Asymmetric Quaternary Center Construction

Brian Raymer
Evans Group Seminar
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Lead References:

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

Asymmetric Quaternary Center Construction

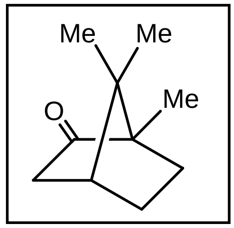
Definition:

Quaternary Center: Carbon with four carbon substituents

Contents:

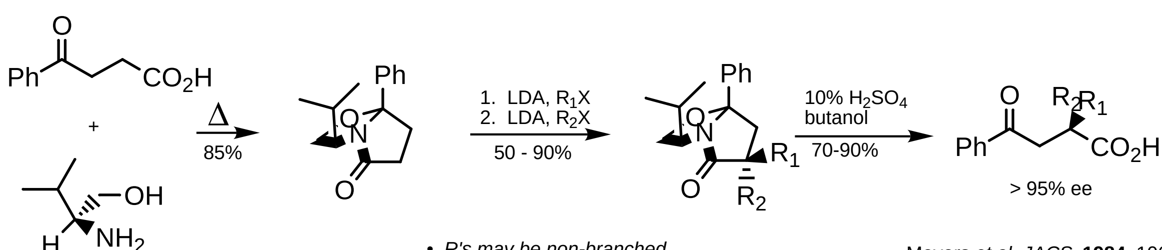
- Enolates and Enamines
- Cycloadditions
- Sigmatropic Rearrangements
- Cyclopropanation
- Palladium Mediated Construction
- Lewis Acid Catalyzed Rearrangements
- Radical Cyclizations

Natural Products from Camphor



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

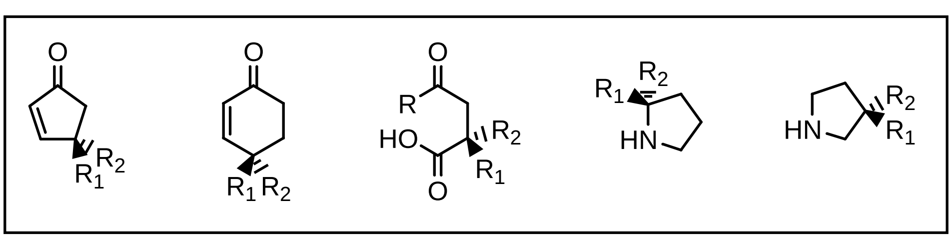
Meyers Bicyclic Lactams



valine dx.

- *R's may be non-branched alkyl, allyl or benzyl*

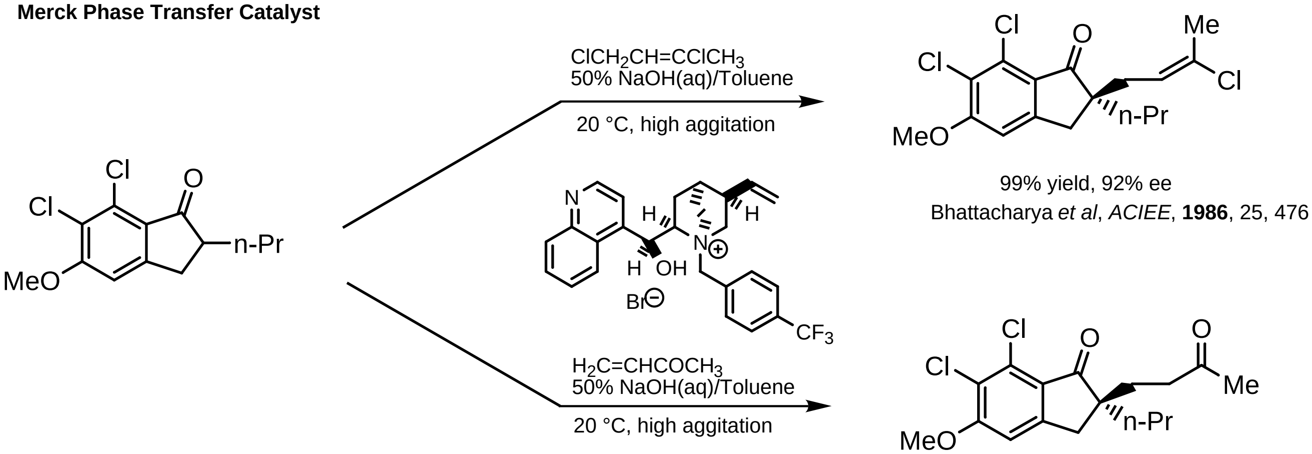
Meyers *et al*, *JACS*, **1984**, 106, 1146



Review: Meyers, Brengel, *CC*, **1997**, 1

Enolate Alkylation and Michael Additions

Merck Phase Transfer Catalyst

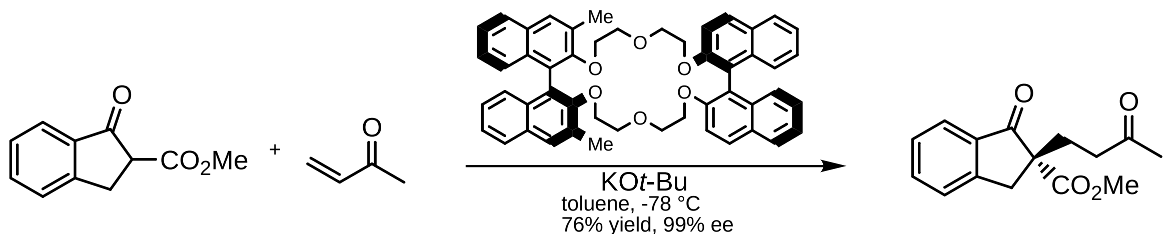


Bhattacharya *et al*, *ACIEE*, **1986**, 25, 476

95% yield, 80% ee

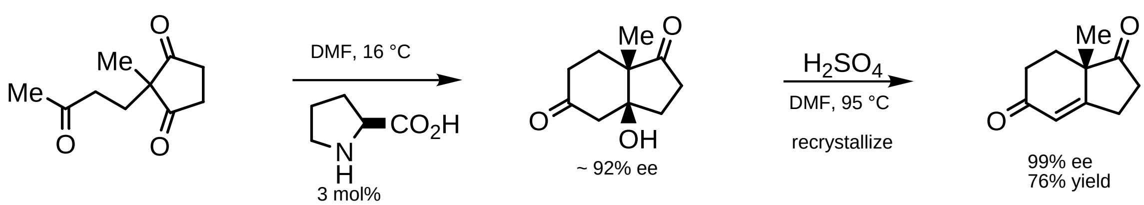
Karady *et al*, *JOC*, **1986**, 51, 4710

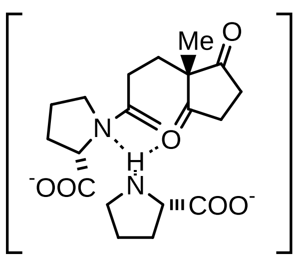
Cram Binol Derived Catalyst



Cram *et al*, *CC*, **1981**, 625

Desymmeterization: Amino-acid catalyzed Robinson Annulation





- *Dilution studies suggest three-center hydrogen bond.*
- *Nonlinear relatinship 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

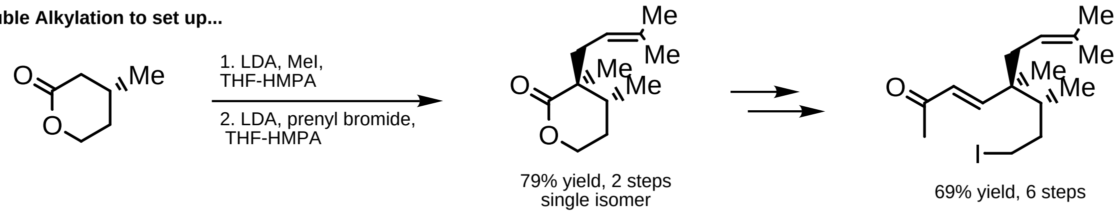
Wieland-Miescher ketone:
Buchschacher, Furst, Gutzwiller, *Org. Synth.*, VII, 368

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

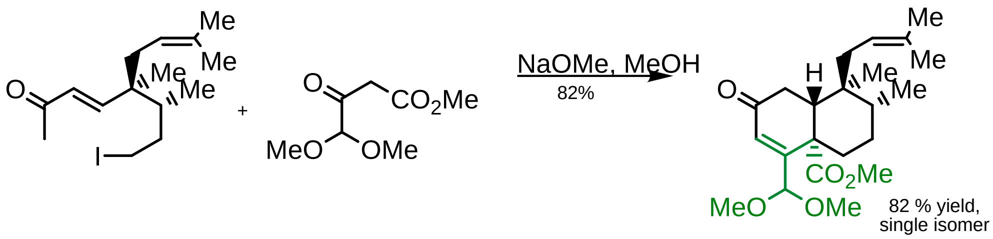
For additional examples: W. Trotter Seminar, April 1997

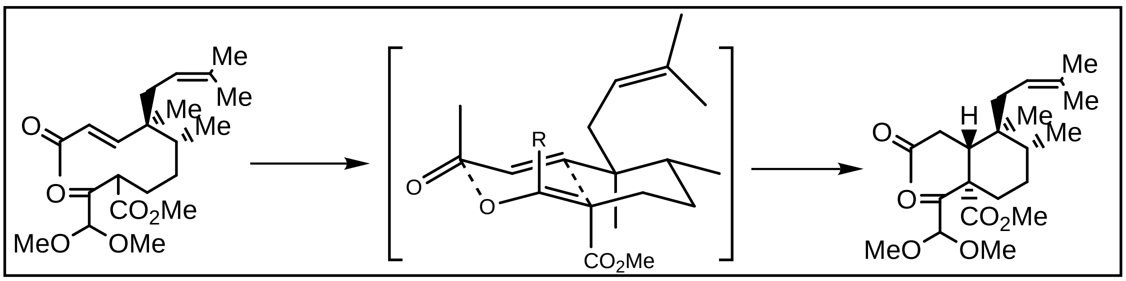
Tanabalin: Intermolecular Alkylation-Intramolecular Robinson Annulation

Double Alkylation to set up...



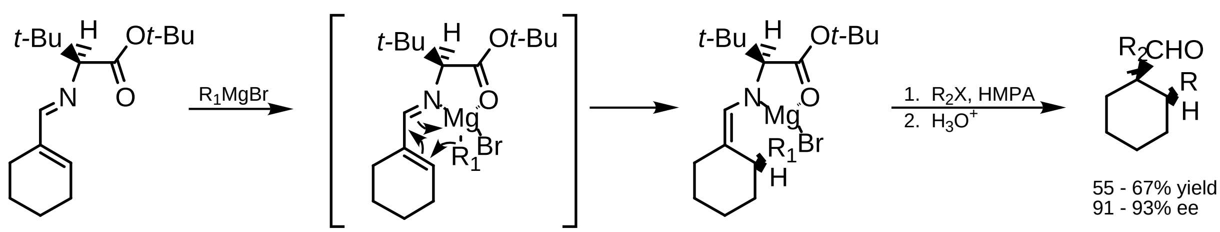
...an alkylation and then a Robinson Annelation.





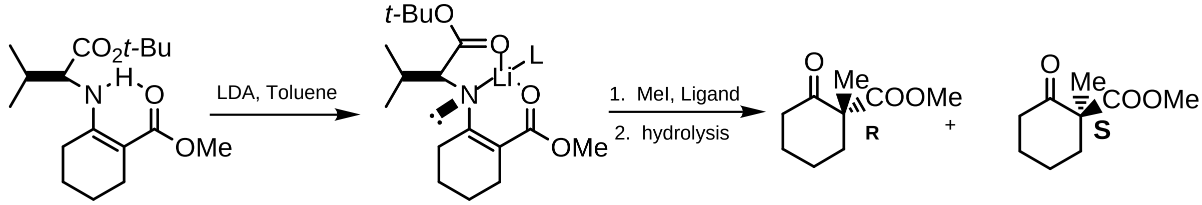
Watanabe, *et al*, *TL*, **1999**, 40, 2545

Asymmetric Grignard Addition and Asymmetric Enamine Alkylation



R_1 = Ph, vinyl
R_2X = MeI, BnI, allylBr, EtI, MOMCl

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

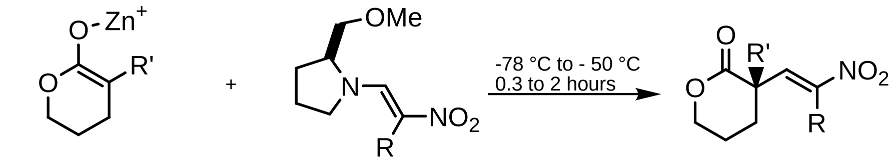


Ligand: 1.0 eq. HMPA	57% yield,	>99:1 (R)
2.0 eq. THF	63% yield,	96:4 (S)

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

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

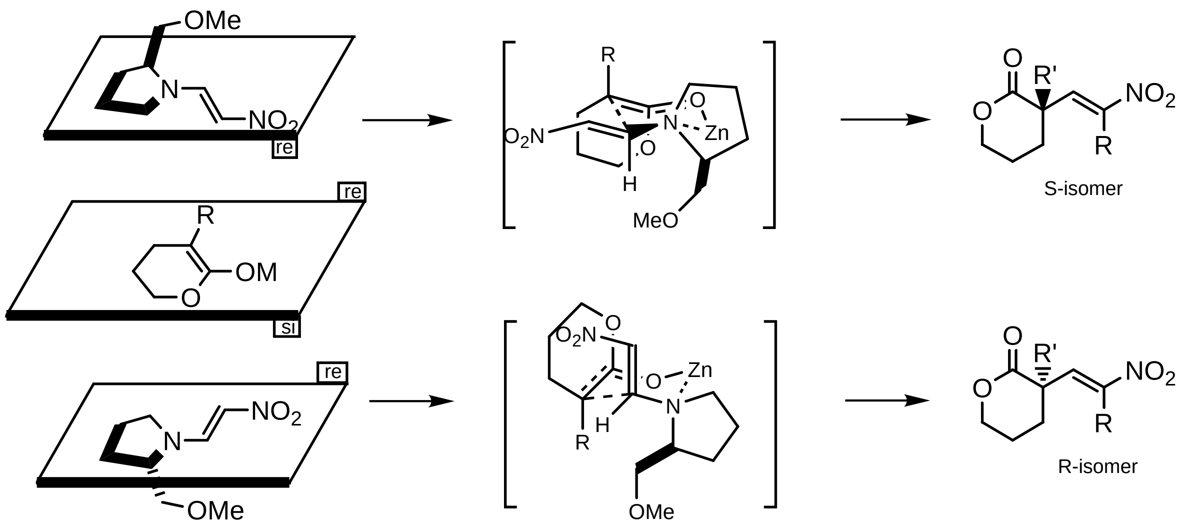
Chiral Leaving Groups: Nitroolefination



3.0 eq.
R'=Me, Et, allyl

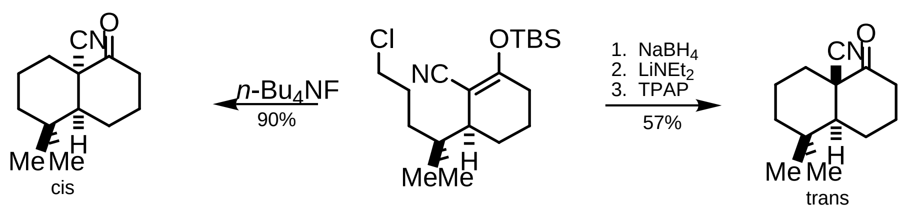
R=H, Me, Et,

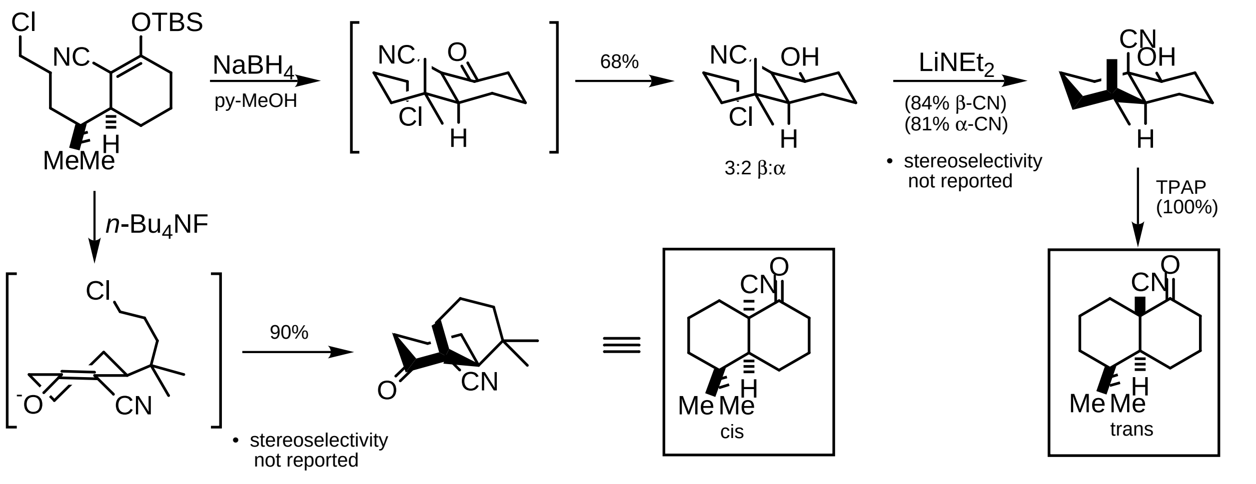
74 - 96% ee
54 - 86% yield



Fuji *et al*, *JACS*, **1989**, 111, 7923

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

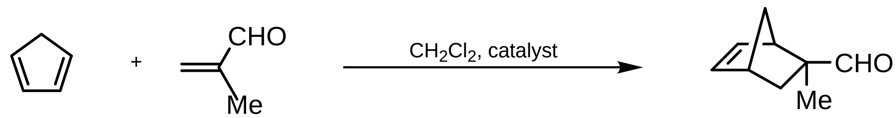


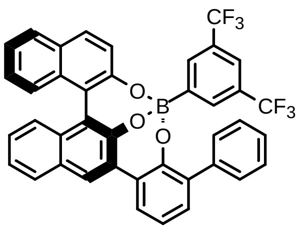


see also: Stork, Boeckman, *JACS*, **1973**, 95, 2016
Effects of counterion on on nitrile anion orientation.

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

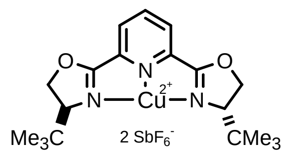
Catalytic Enantioselective Diels-Alder





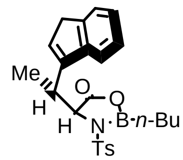
Yamamoto
4.0 eq. diene
5 mol %cat.
-78 °C, 1.5 h
96% yield, 99%ee,
exo:endo >90%?

JACS, **1996**, 118, 3049



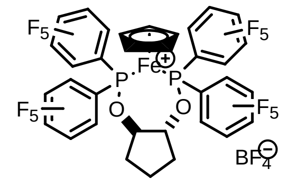
Evans
1.2 eq. diene
5 mol % cat.
-40 °C, 8 h
100% conv., 92% ee,
exo:endo=97:3

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

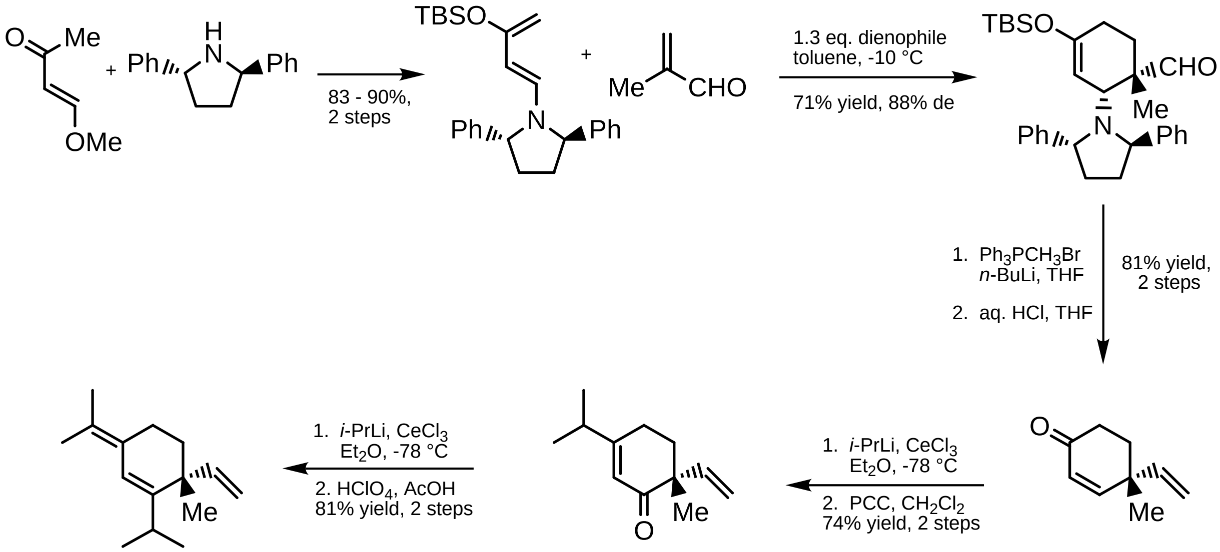


Kundig
1.1 eq. diene
5 mol % cat.
-20 °C, 22 h
91 % yield, 98% ee,
exo:endo=97:3

ACIEE, **1994**, 33, 1856

Diels-Alder in Synthesis of Elemene

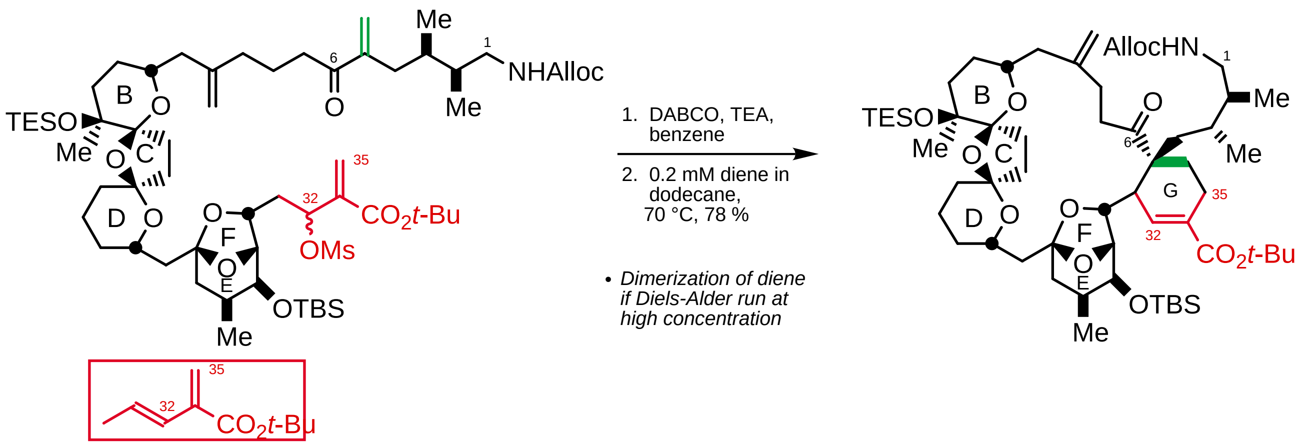
Elemene: Chiral Amino Siloxy Diene Diels-Alder

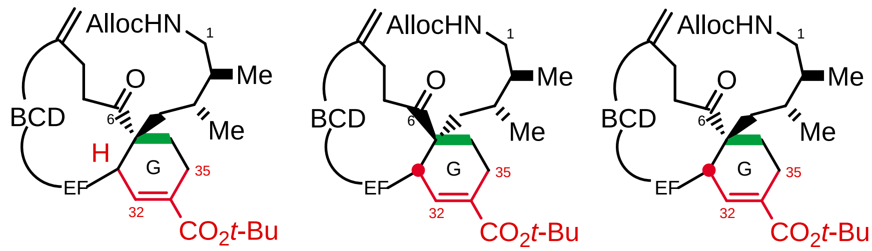


(-)-α-Elemene

Rawal, Kozmin, *JACS*, **1999**, 121, 9562

Pinnatoxin Diels-Alder

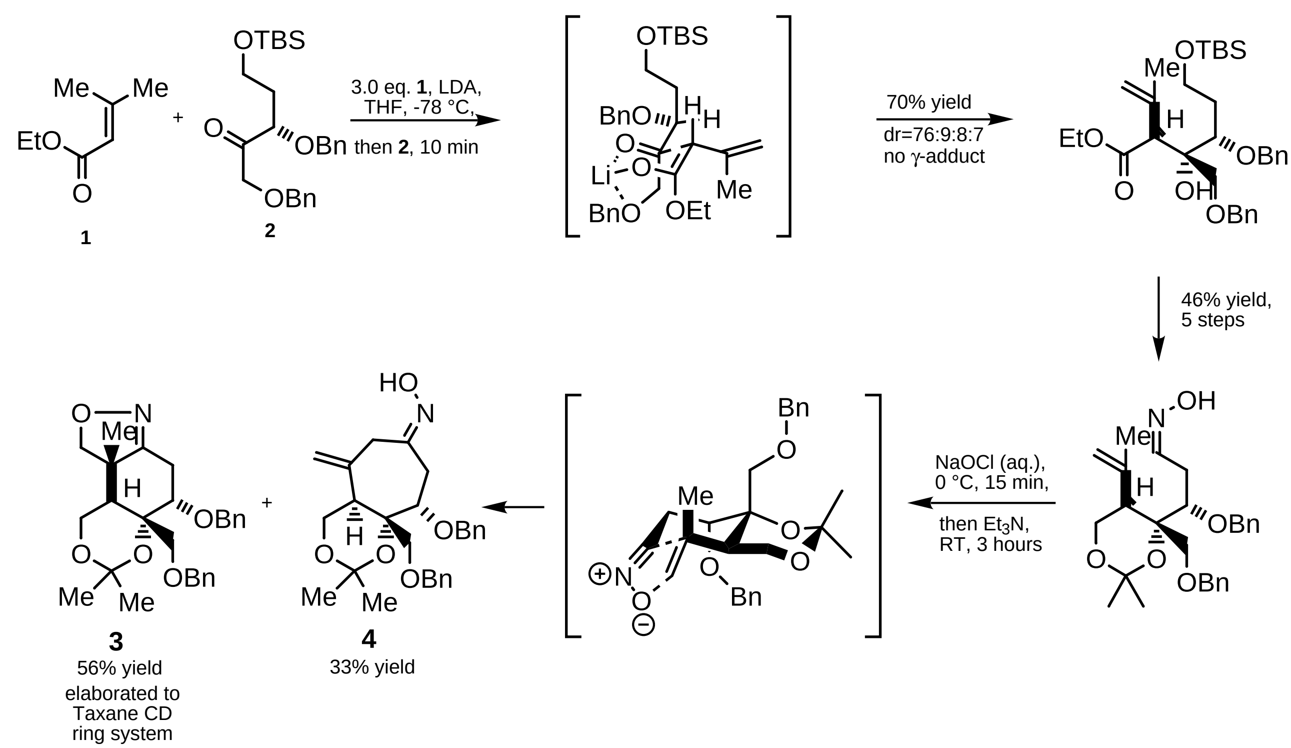




Reaction Conditions	A, desired exo product	B, undesired exo product	C, endo product
toluene, 100 °C	33 %	33 %	33 %
dodecane, 70 °C	43 %	39 %	17 %

Kishi *et al*, *JACS*, **1998**, 120, 7647

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

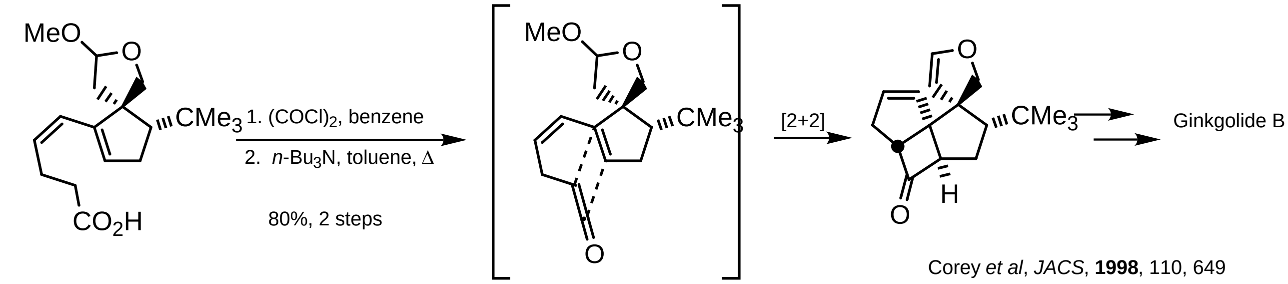


see also: D. Halstead Seminar
Nitrile Oxide Cycloadditions

Takahashi *et al*, *JOC*, **1998**, 63, 5742

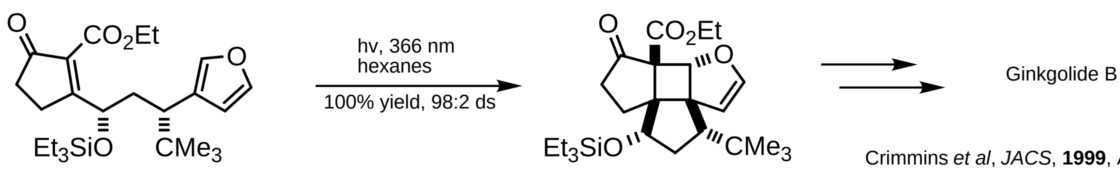
Ginkgolide B Syntheses: 2+2 Cycloadditions

Ketene [2+2]:



Corey *et al*, *JACS*, **1998**, 110, 649

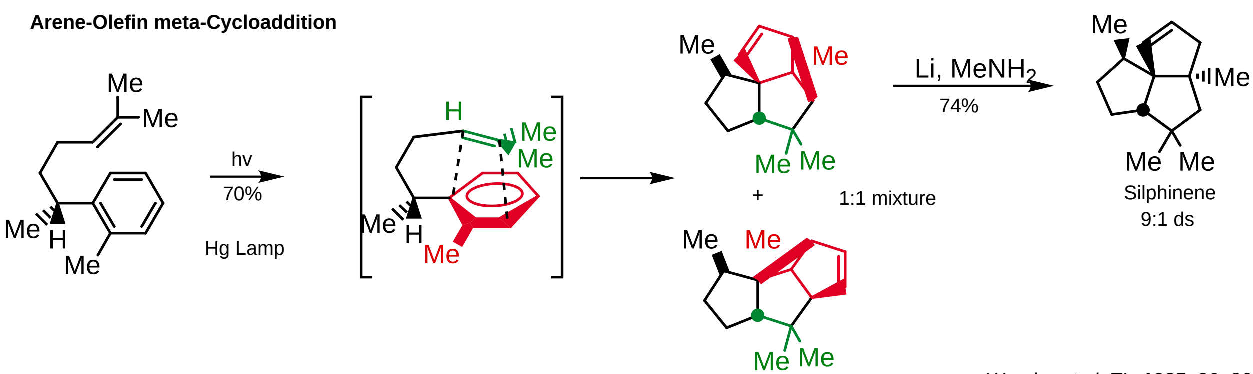
Enone-Furan [2+2]:



Crimmins *et al*, *JACS*, **1999**, ASAP

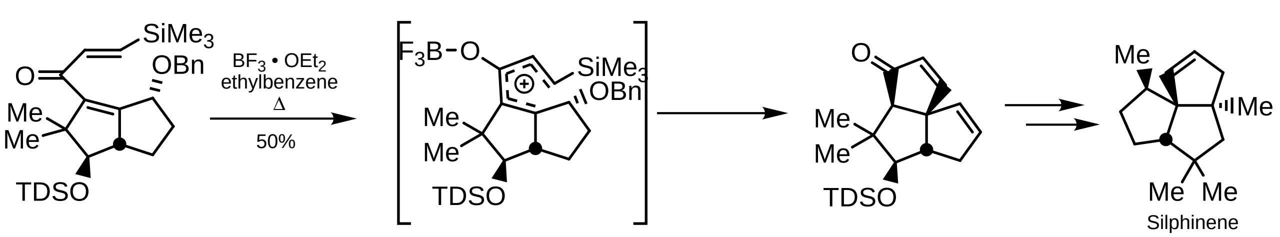
Silphinene: Arene-Olefin meta-Cycloaddition and Nazarov Cyclization

Arene-Olefin meta-Cycloaddition



Wender *et al*, *TL*, **1985**, 26, 2625

Nazarov Cyclization



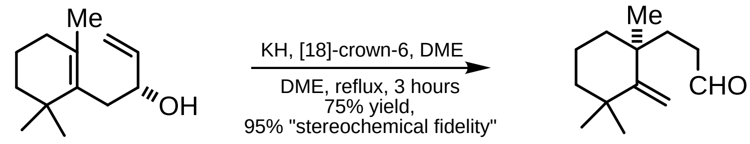
TDS = Thexyldimethylsilyl

Franck-Neumannet *al*, *Tet*, **1997**, 53, 2103

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

Ireland-Claisen and Anionic Oxy-Cope

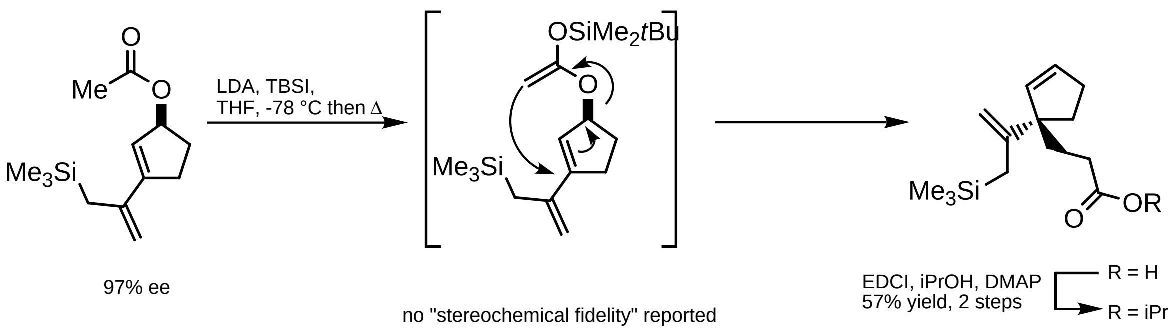
(+)-Dihydromayurone: Anionic Oxy-Cope



no ee reported

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

Aspidophytine: Ireland-Claisen

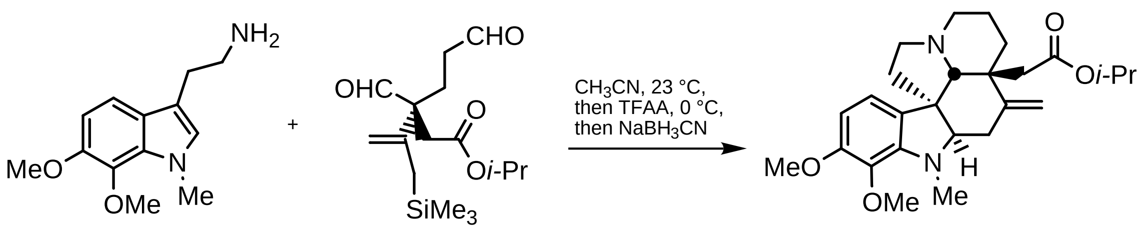


97% ee

no "stereochemical fidelity" reported

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

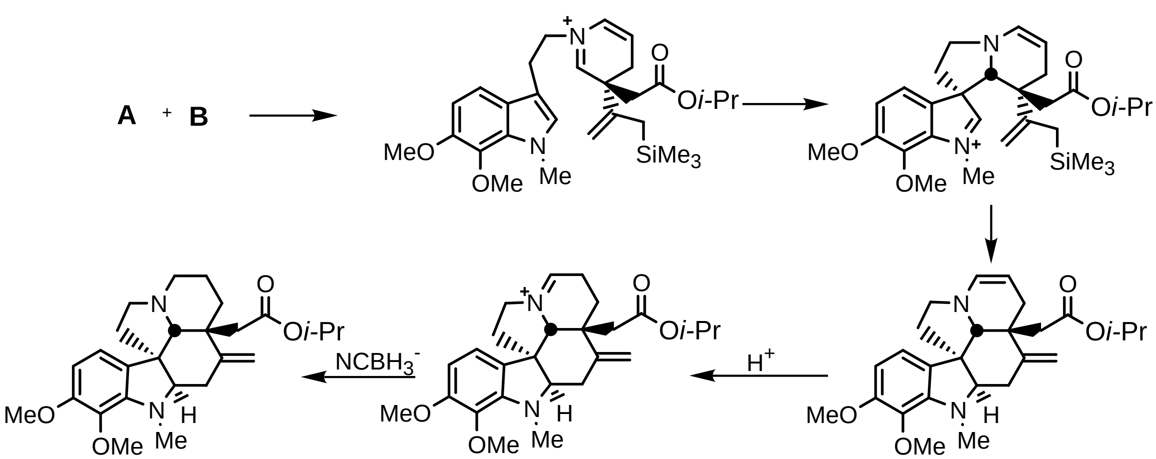
Enamine Alkylation: Aspidophytine



A **B**

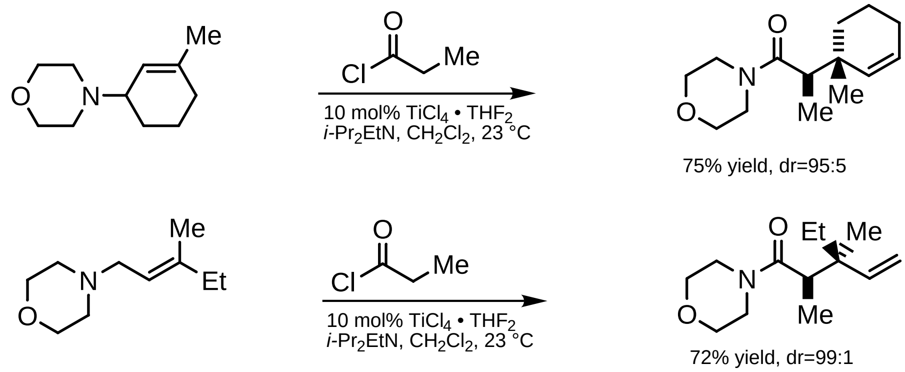
B Quaternary Center
set by Ireland-Claisen

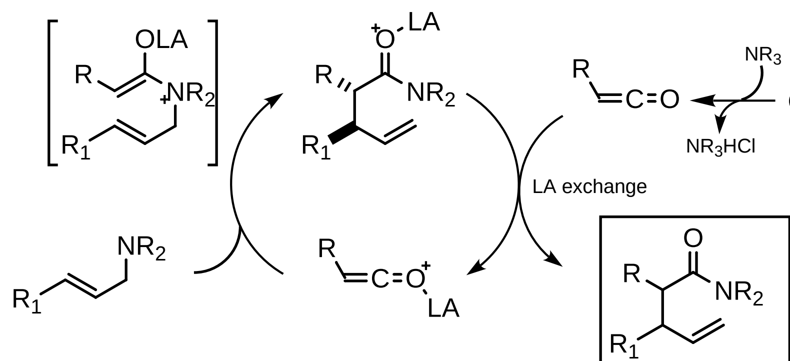
66% yield
selectivity not reported



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

Lewis-Acid Catalyzed Claisen Rearrangement

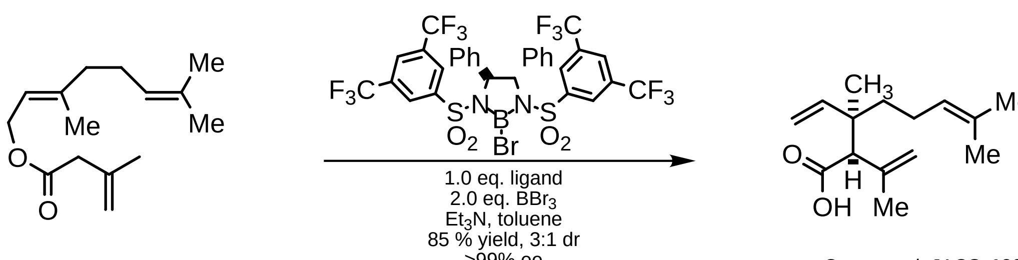




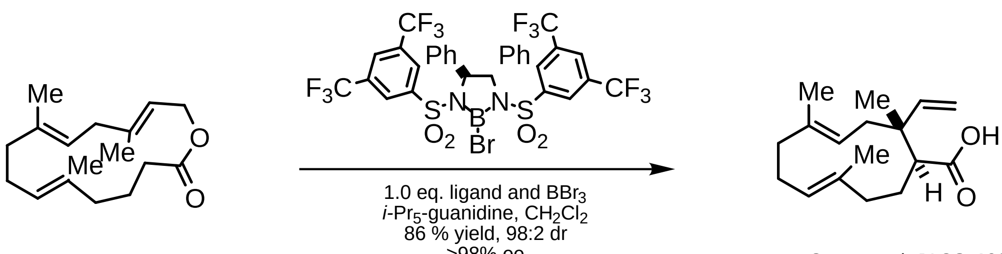
■ enantioselective version under development

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

Stoichiometric Enantioselective Claisen Rearrangement



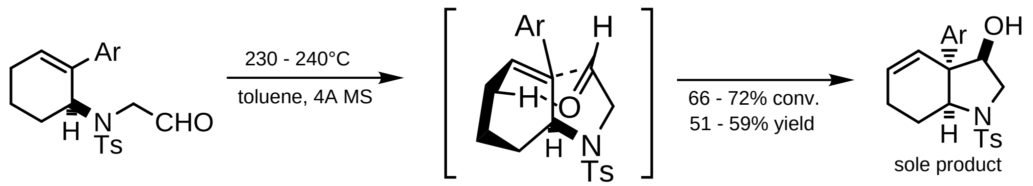
Corey *et al*, *JACS*, **1995**, 117, 193

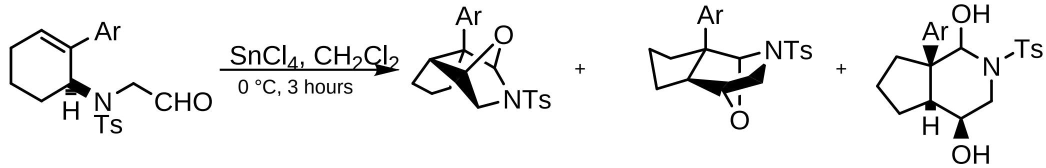


Corey *et al*, *JACS*, **1996**, 118, 1229

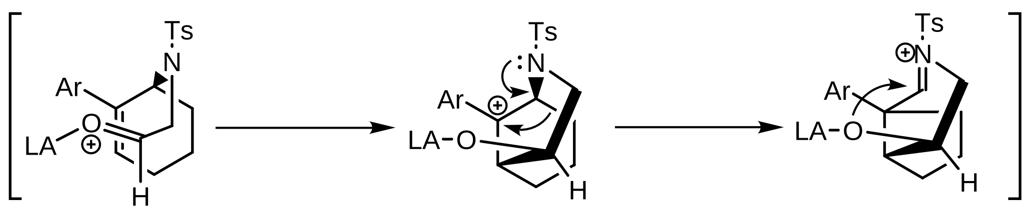
- *strong, hindered base gives best results*
  i-Pr_5-guanidine: Barton's Base

Intramolecular Ene and a Lewis-Acid Catalyzed Rearrangement





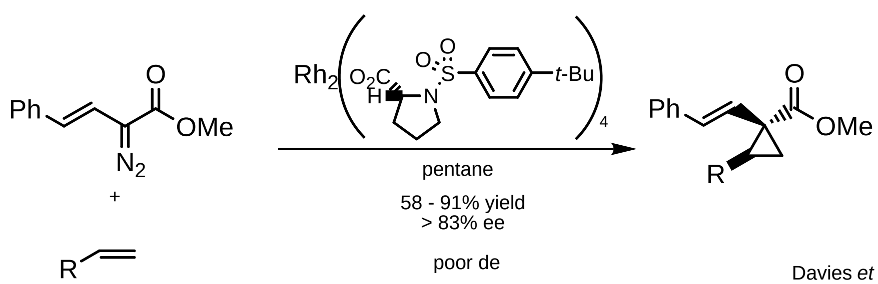
	Yield (%)		
10 mol% $SnCl_4$	89%	0%	0%
100 mol% $SnCl_4$	13%	6%	29%



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

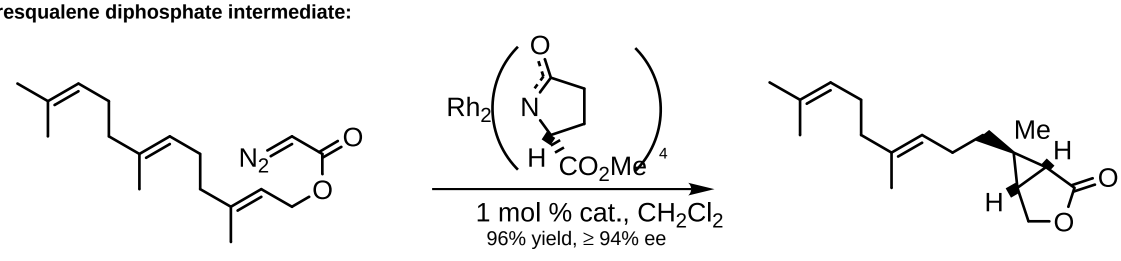
Intermolecular and Intramolecular Cyclopropanations

α **- cyclopropyl esters:**



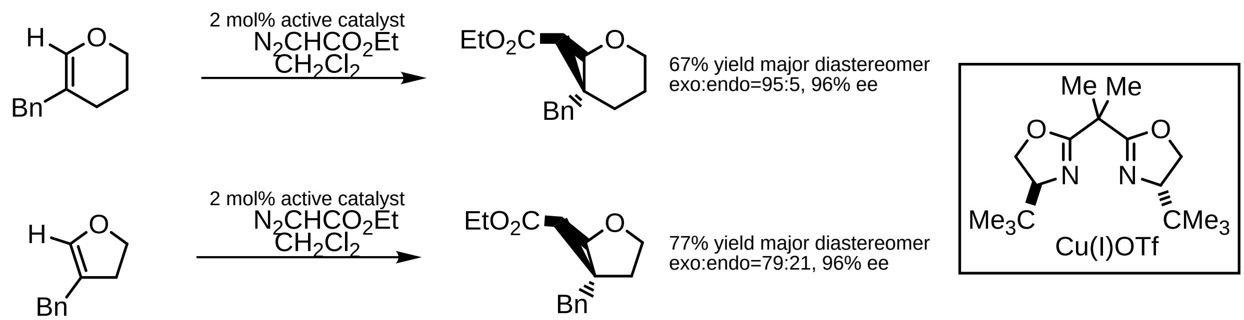
Davies *et al*, *TL*, **1993**, 34, 7243

Presqualene diphosphate intermediate:

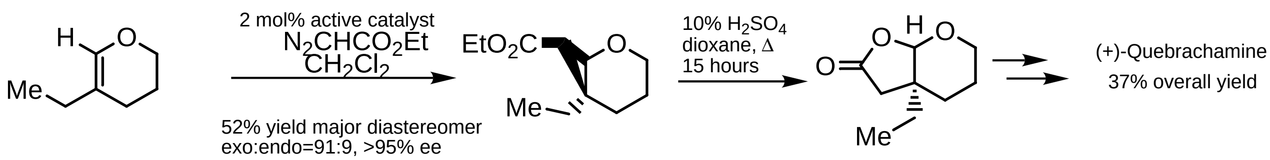


Poulter *et al*, *JOC,* **1995**, 60, 941

Cu (I)-Catalyzed Cyclopropanation of Cyclic Enol Ethers



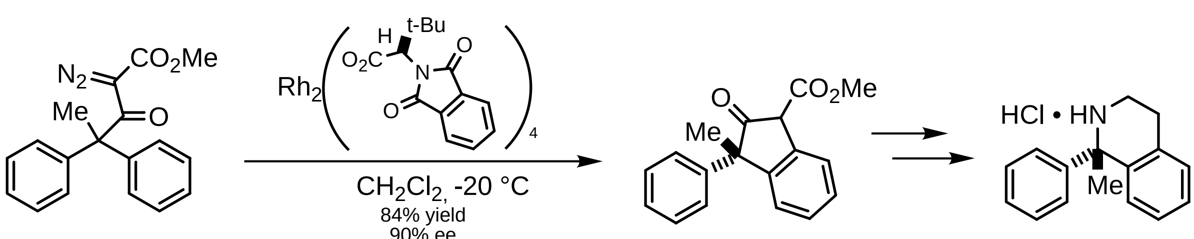
Quebrachamine:



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

Rh Catalyzed C-H insertion

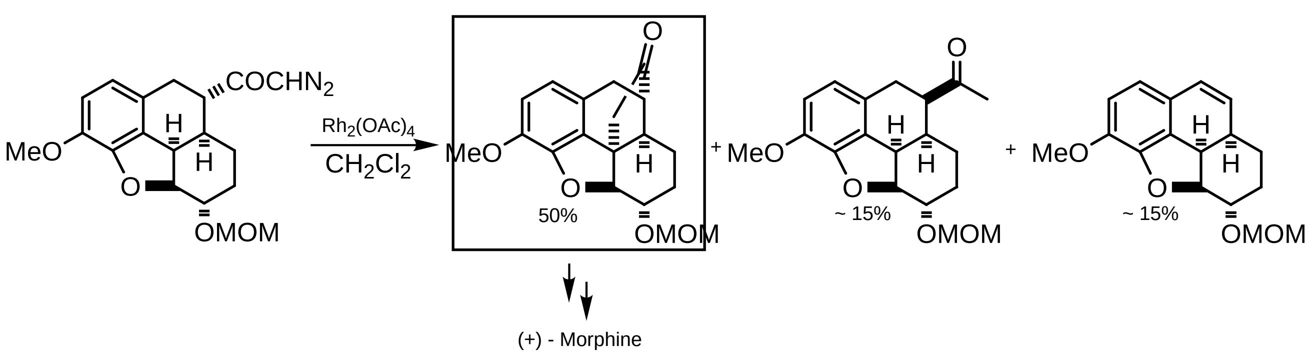
FR115427:



(S)-FR115427

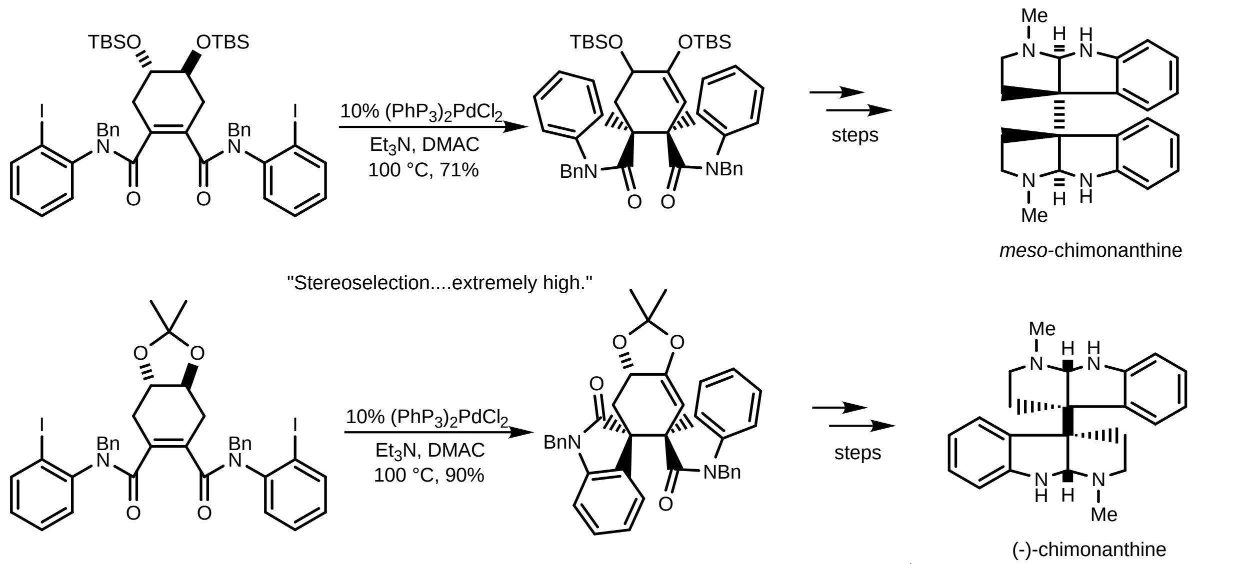
Hashimoto *et al*, *Synlett*, **1996**, 85-86

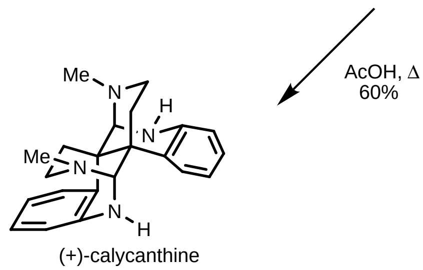
Morphine:



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

Vicinal Stereogenic Quaternary Carbon Centers

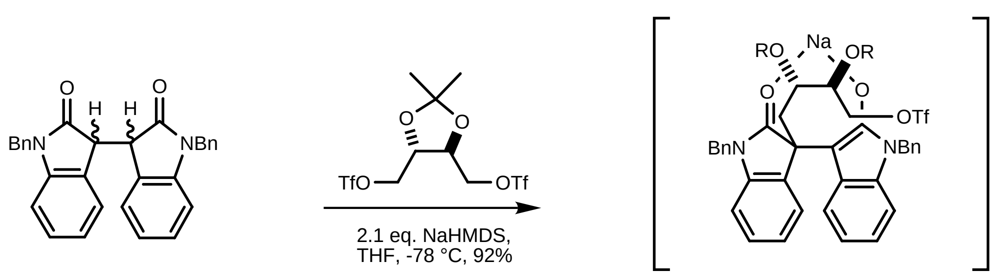




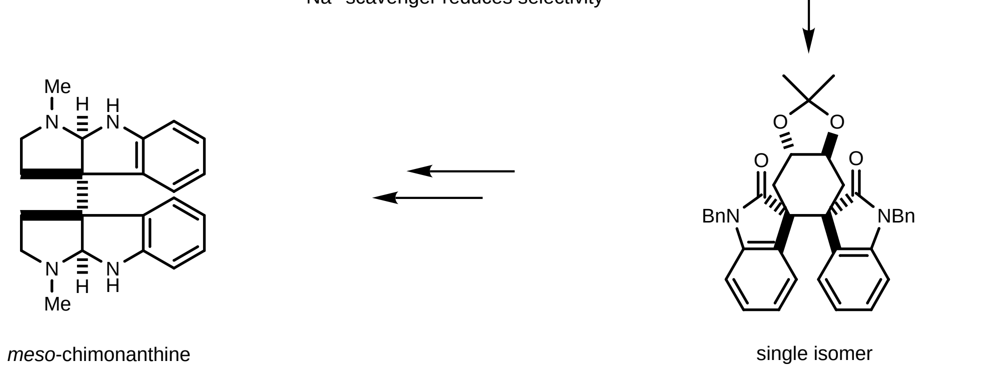
- *TBS substituents prefer a bis-axial orientation*
- *acetonide prefers a bis-equitorial orientation*

Overman *et al*, *JACS*, **1999**, 121, 7702

Chimonanthine Revisited: Dialkylation

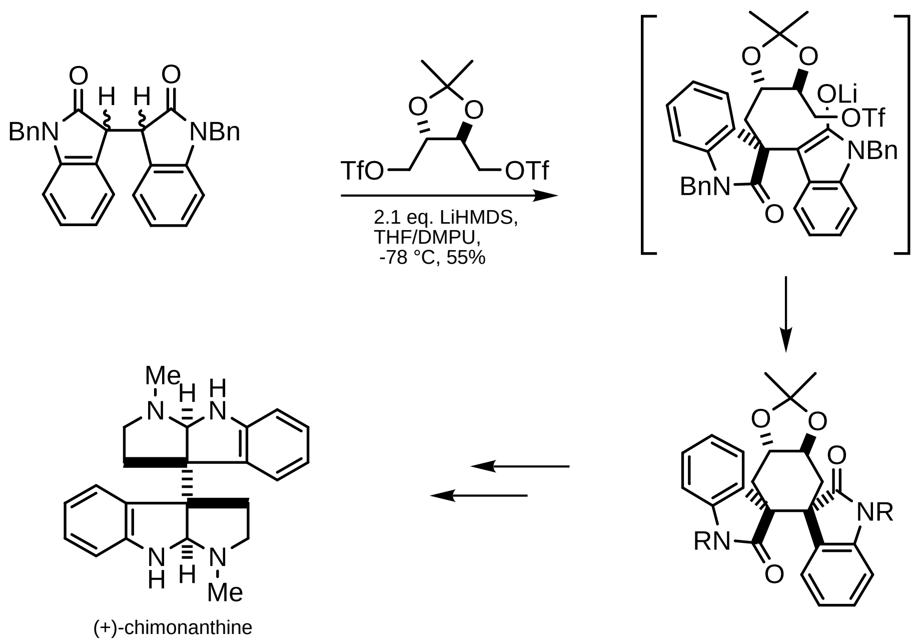


• Na^+ scavenger reduces selectivity



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

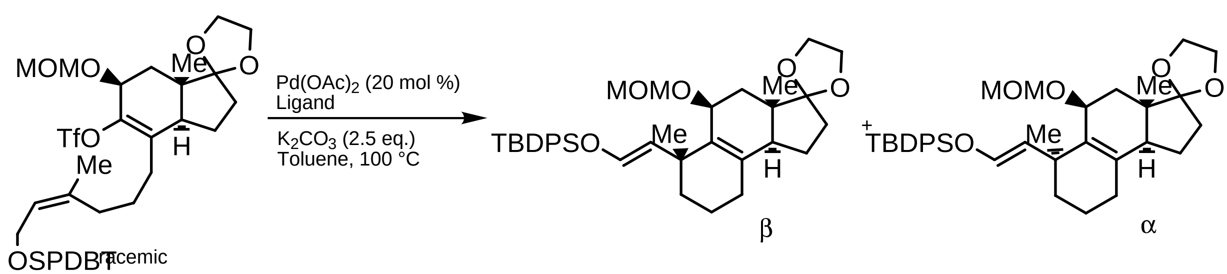
Chimonanthine Revisited: Dialkylation



- *trace amounts of other C_2 isomer*
- *20% cis-spirooxindole formed*

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

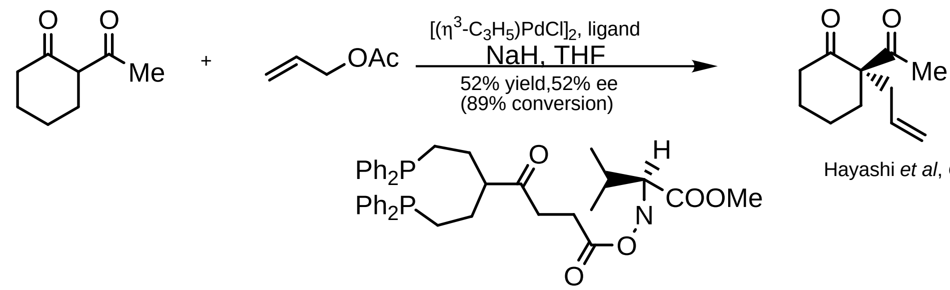
Kinetic Resolution by Asymmetric Heck Reaction



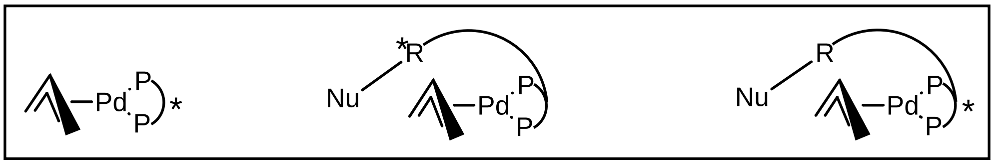
ligand (mol %)	reaction time (h)	Yield %	β:α	% ee of β
(R,R)-CHIRAPHOS (40)	20	14	6:1	4
(R)-BINAP (40)	2	17	5:1	97
(R)-Tol-BINAP (40)	1.5	20	11:1	96

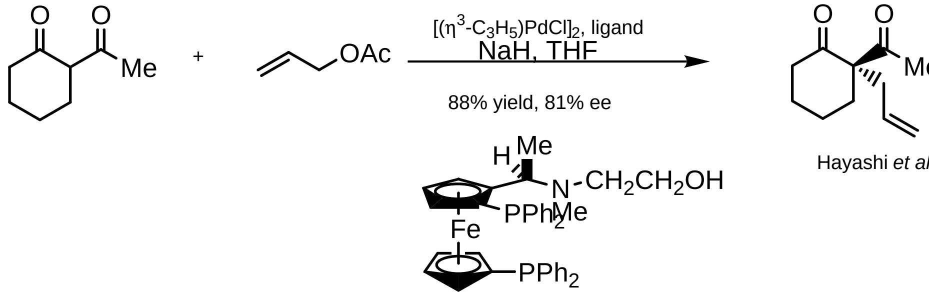
Shibasaki *et al*, *TL,* **1999**, 49, 311

Palladium Catalyzed Allylation



Hayashi *et al*, *CC*, **1982**, 1162

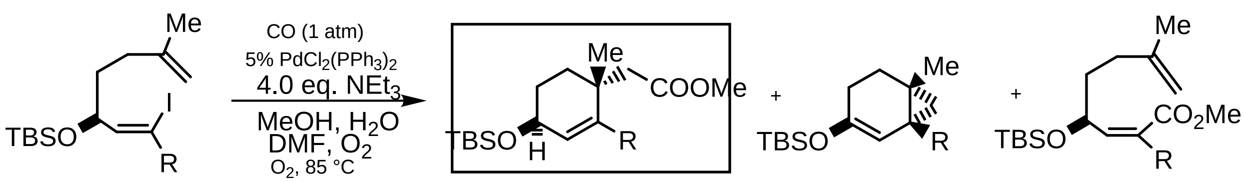




Hayashi *et al*, *JOC*, **1988**, 53, 113

Type II Carbopalladation

Carbopalladation - Carbonylative Esterification:

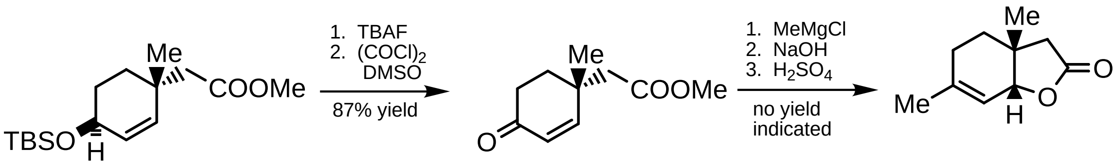


R = H	91% yield, 94% de
R = *n*-Bu	84% yield, 95% de
R = -$(CH_2)_2CH{=}CH_2$	65% yield, 85% de
R = -$(CH_2)_2CH{=}CMe_2$	80% yield, 93% de

less than 2% observed

less than 5% observed

Colvin-Raphael lactone:



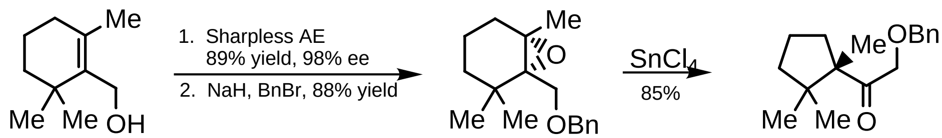
Colvin-Raphael lactone

Precursor for trichodermin and trichodiene

Negishi *et al*, *Org. Lett.*, **1999**, 1, 165

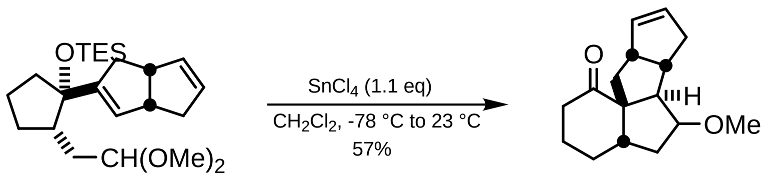
1,2 Rearrangements

Herbertene and Herbertenol:



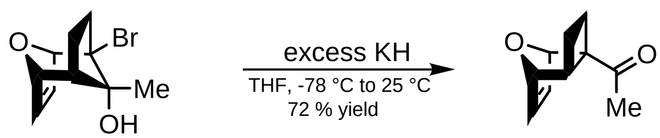
no loss of ee
Abad *et al*, *JOC*, **1999**, 64, 1741

Magellanine:



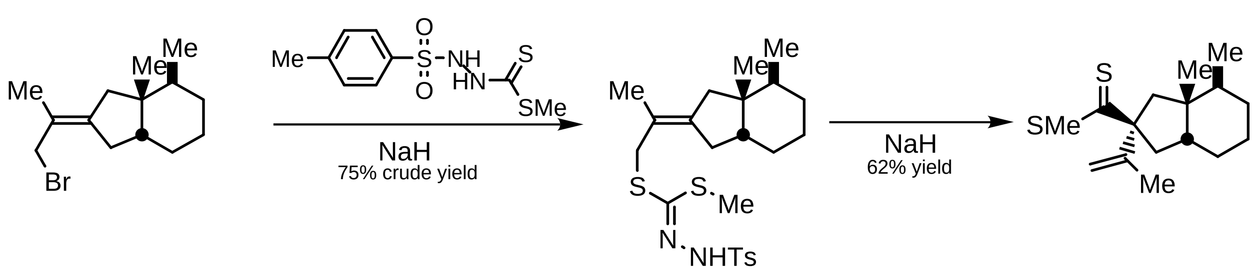
Overman *et al*, *JACS*, **1993**, 115, 2992

Cyclobutene adduct:



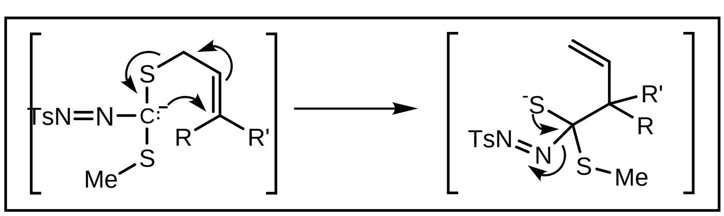
Harmata *et al*, *Synthesis*, **1999**, 1534

Bakkenolide: 2,3 Rearrangement



allylic carbazate

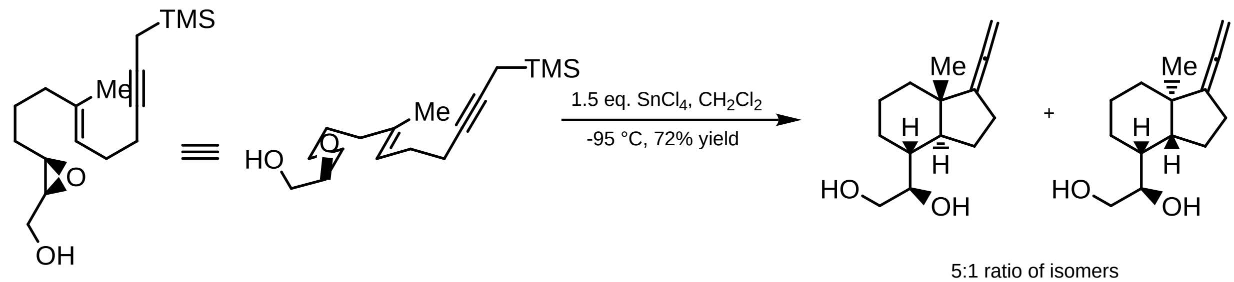
highly stereoselective



Evans, *et al*, *JACS*, **1977,** 99, 5453

Cationic Cyclizations

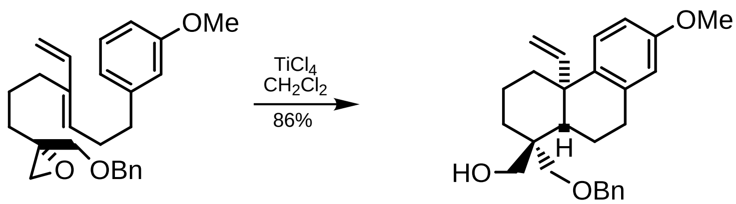
Vitamin D metabolite precursor:



5:1 ratio of isomers

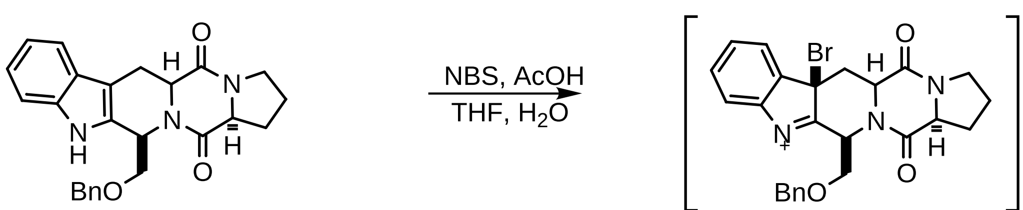
Takano *et al*, *CC*, **1989**, 1893

Neotripterifordin:

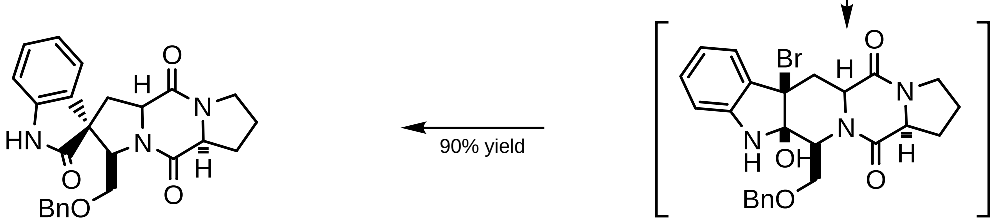


Corey *et al*, *JACS*, **1997**, 119, 9929

Spirotryprostatin A



- *TBS protected hydroxyl gives same stereochemistry*

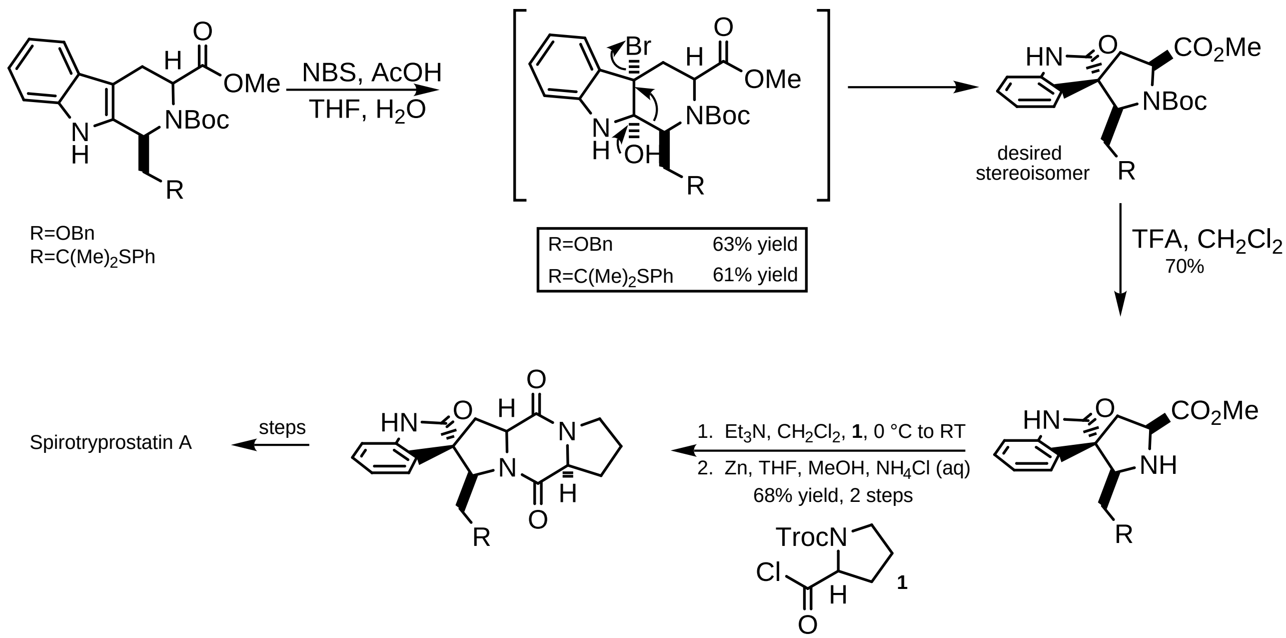


undesired stereoisomer

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

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

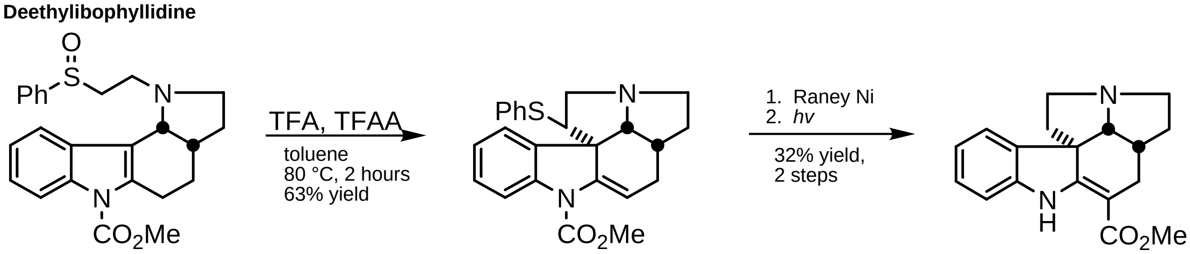
Spirotryprostatin A



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

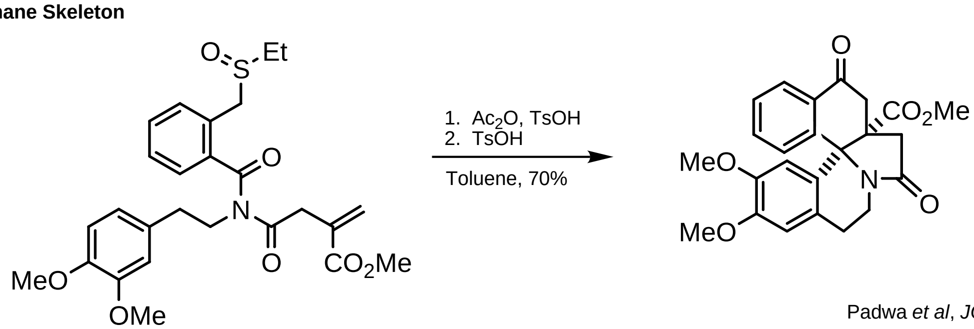
Pummerer Rearrangement

Deethylibophyllidine

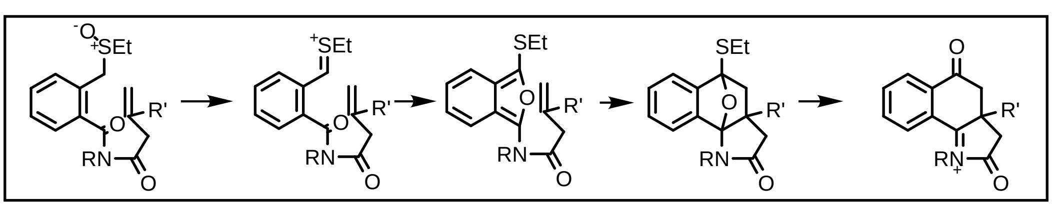


Bonjoch *et al*, *JOC*, **1996**, 61, 7107

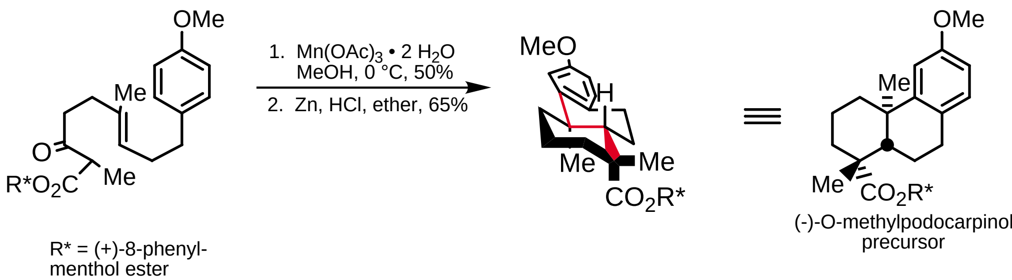
Erythrinane Skeleton



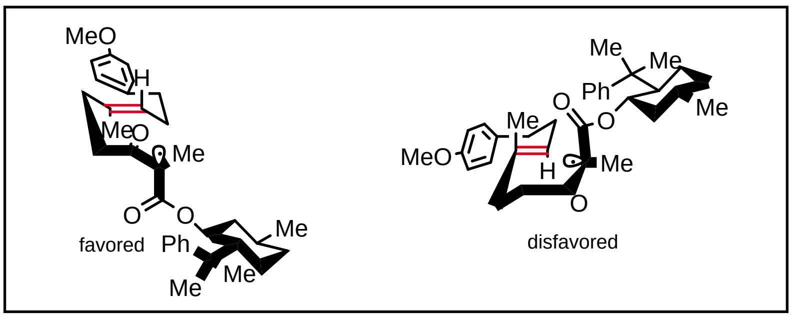
Padwa *et al*, *JOC*, **1996**, 61, 4888



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