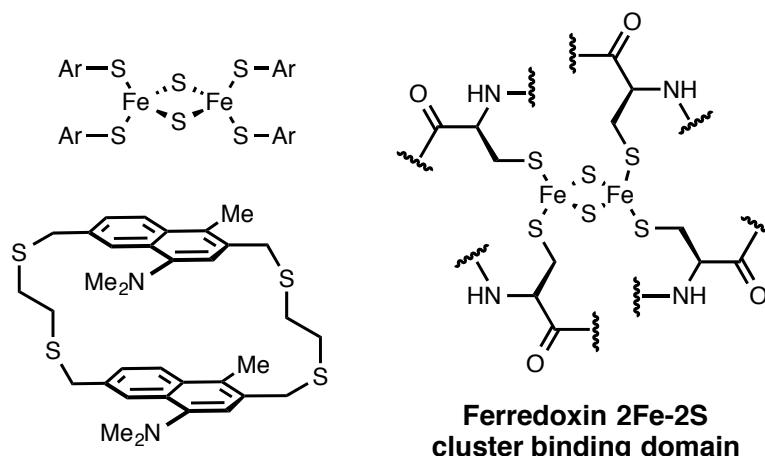
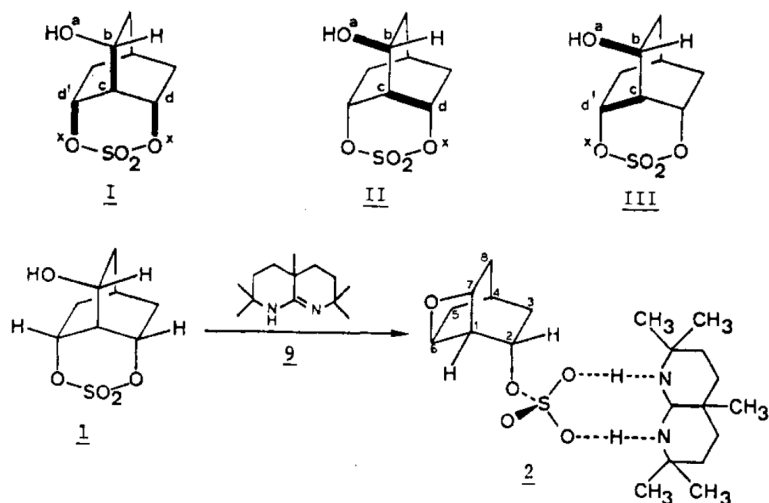


Selected Topics in the Career of Scott E. Denmark

January 14th, 2016

- ◆ Born: Lynbrook, NY 1953
- ◆ B. S. – MIT 1975
 - Richard H. Holm
 - Ferredoxin analogs
 - Daniel S. Kemp
 - Functionalized cyclophanes
- ◆ D.Sc.Tech. – ETH Zürich 1980
 - Albert Eschenmoser
 - Stereochemistry of S_N' reaction
- ◆ Reynold C. Fuson Professor of Chemistry - UIUC



Holm, R. H.; et al. *J. Am. Chem. Soc.* **1975**, *97*, 1032-1045.

Kemp, D. S.; et al. *J. Org. Chem.* **1979**, *44*, 4469-4473.

Denmark, S. E. *J. Org. Chem.* **1981**, *46*, 3144-3147.

Presentation Outline

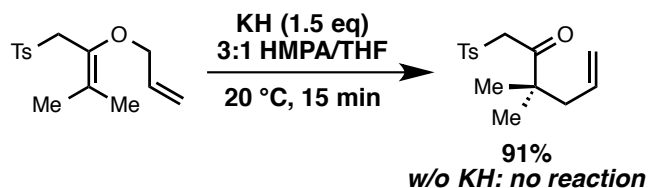
- 1. Carbanion-Accelerated Claisen Rearrangement**
- 2. Allyl-Si and Allyl-Sn Additions**
- 3. Si-Enolate Aldol Reactions**
- 4. R-Si Cross-Coupling Reactions**
- 5. Lewis Base Catalysis**
- 6. Nitroalkene Cycloaddition Chemistry**

Not covered:

- Phase Transfer Catalysis***
- Assorted Organometallic Chemistry***
- Phosphorus-Stabilized Anions***
- Dioxirane Chemistry***
- Silicon-Directed Nazarov Cyclization***

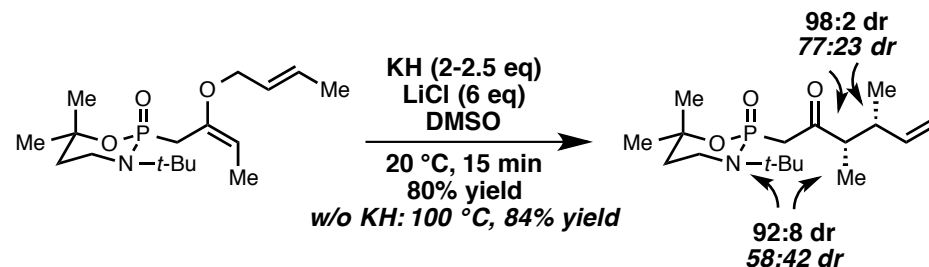
Carbanion-Accelerated Claisen Rearrangement

◆ Initial study

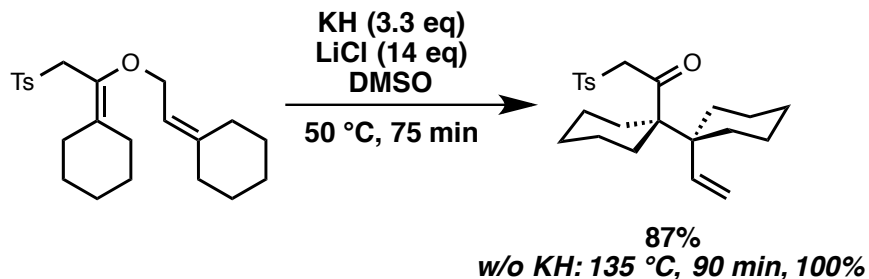


- Stereosel. Consistent w/ chair-like TS[‡]

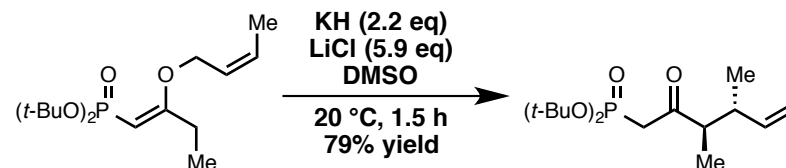
◆ Asymmetric Claisen



◆ Vicinal quat. centers

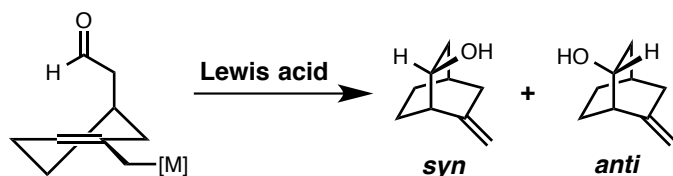


◆ Stereocenters on HWE reagents



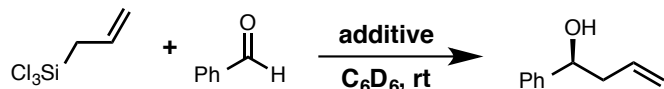
Allylmetal Addition

◆ Early model studies



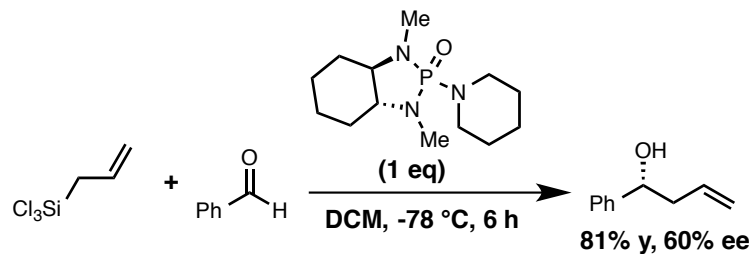
-[M] = SiMe₃: poor selectivity
 -[M] = SnBu₃: 82-97% *syn*

◆ Preliminary Lewis base studies

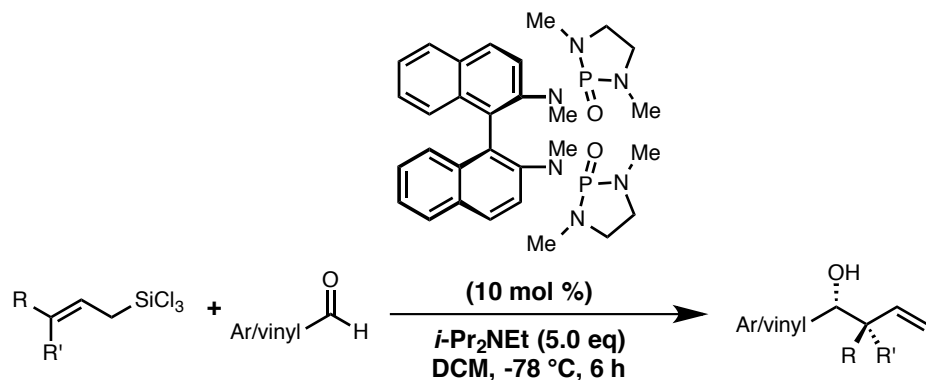
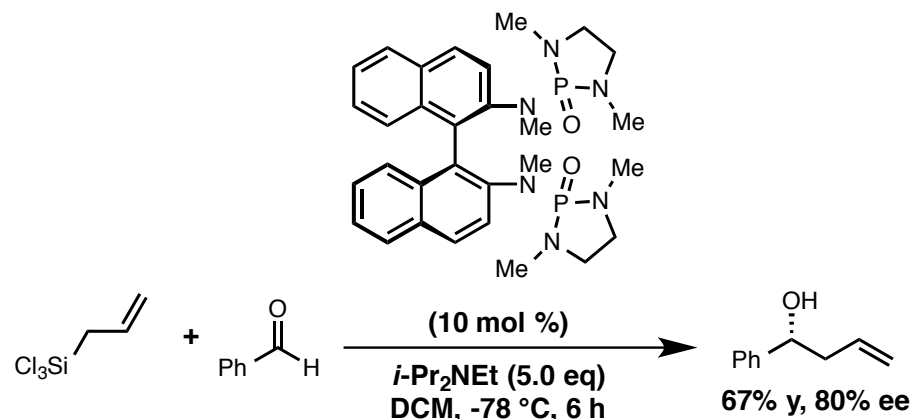


-DMF (1 eq)
 -HMPA (1 eq)

70 h 83% conv.
 4 min 63% conv.



◆ Enantioselective catalysis

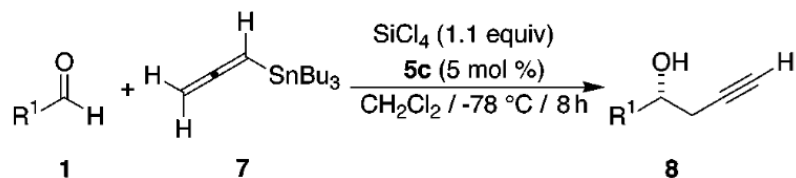


57-92% y,
 (E) gives 99:1 *anti*:*syn*
 (Z) gives ≥95:5 *syn*:*anti*
 81-96% ee

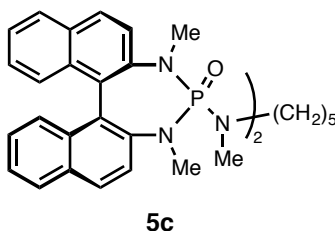
- Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655-1660.
 Denmark, S. E.; Weber, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 7970-7971.
 Denmark, S. E.; et al. *Tetrahedron* **1989**, *45*, 1053-1065.
 Denmark, S. E.; et al. *J. Org. Chem.* **1994**, *59*, 6161-6163.
 Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2000**, *122*, 12021-12022.
 Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488-9489.

Allylmetal Addition

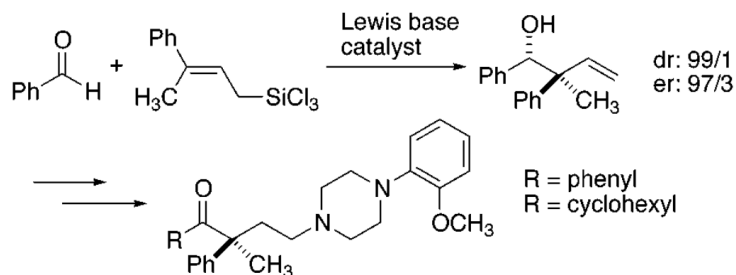
◆ Propargylation



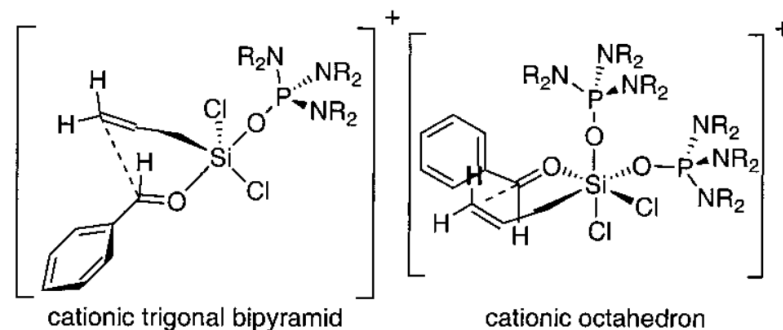
8a: R¹ = Ph 81% (97% ee (*R*))
8b: R¹ = cinnamyl 90% (87% ee (*R*))
8c: R¹ = 2-naphthyl 95% (93% ee (*R*))



◆ Synthesis of serotonin antagonist LY426965

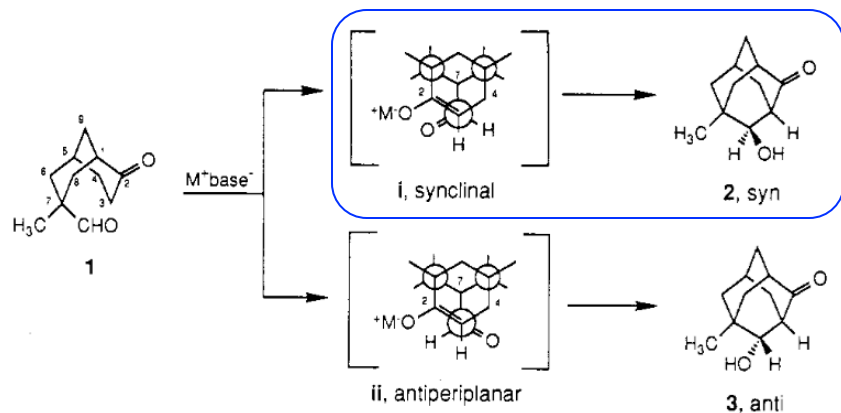


◆ Stereochemical model

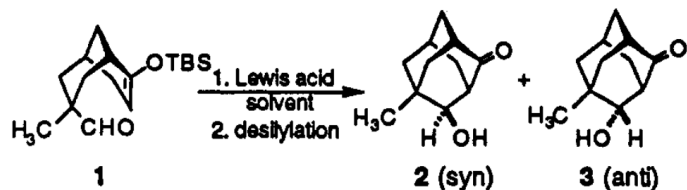


- Evidence shows always chair-like TS[‡] with phosphoramidate catalysis

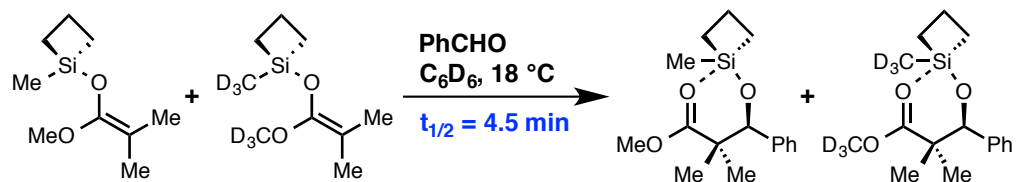
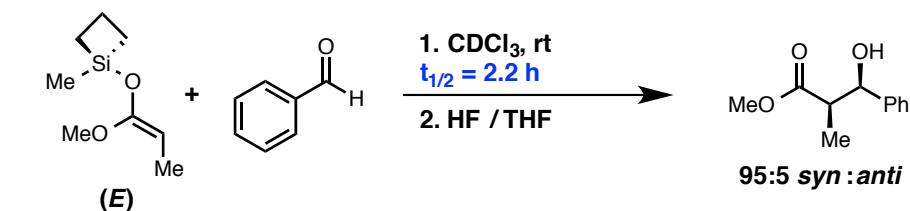
Enoxysilacyclobutane Aldol



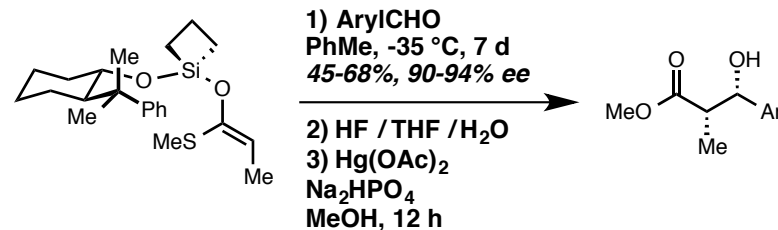
◆ 59-96% stereoselectivity



entry	Lewis acid	syn/anti ^b	syn/anti ^{b,c}	$\Delta\Delta G^\ddagger, ^c$ kcal/mol
1	TiCl ₄	21/79	25/75	-0.43



- ◆ Fast, uncatalyzed
- ◆ Direct [Si]-group transfer
- ◆ Non-Zimmerman-Traxler selectivity
- ◆ Boat-like TS[‡] proposed



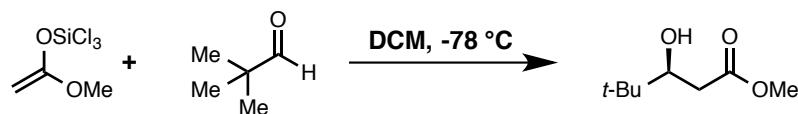
Denmark, S. E.; Henke, B. R. *J. Am. Chem. Soc.* **1991**, *113*, 2177-2194.

Denmark, S. E.; Lee, W. *J. Org. Chem.* **1994**, *59*, 707-709.

Denmark, S. E.; Griedel, B. D.; Coe, Diane M. *J. Org. Chem.* **1993**, *58*, 988-990.

Denmark, S. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 5136-5138.

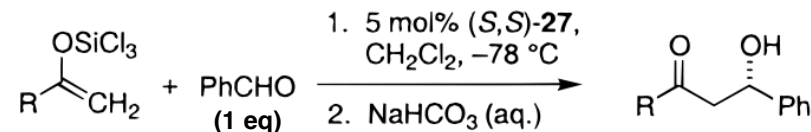
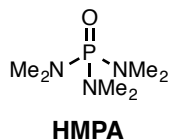
Trichlorosilyl Enolates



-No additive
-HMPA (10 mol %)

120 min
<3 min

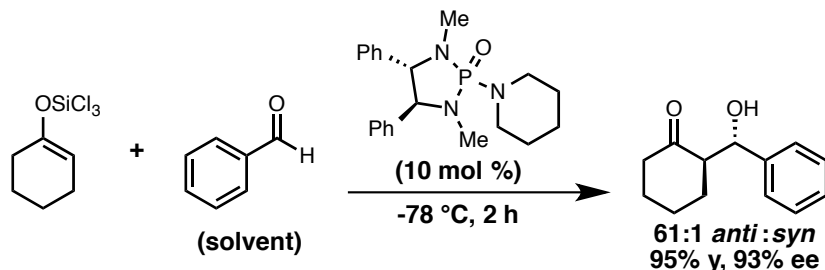
50% yield
100% yield



1. 5 mol% (*S,S*)-**27**,
CH₂Cl₂, -78 °C
2. NaHCO₃ (aq.)

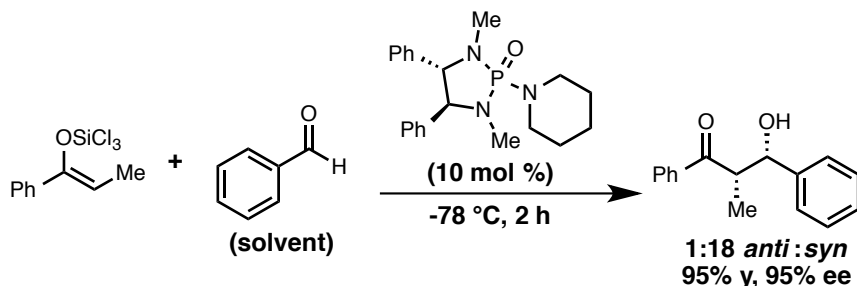
entry	enolate	R	product	er ^b	yield, ^c %
1	1	Me	(-)- 12	14.6/1 ^d	98
2	2	<i>n</i> -Bu	(-)- 13	12.0/1	98
3	3	<i>i</i> -Bu	(-)- 14	10.1/1	95
4	4	<i>i</i> -Pr	(-)- 15	9.75/1	97
5	5	<i>t</i> -Bu	(-)- 16	3.17/1	95
6	6	Ph	(-)- 17	2.92/1	93
7	7	TBSOCH ₂	(-)- 18	13.5/1	94

^a Reactions performed at 0.5 M for 2 h. ^b Ratio of the *S/R* isomer;



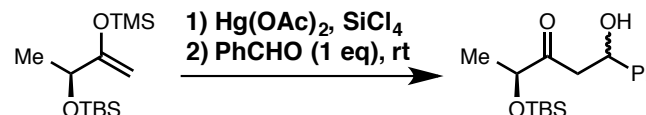
(10 mol %)
-78 °C, 2 h

61:1 *anti:syn*
95% y, 93% ee



(10 mol %)
-78 °C, 2 h

1:18 *anti:syn*
95% y, 95% ee



1) Hg(OAc)₂, SiCl₄
2) PhCHO (1 eq), rt

Additive

yield

anti:syn

-No additive

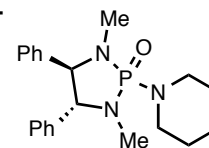
82%

1.2:1

-

85%

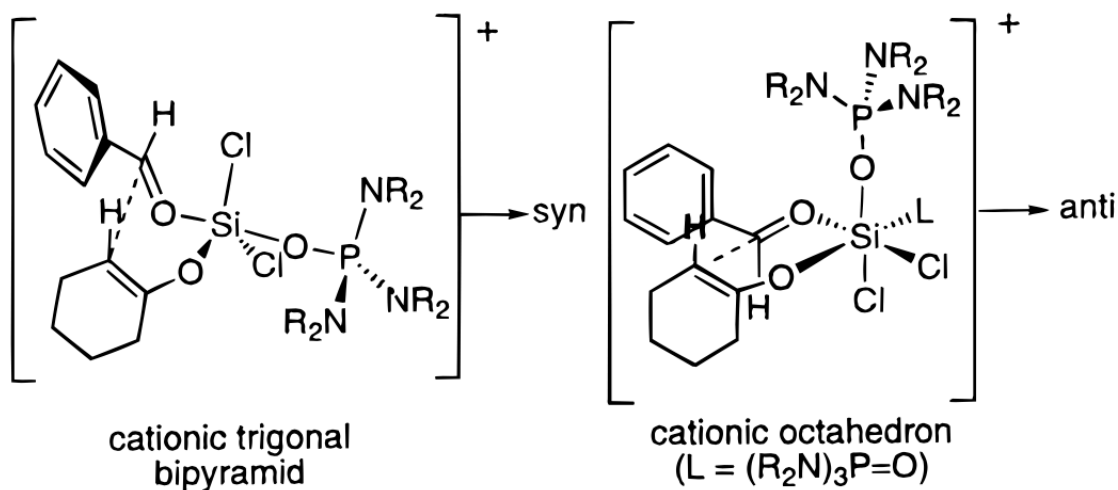
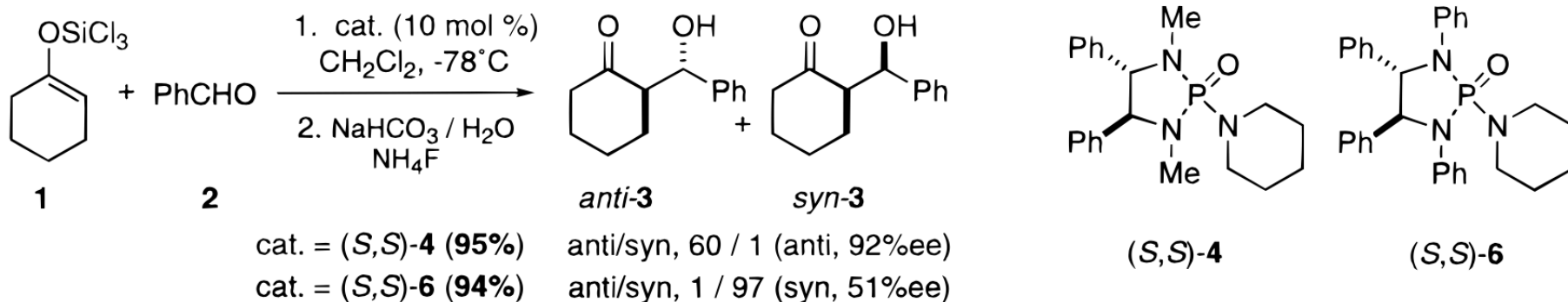
1:73



(5 mol %)

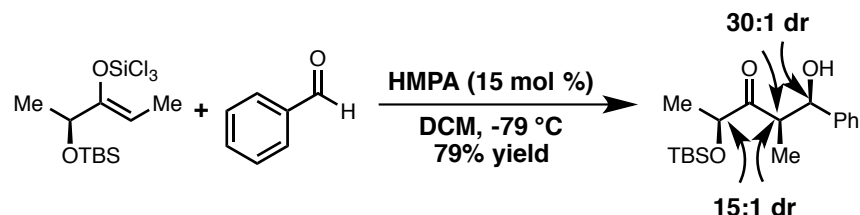
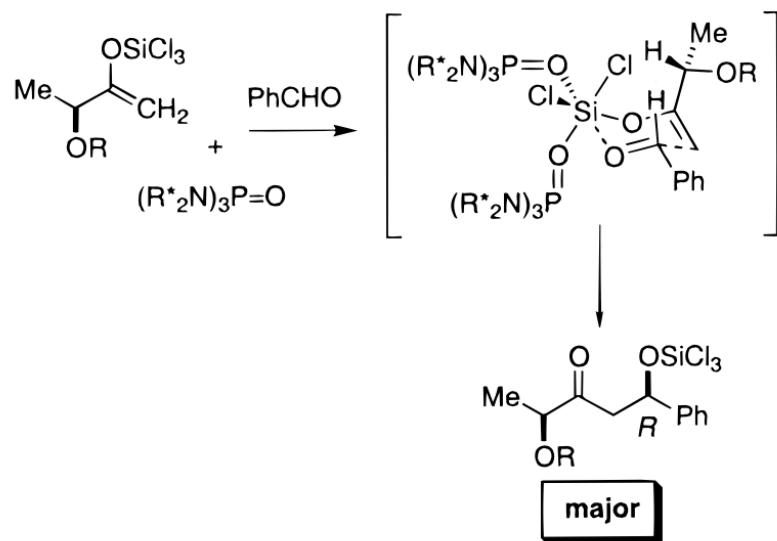
- ◆ Phosphoramidate enantiomer gives 1:1.5 *anti:syn*
- ◆ Electron-poor aldehydes give higher dr's
- ◆ Stereocenter on aldehyde: Felkin-Anh

Mechanistic Duality

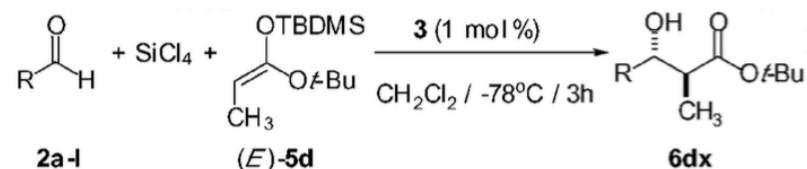


Trichlorosilyl Enolates

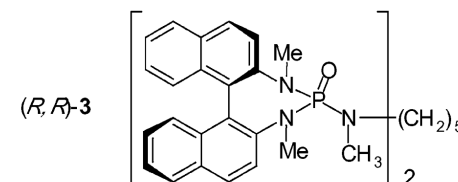
- ◆ **Syn-selectivity of catalyzed reaction: two-ligand mechanism, chair TS[‡]**



- ◆ **Silyl ketene acetals**



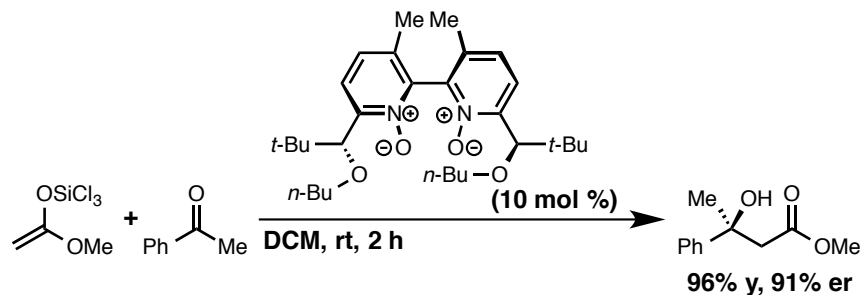
entry	R	product	yield, % ^b	dr ^c	er ^d
1	C ₆ H ₅ (2a)	6da ^e	93	99:1	>99:1
2	1-naphthyl (2b)	6db	98	96:4	97:3
3	2-naphthyl (2c)	6dc	95	>99:1	>99:1
4	4-CH ₃ OC ₆ H ₄ (2e)	6de	88	>99:1	99:1
5	4-CF ₃ C ₆ H ₄ (2f)	6df	93	>99:1	96:4
6	(<i>E</i>)-PhCH=CH (2g)	6dg	98	>99:1	>99:1
7	(<i>E</i>)-PhCH=C(CH ₃) (2h)	6dh	90	>99:1	96:4
8	phenyl propargyl (2l)	6dl	92	96:4	84:16



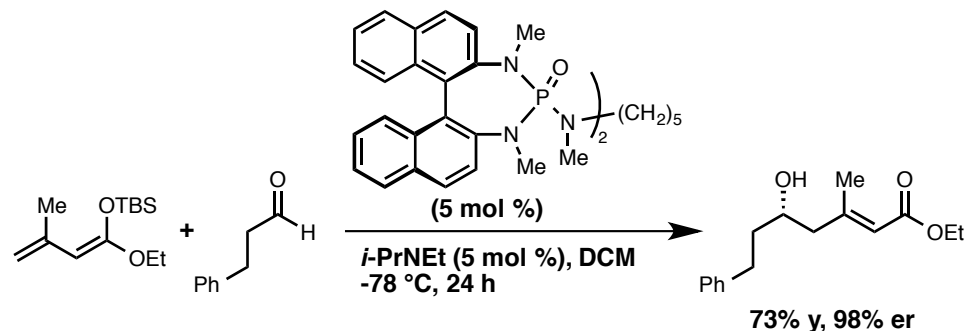
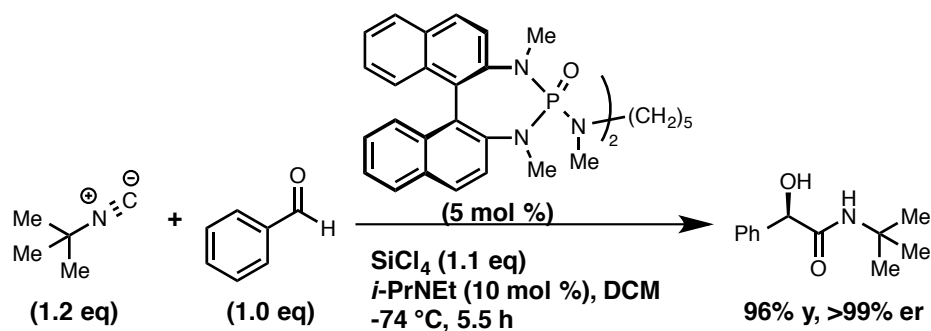
- ◆ **Bidentate ligand encourages chair-like TS[‡]**
- ◆ **Alkyl substrates:**
49-71% y, 89-93% dr, 68-95% er

Method Expansion

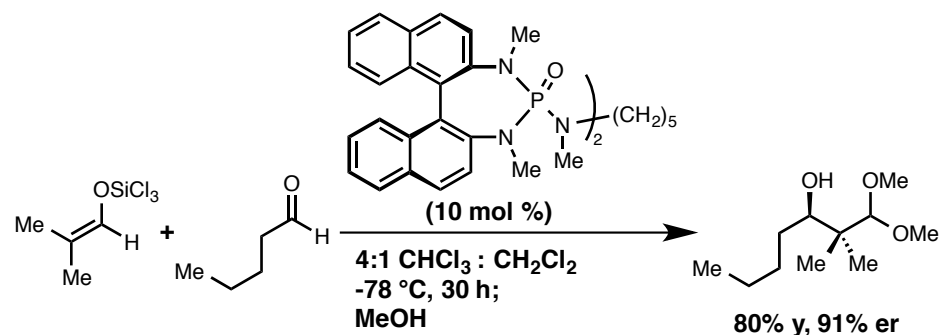
◆ Addition to ketones



◆ Vinylogous aldol

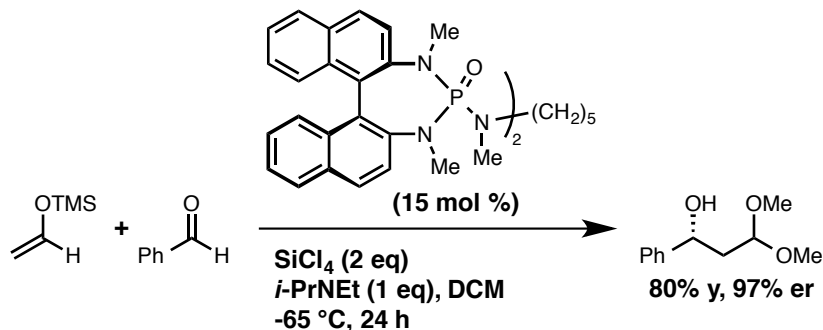
◆ “The First Catalytic, Asymmetric α -Additions of Isocyanides”

◆ Crossed-aldol of aldehydes

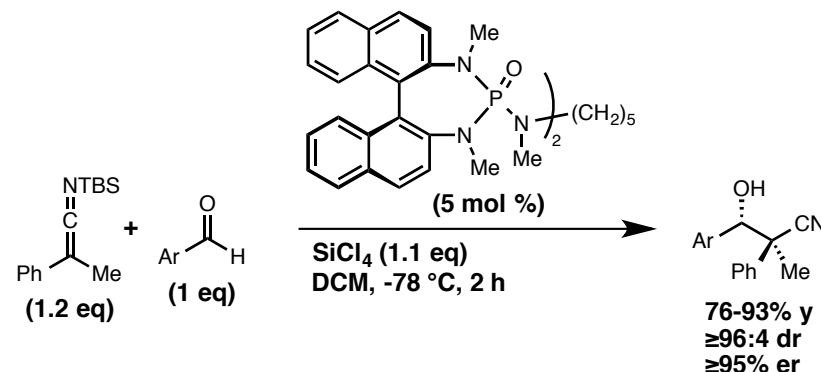
Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2002**, *124*, 4233-4235.Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7825-7827.Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 7800-7801.Denmark, S. E.; Bui, T. *PNAS* **2004**, *101*, 5439-5444.

Trialkylsilyl Nucleophiles

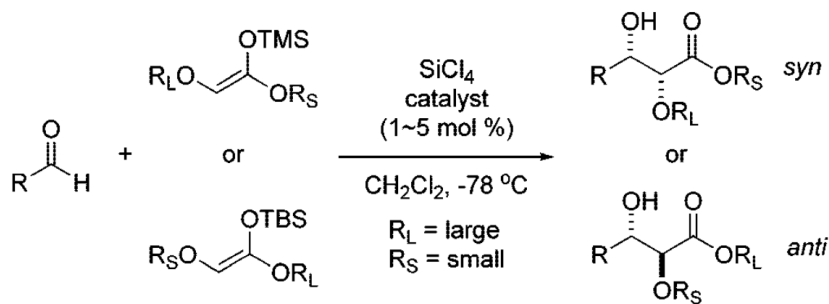
◆ Acetaldehyde-derived enolate



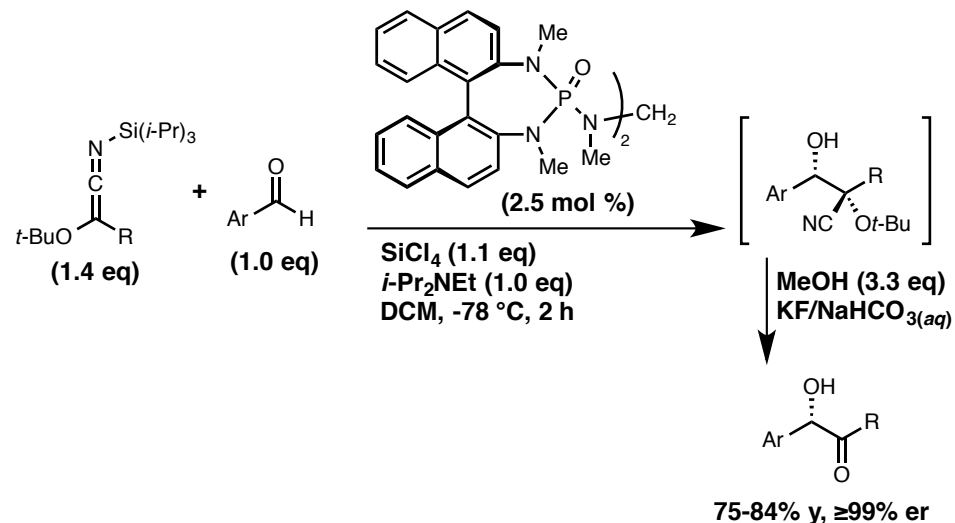
◆ Silyl ketene imine addition



◆ Glycolate-derived enolate

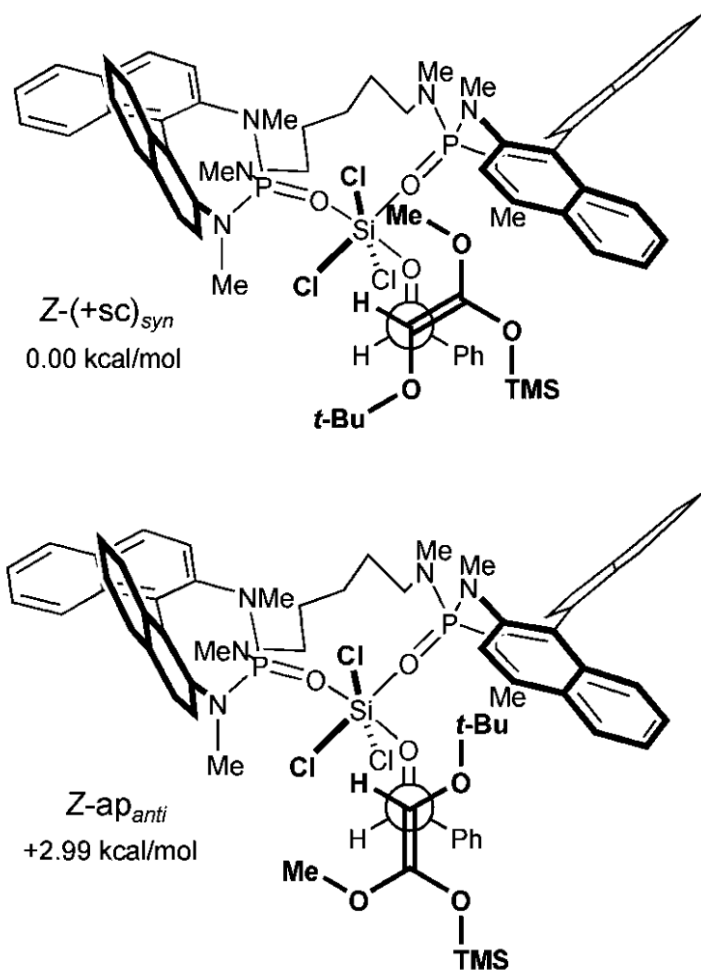


◆ Silyl oxyketene imine addition

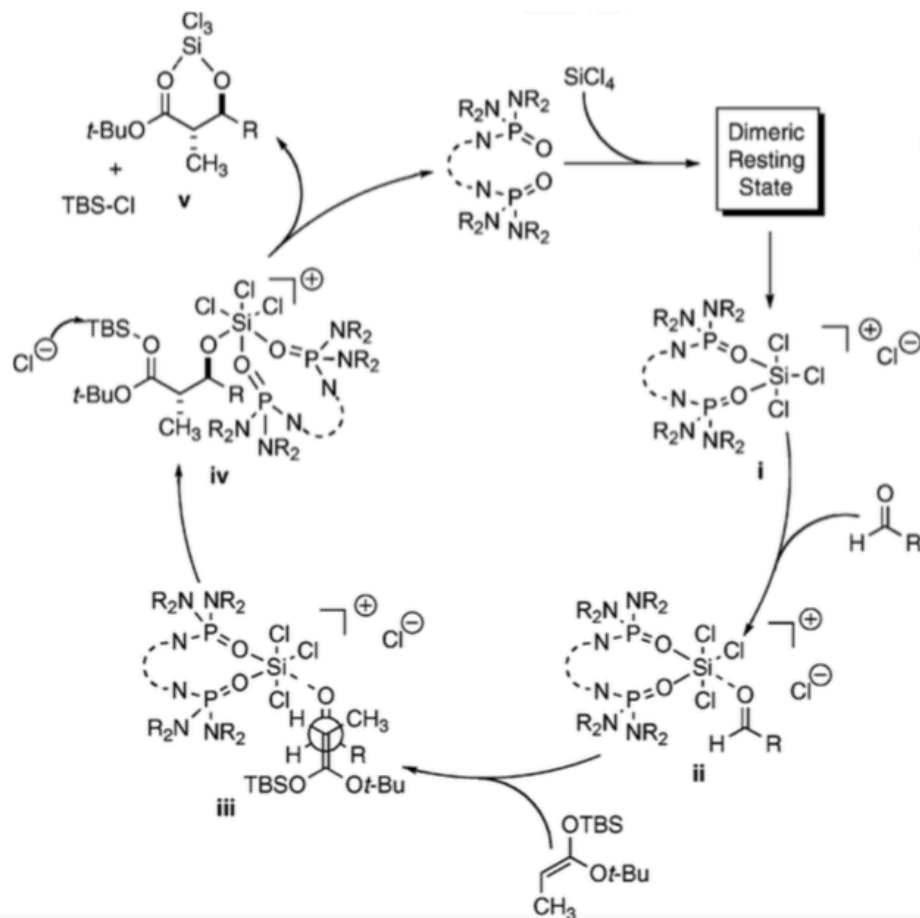
Denmark, S. E.; Bui, T. *J. Org. Chem.* **2005**, *70*, 10190-10193.Denmark, S. E.; Chung, W. *J. Org. Chem.* **2005**, *73*, 4582-4595.Denmark, S. E.; et al. *J. Am. Chem. Soc.* **2007**, *129*, 14864-14865.Denmark, S. E.; Wilson, T. W. *Nat. Chem.* **2010**, *2*, 937-943.

Trialkylsilyl Nucleophiles: Mechanism

◆ Stereochemical model for bidentate ligand



◆ Full catalytic cycle

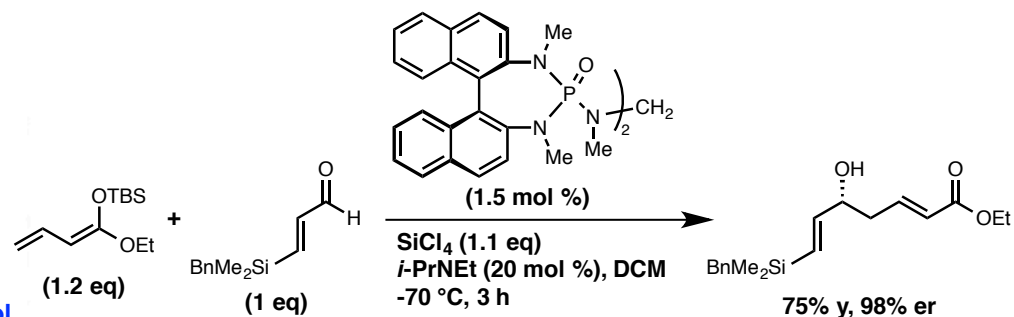
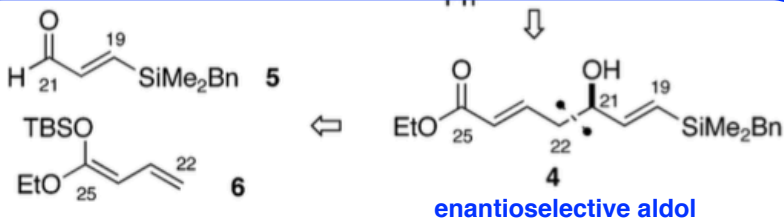
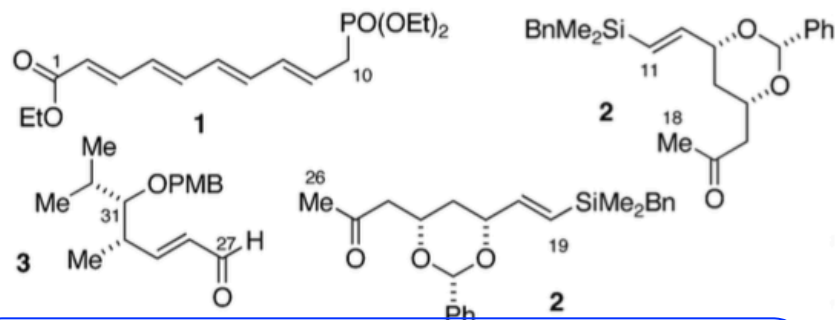
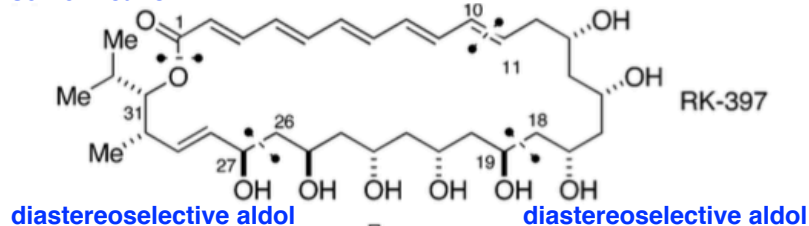


Total Synthesis

◆ Synthesis of antifungal RK-397

transesterification

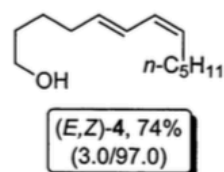
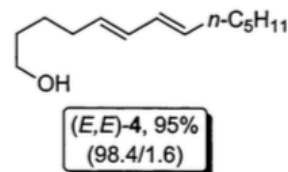
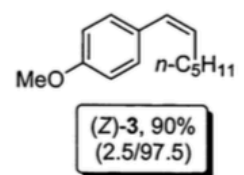
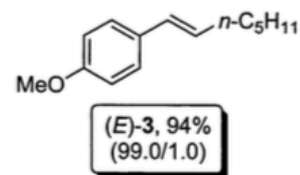
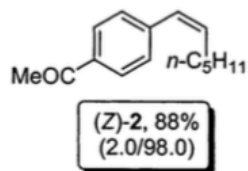
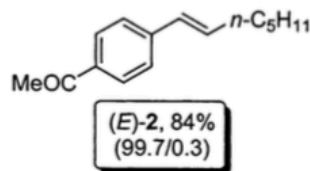
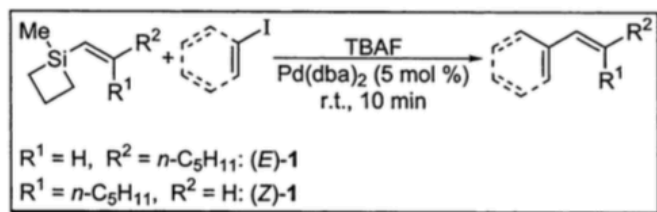
HWE



◆ 20 steps

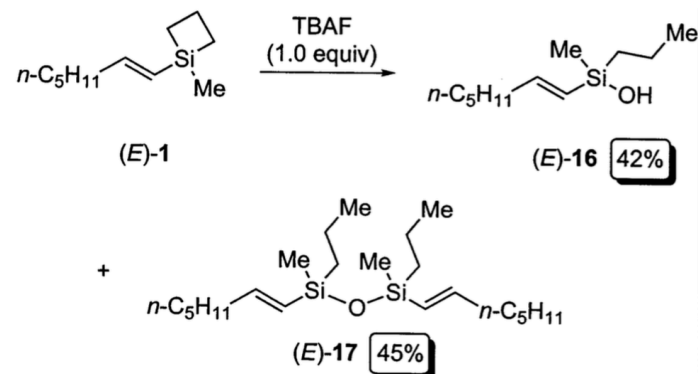
R-Si Cross-Coupling

◆ Silacyclobutanes

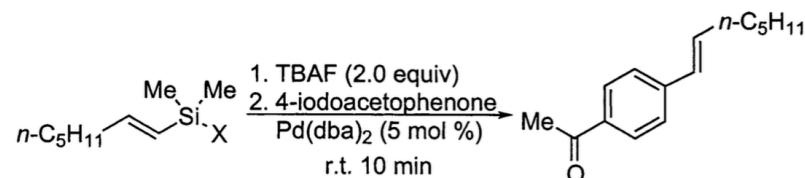


◆ Also works with Ar-Si

◆ Exceptional exotherm observed when adding TBAF to silacyclobutane

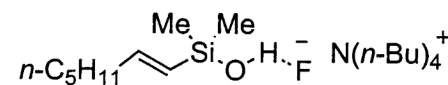


◆ Vinylsilanol reactivity



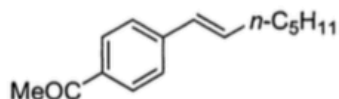
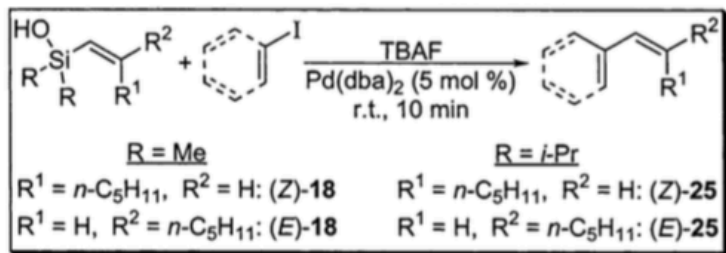
X = OH: (E)-18	79%
X = OSi(Me) ₂ C ₇ H ₁₃ : (E)-19	82%
X = F: (E)-20	78%

○ via

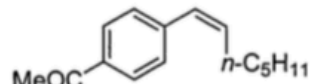


R-Si Cross-Coupling

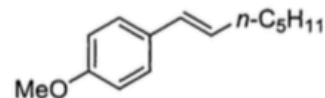
◆ Silanol cross-coupling

**(E)-2**

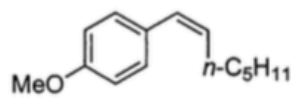
R = Me: 93%, (96.5/3.5)
R = *i*-Pr: 80%, (99.5/0.5)

**(Z)-2**

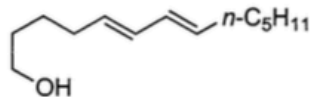
R = Me: 92%, (4.8/95.2)
R = *i*-Pr: 86%, (1.0/99.0)

**(E)-3**

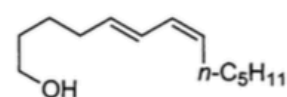
R = Me: 95%, (97.2/2.8)

**(Z)-3**

R = Me: 94%, (2.6/97.4)

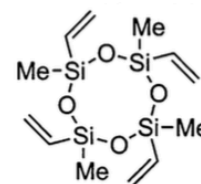
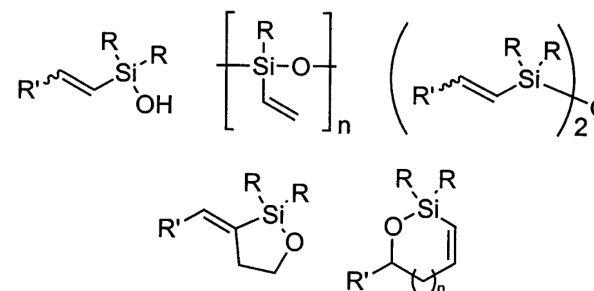
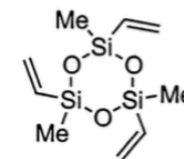
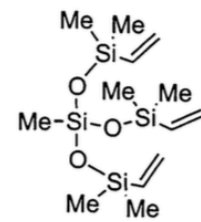
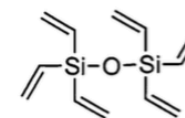
**(E,E)-4**

R = Me: 91%, (95.8/4.2)
R = *i*-Pr: 87%, (97.8/2.2)

**(E,Z)-4**

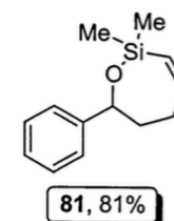
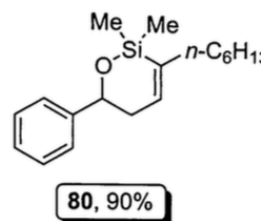
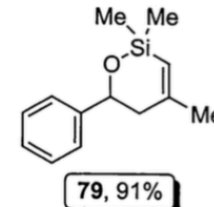
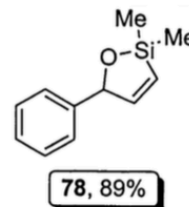
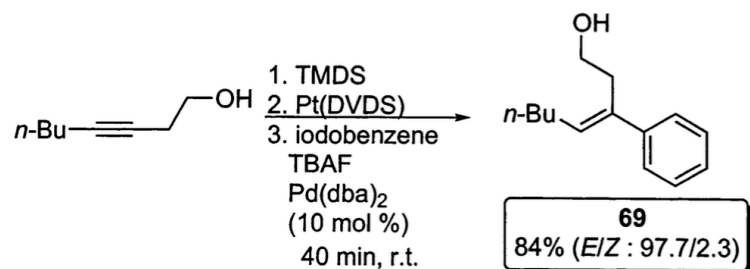
R = Me: 72%, (4.6/95.4)

◆ Reagent availability

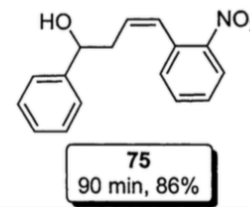
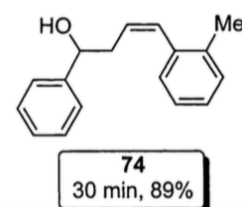
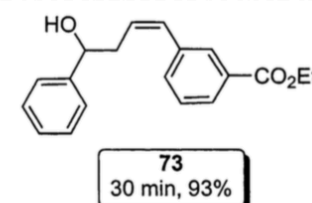
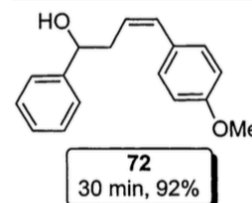
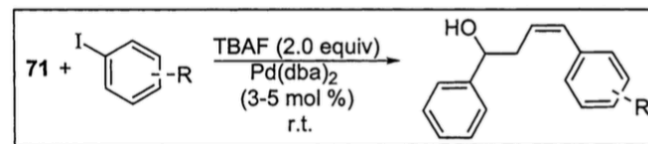
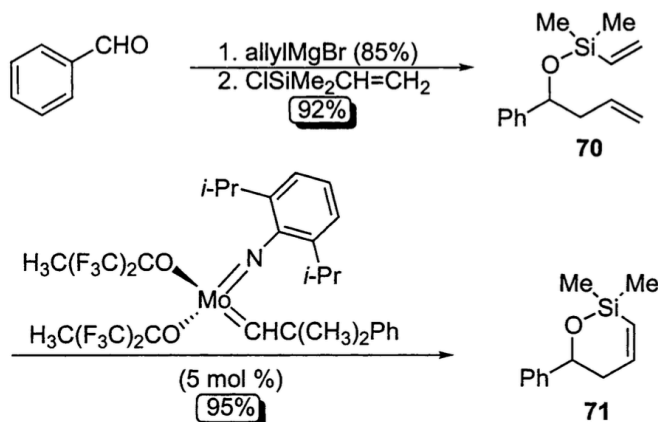
**45**
\$0.76/g**46**
\$4.60/g**47**
\$3.30/g**48**
\$5.30/g

Sequential processes

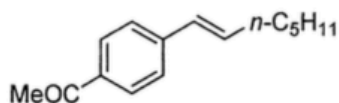
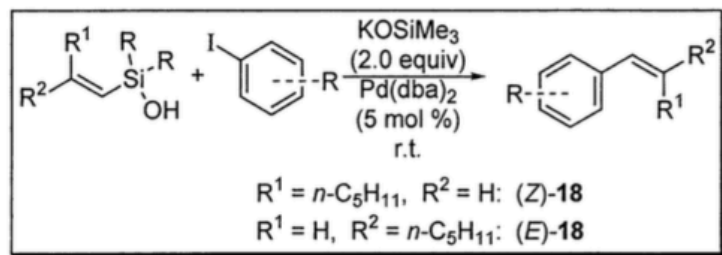
◆ “Net hydroarylation”



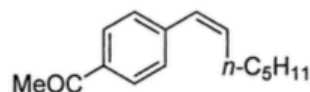
◆ Metathesis-coupling: “aryl-homoallylation”



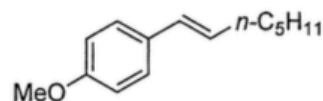
Fluoride-Free Cross-Coupling Reactions



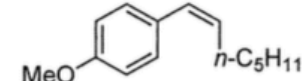
9 h, 82%
(98.8/1.2)



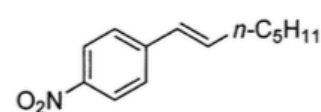
13 h, 83%
(2.9/97.1)



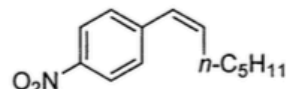
1 h, 88%
(99.3/0.7)



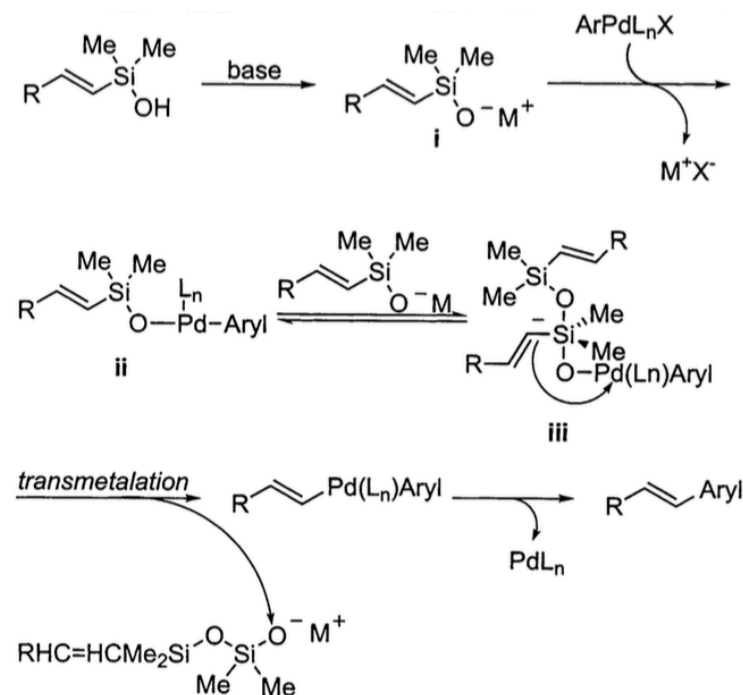
9.5 h, 91%
(1.1/98.9)



15 min, 95%
(98.5/1.5)

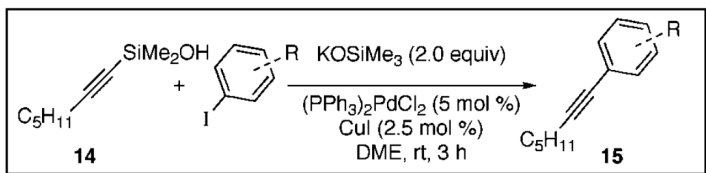


15 min, 85%
(3.8/96.2)

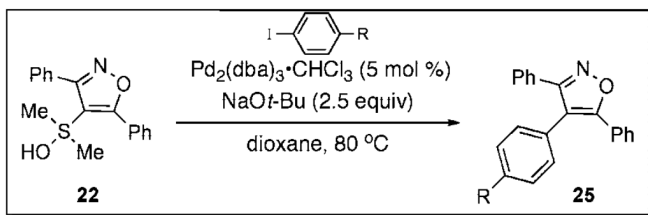
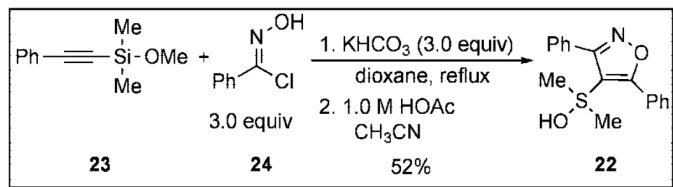
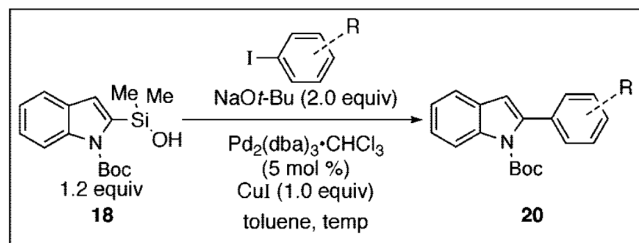


Fluoride-Free Cross-Coupling Reactions

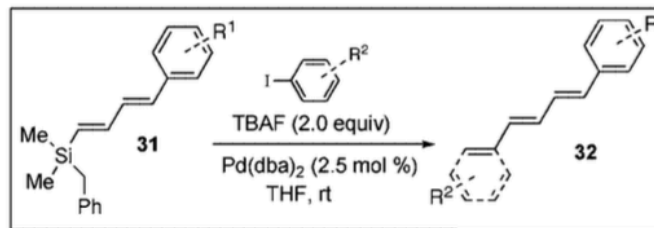
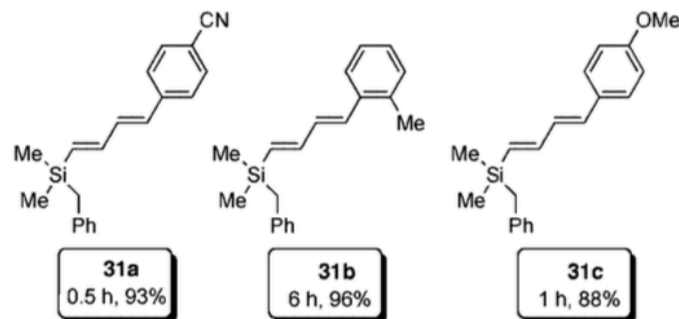
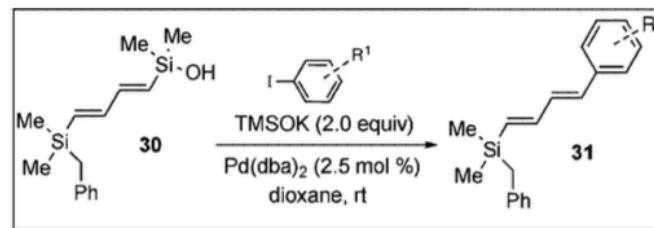
◆ Alkynylsilanols



◆ Heterocyclic silanolates

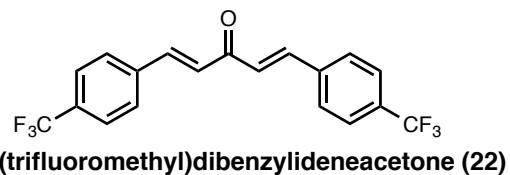
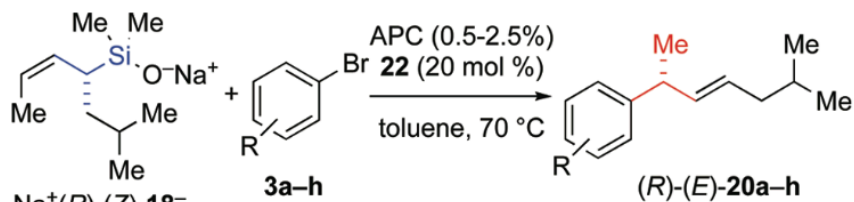
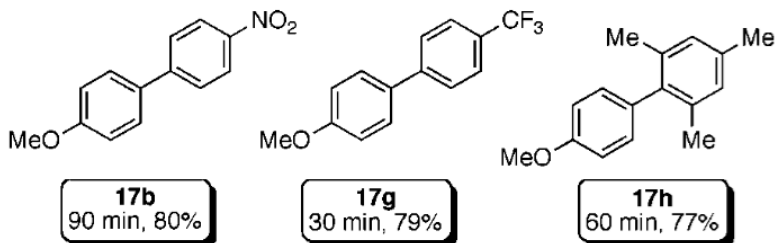
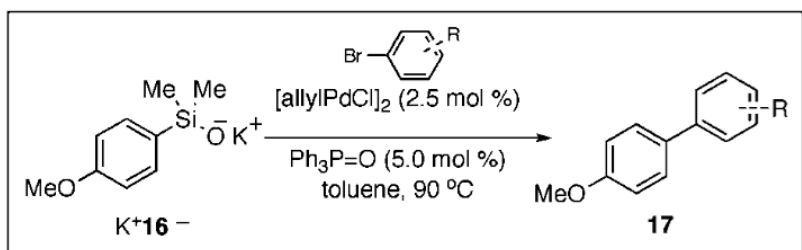


◆ Sequential cross-coupling

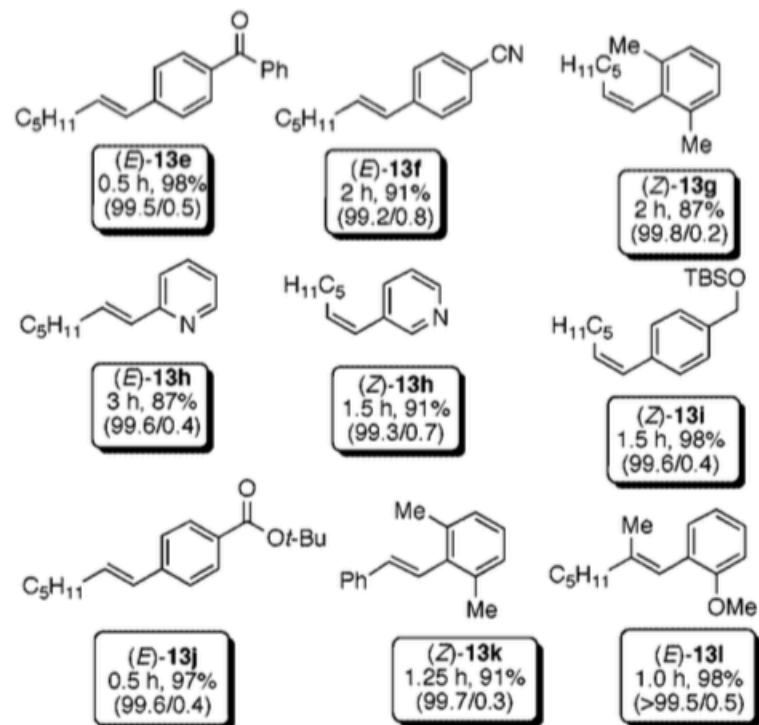
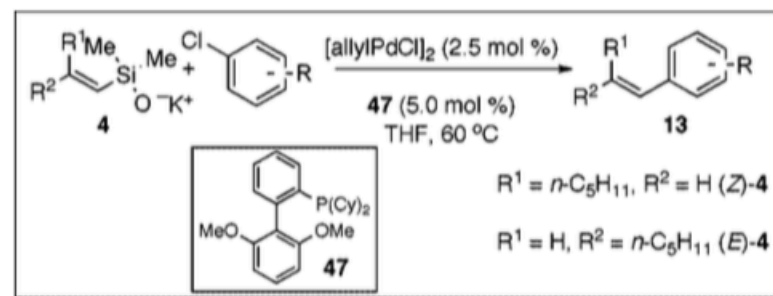


Silanolate Salts

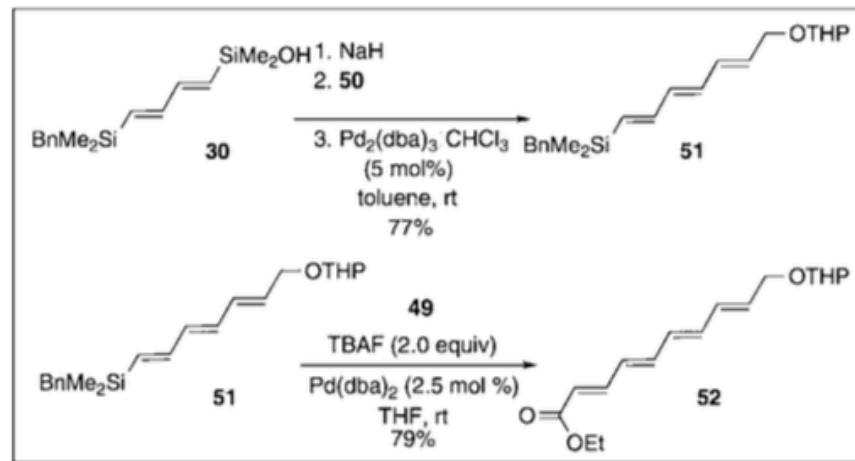
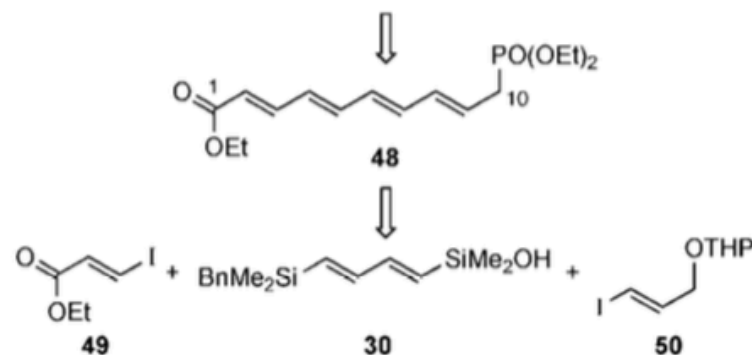
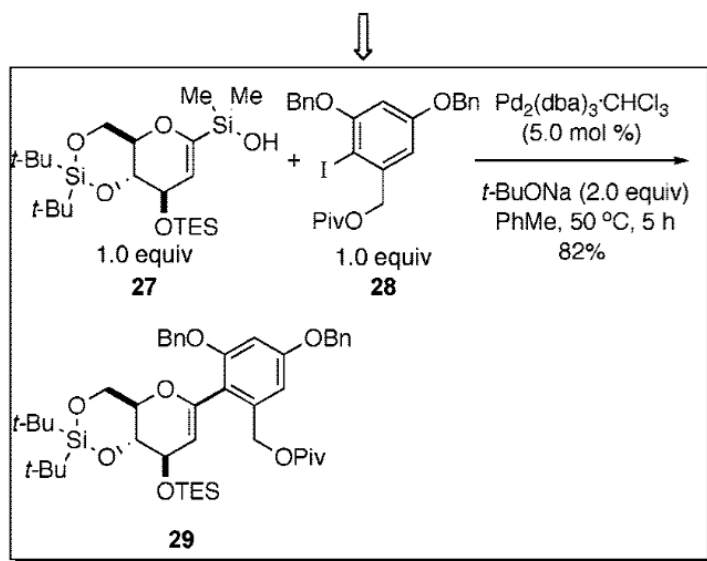
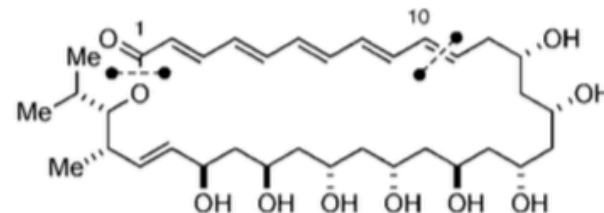
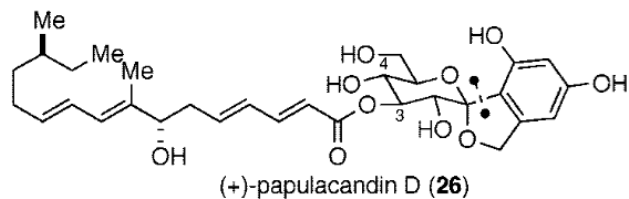
◆ Cross-coupling with aryl bromides



◆ Cross-coupling with aryl chlorides

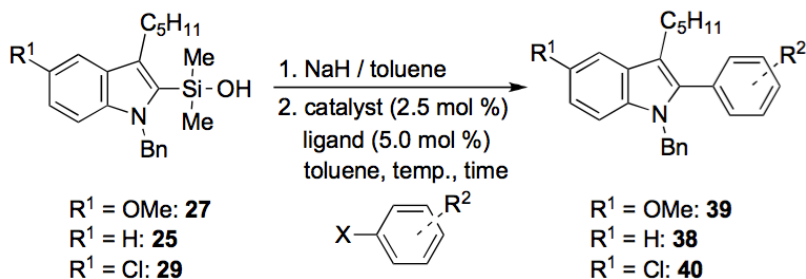
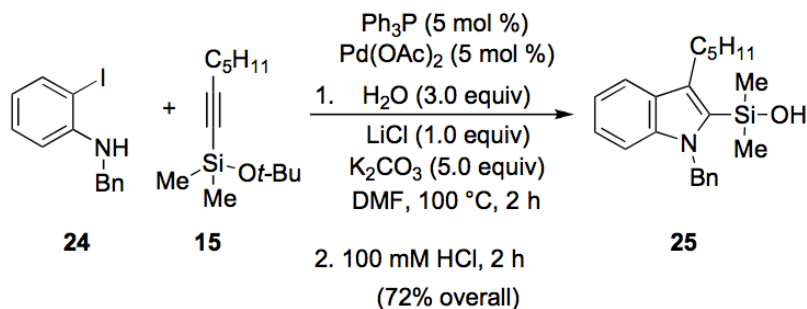


Synthetic Applications

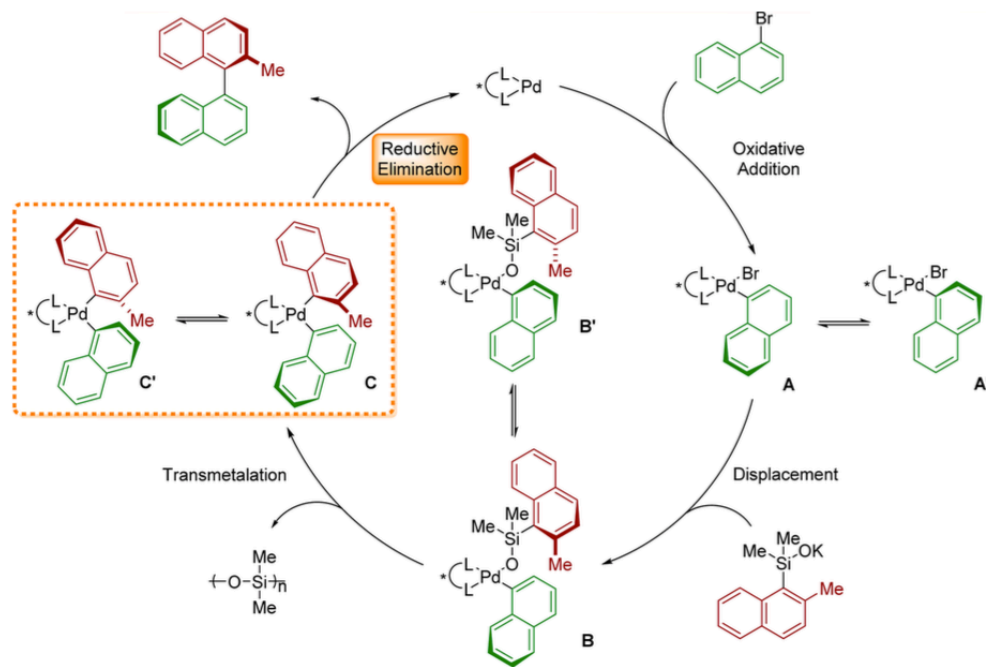
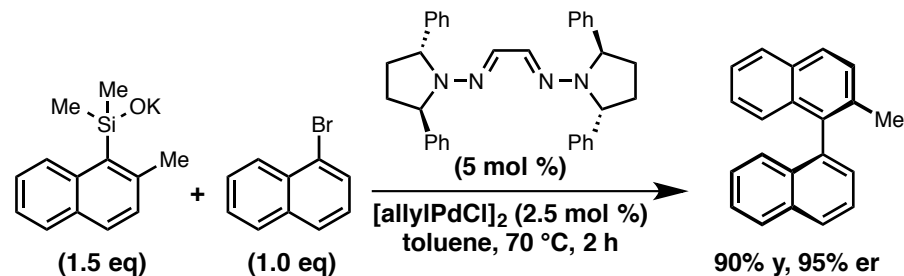


Further Developments

◆ Sequential Larock annulation-coupling

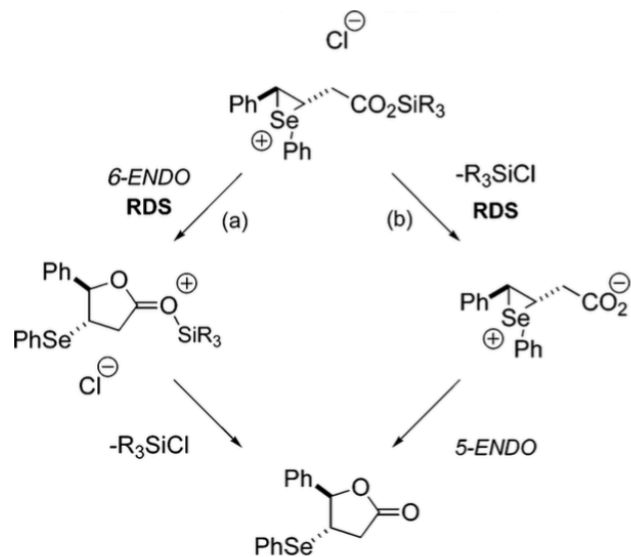
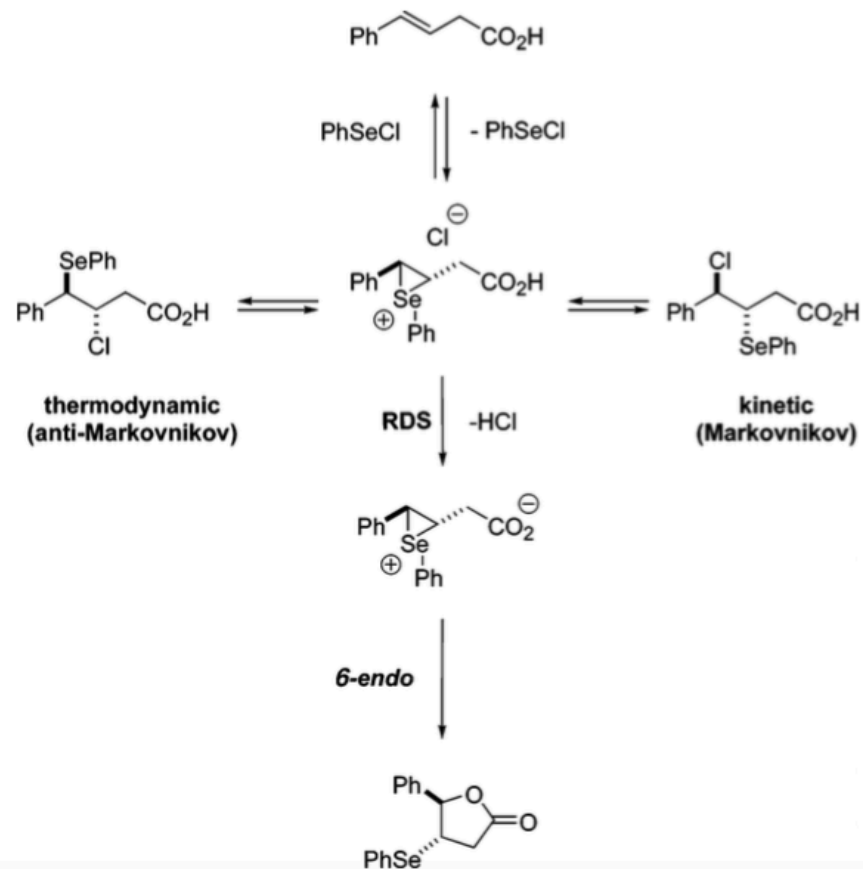
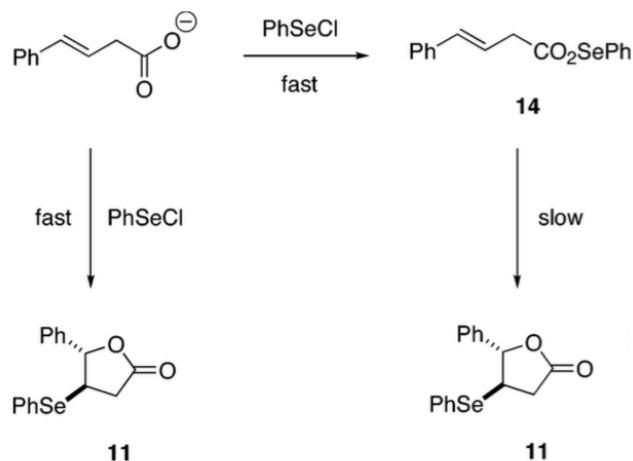


◆ Enantioselective cross-coupling



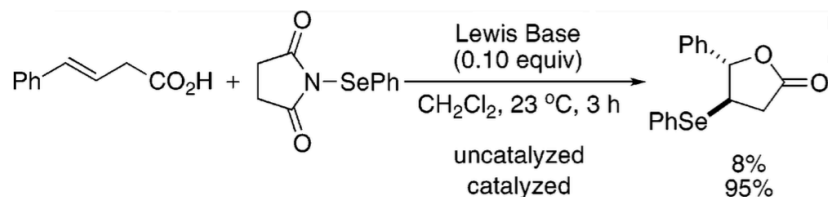
DiarylPd(II) complexes C and C' are the common intermediates.
 Reductive elimination is likely the stereodetermining step.

Mechanism of Selenolactonization



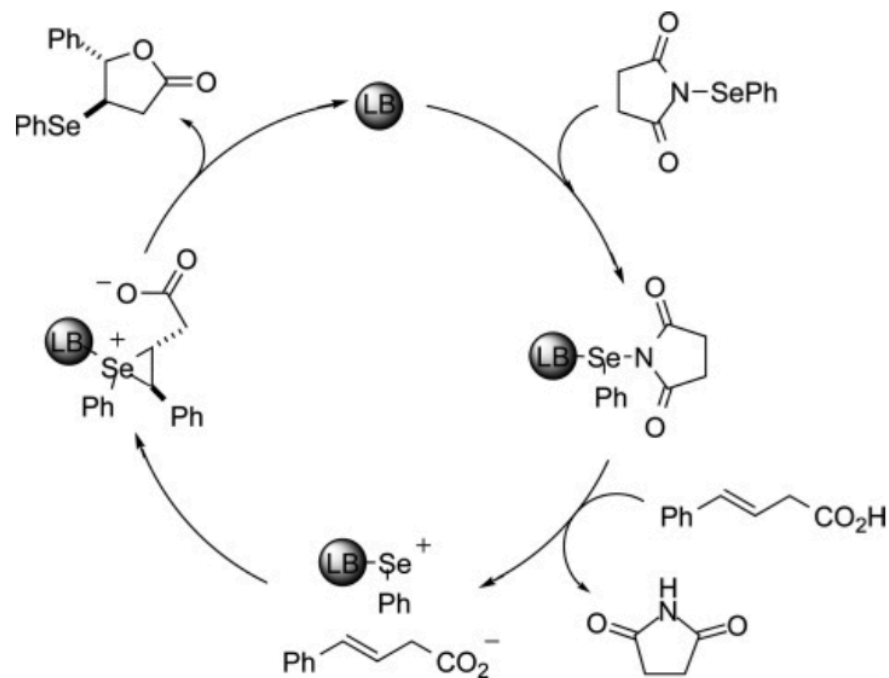
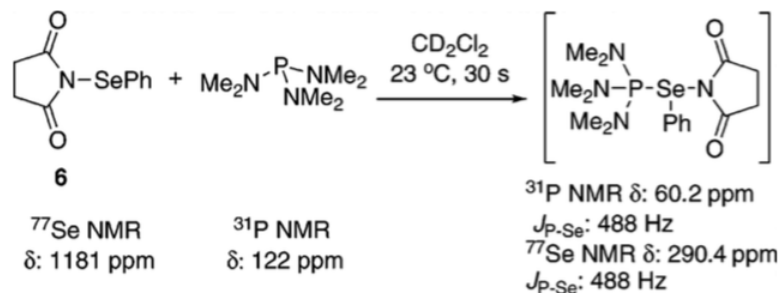
◆ VT-NMR and React-IR

Catalytic Selenocyclization

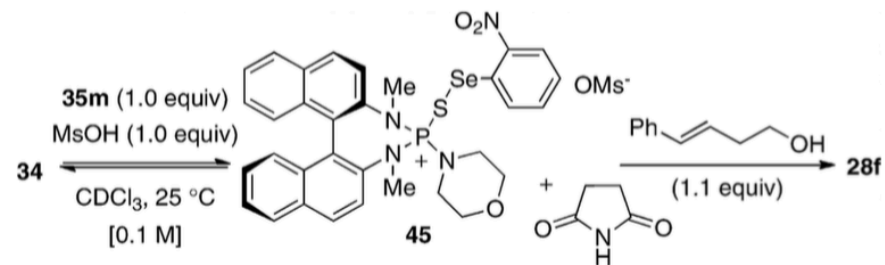
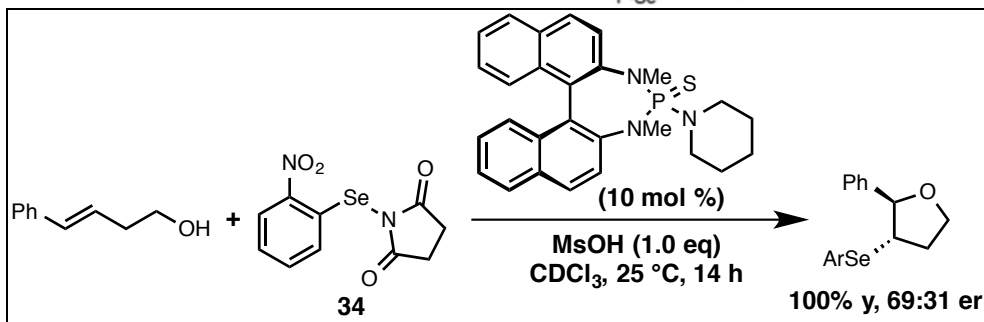


entry	Lewis base catalyst	yield, ^a %
1	(Me ₂ N) ₃ P=O (7)	55
2	(Me ₂ N) ₃ P=S (8)	89
3	(Me ₂ N) ₃ P=Se (9)	95

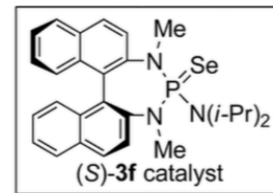
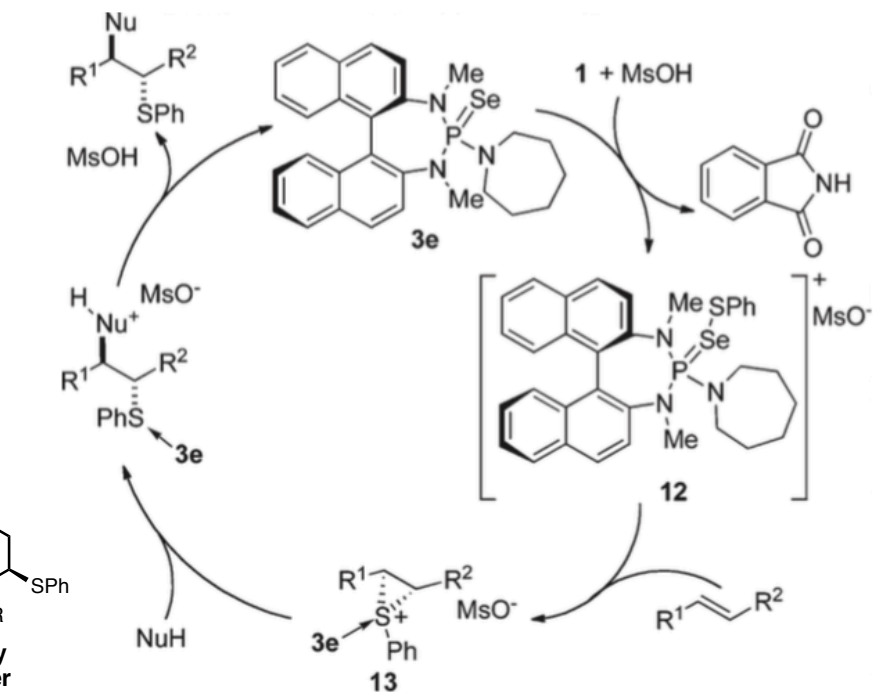
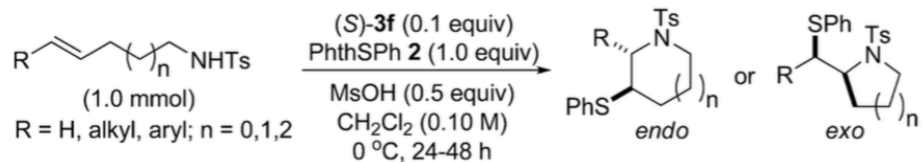
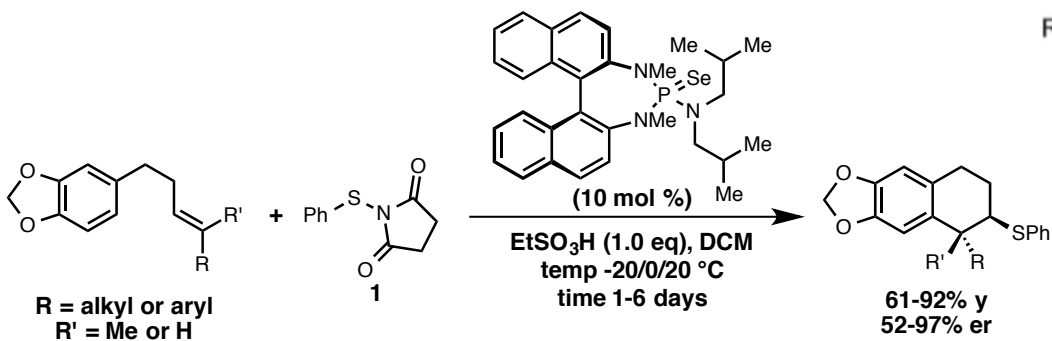
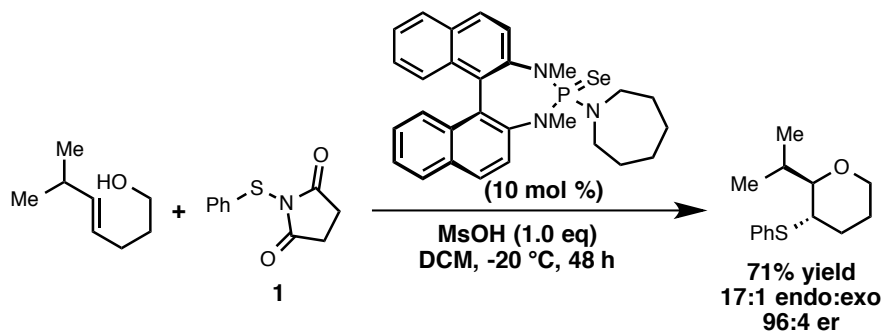
^a Isolated yield of chromatographically homogeneous material



◆ VT-NMR and React-IR

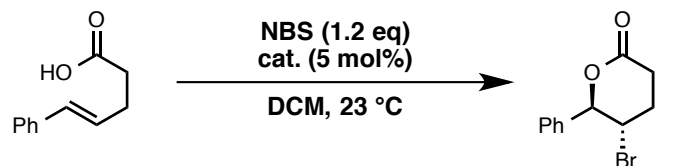


Catalytic Enantioselective Thiocyclization

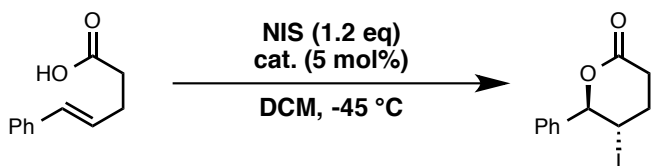


R=aryl: endo
R=alkyl or H: exo
68-93% yield
63-97% er

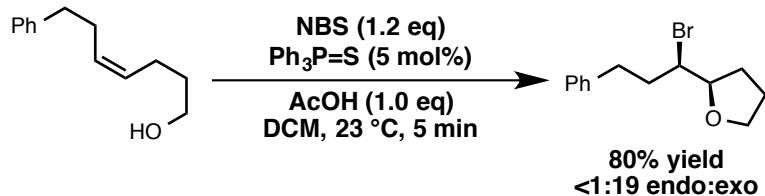
Catalytic Halocyclization



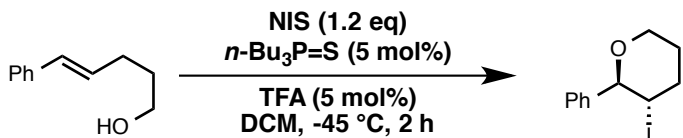
-No catalyst 180 min 13% yield 25:1 endo:exo
 -Ph₃P=S 8 min 82% yield 91:1 endo:exo



-No catalyst 2 h 4% yield 9.5:1 endo:exo
 -Ph₃P=S 1 h 92% yield 5.5:1 endo:exo

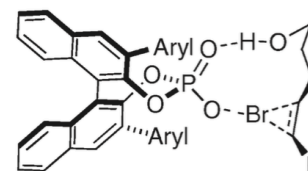
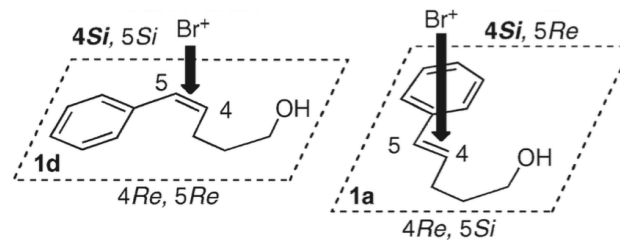
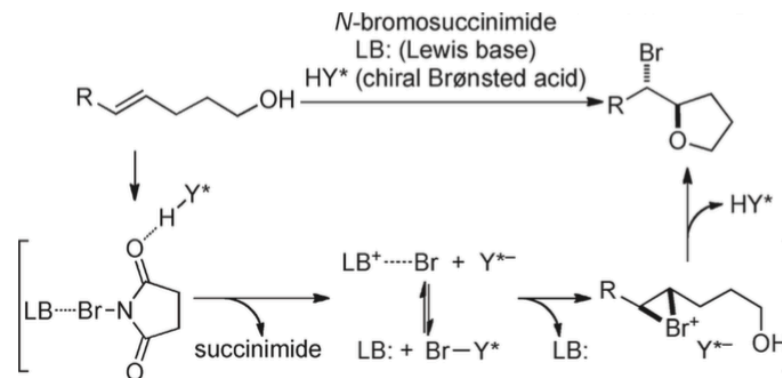
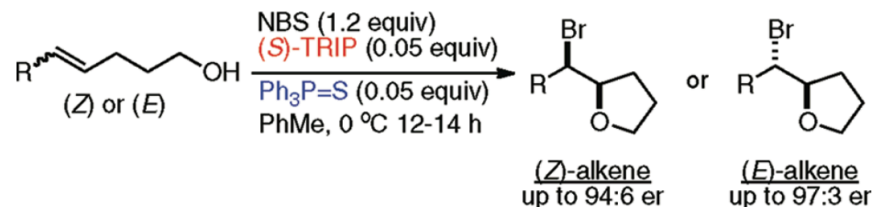


80% yield
 <1:19 endo:exo



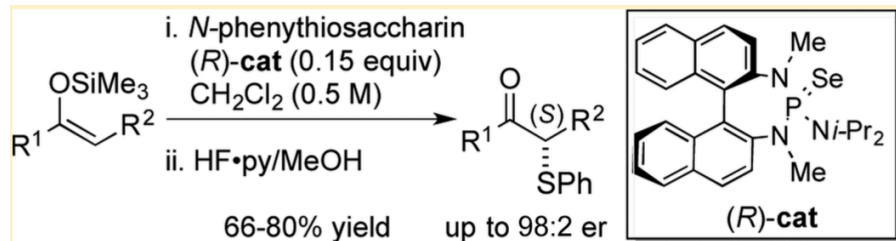
75% yield
 23:1 endo:exo

Chiral Brønsted acid / Achiral Lewis Base Cooperative Catalysis

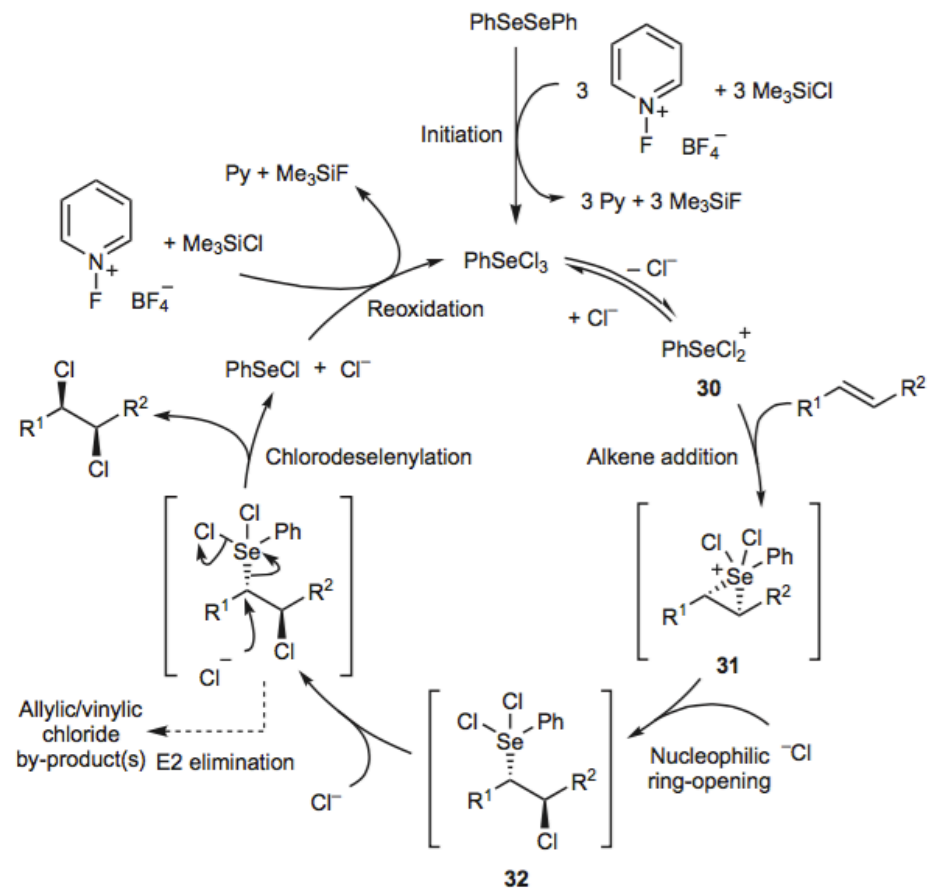
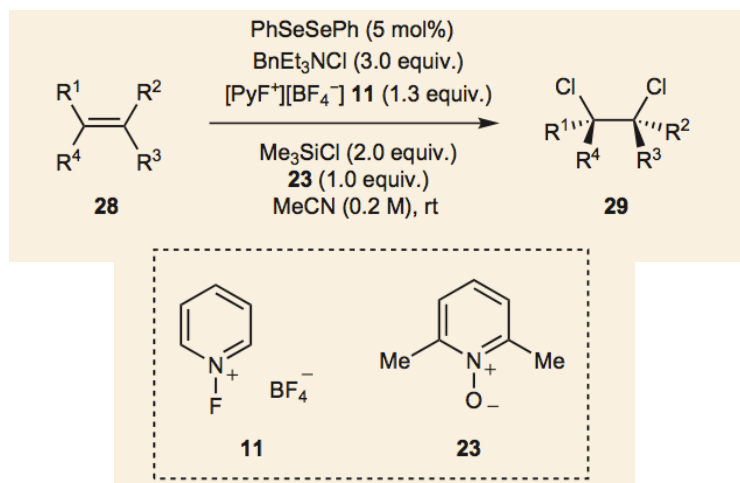


Miscellaneous Intermolecular Reactions

◆ Silyl enol ether α -sulfenylation

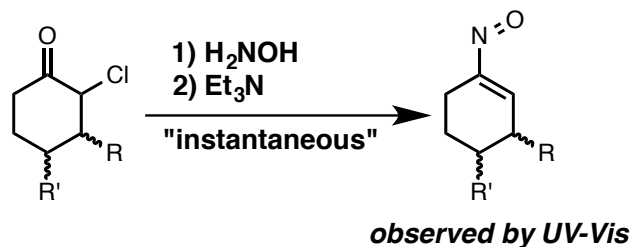


◆ Syn-dichlorination

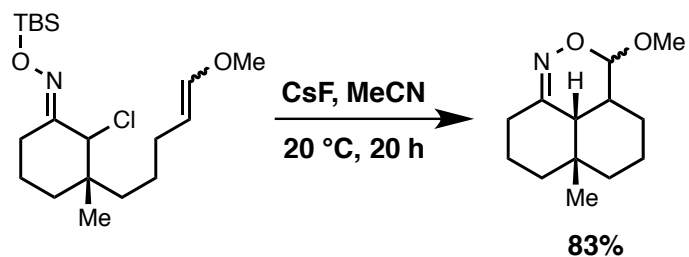


Early Studies

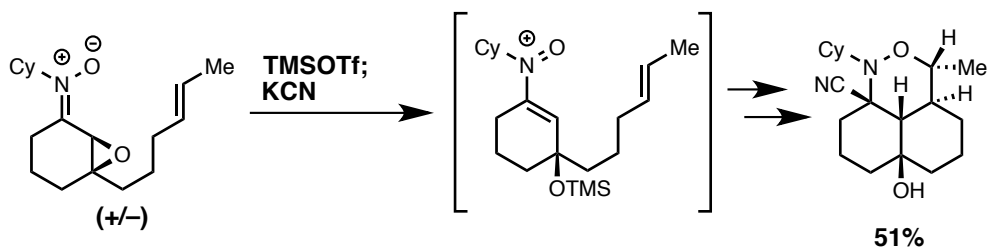
◆ Nitrosoalkene synthesis



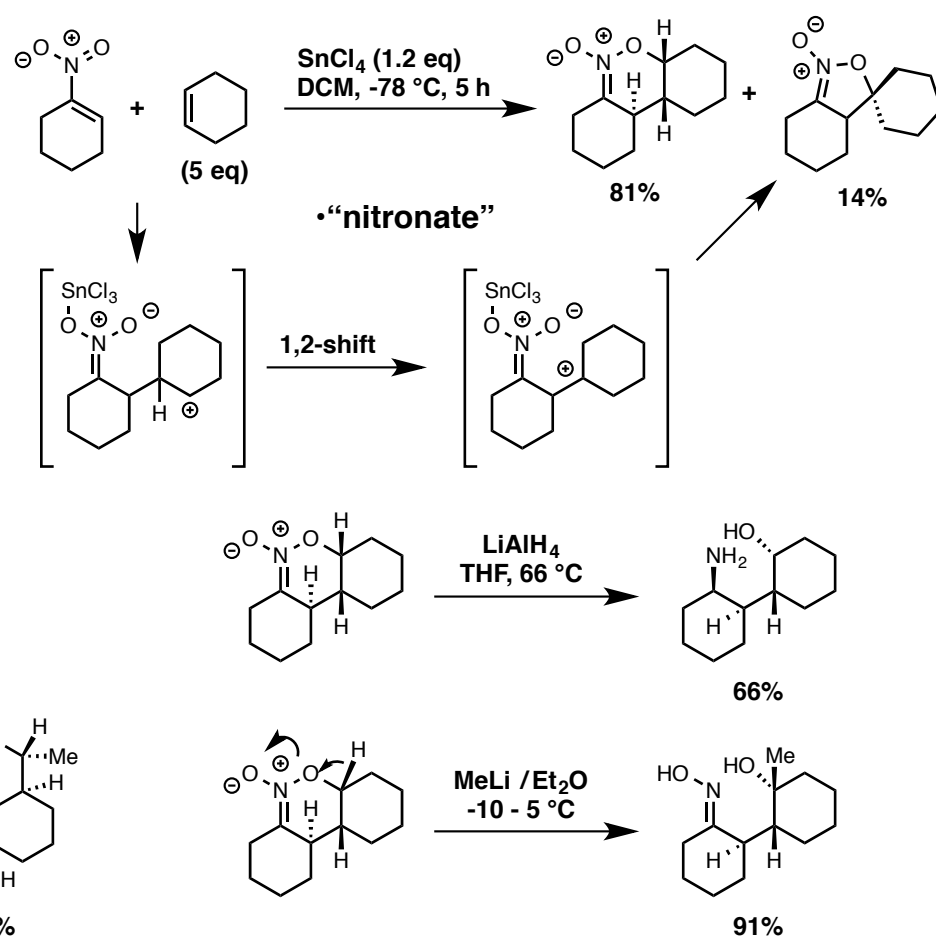
◆ Intramolecular nitrosoalkene [4+2]



◆ Intramolecular vinylnitrosium [4+2]

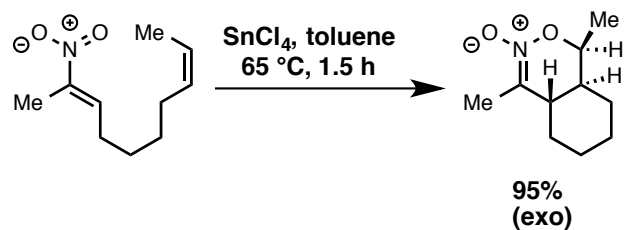


◆ Intermolecular nitroalkene [4+2]

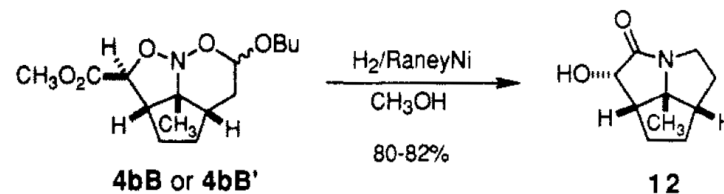


Intramolecular cyclization

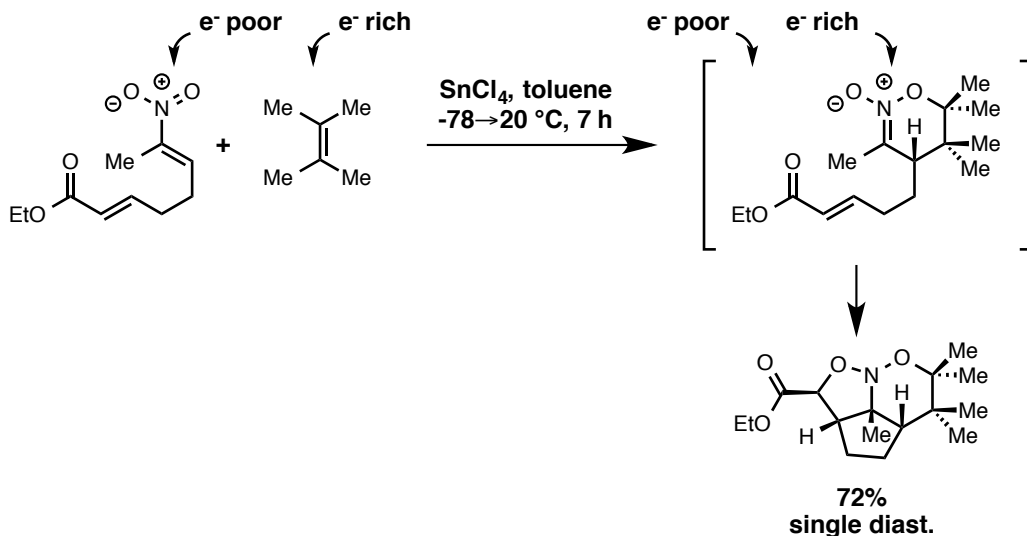
◆ Intramolecular nitroalkene [4+2]



◆ Reduction to lactone

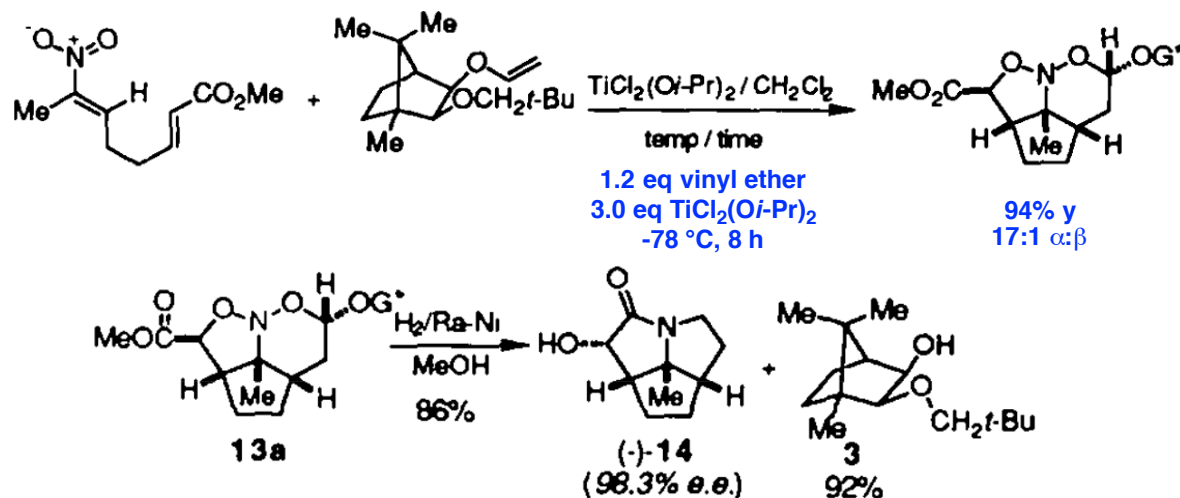


◆ Tandem [4+2]-[3+2]

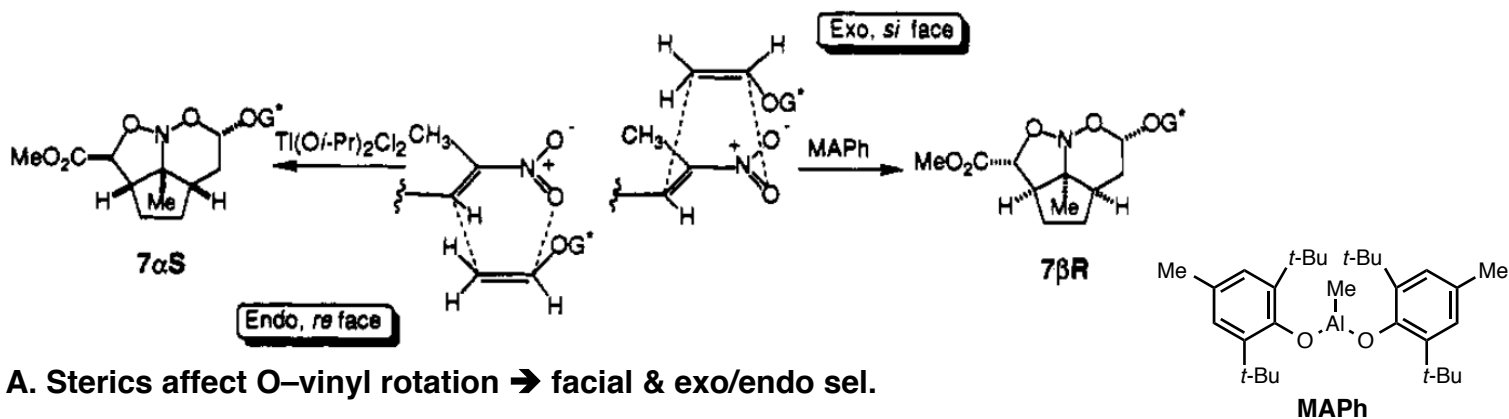


Tandem Cycloaddition Stereochemistry

◆ Chiral auxiliary for asymmetric process



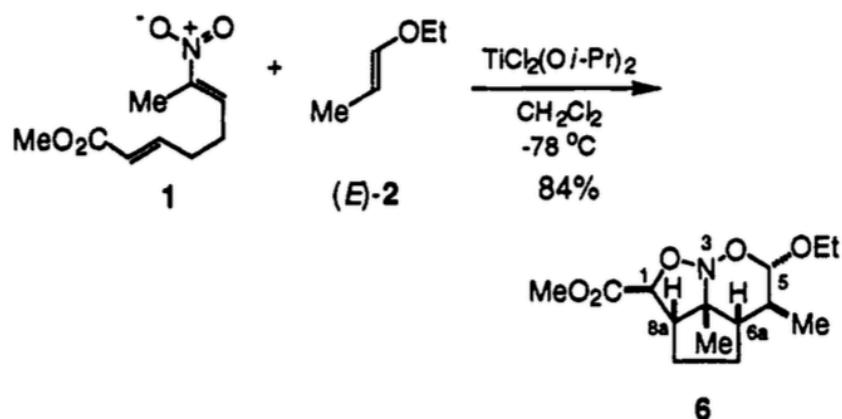
◆ Reversal of stereoselectivity by Lewis acid



- L. A. Sterics affect O–vinyl rotation → facial & exo/endo sel.

Additional Substrates

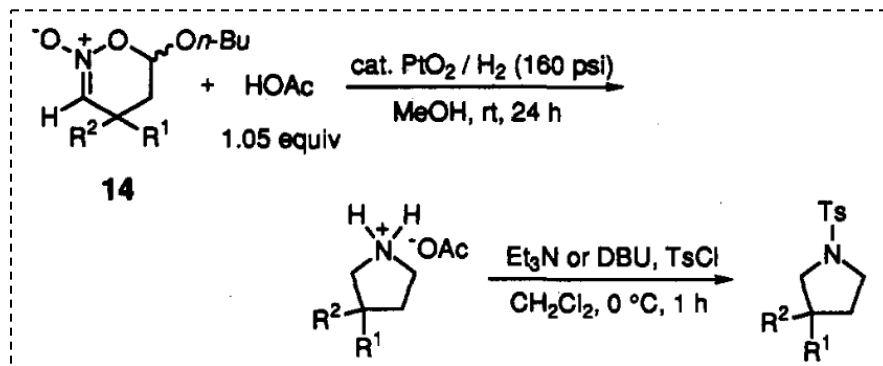
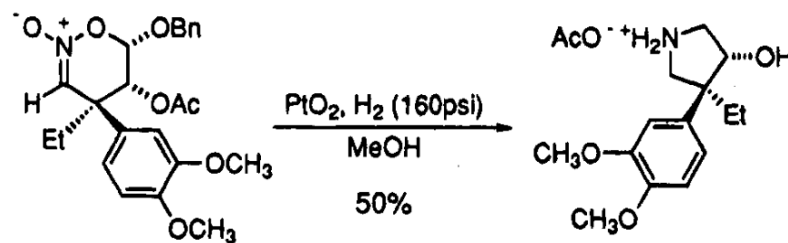
◆ Propenyl ethers

Table I. Effect of Reaction Time on the Anomer Ratio of **6** and **7^a**

entry	1-propenyl ether	time, h	OEt(C(5)), (α : β)
1	(E) - 2	1	95:5 ^b
2	(E) - 2	3	95:5 ^b
3	(E) - 2	5	95:5 ^b
4	(E) - 2	8	95:5 ^b
5	(Z) - 2	1	1.3:1 ^c
6	(Z) - 2	3	1:8 ^c

◆ 2-(Acyloxy)vinyl ethers

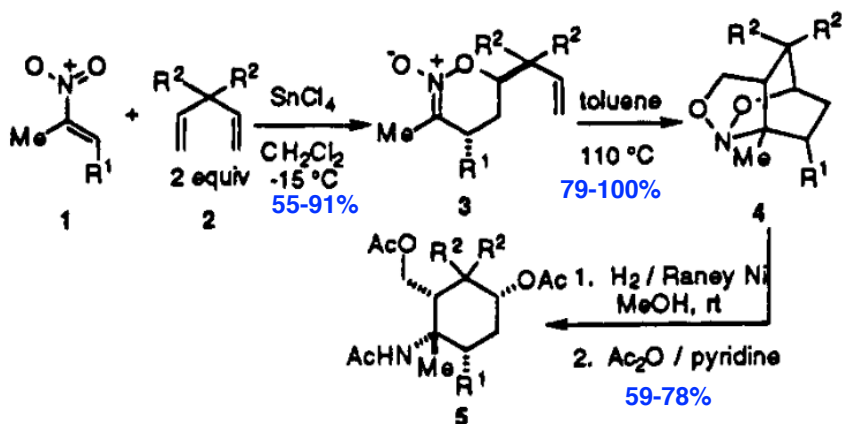
- Higher [O] state



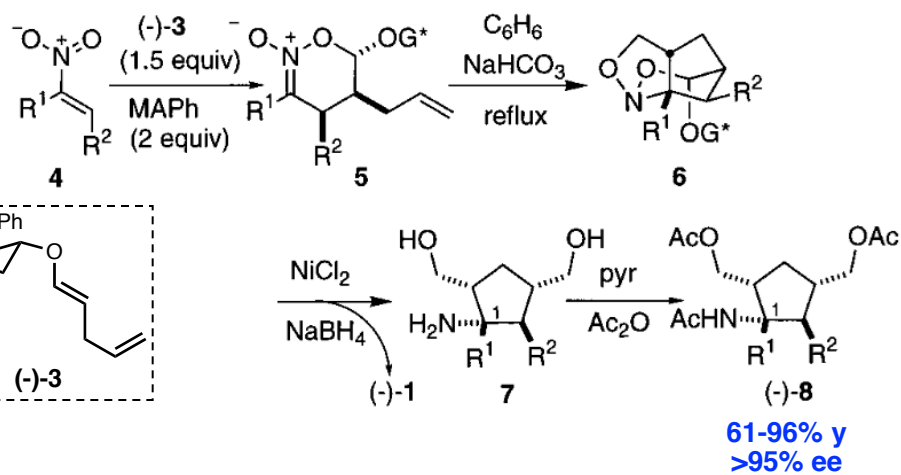
Additional Substrates

◆ Dienes

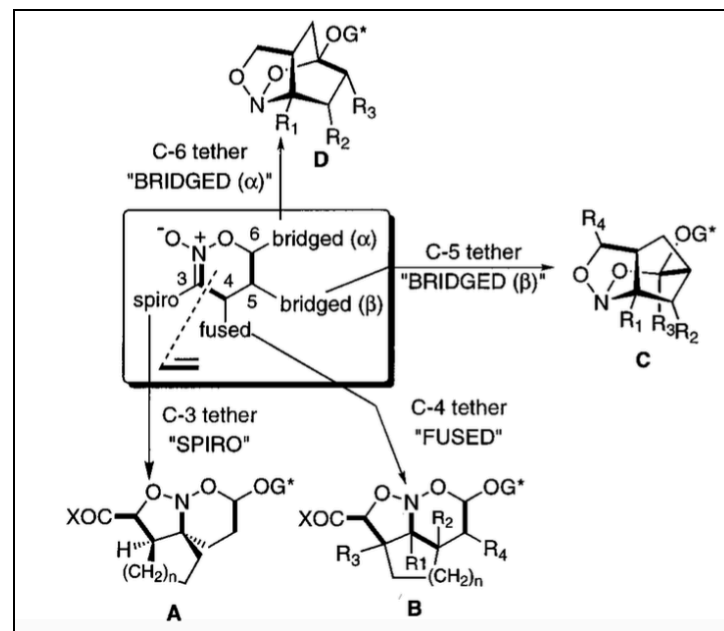
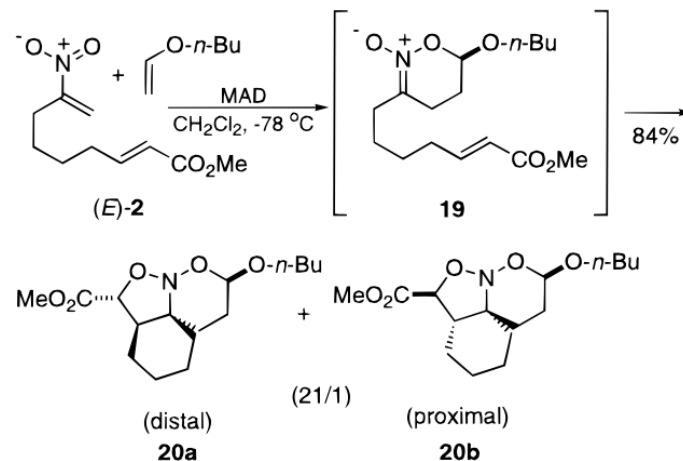
○ Bridged products



○ Aminocyclopentanes

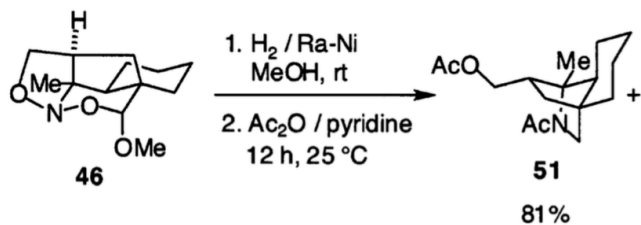
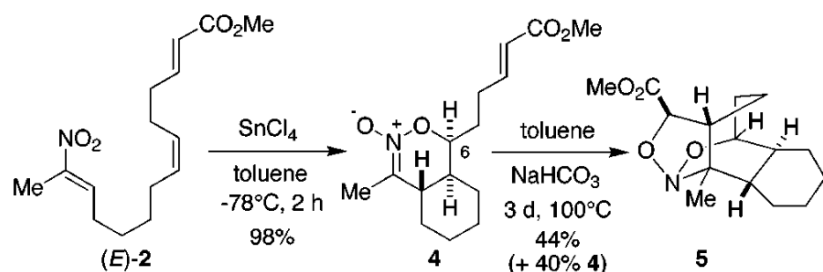
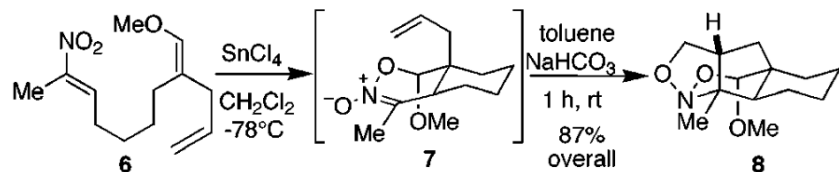


○ Spiro products

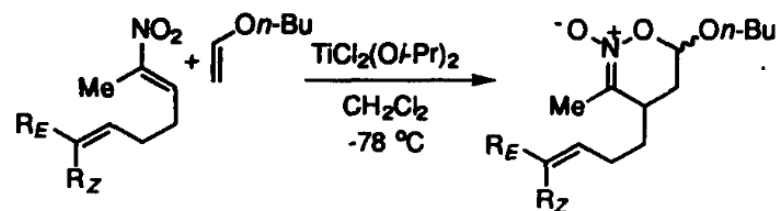


Additional Substrates

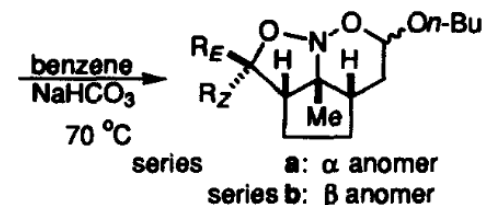
◆ Double-intramolecular cycloaddition



◆ Unactivated dipolarophiles



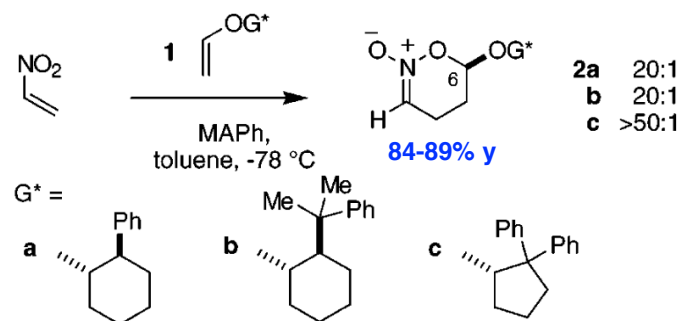
$\text{R}_E = \text{H, Me}$
 $\text{R}_Z = \text{H, Me}$



series
 series **a**: α anomer
 series **b**: β anomer

70-83%

◆ Nitroethylene



Denmark, S. E.; Senanayake, C. B. W. *Tetrahedron* **1996**, *52*, 11579-11600.

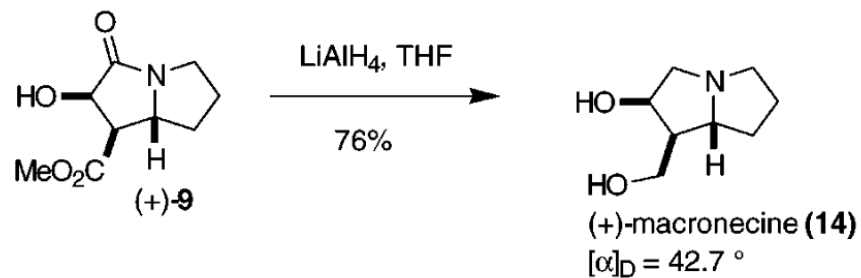
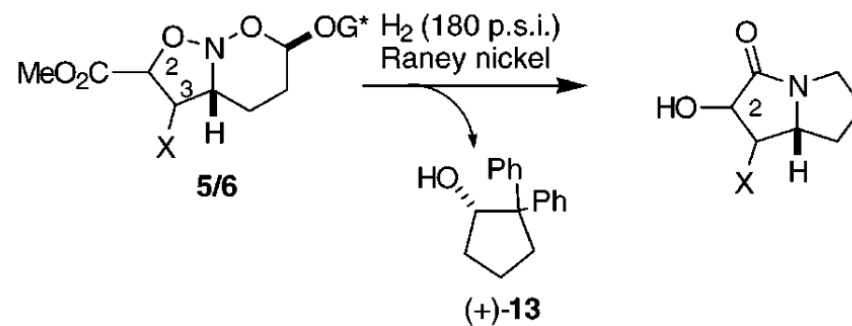
Denmark, S. E.; Gomez, L. *Org. Lett.* **2001**, *3*, 2907-2910.

Denmark, S. E.; Gomez, L. *J. Org. Chem.* **2003**, *68*, 8015-8024.

Denmark, S. E.; Hurd, A. R. *J. Org. Chem.* **1998**, *63*, 3045-3050.

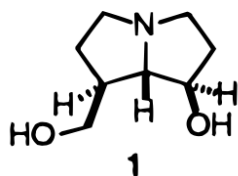
Additional Substrates

◆ Nitroethylene

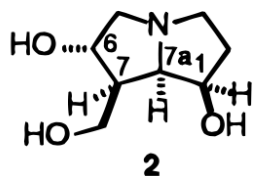


Application to Synthesis

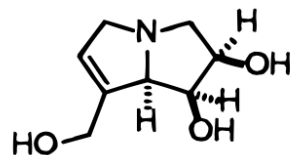
◆ Pyrrolidine natural products



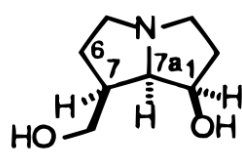
(-)-hastanecine



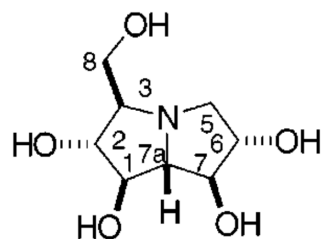
(-)-rosmarinecine



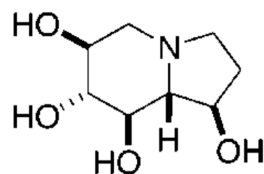
(-)-crotanecine



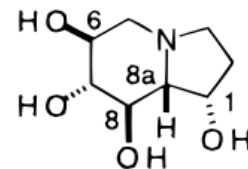
(-)-platynecine



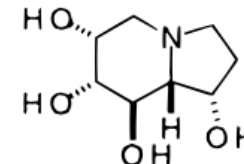
(+)-casuarine (1)



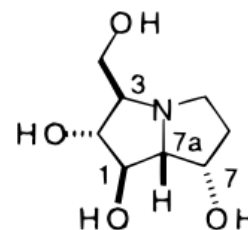
1-epicastanospermine



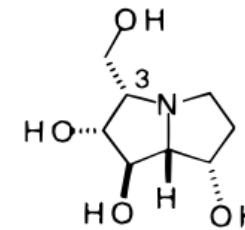
(+)-castanospermine ((+)-1)



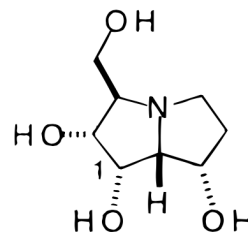
(+)-6-epicastanospermine ((+)-2)



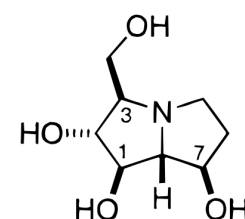
(+)-australine ((+)-3)



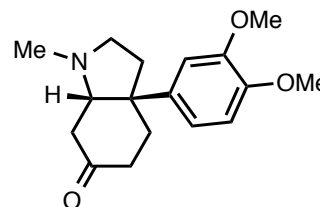
(+)-3-epiaustraline ((+)-4)



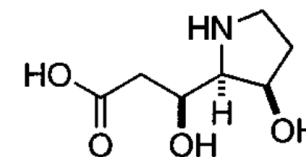
(+)-1-epiaustraline ((+)-5)



(+)-7-Epiaustraline ((+)-1)



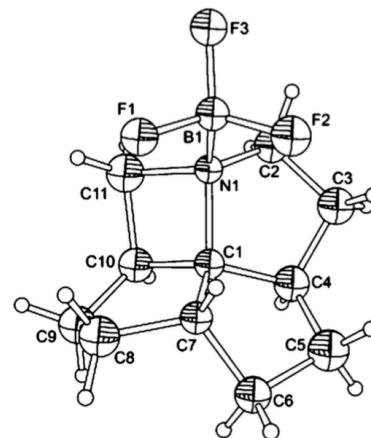
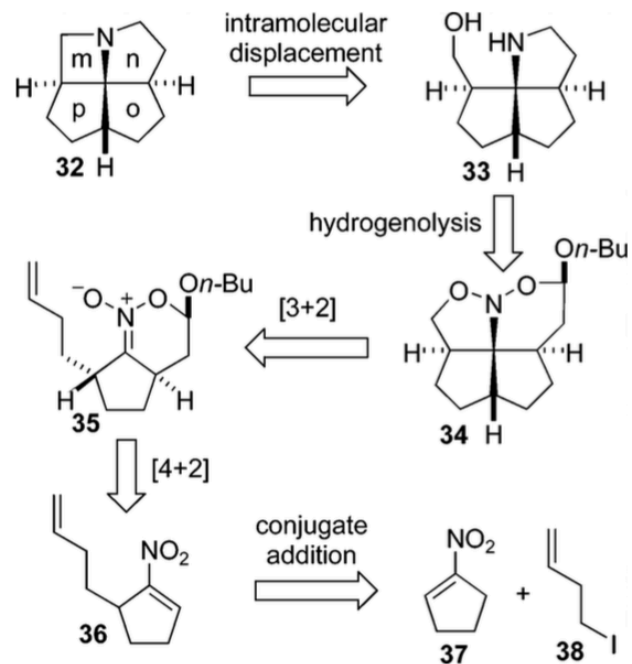
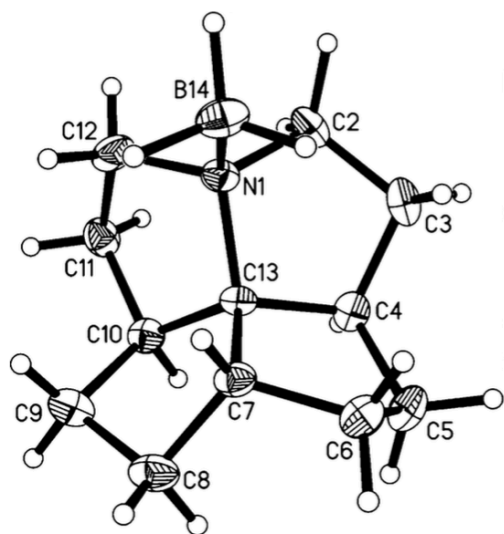
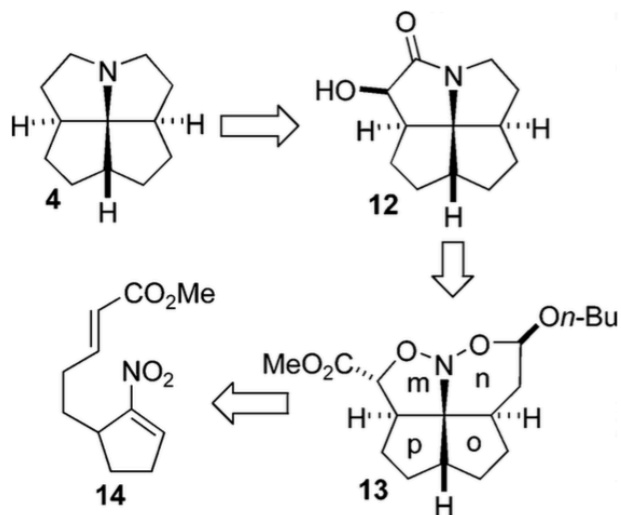
(-)-mesembrine



(-)-detoxinine (1)

Application to Synthesis

◆ 1-Azafenestranes



Application to Synthesis

◆ Complex natural product cores

