

Asymmetric Quaternary Center Construction

Brian Raymer
Evans Group Seminar
October 22, 1999

Lead References:

Corey, Guzman-Perez, *ACIEE*, **1998**, 37, 388 - 401
Fuji, *Chem. Rev.*, **1993**, 93, 2037-2066

Asymmetric Quaternary Center Construction

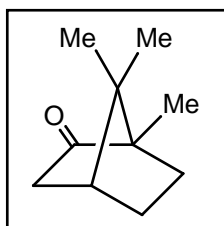
Definition:

Quaternary Center: Carbon with four carbon substituents

Contents:

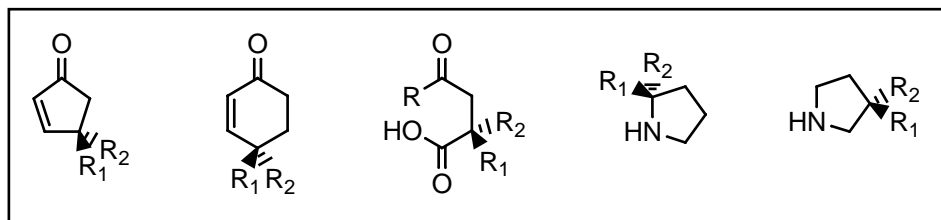
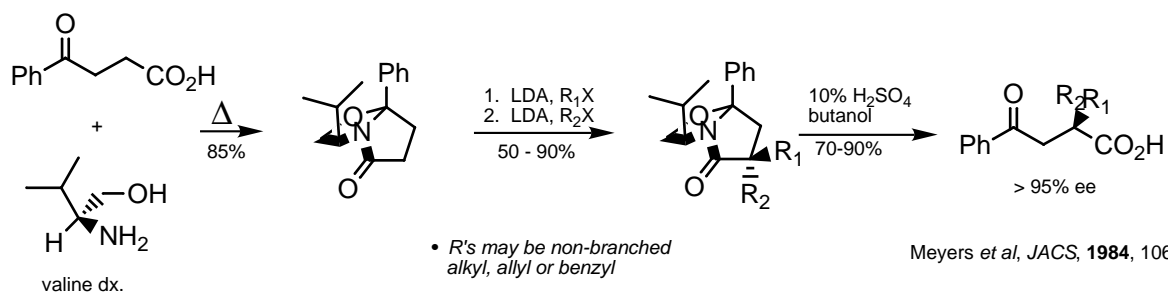
- Enolates and Enamines
- Cycloadditions
- Sigmatropic Rearrangements
- Cyclopropanation
- Palladium Mediated Construction
- Lewis Acid Catalyzed Rearrangements
- Radical Cyclizations

Natural Products from Camphor



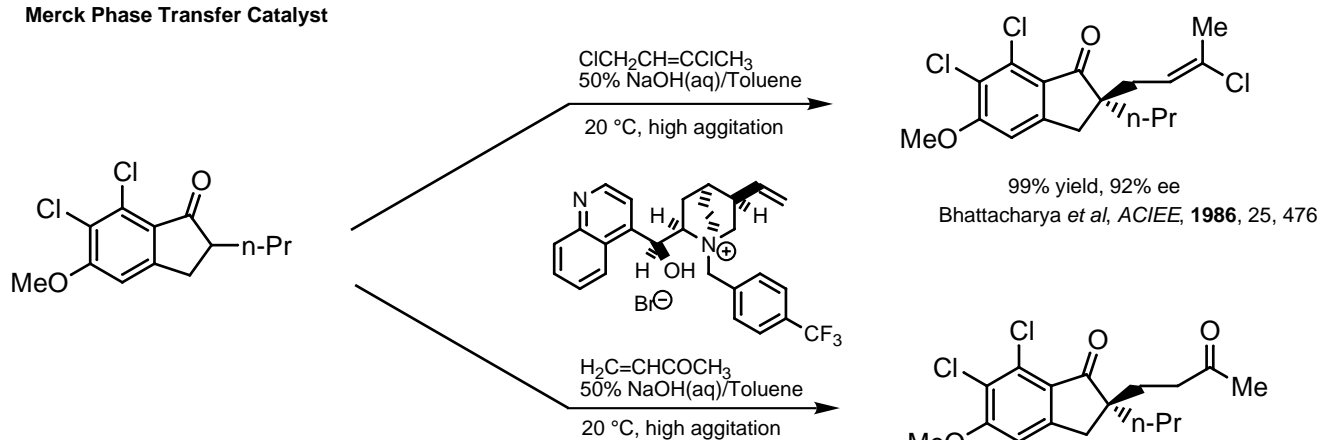
Money, *Nat. Prod. Rep.*, **1985**, 2, 253

Meyers Bicyclic Lactams

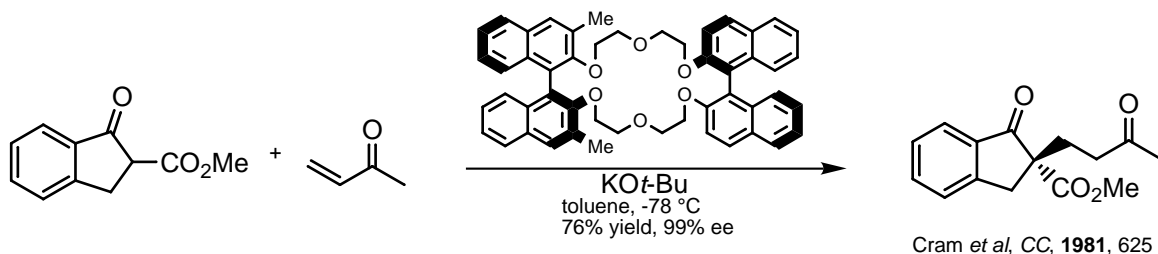


Enolate Alkylation and Michael Additions

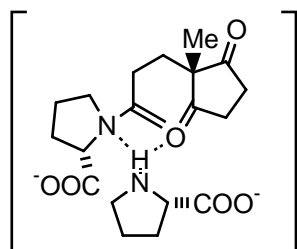
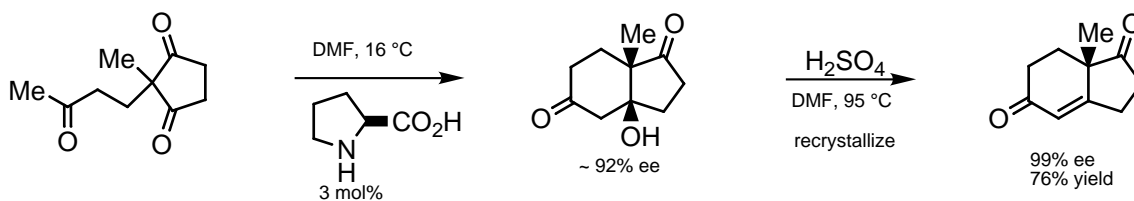
Merck Phase Transfer Catalyst



Cram Binol Derived Catalyst



Desymmetrization: Amino-acid catalyzed Robinson Annulation



- Dilution studies suggest three-center hydrogen bond.
- Nonlinear relationship between enantiomeric purity of (S)-proline and product observed.

Puchot *et al*, *CC*, **1985**, 441.
 Kagan *et al*, *JACS*, **1986**, 108, 2353

Hajos, Parrish, *Org. Synth.*, VII, 363
 Hajos, Parrish, *JOC*, **1974**, 1615

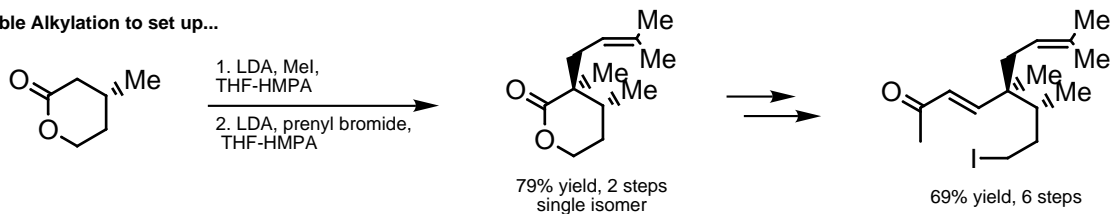
Wieland-Miescher ketone:
 Buchschacher, Furst, Gutzwiller, *Org. Synth.*, VII, 368

See also: Corey, Virgil, *JACS*, **1990**, 112, 6431

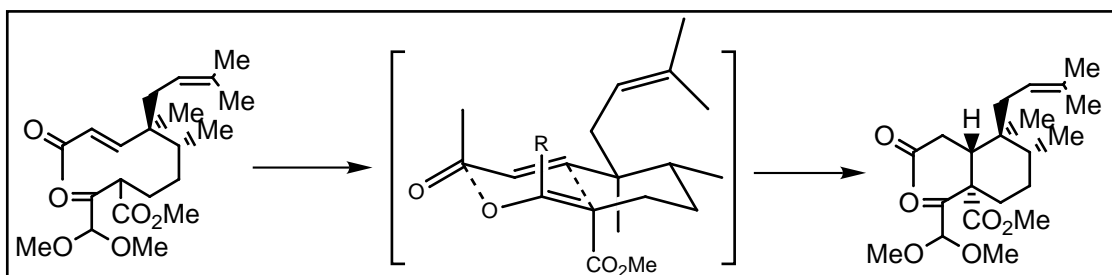
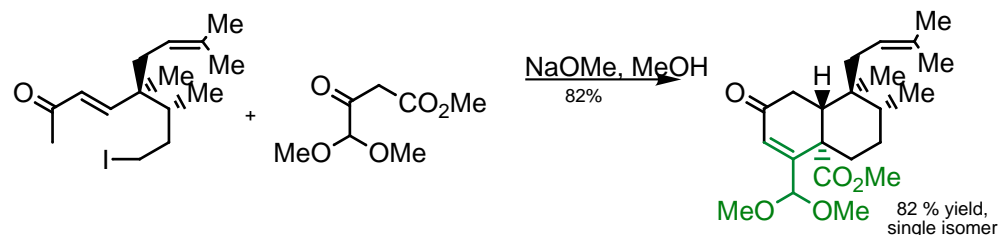
For additional examples: W. Trotter Seminar, April 1997

Tanabalin: Intermolecular Alkylation-Intramolecular Robinson Annulation

Double Alkylation to set up...

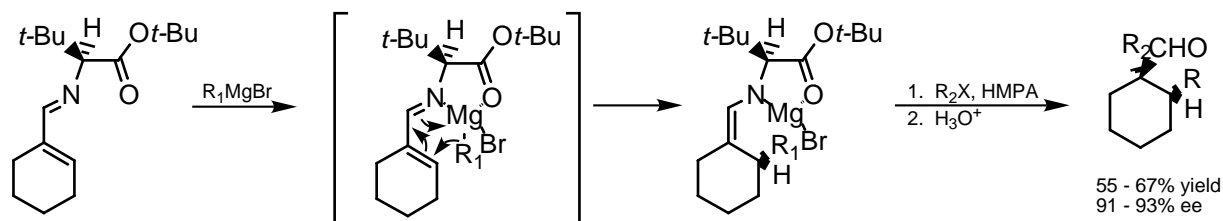


...an alkylation and then a Robinson Annulation.



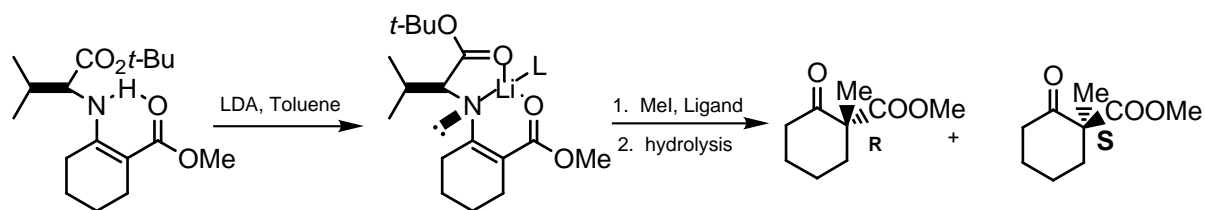
Watanabe, *et al*, *TL*, **1999**, 40, 2545

Asymmetric Grignard Addition and Asymmetric Enamine Alkylation



R₁ = Ph, vinyl
R₂X = MeI, BnI, allylBr, EtI, MOMCl

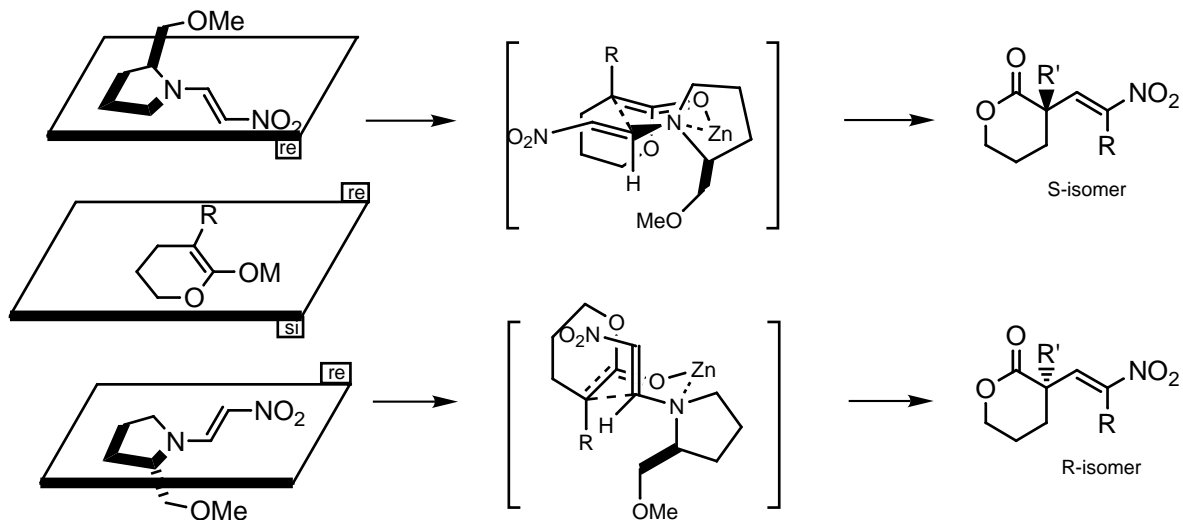
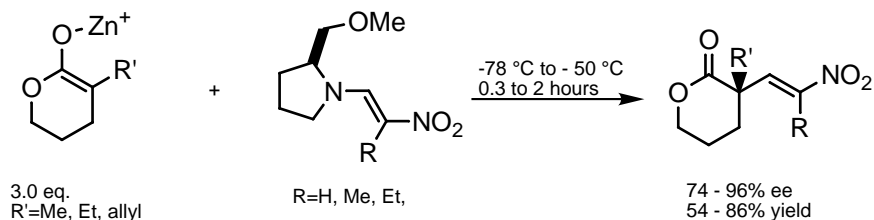
Koga *et al*, *Tet*, **1981**, 37, 3951



- strongly ligating HMPA suppresses underside attack
- weakly ligating THF replaced by alkyl halide before alkylation

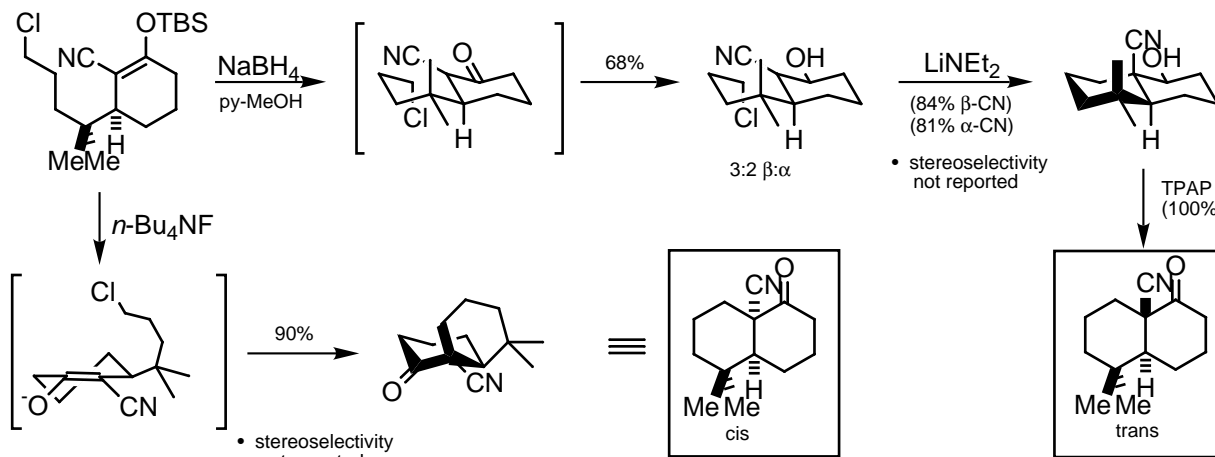
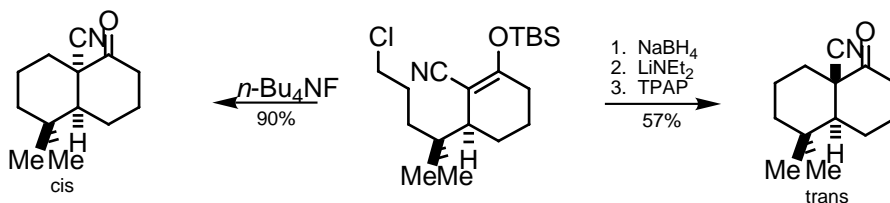
Koga *et al*, *JACS*, **1984**, 106, 2718

Chiral Leaving Groups: Nitroolefination



Fuji et al, JACS, 1989, 111, 7923

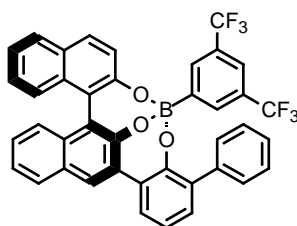
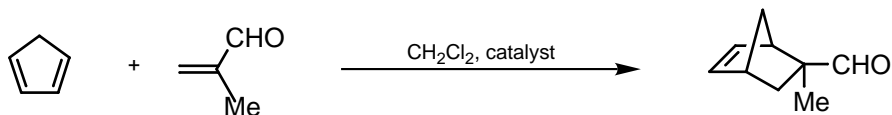
cis- and trans-Decalins: β -Siloxy Unsaturated Nitriles



see also: Stork, Boeckman, JACS, 1973, 95, 2016
Effects of counterion on nitrile anion orientation.

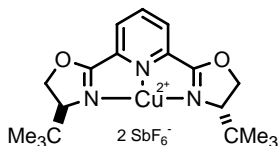
Fleming et al, Org. Lett., 1999, ASAP

Catalytic Enantioselective Diels-Alder



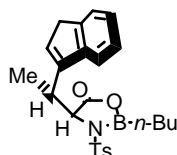
Yamamoto
4.0 eq. diene
5 mol % cat.
-78 °C, 1.5 h
96% yield, 99% ee,
exo:endo >90%?

JACS, 1996, 118, 3049



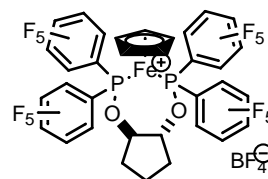
Evans
1.2 eq. diene
5 mol % cat.
-40 °C, 8 h
100% conv., 92% ee,
exo:endo=97:3

ACIEE, 1995, 34, 798



Corey
5.0 eq. diene
10 mol % cat.
-94 °C, 2 h
99% yield, 90 % ee,
exo:endo=88:12

JACS, 1991, 113, 8966

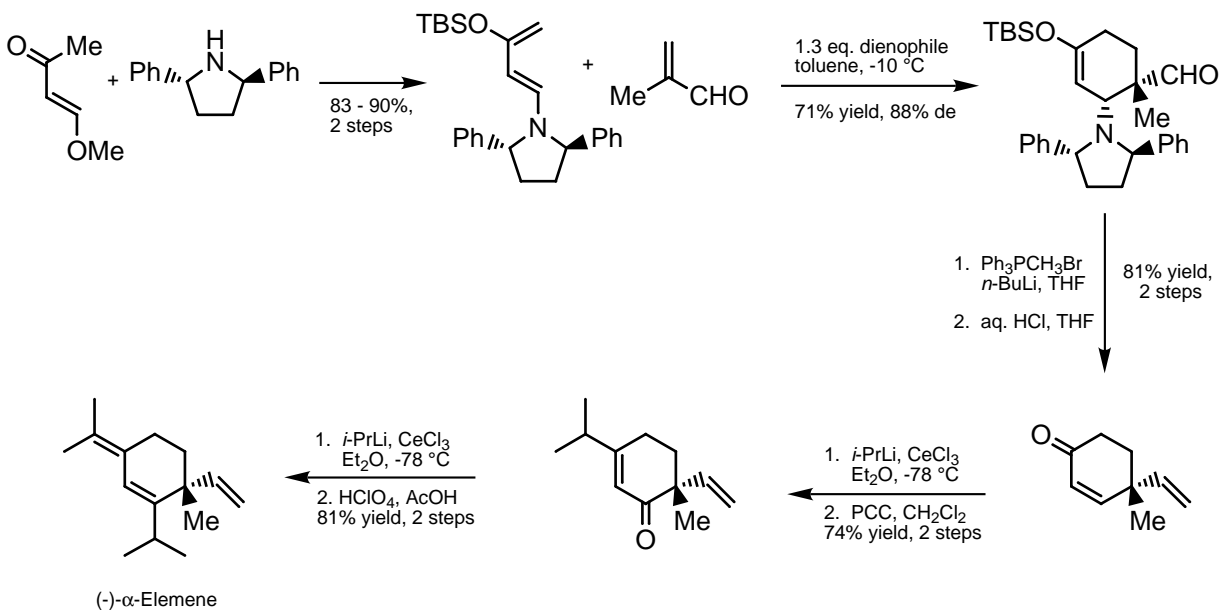


Kundig
1.1 eq. diene
5 mol % cat.
-20 °C, 22 h
91 % yield, 98% ee,
exo:endo=97:3

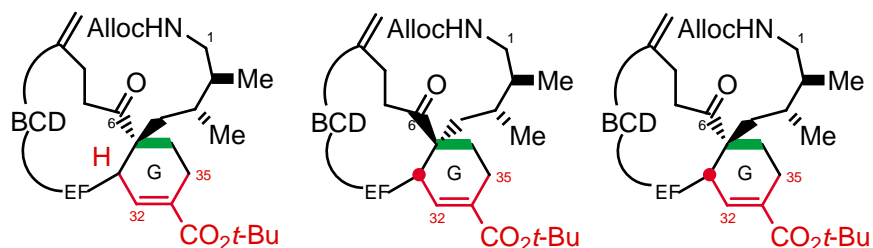
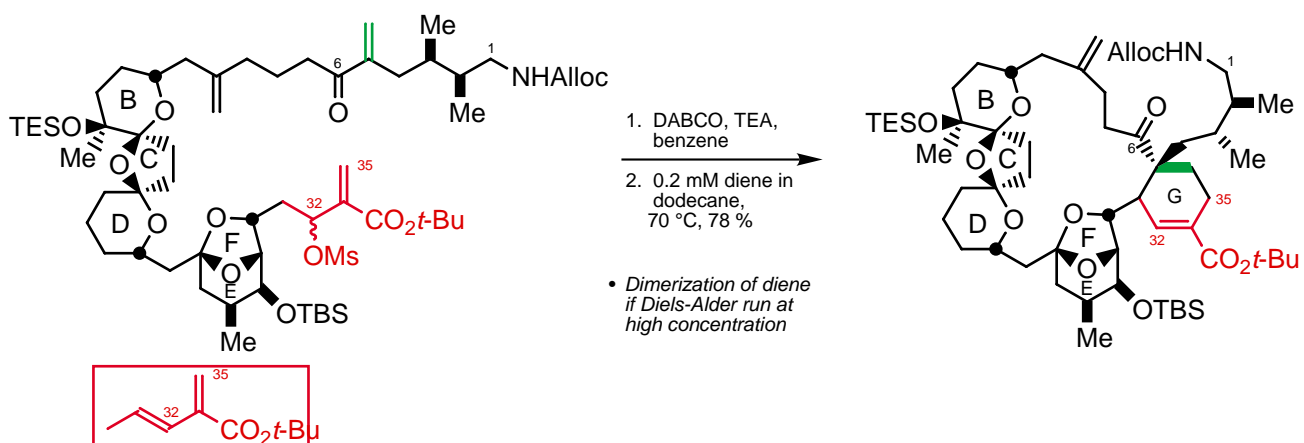
ACIEE, 1994, 33, 1856

Diels-Alder in Synthesis of Elemene

Elemene: Chiral Amino Siloxy Diene Diels-Alder



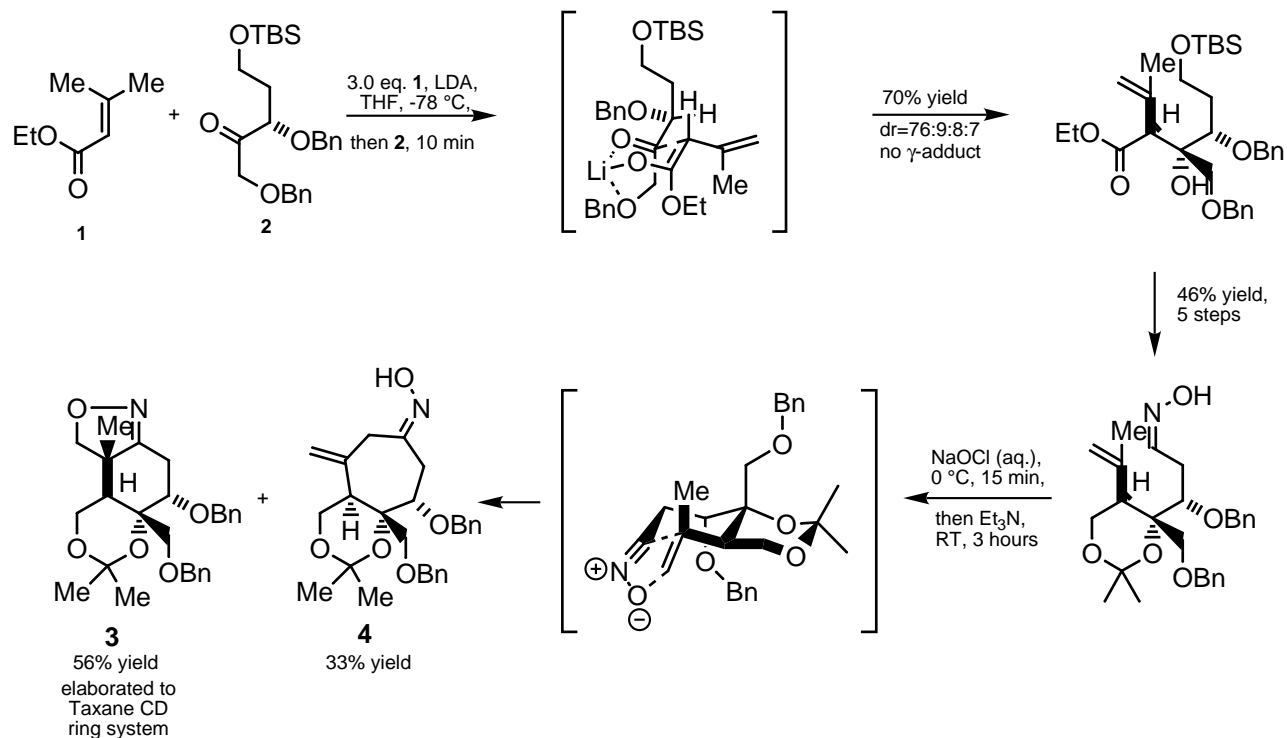
Pinnatoxin Diels-Alder



Reaction Conditions	A. desired exo product	B. undesired exo product	C. endo product
toluene, 100 °C	33 %	33 %	33 %
dodecane, 70 °C	43 %	39 %	17 %

Kishi et al, JACS, 1998, 120, 7647

Taxane CD ring system: 1,2-Addition and [3+2] Cycloaddition

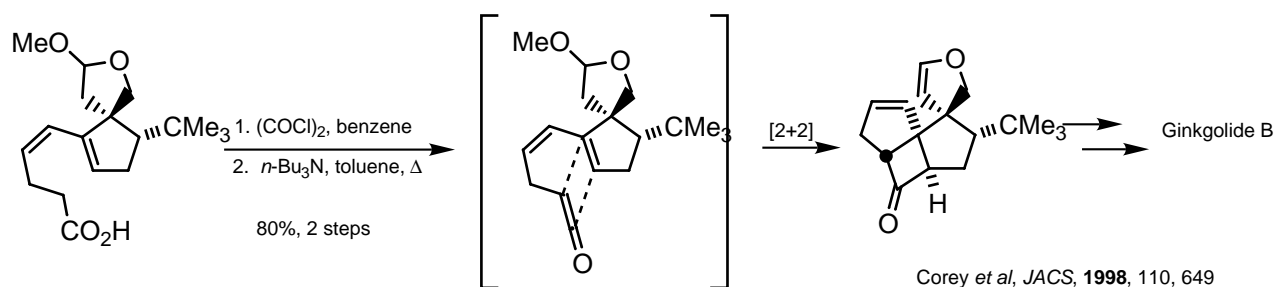


see also: D. Halstead Seminar
Nitrile Oxide Cycloadditions

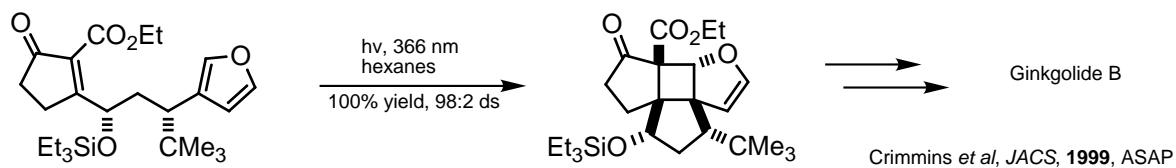
Takahashi et al, JOC, 1998, 63, 5742

Ginkgolide B Syntheses: 2+2 Cycloadditions

Ketene [2+2]:

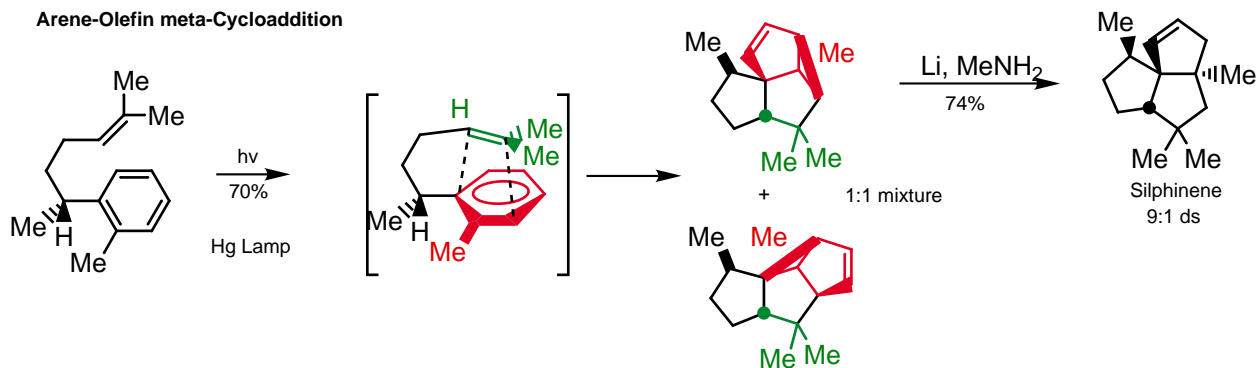


Enone-Furan [2+2]:

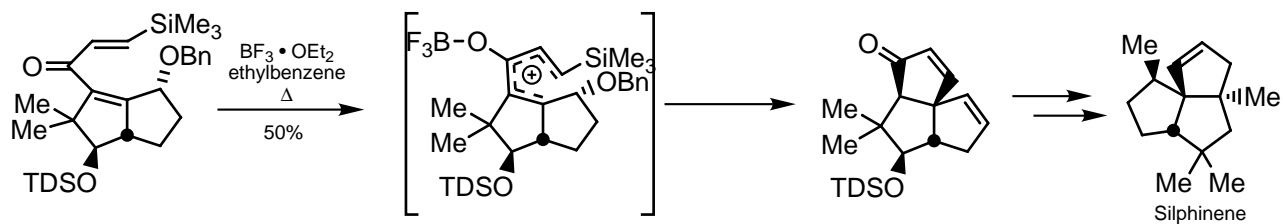


Silphinene: Arene-Olefin meta-Cycloaddition and Nazarov Cyclization

Arene-Olefin meta-Cycloaddition



Nazarov Cyclization



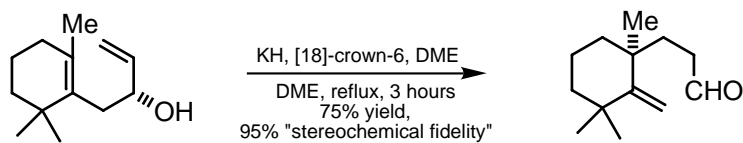
TDS = Tethylsilyl

Franck-Neumann *et al*, *Tet*, **1997**, 53, 2103

see also: Polyquinane Synthesis Seminar
G. Peterson, Feb. 5, 1999

Ireland-Claisen and Anionic Oxy-Cope

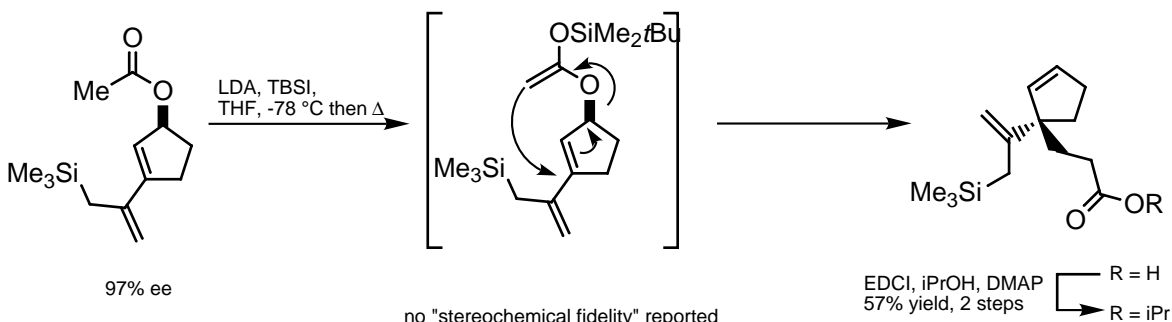
(+)-Dihydromayurone: Anionic Oxy-Cope



no ee reported

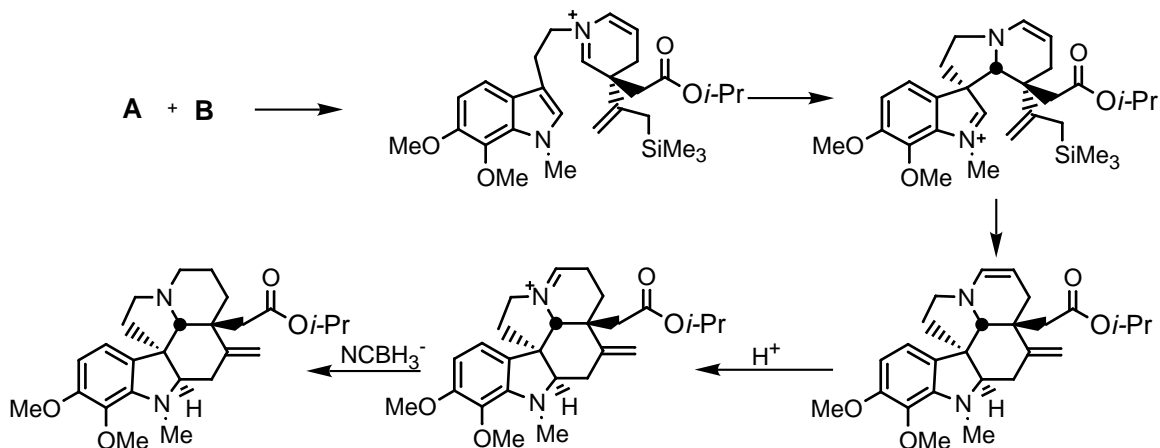
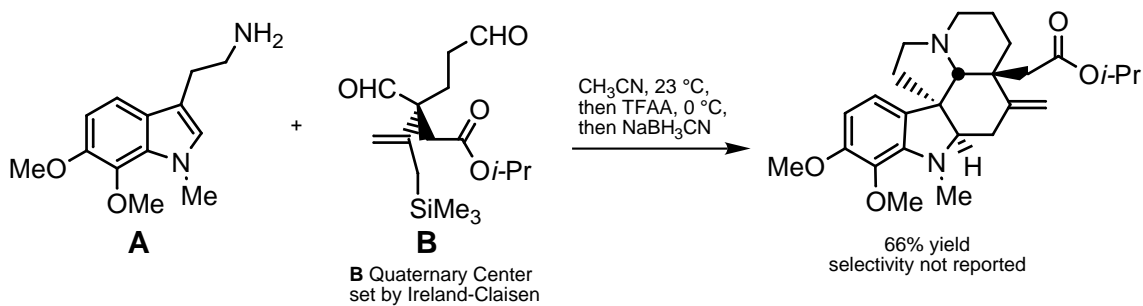
Lee, Shin, Kim, *JACS*, **1990**, 112, 260

Aspidophytine: Ireland-Claisen



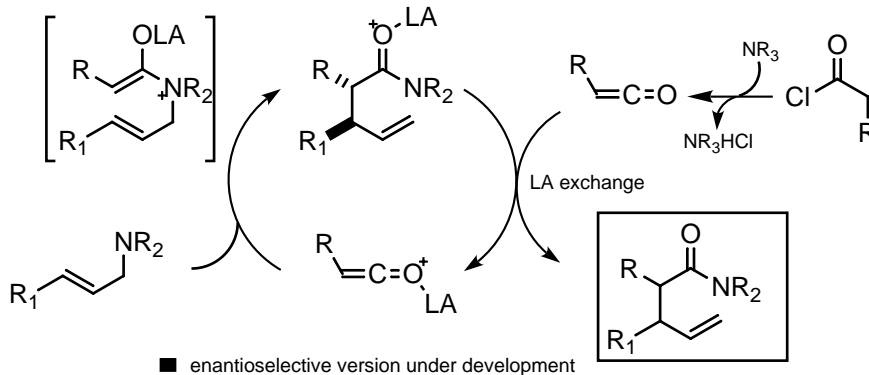
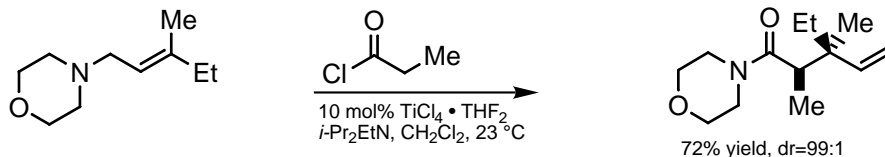
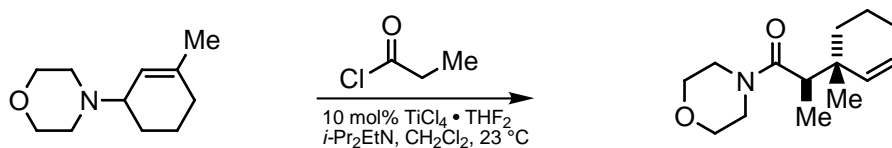
Corey *et al*, *JACS*, **1999**, 121, 6771

Enamine Alkylation: Aspidophytine



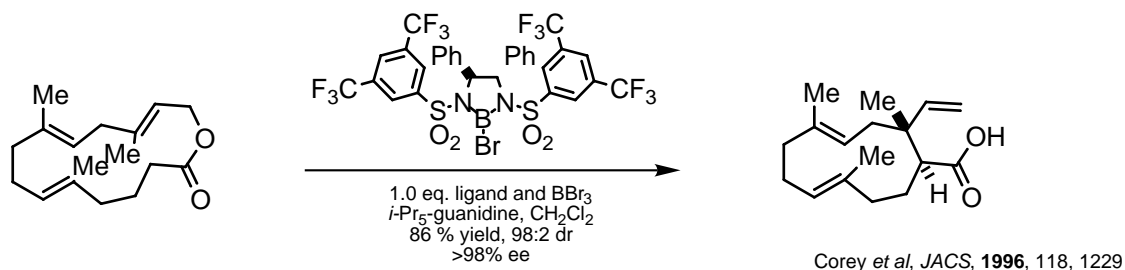
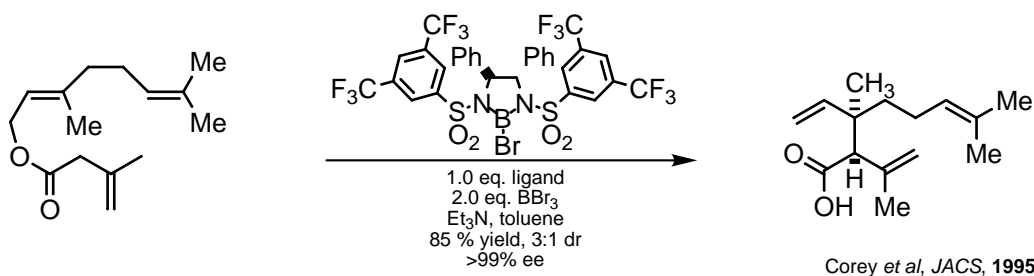
Corey *et al*, *JACS*, **1999**, 121, 6771

Lewis-Acid Catalyzed Claisen Rearrangement



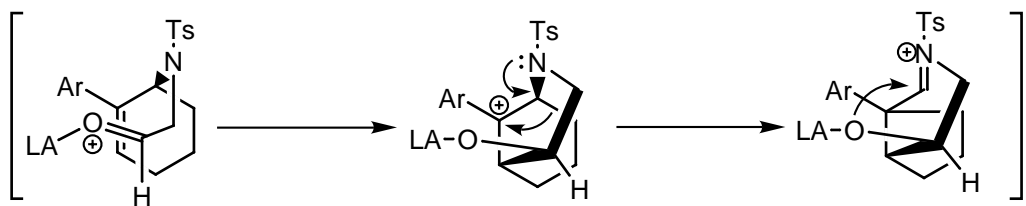
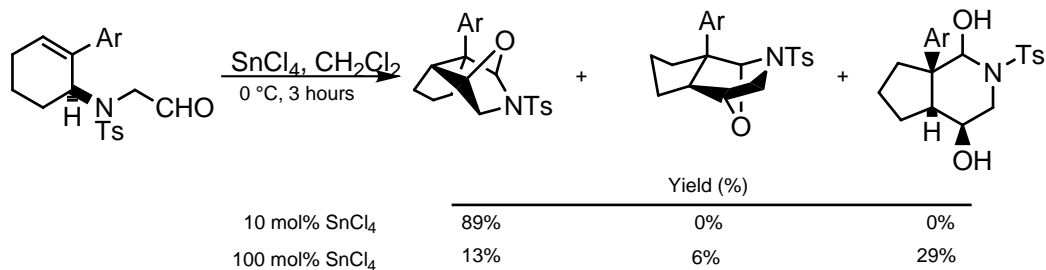
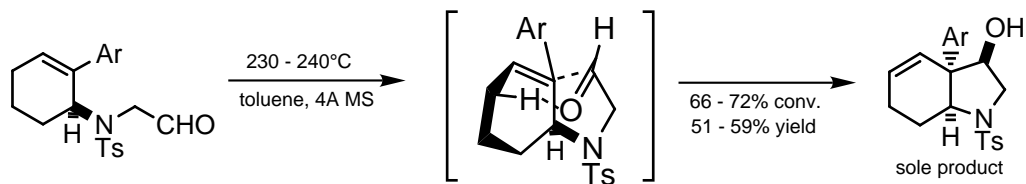
MacMillan, Yoon, Dong, *JACS*, **1999**, 121, 9726

Stoichiometric Enantioselective Claisen Rearrangement



- strong, hindered base gives best results
i- Pr_5 -guanidine: Barton's Base

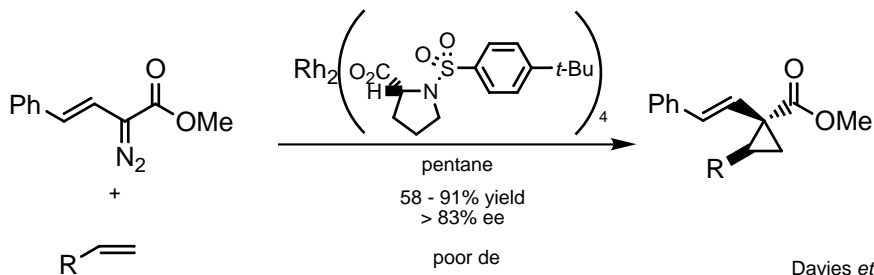
Intramolecular Ene and a Lewis-Acid Catalyzed Rearrangement



Mori *et al*, *JOC*, **1998**, 63, 7586

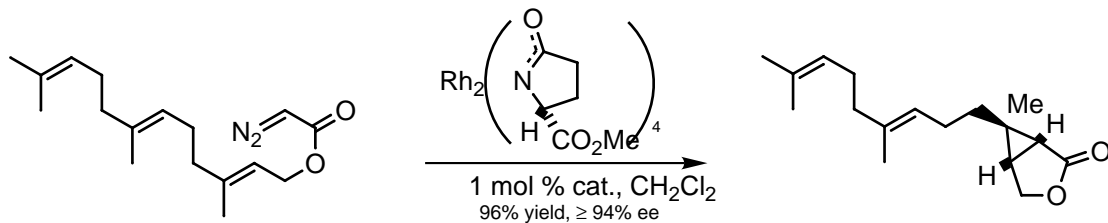
Intermolecular and Intramolecular Cyclopropanations

α - cyclopropyl esters:



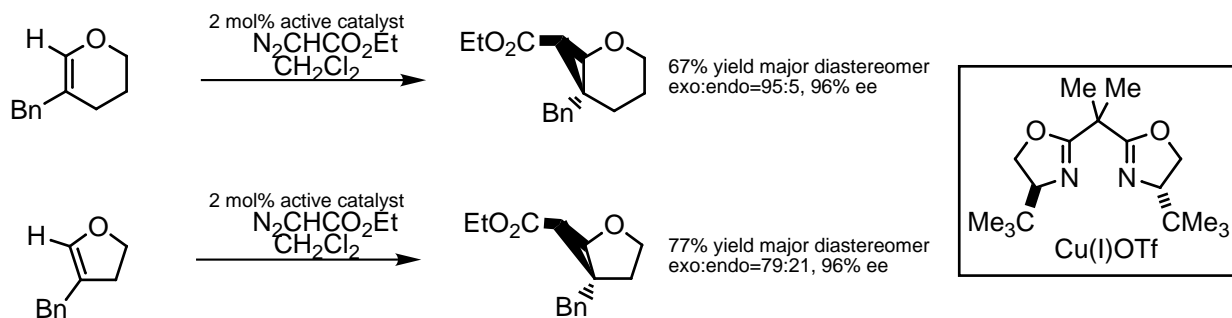
Davies *et al*, *TL*, **1993**, 34, 7243

Presqualene diphosphate intermediate:

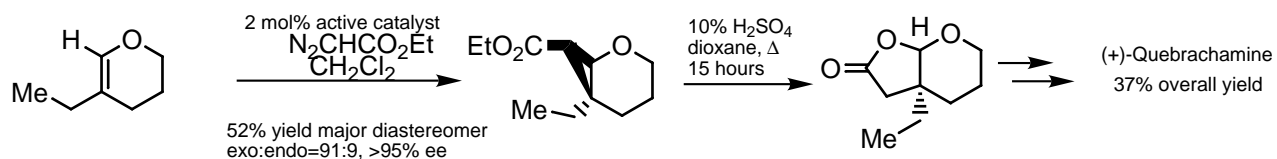


Poulter *et al*, *JOC*, **1995**, 60, 941

Cu (I)-Catalyzed Cyclopropanation of Cyclic Enol Ethers



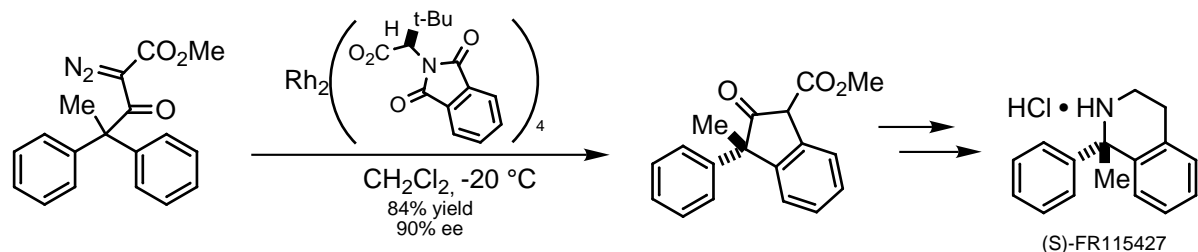
Quebrachamine:



Andersson et al, *JOC*, **1998**, 63, 6007

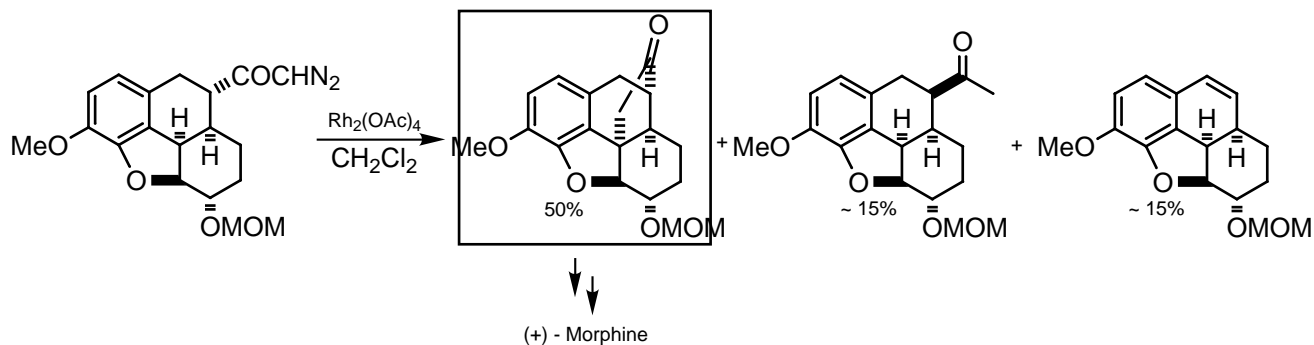
Rh Catalyzed C-H insertion

FR115427:



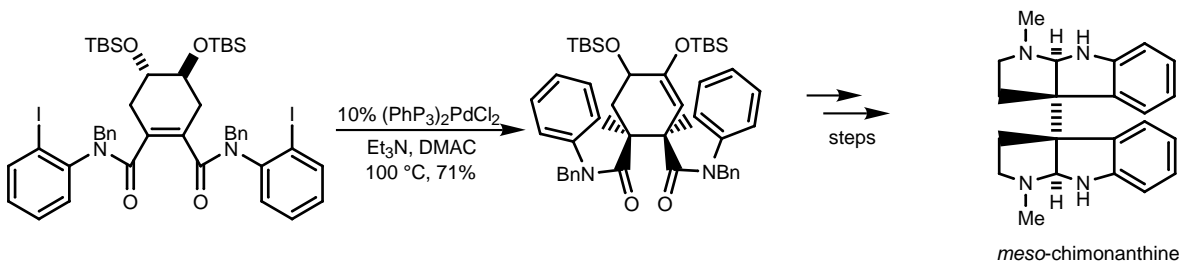
Hashimoto et al, *Synlett*, **1996**, 85-86

Morphine:

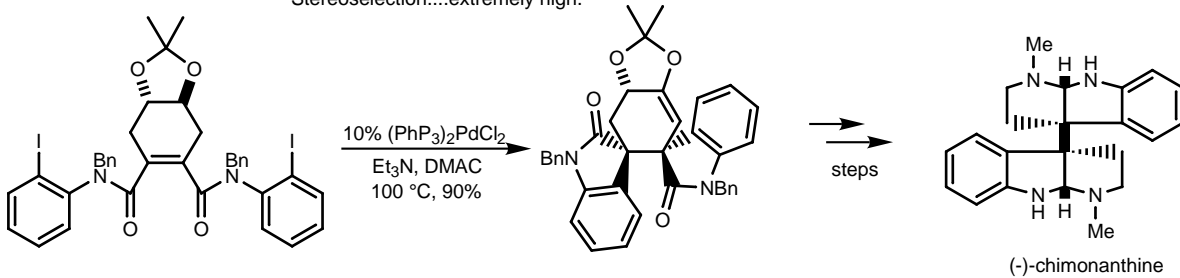


White, Hrciar, Stappenbeck, *JOC*, **1997**, 62, 5250

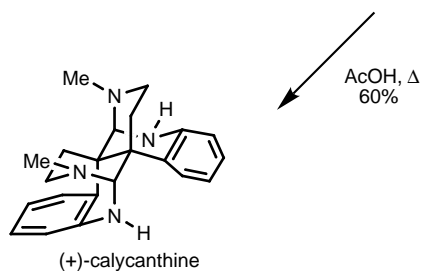
Vicinal Stereogenic Quaternary Carbon Centers



"Stereoselection....extremely high."

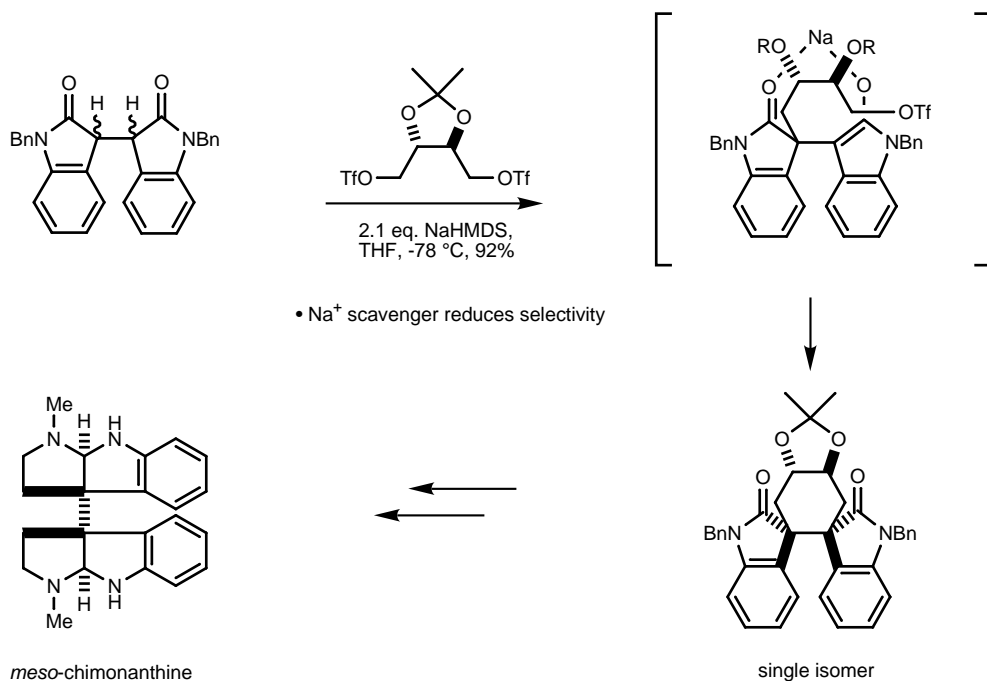


- TBS substituents prefer a bis-axial orientation
- acetonide prefers a bis-equatorial orientation



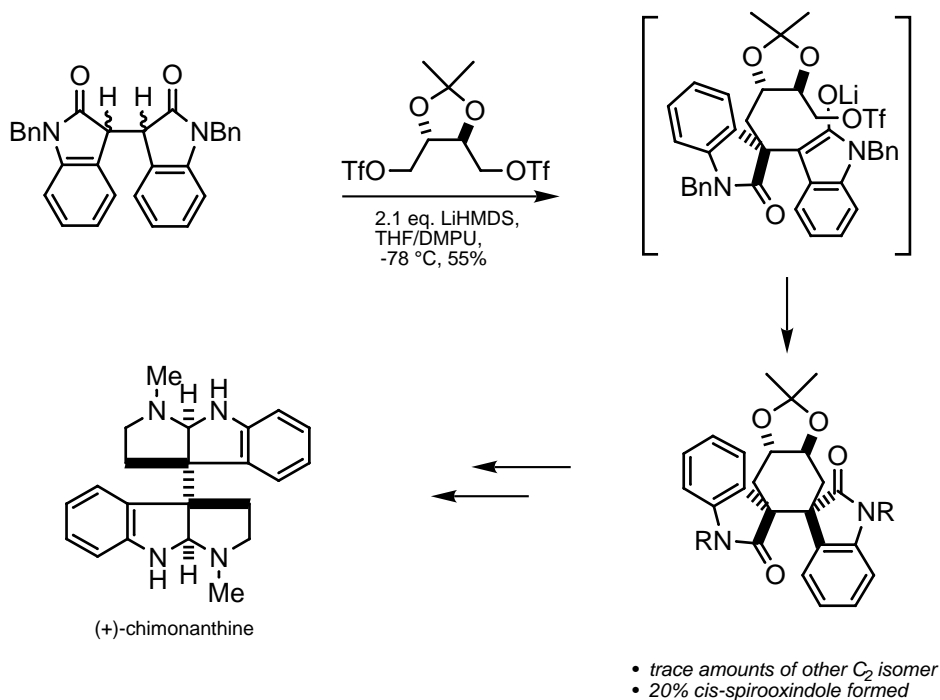
Overman et al, JACS, 1999, 121, 7702

Chimonanthine Revisited: Dialkylation



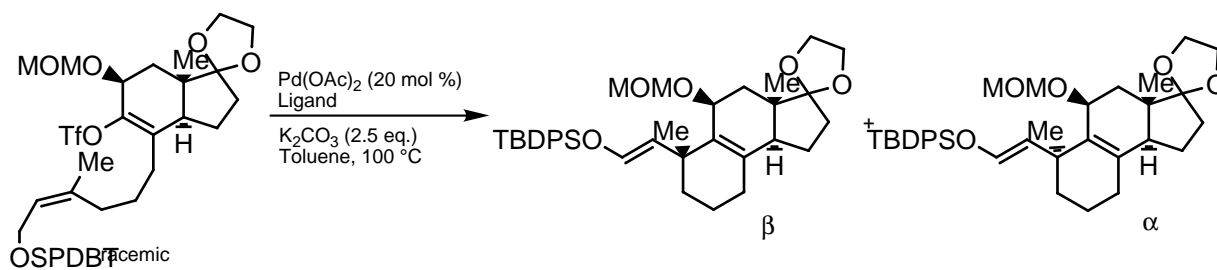
Overman, et al, ACIEE, 1999, accepted

Chimonanthine Revisited: Dialkylation



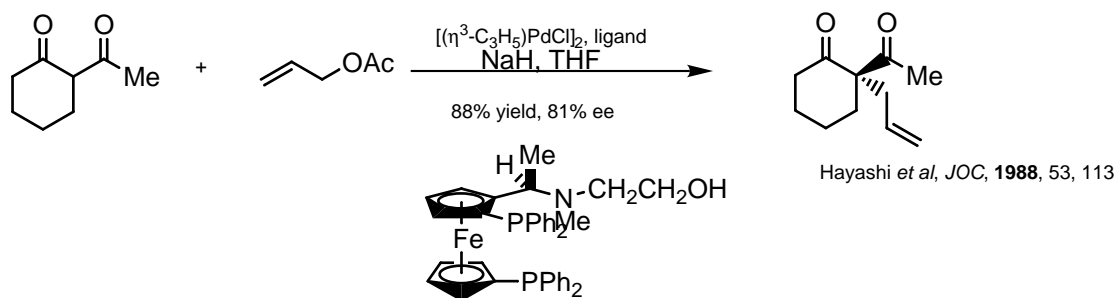
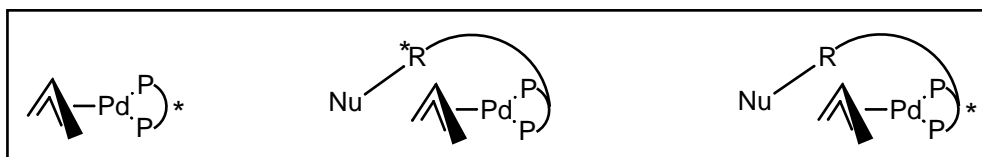
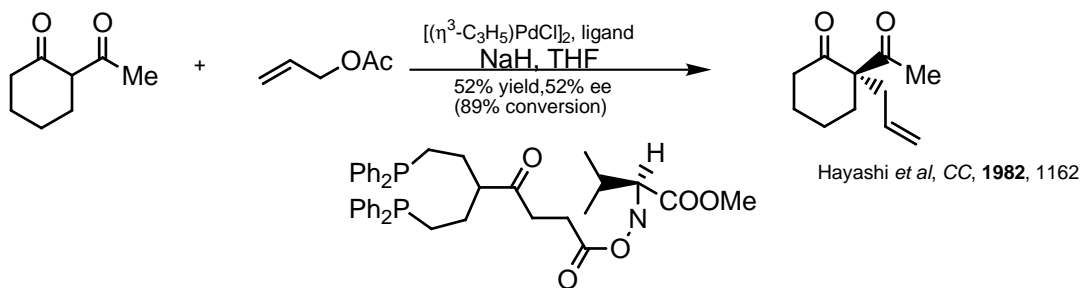
Overman, *et al*, *ACIEE*, **1999**, accepted

Kinetic Resolution by Asymmetric Heck Reaction



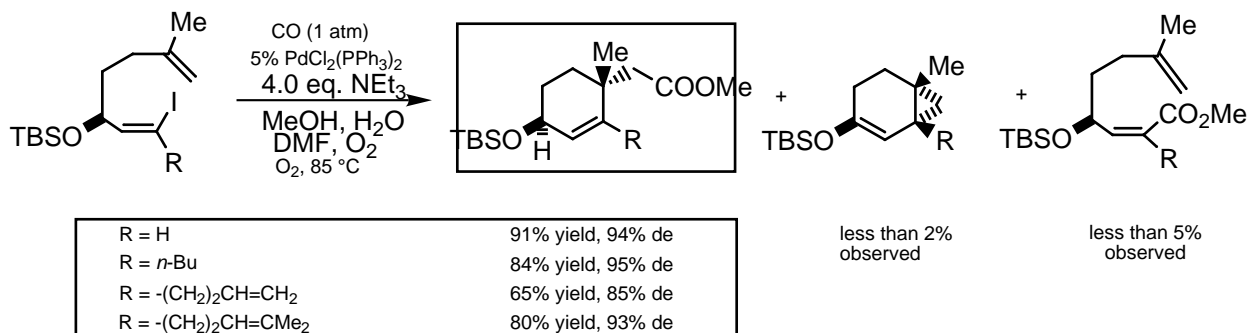
ligand (mol %)	reaction time (h)	Yield %	β : α	% ee of β
(R,R)-CHIRAPHOS (40)	20	14	6:1	4
(R)-BINAP (40)	2	17	5:1	97
(R)-Tol-BINAP (40)	1.5	20	11:1	96

Palladium Catalyzed Allylation

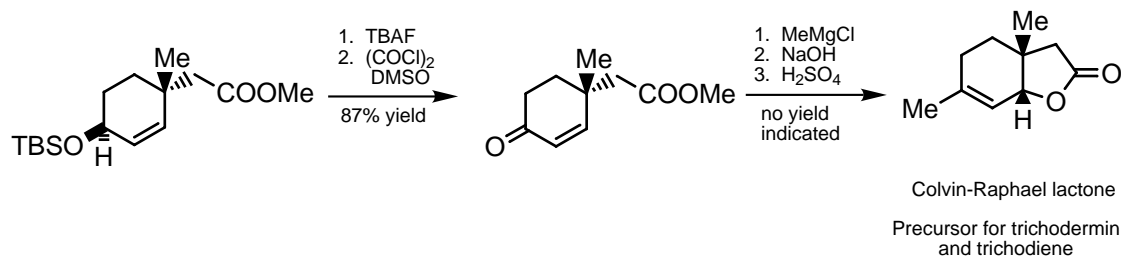


Type II Carbopalladation

Carbopalladation - Carbonylative Esterification:

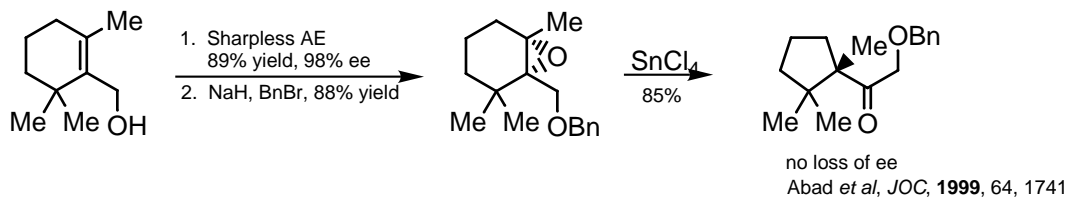


Colvin-Raphael lactone:

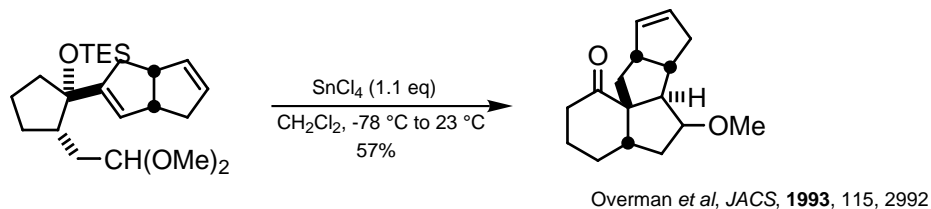


1,2 Rearrangements

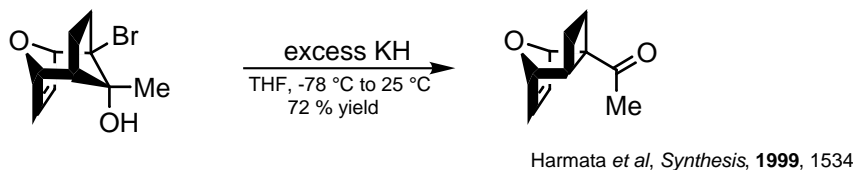
Herbertene and Herbertenol:



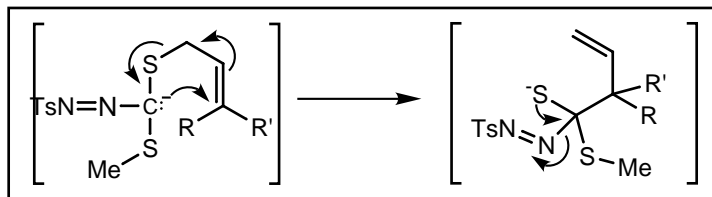
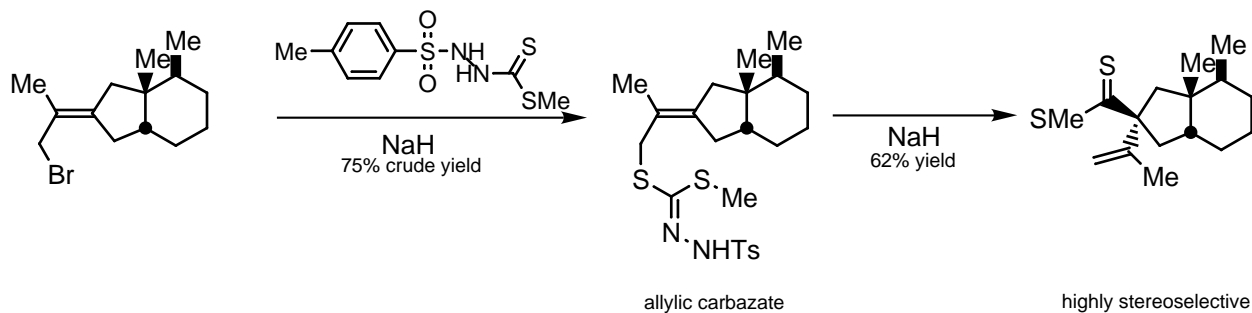
Magellanine:



Cyclobutene adduct:

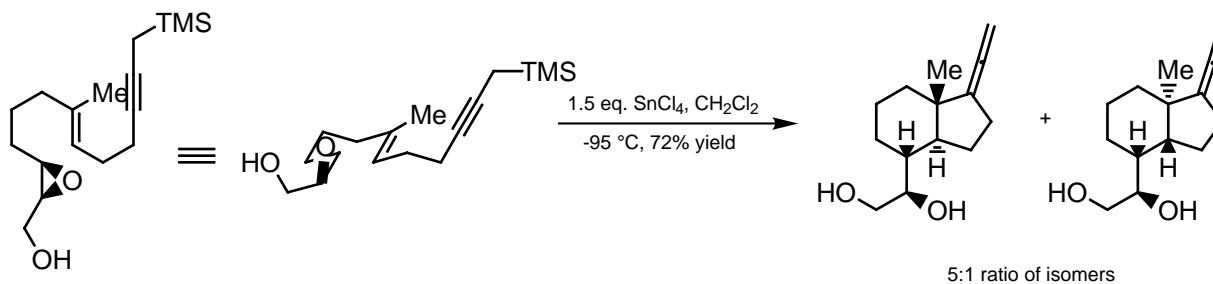


Bakkenolide: 2,3 Rearrangement



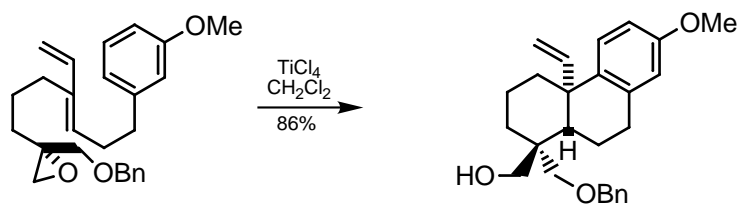
Cationic Cyclizations

Vitamin D metabolite precursor:



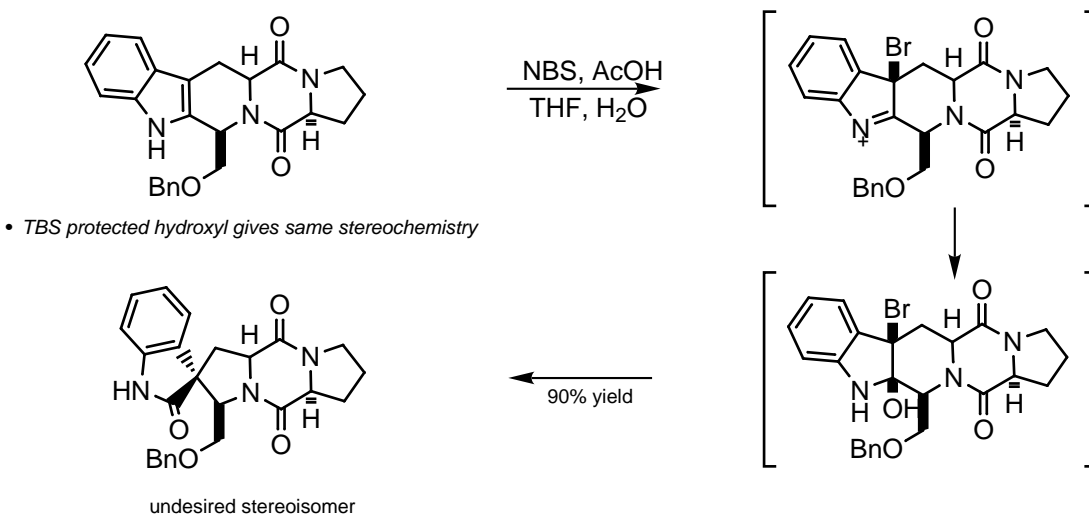
Takano *et al*, *CC*, **1989**, 1893

Neotripterifordin:



Corey *et al*, *JACS*, **1997**, 119, 9929

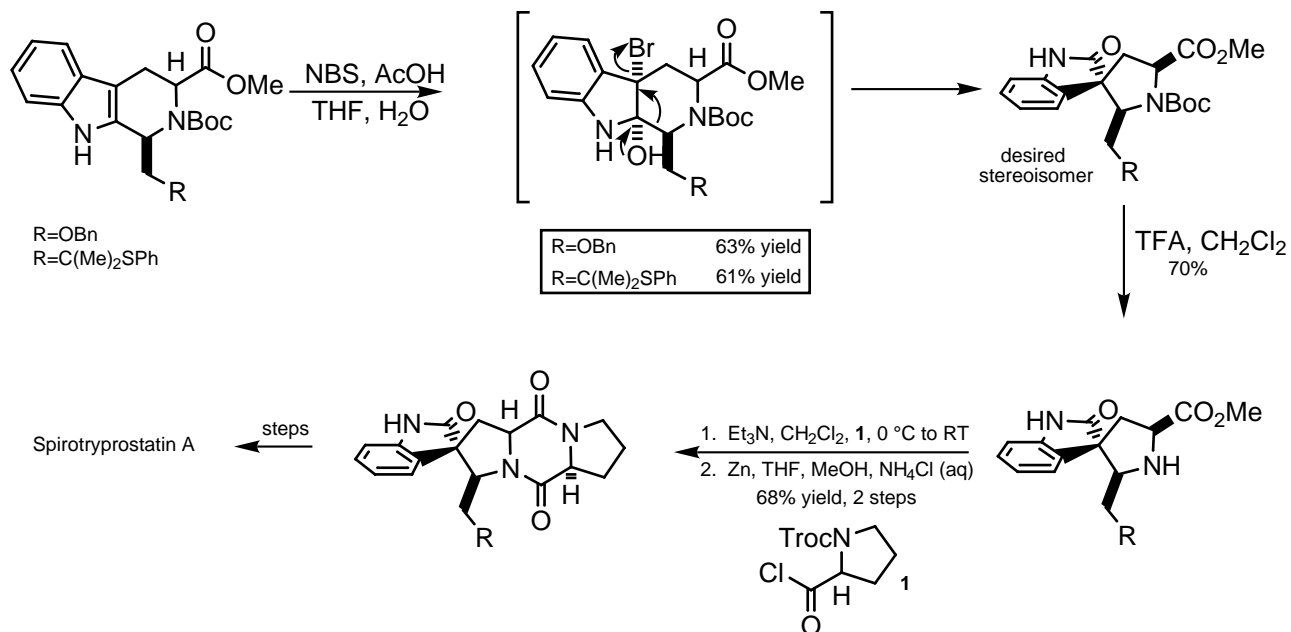
Spirotryprostatin A



- Other conditions: OsO_4 , pyr, THF, then NaHSO_3 (19%) or $t\text{-BuOCl}$, THF, then H_2O , MeOH (42%)

Danishefsky *et al*, *JACS*, **1999**, 121, 2147

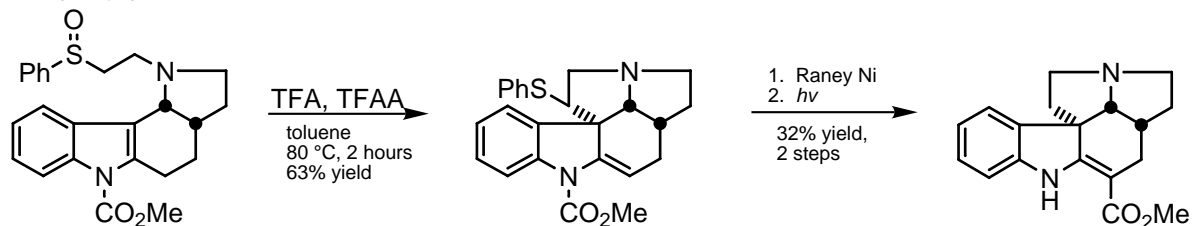
Spirotryprostatin A



Danishefsky *et al*, *JACS*, **1999**, 121, 2147

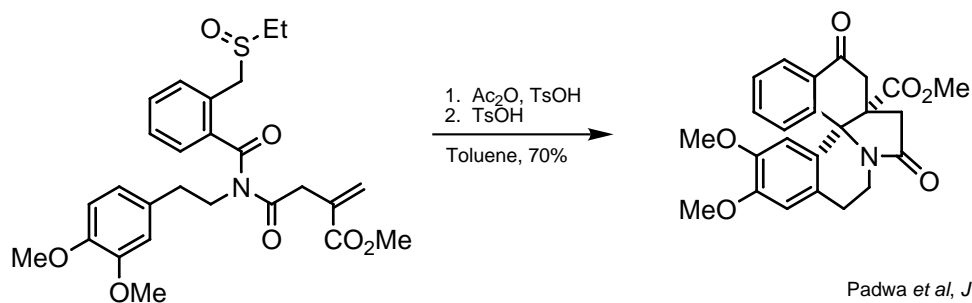
Pummerer Rearrangement

Deethylbophyllidine

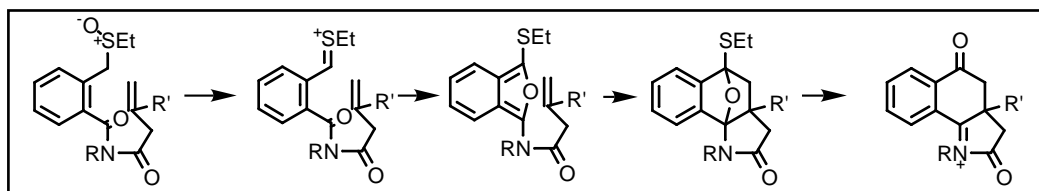


Bonjoch *et al*, *JOC*, **1996**, 61, 7107

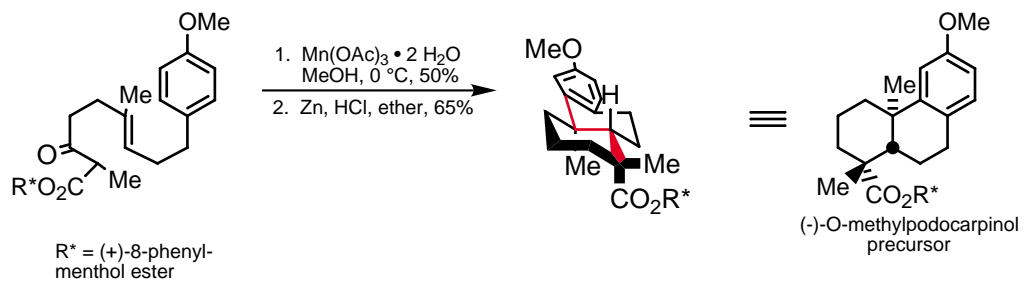
Erythrinane Skeleton



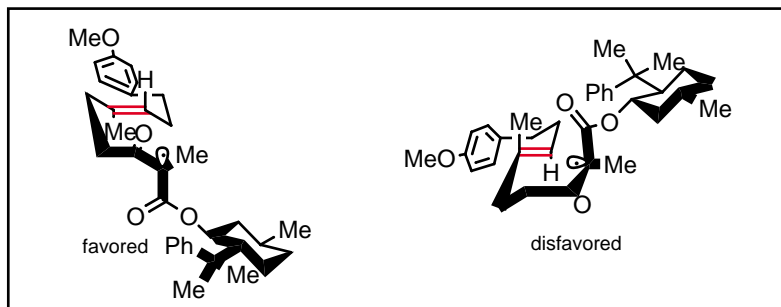
Padwa *et al*, *JOC*, **1996**, 61, 4888



Mn(III) Mediated Radical Cyclization



- 82% *de* after cyclization
- 50% major and 6% minor diastereomer isolated



Lanthanide Triflate Catalysis: Yang et al, *JACS*, **1999**, 121, 5579
 see also: V. Cee Seminar on Mn(III) radicals, April 27, 1999

Snider et al, *JOC*, **1993**, 58, 7640