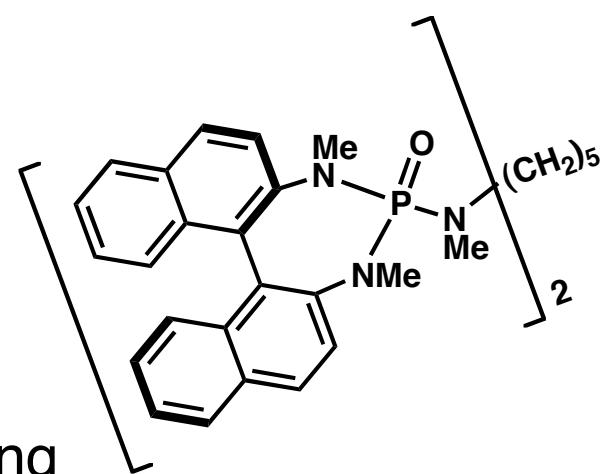
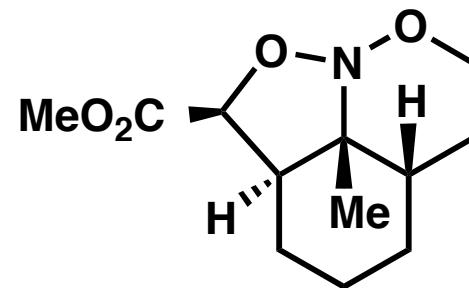
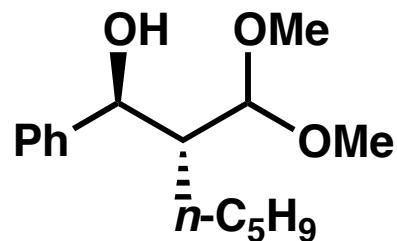
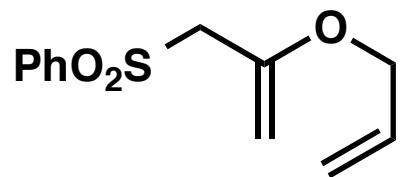
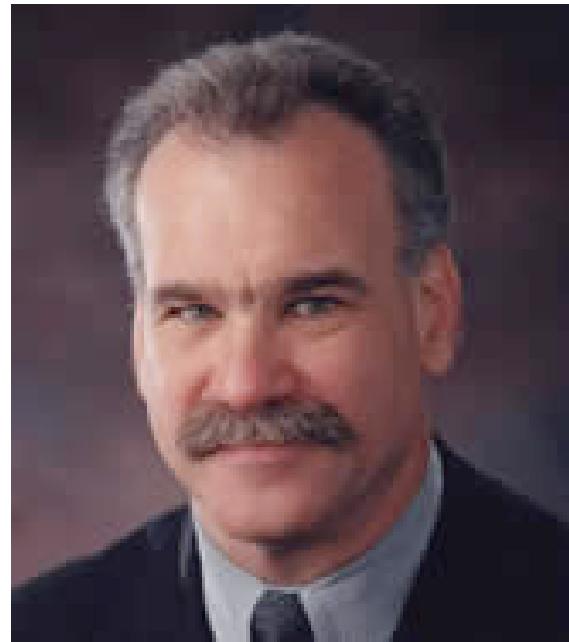
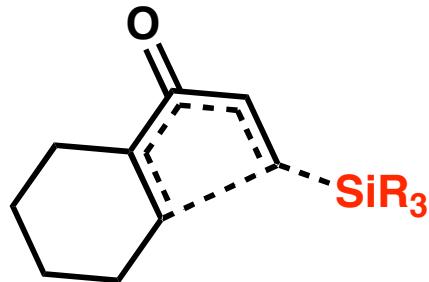
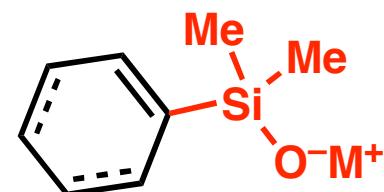


A Perspective on Professor Scott Eric Denmark: The Man, The Myth, The Chemist



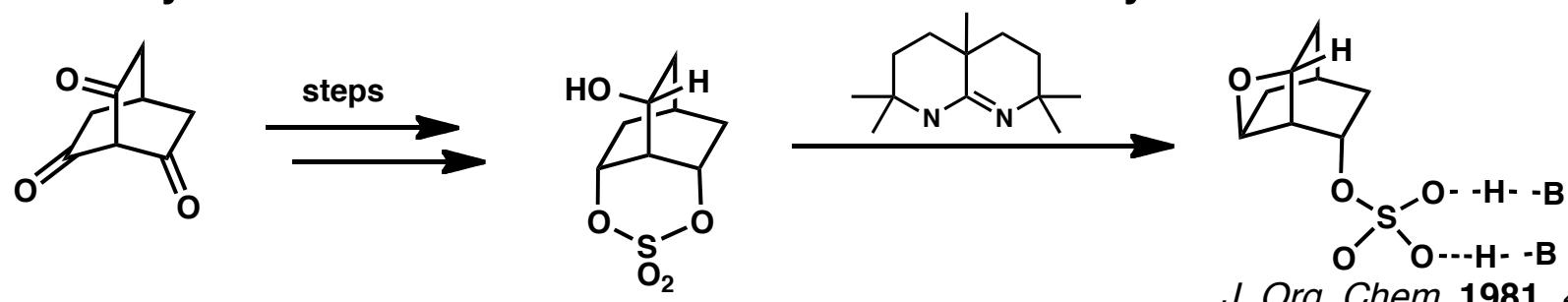
Russell C. Smith
Stoltz/Reisman Group Meeting

January 24, 2011



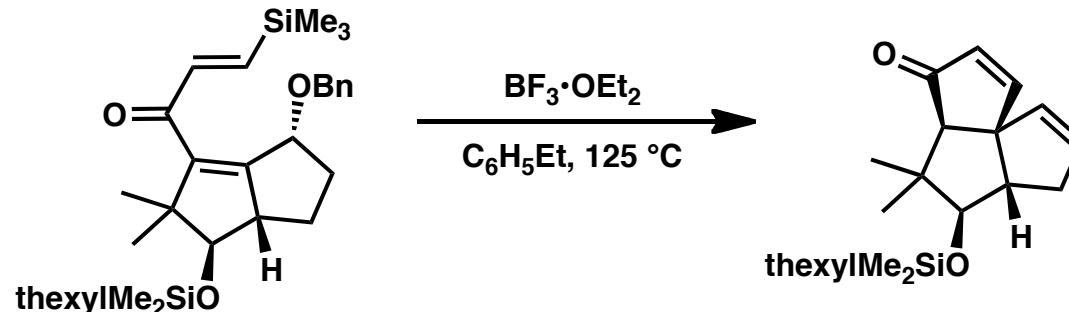
From Humble Beginnings...

- Born in Lynbrook, New York on 17 June 1953
- Obtained an S. B. degree from M.I.T. in 1975
 - Conducted research with both Richard H. Holm (ferredoxin analogs) and Daniel S. Kemp (functionalized cyclophanes).
- Received D. Sc. Tech degree in 1980
 - Prof. Dr. Albert Eschenmoser (“On the Stereochemistry of the S N’ Reaction”).
- 1980 – Independent career as assistant professor at the University of Illinois at Urbana-Champaign.
- 1986 – Associate Professor
- 1987 – Full Professor
- 1991 – Reynold C. Fuson Professor of Chemistry.

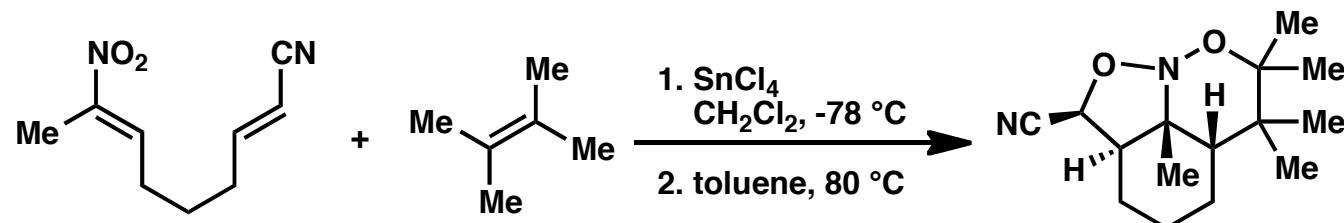


To A Thriving Career In Organic Chemistry: Outline

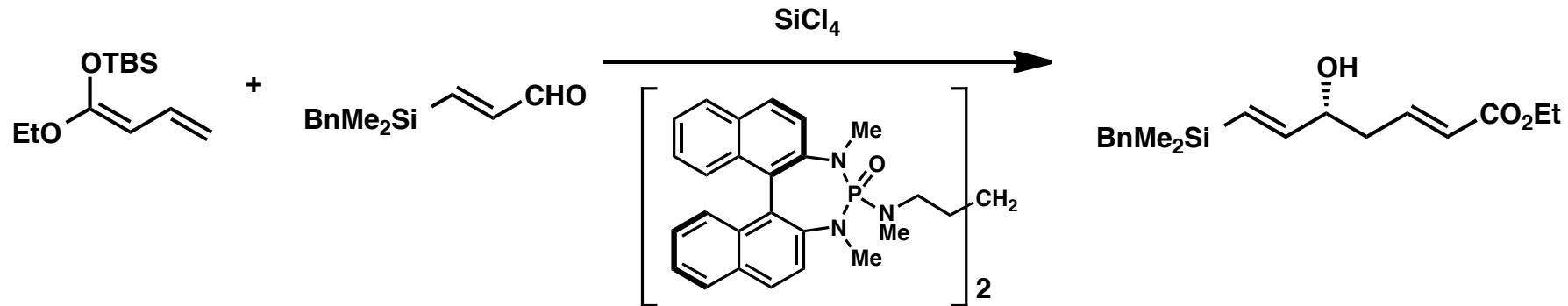
- Silicon-Directed Nazarov Cyclization



- Inter/Intramolecular [4+2]/[3+2] Cycloaddition of Nitro Olefins

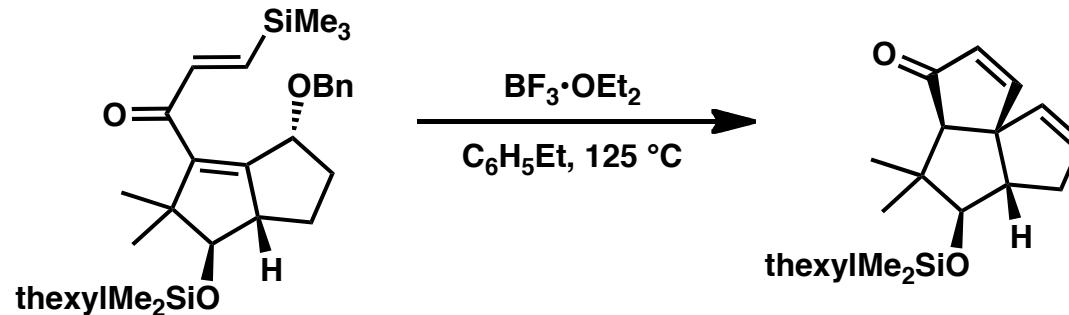


- Lewis-Base Activation of Lewis Acids – Enantioselective Carbon-Carbon Bond Formation

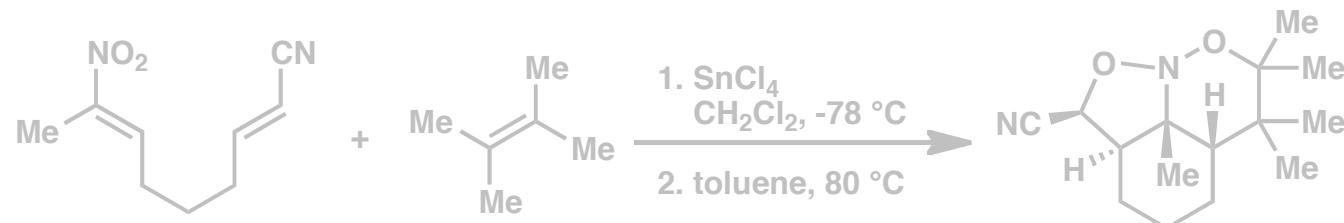


To A Thriving Career In Organic Chemistry: Outline

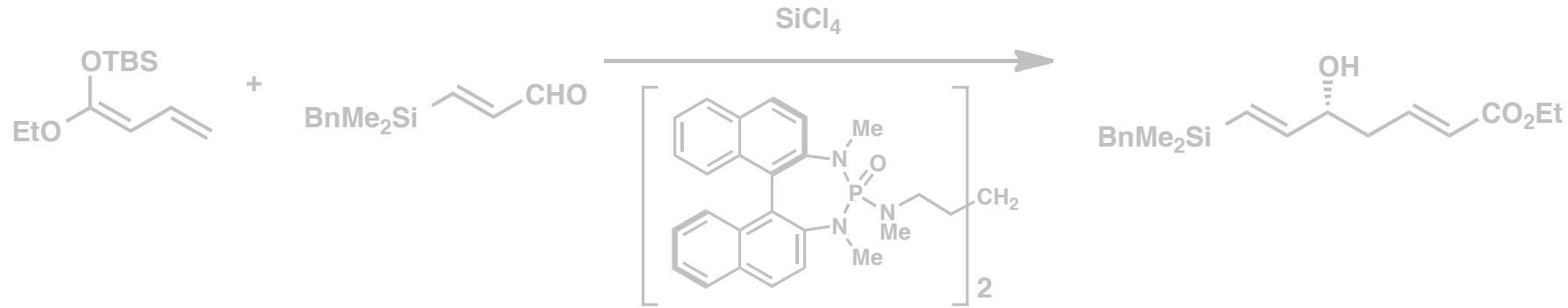
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- Inter/Intramolecular [4+2]/[3+2] Cycloaddition of Nitro Olefins

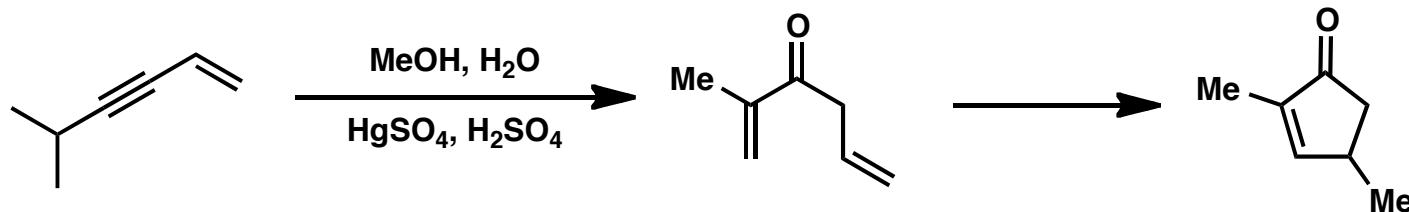


- Lewis-Base Activation of Lewis Acids – Enantioselective Carbon-Carbon Bond Formation

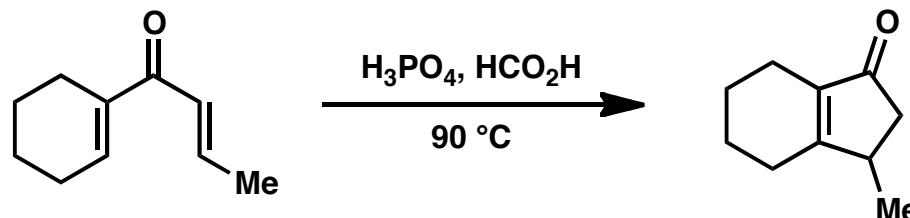


Nazarov Cyclization – Background

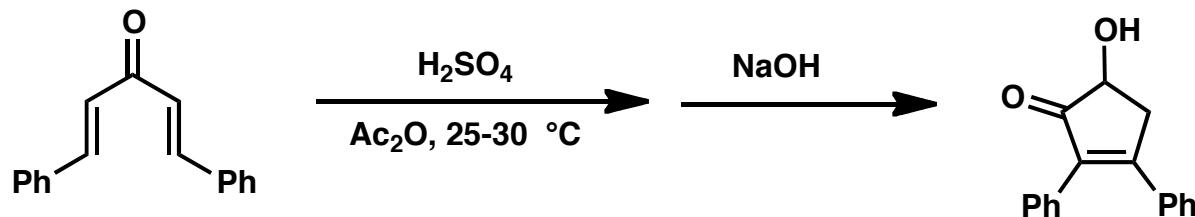
- Named after the Russian chemist I. N. Nazarov (1900-1957)



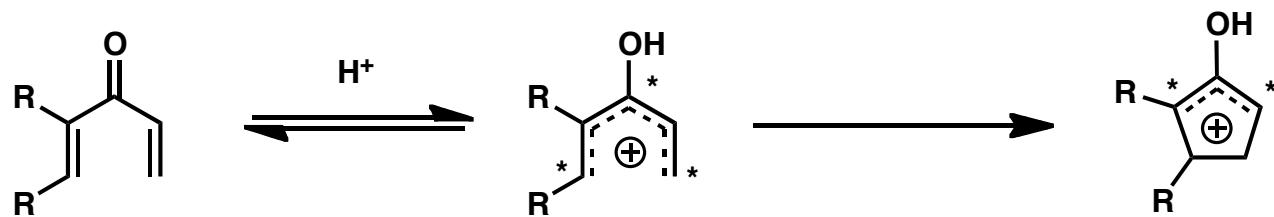
- Proved later that the cyclization proceeds through a divinyl ketone



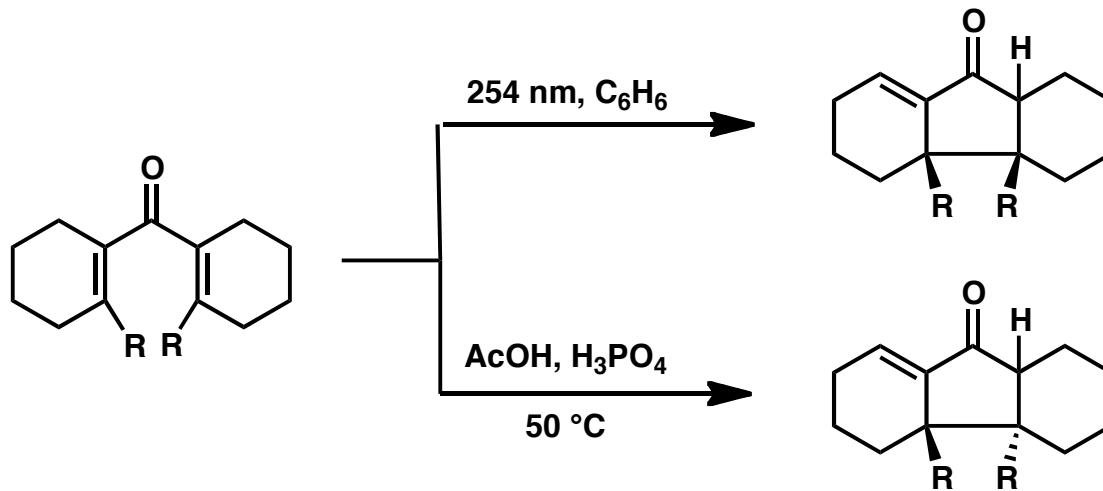
- Incorporation of nucleophile gave further insight into mechanism



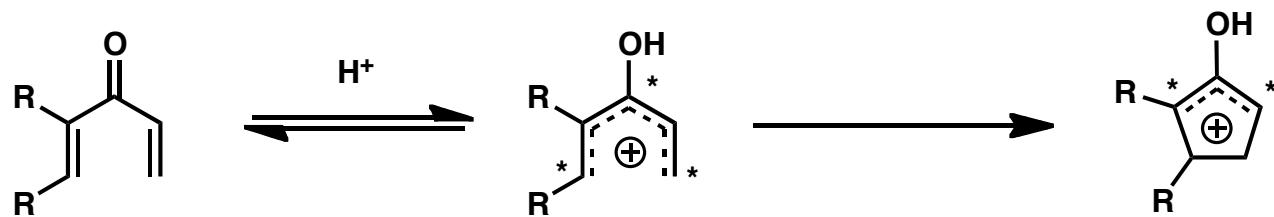
Nazarov Cyclization – Mechanism



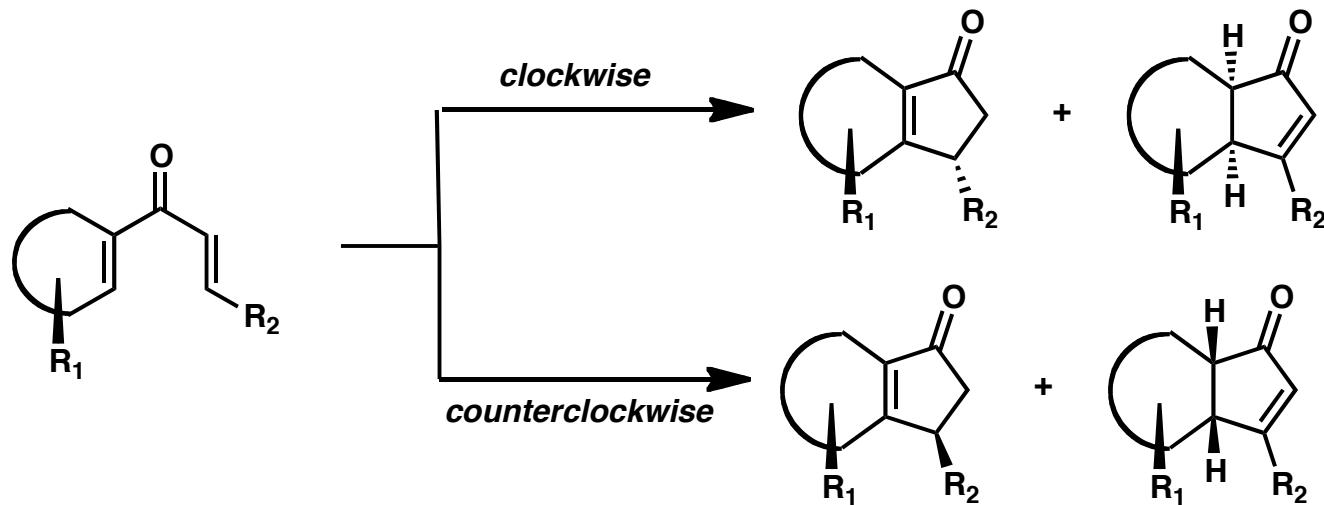
- Promoted by thermal or photochemical initiation



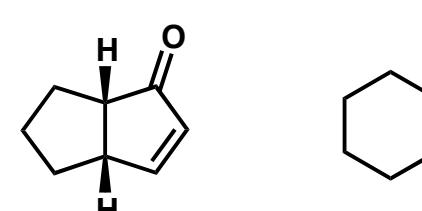
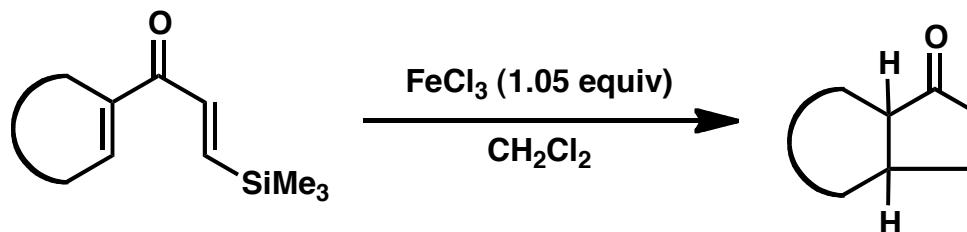
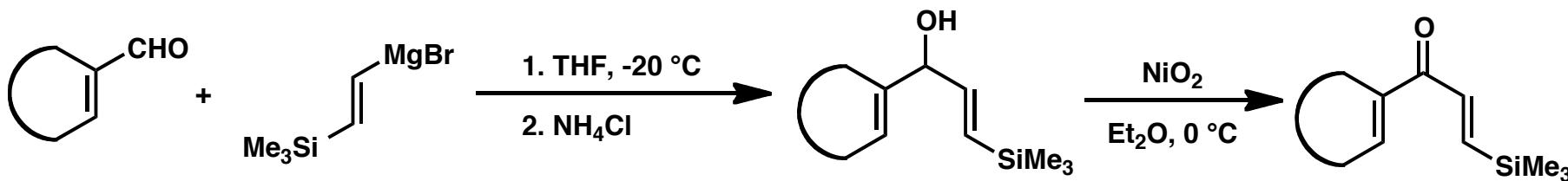
Nazarov Cyclization – Mechanism



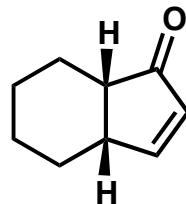
- Remote substituents can cause changes in the *torquoselectivity* of the cyclization



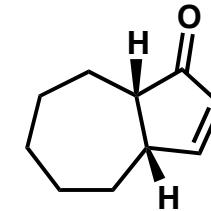
Silicon-Directed Nazarov Cyclization



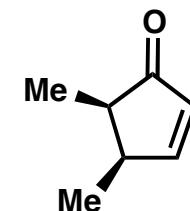
55%, 100% *cis*



84%, 100% *cis*



74%, 85/15 *cis/trans*

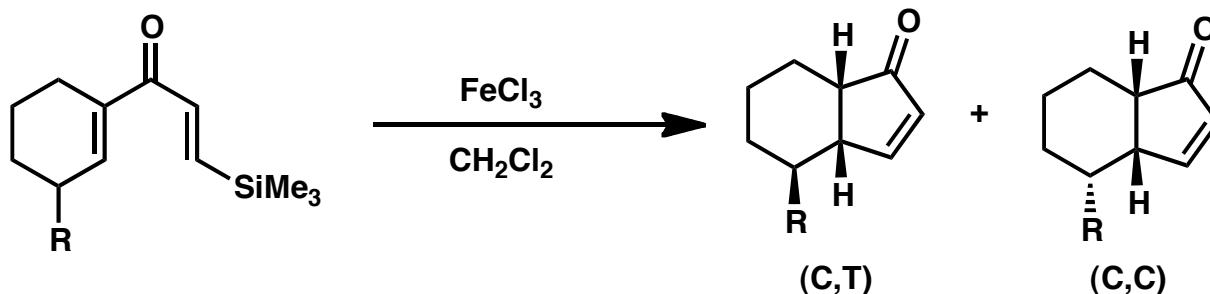


95%, 59/41 *cis/trans*

Use of Si functionality directs collapse of cation

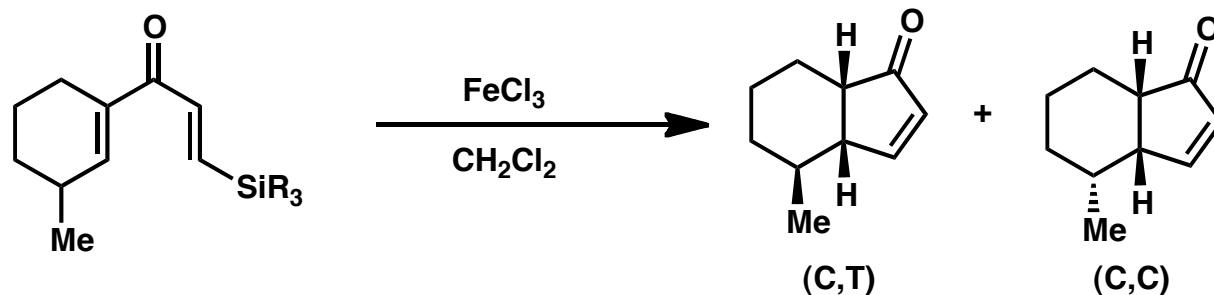
SDNC – Effect of Allylic Position

- Larger substituents promote increased levels of torque selectivity (presence of vinyl silane)

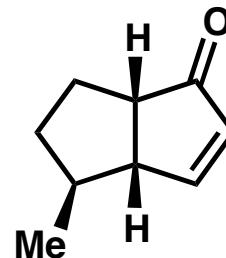


R	(C,T)	(C,C)	yield, %
Me	78	22	99
$\text{CH}_2=\text{CH}_2$	70	30	66
Ph	94	6	76
<i>t</i> -Bu	94	6	63
OCH_2Ph	90	10	76

SDNC – Effect of Silicon Functionality



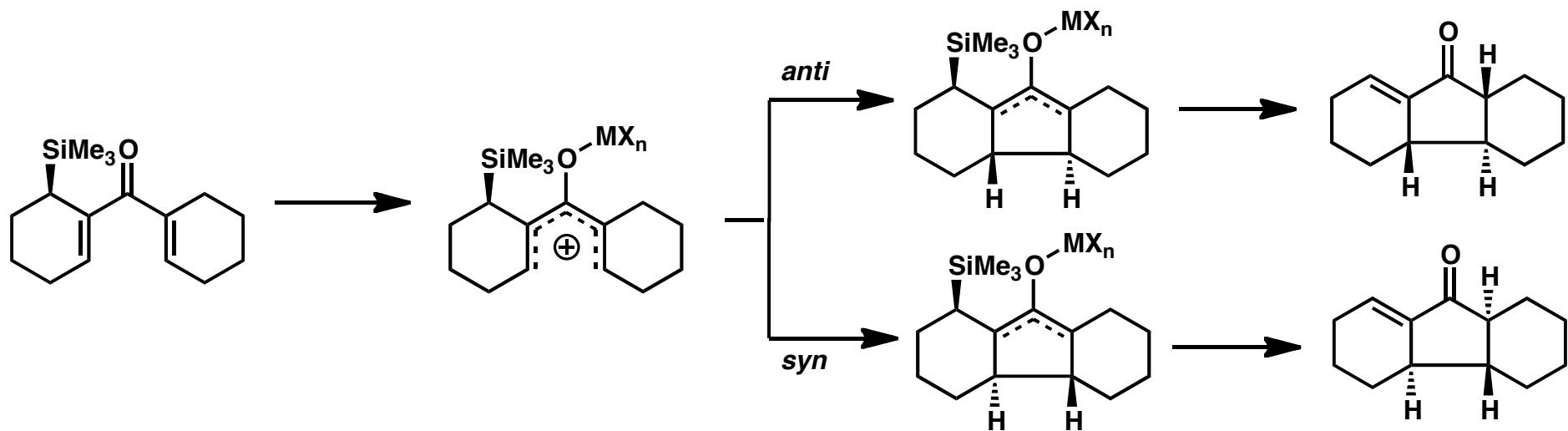
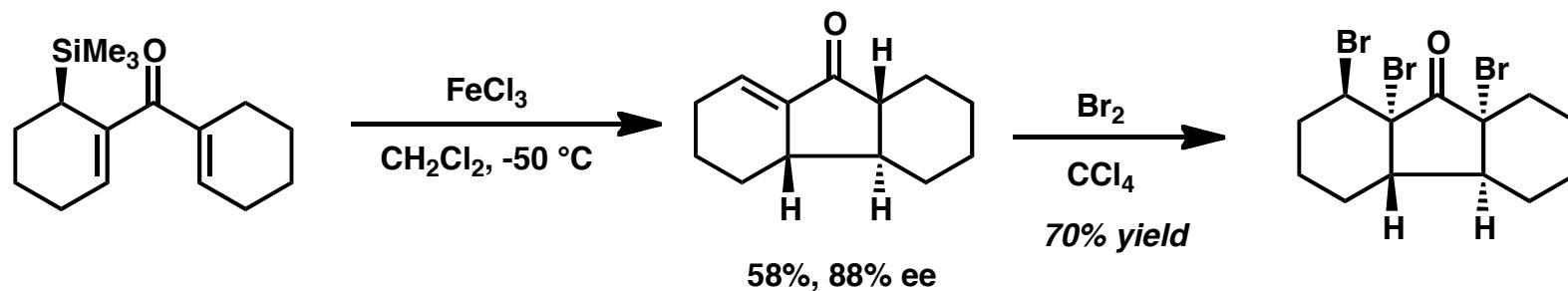
R	(C,T)	(C,C)	yield, %
Me	78	22	99
Me ₂ PhSi	84	16	63
MePh ₂ Si	86	14	83
Ph ₃ Si	87	13	15
i-Pr ₃ Si	90	10	70



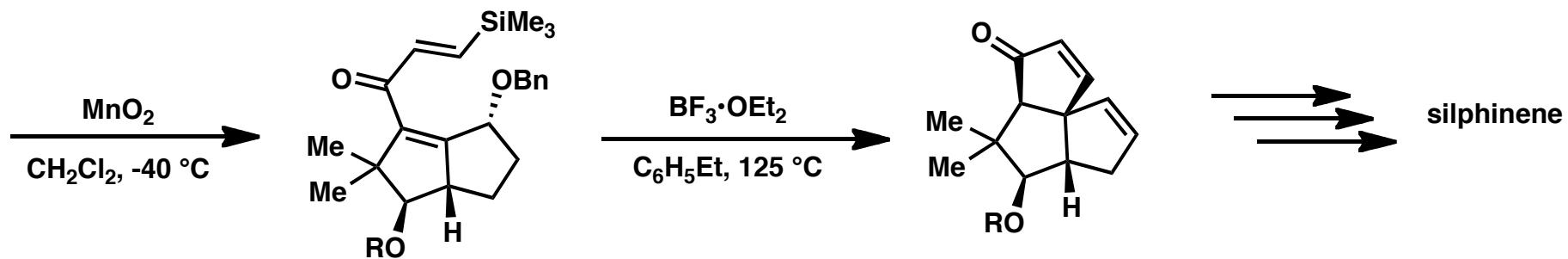
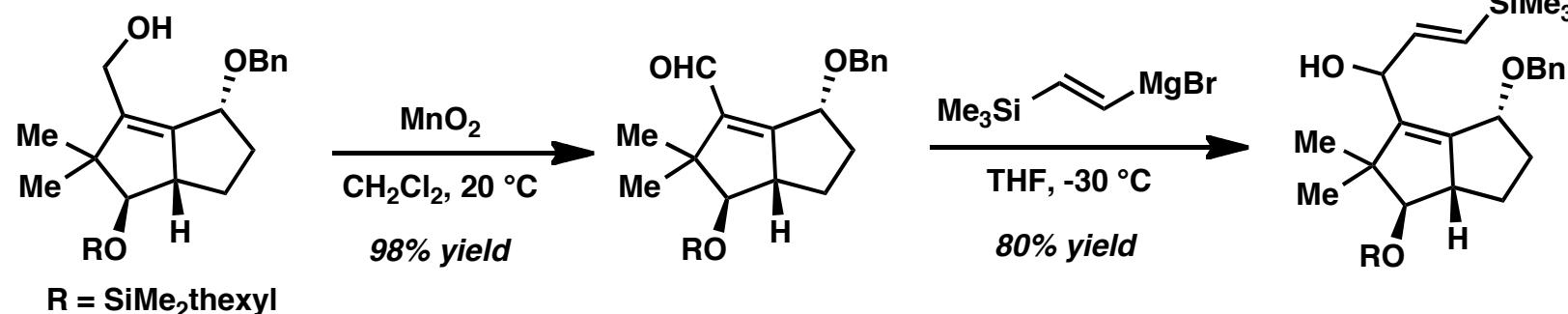
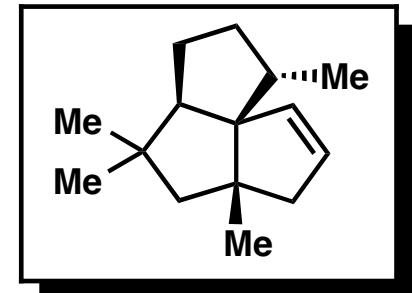
For SiMe₃ = 54/46

for $\text{Si}(i\text{-Pr})_3 = 79/21$

Formation of Enantioenriched Carbocycles Via SDNC



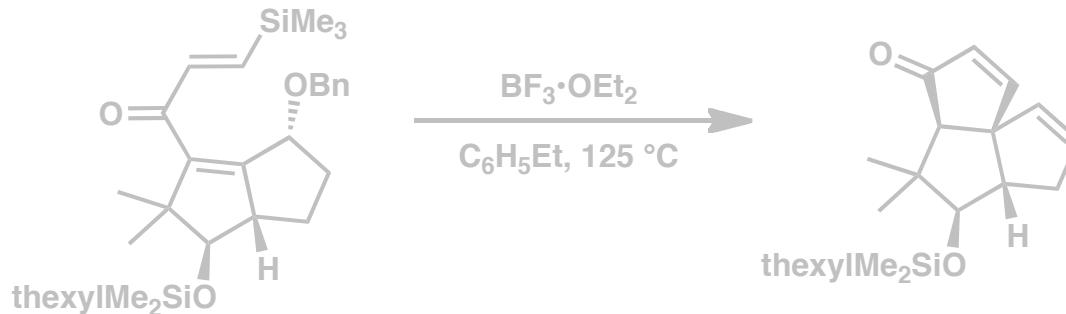
Total Synthesis of Silphinene: Application of SDNC



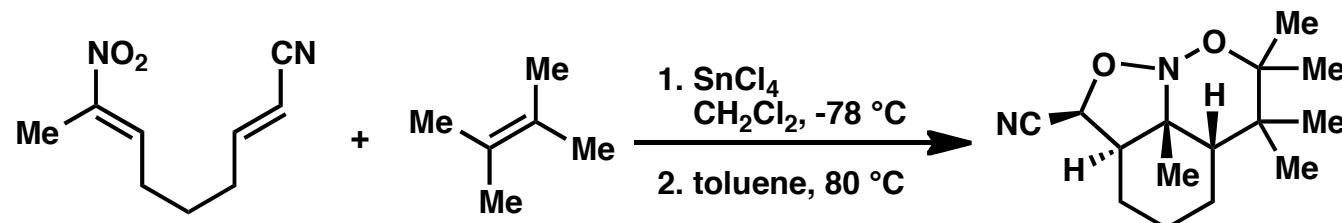
Presence of silicon functionality directs formation of cyclopentenone

To A Thriving Career In Organic Chemistry: Outline

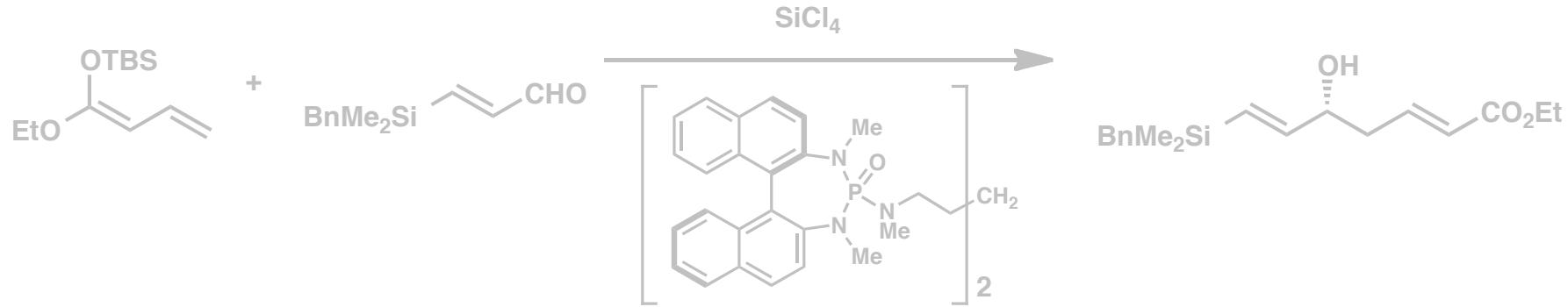
- Silicon-Directed Nazarov Cyclization



- Inter/Intramolecular [4+2]/[3+2] Cycloaddition of Nitro Olefins

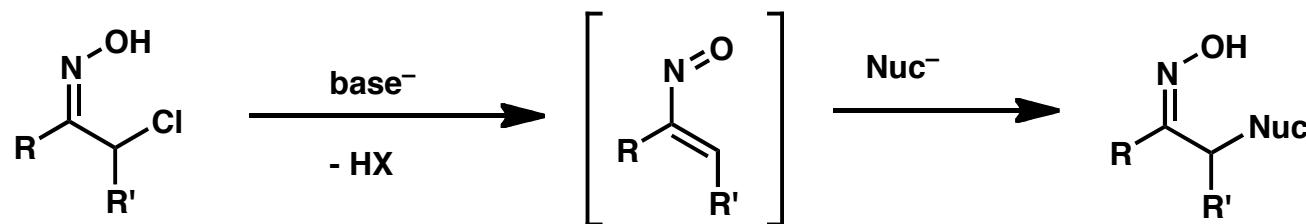


- Lewis-Base Activation of Lewis Acids – Enantioselective Carbon-Carbon Bond Formation

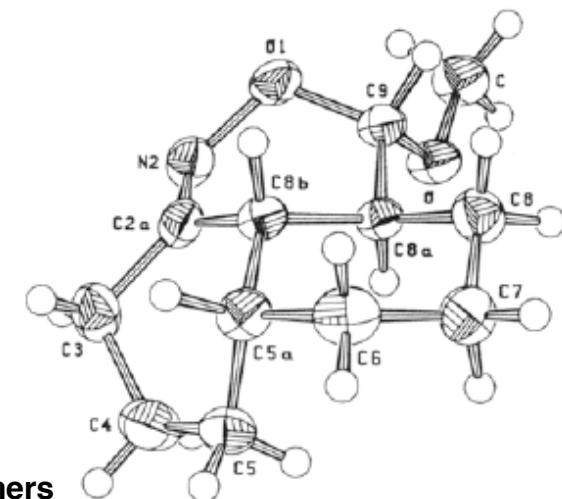
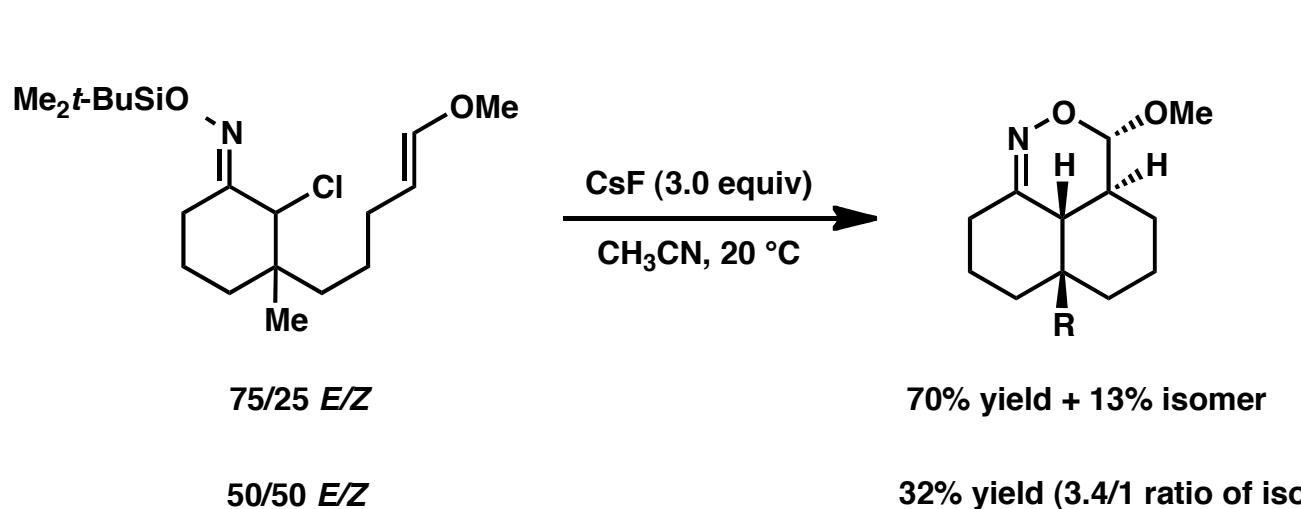


Intramolecular Cycloaddition of Nitrosoalkenes

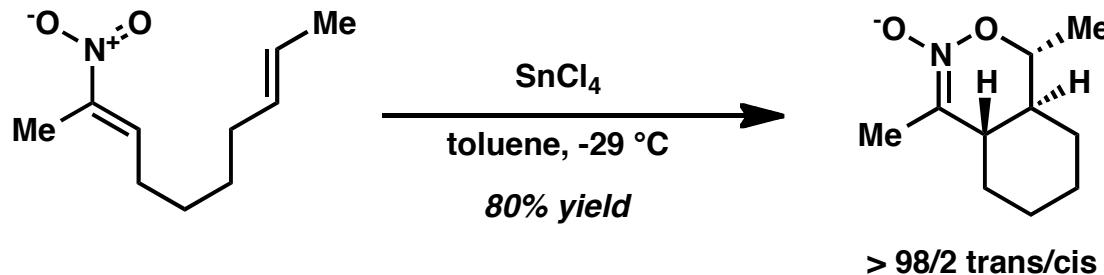
- Reactivity of Nitrosoalkenes



- Intermediate nitrosoalkene can act as 2π or 4π cycloaddition component

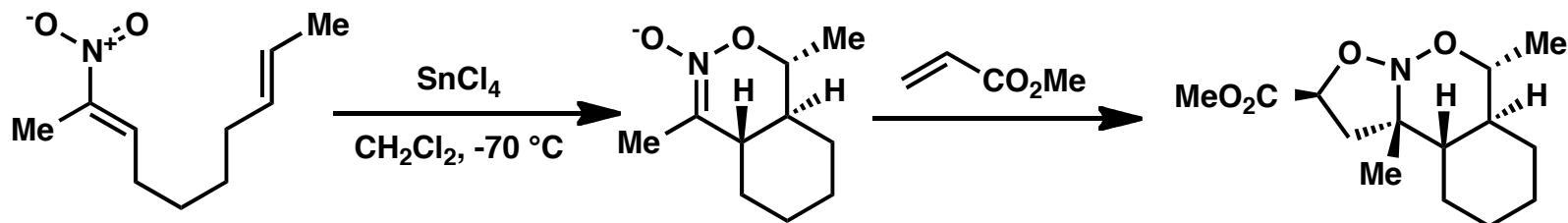
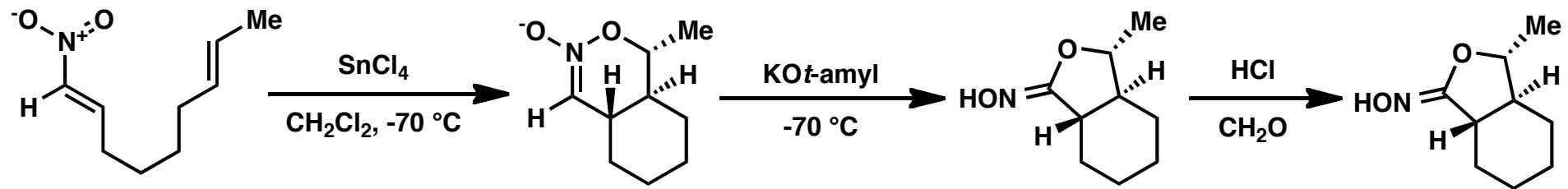


Nitroolefins as 4π Components in Cycloadditions



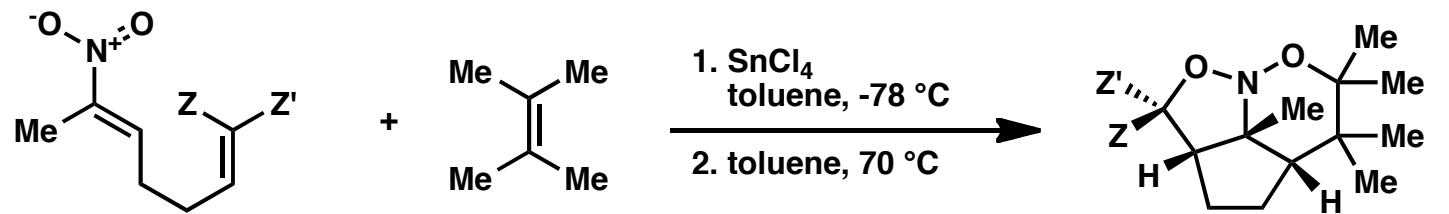
J. Am. Chem. Soc. **1986**, *108*, 1306

- Nitro groups serve as useful functionality for further elaboration

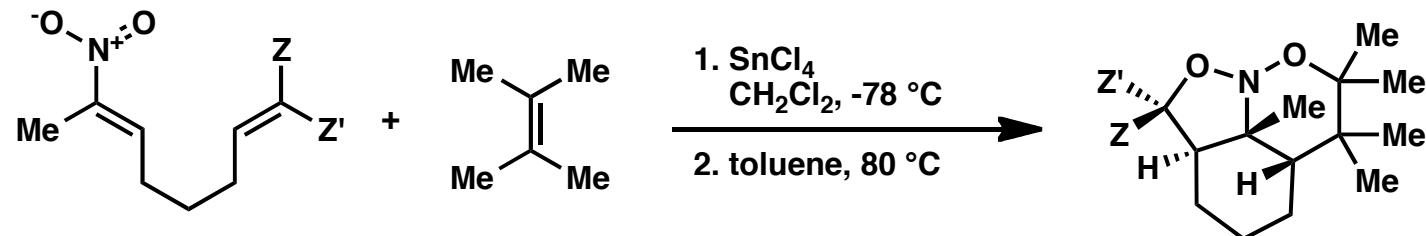


Helv. Chim. Acta. **1986**, *69*, 1971

Intramolecular [3+2] Cycloaddition



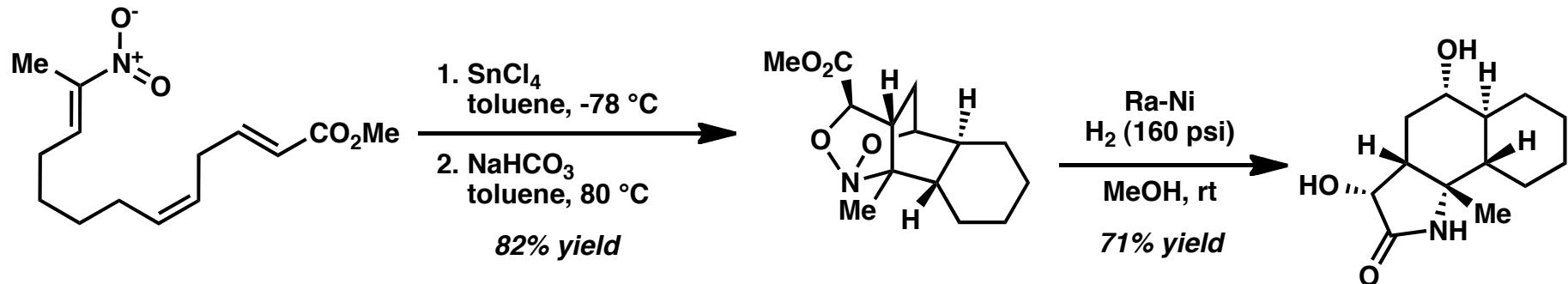
Z	Z'	time, h [4+2]	time, h [3+2]	ds	yield, %
H	CO_2Et	7	0	>100:1	72
CO_2Et	H	8	3	20:1	78



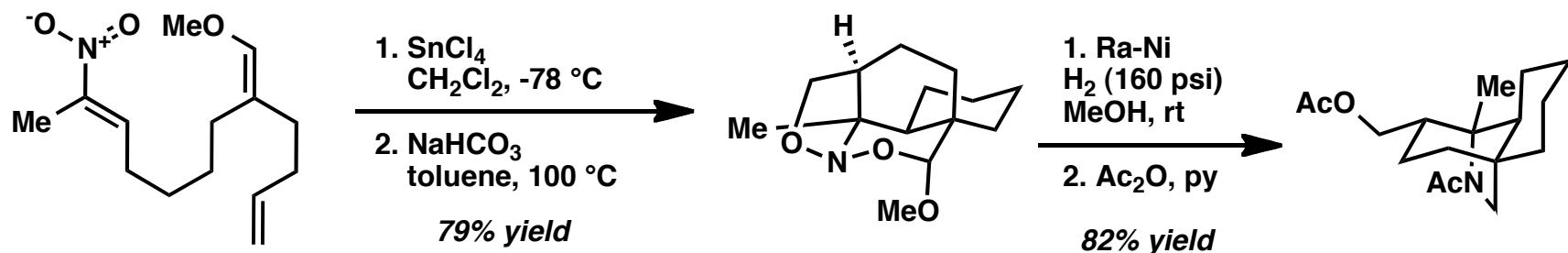
Z	Z'	time, min [4+2]	time, h [3+2]	ds	yield, %
H	CO_2Et	25	7	>100:1	93
CO_2Et	H	10	14	2.6:1	90

Tandem Double Intramolecular [4+2]/[3+2] Cycloaddition

- Fused/bridged C(6)

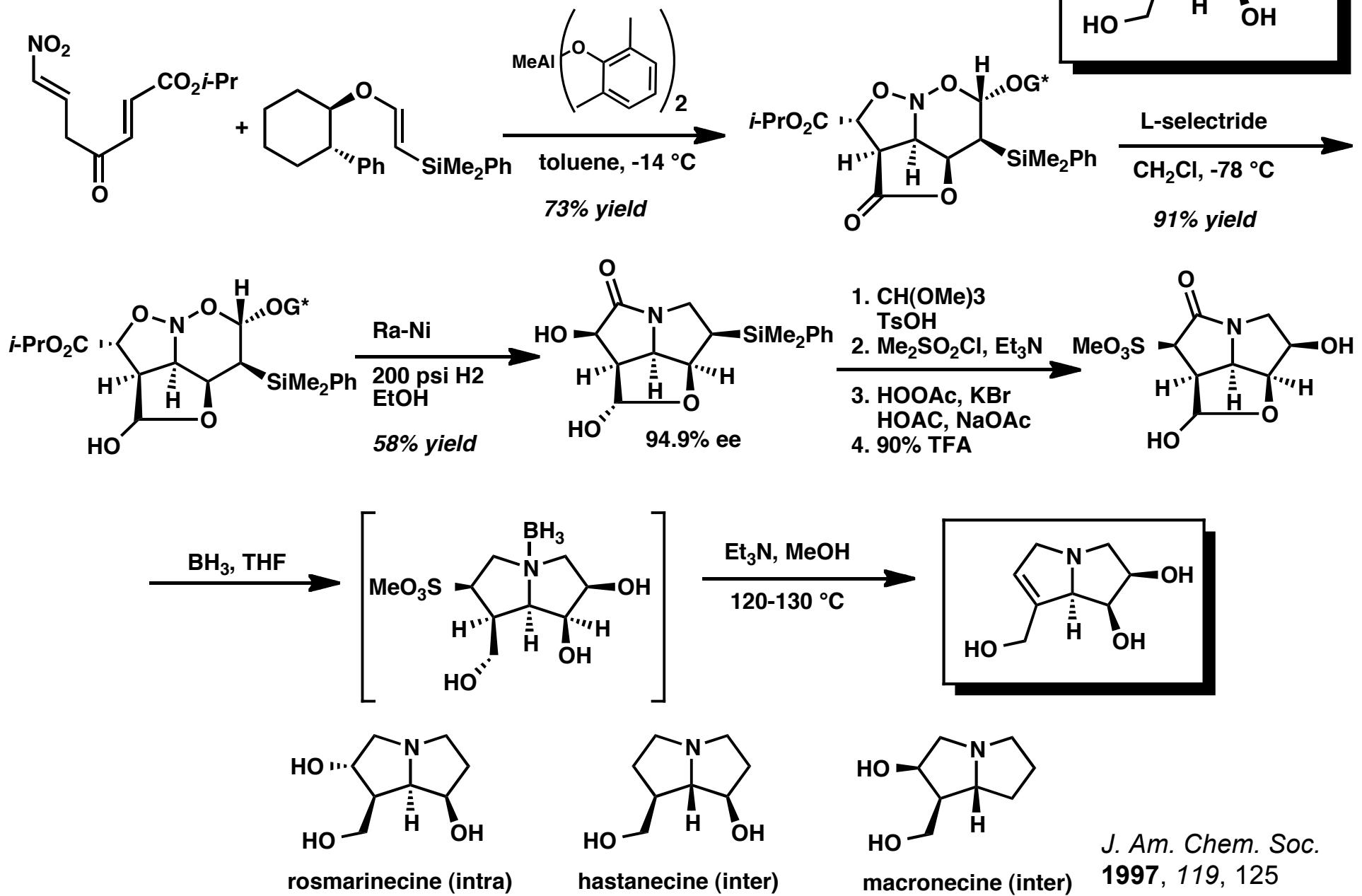


- Fused/bridged C(5)

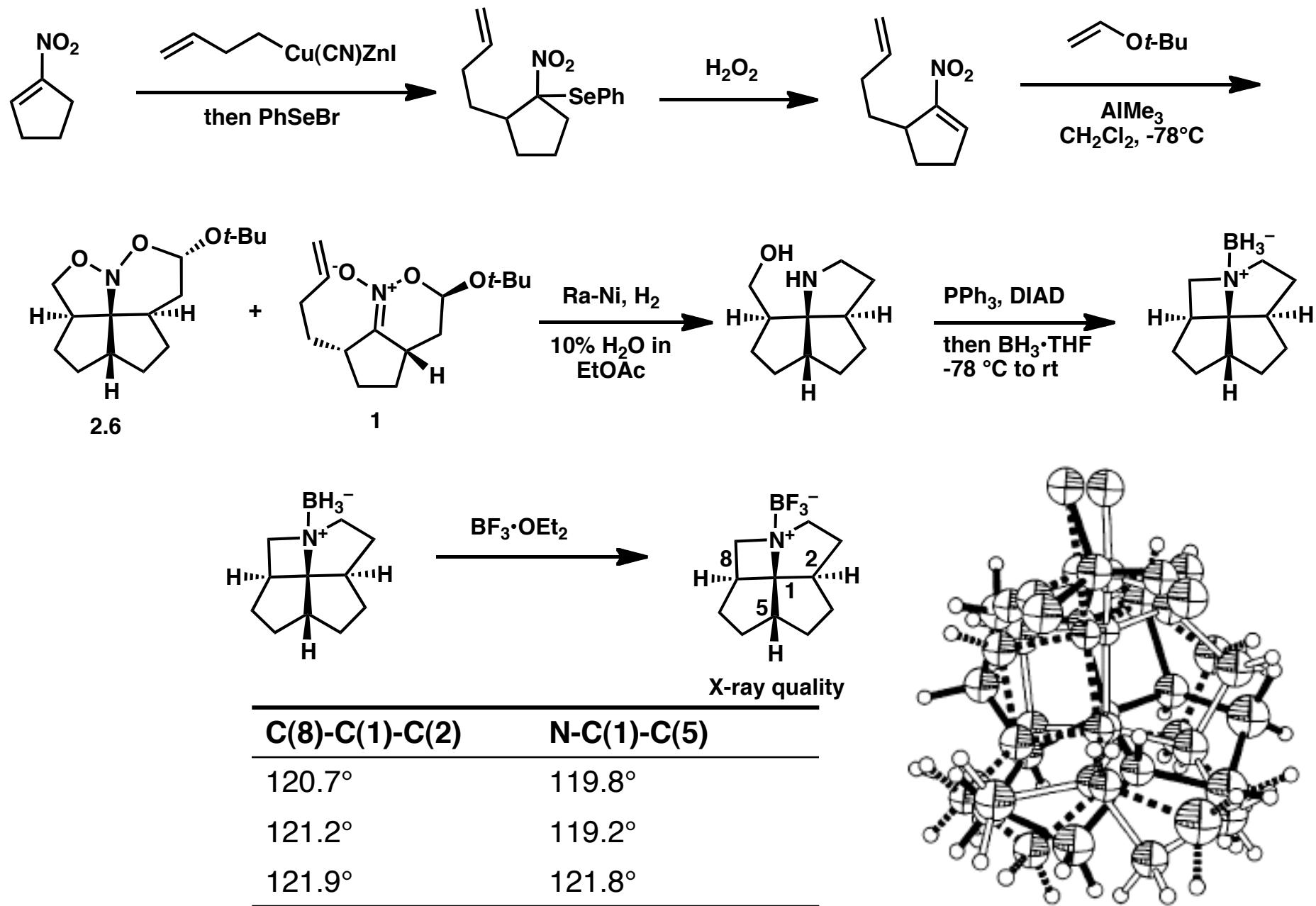


Cycloaddition can be rendered diastereoselective by presence of chiral auxiliary

Total Synthesis of (+)-Crotanecine

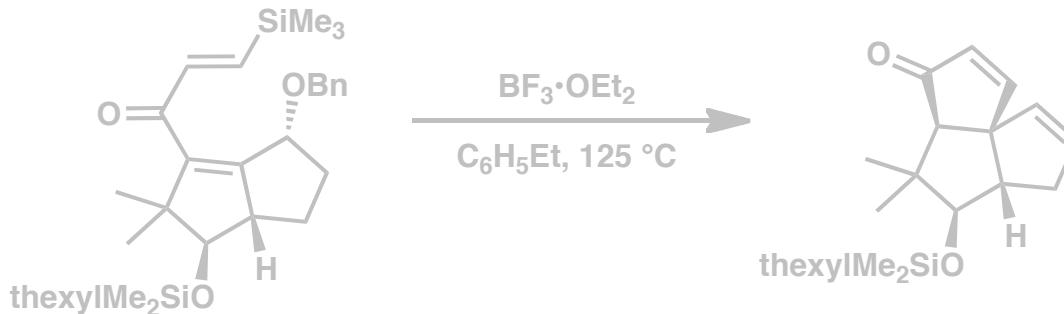


1-Azafenestrane: Planarization of sp^3 Carbon Center

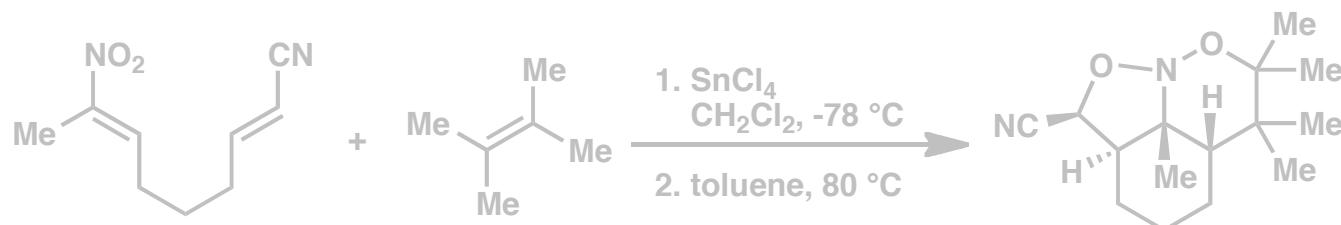


To A Thriving Career In Organic Chemistry: Outline

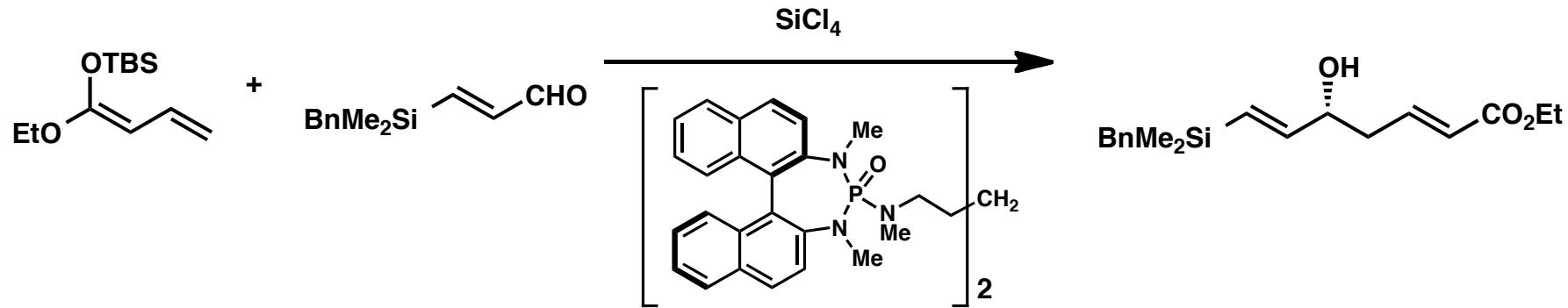
- Silicon-Directed Nazarov Cyclization



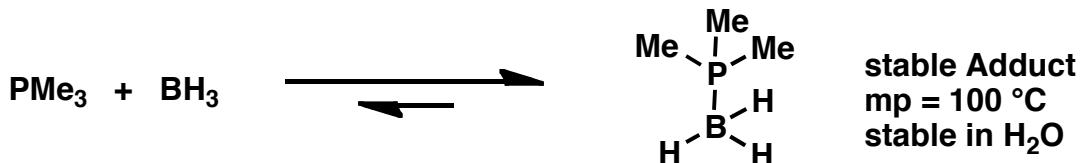
- Inter/Intramolecular [4+2]/[3+2] Cycloaddition of Nitro Olefins



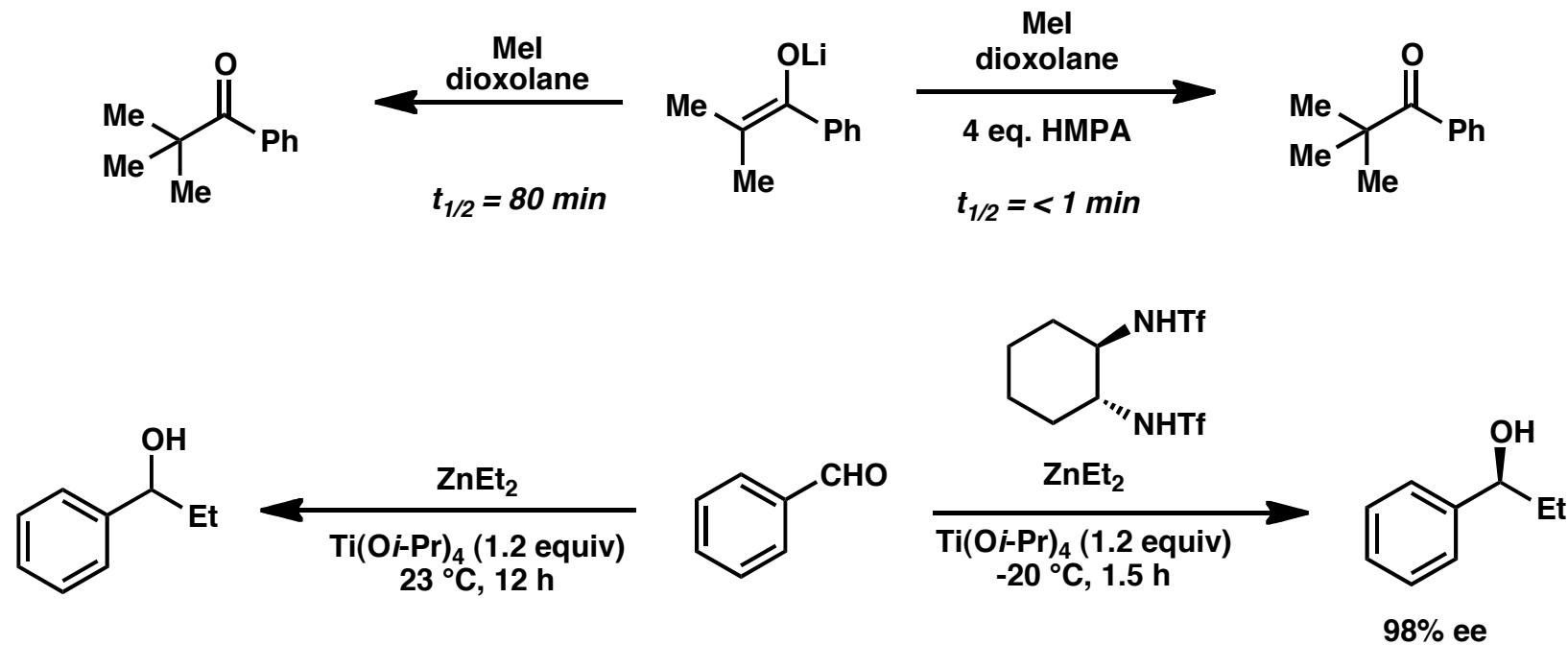
- Lewis-Base Activation of Lewis Acids – Enantioselective Carbon-Carbon Bond Formation



Lewis-Base Activation of Lewis Acids

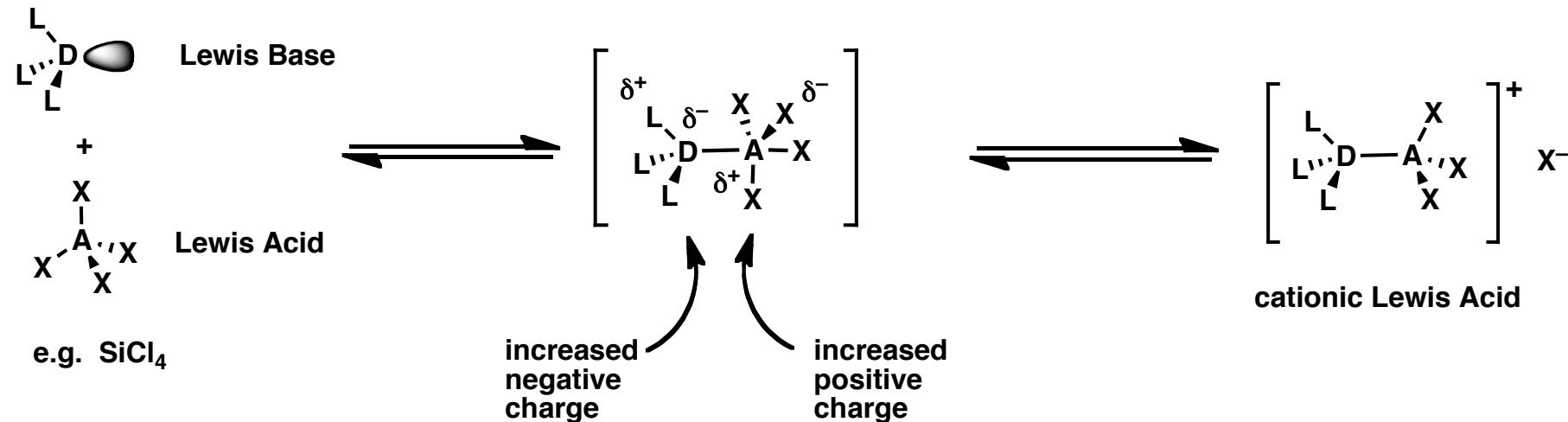
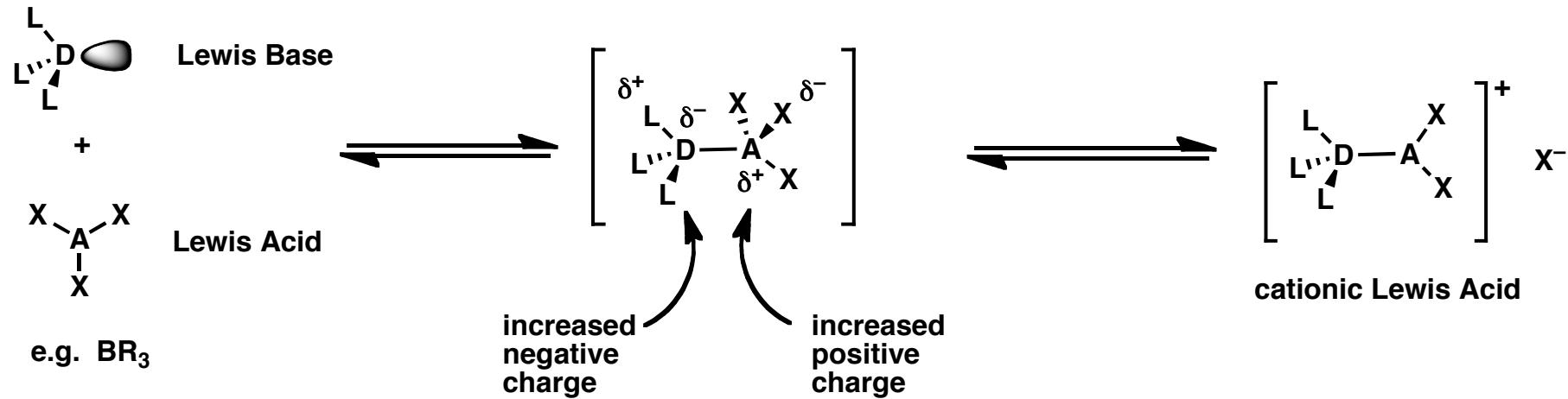


- Preparative Examples



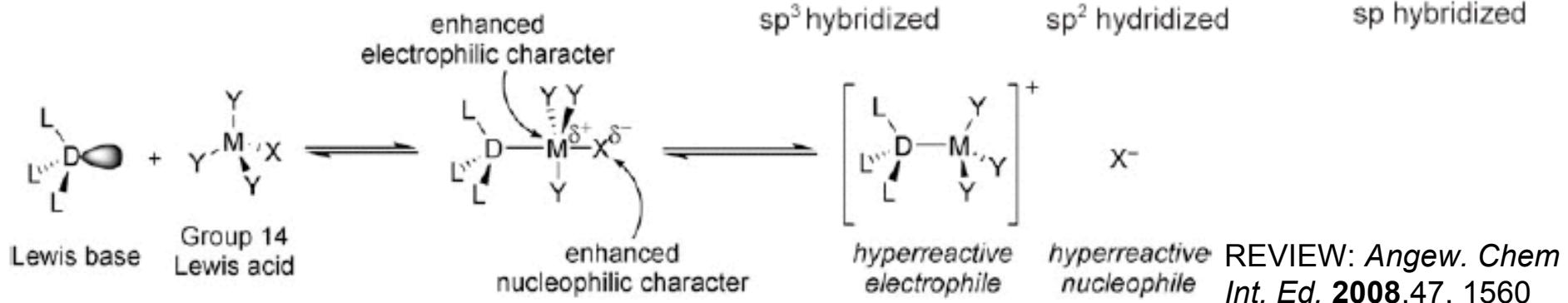
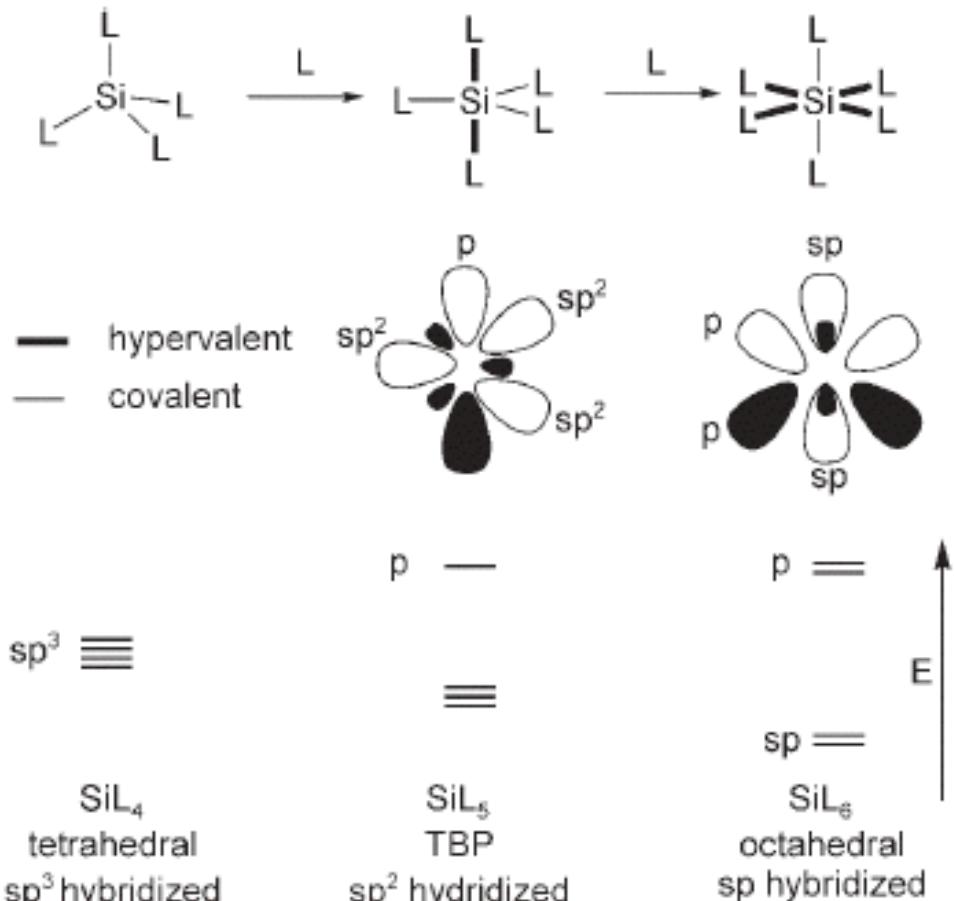
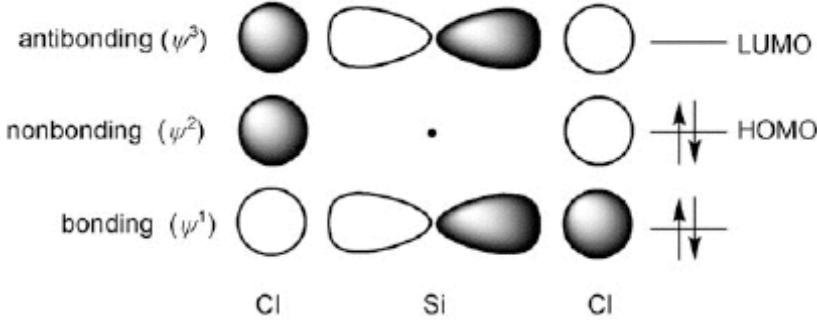
Lewis-Base Activation of Lewis Acids – Principles

- Gutmann Analysis



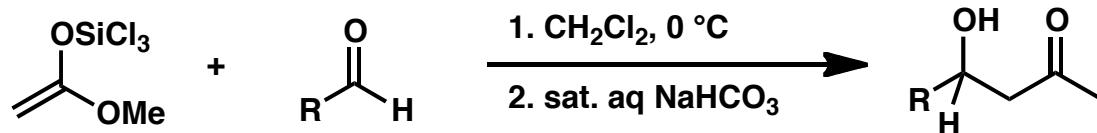
Lewis-Base Activation of Lewis Acids – Principles

- Hybridization of Silicon

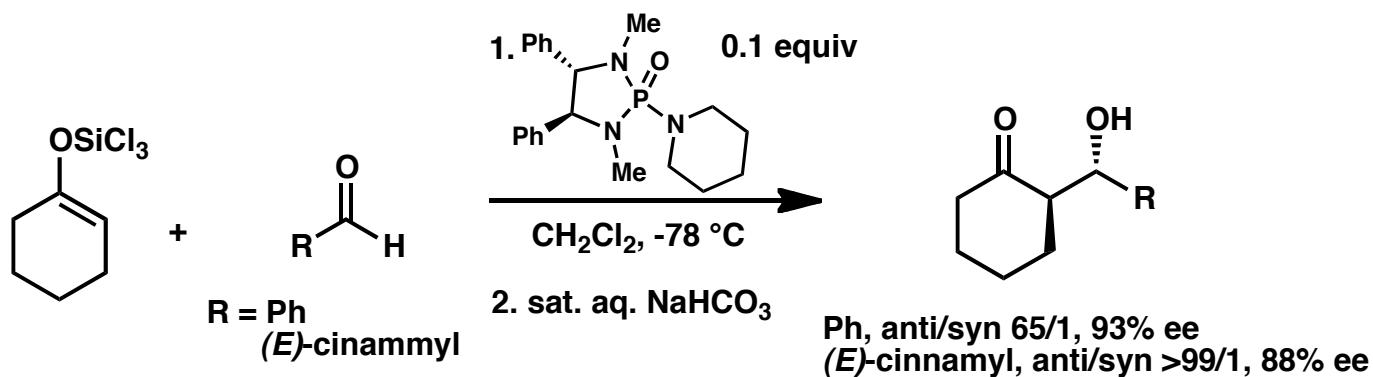


Aldol Reaction of Silicon-Substituted Enolates

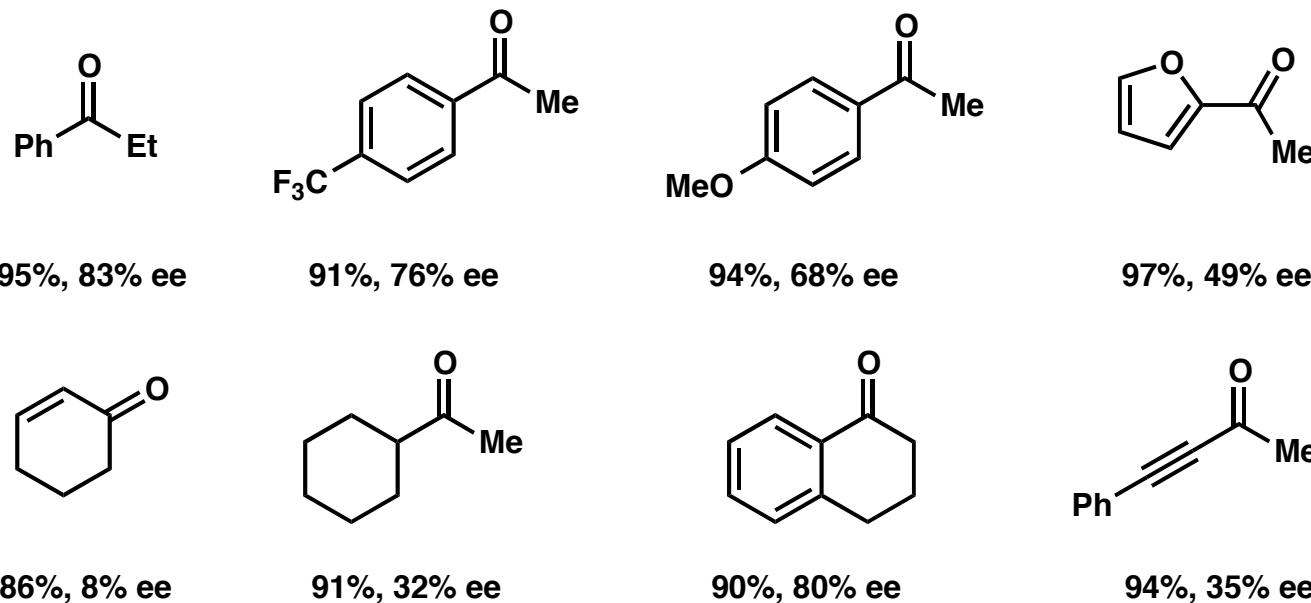
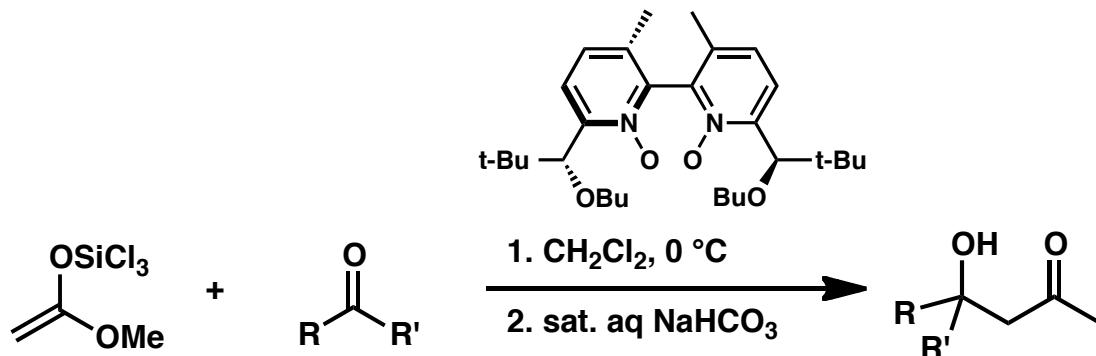
- Uncatalyzed



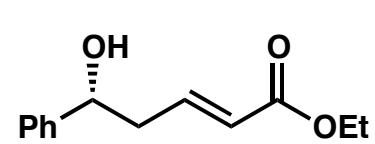
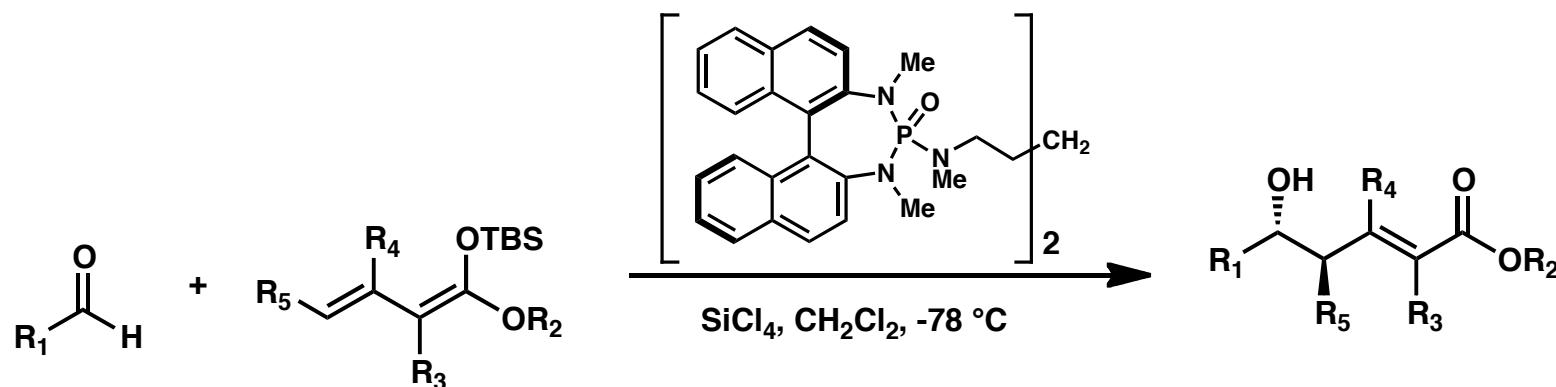
R	yield, %
Ph	98
Cy	96
t-Bu	99
(E)-cinnamyl	89



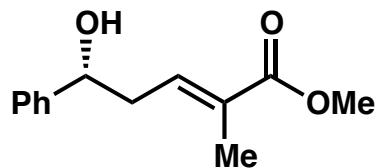
Addition to Ketones – Silyl Ketene Acetals



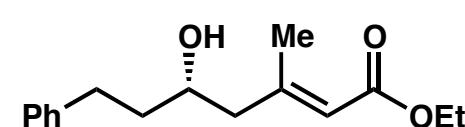
Vinylogous Aldol



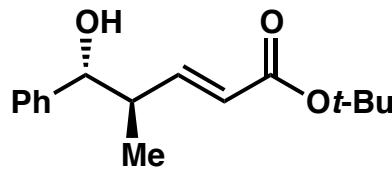
89%, >99:1 γ/α , 98% ee



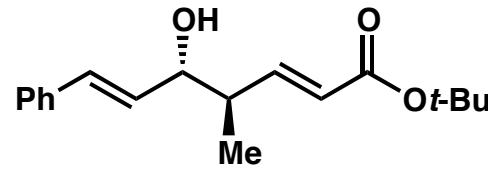
93%, >99:1 γ/α , 99% ee



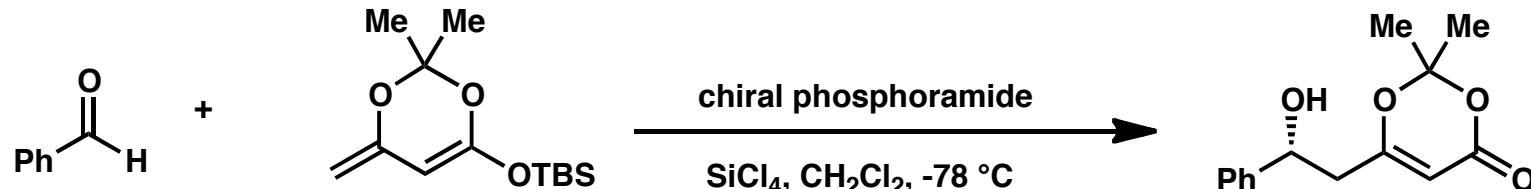
73%, >99:1 γ/α , 95% ee



92%, >99:1 γ/α , 89% ee, 98% de



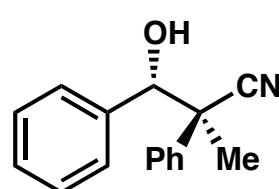
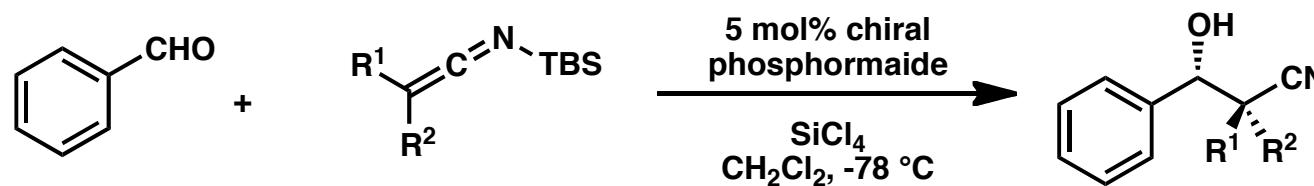
71%, >99:1 γ/α , 82% ee, 98% de



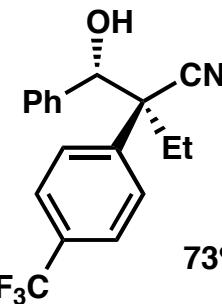
92% yield, >99:1 γ/α , 74% ee

J. Am. Chem. Soc. 2003, 125, 2800

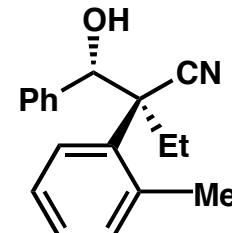
Formation of Quaternary Centers – Silyl Ketene Imines



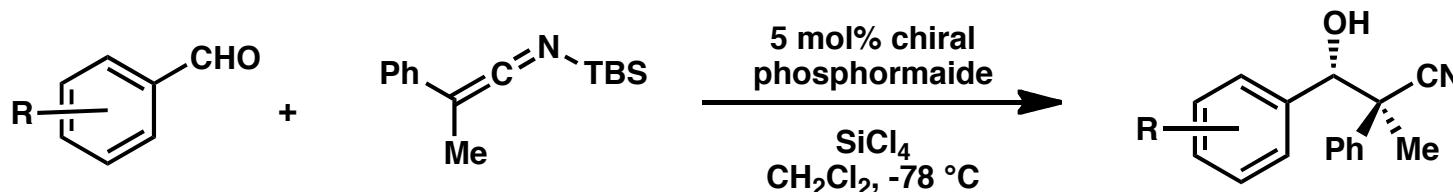
87%, 95/5 dr, 97% ee



73%, 97/3 dr, 99% ee

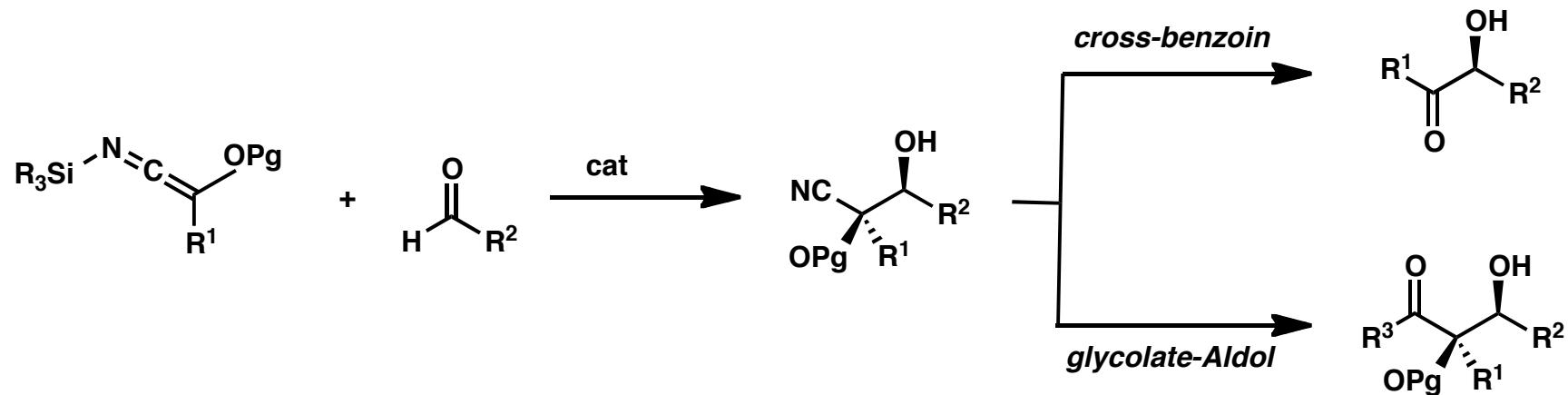


74%, 87/13 dr, 89% ee

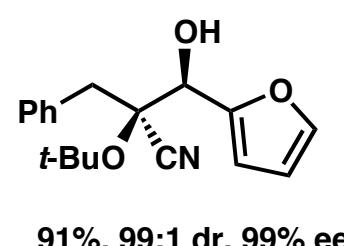
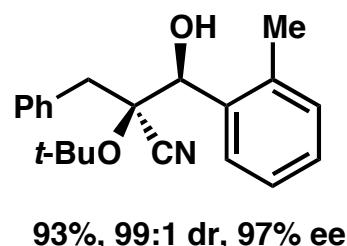
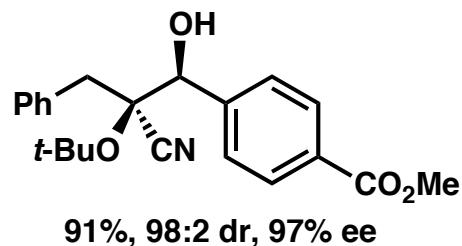
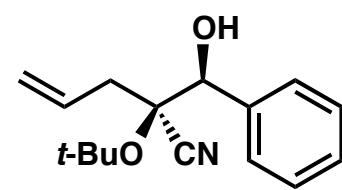
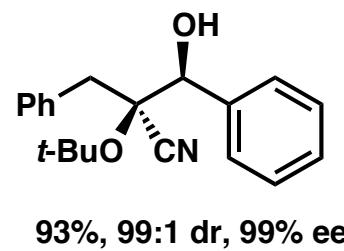
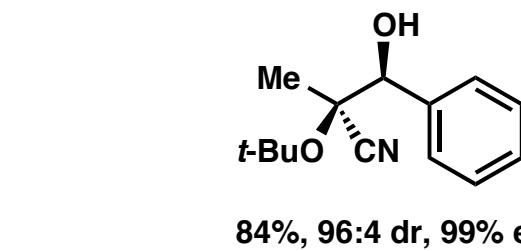
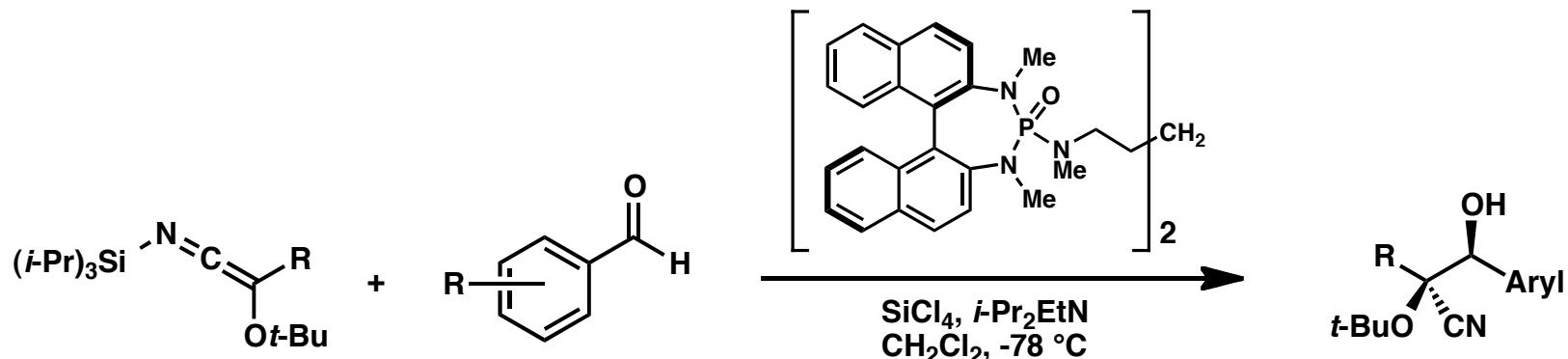
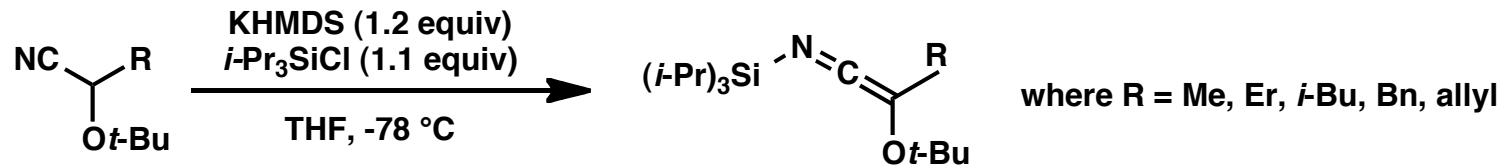


R	dr	ee, %	yield, %
4-CF ₃	>99:1	99	88
2-Me	>99:1	99	84
1-naphthyl	>99:1	97	76
2-furyl	99:1	90	92

N-Silyl Oxyketene Imines – Aldol Surrogates

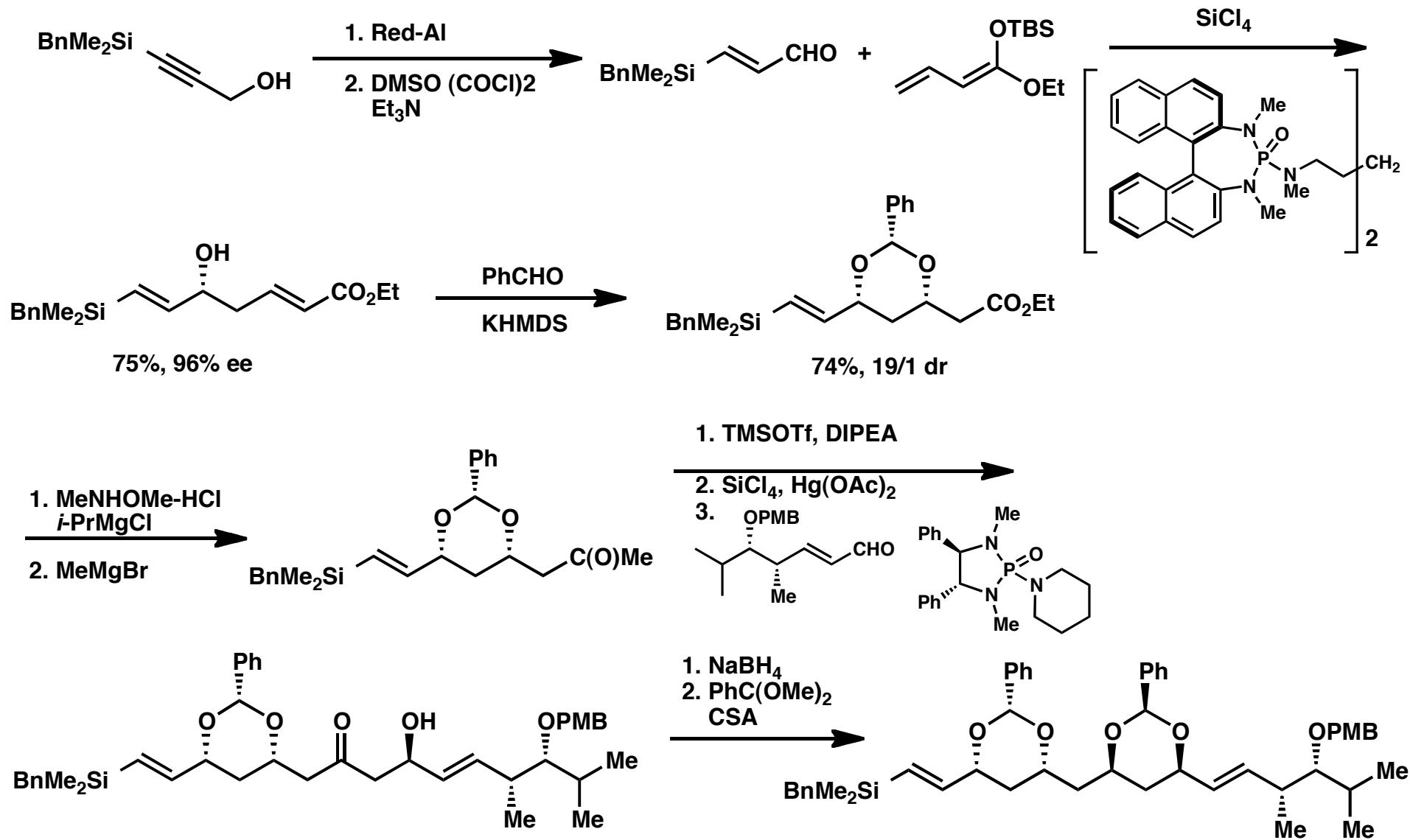


N-Silyl Oxyketene Imines – Aldol Surrogates

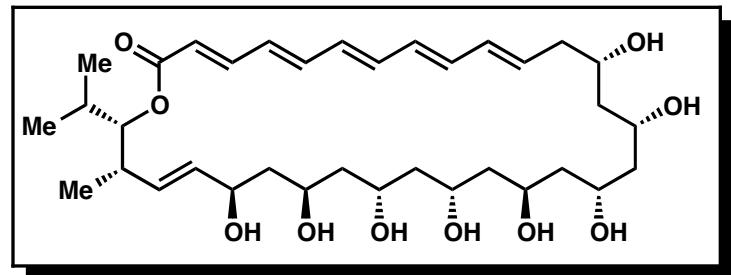


Total Synthesis of RK-397

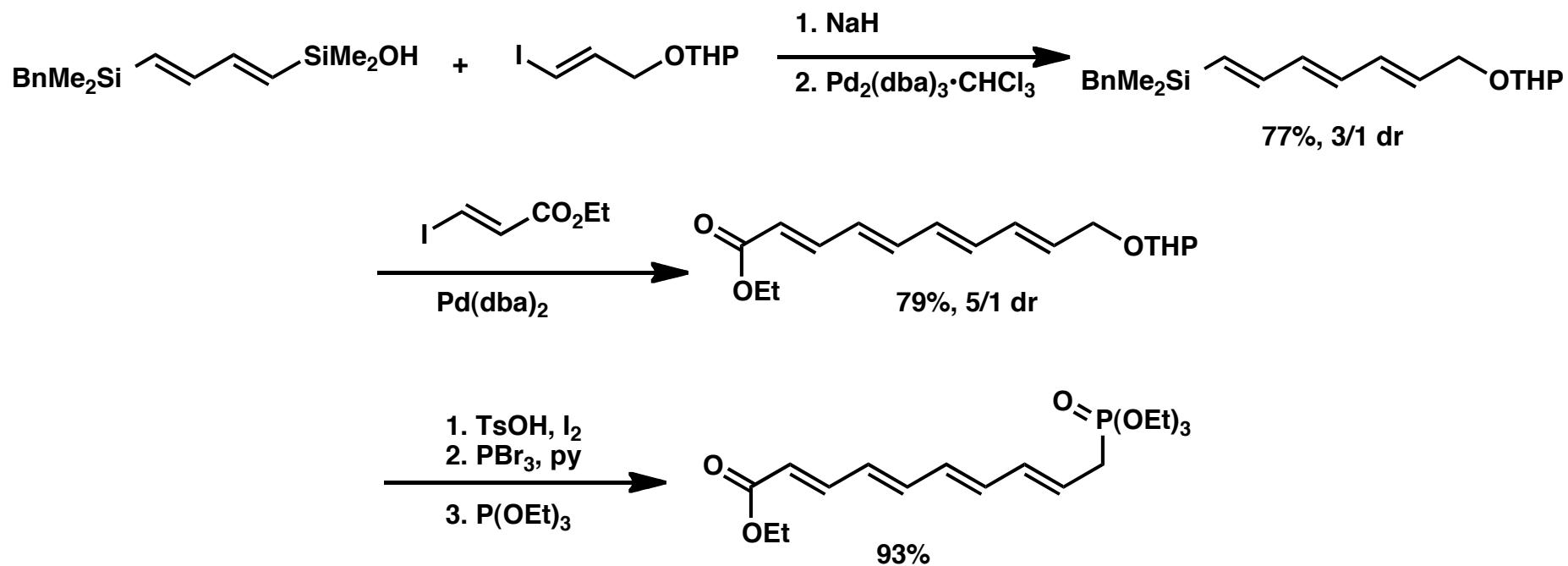
- Synthesis of Polyol Fragment



Total Synthesis of RK-397



- Synthesis of Polyene Fragment



8 of 10 stereocenters were generated by substrate control

Awards/Recognition

- Eli Lilly Research Grantee, 1983
- Beckman Endowment Research Award, 1983
- University of Illinois Center for Advanced Study, Beckman Fellow, Spring 1985
- A. P. Sloan Foundation Fellow, 1985-1987
- NSF Presidential Young Investigator Award, 1985-1990
- Procter and Gamble University Exploratory Research Program Award, 1986-89
- University Scholar, University of Illinois, 1986-1989
- School of Chemical Sciences Teaching Award, University of Illinois, 1986
- Stuart Pharmaceuticals Award in Chemistry, ICI Americas, 1987
- A. C. Cope Scholar Award, American Chemical Society, 1989
- Fellow, American Association for the Advancement of Science, 1990
- Reynold C. Fuson Professor of Chemistry, 1991
- Pedler Medal (Royal Society of Chemistry), 2002-2003
- ACS Award for Creative Work in Synthetic Organic Chemistry, 2003
- Yamada-Koga Prize (Japan Research Foundation for Optically Active Compounds), 2006
- Fellow, Royal Society of Chemistry (FRSC), 2006
- Prelog Medal (ETH-Zürich, Switzerland), 2007
- Robert Robinson Medal and Lectureship (Royal Society of Chemistry), 2009-2010
- H. C. Brown Award for Creative Research in Synthetic Methods (ACS), 2009
- Fellow, American Chemical Society, 2009 (inaugural year)

