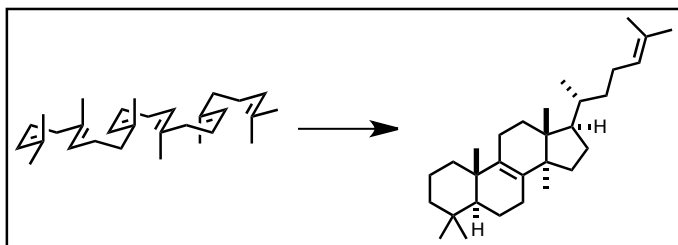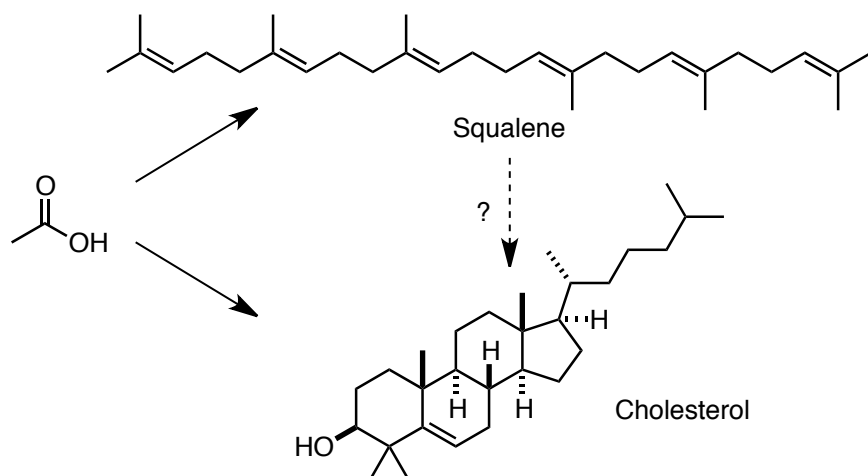# Polyene Cyclizations In Nature And Synthetic Organic Chemistry
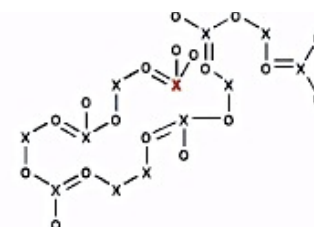
Burns Group Meeting
1/23/2014

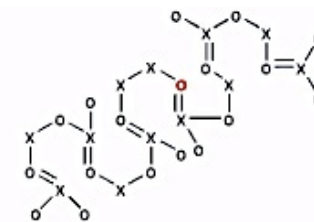## Discovery of Polyene Cyclizations in Nature

- In 1945, Bloch and Rittenberg conducted isotope labeling studies in mice and discovered that both squalene and cholesterol derive from acetic acid
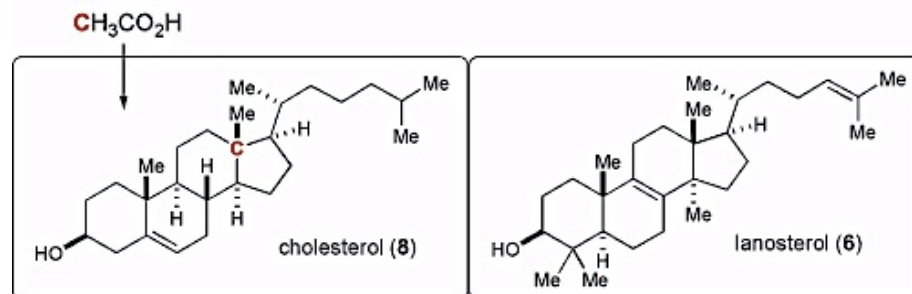

Squalene

Cholesterol

- Before 1950, steroids were commonly believed to come from fatty acids
- Based on their discovery however, Bloch and Rittenberg hypothesized that squalene might be the actual precursor
- Robert Robinson had formulated a proposal on the synthesis of cholesterol from squalene in 1936 already, but the isotope labeling studies disproved his proposal
- Woodward eventually proposed that squalene lines up in a serpentine-like fashion and does a series of methyl and hydride shifts after cyclization (see figure below, x = acetate carboxyl, o = acetate methyl)
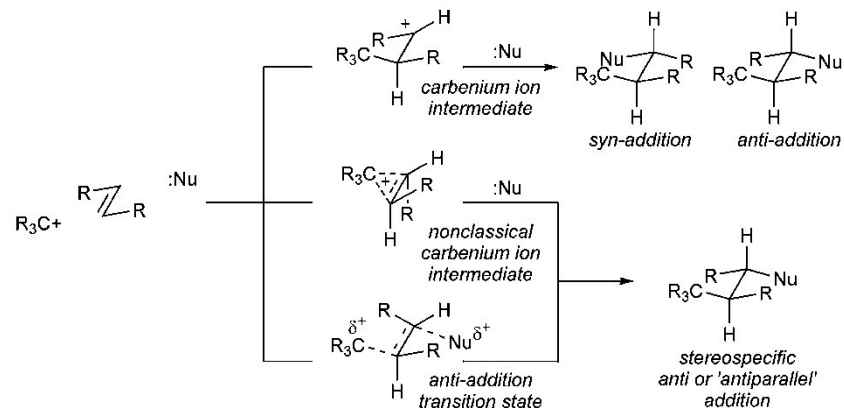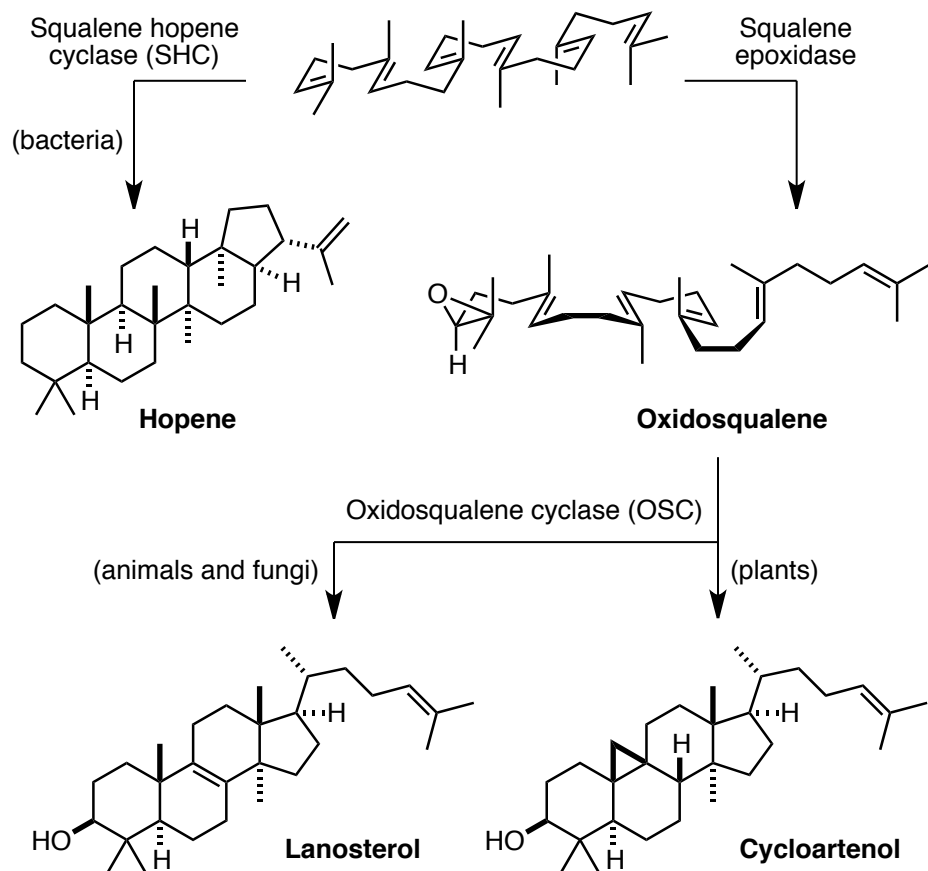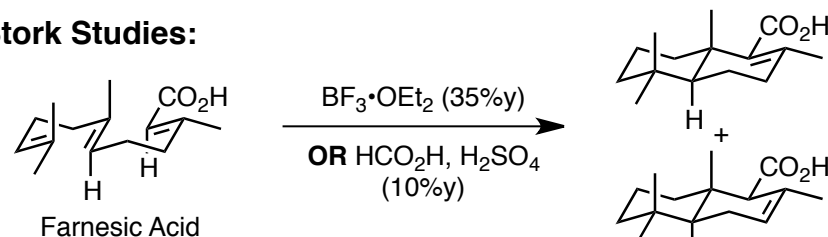

Robinson proposal

Bloch-Woodward proposal

CH_3CO_2H

cholesterol (**8**)

lanosterol (**6**)

Bloch, K.; Rittenberg, D. J. Biol. Chem. 1945, *159*, 45-58

Johnston et. al. Chem. Rev. 2005, *105*, 4730-4756

Enzymatic Pathways For Squalene Cyclization

Squalene hopene cyclase (SHC)

(bacteria)

Hopene

Squalene epoxidase

Oxidosqualene

Oxidosqualene cyclase (OSC)

(animals and fungi)

(plants)

HO

Lanosterol

HO

Cycloartenol

carbenium ion intermediate

:Nu

syn-addition   *anti-addition*

nonclassical carbenium ion intermediate

:Nu

anti-addition transition state

stereospecific anti or 'antiparallel' addition

Stork Studies:

CO_2H

$BF_3 \cdot OEt_2$ (35%y)

OR HCO_2H, H_2SO_4 (10%y)

Farnesic Acid

CO_2H

CO_2H
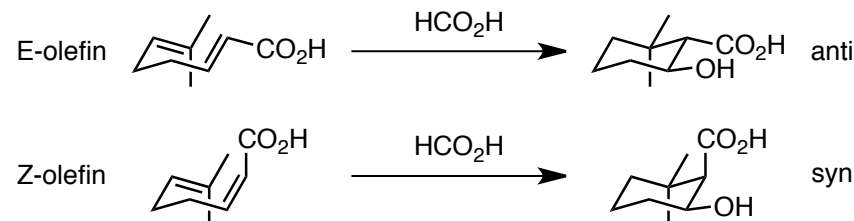
+

- Only products observed are trans-decalins
- Confirms anti-addition hypothesis
- Concerted process, no localized carbocations are formed
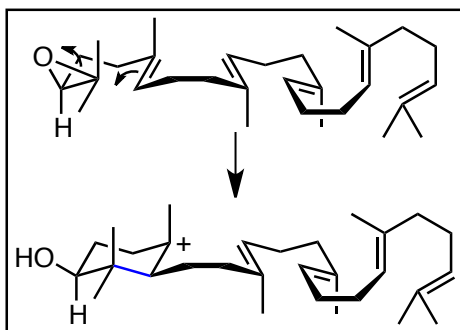
Eschenmoser Studies:

E-olefin CO_2H HCO_2H CO_2H anti
OH

Z-olefin CO_2H HCO_2H CO_2H syn
OH

- Cyclizations occur through chair transition state
- Again, concerted anti-addition is confirmed
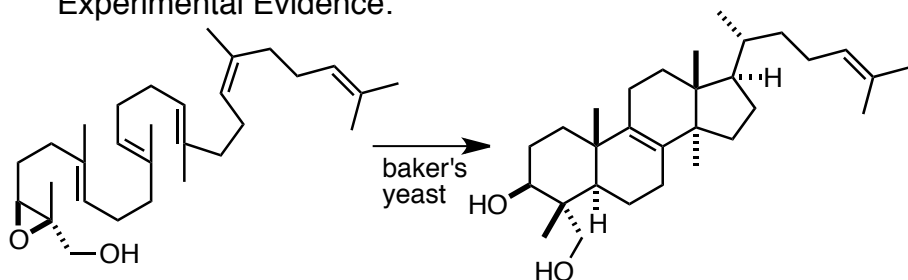
Johnston et. al. Chem. Rev. 2005, *105*, 4730-4756
Stork et. al. J. Am. Chem. Soc. 1955, *77*, 5068
Eschenmoser et. al. Helv. Chim. Acta. 1955, *38*, 222-230

Johnston et. al. Chem. Rev. 2005, *105*, 4730-4756

A-Ring Cyclization:
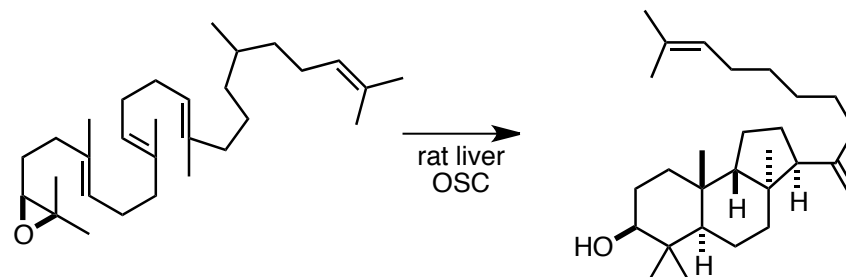

Experimental Evidence:

baker's yeast

- Stereospecific cyclization observed, indicates that trapping of cation is faster than rotation around C2-C3 bond or that the process is concerted
- Influence of substituent R in modified oxidosqualene on rate of cyclization is taken as clear evidence against charge buildup on C2 and instead for a concerted mechanism
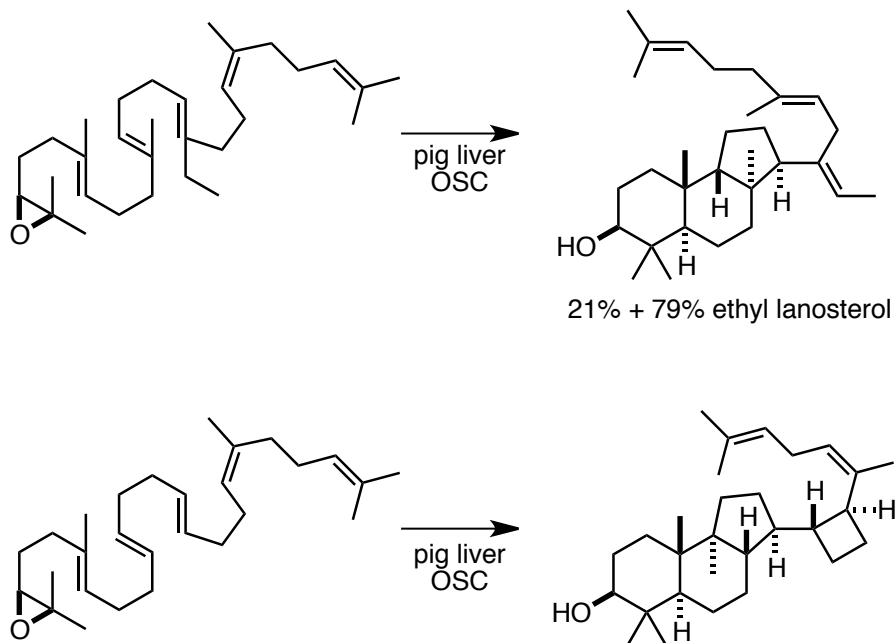

R	Rel. Rates of cyclization
Me	15
Cl	2.4
H	1

Kyler et. al. J. Am. Chem. Soc. 1988, *110*, 4818-4821
Corey et. al. J. Am. Chem. Soc. 1997, *119*, 1277
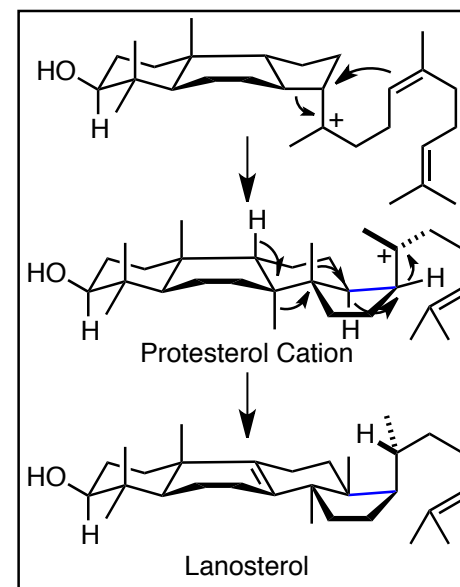
B/C-Ring Cyclization:
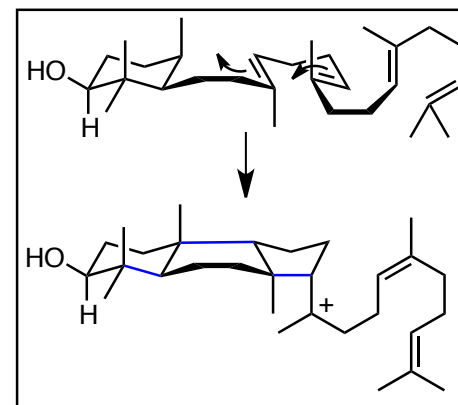
- It is not known whether there is temporal overlap between A and B/C ring formation
- Ring C presents a problem: 6-endo closure creates a secondary carbocation (anti-Markovnikoff addition)
- Evidence for an initial formation of a 5-membered ring and rearrangement to the 6-membered ring is provided by the following experiments:
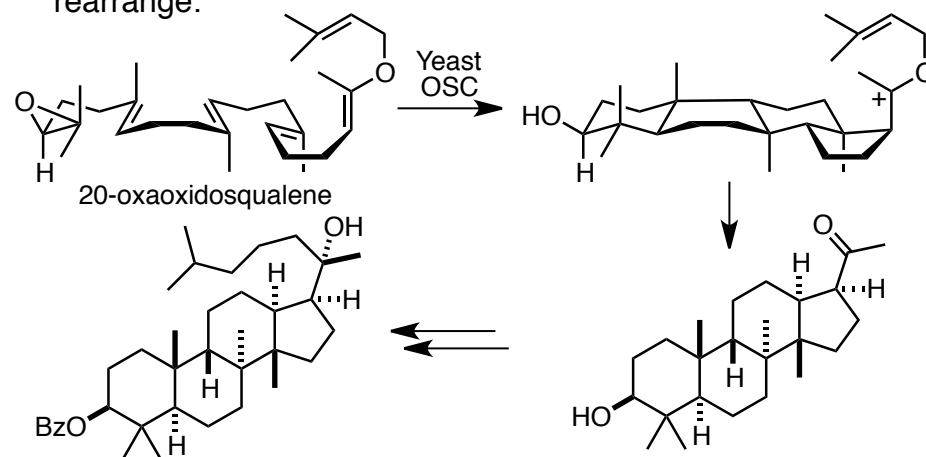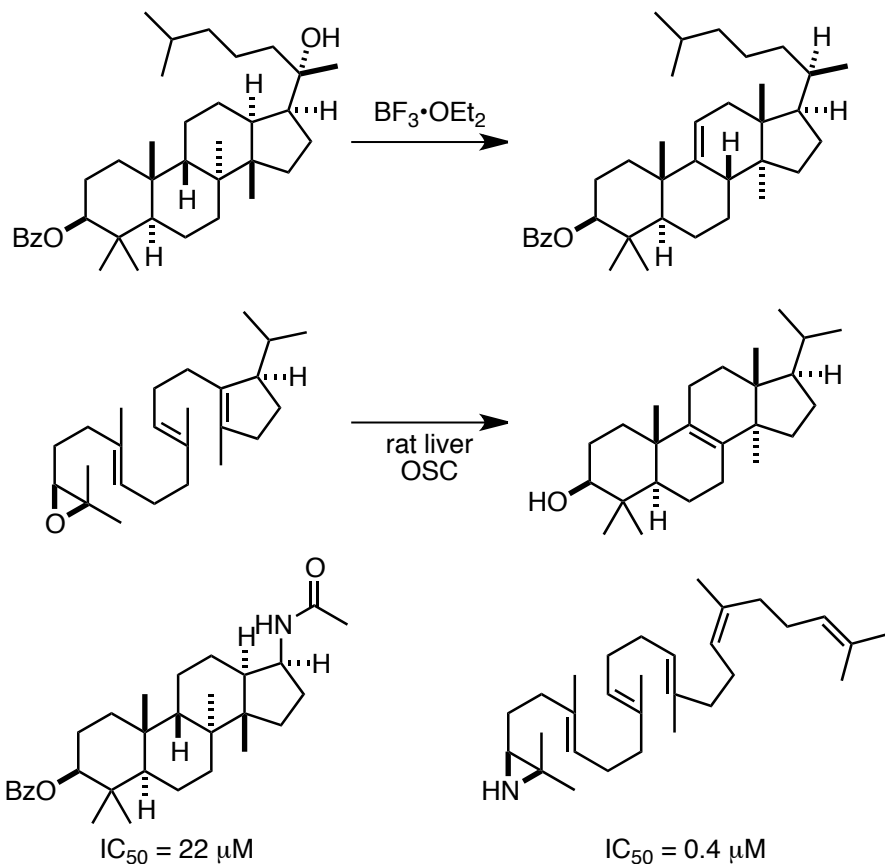

rat liver OSC

Corey et. al. Angew. Chem. Int. Ed. 2000, *39*, 2812-2833

pig liver OSC

21% + 79% ethyl lanosterol

pig liver OSC

D-Ring Cyclization and Elimination:

Protesterol Cation

Lanosterol

- In order to decouple cyclization and rearrangement, Corey et. al. aimed at trapping the protesterol cation before it can rearrange:

Yeast OSC

20-oxaoxidosqualene

Corey et. al. J. Am. Chem. Soc. 1991, *113*, 4025-4026
Corey et. al. Tet. Lett. 1996, *37*, 3287-3290

Corey et. al. Angew. Chem. Int. Ed. 2000, *39*, 2812-2833

IC$_{50}$ = 22 μM

IC$_{50}$ = 0.4 μM

Site-Specific Mutagenesis

- One amino acid residue is altered at a time to observe consequence on protein activity
- First experiments on SHC reported in 1996 by the Poralla group

- Replacement of Asp376 with glutamic acid lowered activity of SHC to 10% of wild type, evidence for the amino acid's role in activating the terminal prenyl group of squalene
- Replacement of His451 with alanine significantly slowed down the cyclization rate. It is believed that His451 bears a positive charge and stabilizes Asp376 during activation of squalene
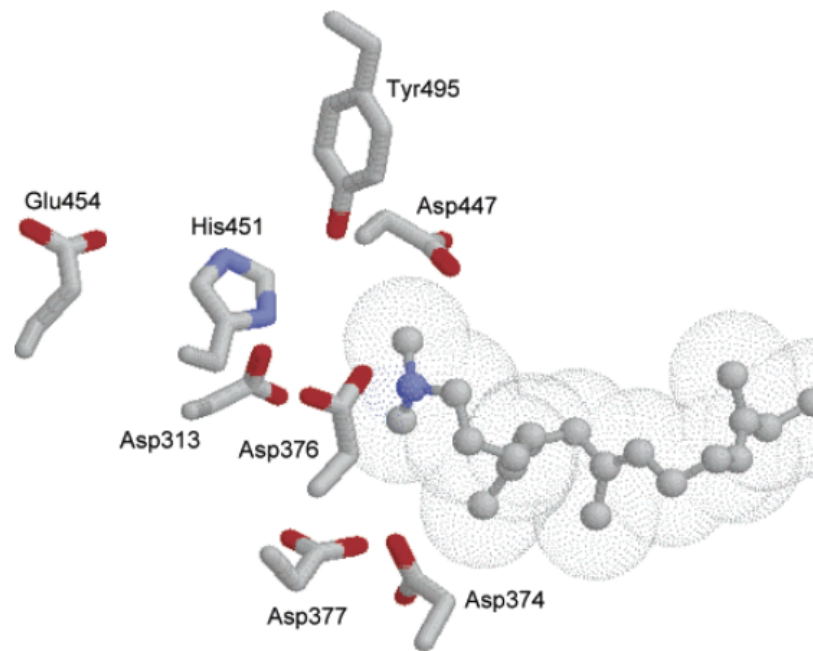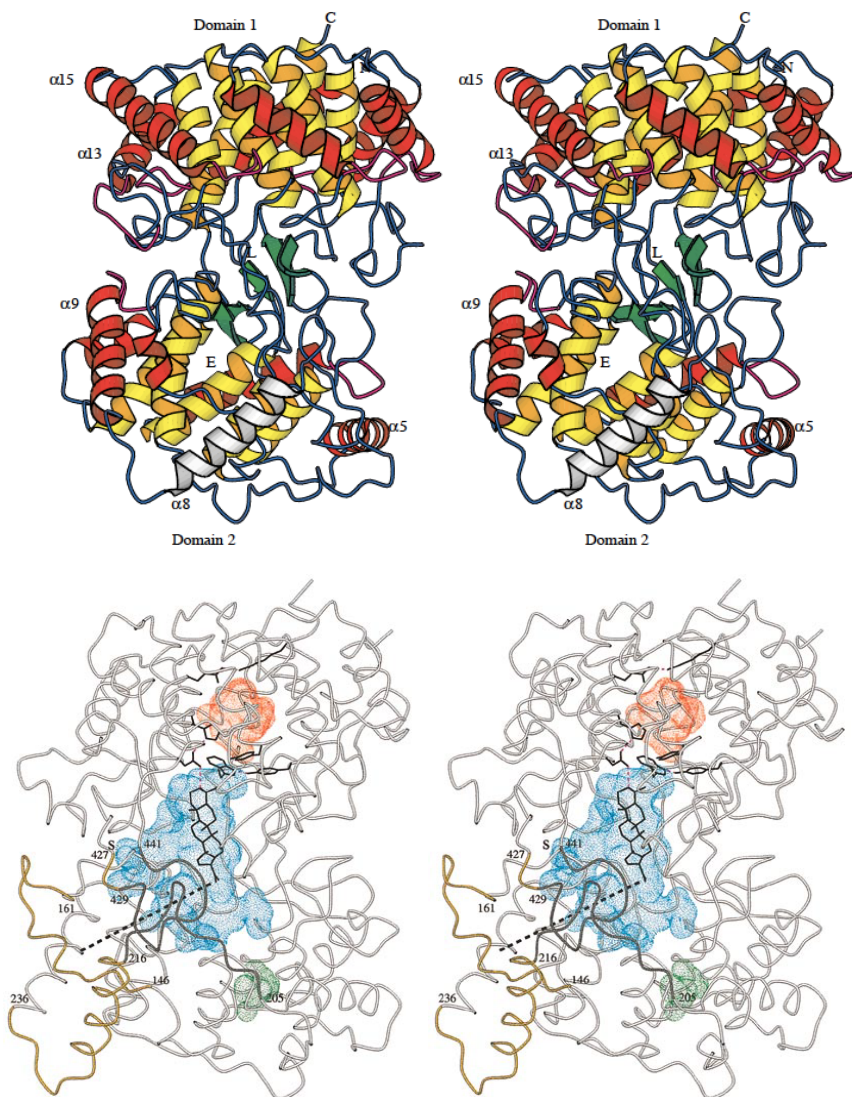
- Rearrangements occur readily, even in nonenzymatic reactions
- Based on the inhibition experiments, the steroid cation prior to rearrangement is only loosely bound to the enzyme
- Enzyme control over the rearrangements is believed to be minimal except for the final deprotonation step, which is very selective and must be rigorously controlled

Corey et. al. J. Am. Chem. Soc. **1991**, *113*, 4025-4026
Corey et. al. Tet. Lett. **1996**, *37*, 3287-3290

Poralla et. al. Eur. J. Biochem. **1996**, *242*, 51-55
Poralla et. al. Tet. Lett. **1999**, *40*, 2121-
Johnston et. al. Chem. Rev. 2005, *105*, 4730-4756

SHC crystal structure (1997)

OSC crystal structure (2004)

- "given the hydrophobic character, water insolubility, and instability of the enzyme, the prospects of such a determination [crystal structure of OSC] in the foreseeable future seem questionable." (Corey, 1997)
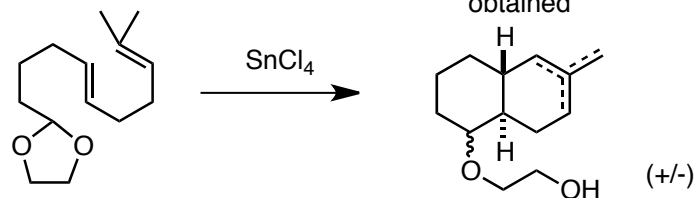

Schulz et. al. Science. **1997**, *277*, 1811-1815
Schulz et. al. J. Mol. Biol. **1999**, *286*, 175-187
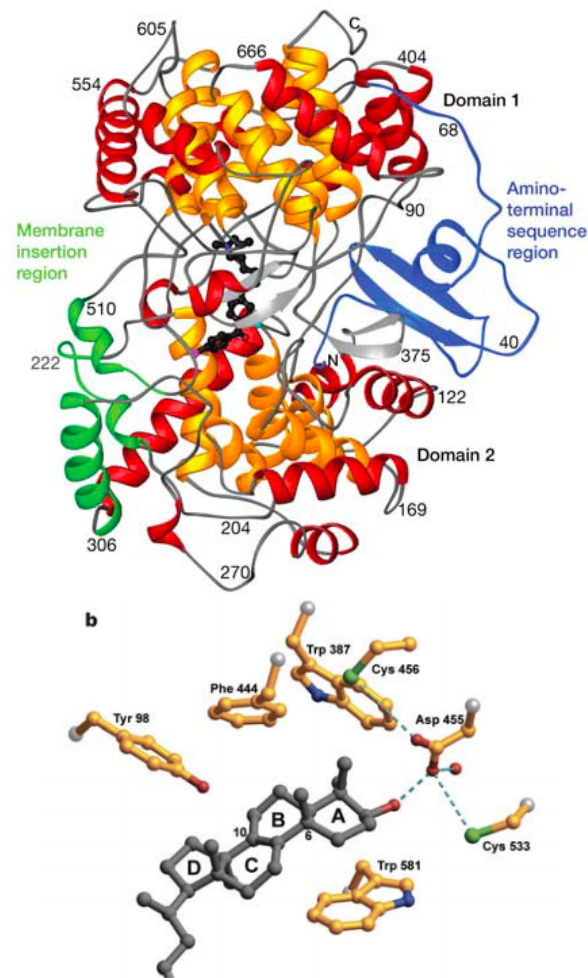
F. Hoffman-La Roche AG. Nature. **2004**, *432*, 118-122
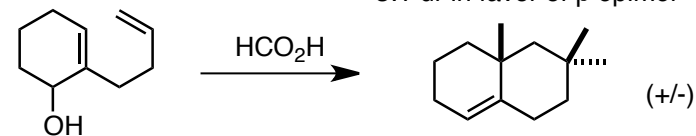Corey et. al. J. Am. Chem. Soc. **1997**, *119*, 1289-1296
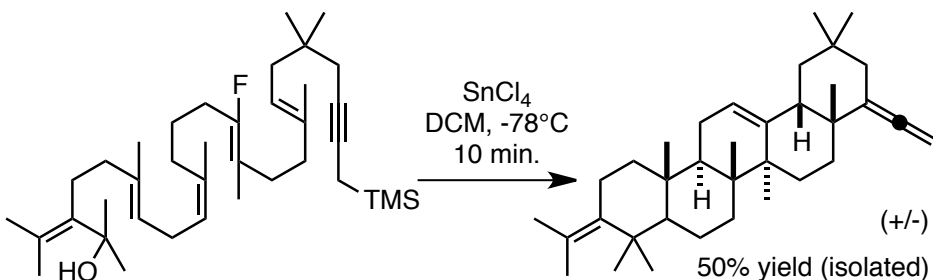
Initiators:
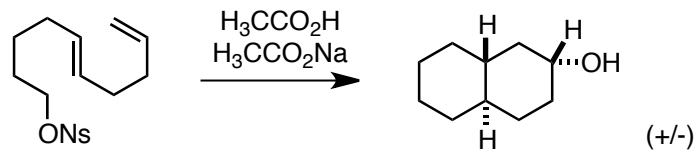
8% yield, no cis-decalin
obtained

(+/-)

91% of crude mixture,
~3:1 dr in favor of β epimer

(+/-)

92% of crude mixture

(+/-)

Carbocation Stabilizers/Acetylenic terminators

50% yield (isolated)

(+/-)

- F-substituent stabilizes the carbocation to bias for
  6-membered ring formation as well as to promote complete
  cyclization of polyene substrate
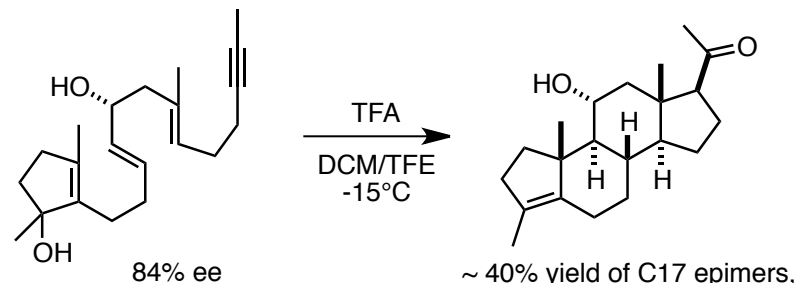
Johnson et. al. J. Am. Chem. Soc. 1964, *86*, 1959-1966
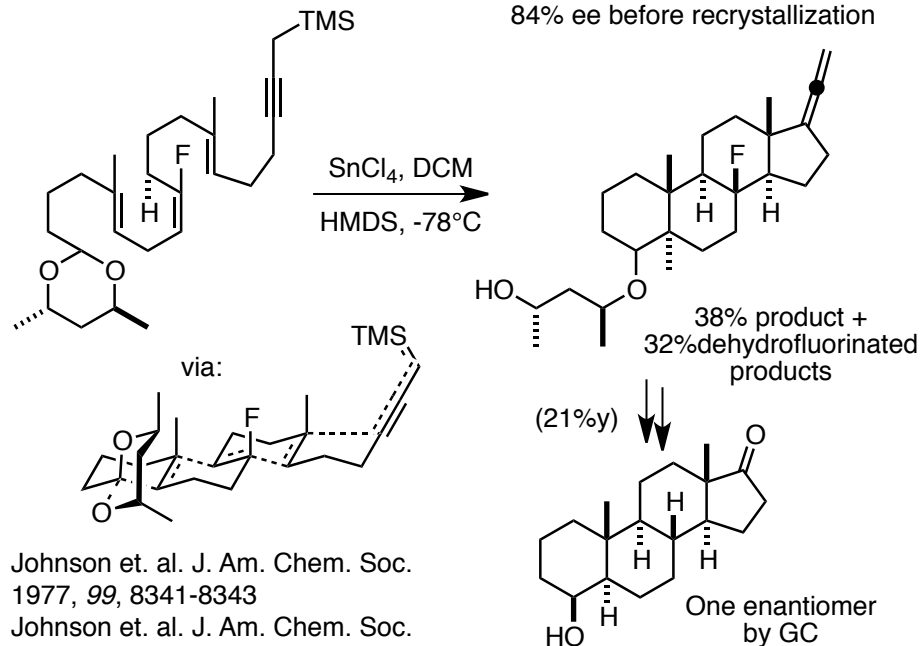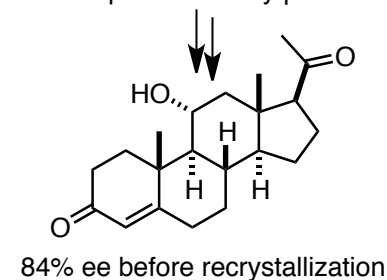Johnson et. al. J. Am. Chem. Soc. 1967, *89*, 170-172
Johnson et. al. J. Am. Chem. Soc. 1964, *86*, 1972-1978
Johnson et. al. J. Org. Chem. 1994, *59*, 2324-2335

First Asymmetric Syntheses of Steroids:

84% ee

~ 40% yield of C17 epimers,
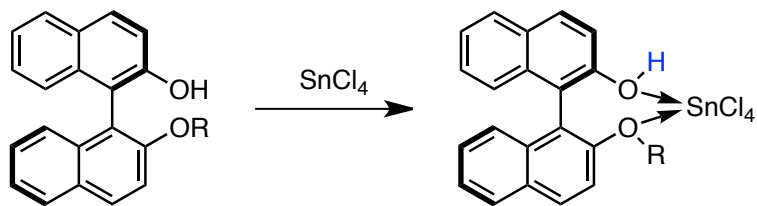"predominantly β"

84% ee before recrystallization

via:

38% product +
32%dehydrofluorinated
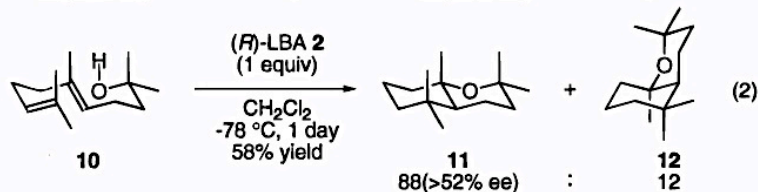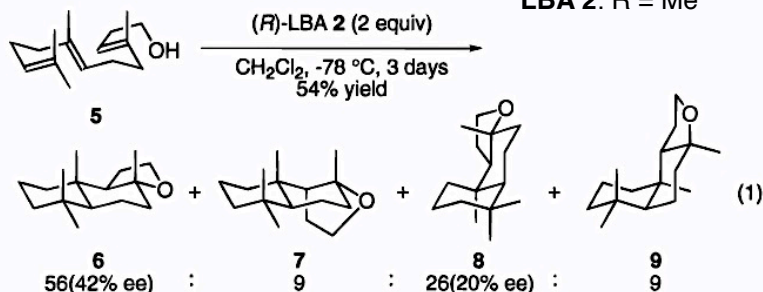products

(21%y)

One enantiomer
by GC

Johnson et. al. J. Am. Chem. Soc.
1977, *99*, 8341-8343
Johnson et. al. J. Am. Chem. Soc.
1993, *115*, 497-504

Yamamoto (1999)

LBA **4**: R = COPh
LBA **2**: R = Me

• Proposed transition state:

favored   *disfavored*

| | **16** | | (R)-LBA **4** | time | **17** | | ratio[c] |
entry	R[1]	R[2]	(equiv)	(day)	yield (%)[a]	ee (%)[b]	**17:18**
1	H	H	1.1	1	98 (79)	69	98:2
2	H	H	0.2	4	98 (76)	77	98:2
3	Br	H	0.2	1	85 (71)	87	89:11
4	Me	H	0.2	4	94	67	97:3
5	OMe	H	1.1	1	84	70	95:5
6	H	Me	1.1	1	80	62	89:11

[a] Unless otherwise noted, GC yields are indicated. Isolated yields are indicated in parentheses. *[b]* Ee values were determined by GC or HPLC analysis of isolated pure product. *[c]* Ratios were determined by GC or HPLC analysis of crude products in which other minor products were included.

• First reported enantioselective polyene cyclization

Corey (2012)
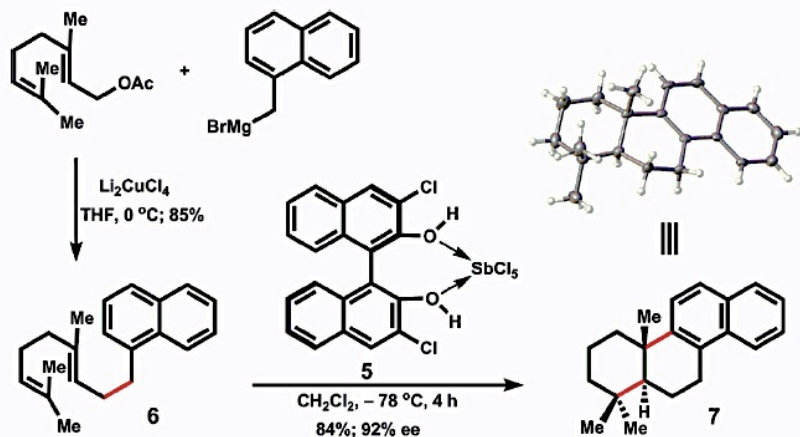
Entry	Substrate	Product	Yield,[a] ee,%[b]
1			80, 91
2			85, 87
3			82, 90 (8:2)[c]

Corey et. al. J. Am. Chem. Soc. **2012**, *134*, 11992-11994

Corey (1995)

62% yield, 90% ee 8:1 selectivity for terminal prenyl group

3 (1 mol%)
K$_2$OsO$_4$ (1 mol%)
K$_3$Fe(CN)$_6$ (3 eq.)
K$_2$CO$_3$ (3 eq.)
^{t}Bu-OH/H$_2$O/Me-C$_6$H$_{11}$, 0°C

(91% yield on farnesyl acetate substrate)

1.) Ms–Cl, pyr DCM
2.) K$_2$CO$_3$, MeOH
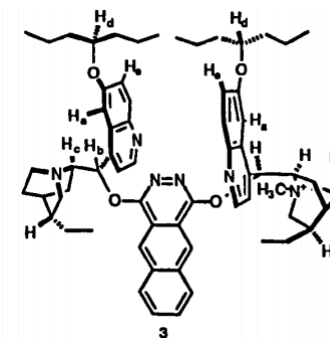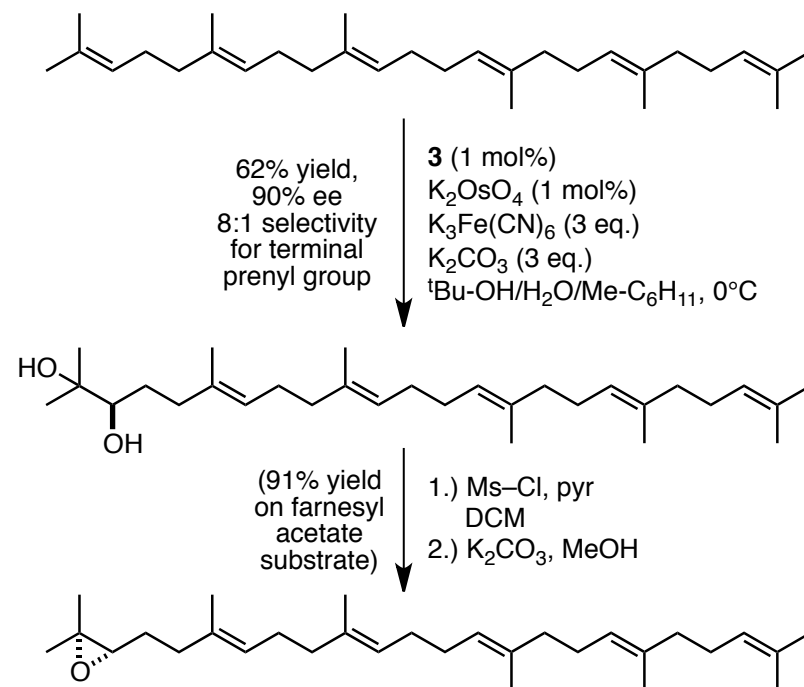
Corey et. al. Tet. Lett. **1995**, *36*, 8741-8744
Corey et. al.

Jacobsen (2010)

3	10%	9% ee
4	12%	25% ee
5	33%	61% ee
6	46%	60% ee
7	52%	87% ee
8	78%	95% ee

- Good correlation between polarizability of arene and %ee, indicative of cation-π interactions

Jacobsen et. al. J. Am. Chem. Soc. **2010**, *132*, 5030-5032
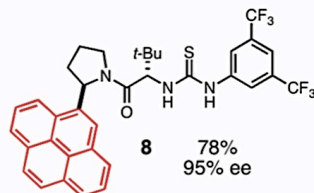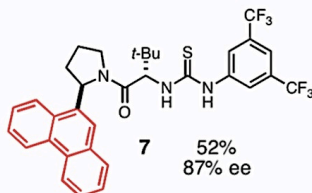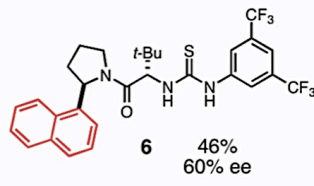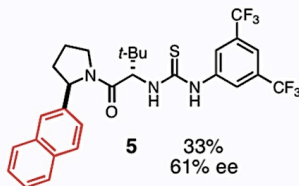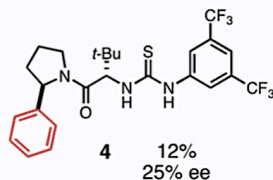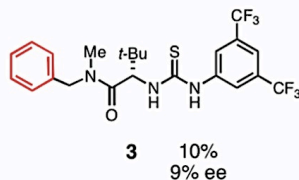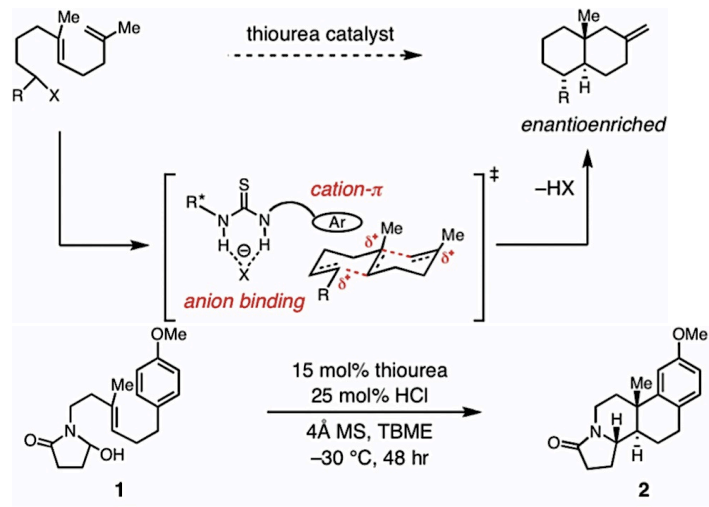
Carreira (2012)
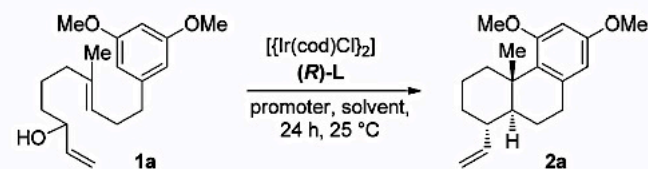
entry	promoter (mol%)	solvent	yield[b]	ee (%)[c]
1	P(O)(OBu)$_2$OH (50)	(CH$_2$Cl)$_2$	42	89
2	Bi(OTf)$_3$ (10)	(CH$_2$Cl)$_2$	71	96
3	Sc(OTf)$_3$ (10)	(CH$_2$Cl)$_2$	91	80
4	In(OTf)$_3$ (10)	(CH$_2$Cl)$_2$	84	88
5	Yb(OTf)$_3$ (10)	(CH$_2$Cl)$_2$	79	94
6	Zn(OTf)$_2$ (10)	(CH$_2$Cl)$_2$	72	>99.5
7	Zn(OTf)$_2$ (10)	dioxane	8	>99.5
8	Zn(OTf)$_2$ (10)	DMF	n.r.	–
9	Zn(OTf)$_2$ (20)	(CH$_2$Cl)$_2$	90	>99.5
10	Zn(OTf)$_2$ (50)	(CH$_2$Cl)$_2$	83	99
11	TfOH (20)	(CH$_2$Cl)$_2$	12	81

[a]Reaction conditions: 1a (0.25 mmol, 1.0 equiv), [{Ir(cod)Cl}$_2$] (4 mol%), (R)-L (16 mol%), promoter, solvent (1.5 mL), 25 °C, 24 h. [b]Yield of 2a after purification by chromatography. [c]Determined by SFC on a chiral stationary phase.

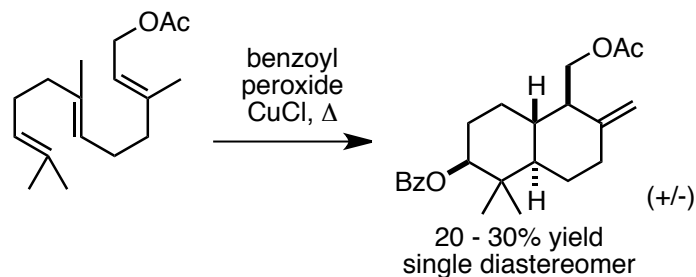## Total Synthesis of (+)-Asperolide C (2013)

d.r. = 9:1, e.r. = 98:2
73% (1 mmol scale)
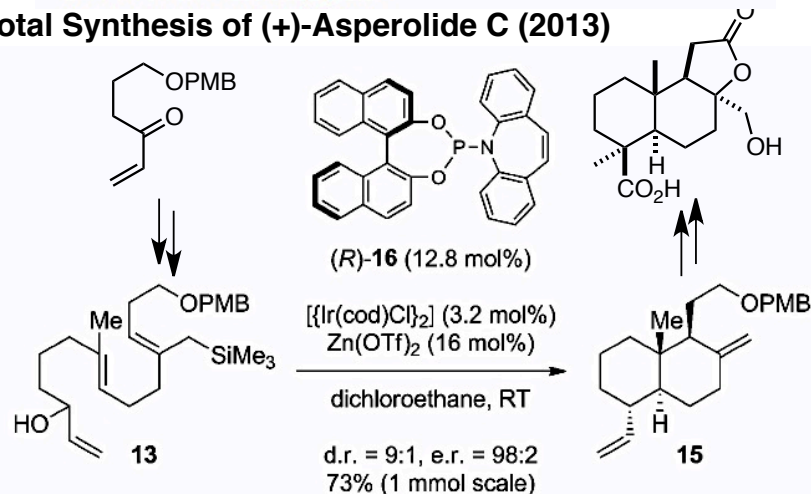
Carreira et. al. J. Am. Chem. Soc. **2012**, *134*, 20276-20278
Carreira et. al. Angew. Chem. Int. Ed. **2013**, *52*, 12166-12169

Breslow (1968)

benzoyl peroxide
CuCl, Δ

20 - 30% yield
single diastereomer
(+/-)

MacMillan (2010)

unsaturated aldehyde **1**

amine catalyst **2**
(Ar = Ph or 1-Naphthyl)

[Ox] | – H₂O, – 1e⁻

3

polycyclic cascade product **5**

[Ox] | – cat. **2**, – H⁺, – 1e⁻

4

catalyst **2**·TFA
Cu(OTf)₂, NaTFA

additive, solvent
23 °C

6 → **7**

entry	catalyst	additive[b]	solvent	yield (%)[c]	ee (%)[d]
1	**2a**, Ar = Ph (20 mol%)	none	MeCN	11	34
2	**2a**, Ar = Ph (20 mol%)	TFA	MeCN	16	35
3[e]	**2a**, Ar = Ph (20 mol%)	TFA	MeCN	42	42
4[e]	**2b**, Ar = 1-Np (20 mol%)	TFA	MeCN	56	74
5[e]	**2b**, Ar = 1-Np (20 mol%)	TFA	*i*-PrCN/DME[f]	54	87
6[e]	**2b**, Ar = 1-Np (30 mol%)	TFA	*i*-PrCN/DME[f]	70	87
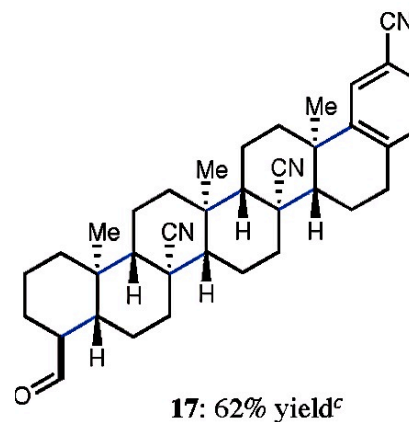
17: 62% yield[c]

6 new C–C bonds

11 contiguous stereocenters

5 all-carbon quaternary stereocenters

92% yield per bond formation

- Vinyl CN substituents needed for polarization of double bonds, resulting in good selectivity for 6-endo-trig over 5-exo-trig

- No %ee reported because of insolubility in HPLC solvents
- > 92%ee's achieved for pentacyclizations
- Record for highest number rings closed in one step

MacMillan et. al. J. Am. Chem. Soc. **2010**, *132*, 5027-5029

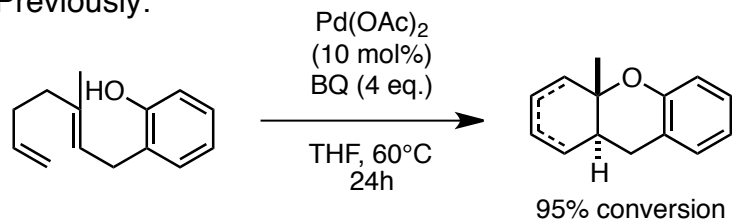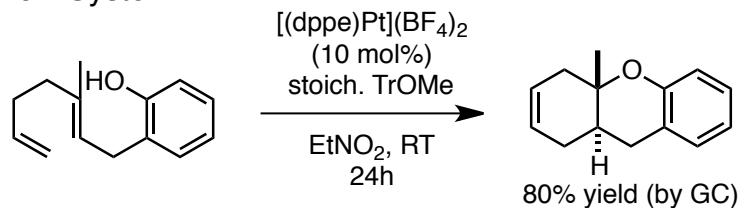MacMillan et. al. J. Am. Chem. Soc. **2010**, *132*, 5027-5029

Gagné (2007)

Previously:

Pd(OAc)$_2$ (10 mol%)
BQ (4 eq.)

THF, 60°C
24h

95% conversion

- β-hydride elimination of Palladium happens unselectively

New System:

[(dppe)Pt](BF$_4$)$_2$ (10 mol%)
stoich. TrOMe

EtNO$_2$, RT
24h

80% yield (by GC)

Proposed Catalytic Cycle:

Gagné (2013)

(S)-(xylyl)-(phanephos) =

Ar =

10 mol%(S)-(xylyl-phanephos)PtI$_2$
25 mol% AgBF$_4$
30 mol% NCC$_6$F$_5$

1.1 equiv TMSOMe
1.1 equiv XeF$_2$
CD$_3$NO$_2$
0 °C
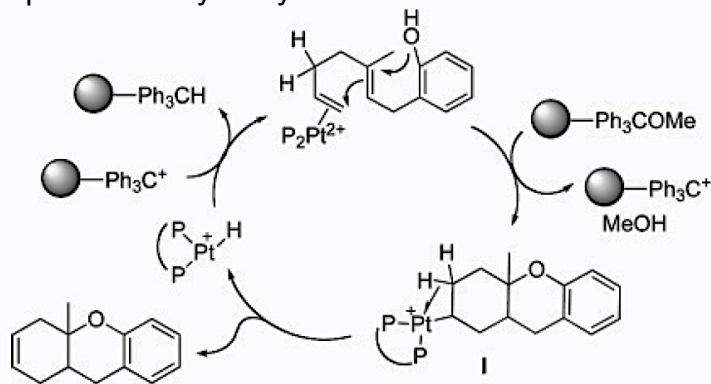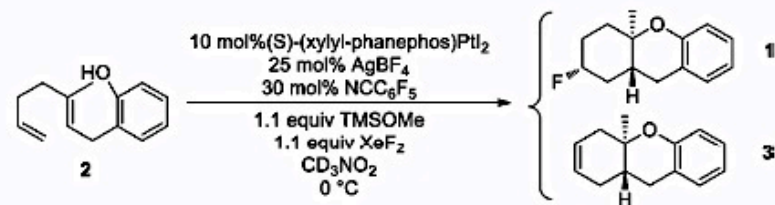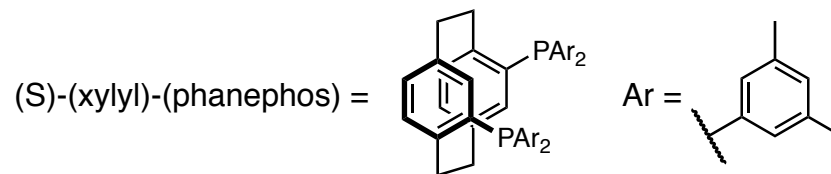
Entry	Polyene	Product	Yield 1 (%ee)[b]	Yield 3[c]
1			67% (75)	14%
2			67% (73)	15%
3[d]			49% (86)	15%[e]
4			56% (81)	16%
5			60% (87)	13%

Gagné et. al. Tetrahedron. **2004**, *60*, 7405-7410
Gagné et. al. J. Am. Chem. Soc. **2007**, *129*, 11880-11881

Gagné et. al. J. Am. Chem. Soc. **2013**, *135*, 628-631

Toste (2010)

Ligand = MeO / PAr₂, MeO / PAr₂ (BIPHEP core)

Ar = 3,5-di-tBu-4-OMe-phenyl (tBu, OMe, tBu)

EtO₂C CO₂Et ... R (alkyne), CO₂H

1a: R = H
1b: R = Me

3% MeO-DTB-BIPHEP(AuCl)₂
3% AgSbF₆
m-xylene, -40°C

[L—Au intermediate with E, E, OH, O, R]

NIS, (R = H)

(1)

EtO₂C, EtO₂C ... O, O, H, R

2a (87% yield, 96% ee)
2b (86% yield, 92% ee, at rt)

EtO₂C, EtO₂C ... O, O, H, I

2c (73% yield, 96% ee)

EtO₂C CO₂Et ... NHTs

4

3% MeO-DTBM-BIPHEP(AuCl)₂
3% AgSbF₆
m-xylene, rt

EtO₂C, EtO₂C ... Ts, N, H

(2)

5 (75% yield, 92% ee)

EtO₂C CO₂Et ... OH, R, X

6a R=X=H
6b R=H, X=OMe
6c R=Me, X=H

5% MeO-DTBM-BIPHEP(AuCl)₂
5% AgSbF₆
m-xylene, rt

EtO₂C ... O, H, R, X

(3)

7a (96% yield, 93% ee)
7b (98% yield, 94% ee)
7c (93% yield, 93% ee)

EtO₂C CO₂Et ... OMe, OMe

8

3% MeO-DTBM-BIPHEP(AuCl)₂
3% AgSbF₆
m-xylene, rt

MeO, OMe, EtO₂C, EtO₂C ... H

(4)

9 (98% yield, 94% ee)
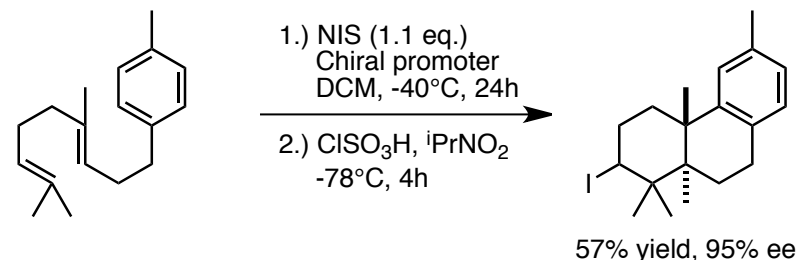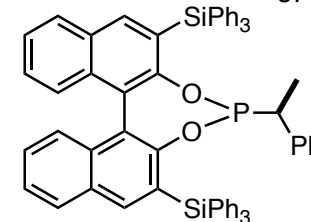
- First reported enantioselective polyene cyclization via alkyne activation

Toste et. al. J. Am. Chem. Soc. **2010**, *132*, 8276-8277

Ishihara (2007)
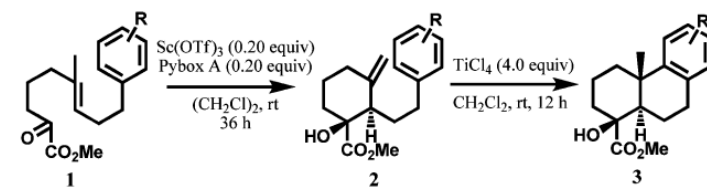
[p-tolyl polyene substrate]

1.) NIS (1.1 eq.)
Chiral promoter
DCM, -40°C, 24h

2.) ClSO₃H, ⁱPrNO₂
-78°C, 4h

[tricyclic product with I]

57% yield, 95% ee

Chiral Promoter: [BINOL-derived phosphoramidite with SiPh₃, O, P, Ph, SiPh₃]

Loh (2010)

[substrate 1 with R, CO₂Me]

Sc(OTf)₃ (0.20 equiv)
Pybox A (0.20 equiv)
(CH₂Cl)₂, rt
36 h

[product 2 with R, HO, H, CO₂Me]

TiCl₄ (4.0 equiv)
CH₂Cl₂, rt, 12 h

[product 3 with R, HO, H, CO₂Me]

1 → **2** → **3**

Entry	R	Substrate	2 Yield[b,c] (%)	2 Ee[d] (%)	3 Yield[b,c] (%)	3 Ee[d] (%)
1	2-OMe	**1**	87	95	85	93
2	4-OMe	**1a**	81	92	75	86
3	—	**1b**	60	93	90	88
4	**4**-Cl	**1c**	83	91	53[e]	87

[Ligand A: bis(indanyl) Pybox structure]

Ligand **A**
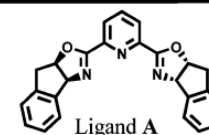
Ishihara et. al. Nature. **2007**, *445*, 900-903
Loh et. al. J. Am. Chem. Soc. **2010**, *132*, 10242-10244