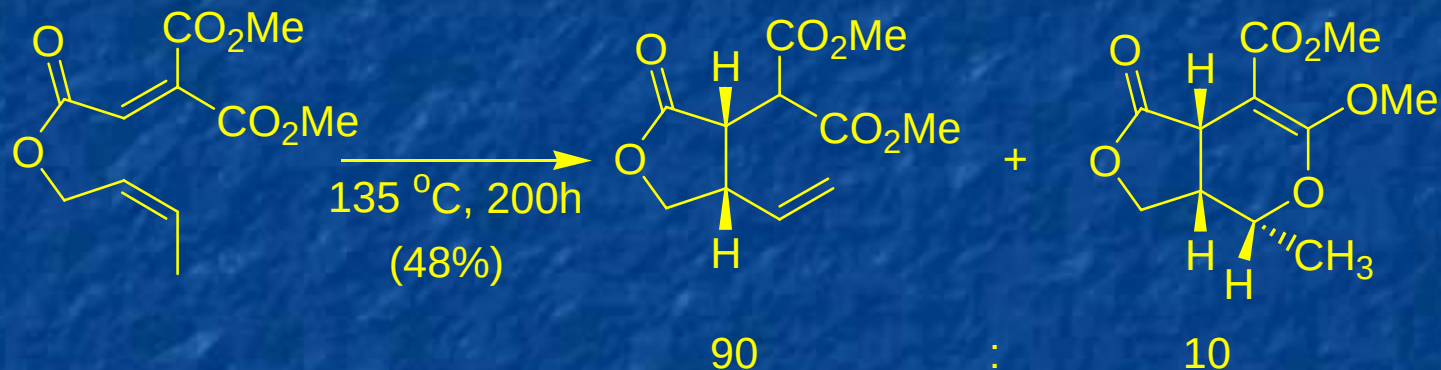
1. Sauer, J.C.; Sausen, G.N. *J. Org. Chem.* **1962**, 27, 2730.
2. Alder, K.; von Brachel, H. *Justus Liebigs Ann. Chem.* **1962**, 651, 141.

Scope and Limitations: Allenes as Enophiles or Enes



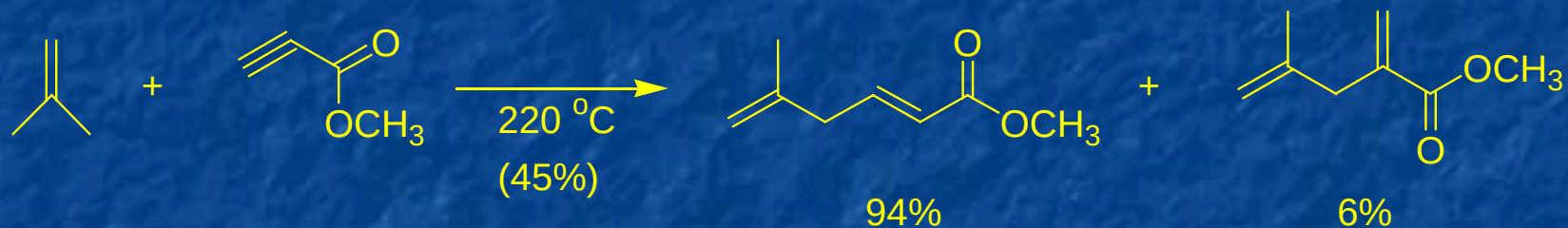
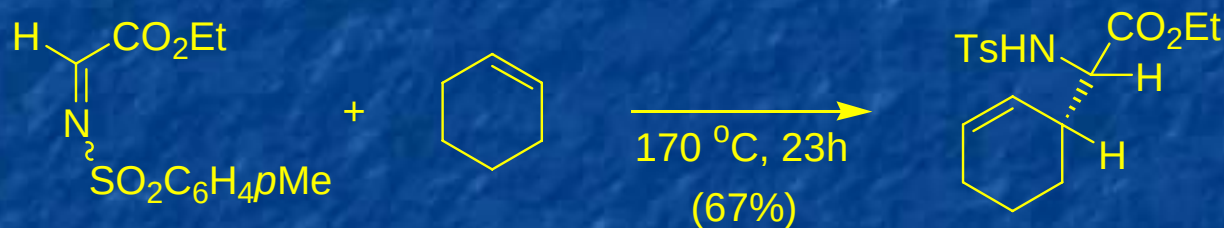
1. Lee, C.B.; Taylor, D.R. *J. Chem. Soc., Perkin. Trans. I* **1977**, 1463.
2. Taylor, D.R.; Write, D.B. *J. Chem. Soc., Perkin Trans. I* **1973**, 956.

Types of Reactions: Thermal Promoted



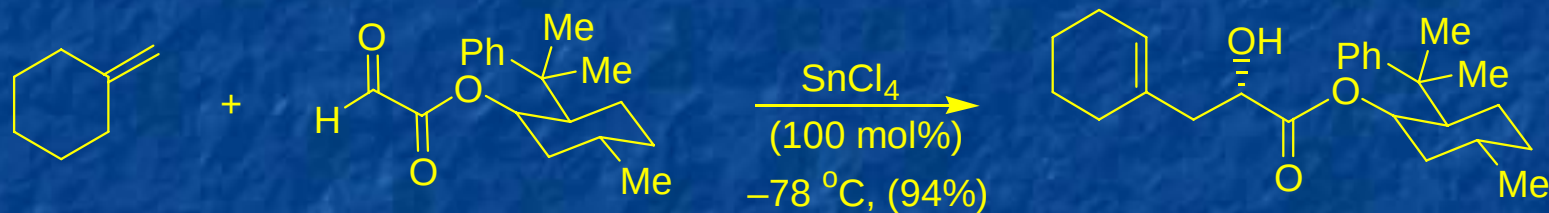
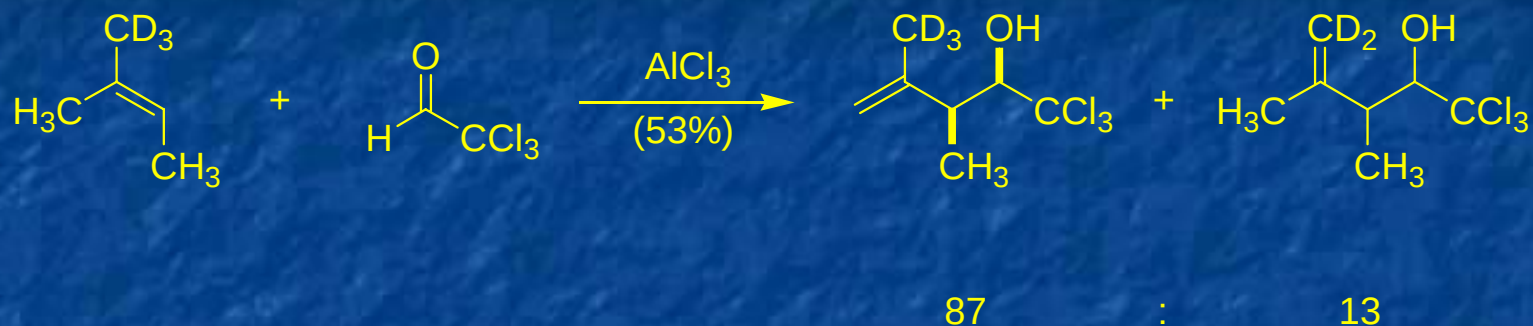
1. Snider, B.B.; Rush, D.M. *J. Org. Chem.* **1979**, 44, 4229.
2. Achmatowicz, O.; Pietraszkiewicz, M. *J. Chem. Soc., Chem. Commun.* **1976**, 484.

Types of Reactions: Thermal Promoted



1. Tschaen, D.M.; Weinreb, S.M. *Tetrahedron Lett.* **1982**, 23, 3015.
2. Alder, K.; von Brachel, H. *Justus Liebigs Ann. Chem.* **1962**, 651, 141.

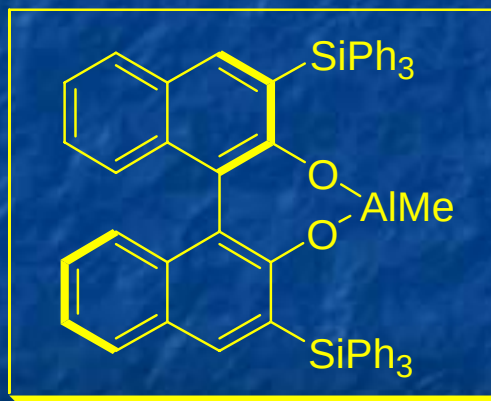
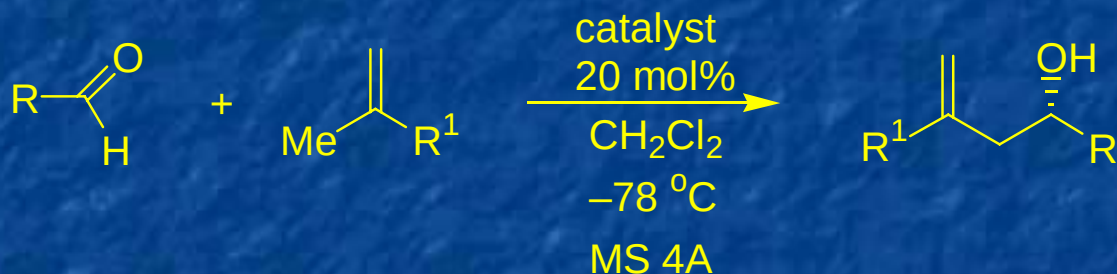
Types of Reactions: Lewis Acid Promoted



1. Benner, J.P.; Gill, G.B.; Parrott, S.J.; Wallace, B.; Begley, M.J. *J. Chem. Soc., Perkin Trans. I* **1984**, 315.
2. Whitesell, J.K.; Bhattacharya, A.; Buchanan, C.M.; Chen, H.H.; Deyo, D.; James, D.; Liu, C.-L.; Minton, M.A. *Tetrahedron* **1986**, 42, 2993.

Types of Reactions: Reactions with Chiral Lewis Acid Catalysts

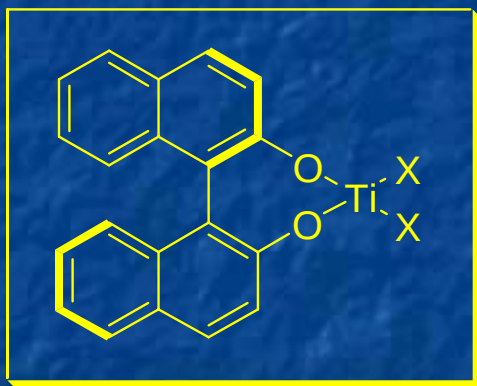
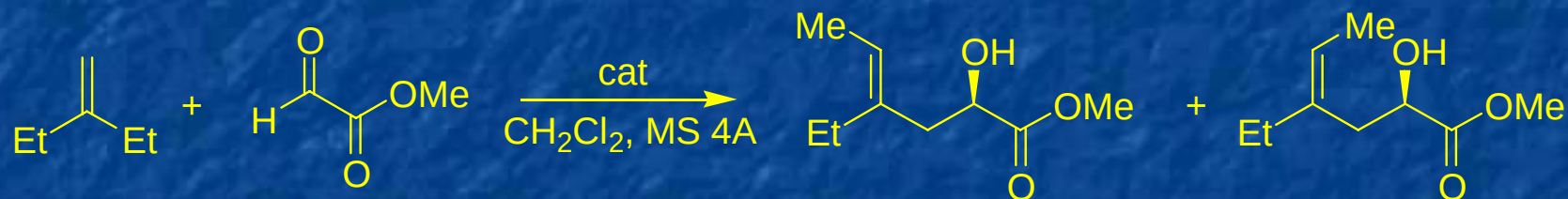
Chiral Aluminium Lewis Acids



1. Maruoka, K.; Hoshino, Y.; Shirasaka, T.; Yamamoto, H. *Tetrahedron Lett.* **1988**, 29, 3967.

Types of Reactions: Reactions with Chiral Lewis Acid Catalysts

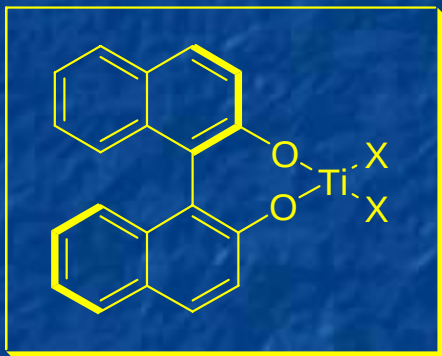
Chiral Titanium Lewis Acids



X = Cl (10 mol%)	89 (75% ee)	: 11	68%
X = Br (5 mol%)	91 (98% ee)	: 9	73%

Types of Reactions: Reactions with Chiral Lewis Acid Catalysts

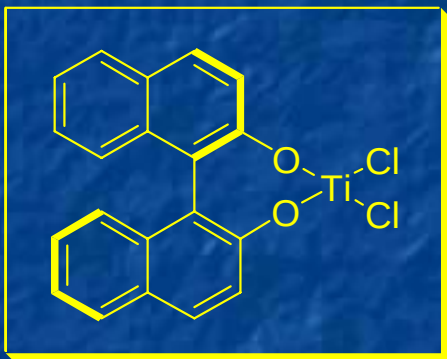
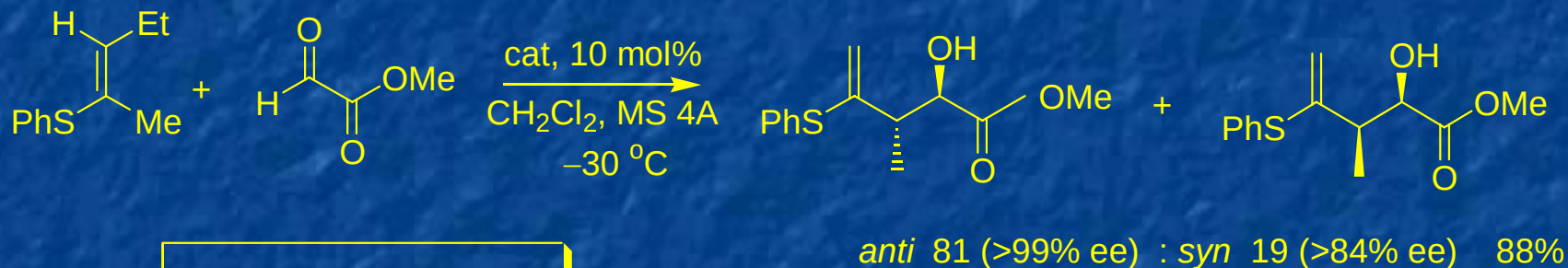
Chiral Titanium Lewis Acids



X = Br (10 mol%)	83 (92% ee)	: 17 (>98% ee)	91%
X = Cl (5 mol%)	87	: 13	73%

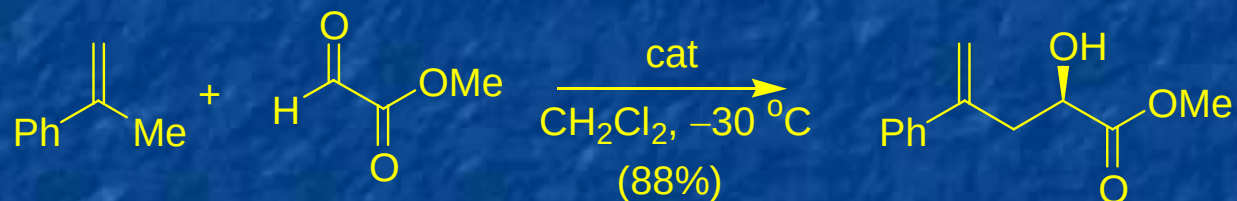
Types of Reactions: Reactions with Chiral Lewis Acid Catalysts

Chiral Titanium Lewis Acids

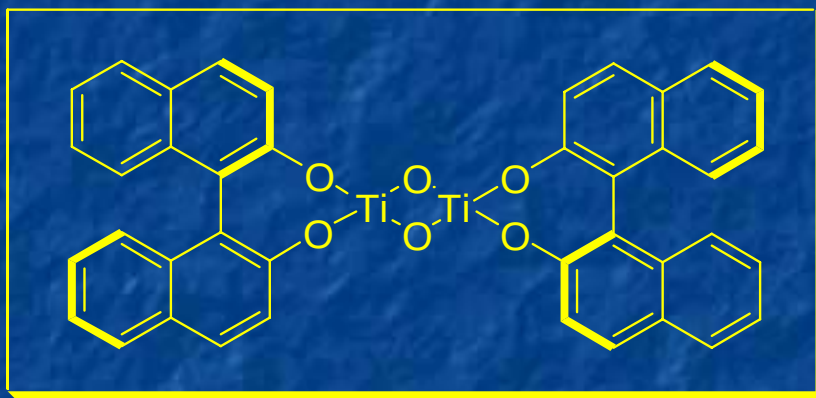


Types of Reactions: Reactions with Chiral Lewis Acid Catalysts

Chiral Titanium Lewis Acids

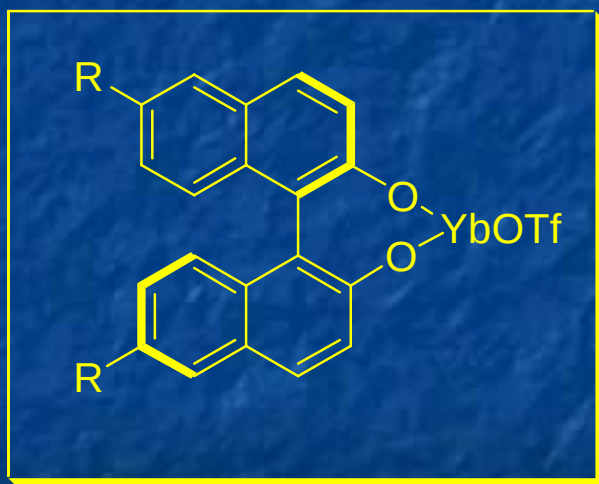
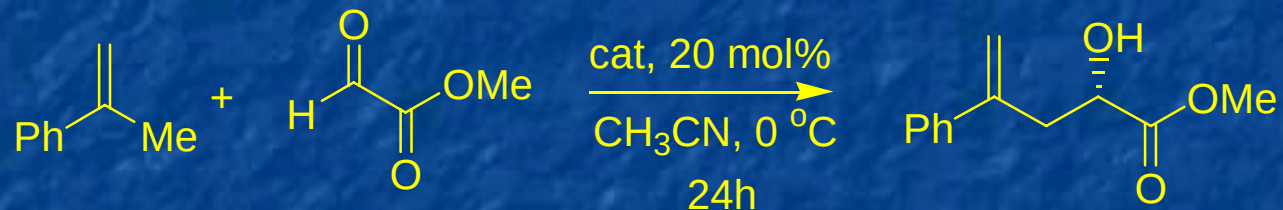


98.7% ee



Types of Reactions: Reactions with Chiral Lewis Acid Catalysts

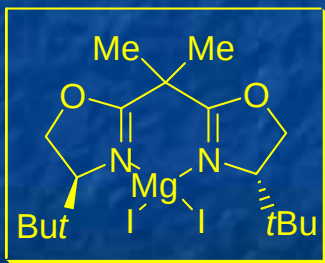
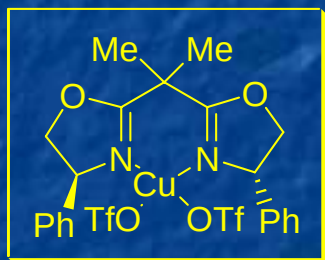
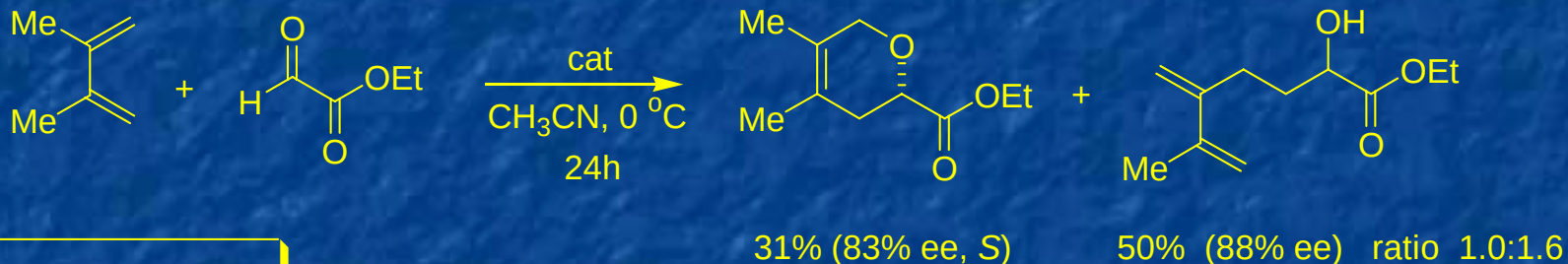
Chiral Ytterbium Lewis Acids



R = H	82	(12% ee, S)
R = Br	78	(38% ee, S)
R = Ph	87	(25% ee, S)
R = CCTMS	83	(29% ee, S)

Types of Reactions: Reactions with Chiral Lewis Acid Catalysts

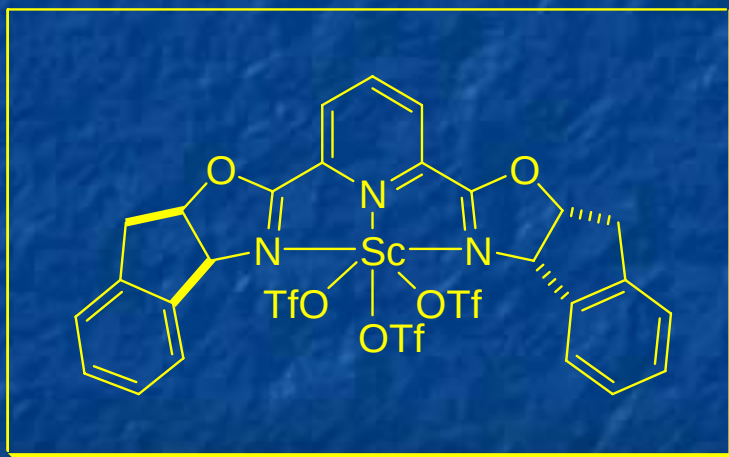
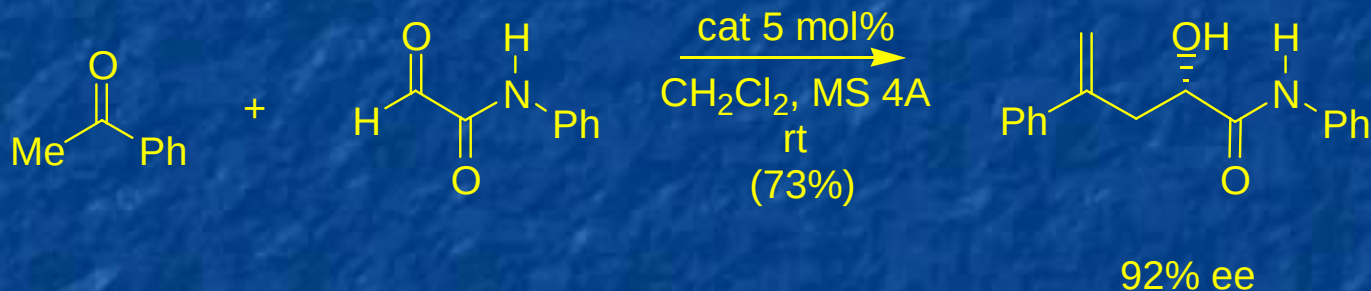
Chiral Copper and Magnesium Lewis Acids



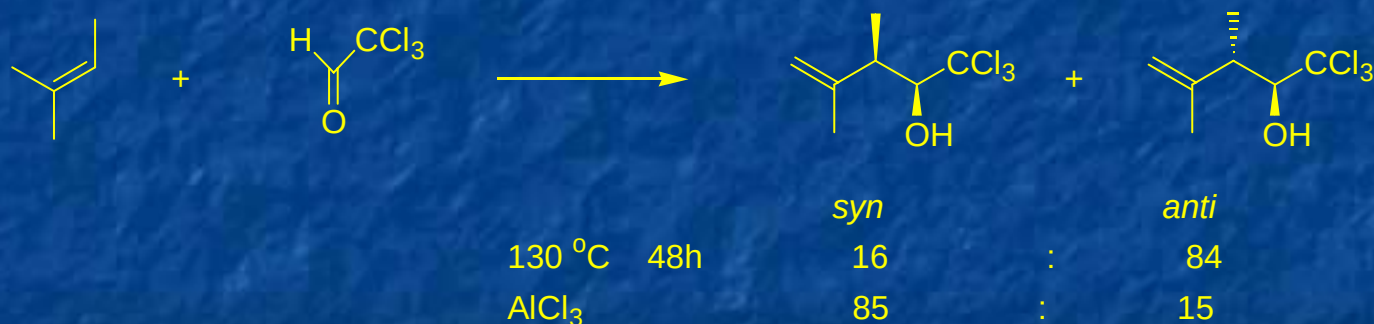
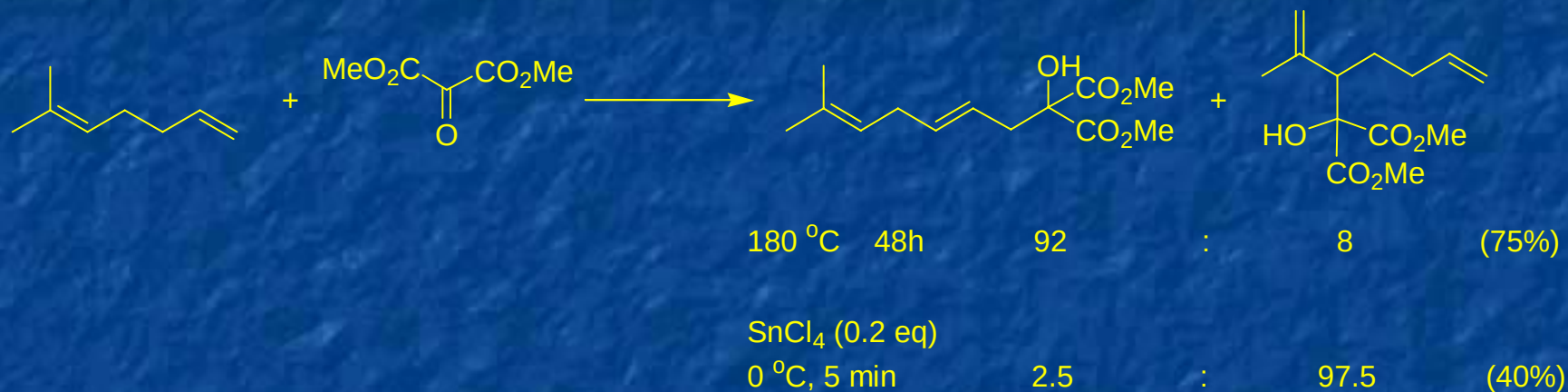
10% (5% ee, S) 20% (10% ee) ratio 1.0:2.0

Types of Reactions: Reactions with Chiral Lewis Acid Catalysts

Chiral Scandium Lewis Acids

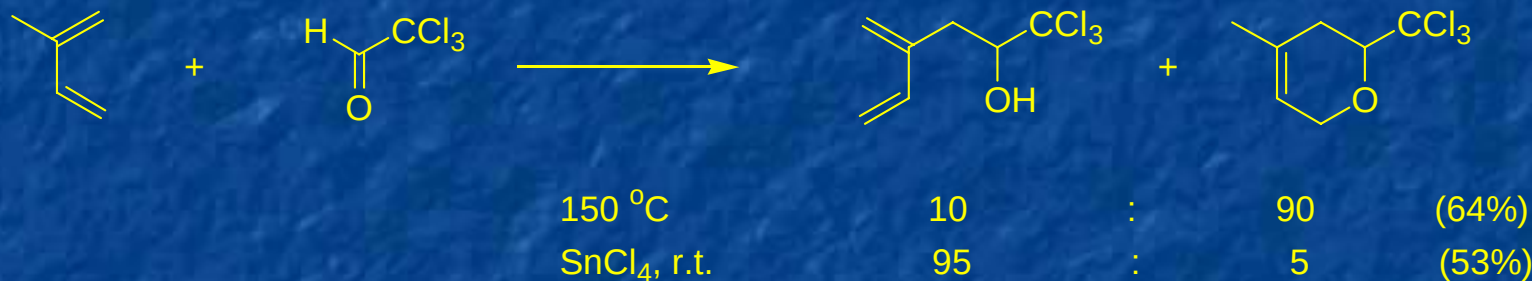


Types of Reactions: Thermal vs Lewis Acid Promoted



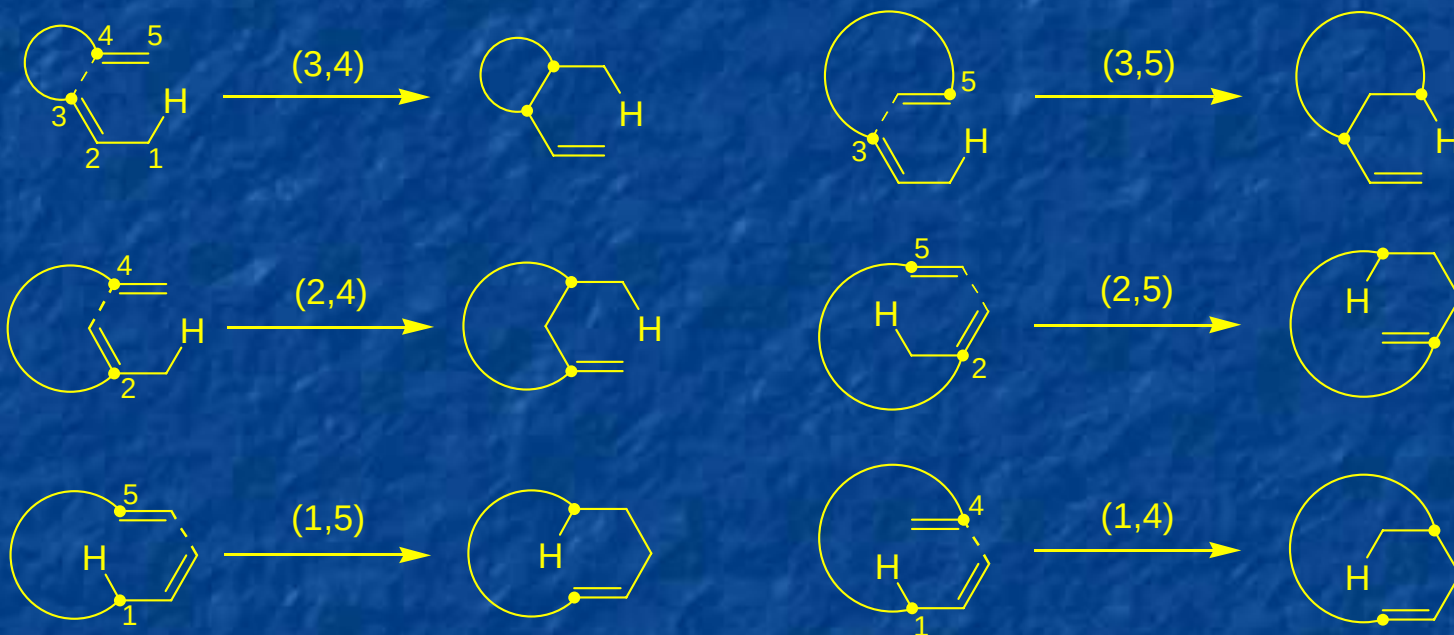
1. Salomon, M.F.; Pardo, S.N.; Salomon, R.G. *J. Org. Chem.* **1984**, 49, 2446.
2. Benner, J.P.; Gill, G.B.; Parrott, S.J.; Wallace, B.; Begley, M.J. *J. Chem. Soc. Perkin Trans I* **1984**, 315.

Types of Reactions: Thermal vs Lewis Acid Promoted



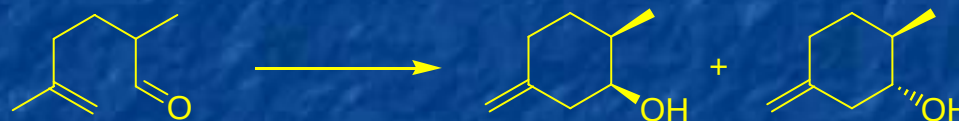
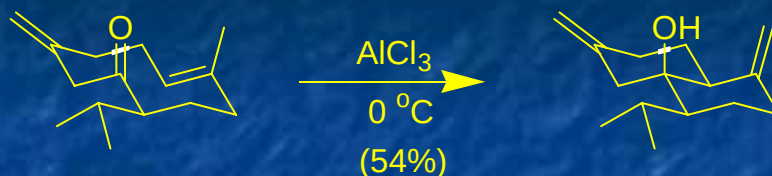
1. Klimova, E.; Arbuzov, Yu. *Chem. Abstr.* **1967**, 67, 108156c.
2. Klimova, E.I.; Treshchova, E.G.; Arbuzov, Yu.A. *Chem. Abstr.* **1968**, 69, 67173b.

Ene Cyclizations

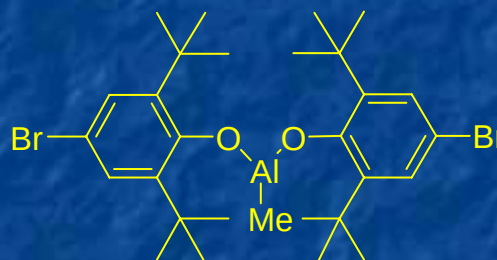


1. Mikami, K.; Sawa, E.; Terada, M. *Tetrahedron: Asymmetry* **1991**, I, 1403.
2. Ziegler, F.E. *Chem. Rev.* **1988**, 88, 1423.

Ene Cyclizations



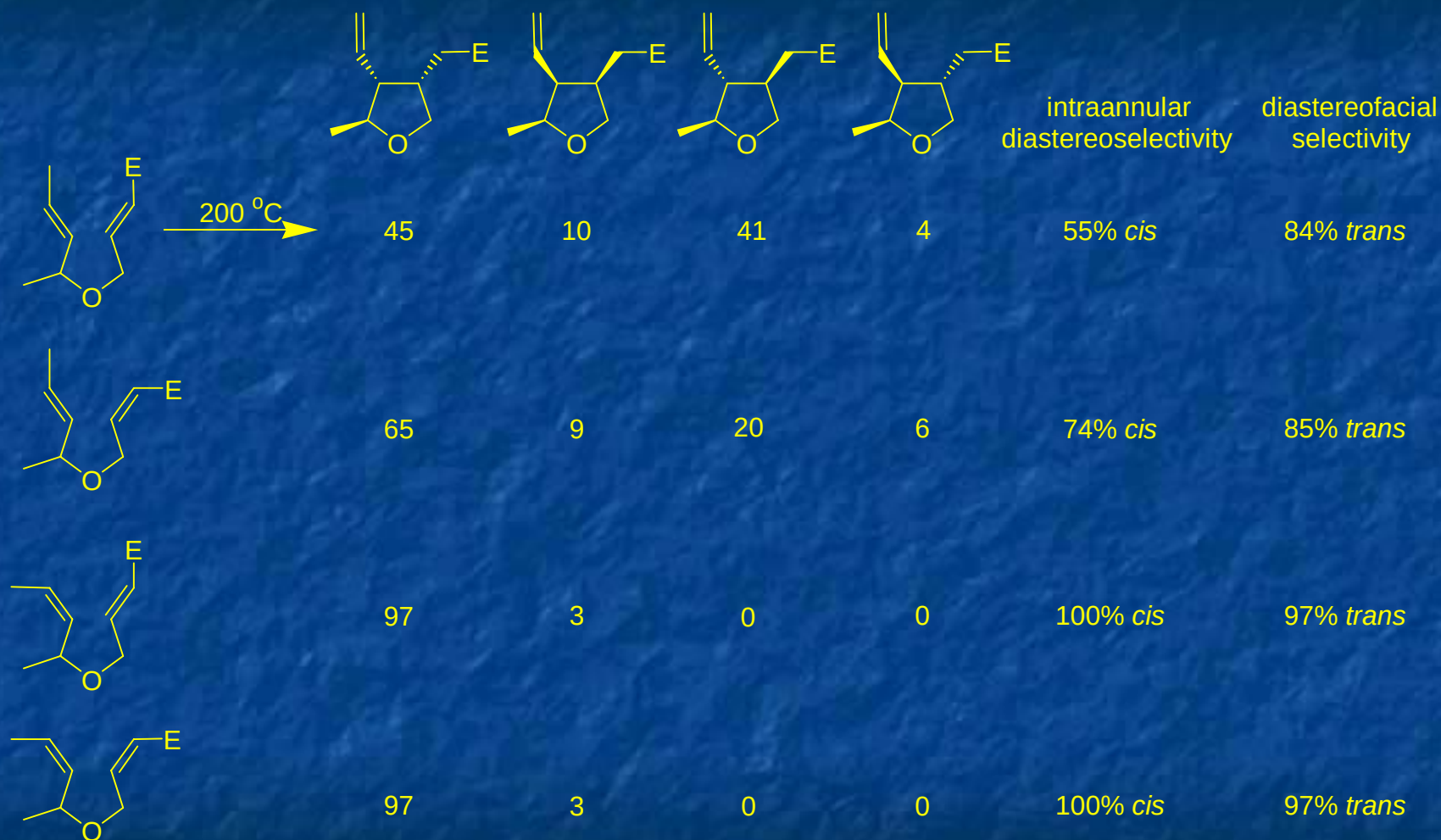
MeAlCl (-78°C)	90	:	10	(65%)
MABR (-78°C)	3	:	97	(85%)



(MABR)

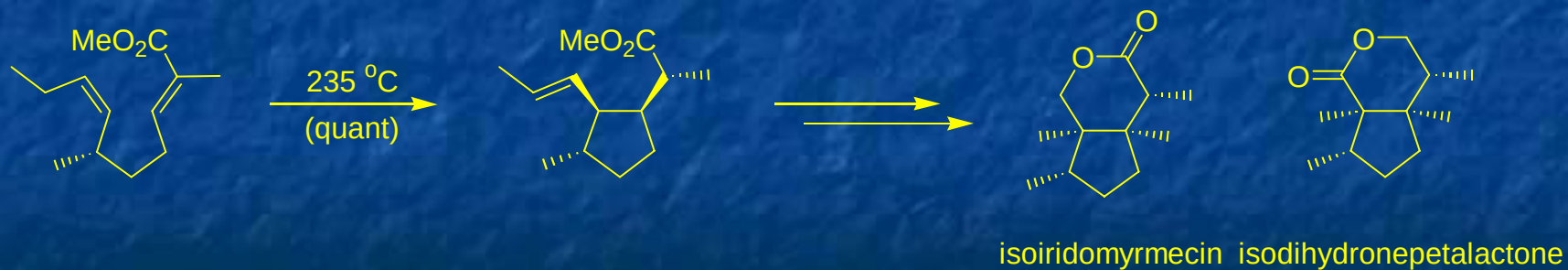
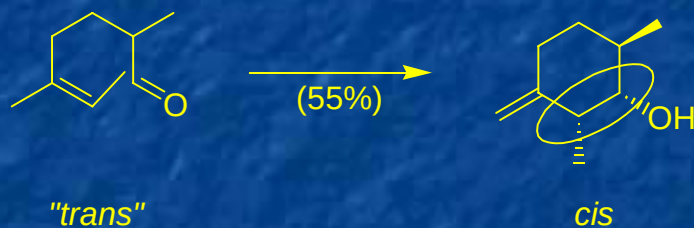
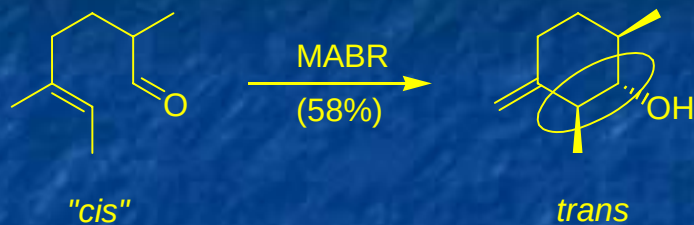
1. Niwa, H.; Iguchi, M.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1976**, 49, 3148.
2. Terada, Y.; Yamamura, S. *Tetrahedron Lett.* **1979**, 1623.
3. Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, 112, 9011.
4. Maruoka, K.; Saito, S.; Ooi, T.; Yamamoto, H. *Synlett* **1991**, 579.

Ene Cyclizations



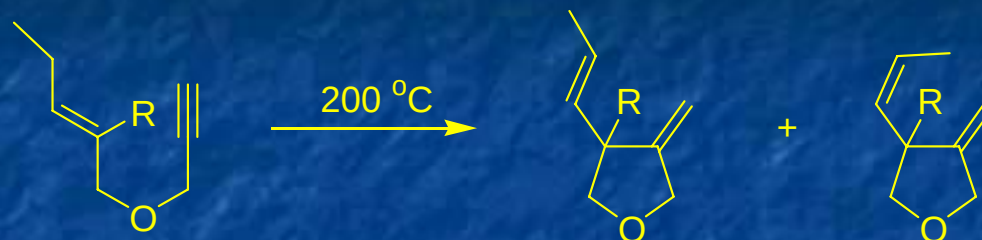
1. Mikami, K.; Takahashi, K.; Nakai, T. *Tetrahedron Lett.* **1989**, 30, 357.
2. Oppolzer, W. *Pure Appl. Chem.* **1981**, 53, 1181.

Ene Cyclizations

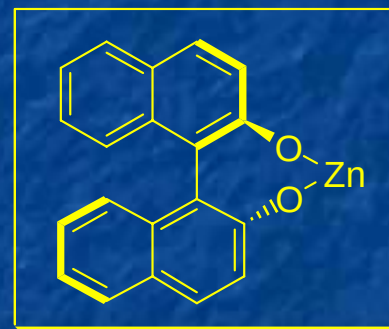
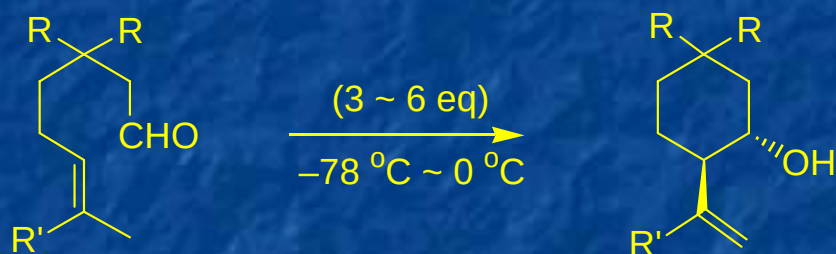


1. Maruoka, K.; Ooi, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 9011.
2. Mikami, K.; Takahashi, K.; Nakai, T. *Synlett* **1989**, 45.

Ene Cyclizations



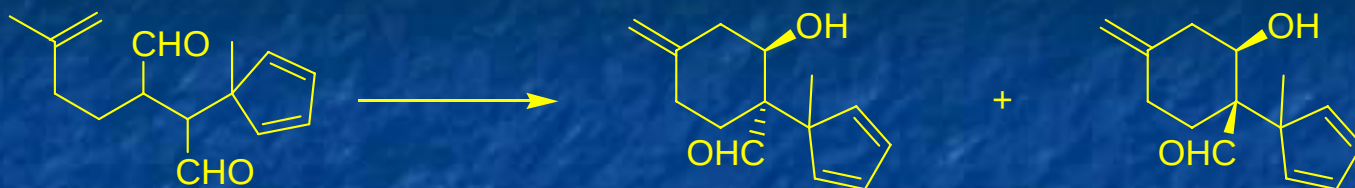
R = H	87	:	13
R = Me	>95	:	<5



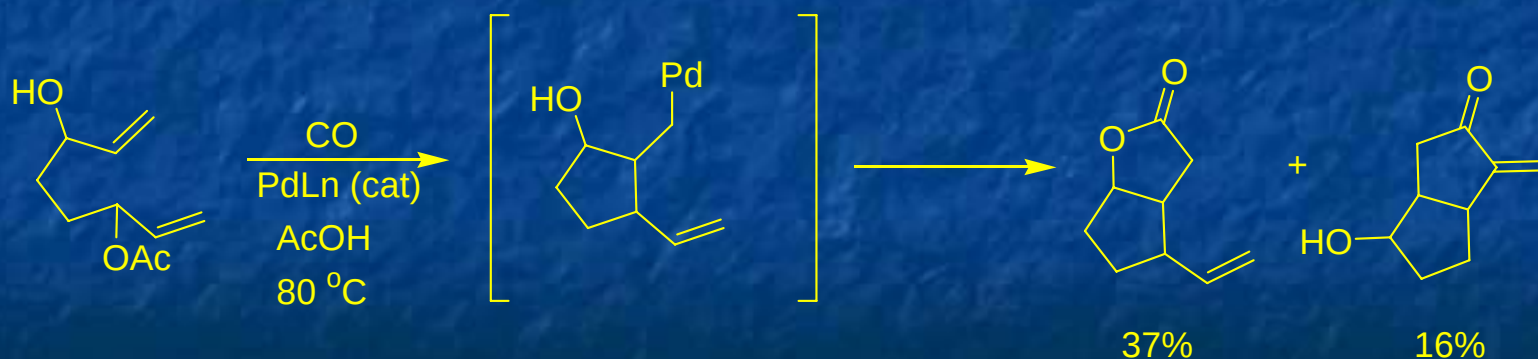
R=Me, R'=Me or $(\text{CH}_2)_2\text{CH}=\text{C}(\text{CH}_3)_2$	~90% (~90% ee)
R=H, R'=Me	31% (0% ee)

1. Mikami, K.; Takahashi, K.; Nakai, T. *Chem. Lett.* **1987**, 2347.
2. Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1986**, 42, 2203.

Ene Cyclizations



Eu(fod) ₃	8	:	1	(-)
(+)-Eu(hfc) ₃	5	:	1	(20% ee)
(+)-Eu(dppm) ₃	4.5	:	1	(31% ee)
(S)-1	4.5	:	1	(38% ee)



1. Ziegler, F.E.; Sobolov, S.B. *J. Am. Chem. Soc.* **1990**, 112, 2749.
2. Yamamoto, K.; Terakado, M.; Murai, K.; Miyazawa, M.; Tsuji, J.; Takahashi, K.; Mikami, K. *Chem. Lett.* **1989**, 955.

Thank You for attention!