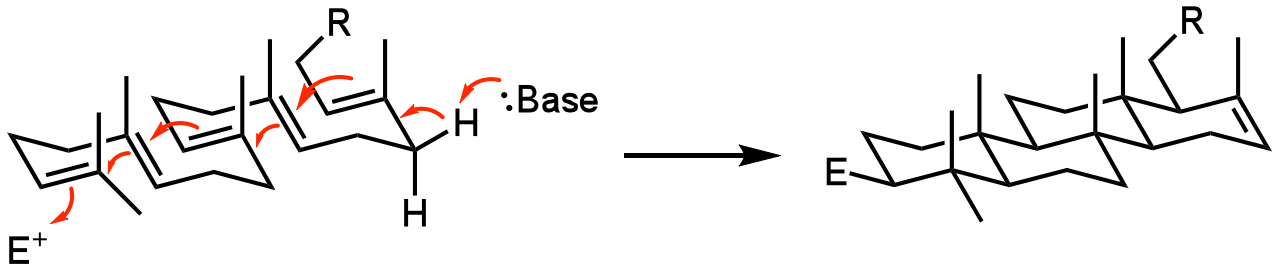
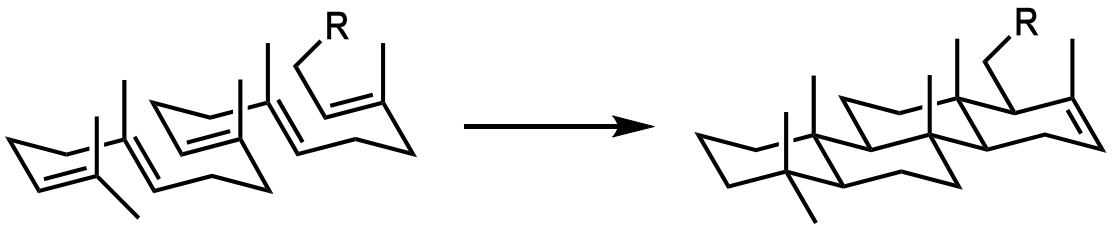
Biomimetic Polyene Cyclization *via* Electrophilic Activation of the Terminal Double Bond



Munmun Mukherjee
Michigan State University
January 16, 2008

Polyene Cyclizations



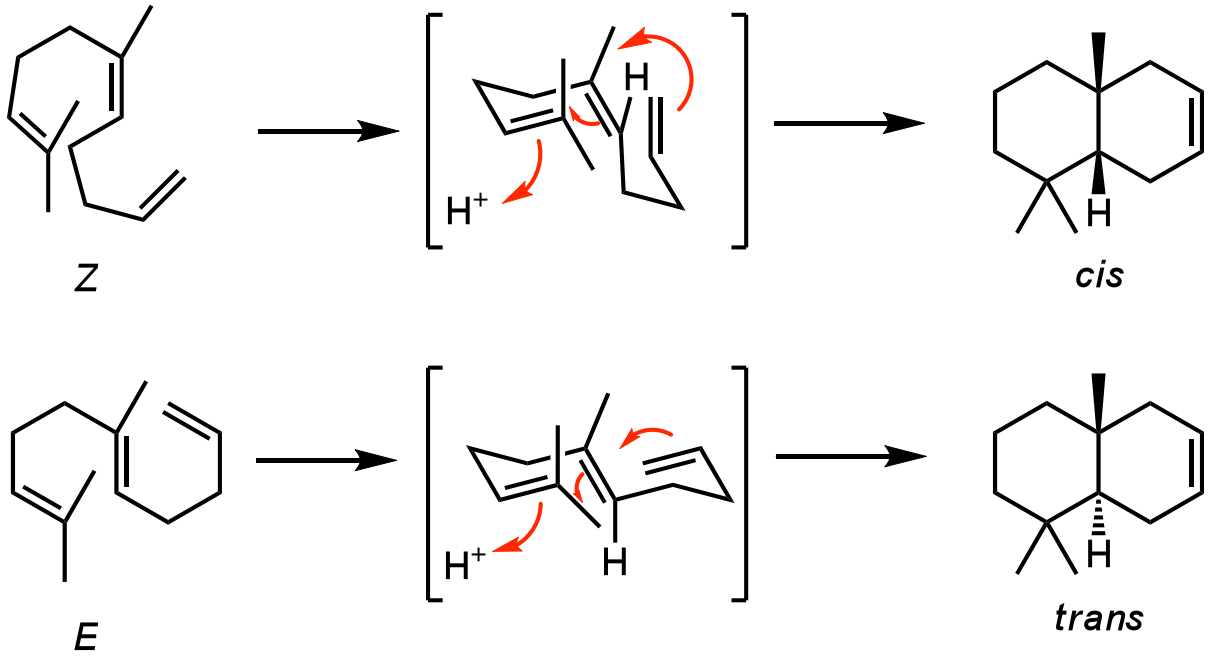
polyprenoids polycyclic systems

Definition: Cascade cyclization of multiple double bonds in an acyclic system which results in the formation of polycyclic compounds

- ❖ Simultaneous formation of several carbon-carbon bonds in one step reaction
- ❖ Multifaceted Selectivity:
  - ring size, number of rings formed
  - relative and absolute stereocontrol (seven to nine stereocentres formed)
- ❖ Ease of formation of quaternary carbons.

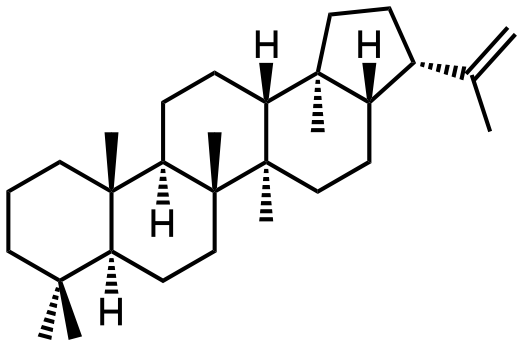
Stork-Eschenmoser Hypothesis

- Polyenes react in defined conformations
- Can predict stereochemistry of cyclization product from starting materials
  - *Z* alkene to *cis* ring fusion
  - *E* alkene to *trans* ring fusion

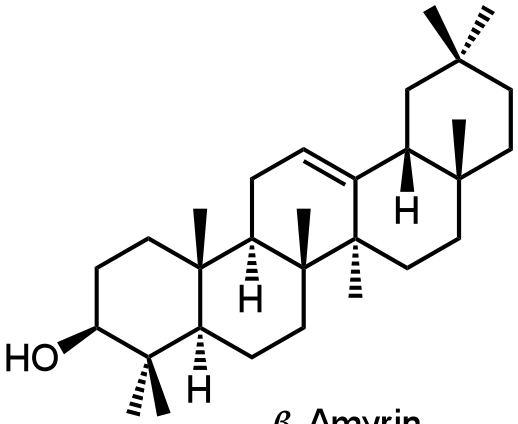


Stork, G.; Burgstrahler, A.W. *J. Am. Chem. Soc.* **1955**, *77*, 5068
Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta.* **1955**, *38*, 1890

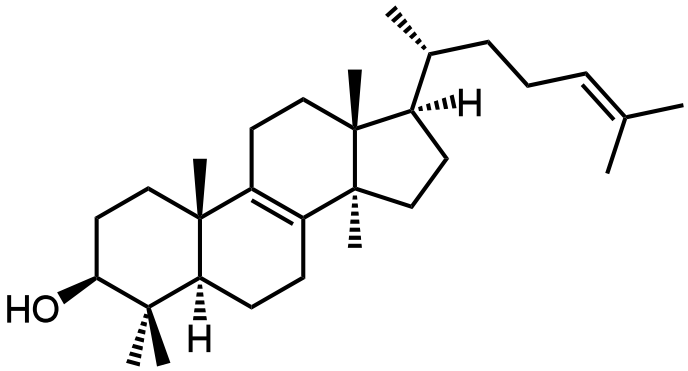
Significance of Biomimetic Synthesis



hopene
(bacteria)



β-Amyrin
(plants)



lanosterol
(animals and fungi)

" The synthesis of such a substrate appears to the chemist particularly difficult, and up till now I have not dared to attempt it"

- Adolf Windaus, 1928 Nobel lecture

" We think that the molecular frameworks of most of natural products arise by intrinsically favorable chemical pathways-favorable enough that the skeleton could have arisen by a non-enzymatic reaction"

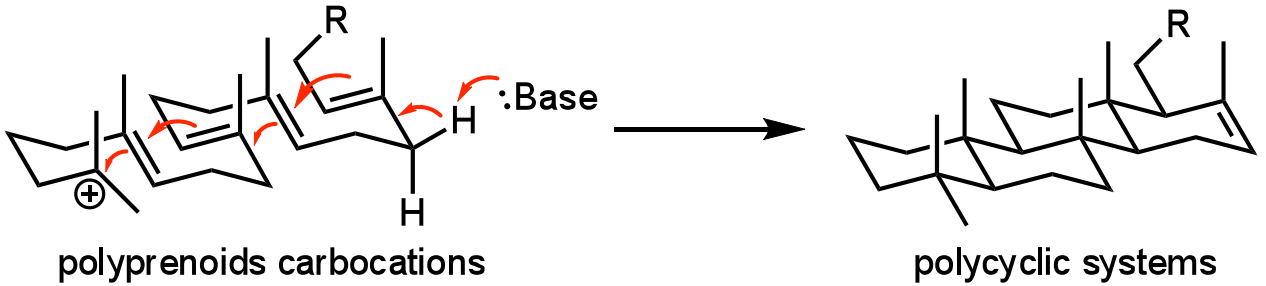
- Clayton Heathcock, 1996

Polyene Cyclizations are ideal reactions for biomimetic approach.

Torre, M. C.; Sierra, M. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 160

Different Approaches Towards Polyene Cyclizations

- Polyene cyclizations occur via a carbocationic intermediate in nature.

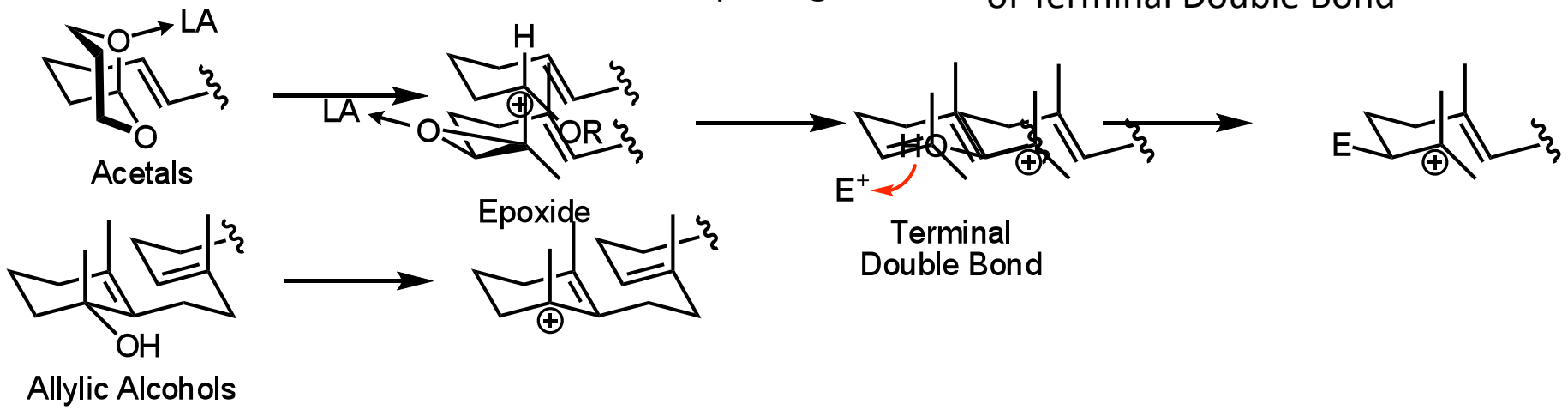


Generation of Carbocation

Leaving Group Elimination

Epoxide Opening

Electrophilic Activation of Terminal Double Bond



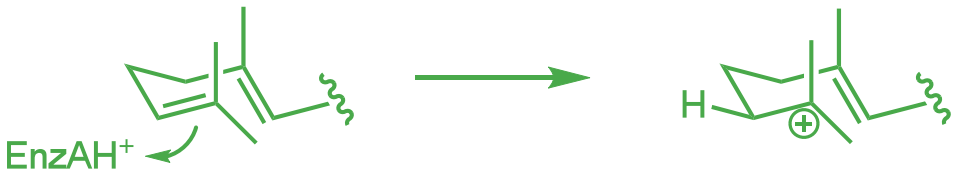
Outline

Activation of Terminal Double Bond

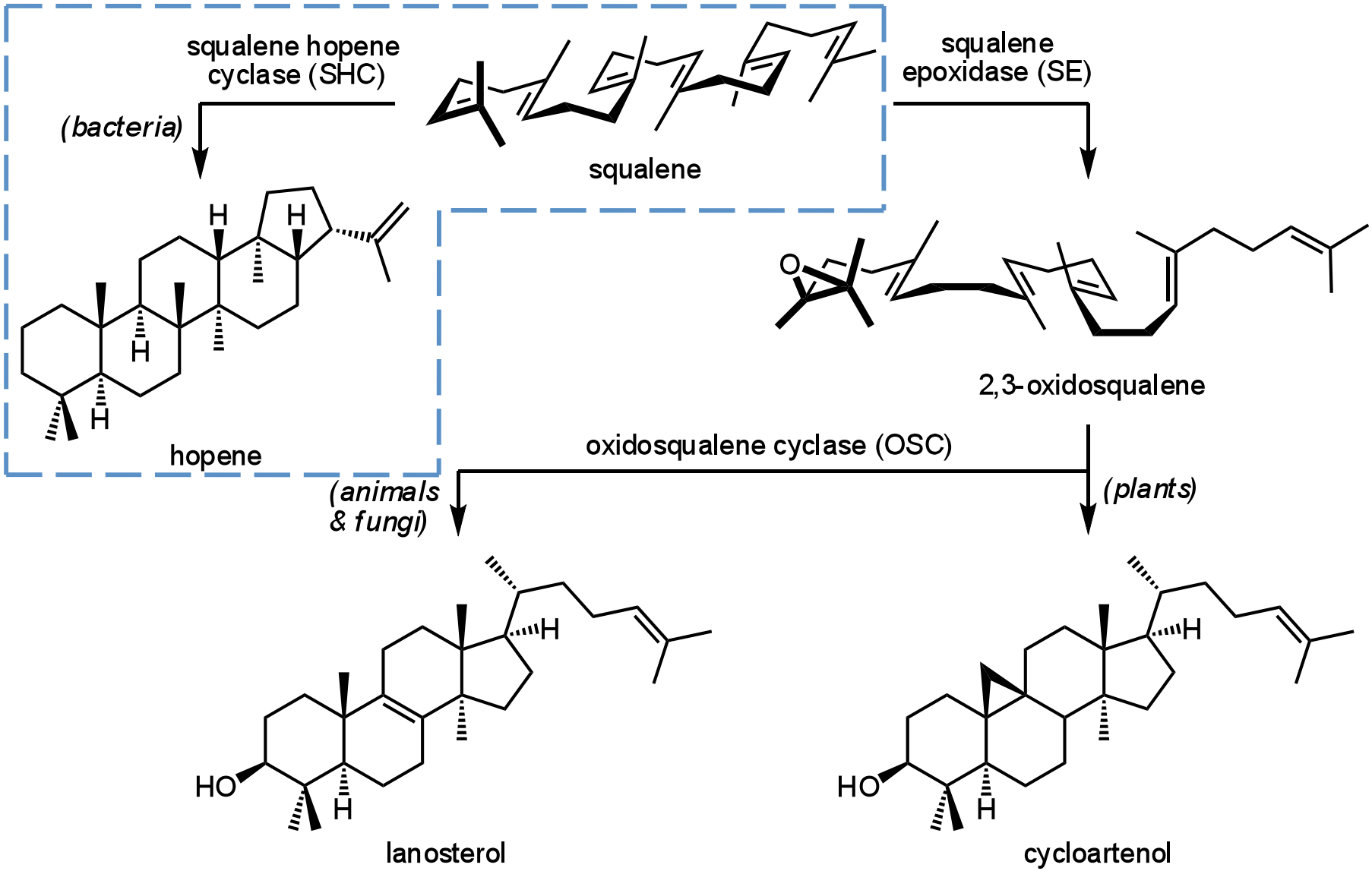
H^+ or X^+

Enzymatic
Polyene Cyclization

Biomimetic
Polyene Cyclization

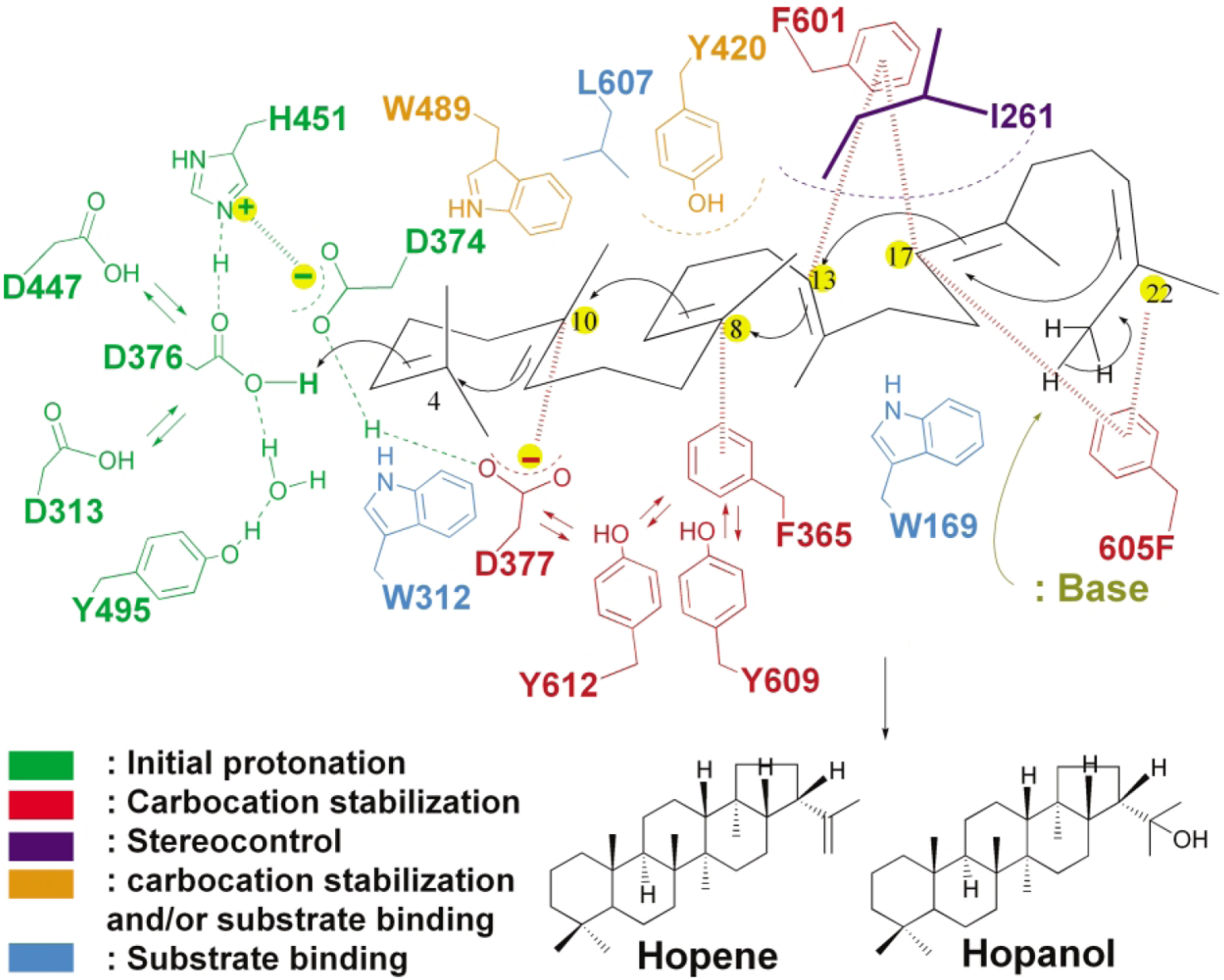


Biosynthesis Pathways with Different Squalene Enzymes



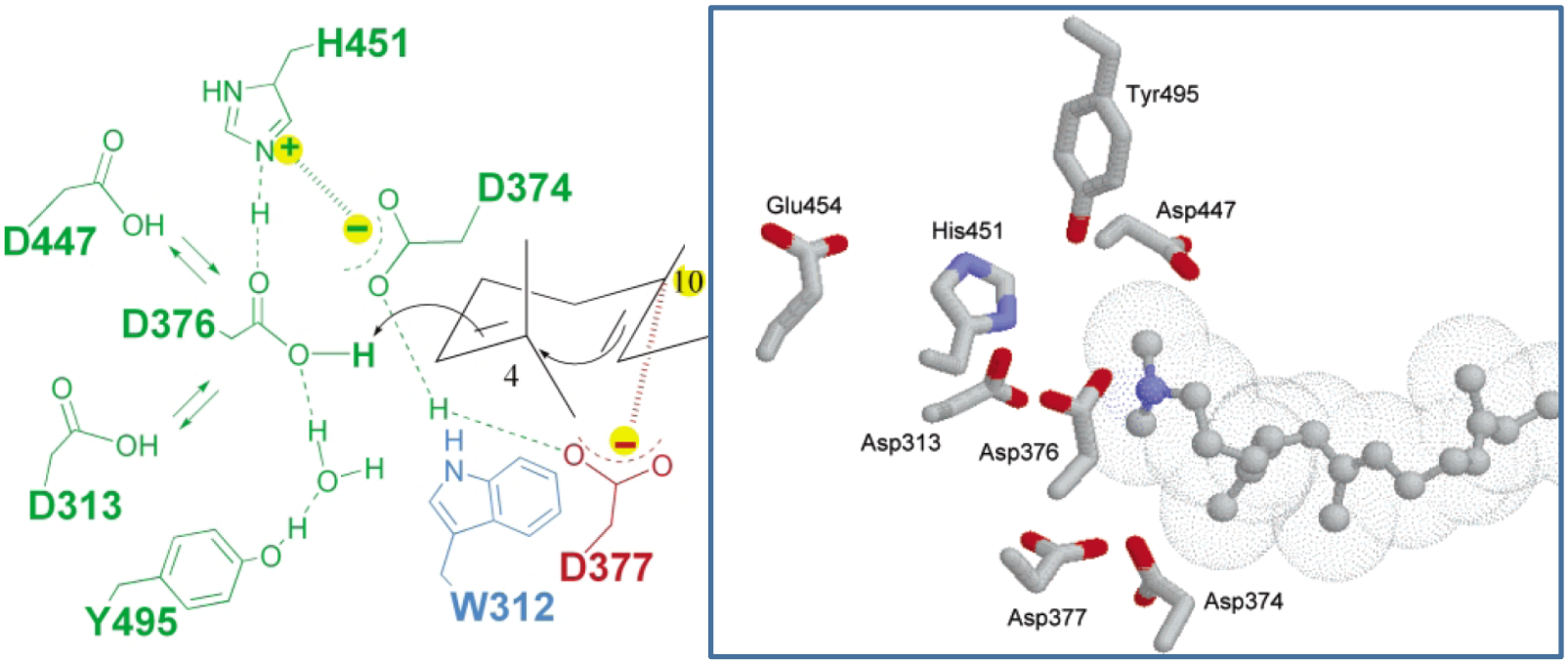
Voser, W.; Mijovic, M. V.; Heusser, H.; Jeger, O.; Ruzicka, L. *Helv. Chim. Acta* **1952**, *35*, 2414

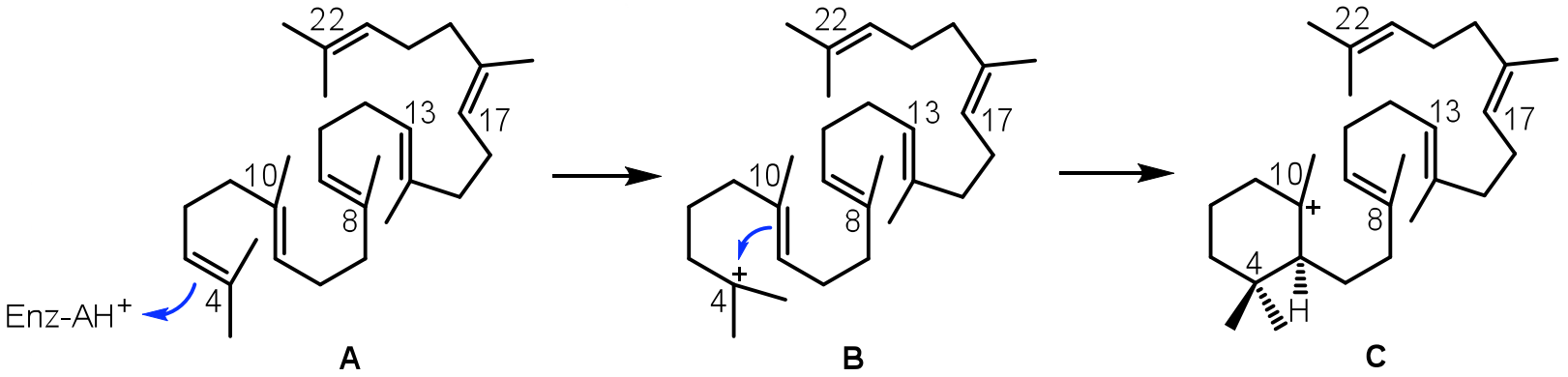
Enzymology: Squalene-Hopene Cyclase



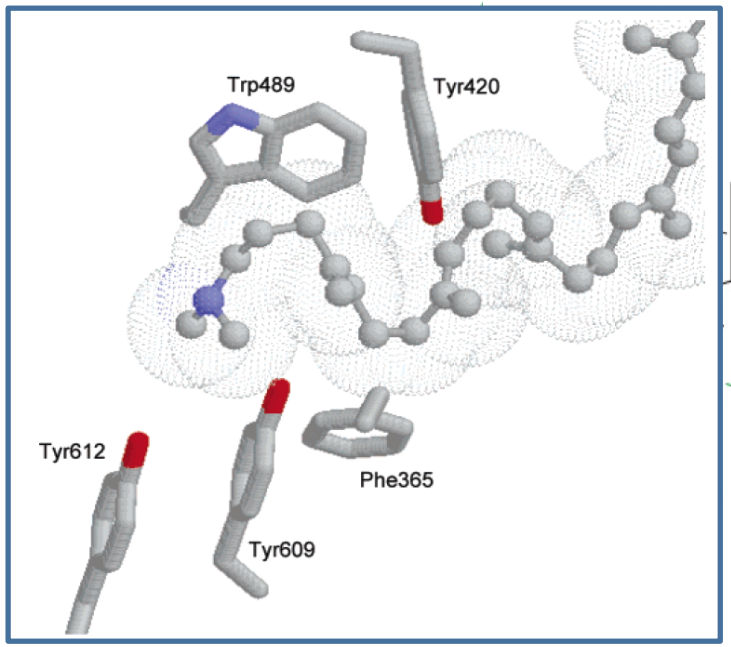
Hoshino, T.; Sato, T. *Chem. Comm.* **2002**, 291

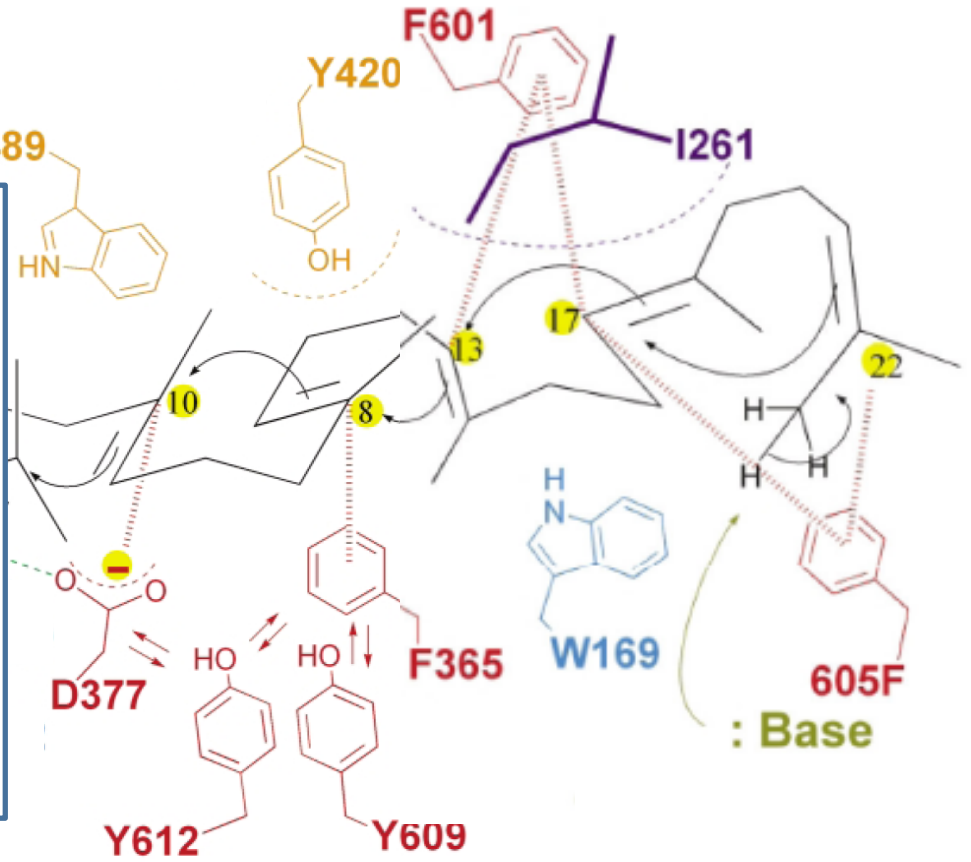
Enzymology: Initial Protonation

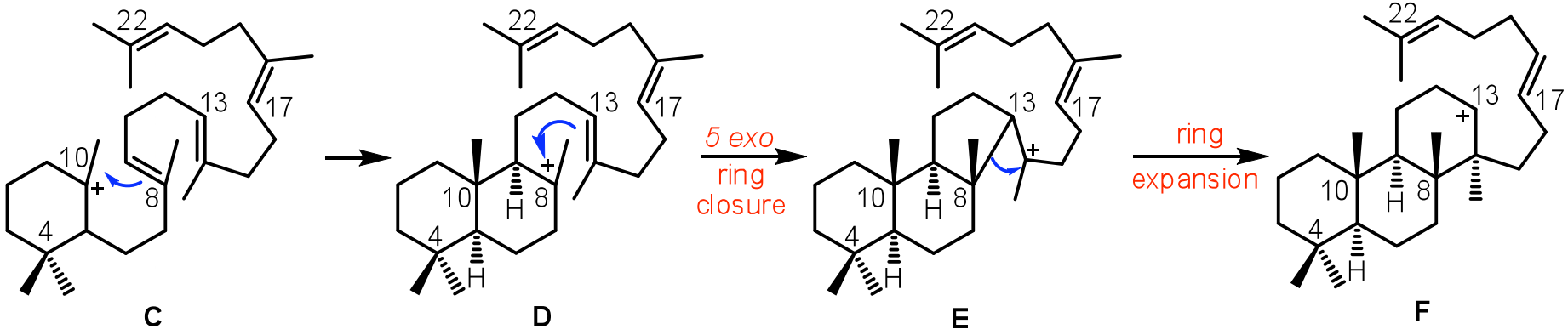




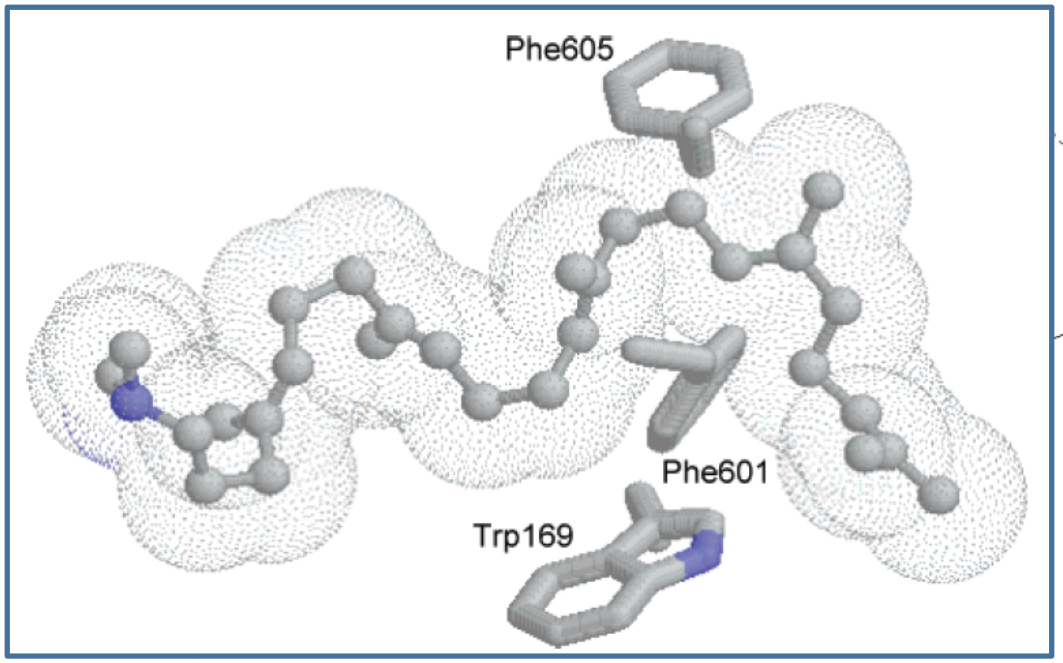
Enzymology: Carbocation Stablization

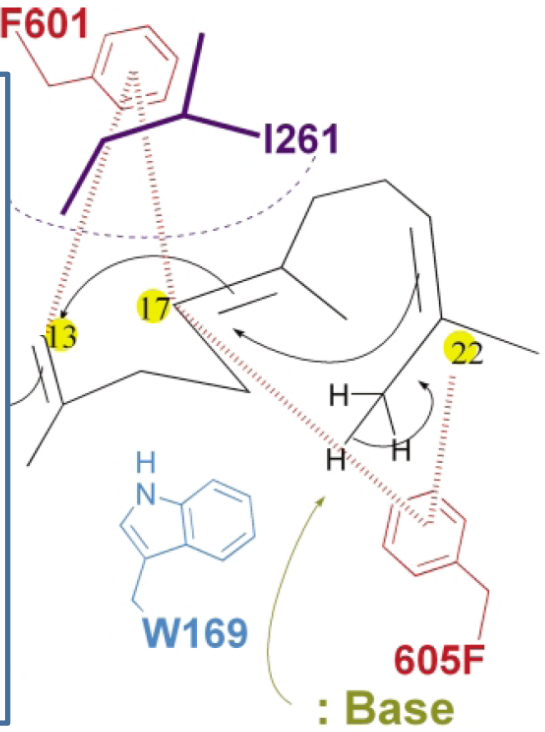


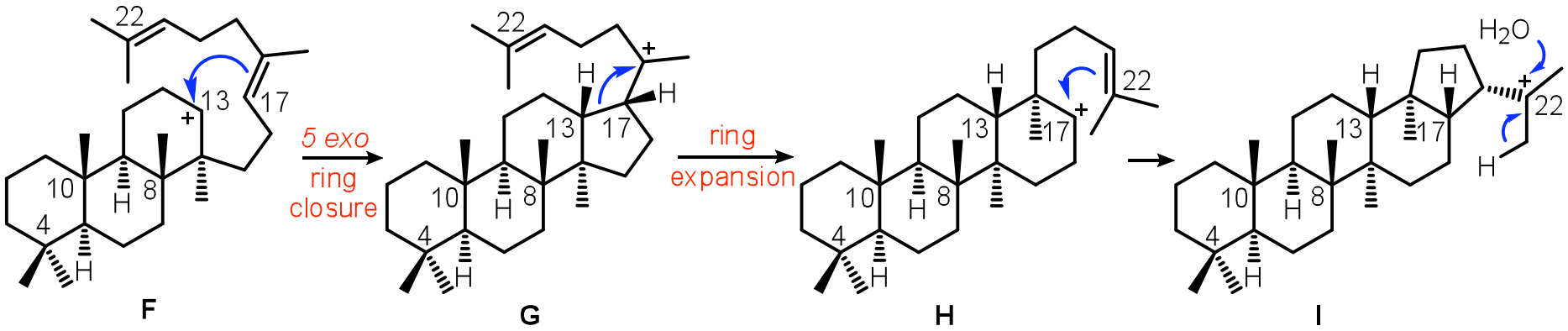




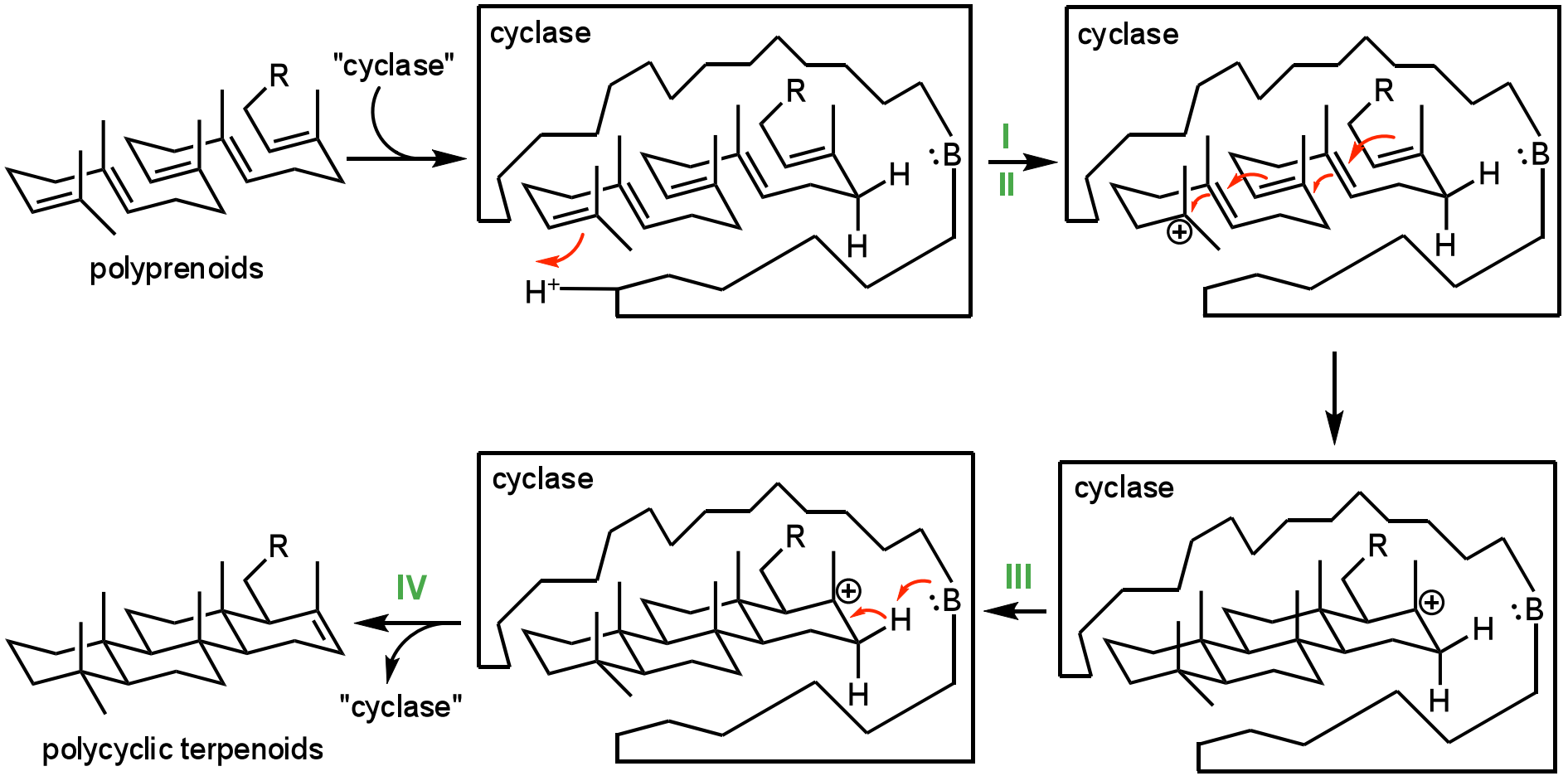
Enzymology: Carbocation Stablization







Inspiration for Biomimetic Synthesis



I : Generation of the carbonium ion

II: Control over the conformation of the substrate

III: Stabilization of intermediates

IV: Quenching of the final carbocation

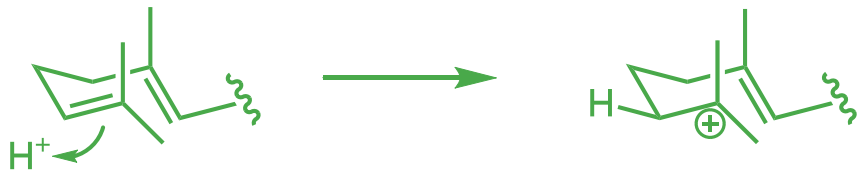
Outline

Activation of Terminal Double Bond

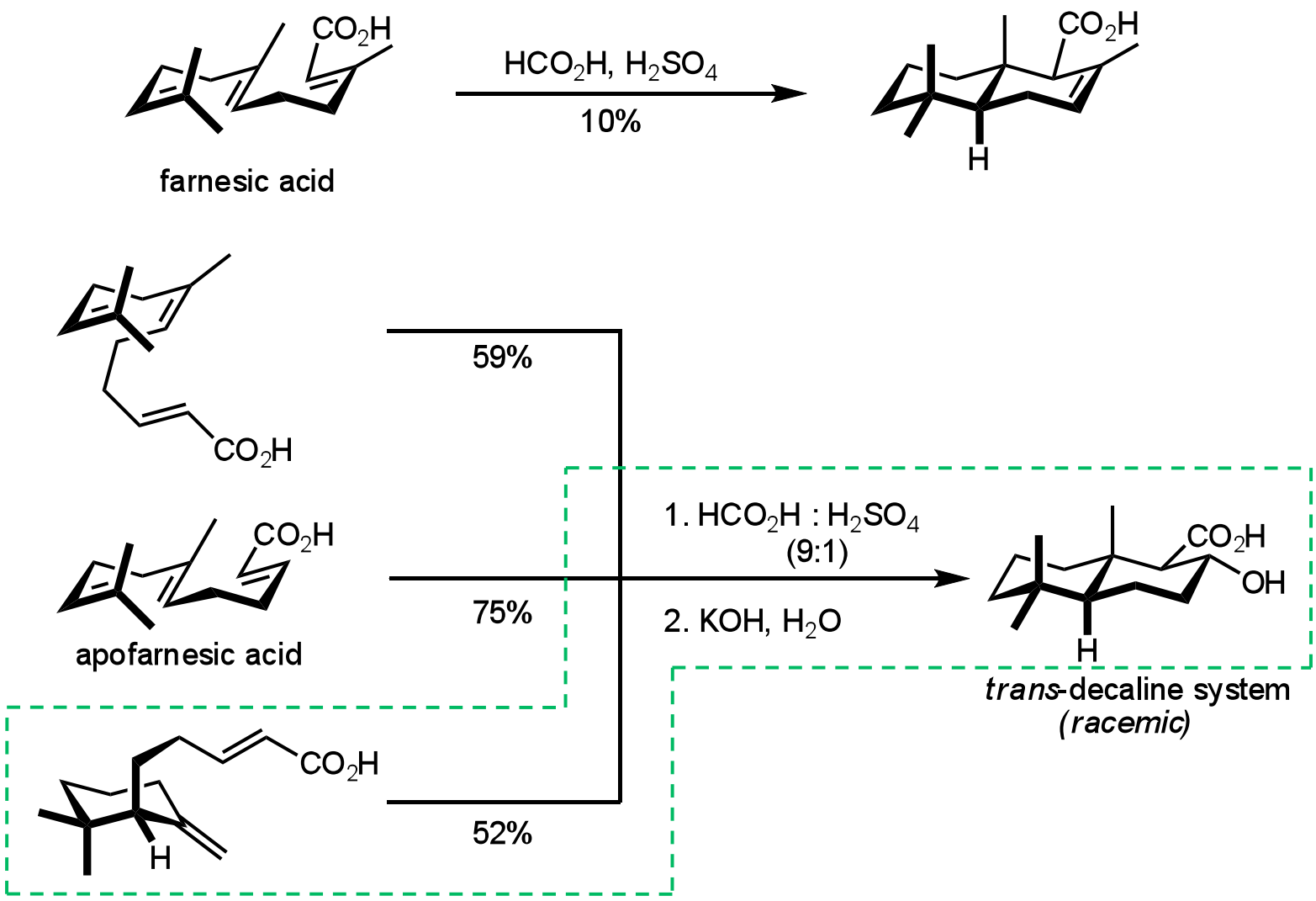
H^+ or X^+

Enzymatic
Polyene Cyclization

Biomimetic
Polyene Cyclization



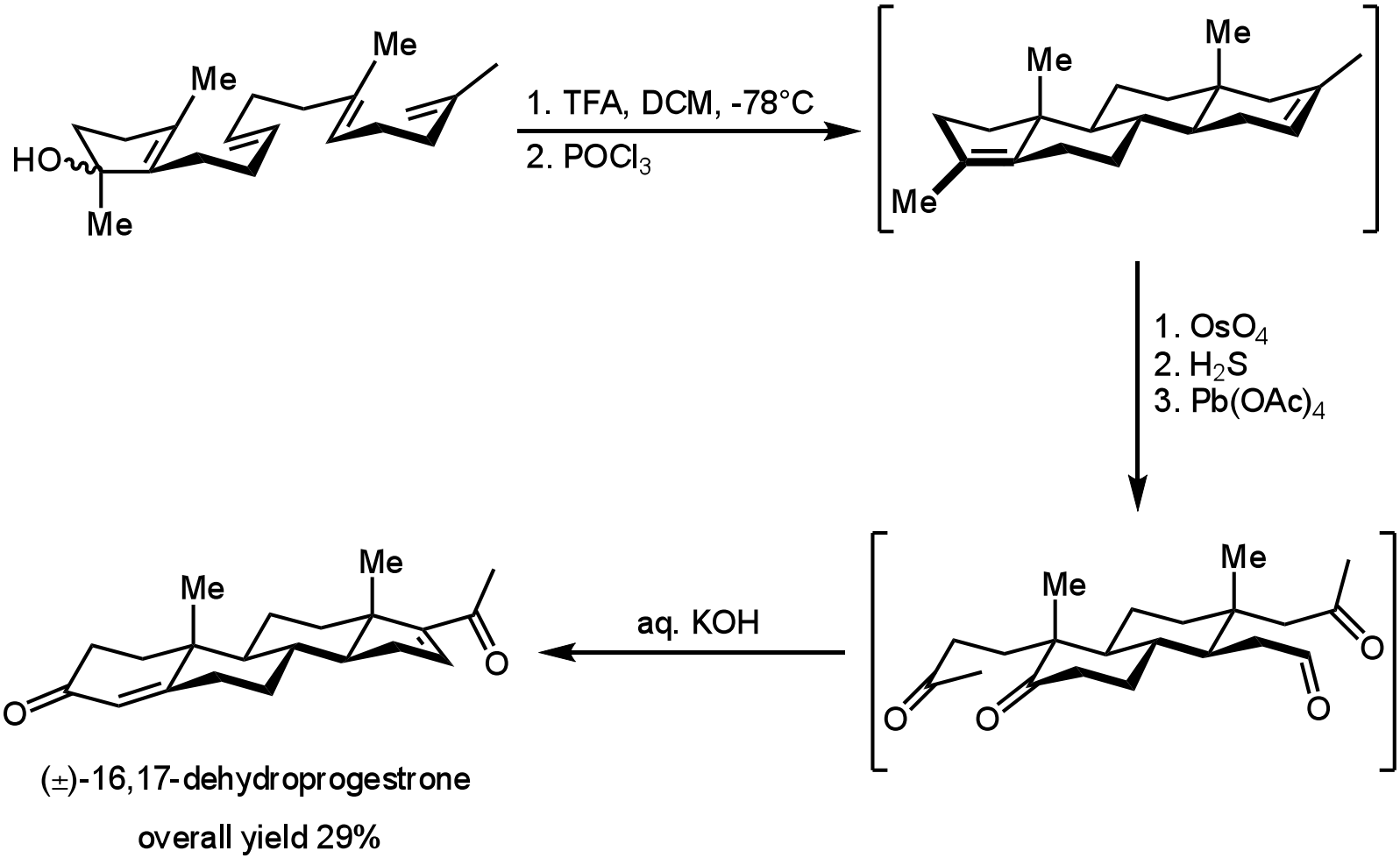
Initial Efforts Towards Biomimetic Synthesis



Stadler, P. A.; Nechvatal, A.; Frey, A. J.; Eschenmoser, A. *Helv. Chim. Acta* **1957**, *40*, 1373

Stadler, P. A.; Eschenmoser, A.; Schinz, H.; Stork, G. *Helv. Chim. Acta* **1957**, *40*, 2191

First Biomimetic Polyene Cyclization in Steroid Synthesis

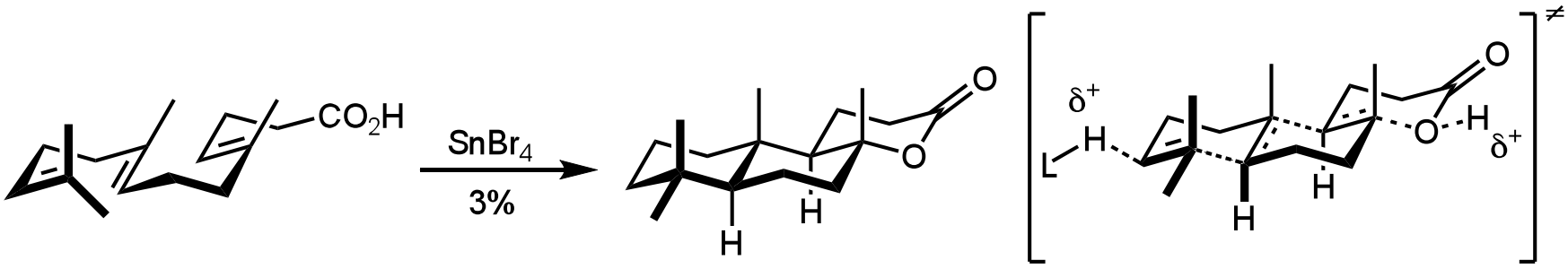


(±)-16,17-dehydroprogestrone

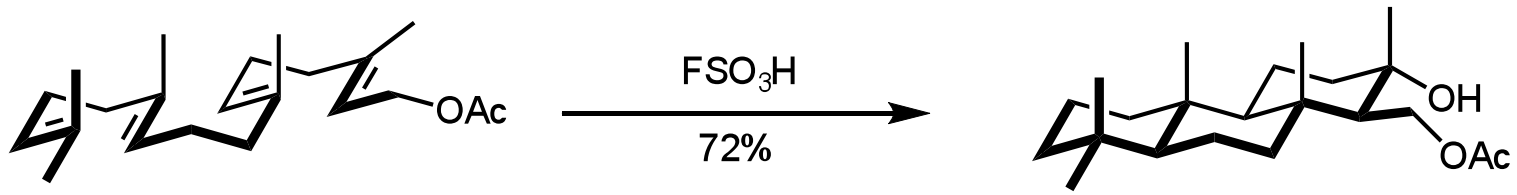
overall yield 29%

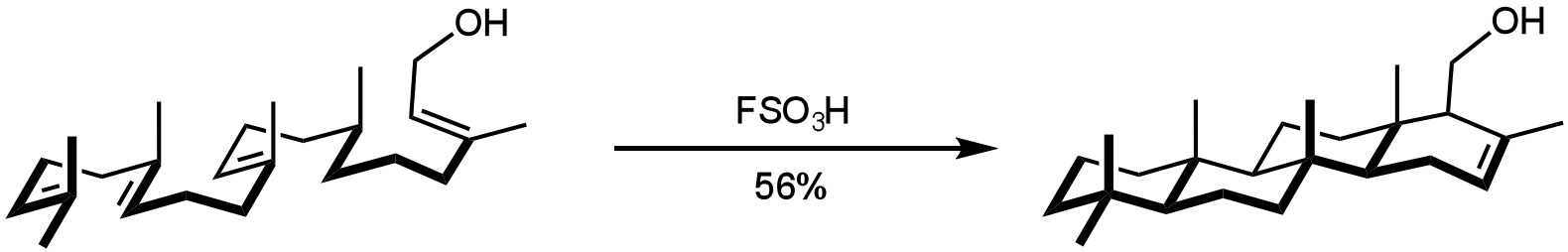
Johnson W. S.; Semmenlhack, M. F.; Sultanbawa, M. U. S.; Dolak, L. A. *J. Am. Chem. Soc.* **1968**, *90*, 2994

Diastereoselective Biomimetic Polyene Cyclization



farnesyl acetic acid — ambreinolide — transition-state double *anti*-addition

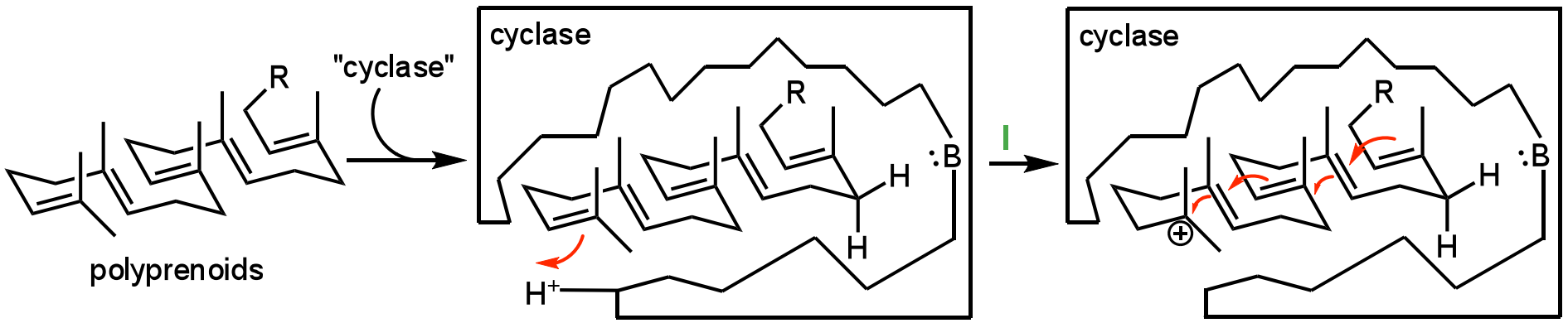




Stadler, P. A.; Eschenmoser, A.; Schinz, H.; Stork, G. *Helv. Chim. Acta* **1957**, *40*, 2191

Vlad, P. F. *Pure & Appl. Chem.* **1993**, *65*, 1329

Asymmetric Induction *via* Chiral Protonation

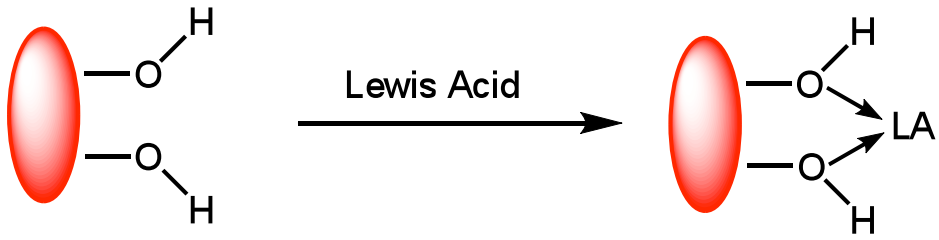


I : Carbonium ion formation

Requirements for an artificial cyclase:

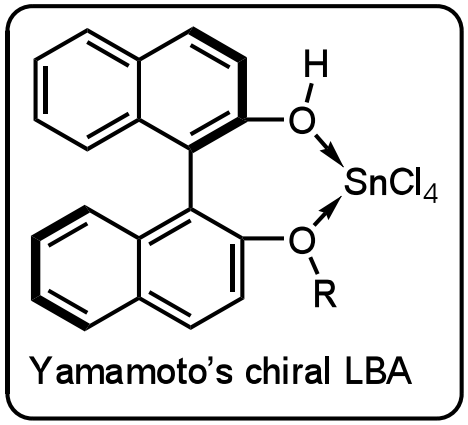
- To recognize the stereoface of a simple olefin that does not bear a directing group.
- To generate a terminal carbocation selectively by protonation.

Lewis Acid Assisted Brønsted Acid Approach



1. Confomationally flexible
2. Low acidity of proton

1. Restricts directional access to proton
2. Increase in acidity of proton

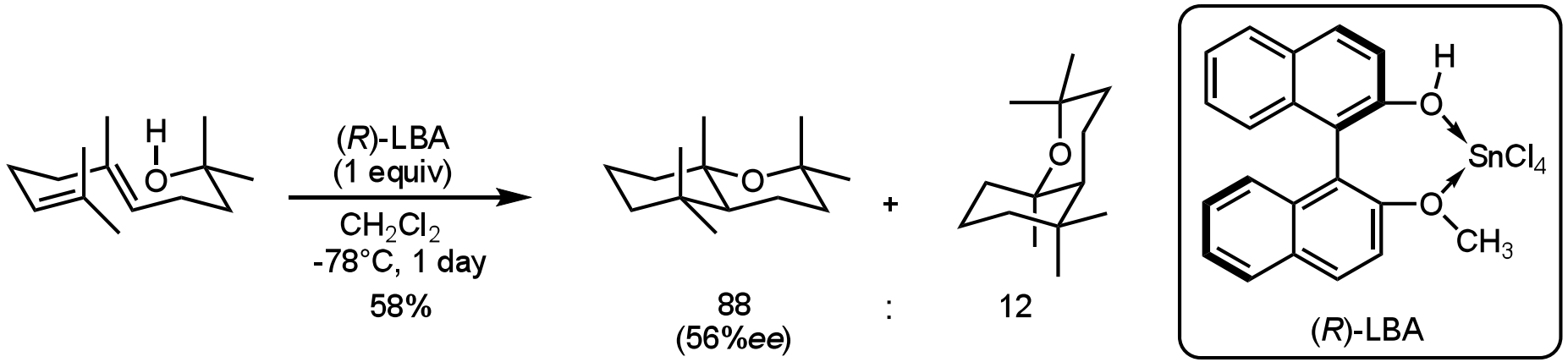


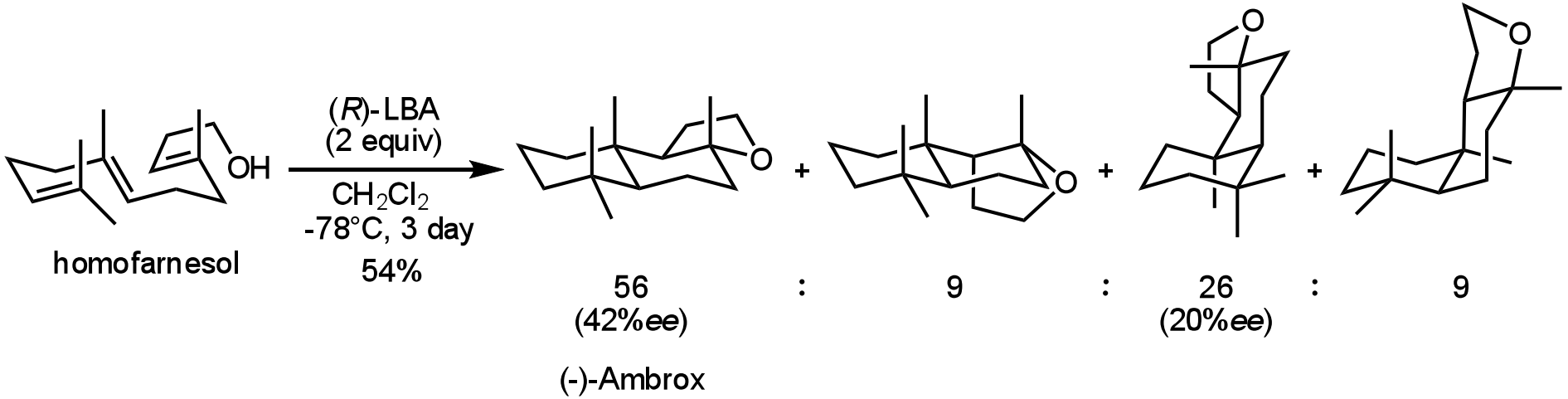
Yamamoto's chiral LBA

Additionally, the bulkiness of BINOL system acts as an artificial cavity and recognizes the terminal olefin of polyprenoids

Yamamoto, H.; Isihara, K.; Nakamura, S. *J. Am. Chem. Soc.* **1999**, *121*, 4906

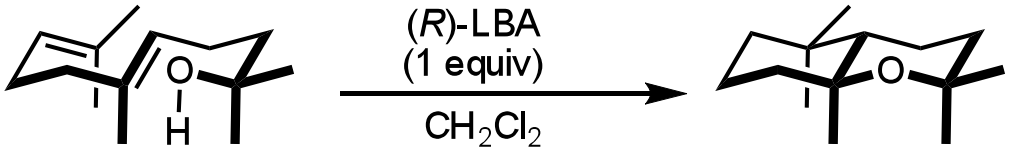
The First Enantioselective Biomimetic Cyclization

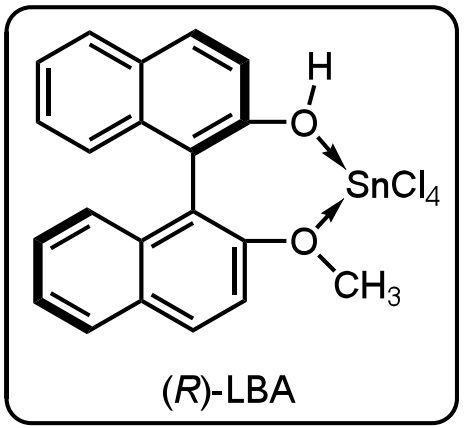




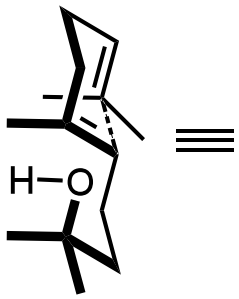
Yamamoto, H.; Isihara, K.; Nakamura, S. *J. Am. Chem. Soc.* **1999**, *121*, 4906

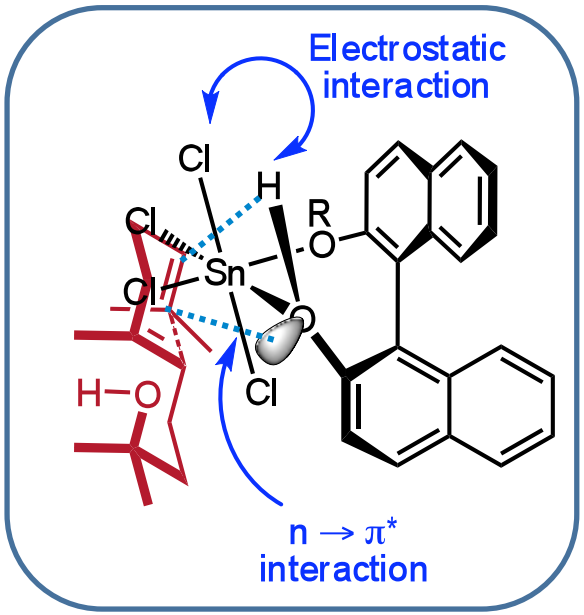
Stereochemical Rationale



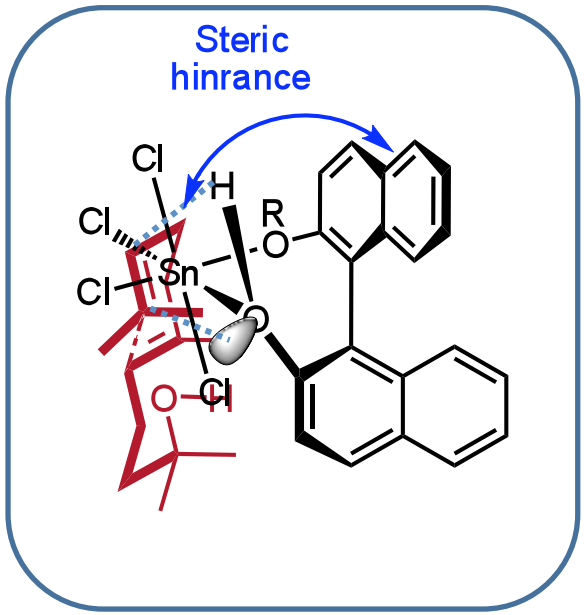


Rotation 90° clockwise





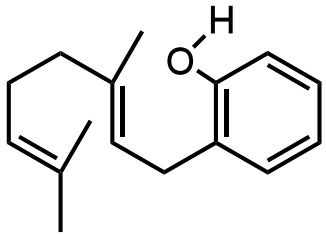
Favored



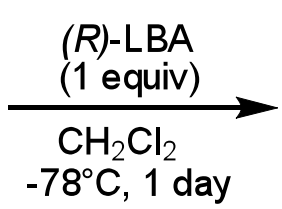
Disfavored

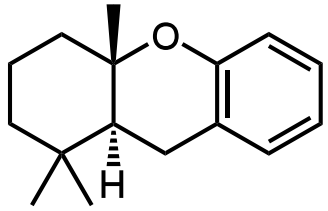
Yamamoto, H.; Isihara, K.; Nakamura, S. *J. Am. Chem. Soc.* **1999**, *121*, 4906

Enantioselective Cyclization of Polyolefinic Phenol Derivatives

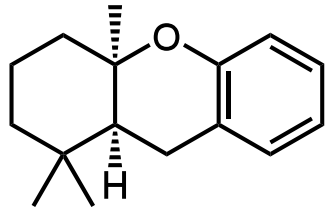


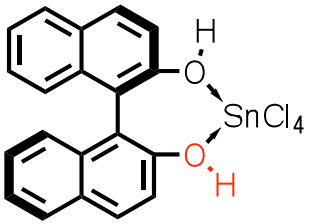
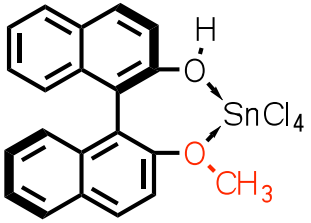
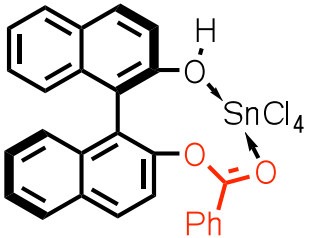
o-geranylphenol





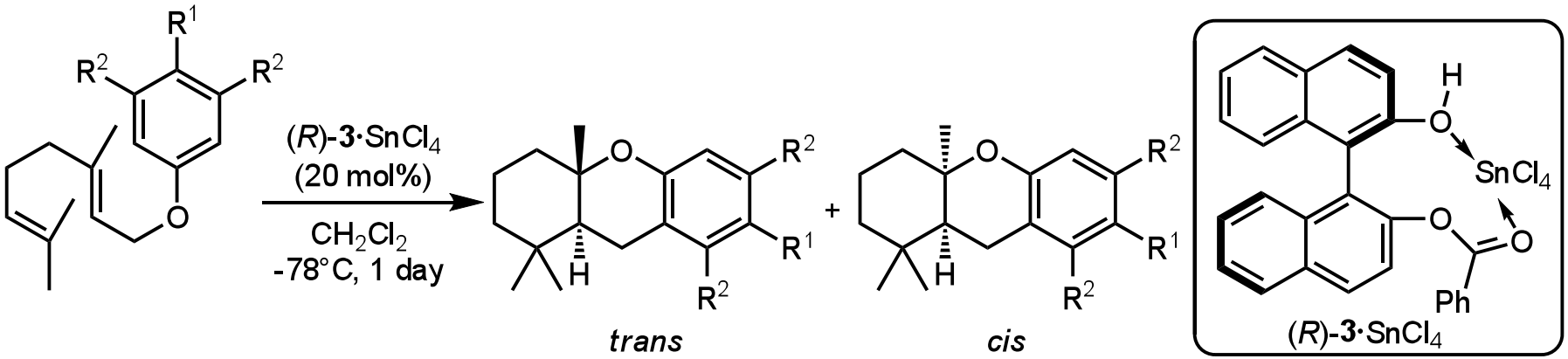
+

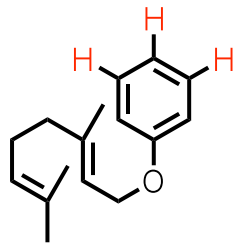
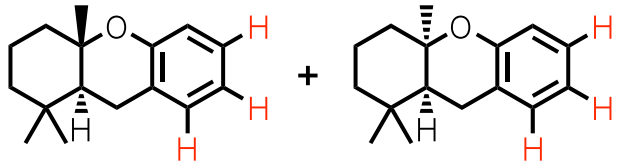
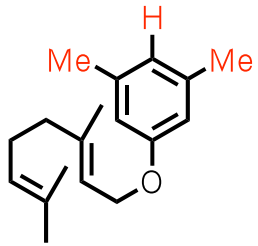
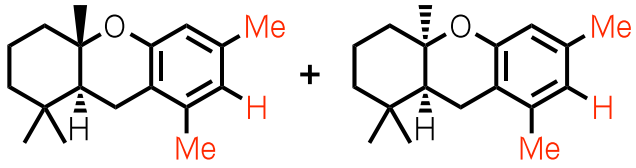


	Yield (trans + cis)	*trans*		*cis*
 (*R*)-**1**·$SnCl_4$	90%	84 (36%*ee*)	:	16 (32%*ee*)
 (*R*)-**2**·$SnCl_4$	89%	>70 (50%*ee*)	:	>20 (34%*ee*)
 (*R*)-**3**·$SnCl_4$	92%	95 (54%*ee*)	:	5 (-)

Yamamoto, H.; Isihara, K.; Nakamura, S. *J. Am. Chem. Soc.* **1999**, *121*, 4906

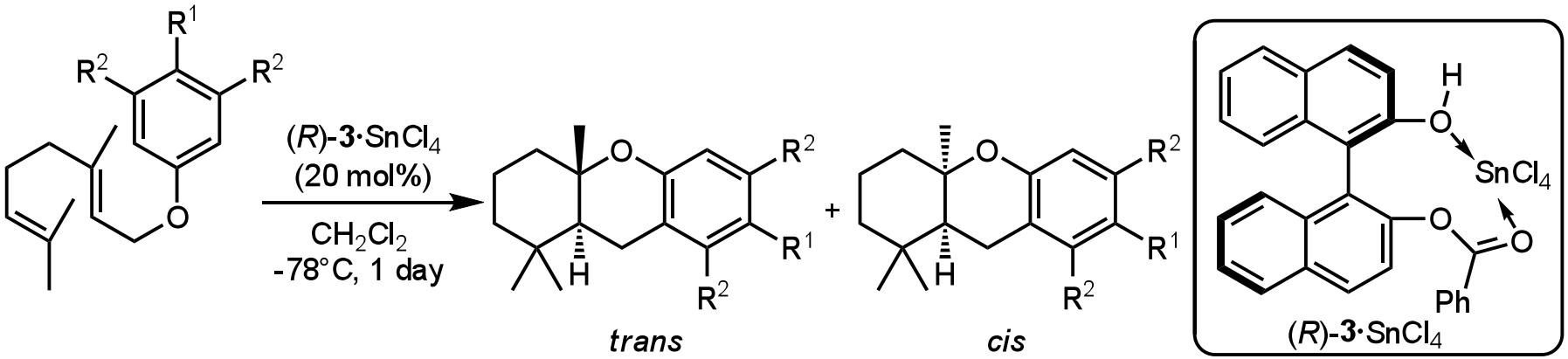
Enantioselective Cyclization of Geranyl Aryl Ether

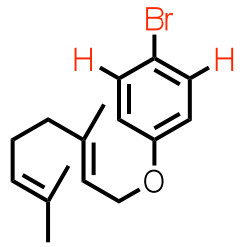
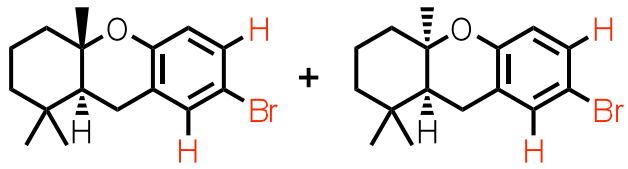
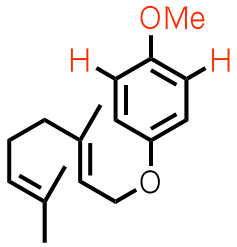
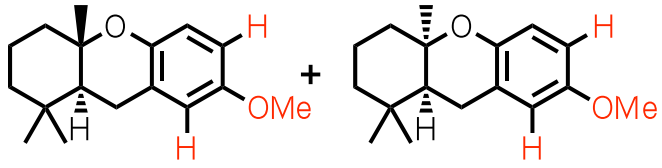


Entry	Reactant	Product	*trans:cis*	Yield (%, trans)	*ee* (%, cis)
1			98:2	98	77
2			91:9	82	46

Yamamoto, H.; Isihara, K.; Nakamura, S. *J. Am. Chem. Soc.* **2000**, *122*, 8131

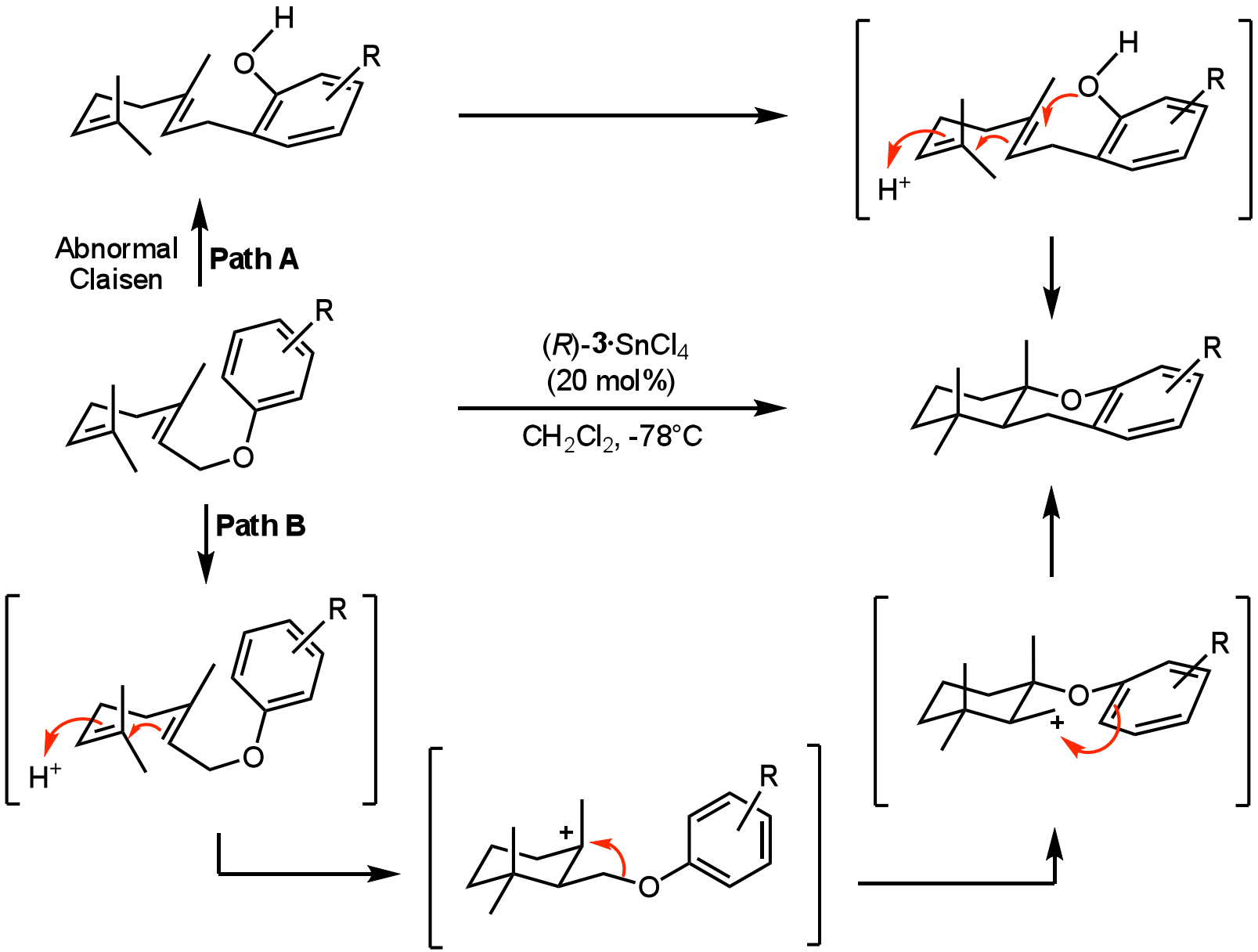
Enantioselective Cyclization of Geranyl Aryl Ether



Entry	Reactant	Product	*trans:cis*	Yield (%, trans)	*ee* (%, cis)
3			89:11	85	87
4			94:6	92	42

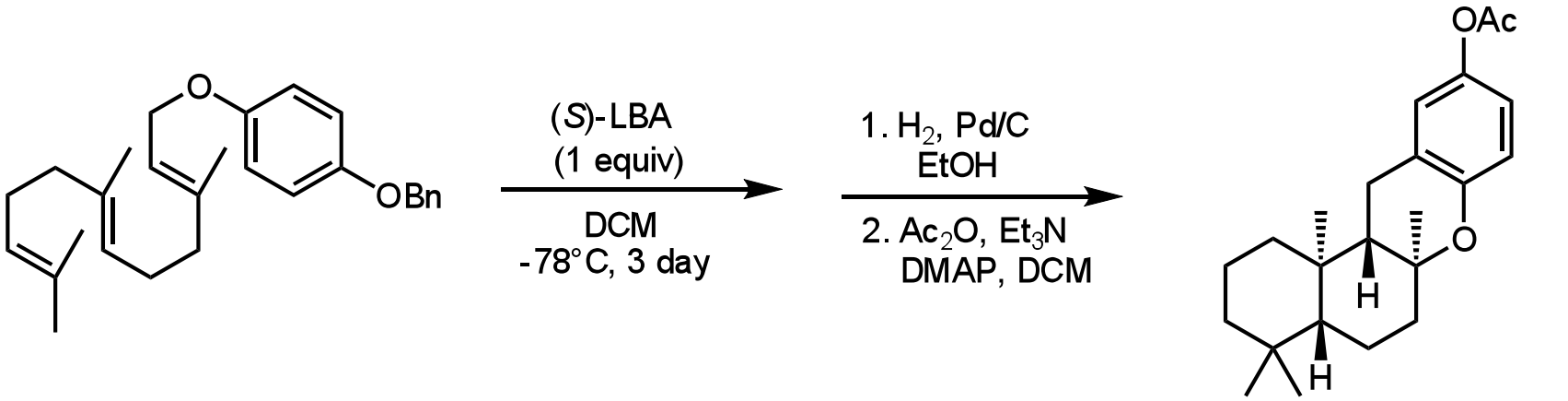
Yamamoto, H.; Isihara, K.; Nakamura, S. *J. Am. Chem. Soc.* **2000**, *122*, 8131

Mechanism of Polyene Cyclization



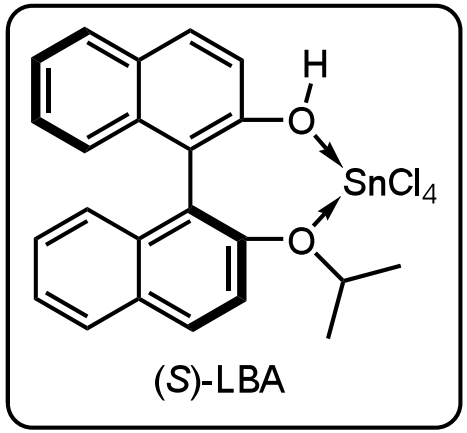
Yamamoto, H.; Isihara, K.; Nakamura, S. *J. Am. Chem. Soc.* **2000**, *122*, 8131

Application to Total Synthesis



(-)-Chromazonarol acetate

40%, 44%*ee*

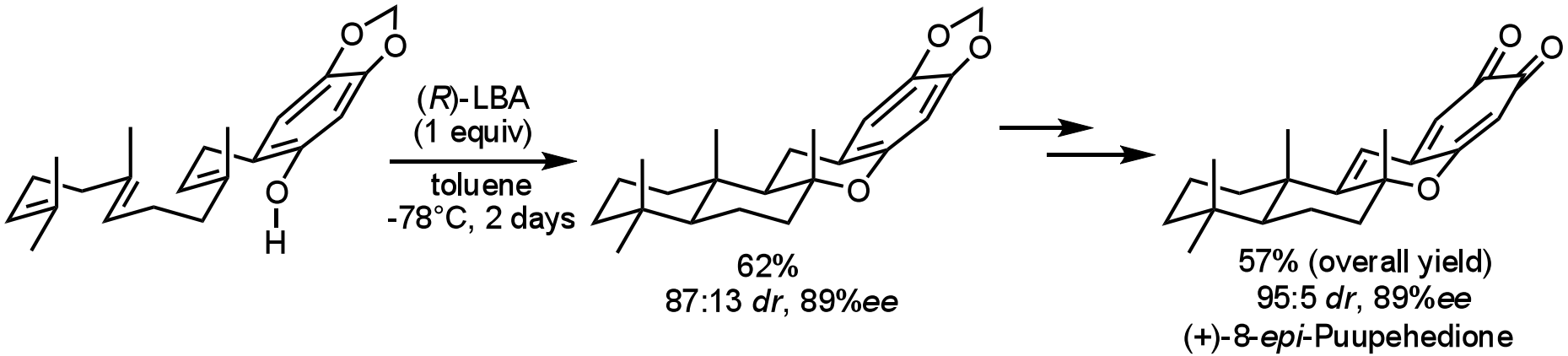


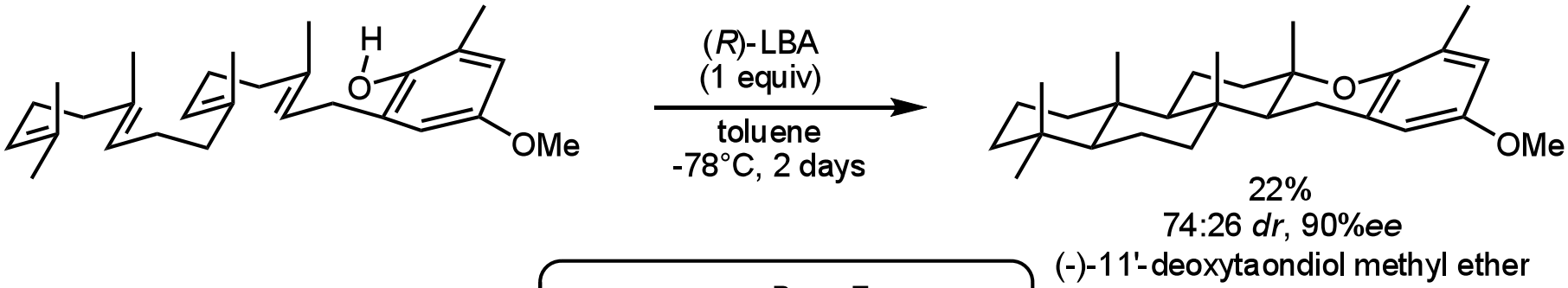
(*S*)-LBA

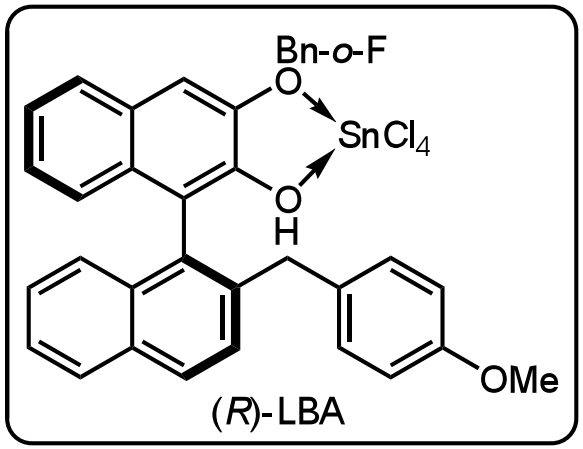
- Control of 4 chiral centres
- Generation of 2 quaternary carbons

Yamamoto, H.; Isihara, K.; Nakamura, S. *J. Am. Chem. Soc.* **2000**, *122*, 8131

A New Artificial Cyclase for Polyolefinic Phenol Derivatives

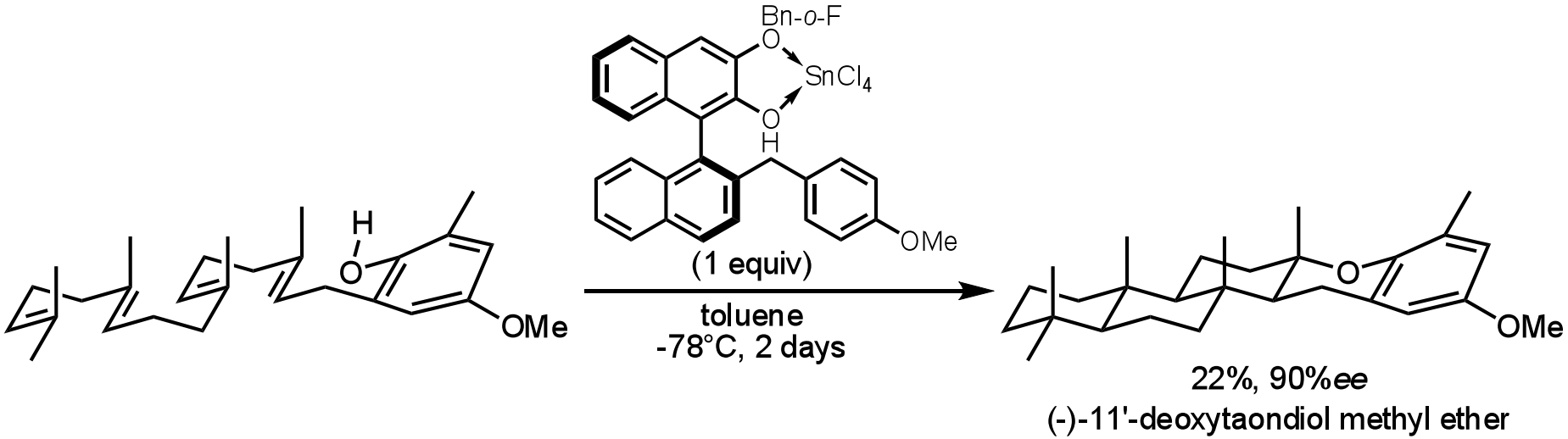






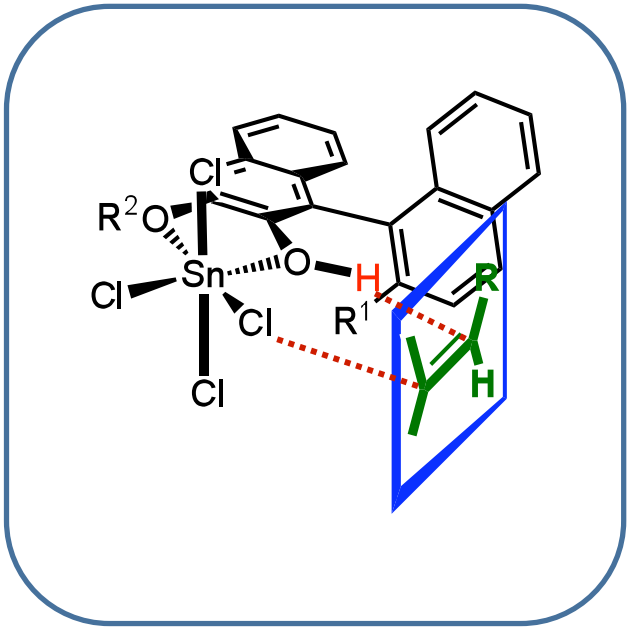
Yamamoto, H.; Isihara, K.; Nakamura, S. *J. Am. Chem. Soc.* **2004**, *126*, 11122

Rationale for Absolute Stereopreference

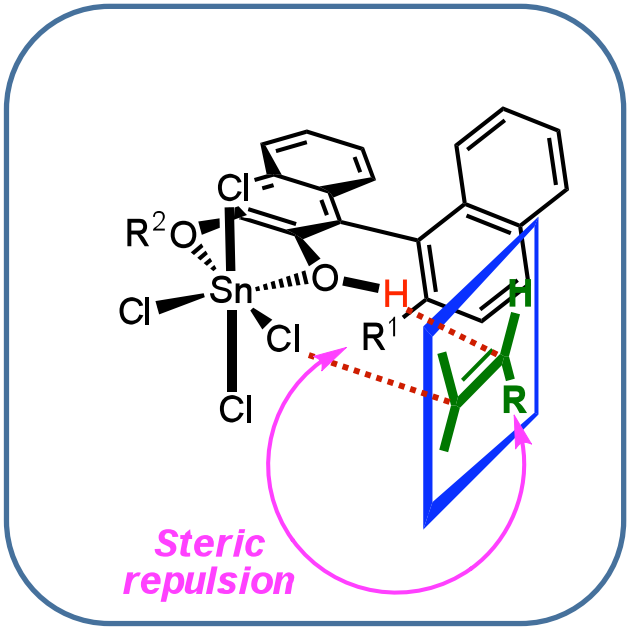


22%, 90%*ee*

(-)-11'-deoxytaondiol methyl ether



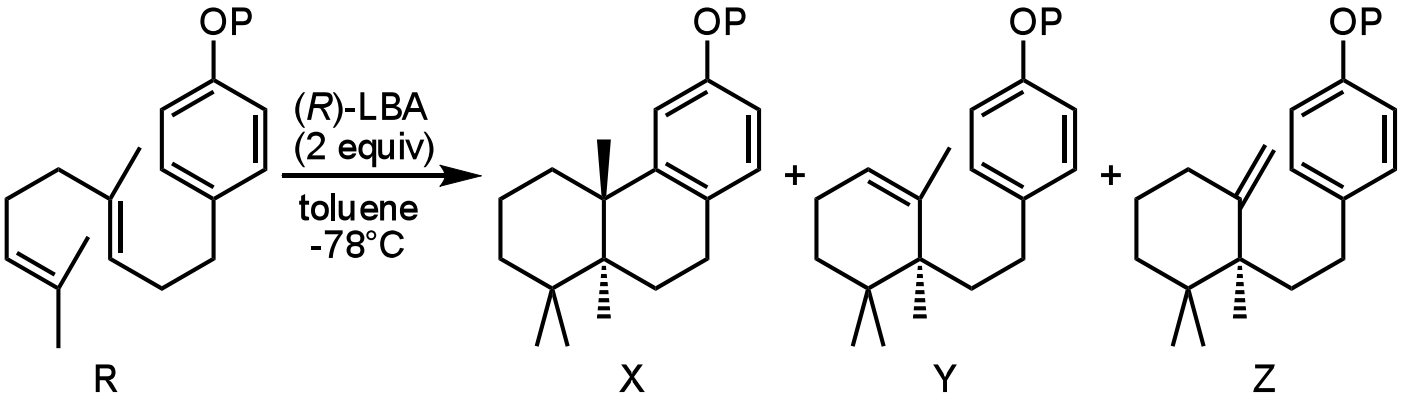
Favored

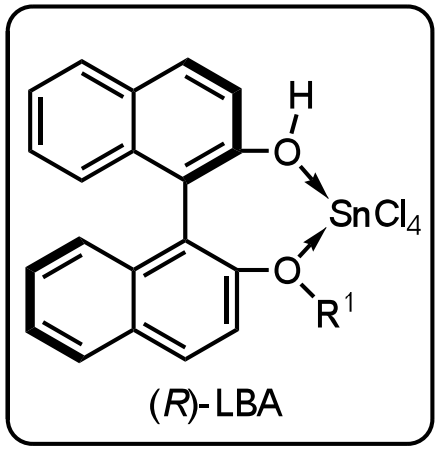


Disfavored

Yamamoto, H.; Isihara, K.; Nakamura, S. *J. Am. Chem. Soc.* **2004**, *126*, 11122

Enantioselective Cyclization of Polyolefinic Phenol Derivatives



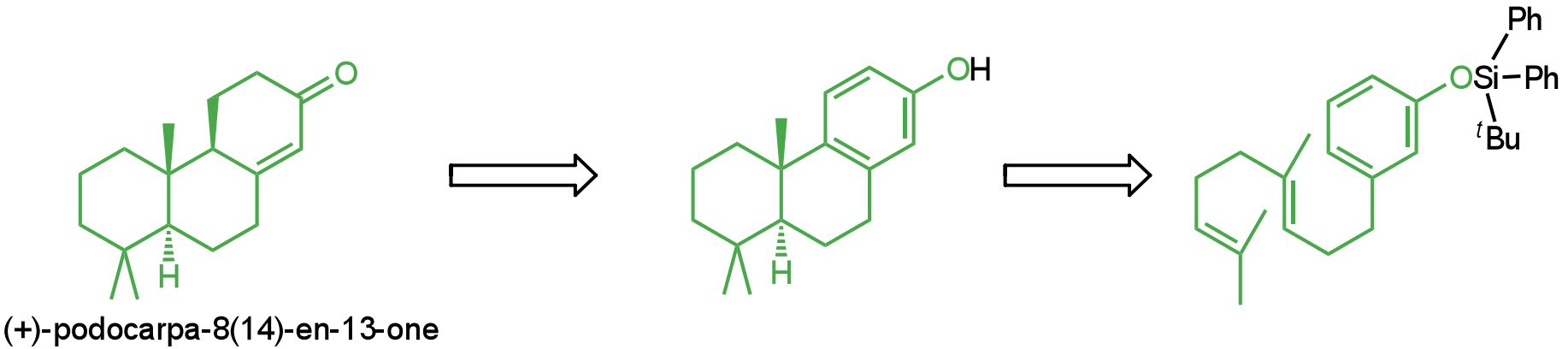


Entry	P	R^1	molar ratio			
			X	Y	Z	R
1	H	Me	87 (49% *ee*)	6	7	0
2	Me	Me	10 (59% *ee*)	36	36	18
3	*t*-$BuPh_2Si$	Me	13 (72% *ee*)	35	35	17
4	*t*-$BuPh_2Si$	*o*-F-Bn	9 (81% *ee*)	44	47	0

Is this mixture of some practical utility?

Yamamoto, H.; Isihara, K.; Ishibashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647

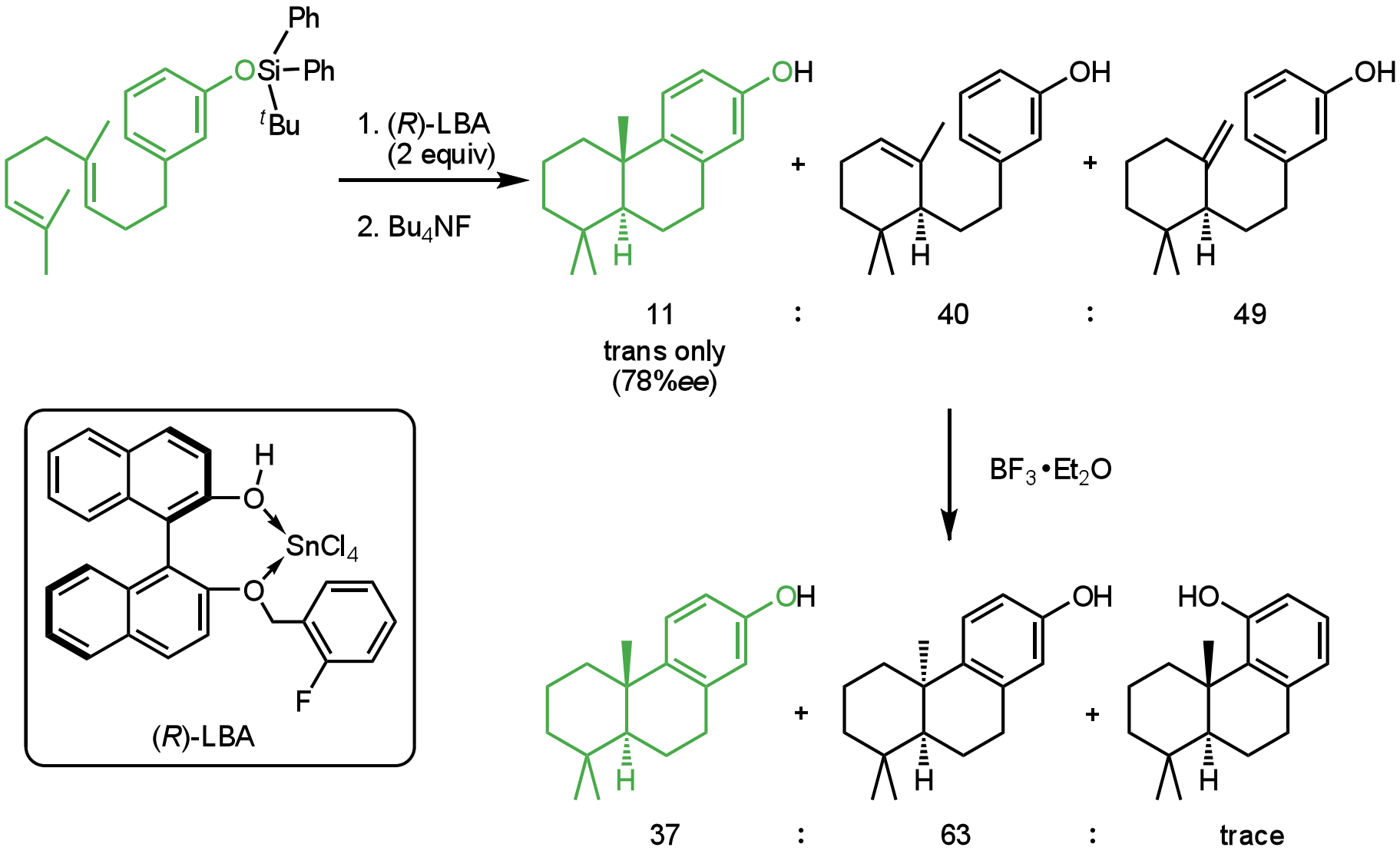
Application to Synthesis of Diterpenoids



(+)-podocarpa-8(14)-en-13-one

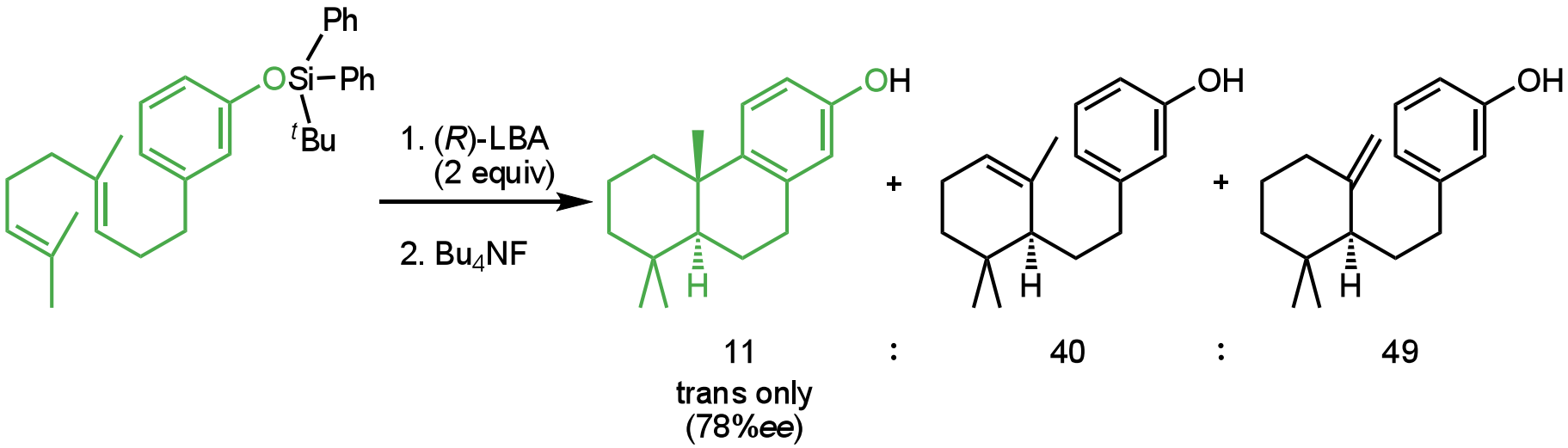
Yamamoto, H.; Isihara, K.; Ishibashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647

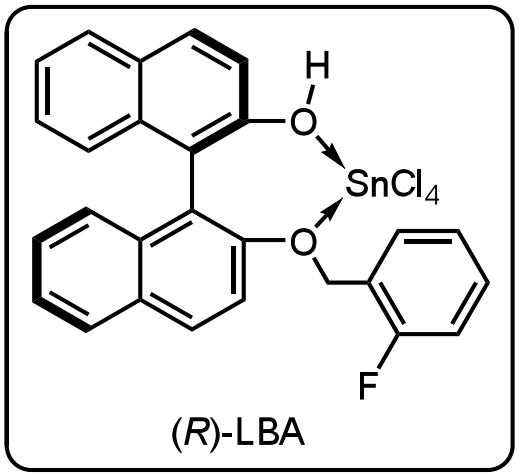
Application to Synthesis of Diterpenoids

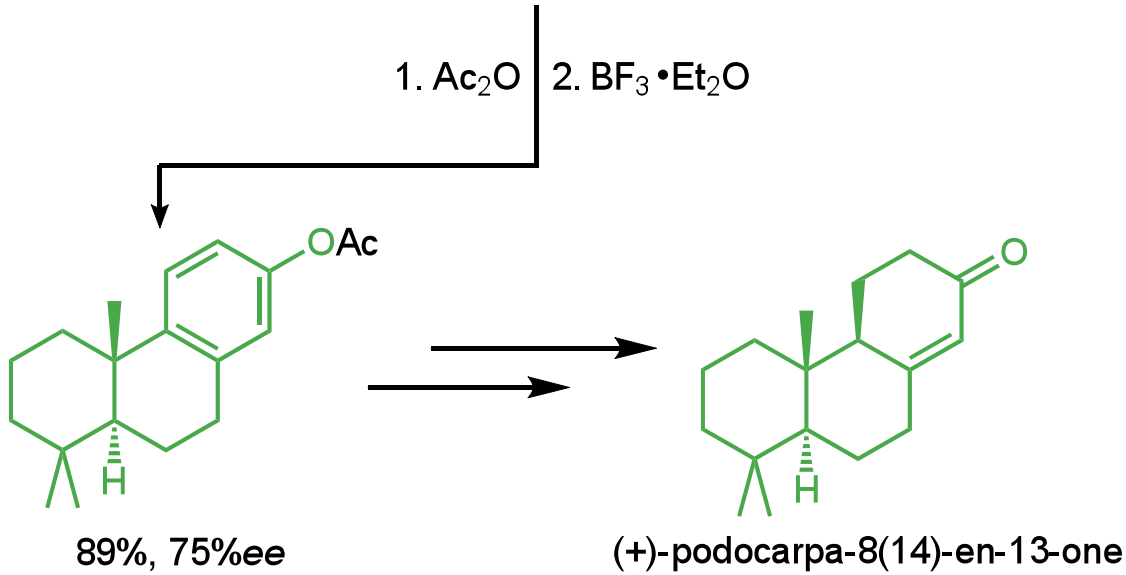


Yamamoto, H.; Isihara, K.; Ishibashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647

Application to Synthesis of Diterpenoids

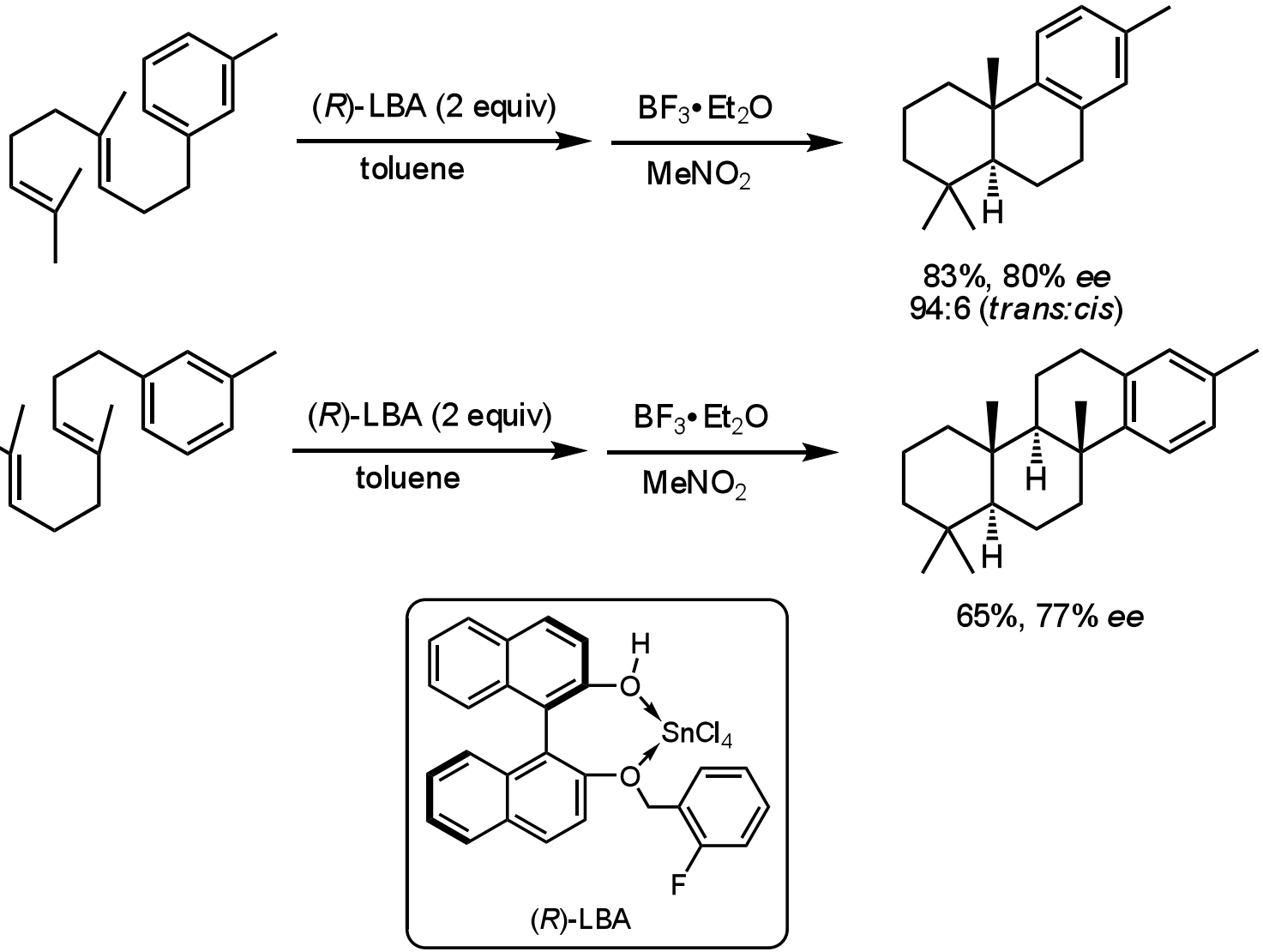






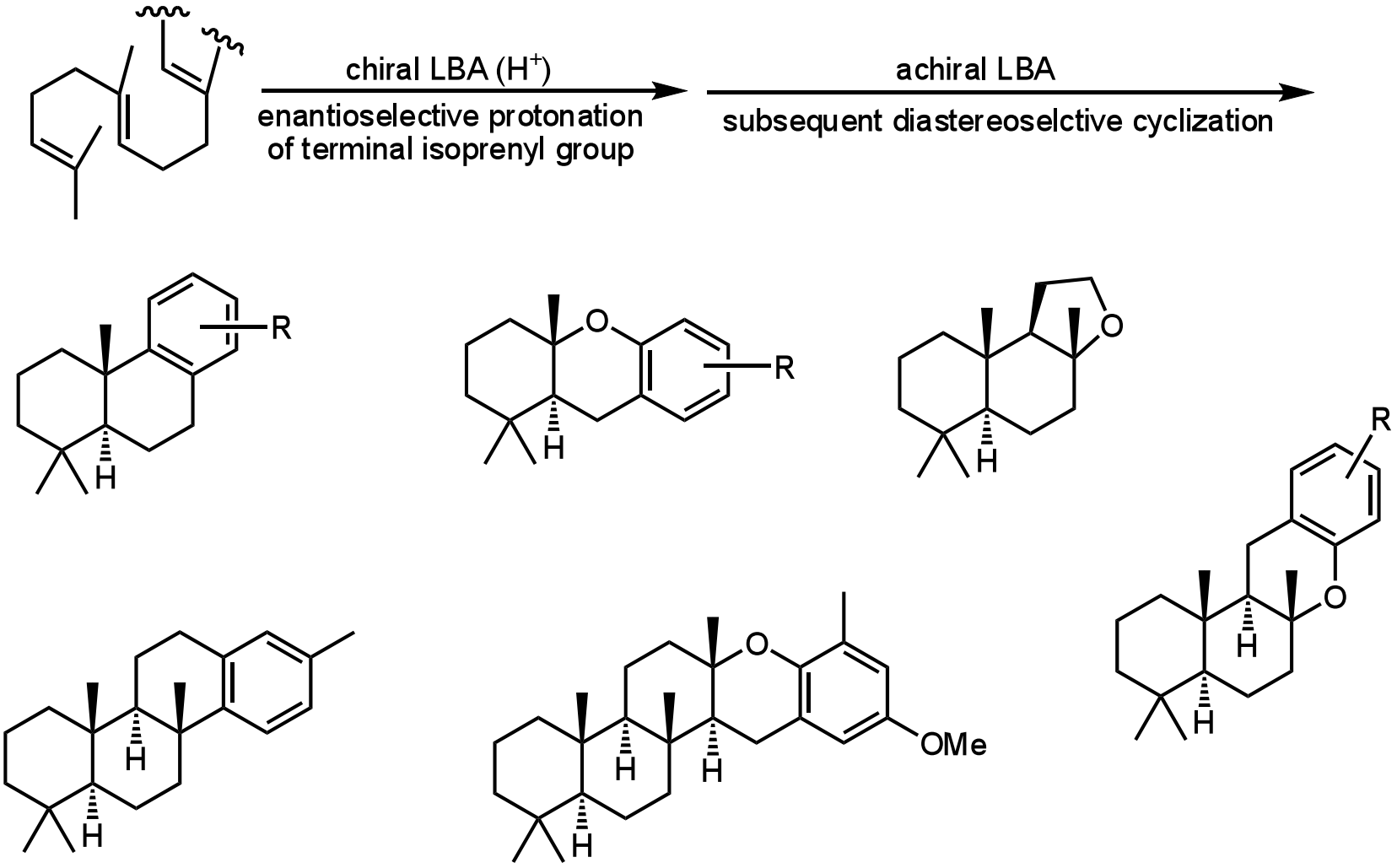
Yamamoto, H.; Isihara, K.; Ishibashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647

Enantioselective Cyclization of Unactivated Polyprenoids



Yamamoto, H.; Isihara, K.; Ishibashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647

Summary


chiral LBA (H+)
enantioselective protonation
of terminal isoprenyl group
achiral LBA
subsequent diastereoselctive cyclization
R
H
O
R
H
O
H
R
O
H
H
O
H
H
OMe
H

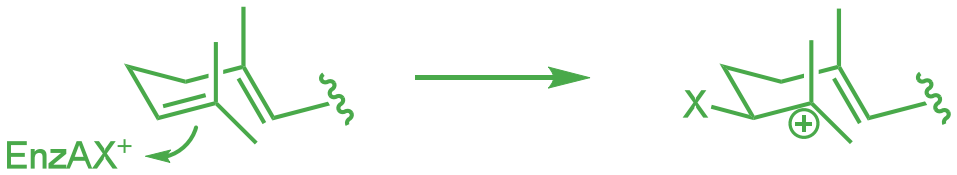
Outline

Activation of Terminal Double Bond

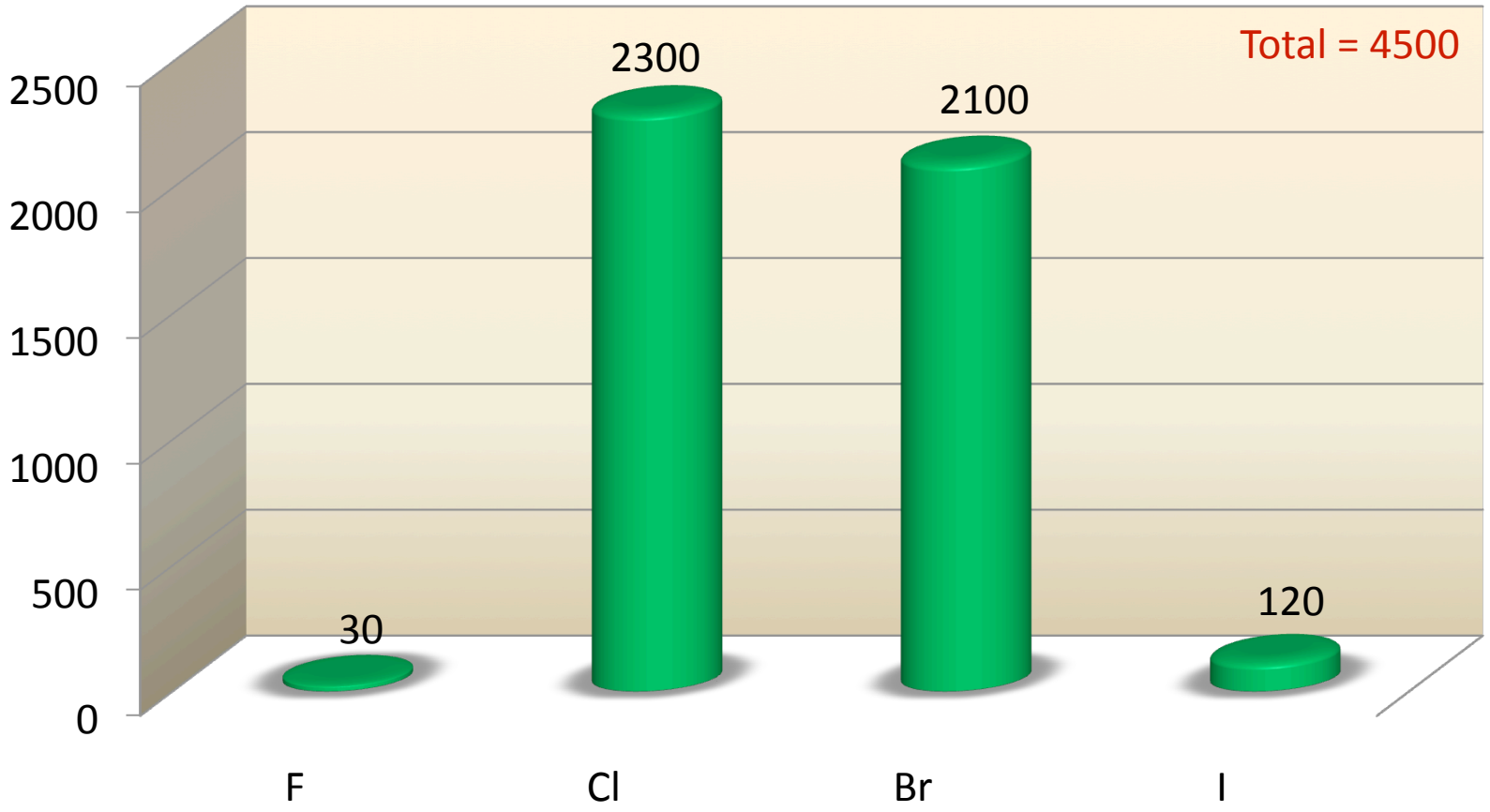
H^+ or X^+

Enzymatic
Polyene Cyclization

Biomimetic
Polyene Cyclization



Nature's Inventory of Organohalogens



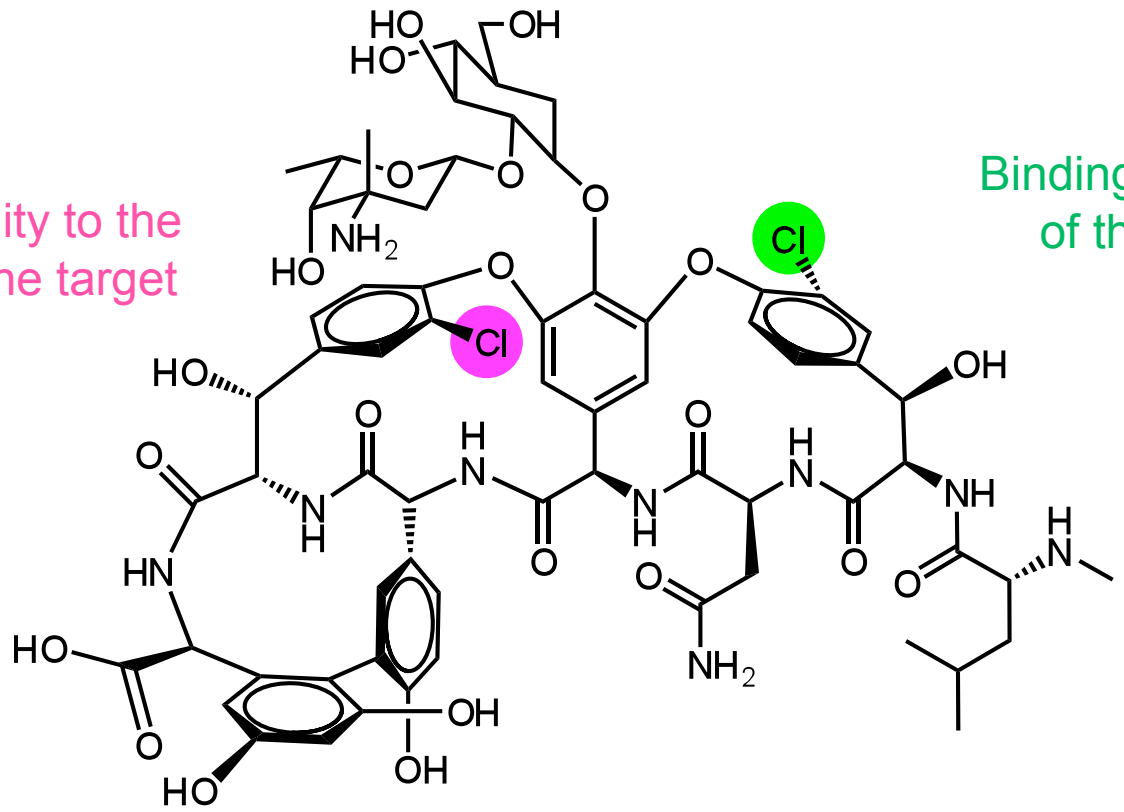
"And that list grows by more than 100 new natural organohalogens per year "
- Gordon W. Gribble

Yarnell, A. *Chemical & Engineering News* **2006**, *84*,12

Importance of Halogens in Natural Products

Binding affinity to the cell-wall of the target

Binding selectivity of the target

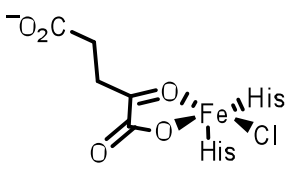


Vancomycin

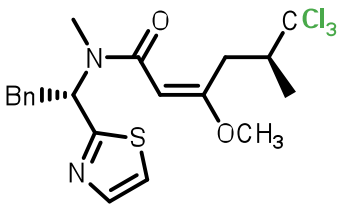
"Nature turns to halogenation in order to fine tune a natural product's biological properties"
-Christopher T. Walsh

Gerhard, U.; Mackay, J.; Maplestone, R.; Williams, D. *J. Am. Chem. Soc*. **1993**, *115*, 232

Diversity in Halogen Installation by Nature

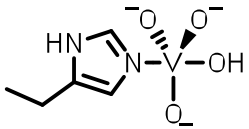


non-heme iron

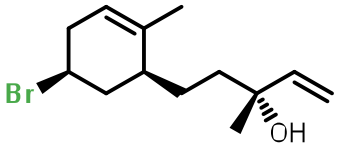


barbamide

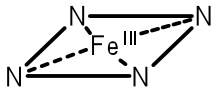
Aliphatic Carbons



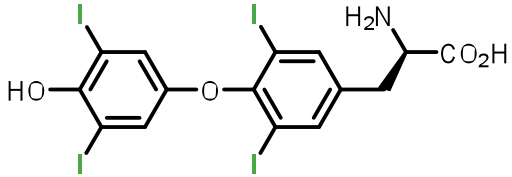
vanadium haloperoxidase



snyderol

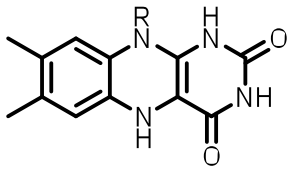


heme iron

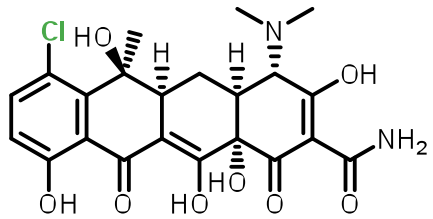


tetraiodothyronine

Aromatic Carbons



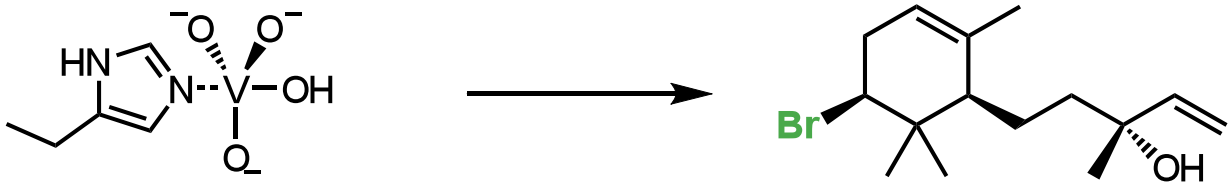
$FADH_2$



chlorotetracyclin

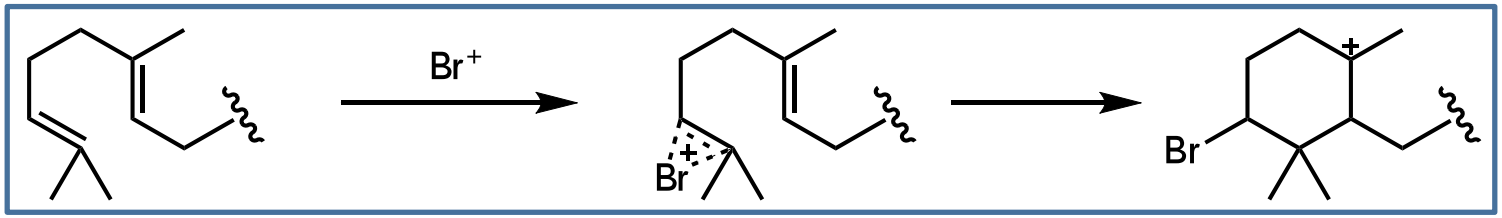
Yarnell, A. *Chemical & Engineering News,* **2006**, *84*,12

Enzymatic Polyene Halocyclization

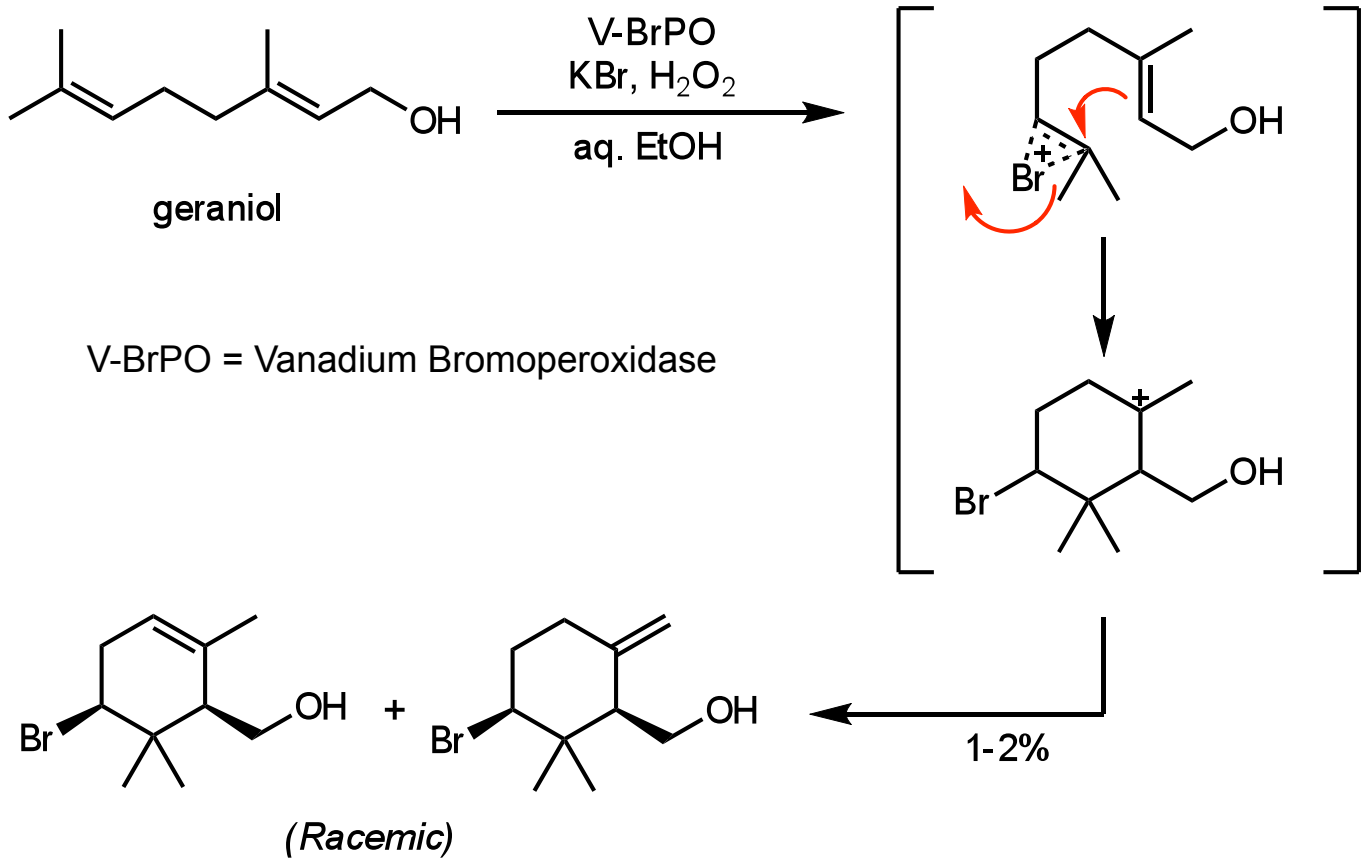


vanadium haloperoxidase

snyderol



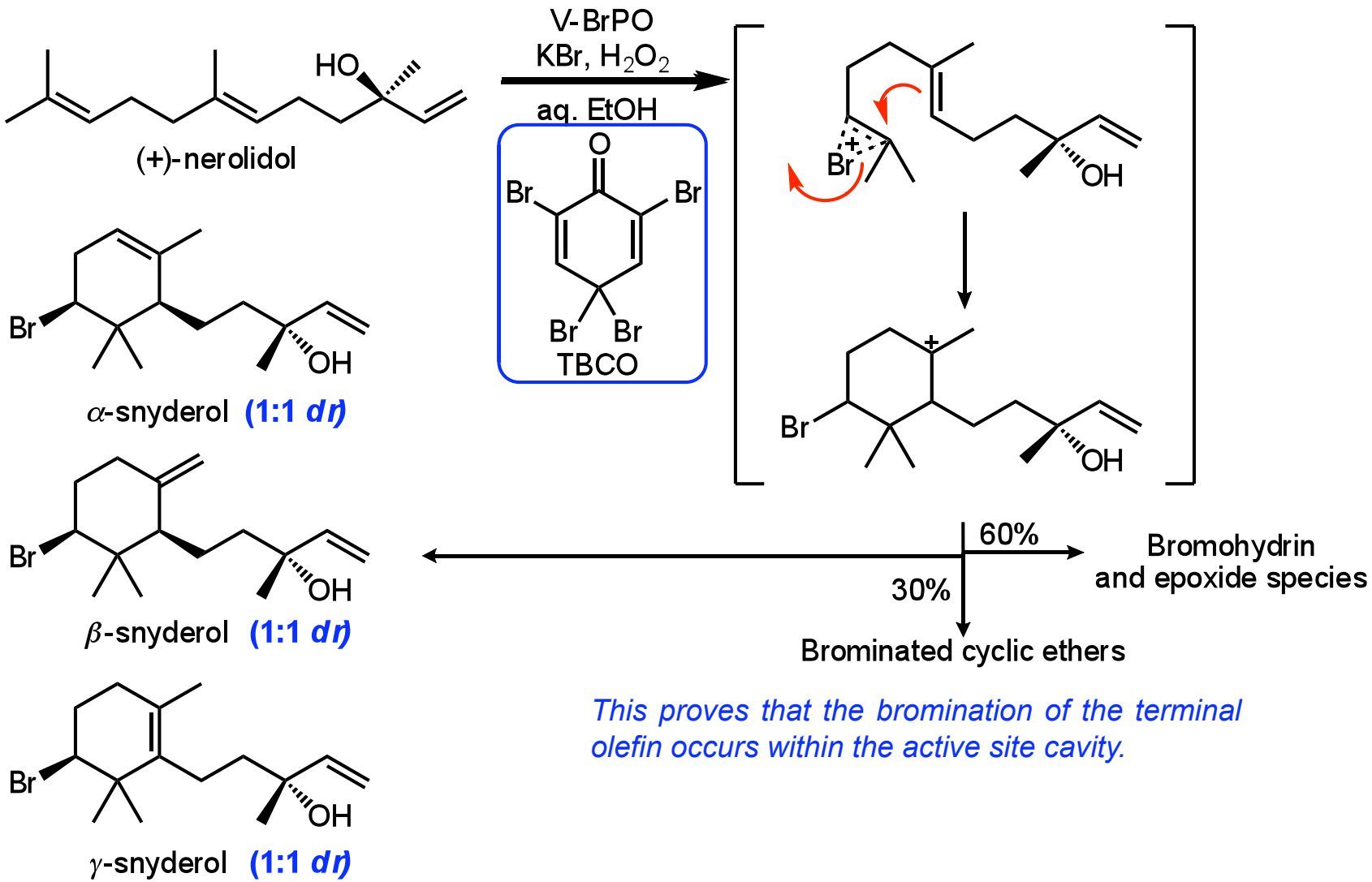
First Evidence of Halocyclization by Vanadium Bromoperoxidase



V-BrPO = Vanadium Bromoperoxidase

Carter-Franklin, J. N.; Parrish, J. D.; Little, R. D.; Butler, A. *J. Am. Chem. Soc.* **2003**, *125*, 3688

Enantioselective Enzymatic Halocyclization



α-snyderol **(1:1 *dr*)**

β-snyderol **(1:1 *dr*)**

γ-snyderol **(1:1 *dr*)**

This proves that the bromination of the terminal olefin occurs within the active site cavity.

Carter-Franklin, J. N.; Butler, A. *J. Am. Chem. Soc.* **2004**, *126*, 15060

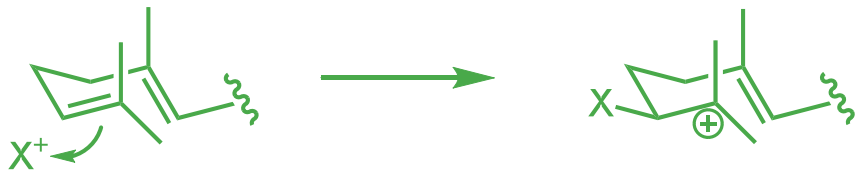
Outline

Activation of Terminal Double Bond

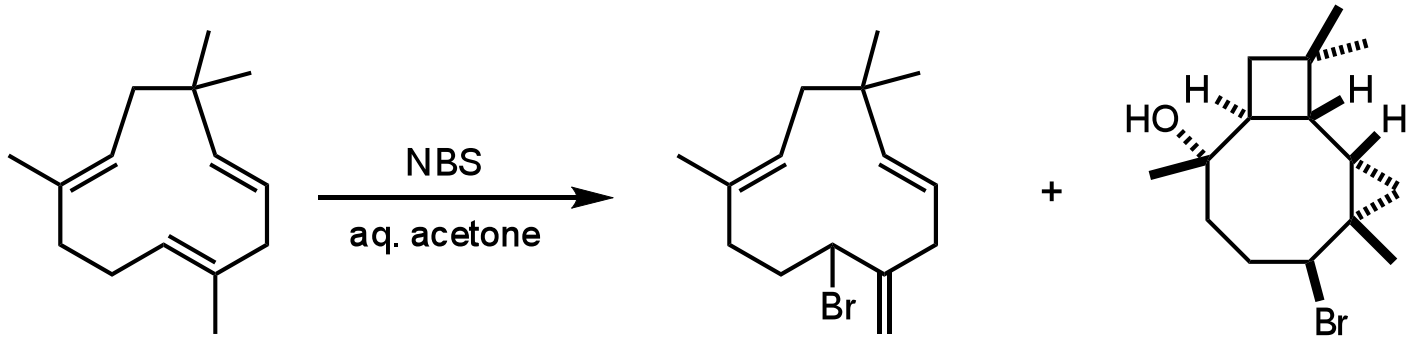
H^+ or X^+

Enzymatic
Polyene Cyclization

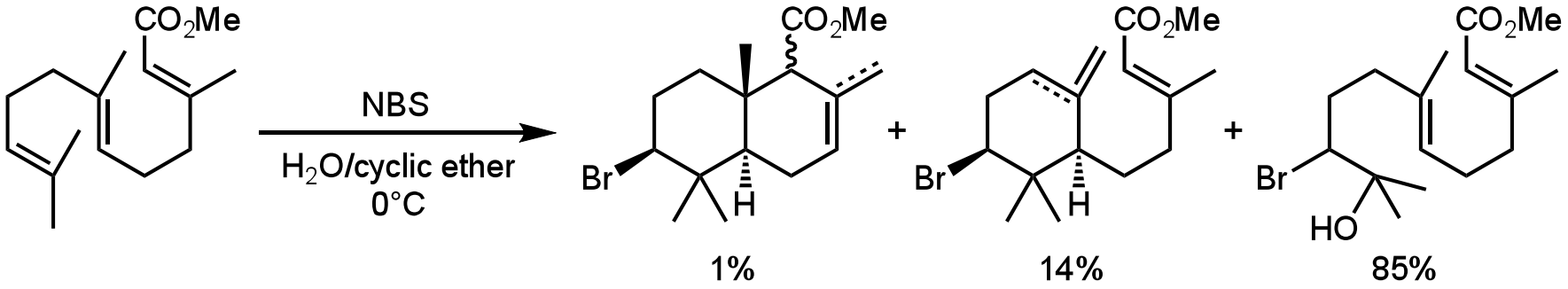
Biomimetic
Polyene Cyclization



Efforts Towards Bromocyclization



humulene 20% 20%

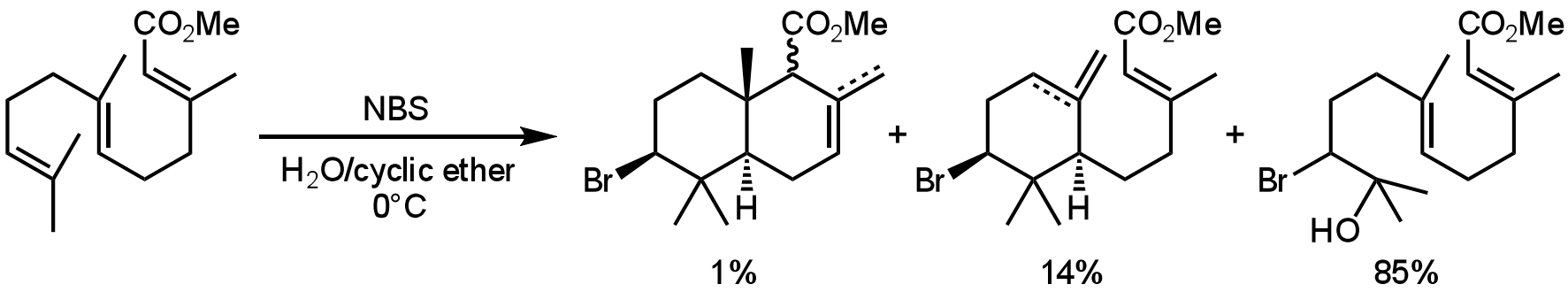


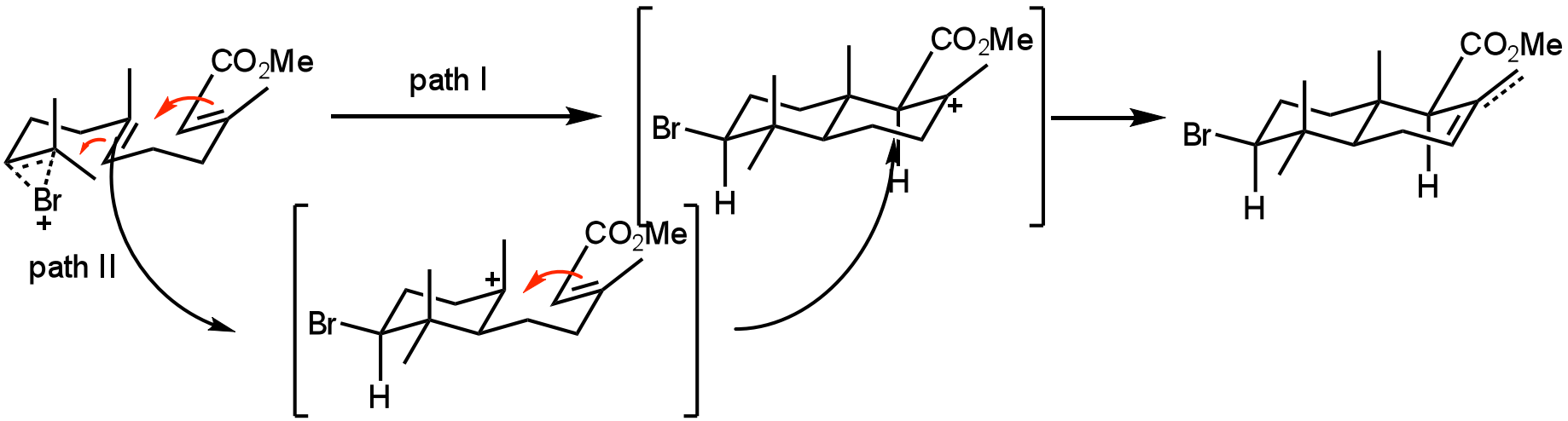
1% 14% 85%

Greenwood, J. M.; Sutherland, J. K.; Torre, A. *Chem. Comm.* **1965**, 410

Tamelen, E. E.; Hessler, E. J. *Chem. Comm.* **1966**, 411

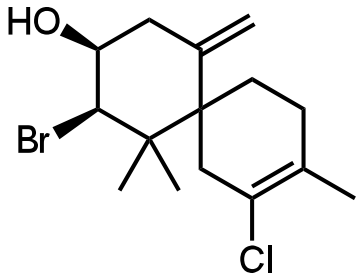
Possible Pathways Towards Bromocyclization



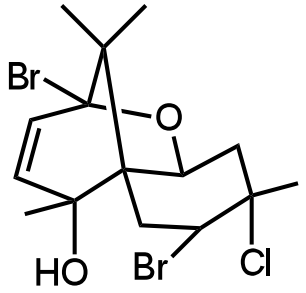


Tamelen, E. E.; Hessler, E. J. *Chem. Comm.* **1966**, 411

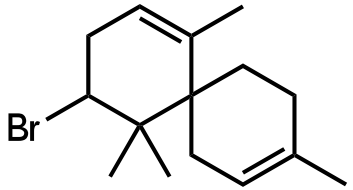
Application to Total Synthesis



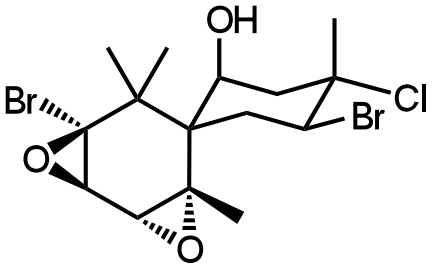
elatol



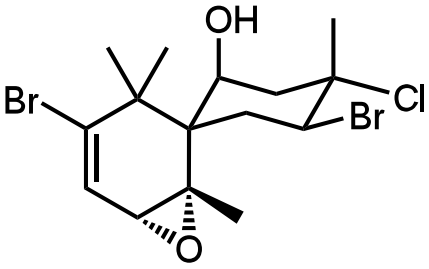
pacifenol



10-bromo-α-chamigrene



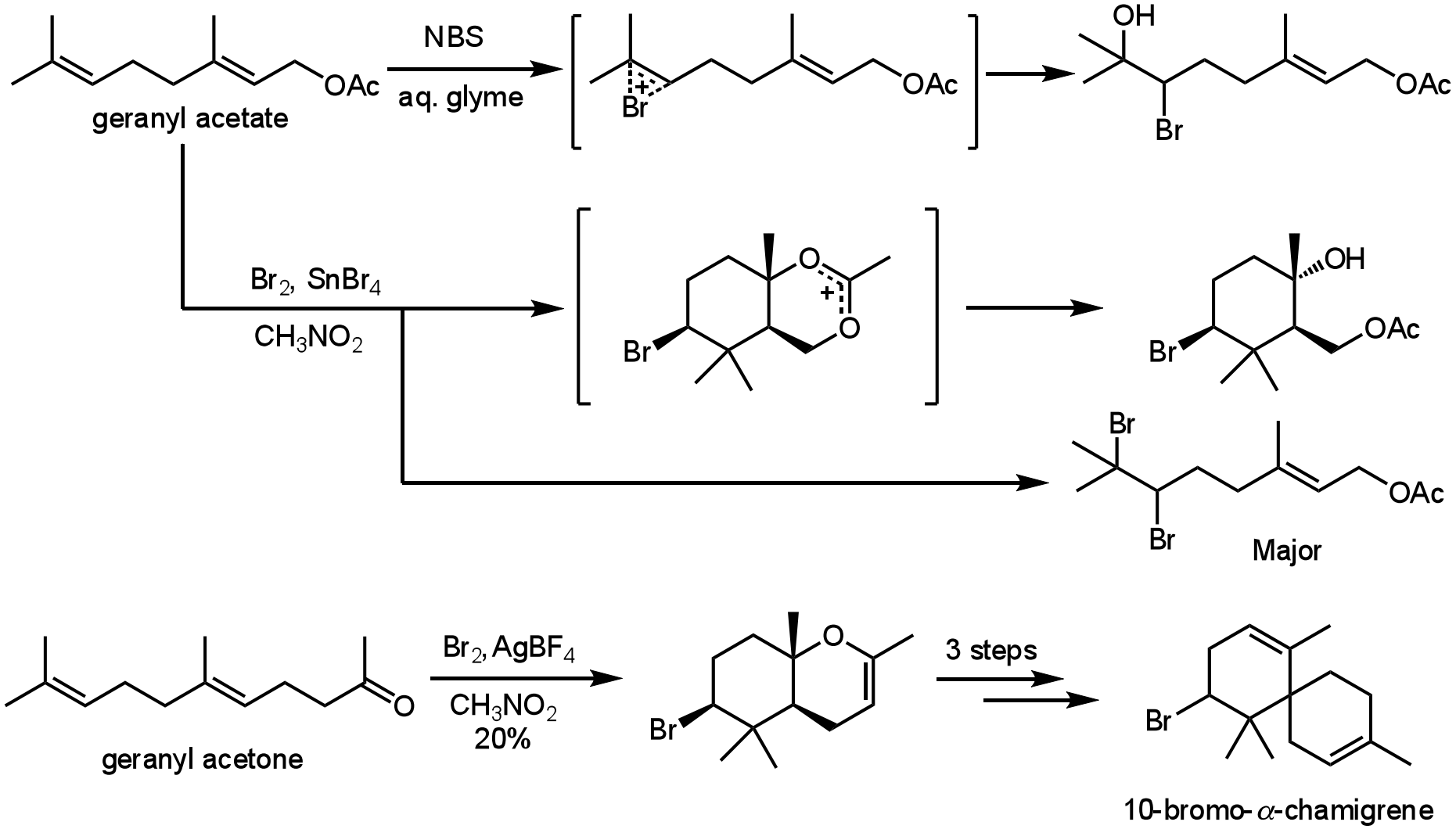
prepacifenol epoxide



prepacifenol

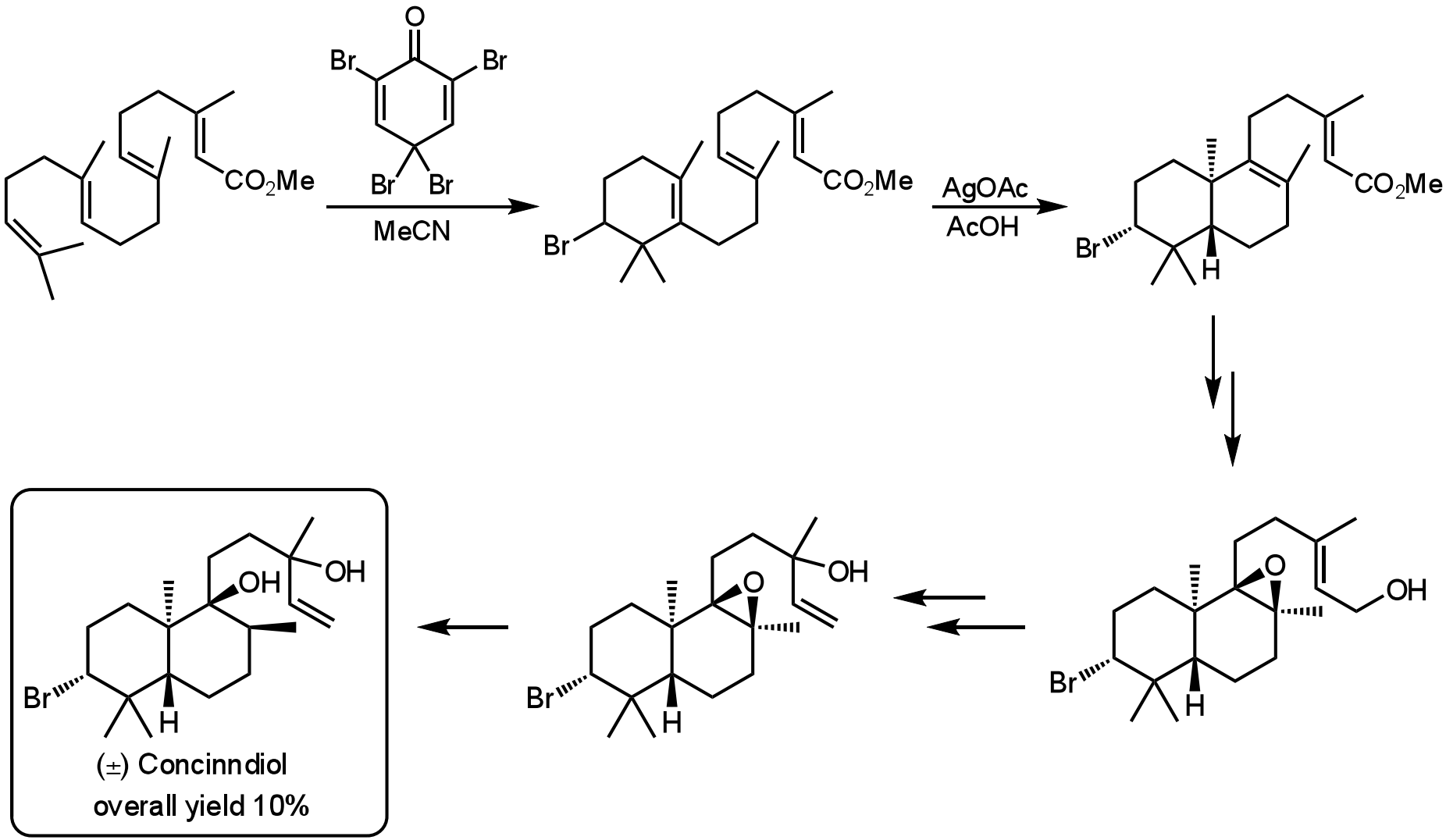
Faulkner, D. J.; Wolinsky, L. E. *J. Org. Chem.* **1976**, *41*, 597

Application to Total Synthesis



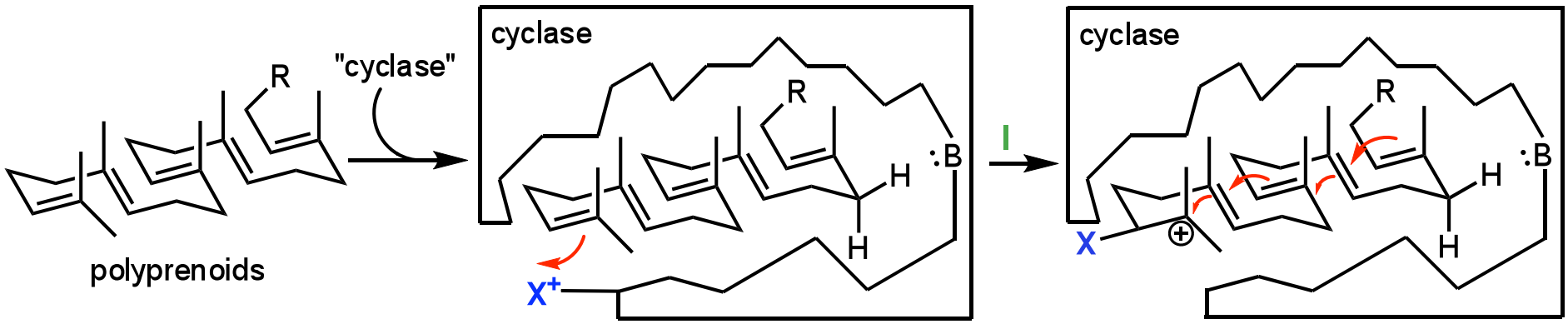
Faulkner, D. J.; Wolinsky, L. E. *J. Org. Chem.* **1976**, *41*, 597

Application to Total Synthesis: (±) Concinndiol



Yamaguchi, Y.; Uyehara, T.; Kato, T. *Tetrahedron Lett.* **1985**, *26*, 343

Asymmetric Induction *via* Chiral Halogenation



I : Carbonium ion formation

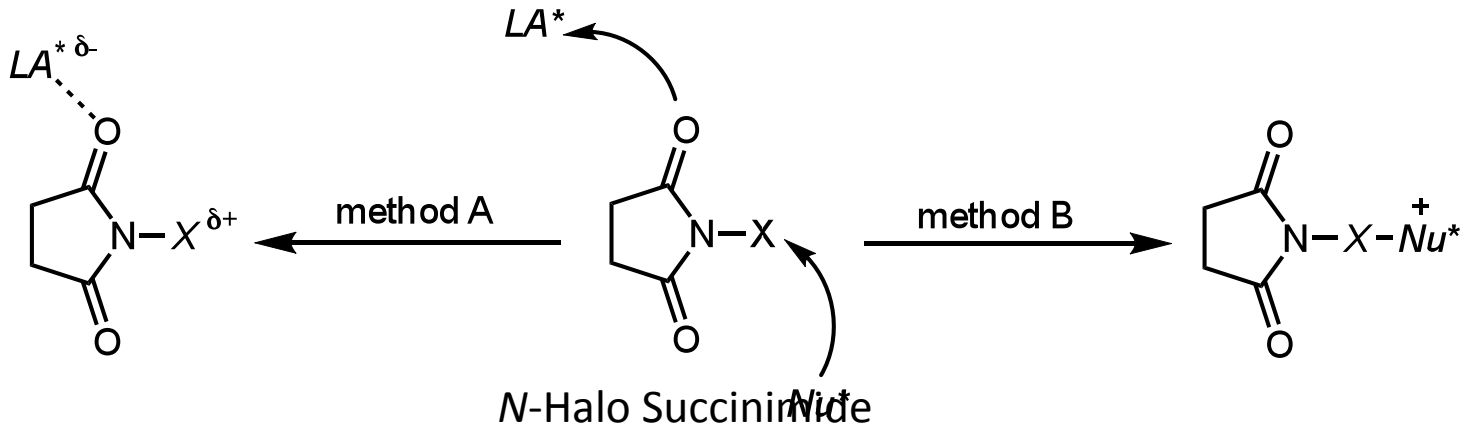
Requirements for an artificial cyclase:

- To recognize the stereoface of a simple olefin that does not bear a directing group.
- To generate a terminal carbocation selectively by halogenation.

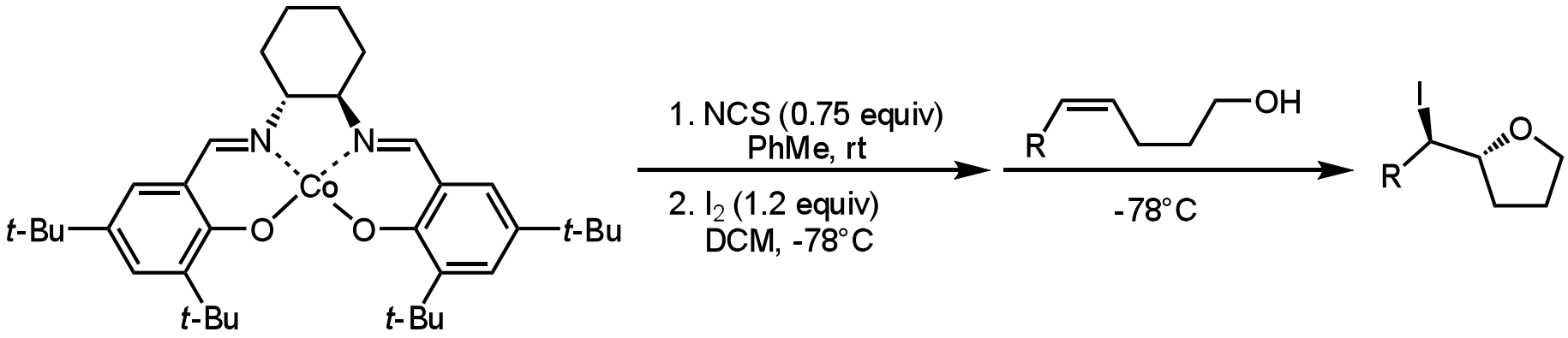
Solution:

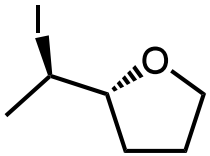
- Using a chiral halonium ion source ⟶ Chiral activators for halogenating reagents

Different Approaches for Asymmetric Activation of Halogenating Reagents

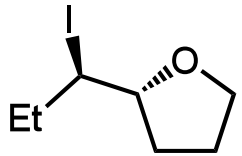


Catalytic Enantioselective Iodocyclization of γ-hydroxy-*cis*-alkenes

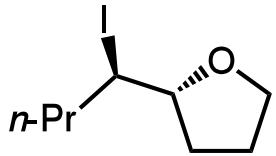




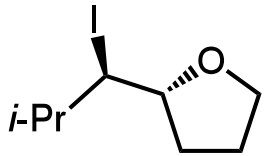
96%, 67%*ee*



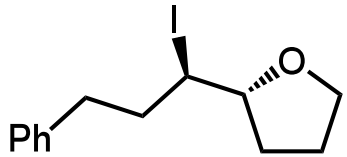
89%, 82%*ee*



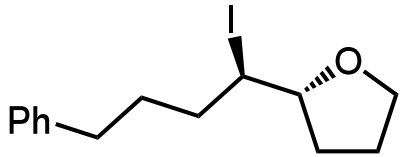
85%, 85%*ee*



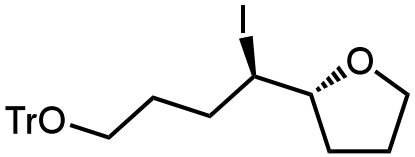
83%, 73%*ee*



94%, 86%*ee*



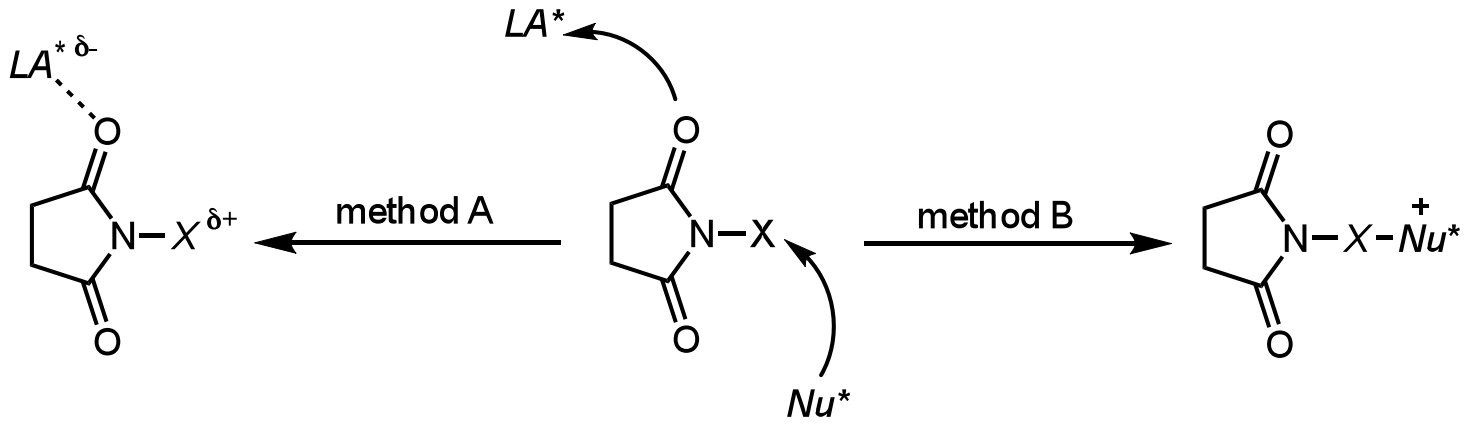
94%, 84%*ee*



89%, 90%*ee*

Kang, S. H.; Lee, S. B.; Park, C. M. *J. Am. Chem. Soc.* **2003**, *125*, 15748

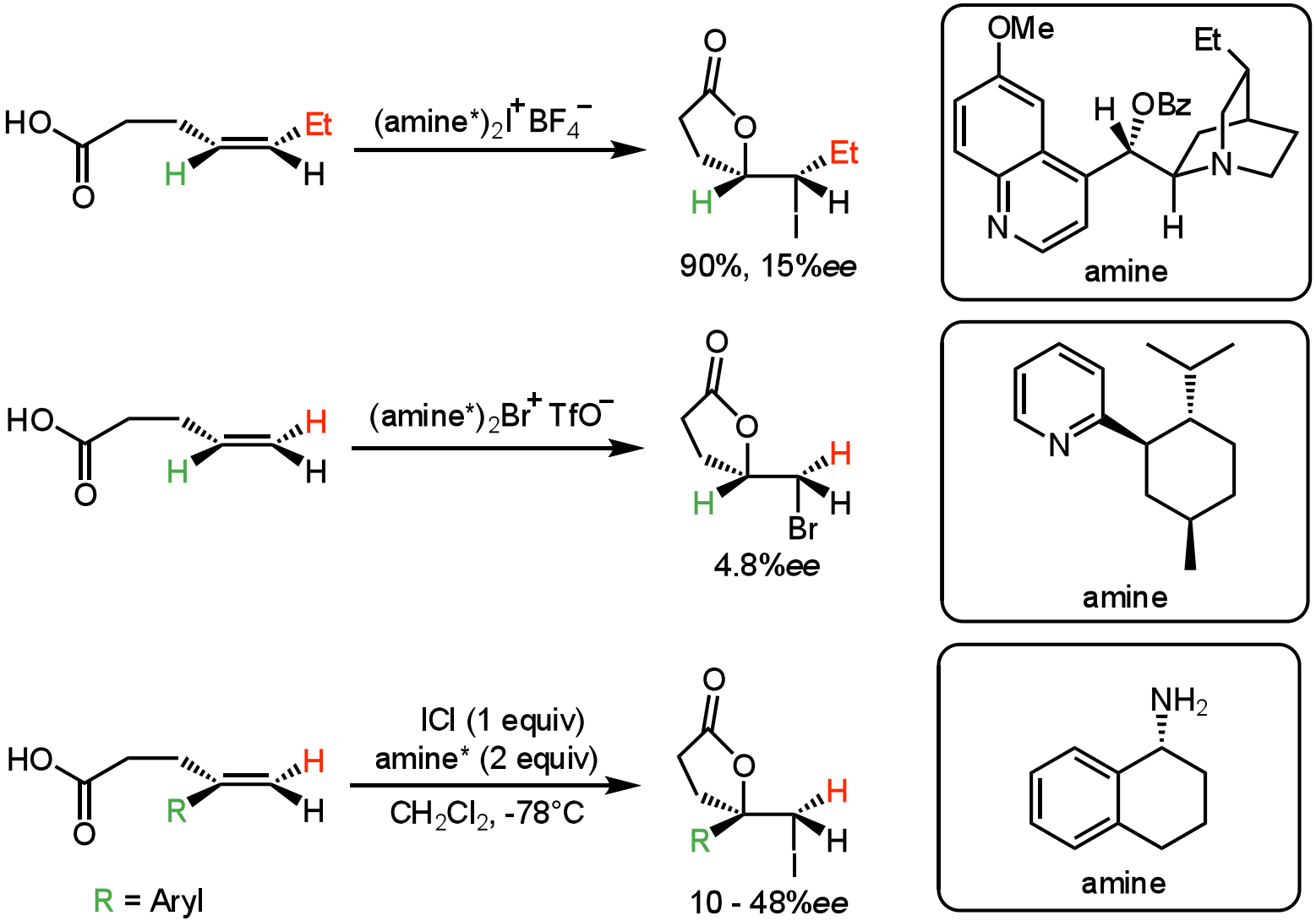
Different Approaches for Asymmetric Activation of Halogenating Reagents



Activation by Lewis Acid

Activation by Chiral Nucleophilic Promoter

Enantioselective Iodolactonization

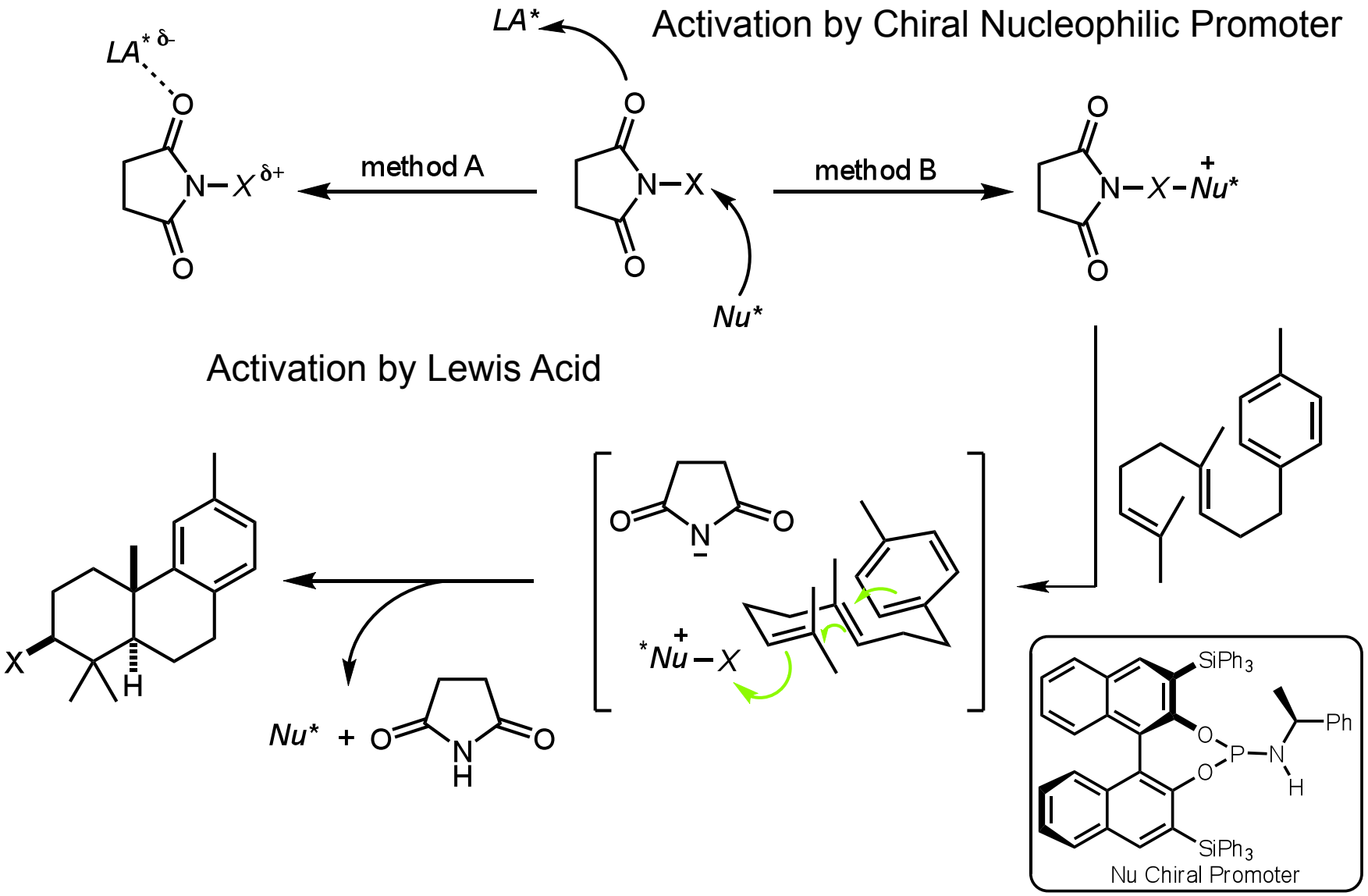


Grossman, R. B.; Trupp, R. J. *Can. J. Chem.* **1998**, *76*, 1233

Cui, X. L.; Brown, R. S *J. Org. Chem.* **2000**, *65*, 5653

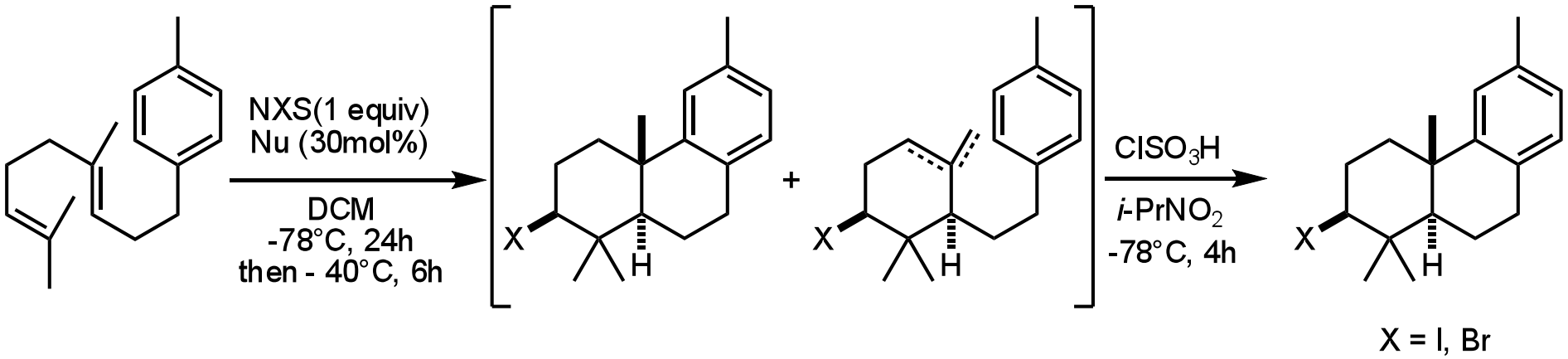
Haas, J., Piguel, S.; Wirth, T. *Org. Lett.* **2002**, *4*, 297

First Enantioselective Halocyclization of Polyprenoids



Isihara, K.; Sakakura, A.; Ukai, A. *Nature*, **2007**, *445*, 900

Reaction Design: Activation by Achiral Nucleophile

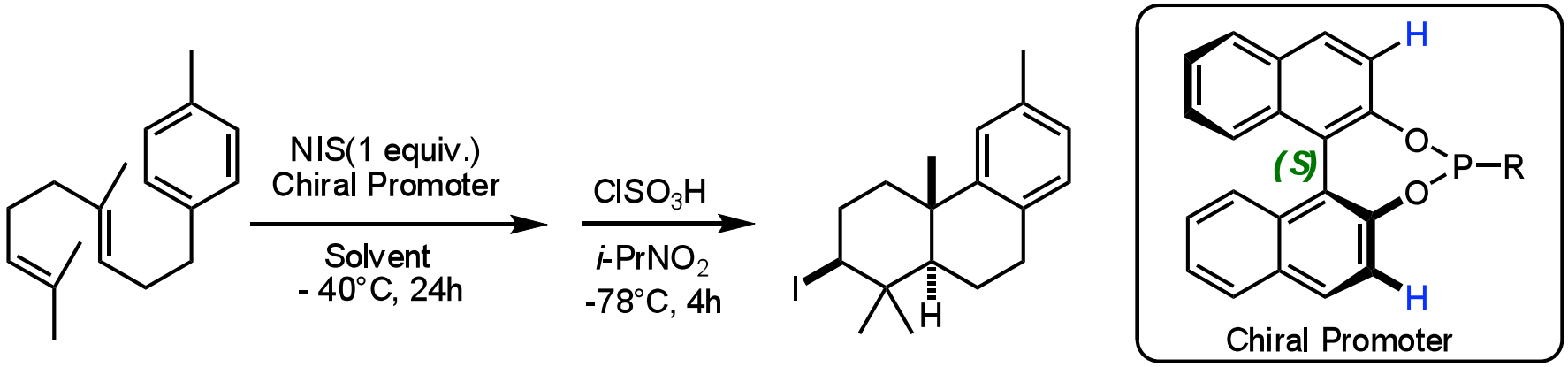


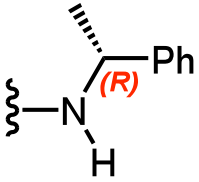
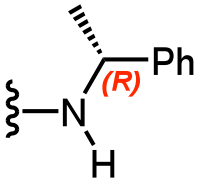
X = I, Br

Entry	Nu	Yield (%)	
		X = I	X = Br
1	PBu_3	99	81
2	PPh_3	67	71
3	$P(OPh)_3$	51	60
4	DMAP	0	0
5	DABCO	0	0
6	No catalyst	3	0

Isihara, K.; Sakakura, A.; Ukai, A. *Nature*, **2007**, *445*, 900

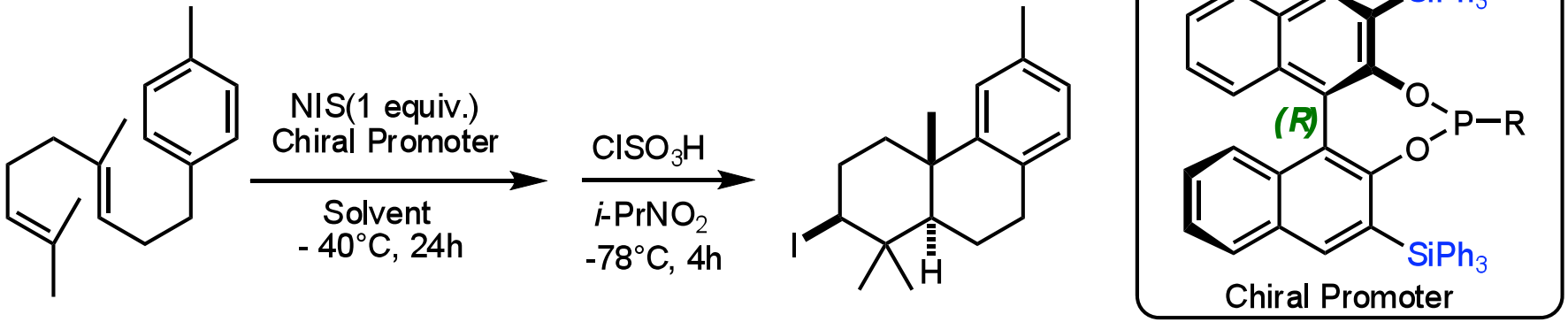
Reaction Design: Screening of Chiral Promoter

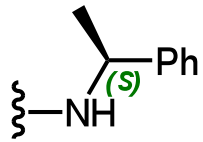
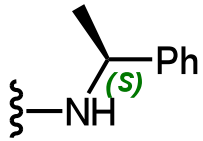
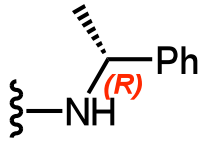
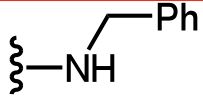


Entry	Chiral Promoter		Solvent	Yield(%)	*ee*(%)
	R	mol%			
1		30	DCM	46	0
2		30	DCM	95	0
3		100	Toluene	11	0

Isihara, K.; Sakakura, A.; Ukai, A. *Nature*, **2007**, *445*, 900

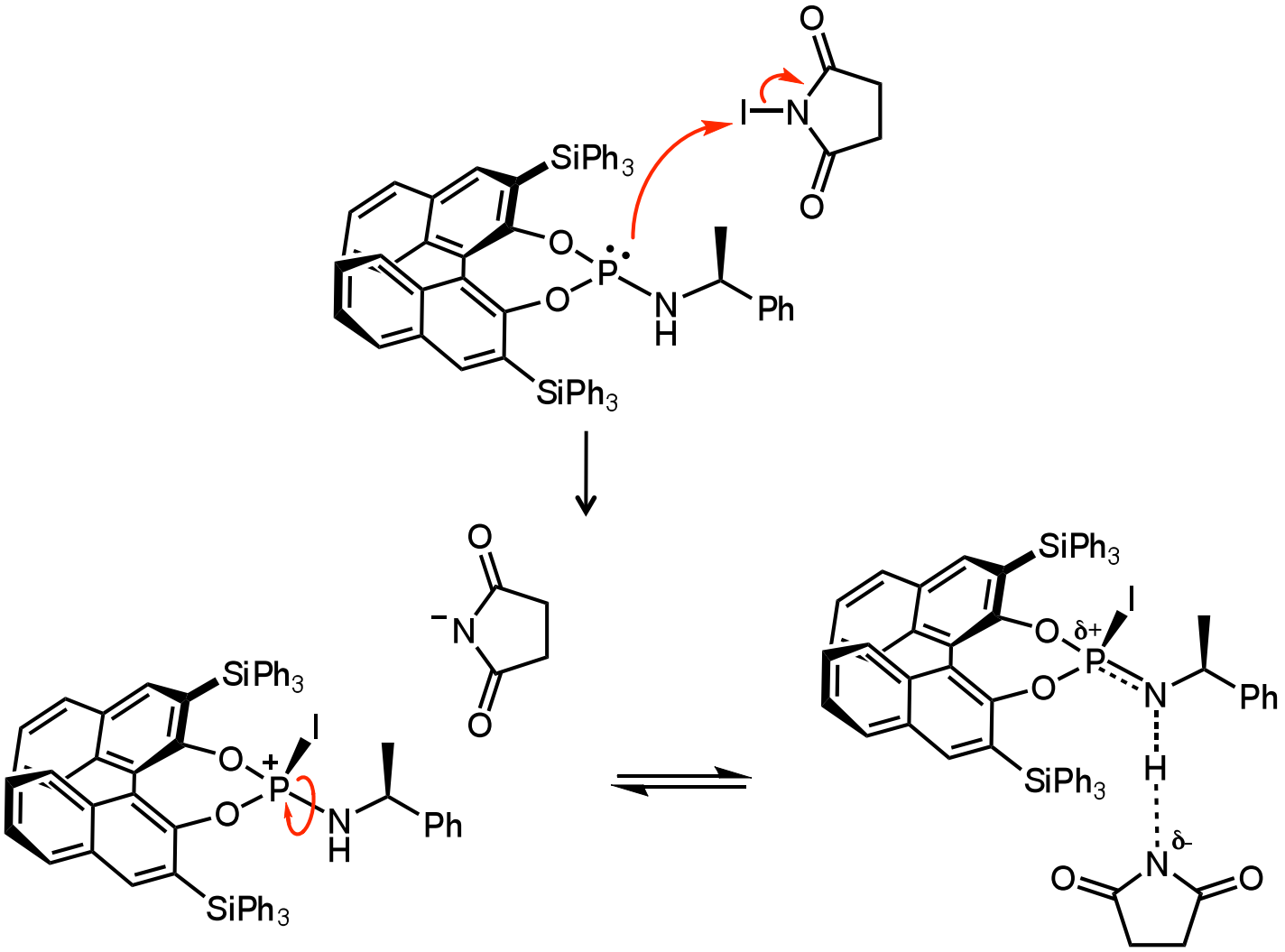
Reaction Design: Screening of Chiral Promoter



Entry	Chiral Promoter R	Chiral Promoter mol%	Solvent	Yield(%)	*ee*(%)
4		100	DCM	95	0
5		100	Toluene	Matched Pair 57	95
6		100	Toluene	Mismatched Pair 0	nd
7		100	Toluene	34	34

Isihara, K.; Sakakura, A.; Ukai, A. *Nature*, **2007**, *445*, 900

Rationale for Solvent Effect: Toluene vs DCM

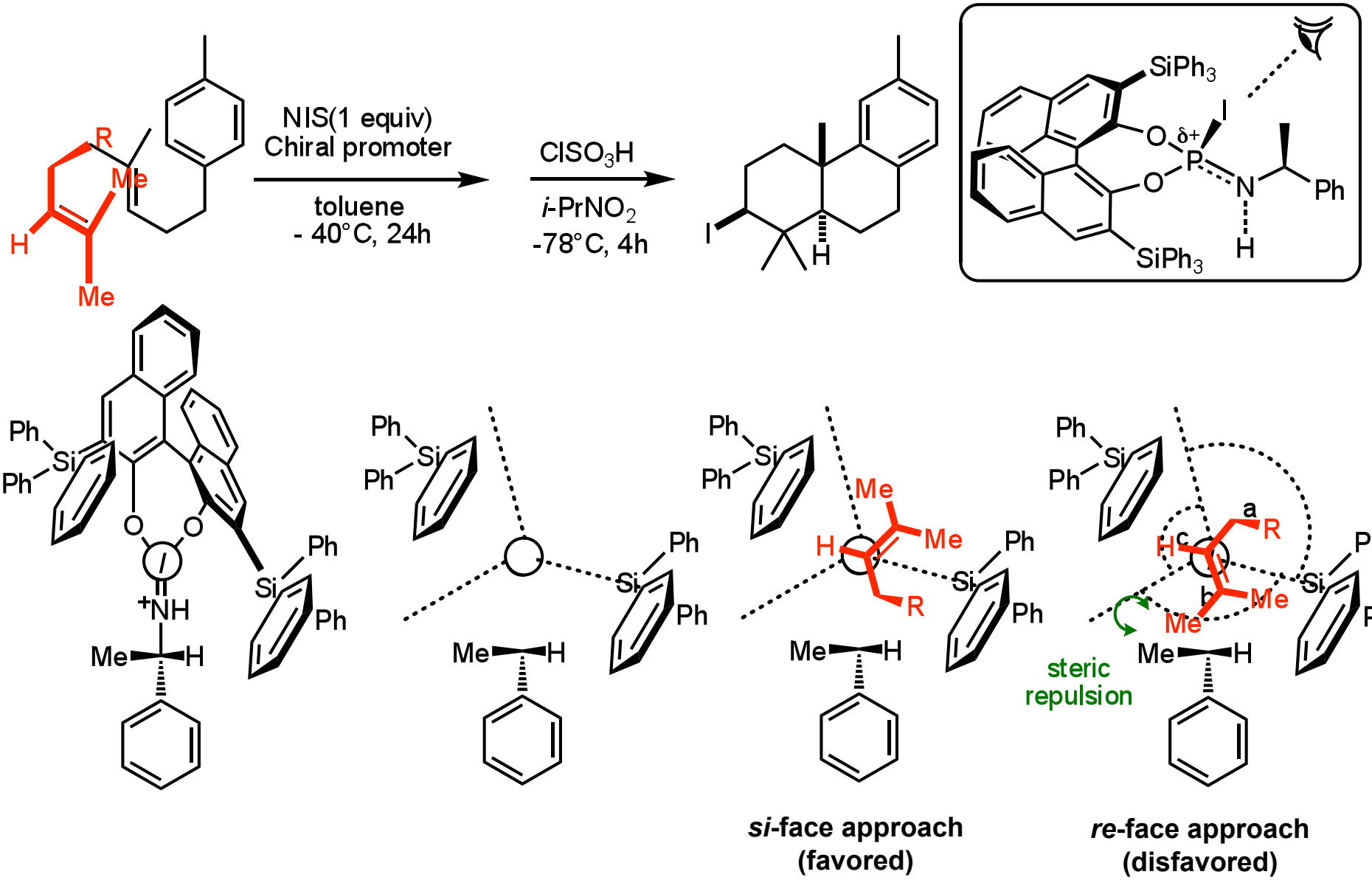


Ionic Species **A**
(more active)
(in dichloromethane)

Tight Ion-pair Species **B**
(less active)
(in toluene)

Isihara, K.; Sakakura, A.; Ukai, A. *Nature*, **2007**, *445*, 900

Rationale for Stereochemical Outcome

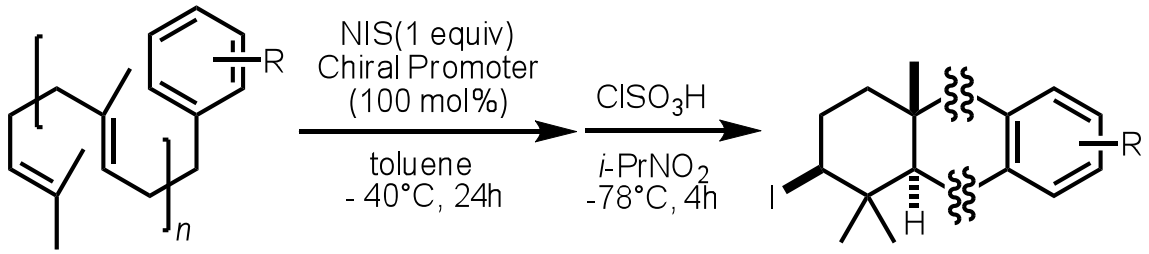


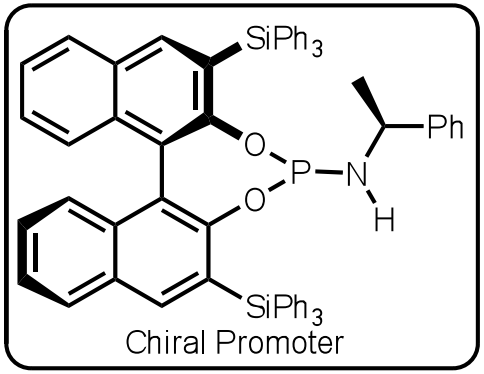
***si*-face approach (favored)**

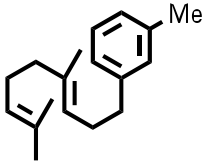
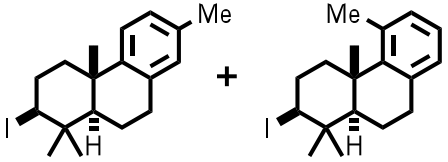
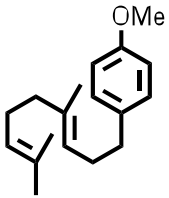
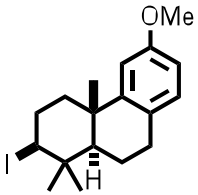
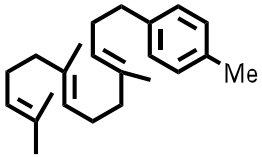
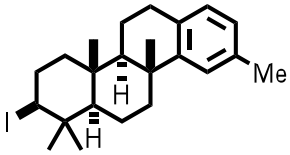
***re*-face approach (disfavored)**

Isihara, K.; Sakakura, A.; Ukai, A. *Nature*, **2007**, *445*, 900

Enantioselective Iodocyclization: Substrate Scope



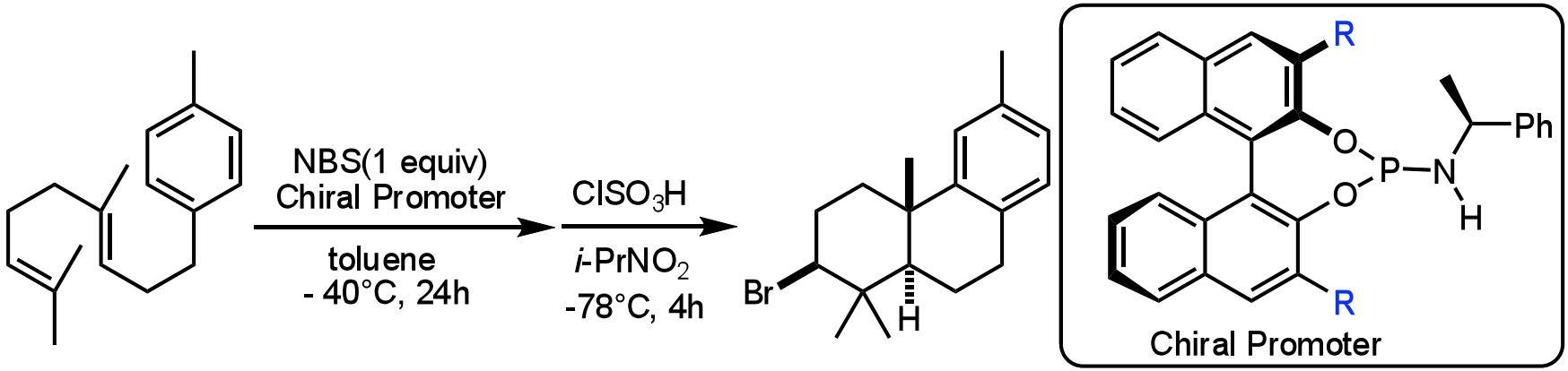


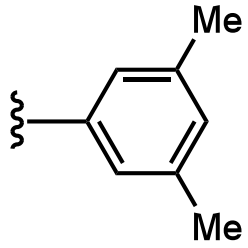
Entry	Reactant	Product	Yield (%)	*ee* (%)	*dr*
1			64 (2:1)	91*	-
2			58	91	-
3			52	99	94:6

* *ee* of major product

Isihara, K.; Sakakura, A.; Ukai, A. *Nature*, **2007**, *445*, 900

Limitation: Enantioselective Bromocyclization

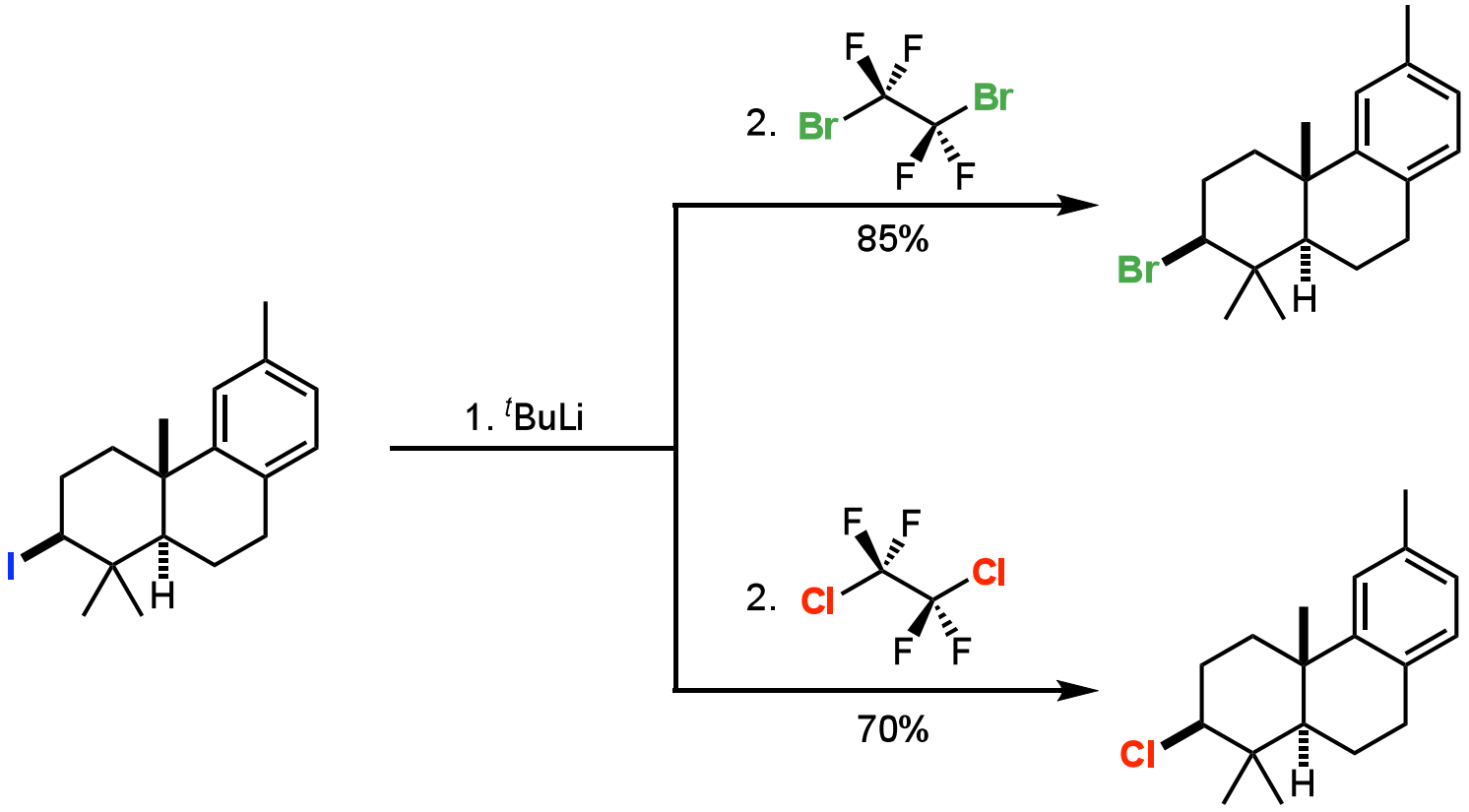


Entry	R	Yield(%)	*ee*(%)
1		29	4
2		75	36

* No reactivity with *N*-Chloro Succinimide

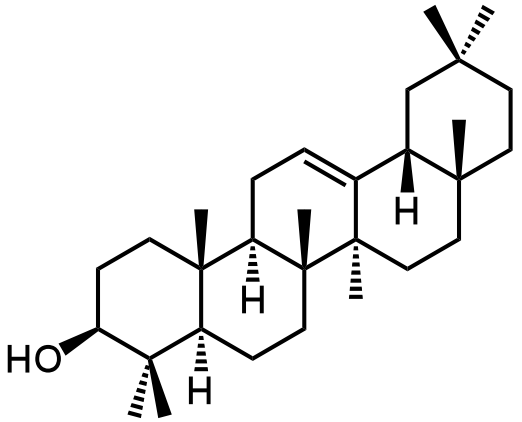
Isihara, K.; Sakakura, A.; Ukai, A. *Nature*, **2007**, *445*, 900

Solution: Stereoselective Transhalogenation



Isihara, K.; Sakakura, A.; Ukai, A. *Nature*, **2007**, *445*, 900

Conclusion



Enzymes can:

- activate unreactive substrates like simple olefin.
- form multiple bonds with multi-faceted selectivity.

Inspiration from nature:

- developing synthetic route following nature's techniques.
- designing artificial cyclase which creates complex organic architechtures

BUT Nature still creates the most selective catalyst!!

Future Prospects:

- Polyene system → (artificial cyclase; enantioselective E^+ addition) → (achiral promoter; subsequent diastereoselctive cyclization) → Polycyclic System

artificial cyclase

catalytic

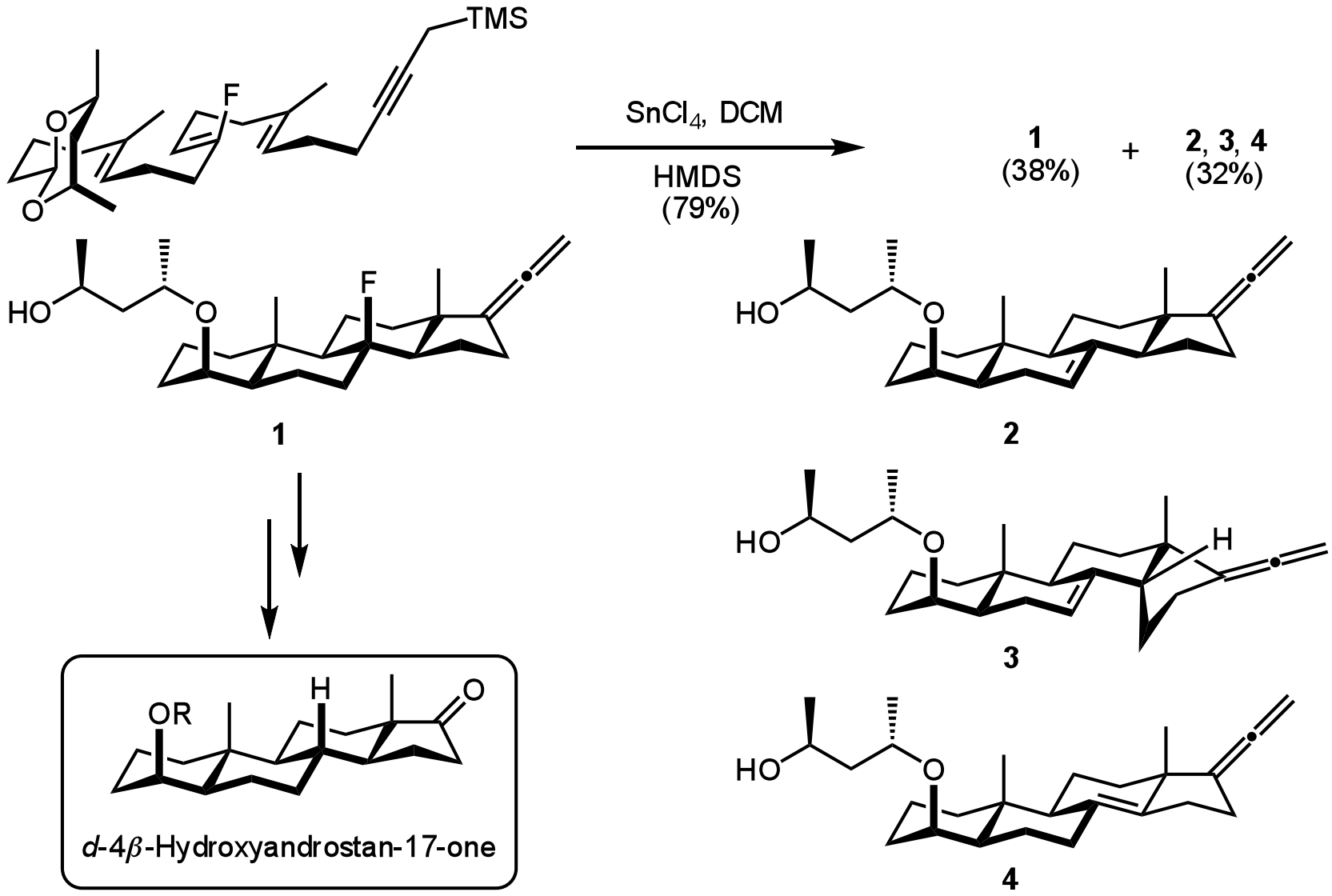
Acknowledgement

Dr. Wulff

Dr. Walker Dr. Borhan

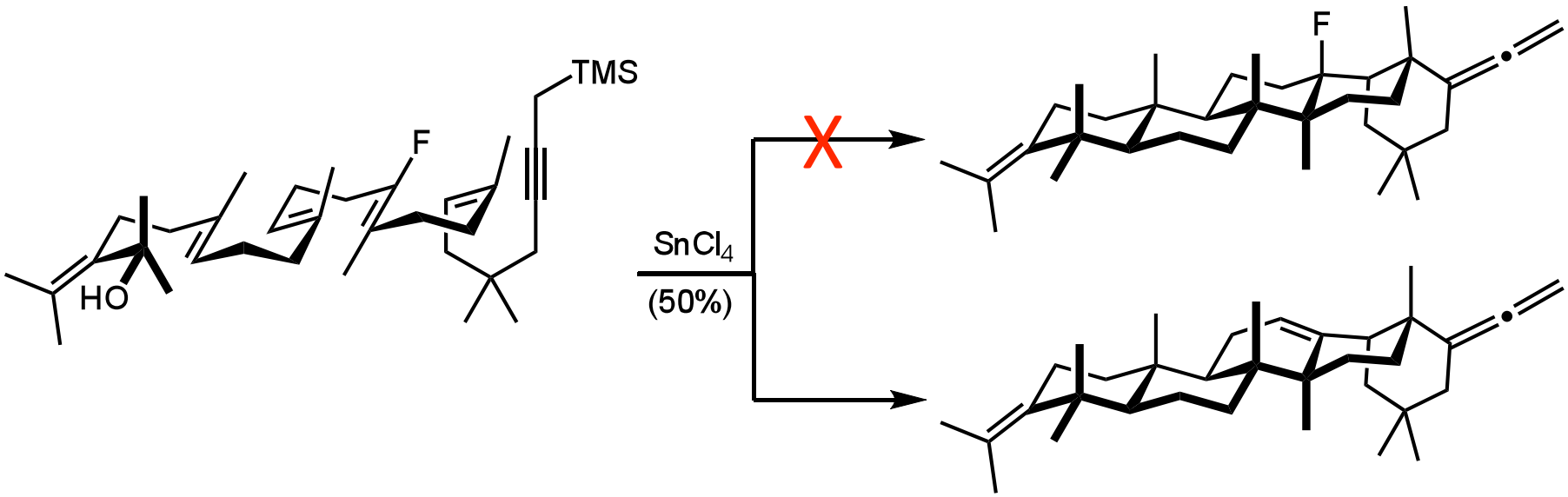
Victor, Ding, Zhenjie, Aman, Alex, Li, Nilanjana,
Dima, Yong, Hong, Wynter, Anil

Different Approaches Towards Polyene Cyclizations: Acetals

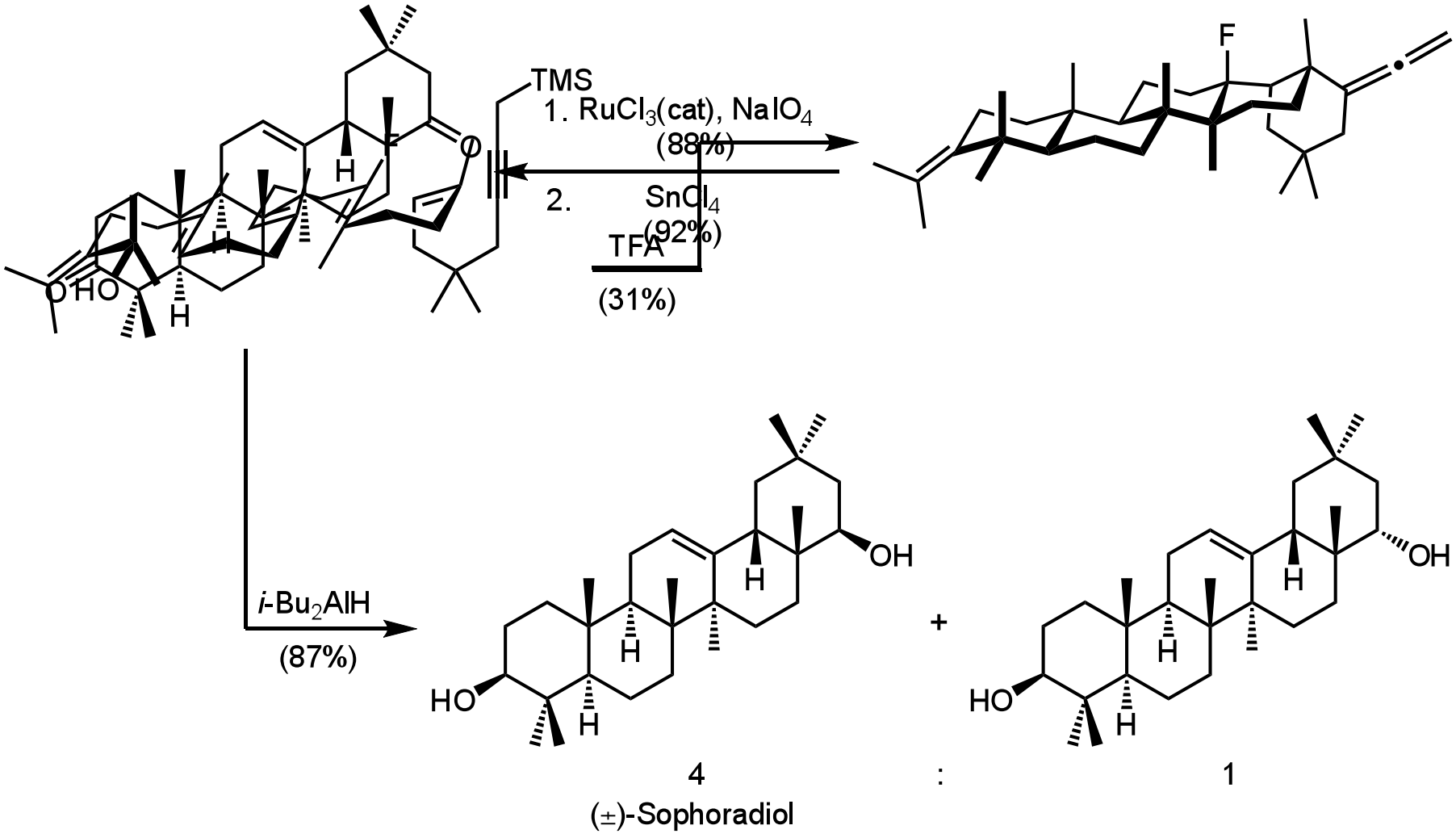


Johnson, W. S.; Fletcher, V. R.; Chenera, B.; Bartlett, W. R.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 497

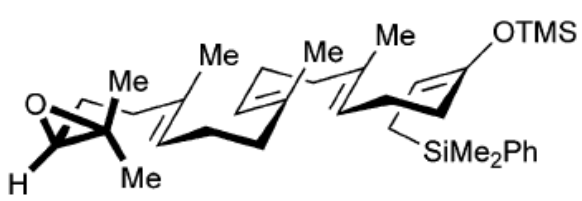
Different Approaches Towards Polyene Cyclizations Allylic Alcohols :- Total synthesis of (-)- Sophoradiol



Different Approaches Towards Polyene Cyclizations
Allylic Alcohols :- Total synthesis of (-)- Sophoradiol

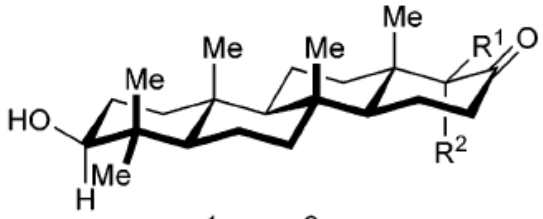


Different Approaches Towards Polyene Cyclizations: Epoxide



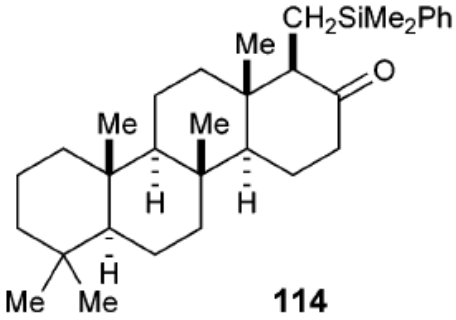
111

1. $MeAlCl_2$
2. HF, CH_3CN
3. KOH, MeOH
(30%)



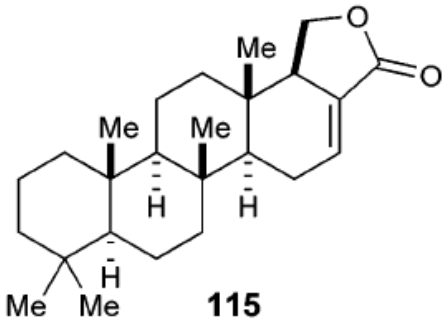
112, R^1=H, R^2=CH_2SiMe_2Ph
113, R^1=CH_2SiMe_2Ph, R^2=H

1. C_6F_5OCSCl
2. Bu_3SnH, AIBN
(89%)



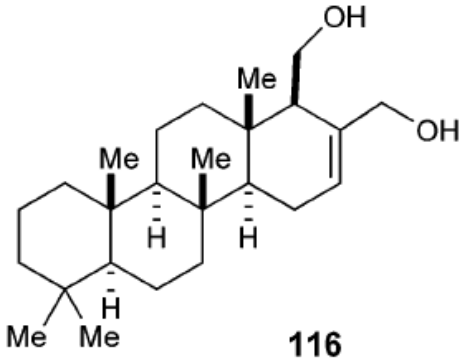
114

1. KHMDS, $PhNTf_2$
2. BF_3•HOAc
3. KF, H_2O_2
4. $Pd(OAc)_2$, dppp, CO
(85%)



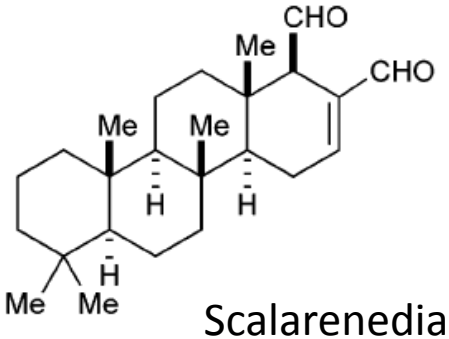
115

$^iBu_2AlH$
(95%)



116

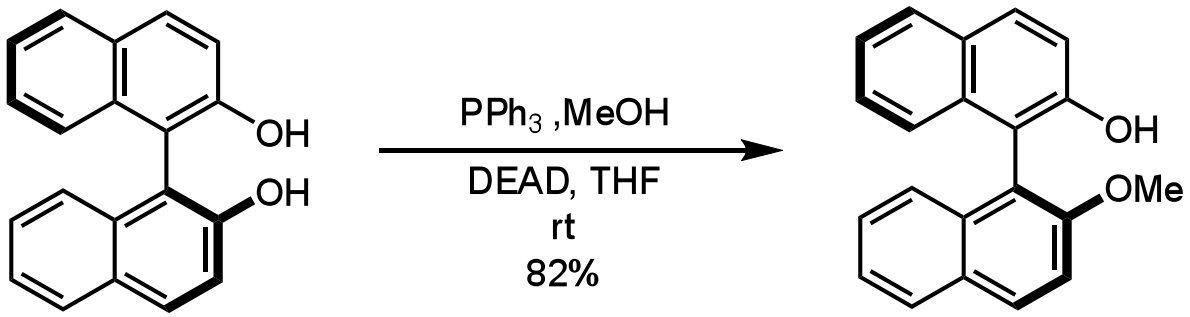
$(COCl)_2$, DMSO
Et_3N
(90%)



Scalarenedial

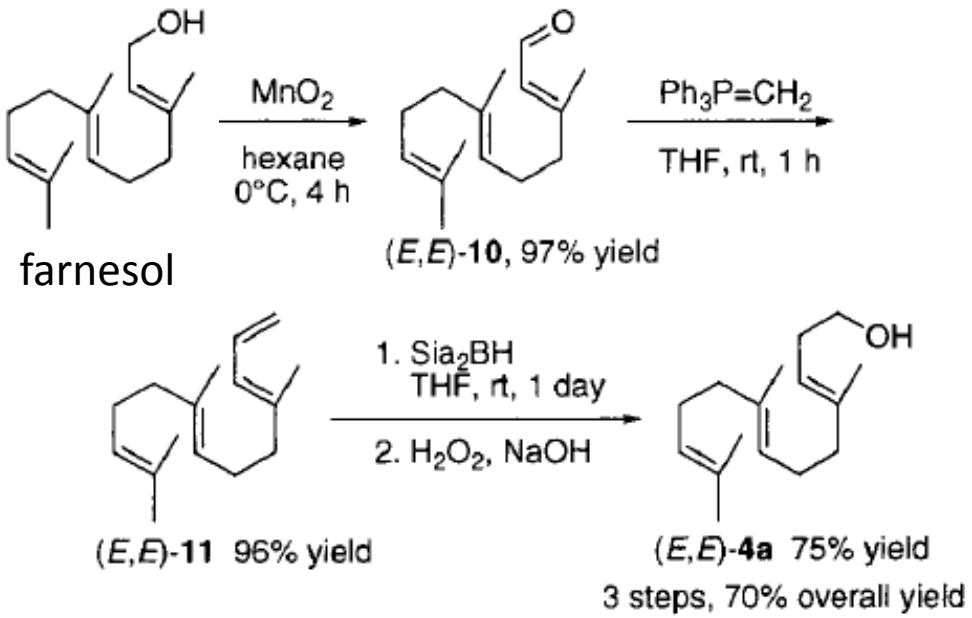
Corey, E. J.; Luo, G.; Lin, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 9927

Preparation of the Catalyst (LBA)



Takashi, M.; Ogasawara, K. Tetrahedron Aysmmetry **1997**, *8*, 3125

Synthesis of Homofarnesol



farnesol

(*E*,*E*)-**10**, 97% yield

(*E*,*E*)-**11** 96% yield

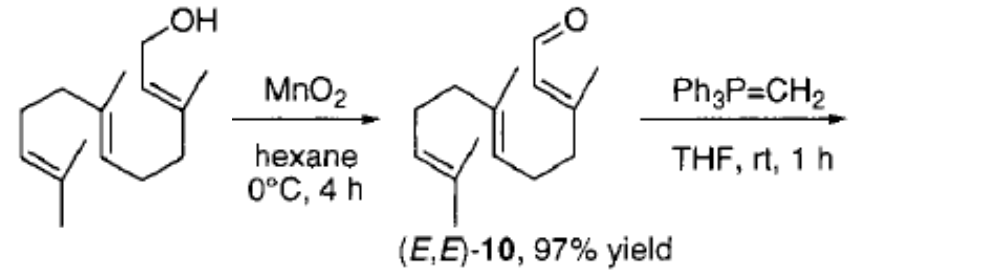
(*E*,*E*)-**4a** 75% yield

3 steps, 70% overall yield

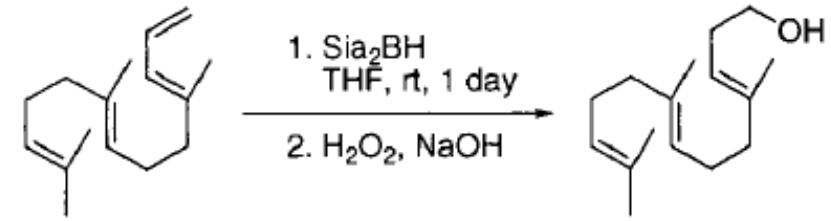
homofarnesol

Yamamoto, H.; Isihara, K.; Ishibashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647

Modified Approach Towards (-)-Ambrox



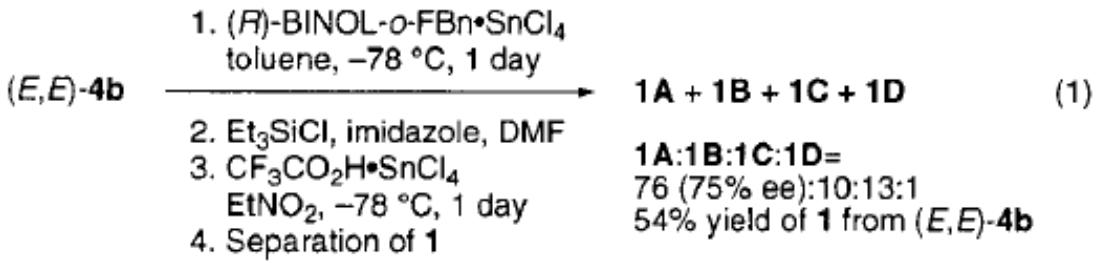
(*E*,*E*)-**10**, 97% yield



(*E*,*E*)-**11** 96% yield

(*E*,*E*)-**4a** 75% yield

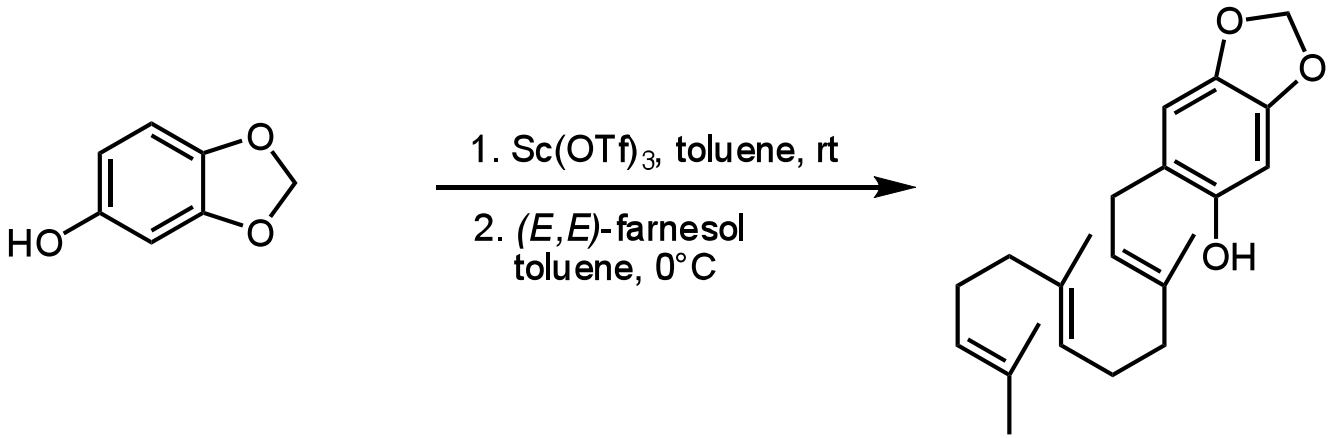
3 steps, 70% overall yield



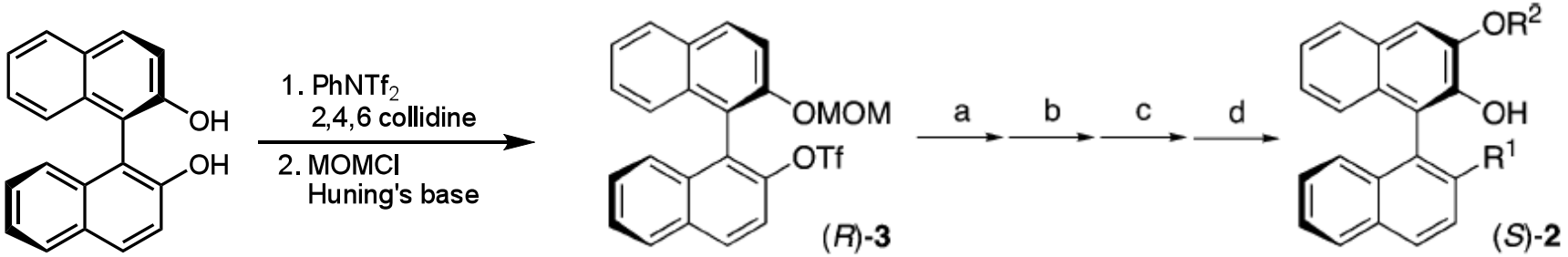
1A = (-) Ambrox

Yamamoto, H.; Isihara, K.; Ishibashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647

A New Artificial Cyclase for Polyolefinic Phenol Derivatives: Substrate and Catalyst



Scheme 1. Synthesis of **2**[a]



[a] Conditions: (a) R^1MgX, $NiCl_2$(dppe), THF, reflux (>95%). (b) BuLi, TMEDA, THF; $B(OMe)_3$; aq HCl; H_2O_2, NaOH, THF (87%). (c) R^2OH, PPh_3, DEAD, THF (>99%). (d) aq HCl, dioxane, reflux (>95%).

Yamamoto, H.; Isihara, K.; Nakamura, S. *J. Am. Chem. Soc.* **2004**, *126*, 11122

Application to Synthesis of Diterpenoids: Possible Reaction Pathways leading to Cis (major) Product

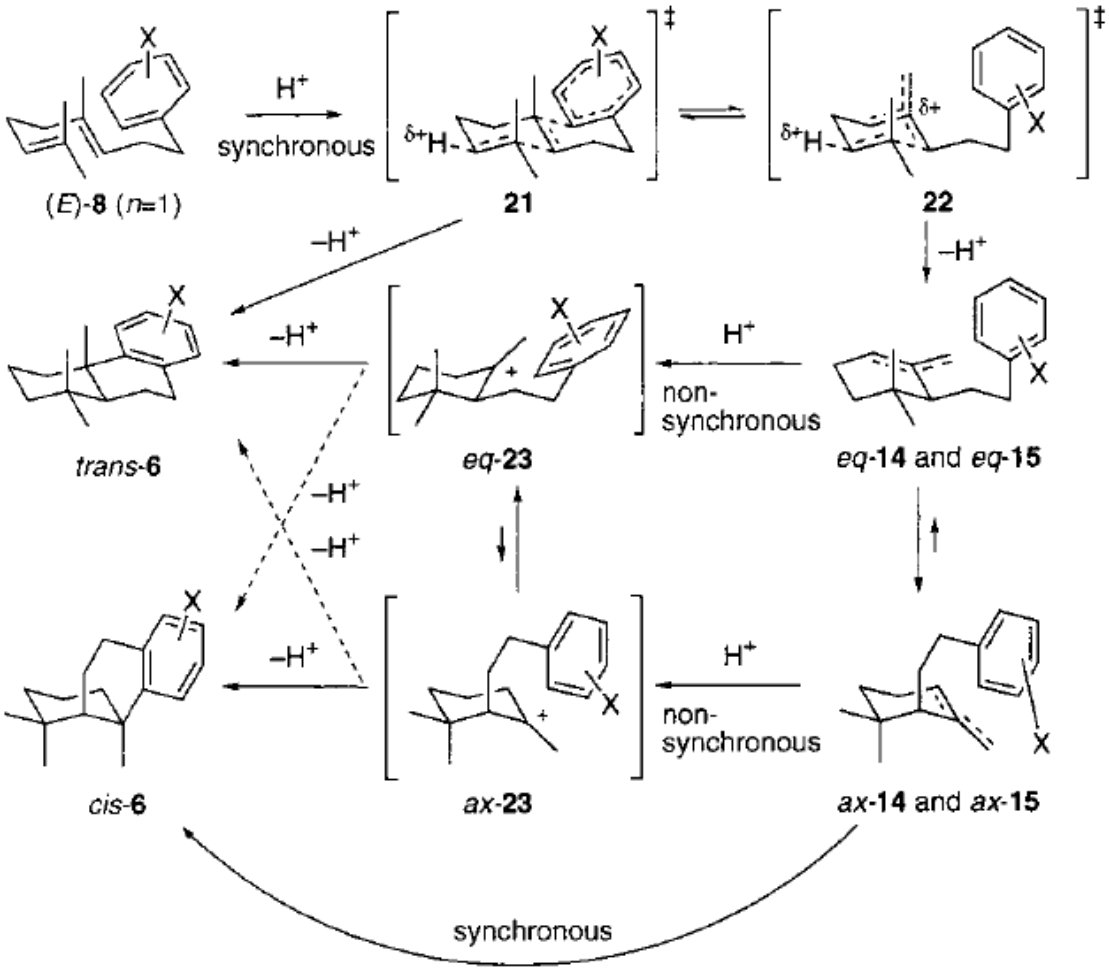
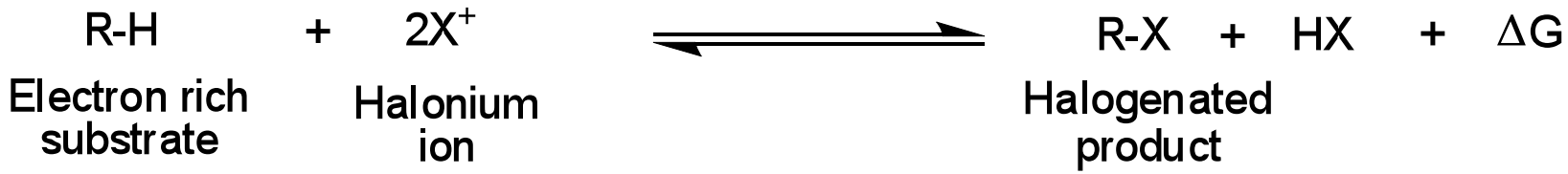


Figure 2. Possible reaction paths for the acid-induced cyclization of (*E*)-**8** ($n = 1$).

Yamamoto, H.; Isihara, K.; Ishibashi, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647

Halogenation Begins

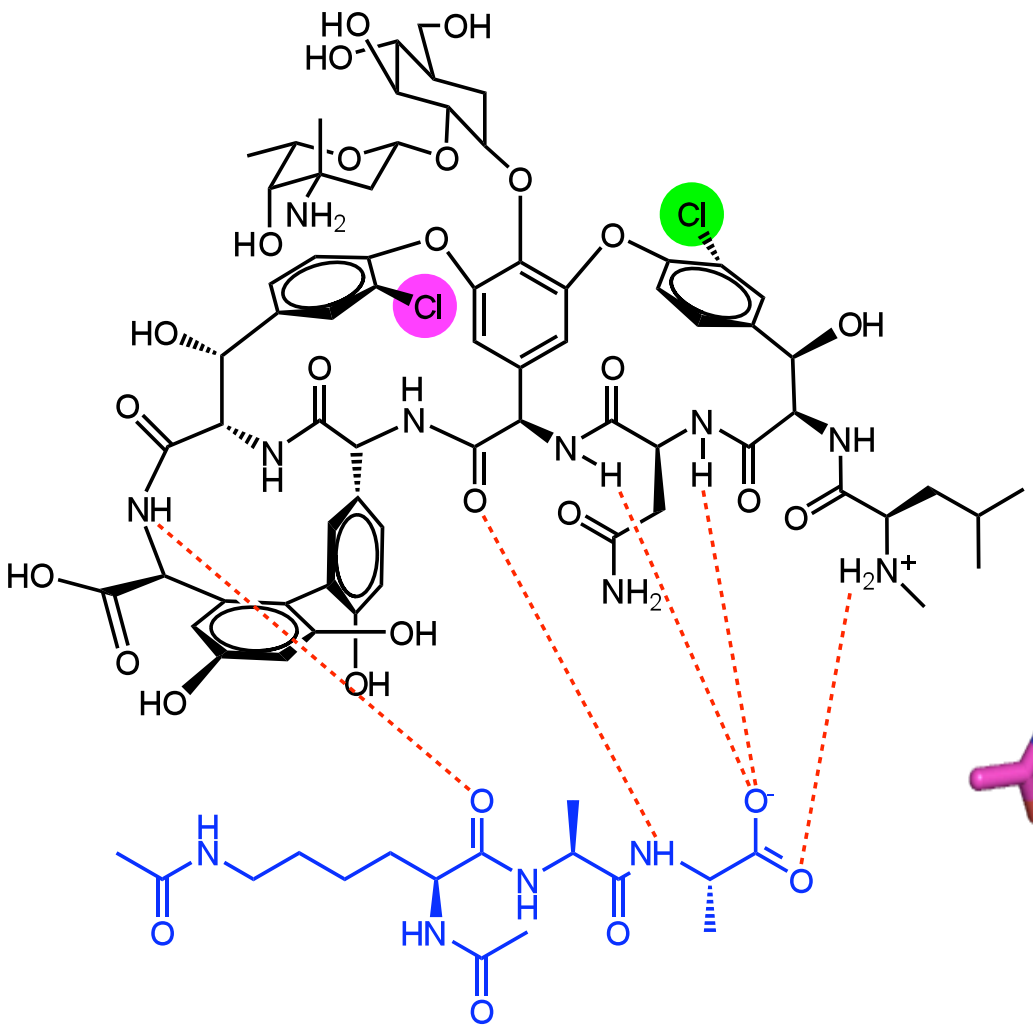
F vs. Cl, Br, I

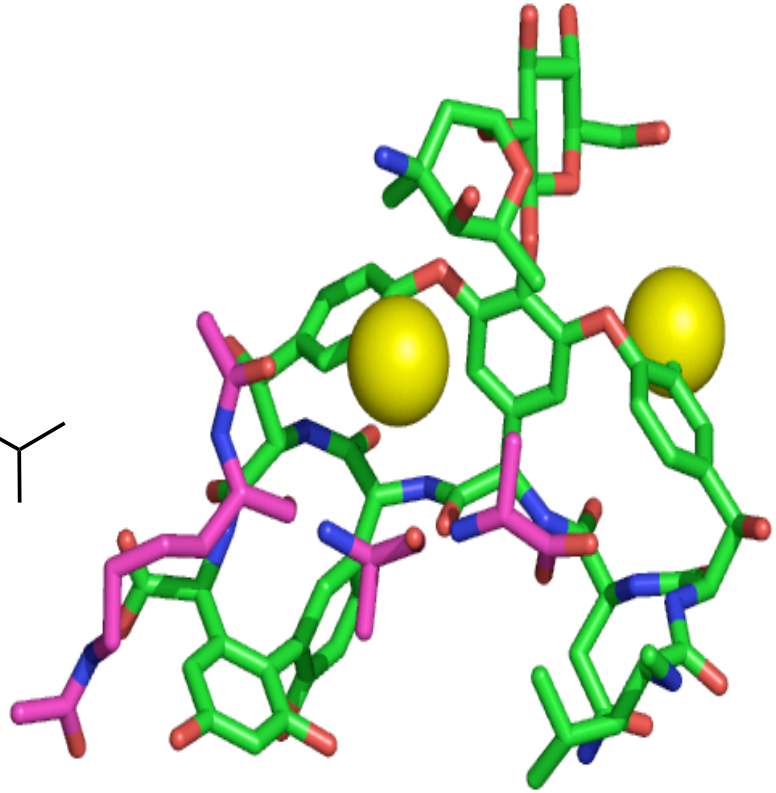


Gibbs Free Energy = $-nFE^o$

Half Reaction	E^o, volts
$2F^- \rightleftharpoons F_2 + 2e^-$	-3.06
$2Cl^- \rightleftharpoons Cl_2 + 2e^-$	-1.36
$2Br^- \rightleftharpoons Br_2 + 2e^-$	-1.07
$2I^- \rightleftharpoons I_2 + 2e^-$	-0.54

Importance of Halogens in Natural Products

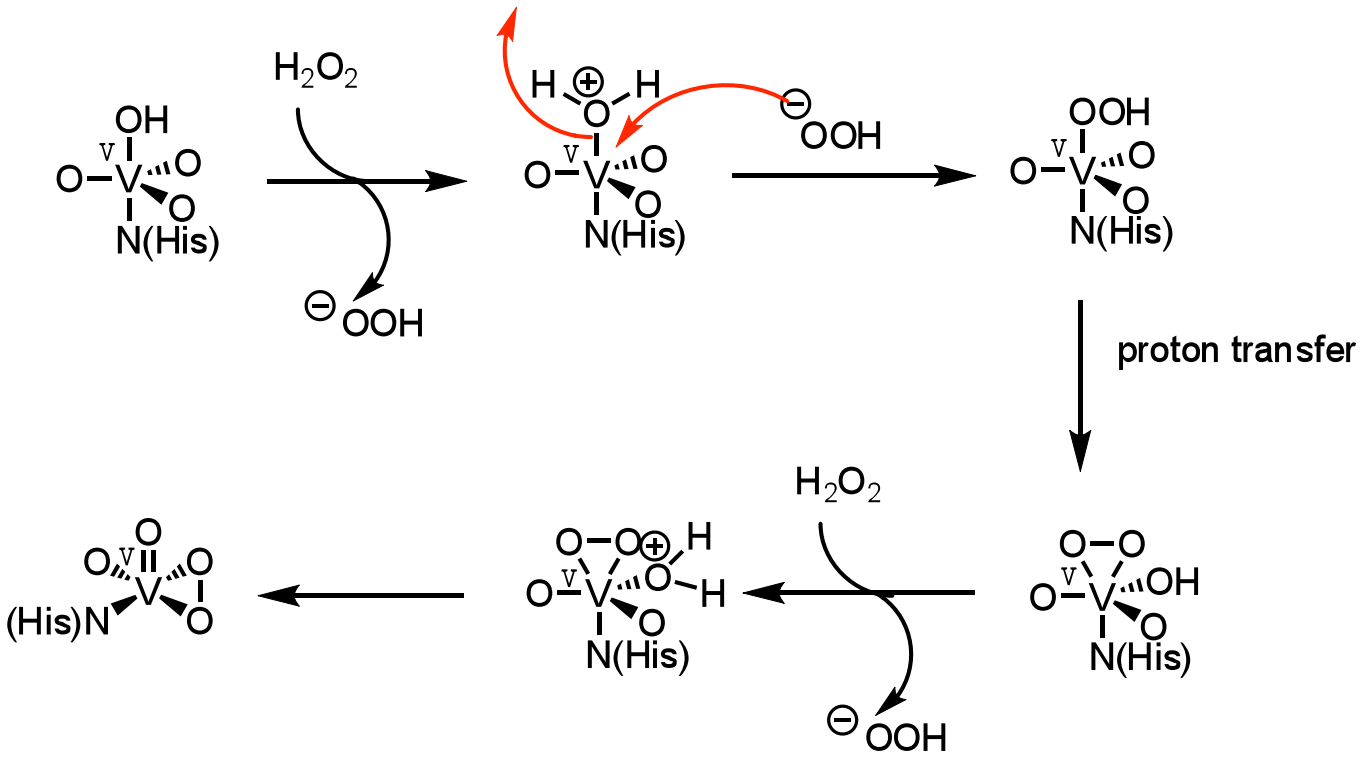




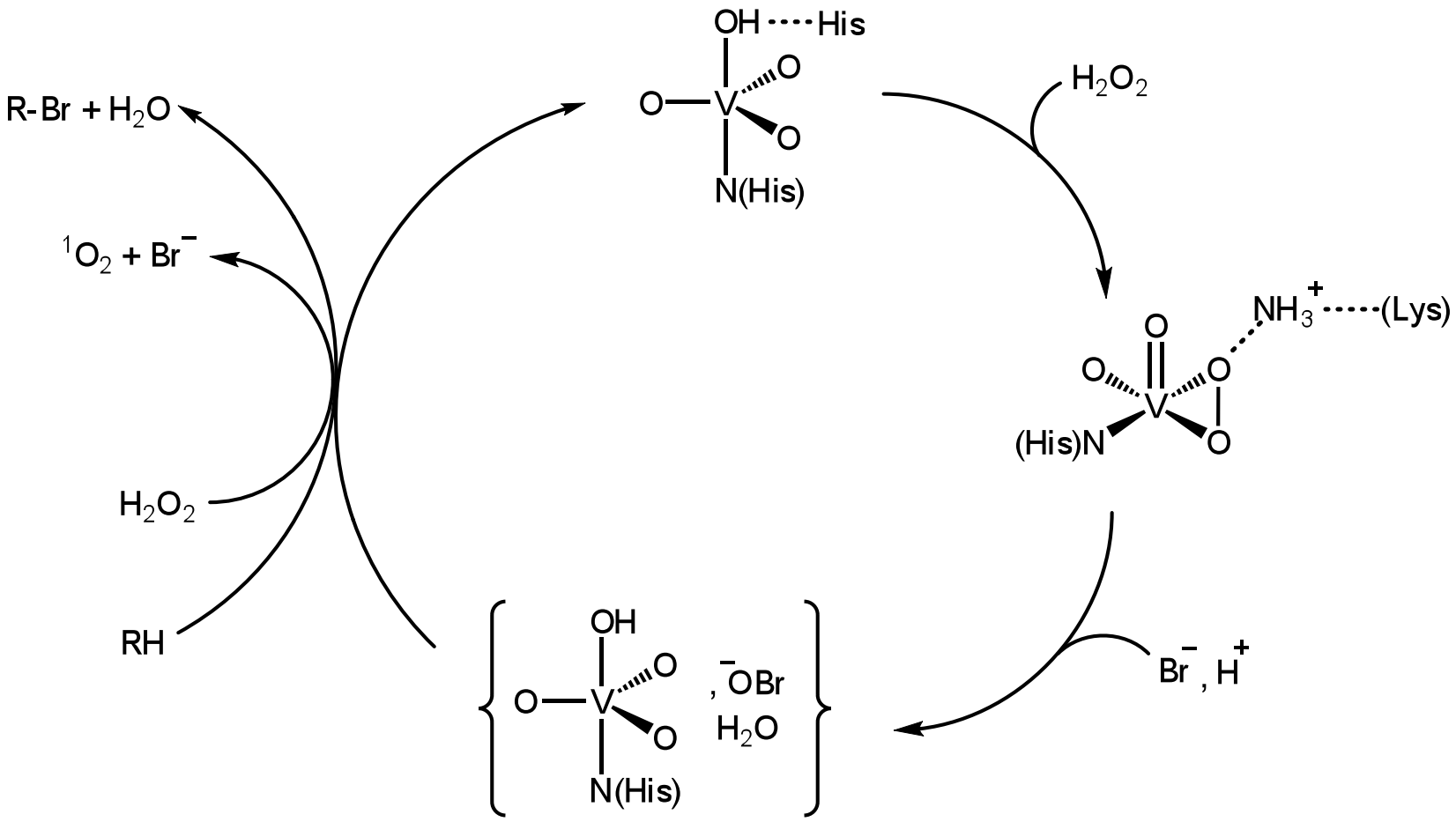
Gerhard, U.; Mackay, J.; Maplestone, R.; Williams, D. *J. Am. Chem. Soc*. **1993**, *115*, 232

Dale, L. B. *Med. Res. Rev* **2001**, *21*, 356

Enzymatic Halocyclization: Mechanism

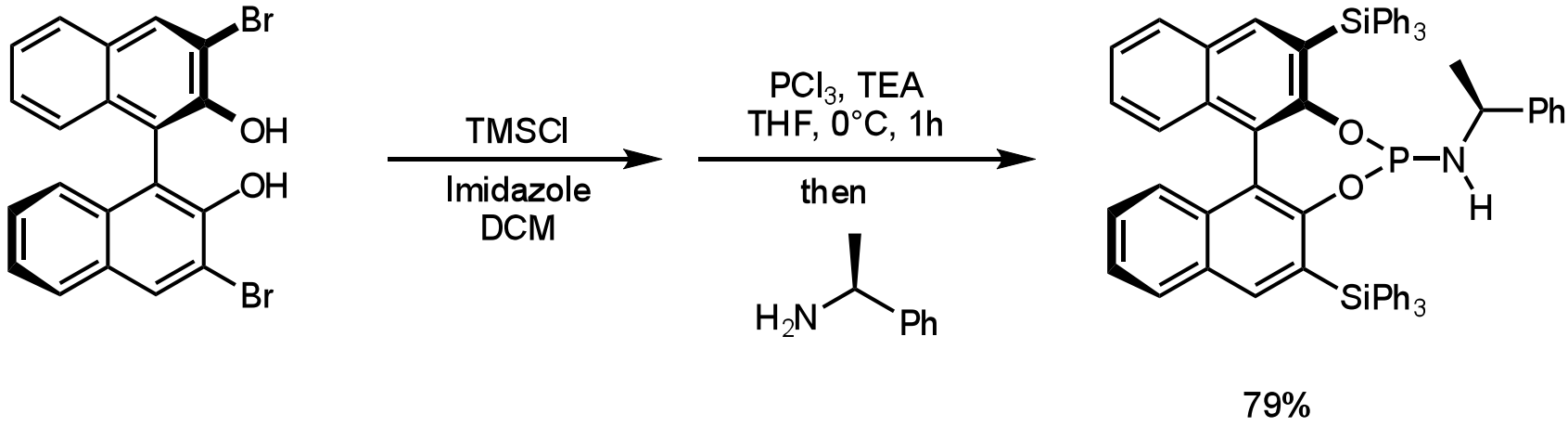


Enzymatic Halocyclization: Mechanism



Everett, R. R.; Soedjak, H. S.; Butler, A. *J. Biol. Chem.* **1990**, *265*, 15671

Preparation of the Catalyst

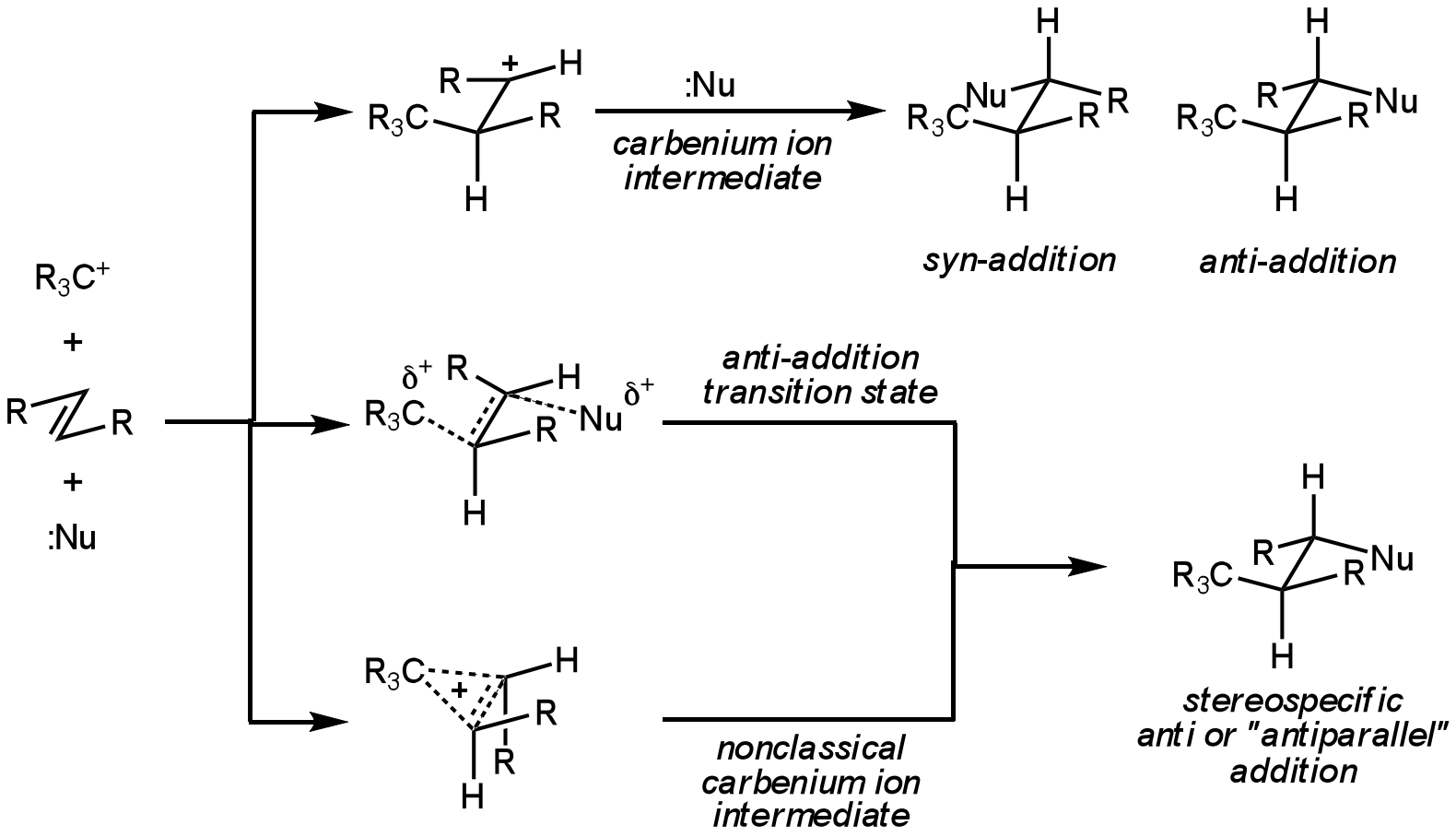


79%

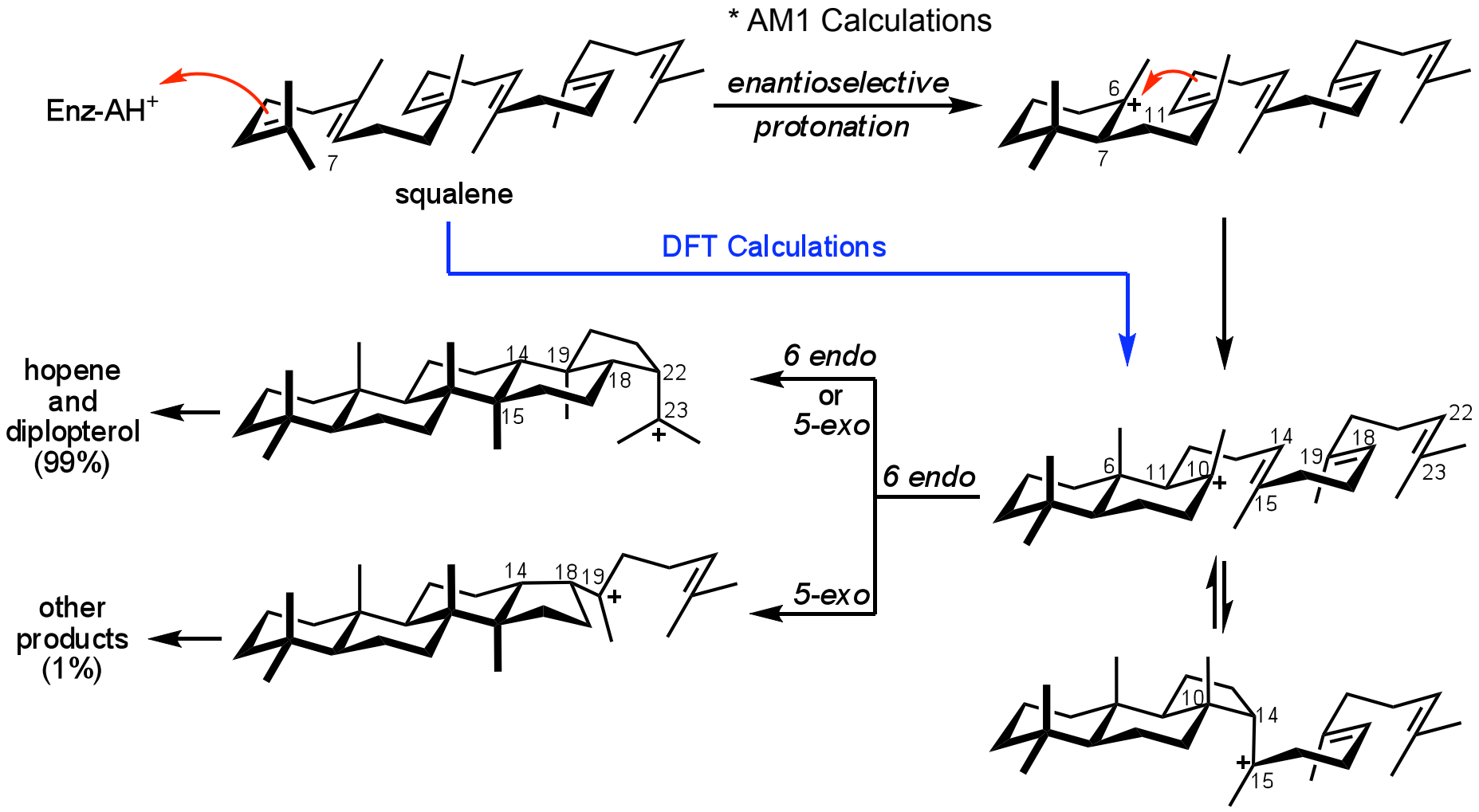
Maruoka, K.; Itoh, T.; Araki. Y.; Shirasaka, T.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2975

Misc…

Mechanistic Possibilities of Polyene Cyclization

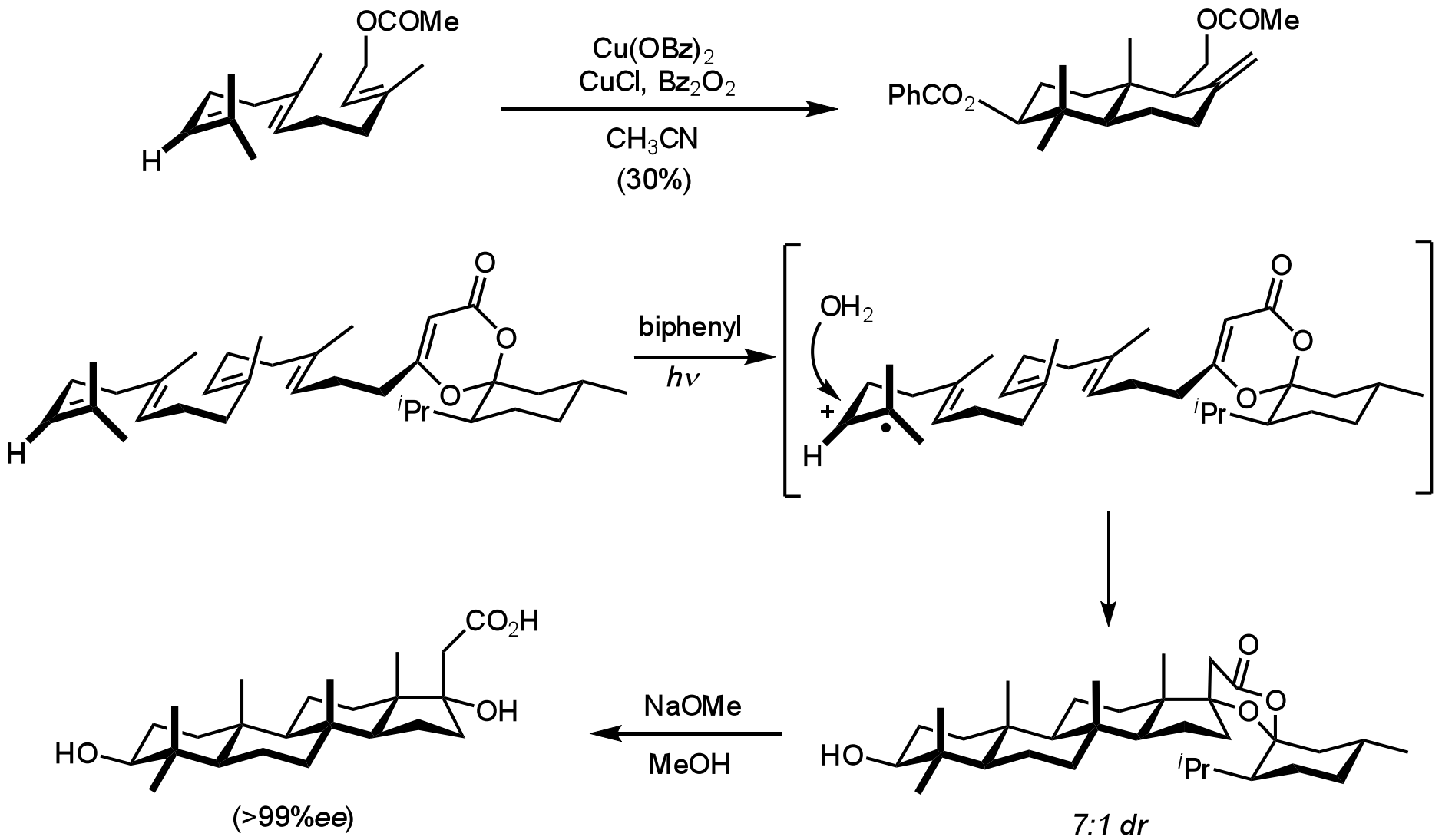


Calculations Supported Mechanism of Cyclization



Rajamani, R.; Gao, J. *J. Am. Chem. Soc.* **2003**, *125,* 12768
Hess, B. A., Jr.; Smentek, L. *Org. Lett.* **2004**, *6,* 1717

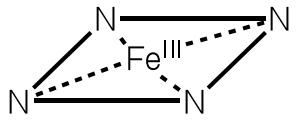
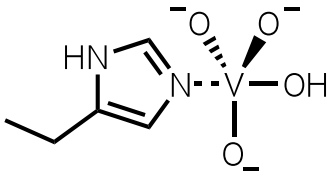
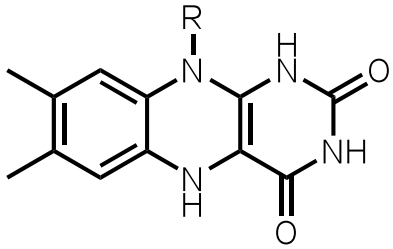
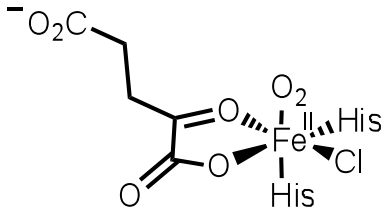
Radical Biomimetic Enantioselective Cyclization



Breslow, R.; Olin, S. S.; Groves, J. T. *Tetrahedron Lett.* **1968**, *9*,1837

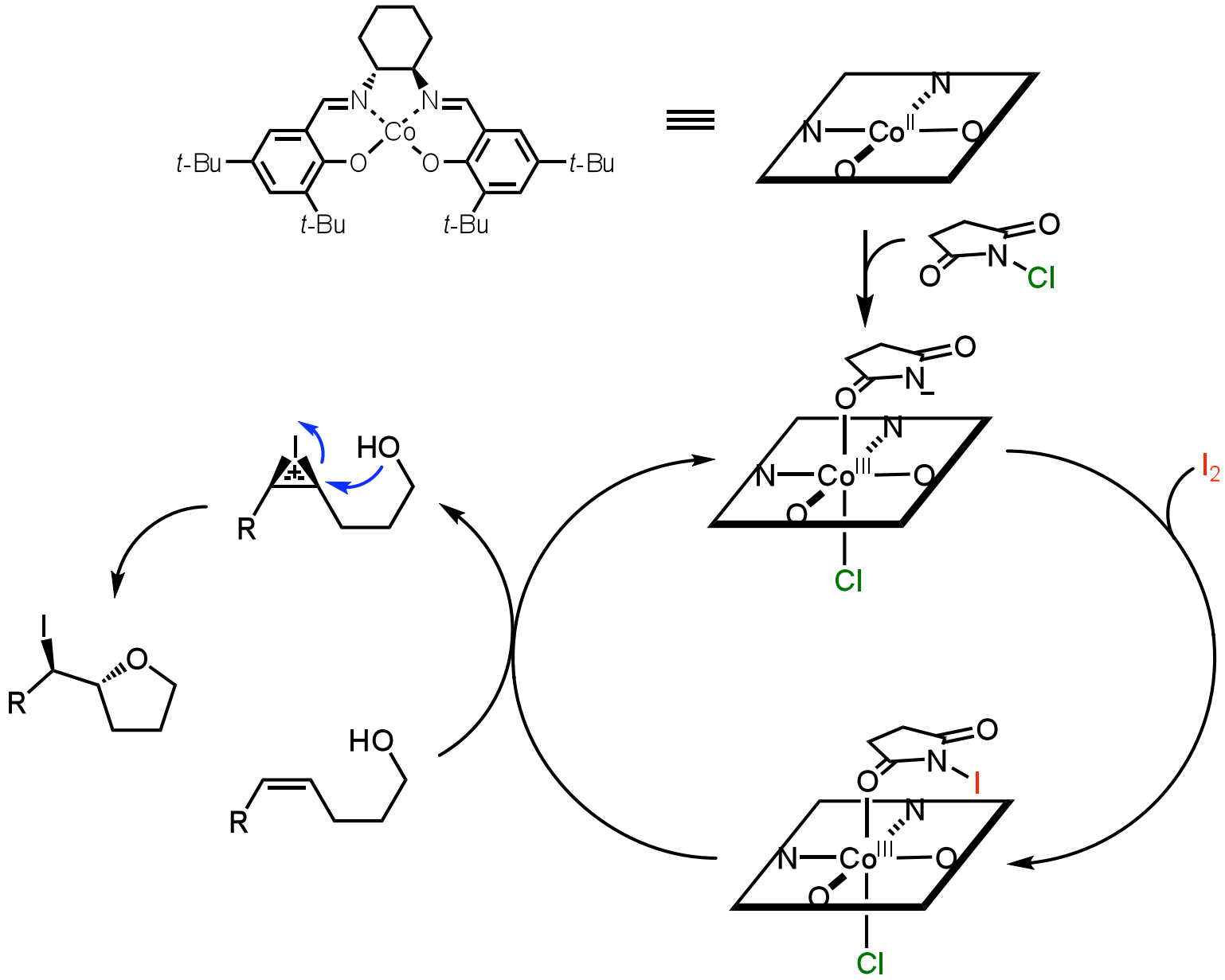
Lallemand, J. Y.; Julia, M.; Mansuy, D. *Tetrahedron Lett.* **1973**, *14*, 4461

Enzyme Halogenation: Halogenase and its cofactors

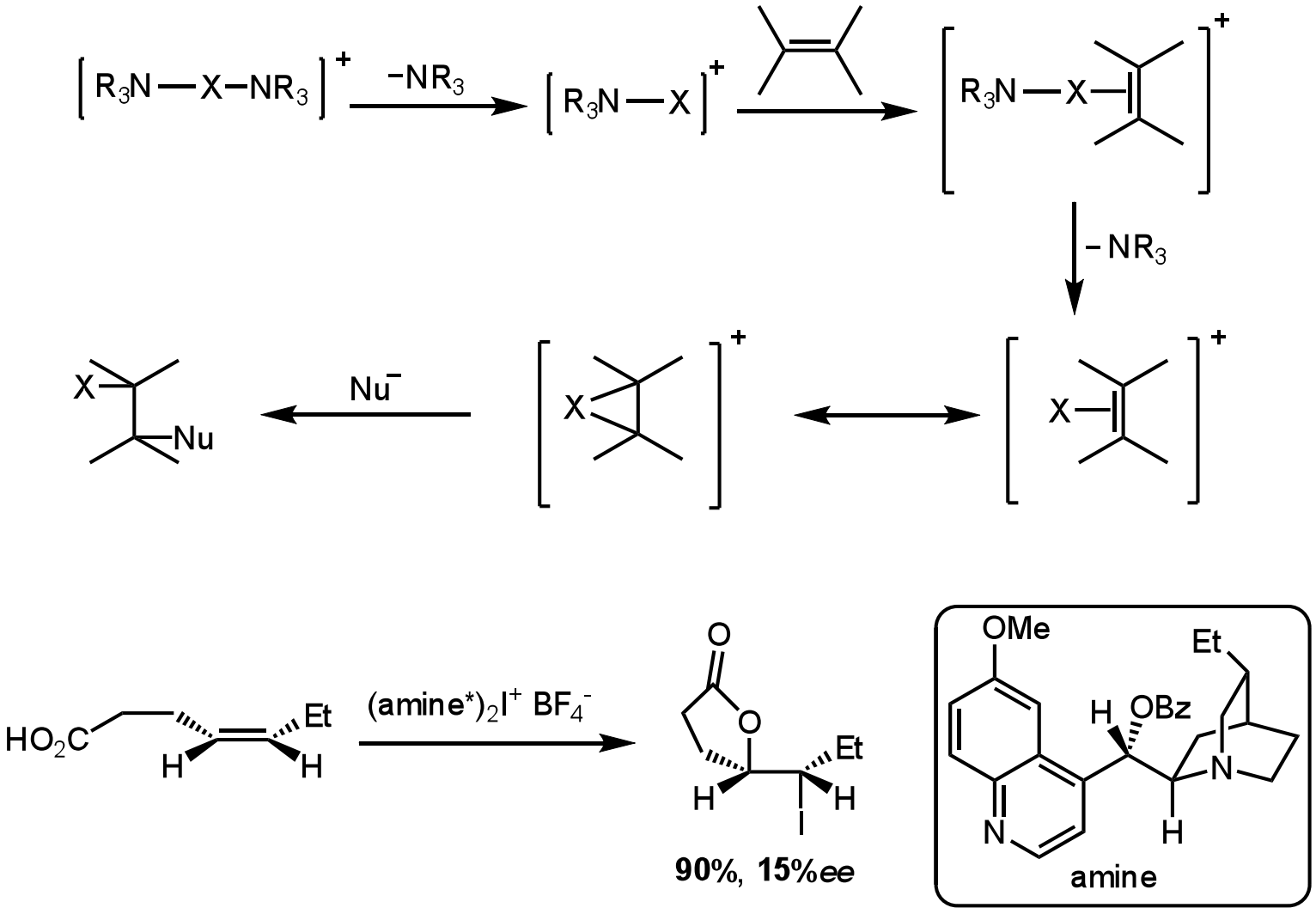
Enzyme Type	Redox Cofactor		Oxidant	Other Cosubstrates
	Name	Structure		
haloperoxidase	heme iron		H_2O_2	halide
haloperoxidase	vanadium		H_2O_2	halide
O_2-dependent halogenase	$FADH_2$		O_2	halide
O_2-dependent halogenase	non-heme iron		O_2	halide, α-ketoglutarate

Walsh, C. T.; Tsodikova, S. G.; Vosburg, D. A.; Yeh, E.; Vaillancourt, F. H. *Chem. Rev.***2006**, *106*, 3364

Possible Mechanism

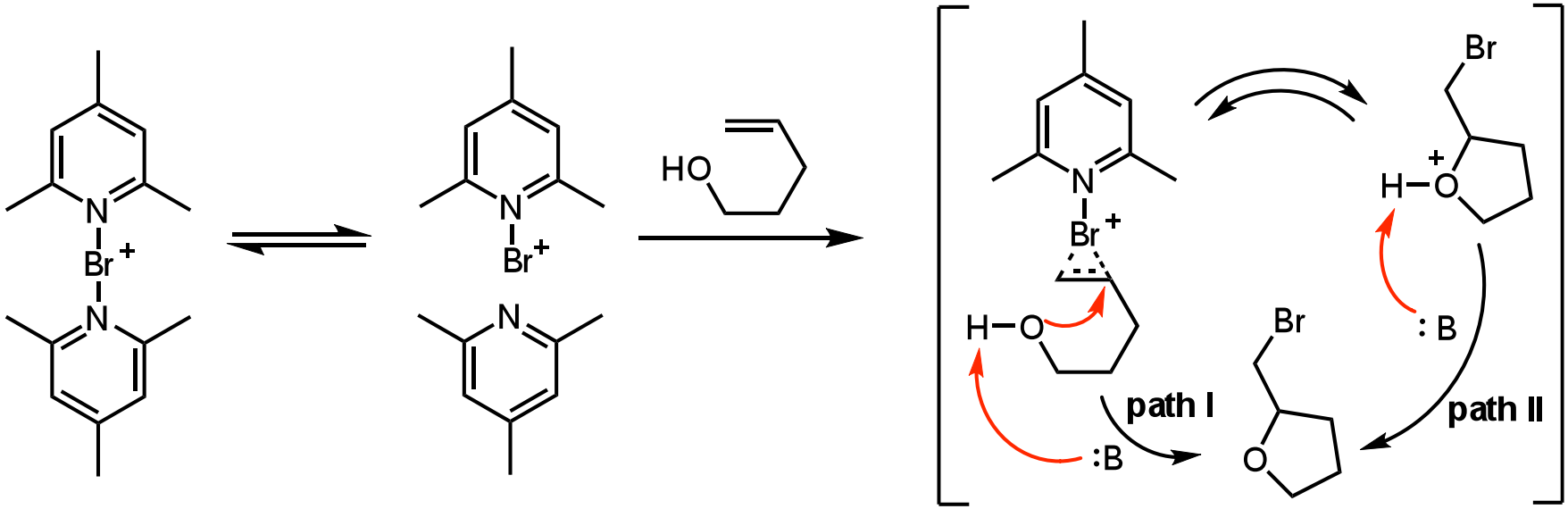


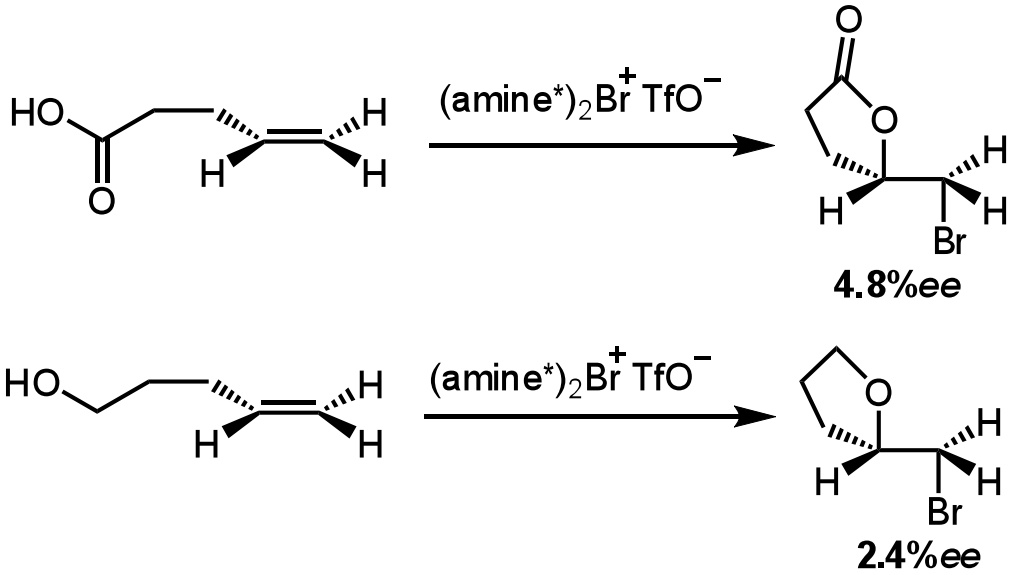
Enantioselective Iodolactonization: Mechanism

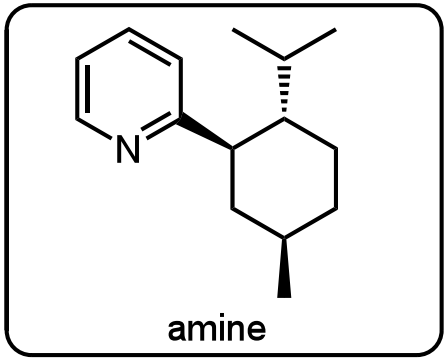


Grossman, R. B.; Trupp, R. J. *Can. J. Chem.* **1998**, *76*, 1233

Iodolactonization: Proof of the Proposed Mechanism







Cui, X. L.; Brown, R. S *J. Org. Chem.* **2000**, *65*, 5653