

Olefin Addition Reactions II: Brominations and Non-Halogens

Evans Group Seminar
November 23, 2009
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Presentation Outline

1. Bromination: The Overall Process

- a) Overall Process / History
- b) Bromonium-Ion (σ -Complex): Formation and Structure
- c) π -Complex: Formation and Structure
- d) Overall Mechanism (calculated)

2. Bromination: Reactions

- a) Substituent Effects / Regioselectivity
- b) Towards Enantioselective Brominations
- c) Bromolactonization / Bromocyclizations

3. Oxymercuration

- a) Overall Process
- b) Reactions

4. Reactions of Tl(III) with Olefins

5. Electrophilic Selenation of Olefins

Selected References

Bromination: The Overall Process

- *Ruasse, M.-F. *Adv. Phys. Org. Chem.* **1993**, *28*, 207;
- *Brown, R.S. *Acc. Chem. Res.* **1997**, *30*, 131;
- *Lenoir, D.; Chiappe, C. *Chem. Eur. J.* **2003**, *9*, 1036;
- Sauers, R.R. *Tetrahedron* **2005**, *61*, 8358;
- Poirier, R.A. *J. Phys. Chem. A*, **2007**, *111*, 13218;
- Poirier, R.A. *J. Phys. Chem. A*, **2008**, *112*, 152.

Bromination: Reactions

- *Pasto, D.J. *J. Am. Chem. Soc.* **1970**, *92*, 7480;
- *Orena, M. *Tetrahedron* **1990**, *46*, 3321;
- *Chamberlin, A.R.; Hehre, W.J. *J. Am. Chem. Soc.* **1987**, *109*, 672;
- *Jayaraman, N. *Tetrahedron*, **2004**, *60*, 5273.

Oxymercuration

- *Pasto, D.J. *J. Am. Chem. Soc.* **1970**, *92*, 7480;
- *Chamberlin, A.R.; Hehre, W.J. *J. Am. Chem. Soc.* **1987**, *109*, 672;
- Perlmutter, P. *Tetrahedron Lett.* **1995**, *36*, 463;
- Perlmutter, P. *Tetrahedron Lett.* **2000**, *41*, 3716.

Reactions of Tl(III)

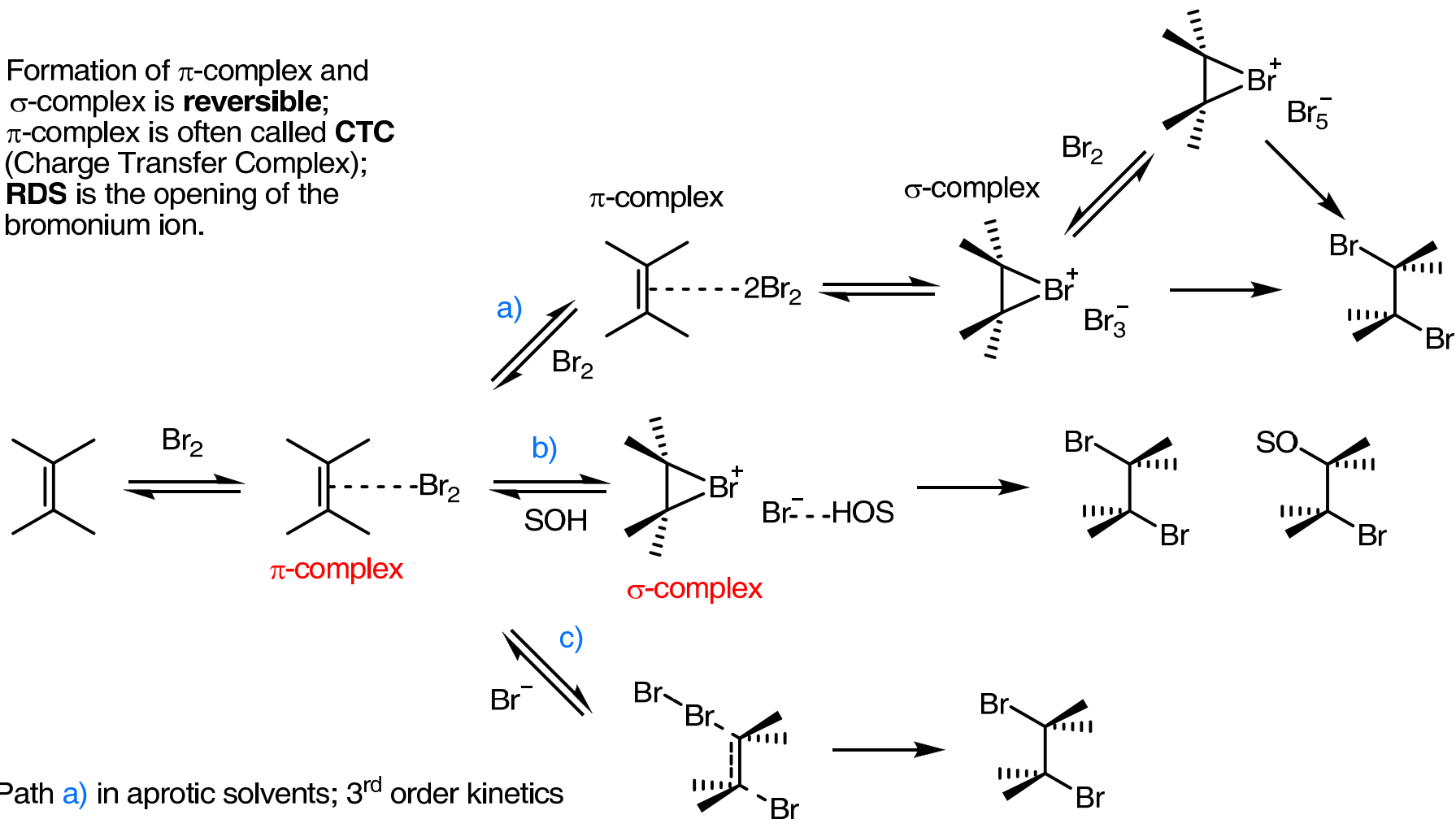
- *Taylor, E.C. *J. Am. Chem. Soc.* **1973**, *95*, 3635;
- *Silva, L.F., Jr. *Quim. Nova* **2000**, *23*, 216;
- Pfaltz, A.; Silva, L.F., Jr. *J. Org. Chem.* **2009**, *74*, 2561.

Electrophilic Selenation

- *Jayaraman, N. *Tetrahedron*, **2004**, *60*, 5273;
- *Wirth, T. *Curr. Org. Chem.* **2006**, *10*, 1893;
- Wirth, T. *Eur. J. Org. Chem.* **2009**, 1649.

Bromination: Overall Reaction Mechanism

- Formation of π -complex and σ -complex is **reversible**;
- π -complex is often called **CTC** (Charge Transfer Complex);
- **RDS** is the opening of the bromonium ion.

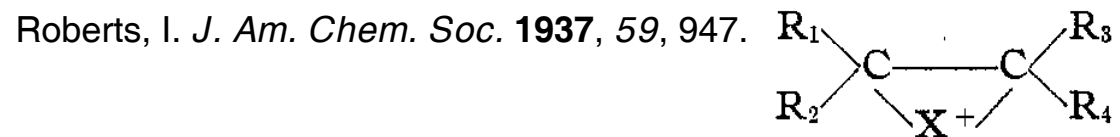


- Path **a)** in aprotic solvents; 3rd order kinetics
- Path **b)** in polar solvents (SOH = AcOH, MeOH); 2nd order kinetics
- Path **c)** in non-polar aprotic solvents with added bromide salts; 2nd order kinetics.

Ruasse, M.-F. *Adv. Phys. Org. Chem.* **1993**, 28, 207;
 Brown, R.S. *Acc. Chem. Res.* **1997**, 30, 131;
 Lenoir, D.; Chiappe, C. *Chem. Eur. J.* **2003**, 9, 1036.

History of the Bromonium Ion

- 1937: Postulation of bromonium ion as origin of anti (trans) selectivity



- 1967: NMR spectra of bromonium ions in $\text{SbF}_5\text{-SO}_2$

Olah, G.A. *J. Am. Chem. Soc.* **1967**, *89*, 4744;
 Olah, G.A. *J. Am. Chem. Soc.* **1969**, *91*, 2113.

- 1969: First bromonium salt (no X-ray)

Wynberg, H. *J. Chem. Soc., Chem. Commun D* **1967**, 907.

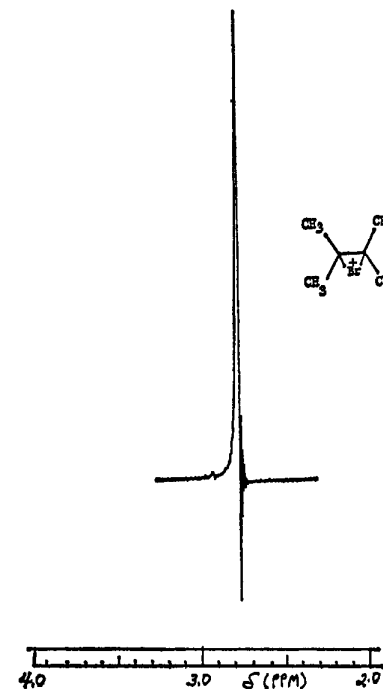
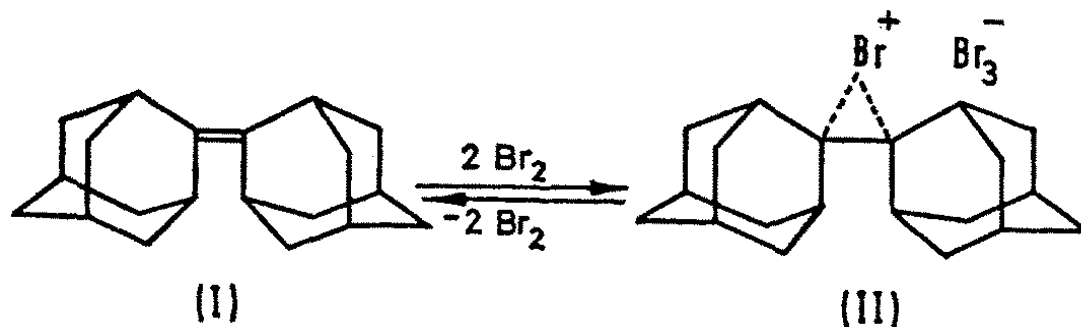
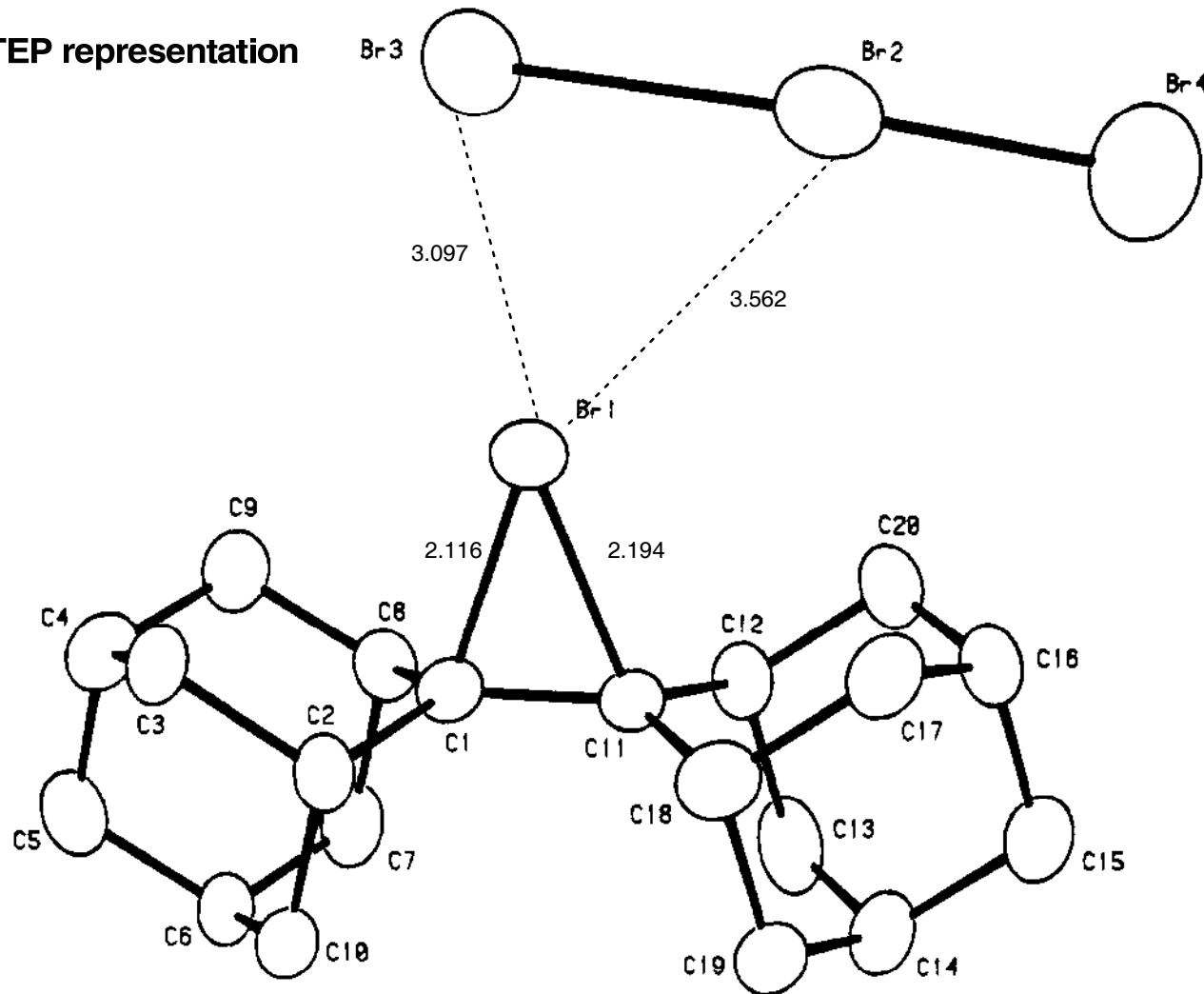


Figure 2. Tetramethylethylenebromonium ion in $\text{SbF}_5\text{-SO}_2$ solution at -60° .

Bromonium Ion Crystal Structure

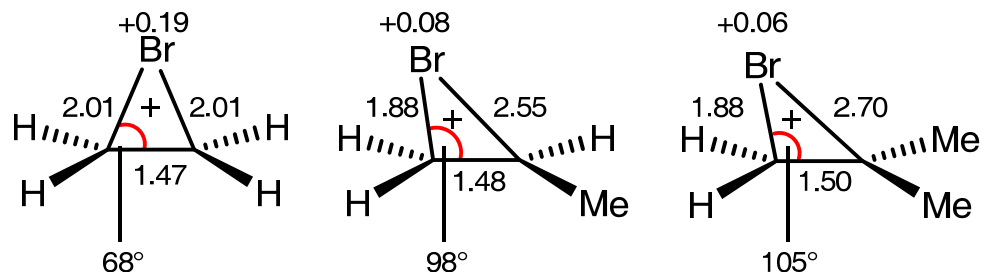
ORTEP representation



Brown, R.S. *J. Am. Chem. Soc.* **1985**, *107*, 4504.

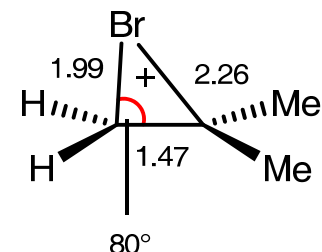
Calculated Bromonium Ion Structures

Semiempirical method (MNDO):



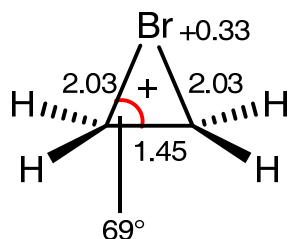
Early calculations show significant decrease of bridging for unsymmetrically substituted bromonium ions:
 Ruasse, M.-F. *J. Chem. Soc., Chem. Commun.* **1990**, 898;
 Ruasse, M.-F. *Adv. Phys. Org. Chem.* **1993**, 28, 207 (Review).

Method that includes correlation (CISD/DZV):



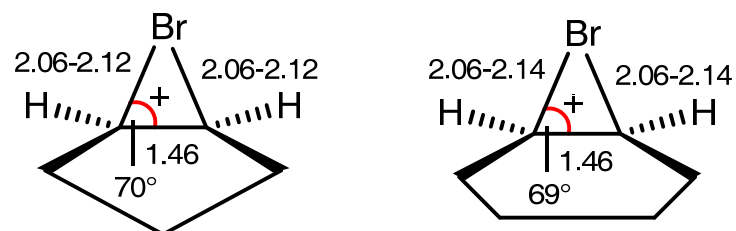
Computed geometry markedly dependent upon method employed. Important: inclusion of electron correlation, polarization functions:
 "The computed structure of the ion becomes more symmetric (more bridged) as the quality of the computational method improves"
 Brown R.S. *J. Org. Chem.* **1994**, 59, 7156.

At MP2/BB2//MP2/SB level:



Damrauer, R.; Hadad, C.M.
J. Org. Chem. **1998**, 63, 9476.

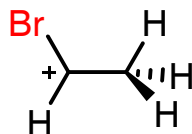
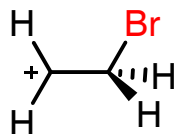
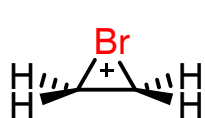
At MP2/6-311G(d,p) & B3LYP/6-311++G(d,p) level



Sigalas, M.P.
Tetrahedron **2003**, 59, 9476.

Bromonium Ion vs. 2-Bromocarocation

Calculations of bromonium ions and 2-bromocarocations:

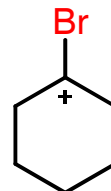
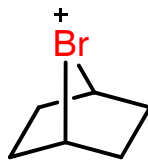
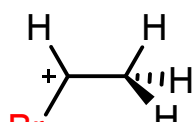
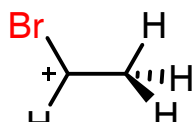
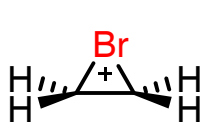


2-bromoethylcation
("cis")

1-bromoethylcation
("trans")

Schaefer, H.F. III,
J. Am. Chem. Soc. **1990**, *112*, 8260:
DZ+d CISD

Calculations of bromonium ions and 1-bromocarocations:



"trans"

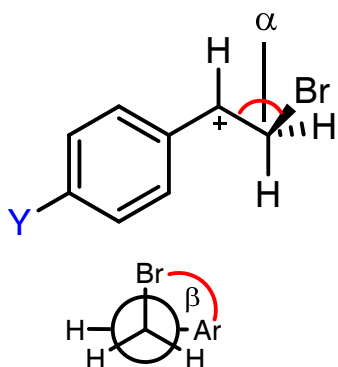
"cis"

Damrauer, R.; Hadad, C.M.
J. Org. Chem. **1998**, *63*, 9476:
MP2/BB2//MP2/SB

Sigalas, M.P.
Tetrahedron **2003**, *59*, 9476:
MP2/6-311G(d,p) & B3LYP/6-311++G(d,p)

Benzylic 2-bromocarocation:

Influence of aryl substituent (Y) on dihedral angles of lowest energy conformation:



Y	σ^+/σ_p	α [°]	β [°]
NH ₂	-1.30	105.3	102.5
OH	-0.92	102.8	102.1
F	-0.07	99.9	101.4
H	0.00	98.8	101.7
CN	0.70	97.4	101.8
NO ₂	0.81	94.7	99.8

B3LYP/6-31+G(d)

Y=H	α [°]
Vacuum	99.4
CCl ₄	101.1
DMSO	103.2

B3LYP/6-31+G(d,p);
LANL2DZ.

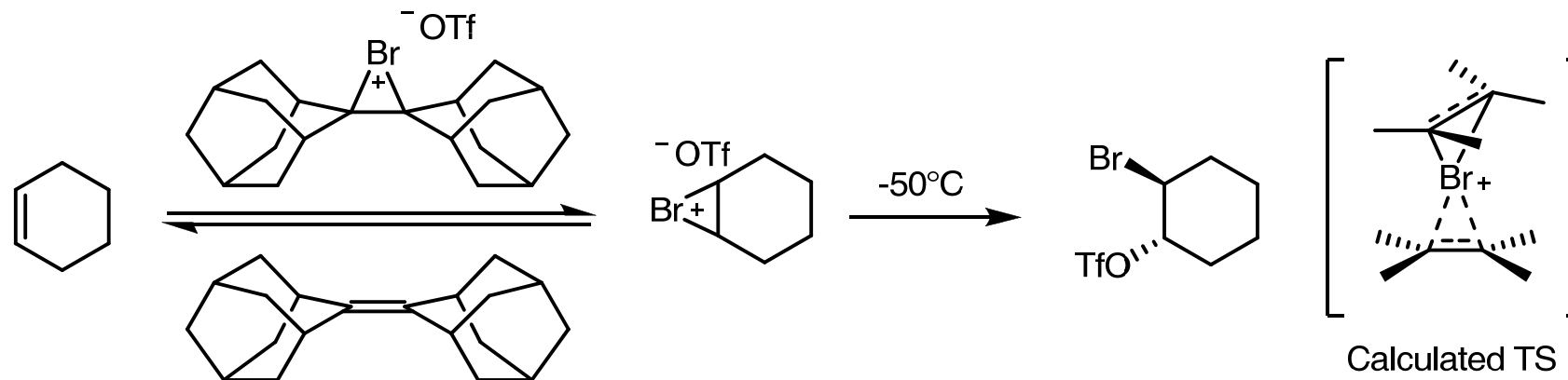
Barrier for rotation (β):
 $\Delta G = 6$ kcal/mol (Y=H)
(vacuum)

Sauers, R.R.
Tetrahedron **2005**, *61*, 8358

Reversibility of Bromonium Ion Formation

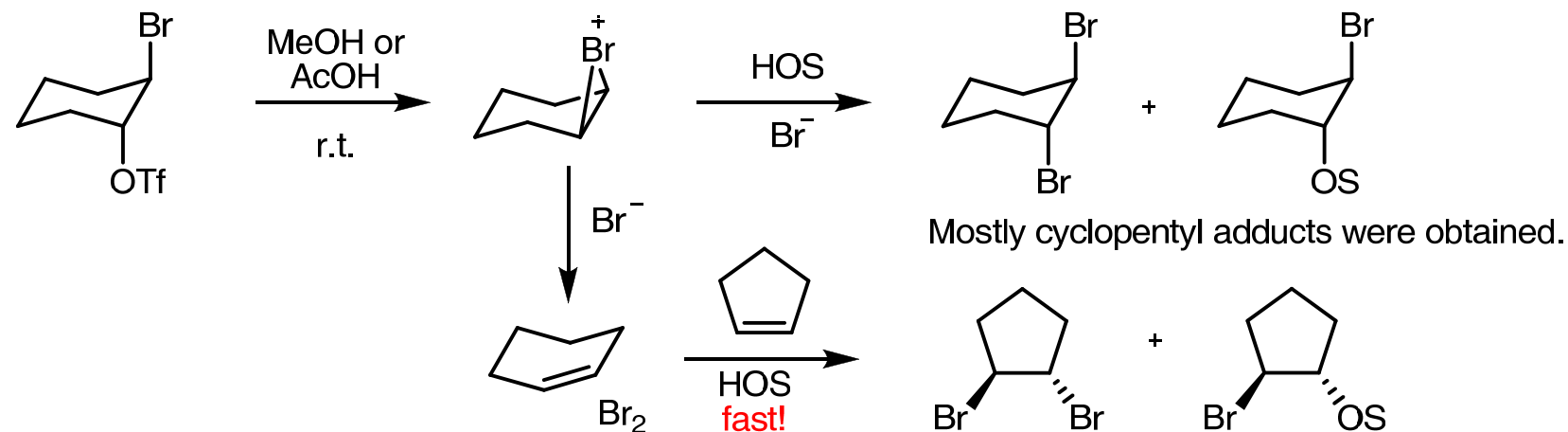
NMR-experiment (cyclohexene- d_{10}): **Bromonium ions undergo fast exchange with olefins**

Bennet, A.J.; Brown R.S. *J. Am.Chem. Soc.* **1991**, *113*, 8532.



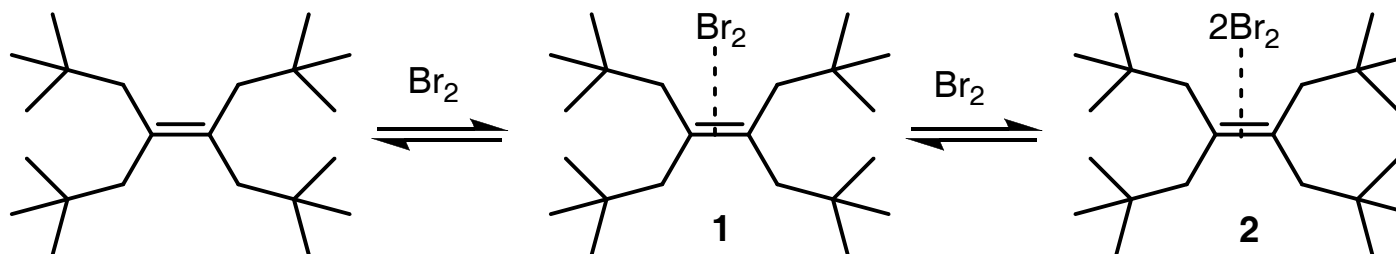
Reversal of bromonium ion formation was found to be general:

Brown R.S. *J. Org. Chem.* **1993**, *58*, 2122.



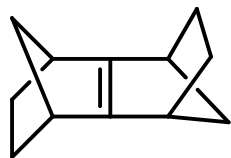
Review: Brown, R.S. *Acc. Chem. Res.* **1997**, *30*, 131.

Evidence for π -Complex

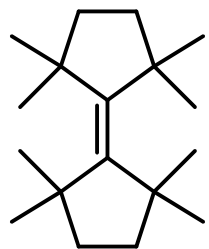


- Tetraeneopentylethylene: Reaction stops at the stage of π -complex
- Ratio of 1 and 2 is dependent on the bromine concentration
- Existence of stable π -complexes formed in equilibrium with reagents in DCE was deduced from concentration-dependant UV spectra
Angew. Chem. Int. Ed. Engl. **1997**, 36, 1284.

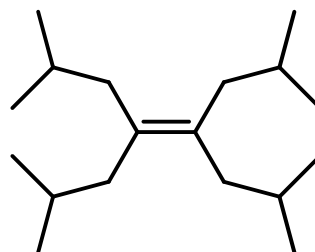
Other sterically congested alkenes:



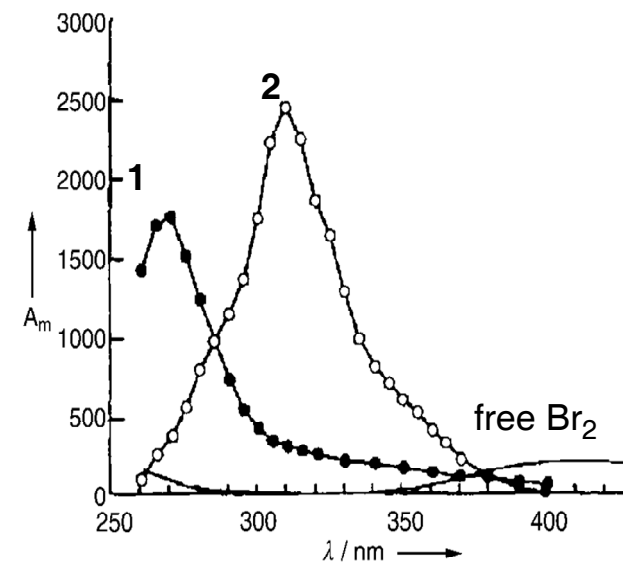
Br_2 adds syn to this olefin:
J. Am. Chem. Soc. **1990**, 102, 3303.



Does not react with Br_2 at all:
Chem. Ber. **1984**, 117, 277.



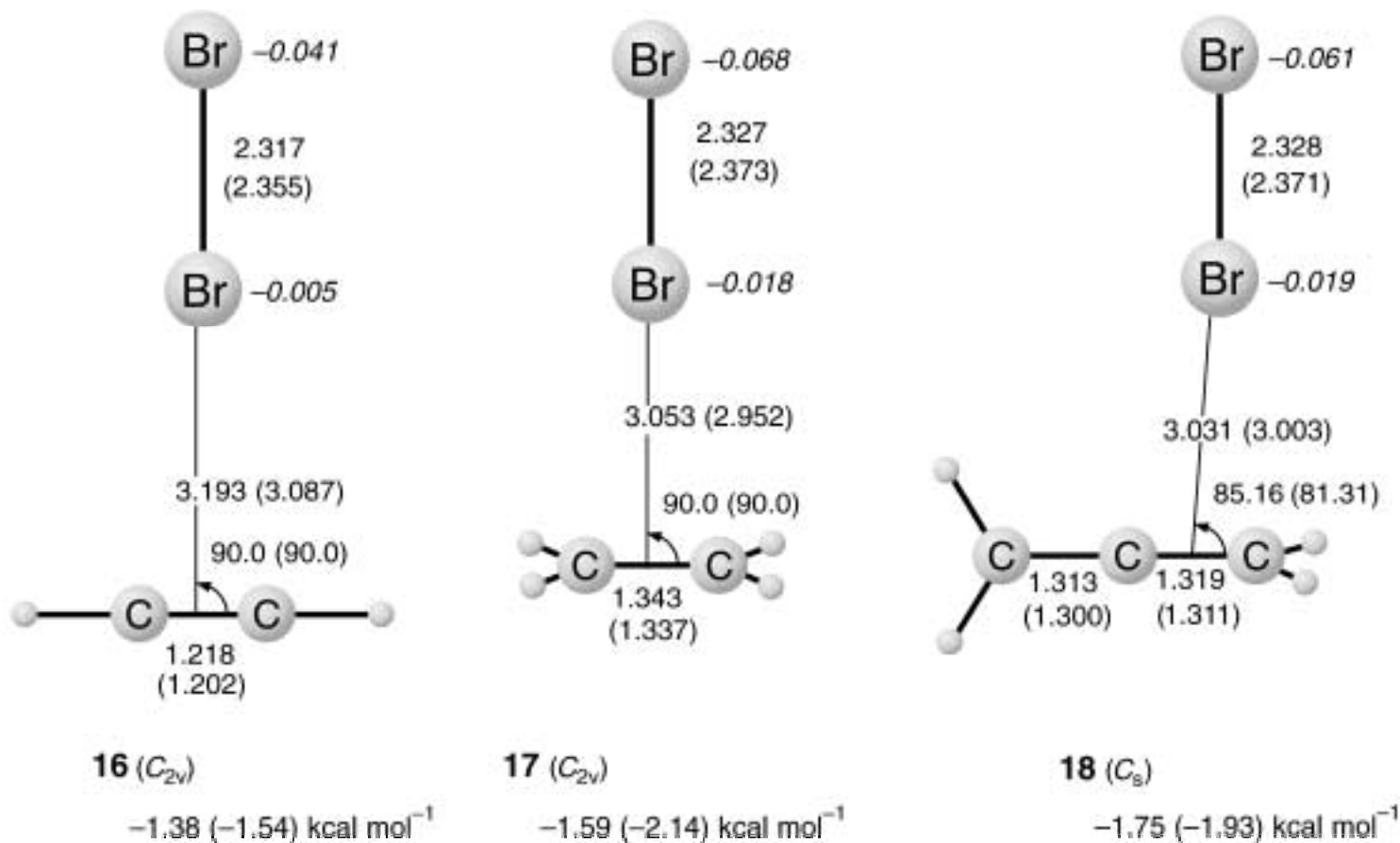
Reaction with Br_2 yields addition-elimination products:
J. Am. Chem. Soc. **1990**, 112, 6310.



Reviews:
Acc. Chem. Res. **1997**, 30, 131;
Chem. Eur. J. **2003**, 9, 1036.

Calculated π -Complexes

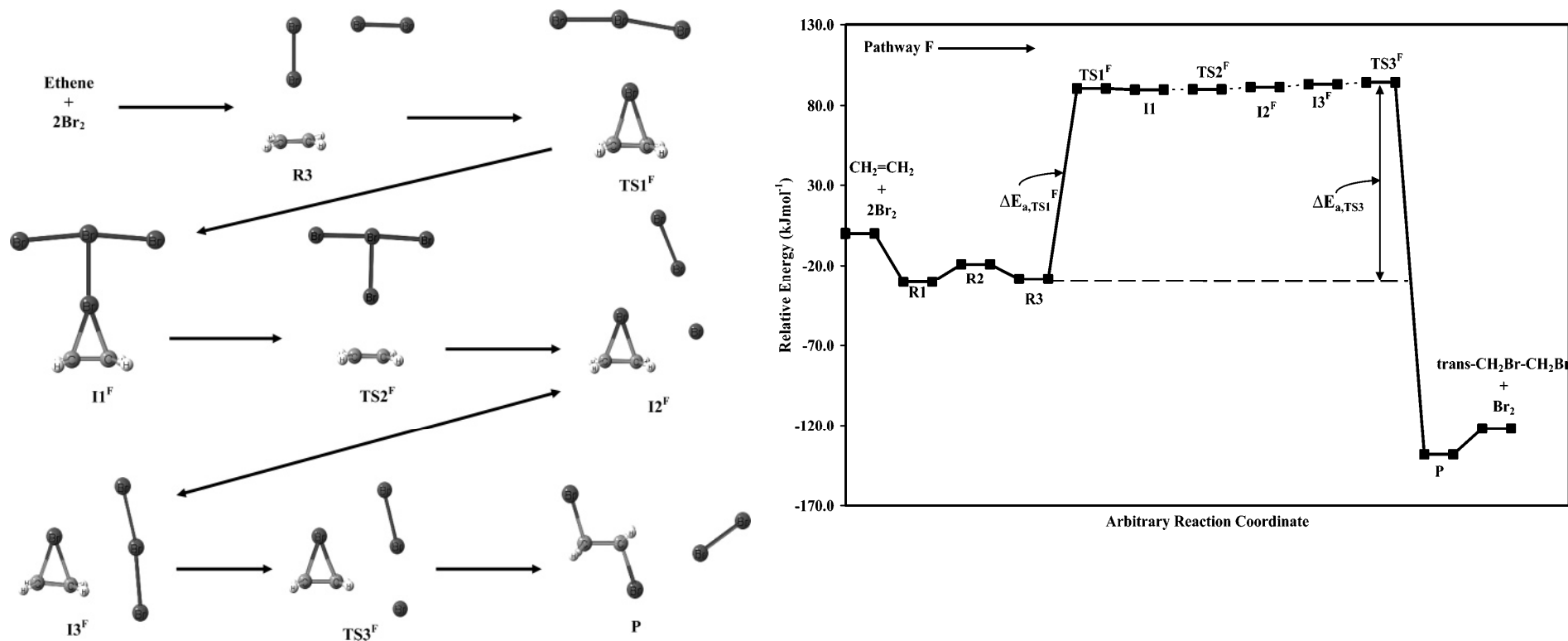
Geometries and complexation energies (both at MP2/6-311+G**) corrected for ZPE and BSSE of 1:1 Br₂ complexes of acetylene, ethylene, and allene. (Data in parantheses at B3LYP6-311+G** level)



Bianchini, R.; Lenoir, D.; Goldberg, N. *Chem. Eur. J.* **1999**, *5*, 1570;
Chiappe, C.; Lenoir, D.; Schleyer, P. v. R. *Chem. Eur. J.* **2002**, *8*, 967;
Review: Lenoir, D.; Chiappe, C. *Chem. Eur. J.* **2003**, *9*, 1036.

Mechanism for the Reaction of Ethene with 2Br₂

„Most likely pathway“ for the **reaction of ethylene with 2Br₂** at the G3MP2B3 level. For TS2^F, I2^F, and I3^F the G3MP2B3 energies were calculated using HF/6-31G(d) optimized geometries.



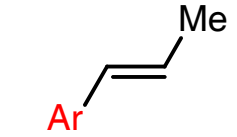

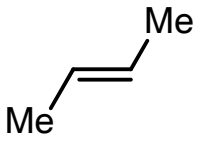

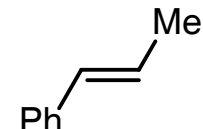
Reaction of Br₂ with ethene, propene, isobutene, fluoroethane, chloroethane:
 Poirier, R.A. *J. Phys. Chem. A*, **2007**, *111*, 13218;
 Reaction of Adamantylideneadamantane (Ad=Ad) with Br₂ and 2Br₂:
 Poirier, R.A. *J. Phys. Chem. A*, **2008**, *112*, 152;

Bromination – Substituent Effects

Alkene	k_{rel}	Kinetics: Substitution effects on bromination rate (Br_2 in MeOH @ 25°C)
$CH_2=CH_2$	1	
$CH_3CH=CH_2$	85	- Bromination rate increases for more substituted alkenes;
$EtCH=CH_2$	105	- Bromination rate decreases for sterically demanding alkyl substituents on the alkene.
$iPrCH=CH_2$	80	
$tBuCH=CH_2$	20	
$(CH_3)_2C=CH_2$	7,960	
$(CH_3)_2C=CHCH_3$	276,000	
$(CH_3)_2C=C(CH_3)_2$	3,025,000	

Ruasse, M.-F. *Adv. Phys. Org. Chem.* **1993**, 28, 207 (Review).

Stereochemical outcome versus structure

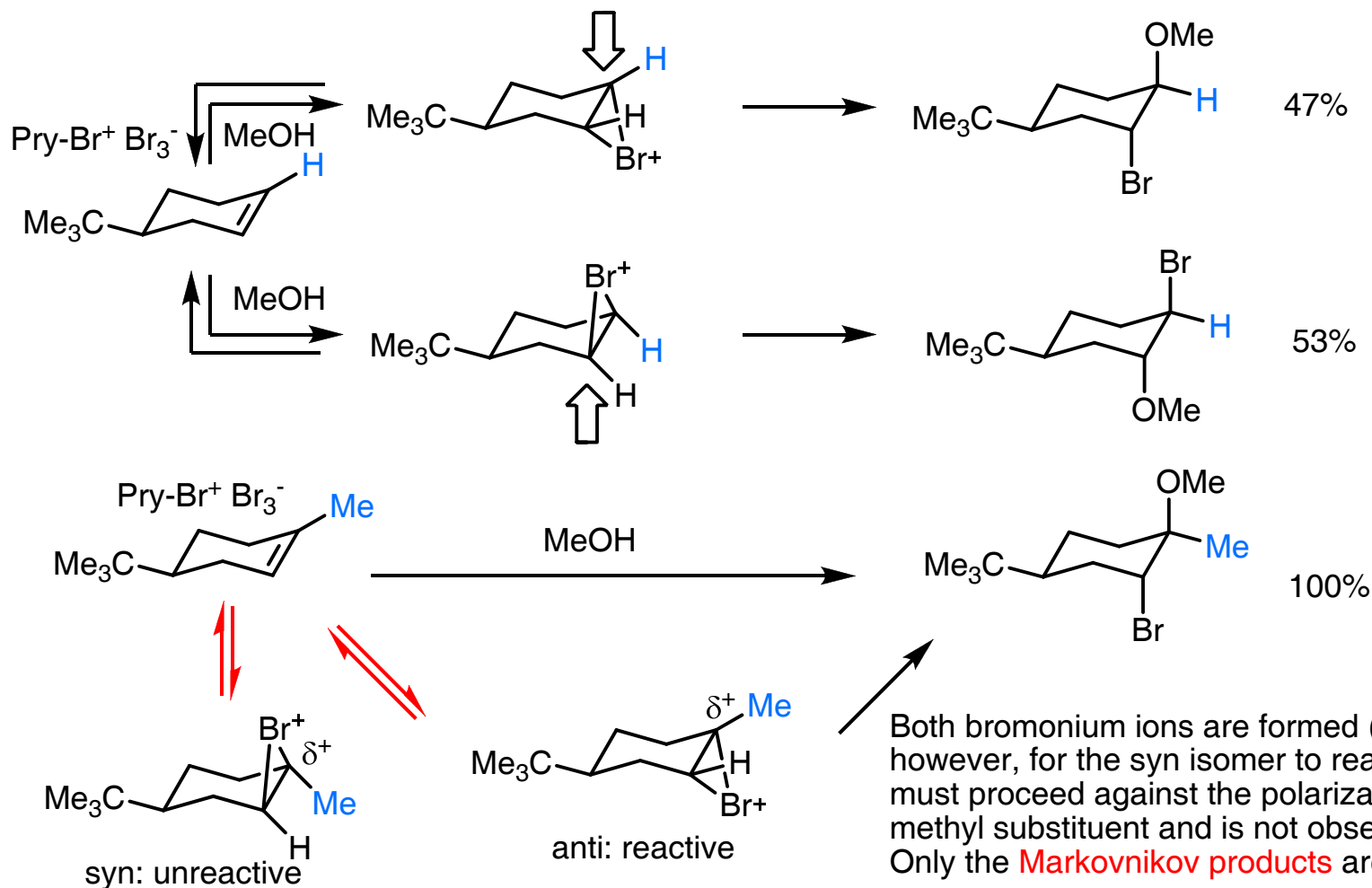
Alkene	% anti addition (Br_2 in HOAc @ 25°C)		% anti addition (Br_2 in CH_2Cl_2 @ 25°C)	% syn addition increases with stabilization of "benzylic carbocation"
	100%	C_6H_5-	81%	
	100%	$4-(OMe)C_6H_4-$	63%	
	73%	$3,5-(CF_3)_2C_6H_3-$	100%	
	83%			

Dubois, J.E. *J. Am. Chem. Soc.* **1978**, 100, 7645;
 Ruasse, M.-F. *Adv. Phys. Org. Chem.* **1993**, 28, 207 (Review).

Bromination: Regioselectivity

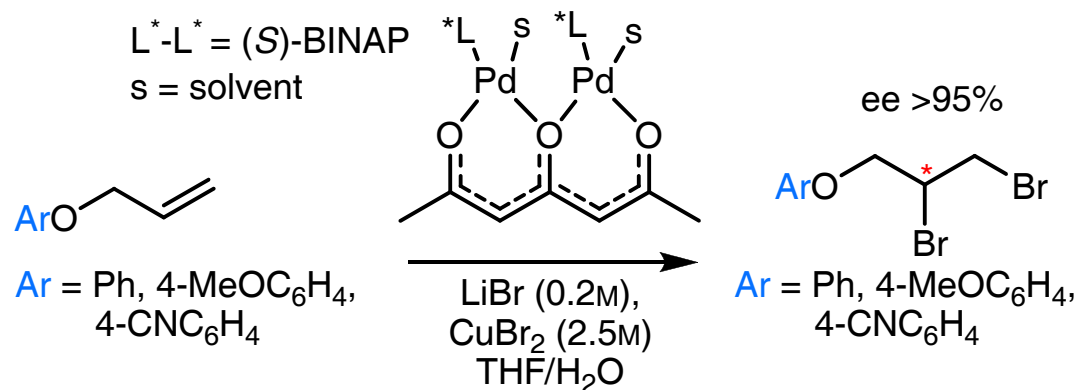
Bromination of cyclohexene derivatives: Pasto, D.J. *J. Am. Chem. Soc.* **1970**, *92*, 7480.

Trans-diaxial opening of bromonium ions may be viewed as an extension of the Fürst-Plattner Rule for epoxide opening (Fürst, A.; Plattner, P.A. *Helv. Chim. Acta* **1949**, *32*, 275).



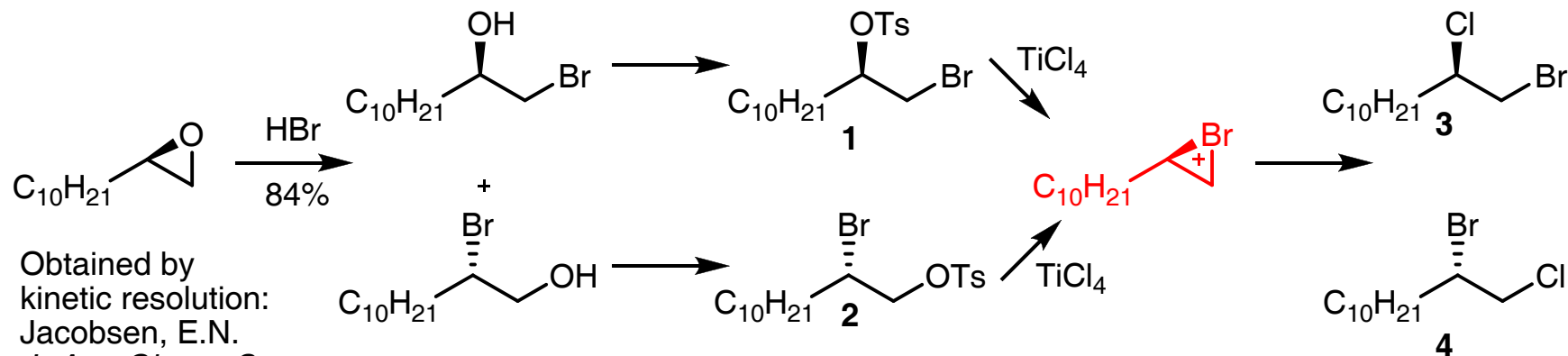
„Enantioselective“ Bromination

Palladium(II)-catalyzed asymmetric 1,2-dibromo synthesis: Henry, P.M. *Org. Lett.* **2003**, 5, 439.



- Works also with 1,2-disubstituted alkenes.
- However, method has never been applied or reproduced;
- source of Pd is not specified;
- only limited supporting information

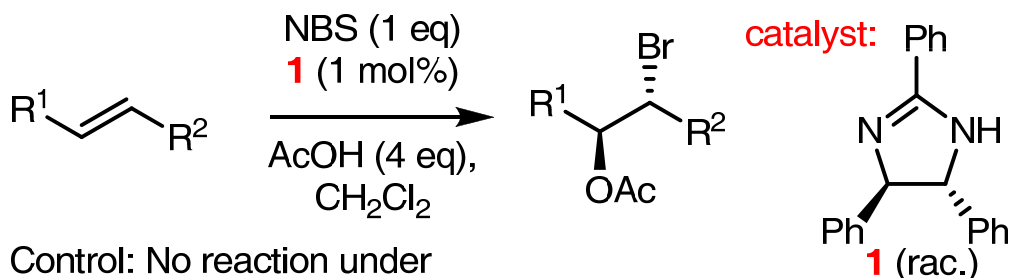
Generation and trapping of enantiopure bromonium ions: Braddock, D.C. *Chem. Commun.* **2009**, 1082.



Same product ratio (**3:4 = 6:1**) was obtained for both, the reaction of **1** with TiCl₄ and **2** with TiCl₄.
 → Mechanism via enantiopure bromonium ion.

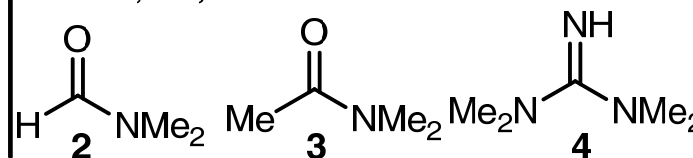
Towards Enantioselective Bromination

Amidines as organocatalysts for transfer of electrophilic bromine from NBS to alkenes: Braddock, D.C. *Tetrahedron Lett.* **2007**, *48*, 5948.

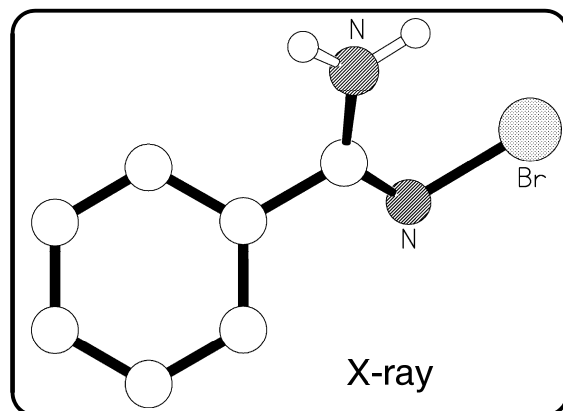
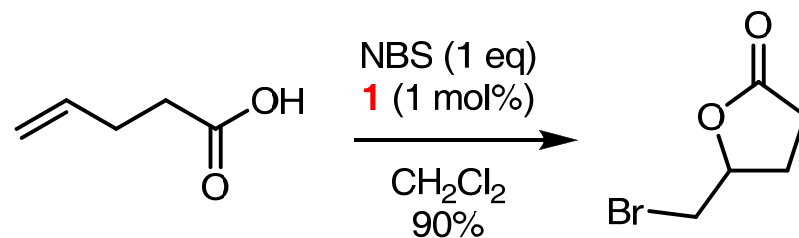
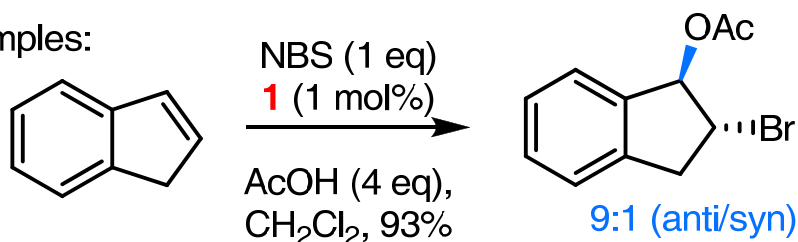


Control: No reaction under these conditions w/o catalyst

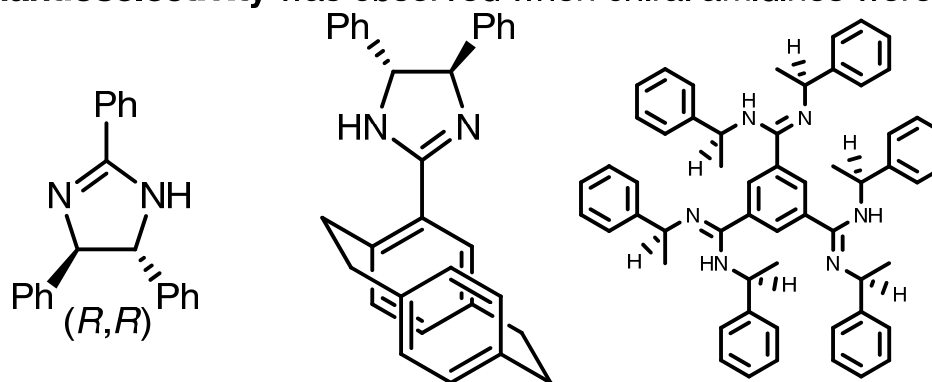
Other catalysts for bromolactonization (**2,3**) and bromoacetoxylation (**4**): Braddock, D.C. *Tetrahedron Lett.* **2007**, *48*, 915.



Examples:



No enantioselectivity was observed when chiral amidines were used:

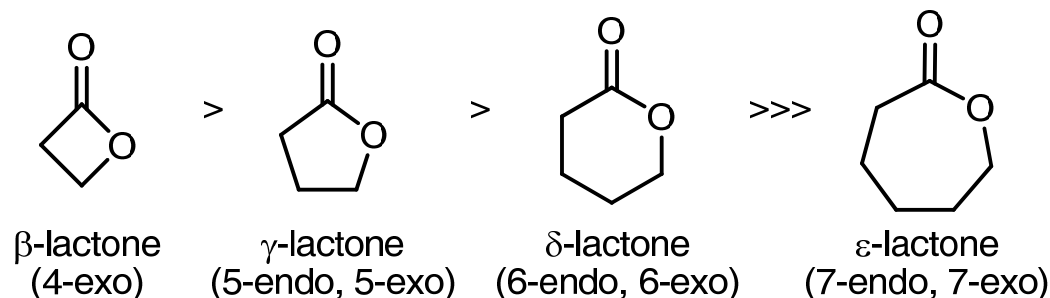


"..catalytic asymmetric bromination via an asymmetric bromonium ion remains an unsolved problem."

Bromolactonization

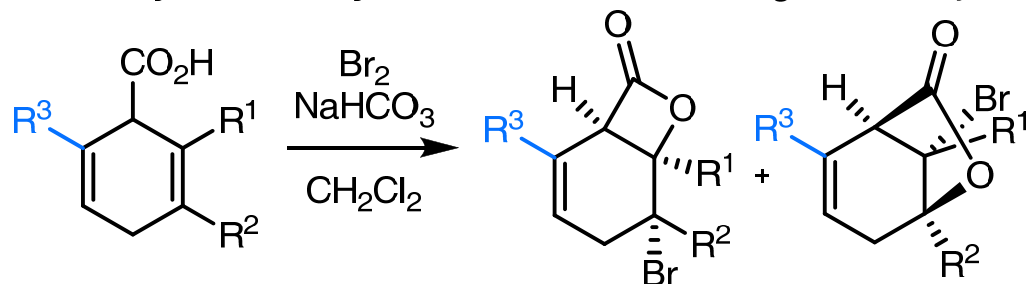
- **Bromolactonizations** are **kinetically controlled**.
(For Iodolactonizations and mercury-promoted cyclizations kinetic *and* thermodynamic control is possible, depending on reaction conditions)

- For **symmetrically** substituted olefins **entropy** factors control the regiochemistry.
Given a choice, the order of preference *usually* is:



Reviews on halolactonization:
J. Mulzer, in *Org. Synth. Highlights* **1991**, p. 158-64; Jayaraman, N. *Tetrahedron*, **2004**, *60*, 5273 (including an overview of reagents and conditions)

- For **unsymmetrically** substituted olefins the regiochemistry is under **Markovnikov** control.



1. R ¹ = Me, R ² = H	52%	-
2. R ¹ = H, R ² = Me	-	71%
3. R ¹ = H, R ² = H	59%	-
4. R ¹ = Me, R ² = Me	trace	80%
5. R ¹ = H, R ² = Me, R ³ = Me	trace	93%

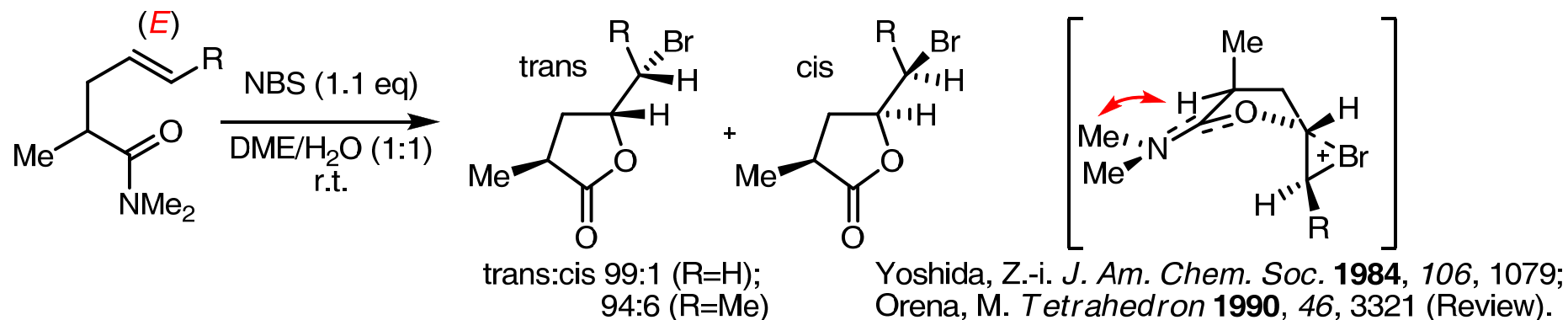
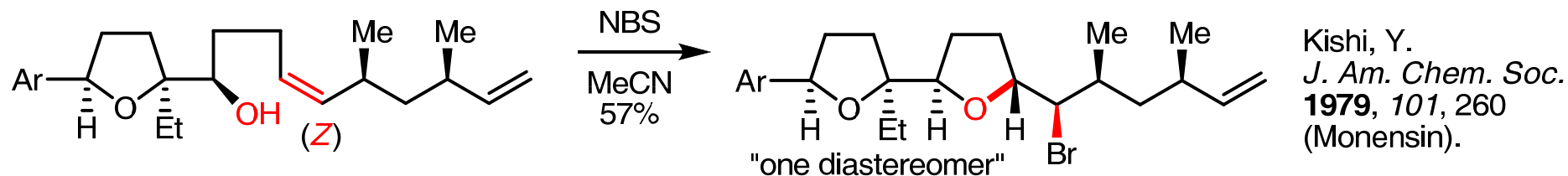
Only major product was isolated (recryst.),
product ratio was not determined.

Needham, L.L. *J. Org. Chem.* **1975**, *40*, 2843.

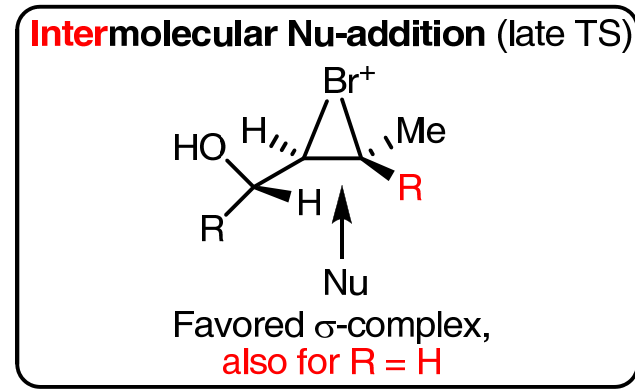
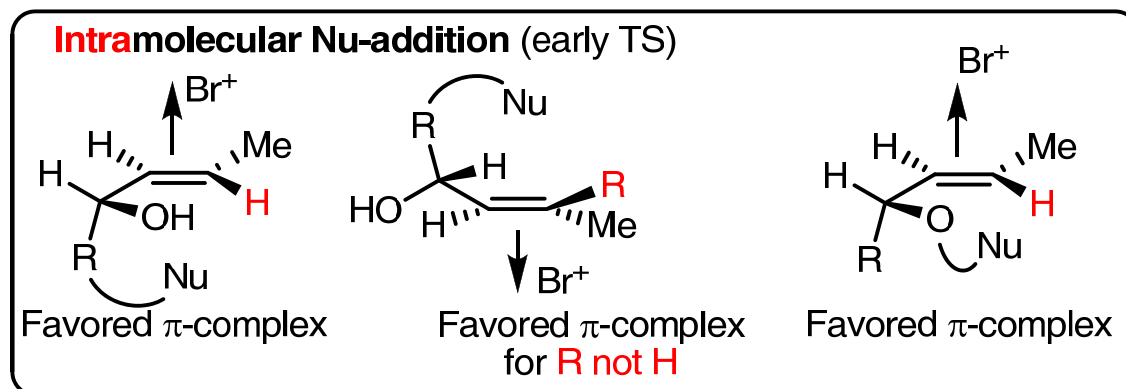
Entry 4 and **entry 5**: Steric effects play a role, too!

Bromocyclization

Examples for acyclic stereocontrol:



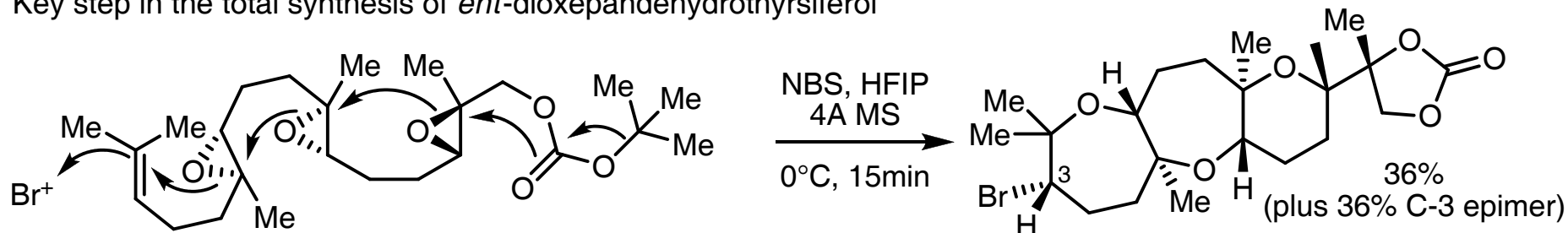
Model for acyclic stereocontrol: Chamberlin, A.R.; Hehre, W.J. *J. Am. Chem. Soc.* **1987**, 109, 672.
 See: Seminar Bichu Cheng, 11/20/2009.



Bromocyclization: Cascades

Example for bromonium-initiated epoxide-opening cascade:

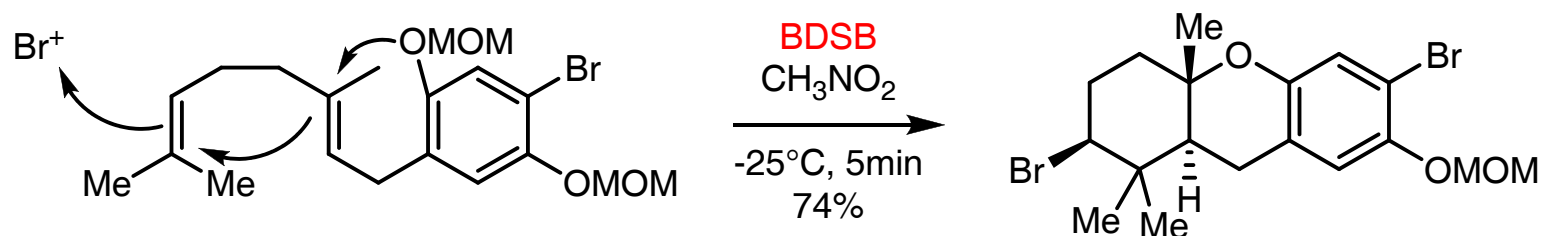
Key step in the total synthesis of *ent*-dioxepandehydrothysiferol



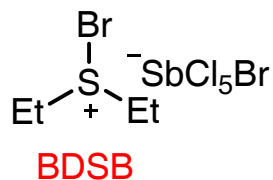
Jamison, T.F. *J. Am. Chem. Soc.* **2009**, *131*, 12084.

Bromonium-Induced Polyene Cyclizations

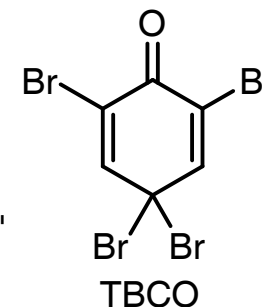
Key step in the total synthesis of 4-isocymobarbatol



Snyder, S.A. *Angew. Chem. Int. Ed.* **2009**, *48*, 7899.

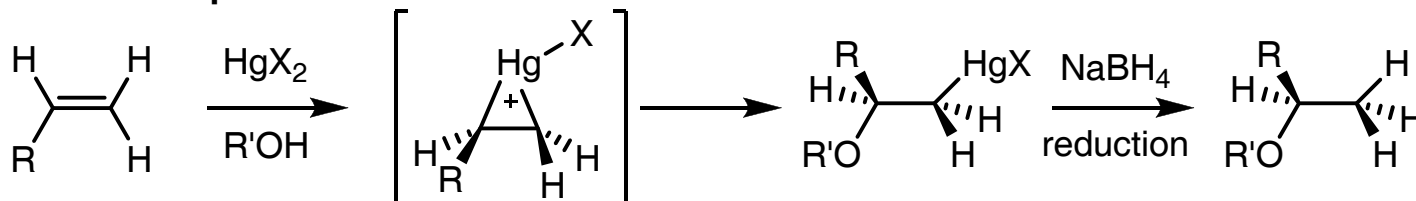


- BDSB was found to be superior to TBCO, NBS/PPh₃, Br₂/AgBF₄
- BDSB: "Reagent for powerful electrophilic bromination. Finally enables direct formation of cation- π cyclization products with essentially every class of standard terpene substrate with predictable stereochemistry."
- "...render this transformation asymmetric .. is the subject of current study."



Oxymercuration I

The overall process:



Kinetics: Halpern, X.Y. *J. Am. Chem. Soc.* **1967**, *89*, 6427.

Reduction: NaBH_4 : Pasto, D.J. *J. Am. Chem. Soc.* **1969**, *91*, 719;

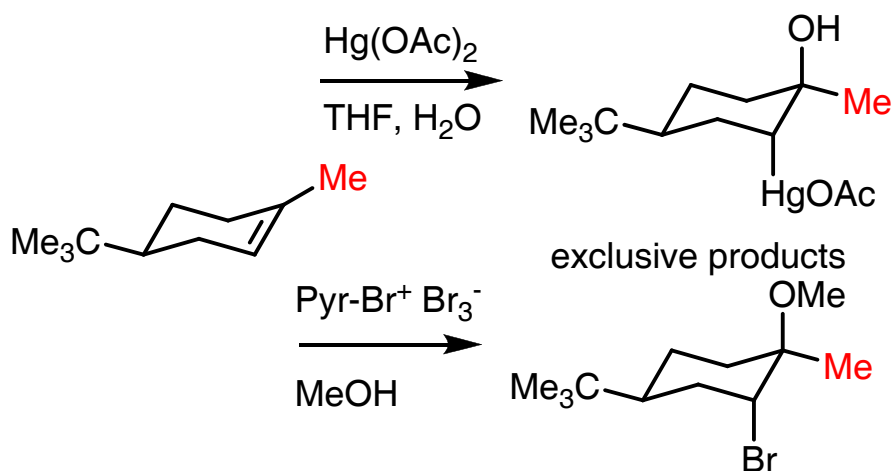
Bu_3SnH : Whitesides, G.M. *J. Am. Chem. Soc.* **1970**, *92*, 6611.

Overview: Brown, X.Y. *J. Org. Chem.* **1981**, *46*, 3810.

- Mercury(II) salts used: $\text{Hg}(\text{OAc})_2$, $\text{Hg}(\text{TFA})_2$, $\text{Hg}(\text{NO}_3)_2$, $\text{Hg}(\text{OMs})_2$
- anti addition to alkene
- Markovnikov products
- complementary to hydroboration
- reduction: nonstereoselective radical chain process

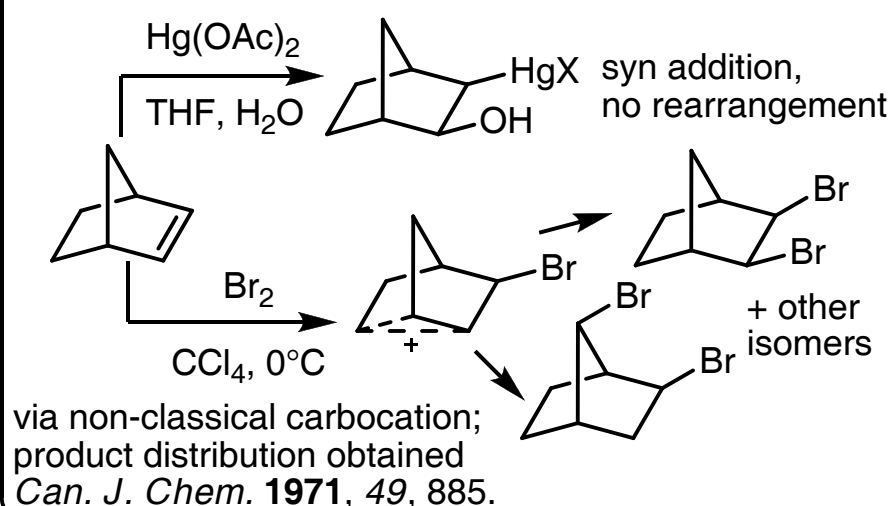
Oxy-mercuration and bromination follow identical pathways:

Pasto, D.J. *J. Am. Chem. Soc.* **1970**, *92*, 7480



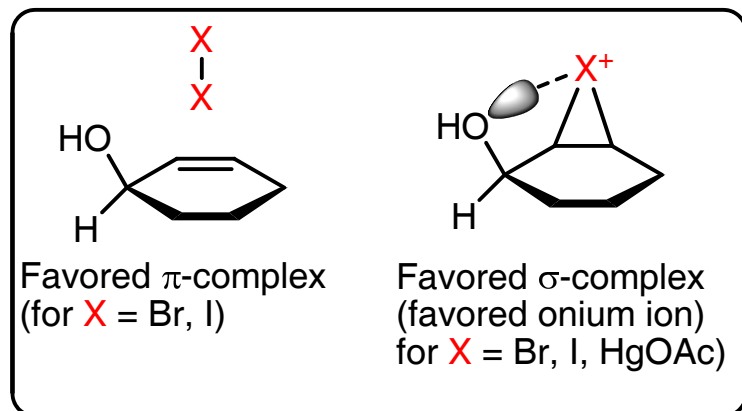
Pasto, D.J. *J. Am. Chem. Soc.* **1970**, *92*, 7480

Bromonium and mercurium ions: Differences

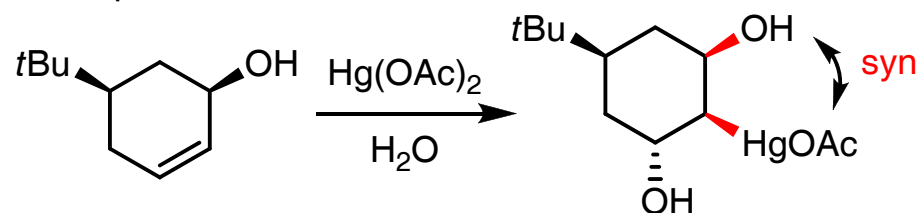


Oxymercuration II

Model for cyclic systems: Chamberlin, A.R.; Hehre, W.J. *J. Am. Chem. Soc.* **1987**, *109*, 672.

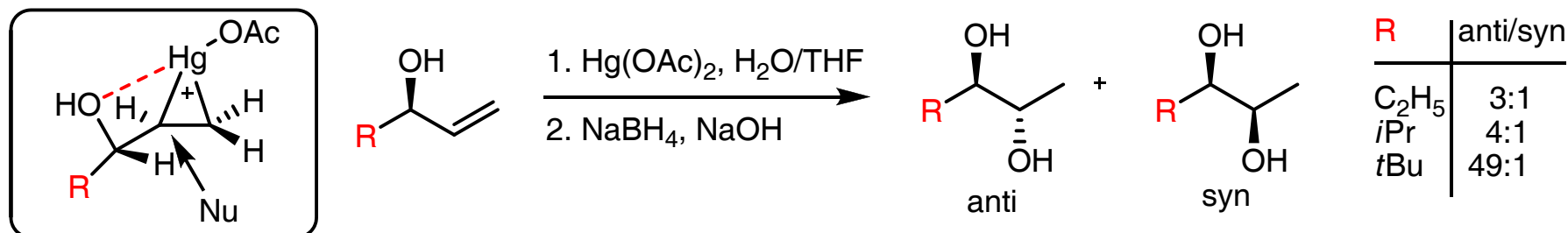


Example:

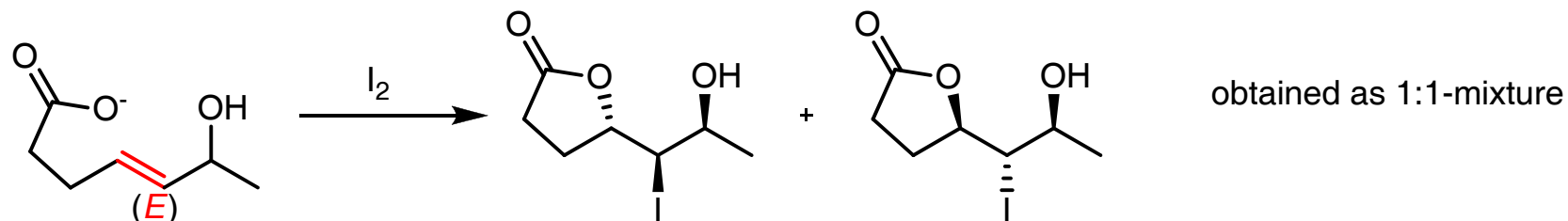


J. Chem. Soc. B **1970**, 1382.

Model for acyclic allylic alcohols: Giese, B. *Tetrahedron Lett.* **1985**, *26*, 1197.



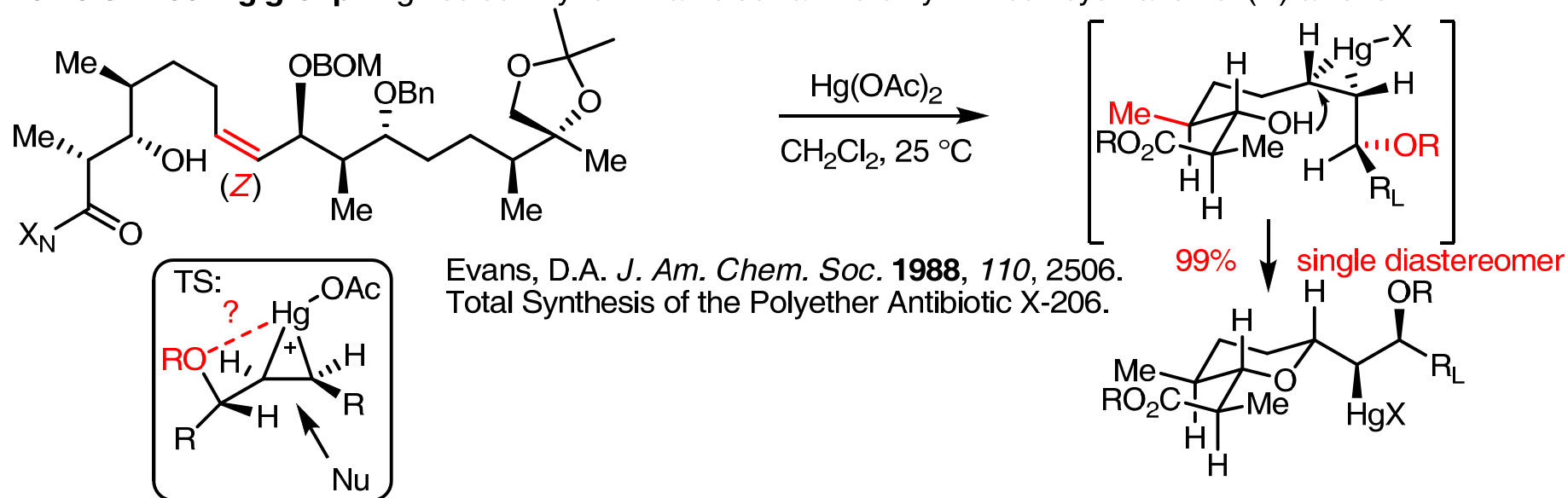
Remote directing group: No selectivity for intramolecular halocyclization of (*E*)-alkenes:



Chamberlin, A.R.; Hehre, W.J. *J. Am. Chem. Soc.* **1987**, *109*, 672.

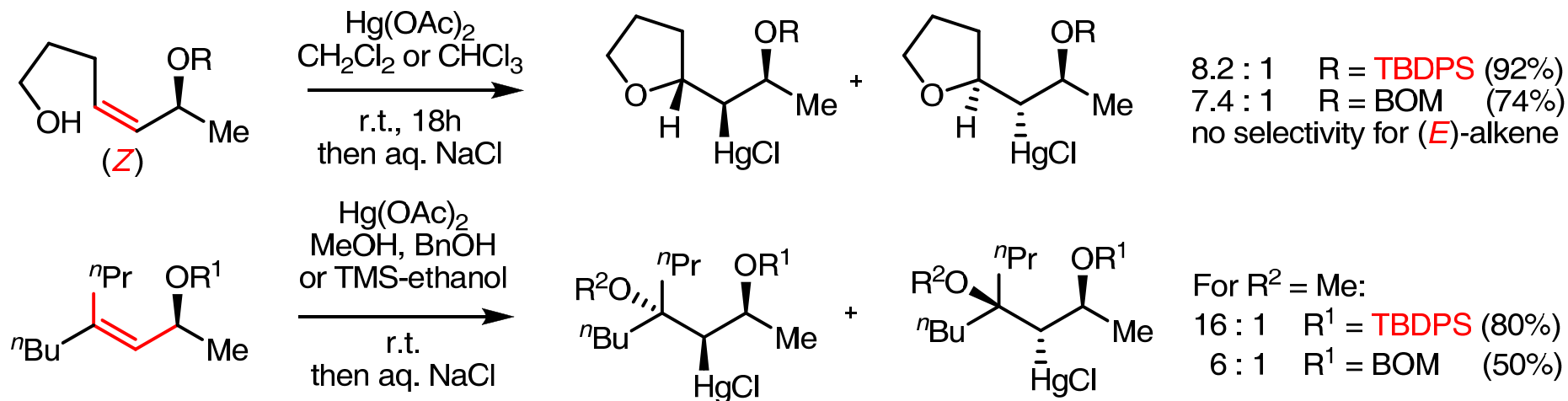
Oxymercuration III

Remote directing group: High selectivity for intramolecular mercury-induced cyclization of (*Z*)-alkene:



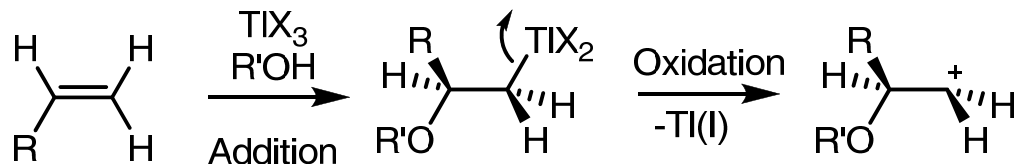
***tert*-Butyldiphenylsilyl hydroxyl (TBDPSO-) as remote directing group:**

Perlmutter, P. *Tetrahedron Lett.* **1995**, *36*, 463; *Tetrahedron Lett.* **2000**, *41*, 3716.



Reactions of Tl(III) with Olefins I

The overall process:

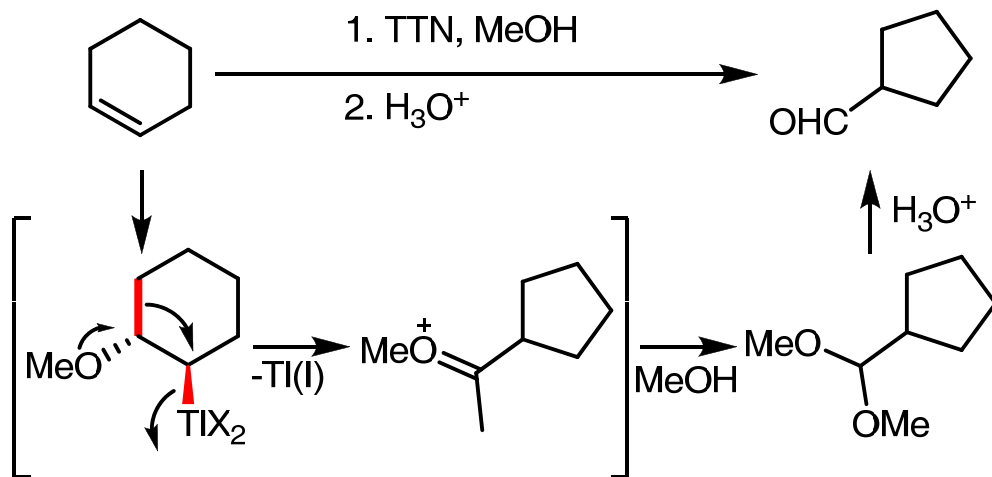


- Thallium(III) mostly used as $Tl(NO_3)_3$ salt
- Anti addition to alkene
- Markovnikov addition
- Oxidation step analogous to solvolysis of C-Tl(III) bond
- Wagner-Meerwein rearrangement occurs along with oxidation (concerted)

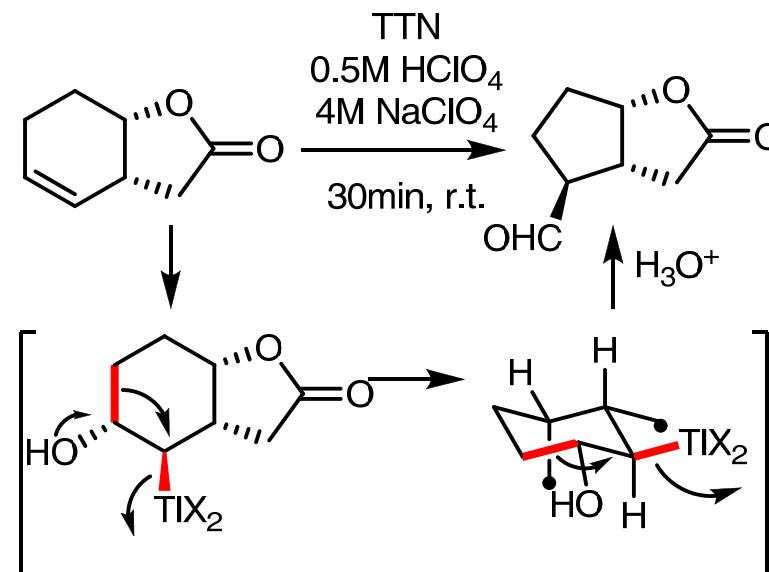
Tl(III)-induced ring contractions:

Seminal Publications (all using $Tl(OAc)_3$): Kabbe, H.-J. *Justus Liebigs Ann. Chem.* **1962**, 656, 204; Lee, J.B.; Price, M.J. *Tetrahedron Lett.* **1962**, 3, 1155; Winstein, S.J. *Org. Chem.* **1963**, 28, 605.

Examples: **TTN = $Tl(NO_3)_2$**



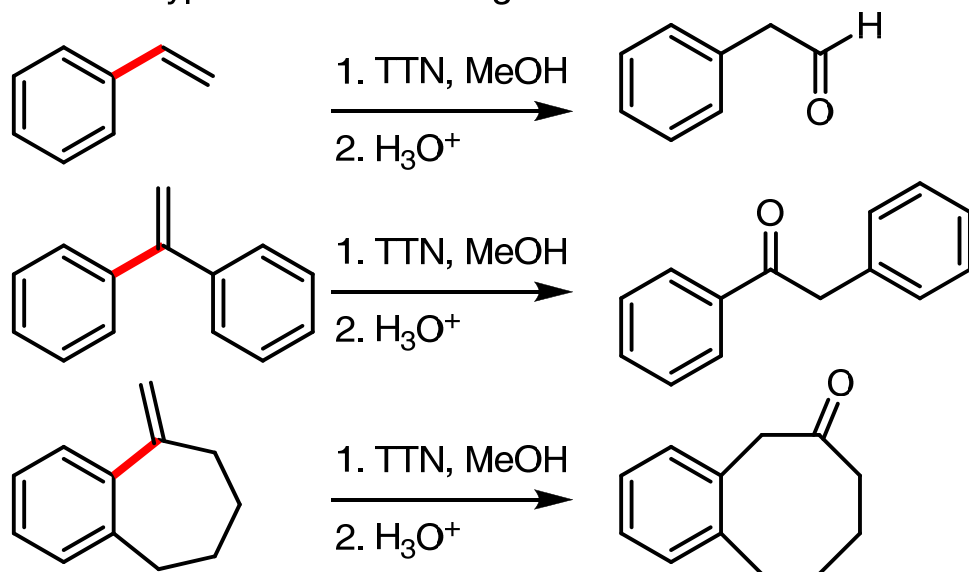
Taylor, E.C. *Tetrahedron Lett.* **1970**, 11, 5275.



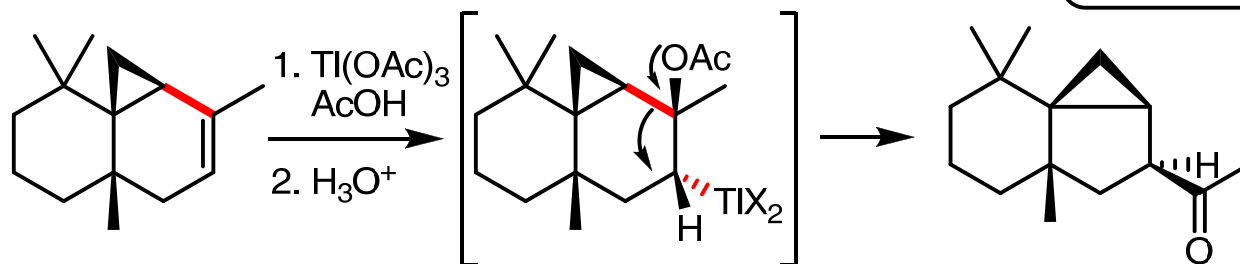
Corey, E.J. *Tetrahedron Lett.* **1971**, 12, 4753.

Reactions of Tl(III) with Olefins II

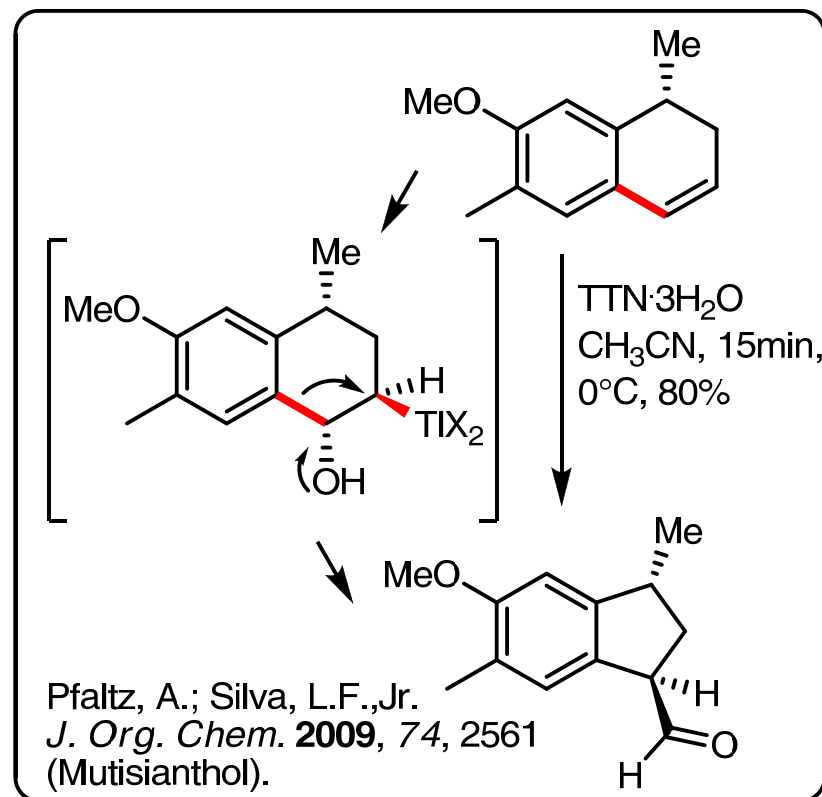
TTN is mostly used for ring-contractions. Examples for other types of reaction are given below:



Taylor, E.C. *J. Am. Chem. Soc.* **1973**, *95*, 3635;
Taylor, E.C. *Tetrahedron Lett.* **1977**, *17*, 1827.



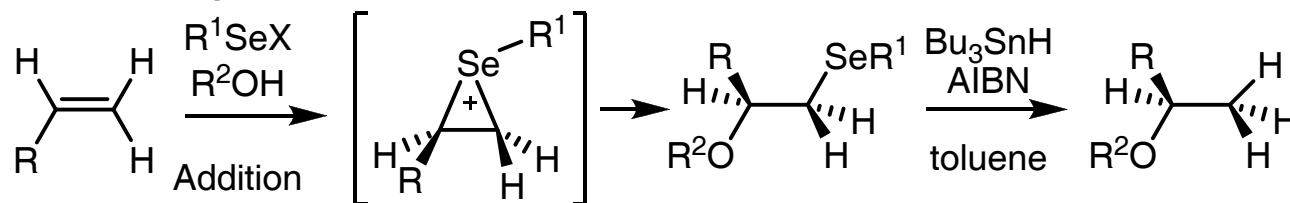
Inoue, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2439.



Review: Silva, L.F., Jr
Quim. Nova **2000**, *23*, 216.

Reaction of Electrophilic Selenium with Olefins I

The overall process:



- Se^+ sources: $PhSeCl$, $PhSePF_6$ and others.
- anti addition to alkenes, also in benzylic position!
- Markovnikov products
- reduction: nonstereoselective radical chain process
- alternative to reduction: H_2O_2 , selenoxidepyrolysis

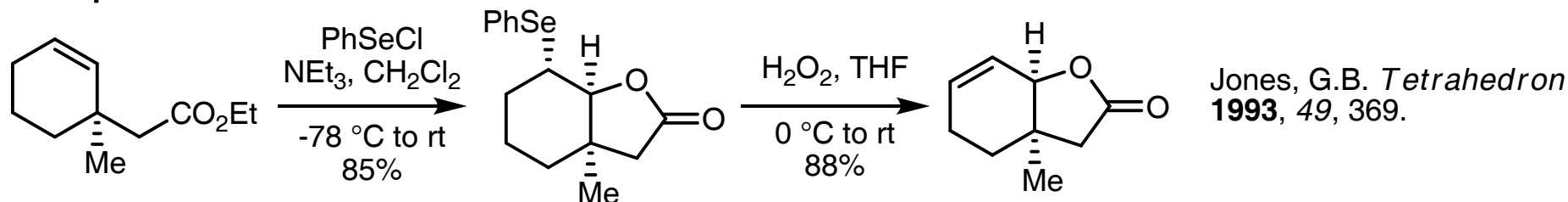
Seminal: Sharpless, K.B. *J. Org. Chem.* **1974**, *39*, 429.

Reviews: Selenolactonization: Jayaraman, N. *Tetrahedron*, **2004**, *60*, 5273.

Selenium electrophiles: Wirth, T. *Eur. J. Org. Chem.* **2009**, 1649.

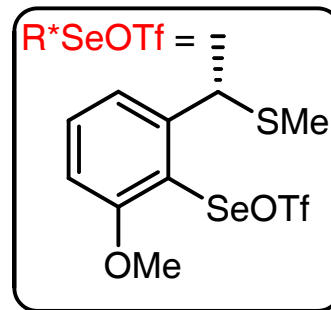
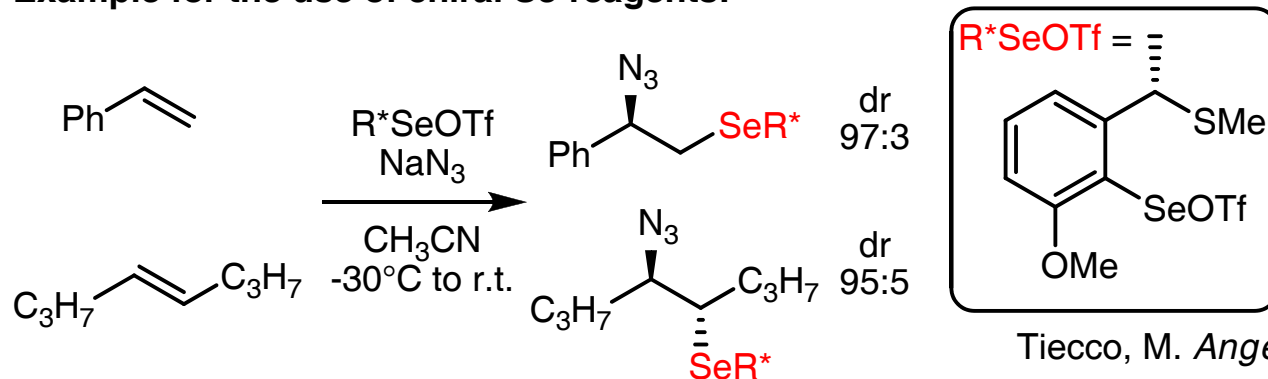
Chiral electrophilic Se-reagents: Wirth, T. *Curr. Org. Chem.* **2006**, *10*, 1893.

Example for selenolactonization:



Jones, G.B. *Tetrahedron* **1993**, *49*, 369.

Example for the use of chiral Se-reagents:

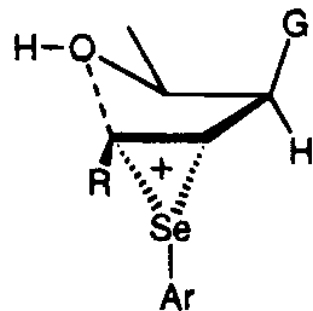
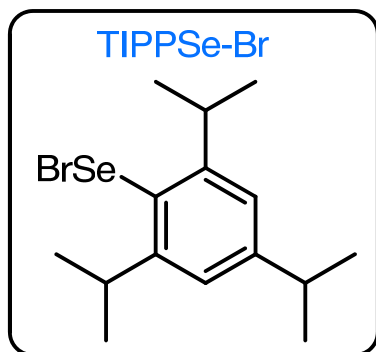
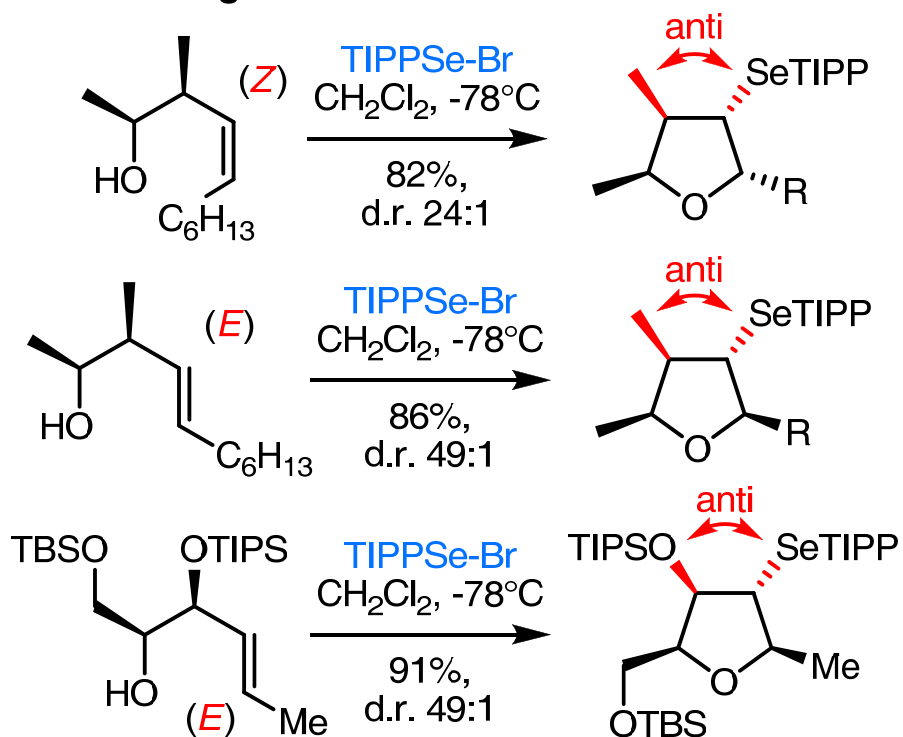


Electrophilic Se-reagents were also used to effect asymmetric hydroxyselenation, methoxy-selenation and cyclofunctionalization reactions. High facial selectivity, mild reaction conditions.

Tiecco, M. *Angew. Chem. Int. Ed.* **2003**, *42*, 3131.

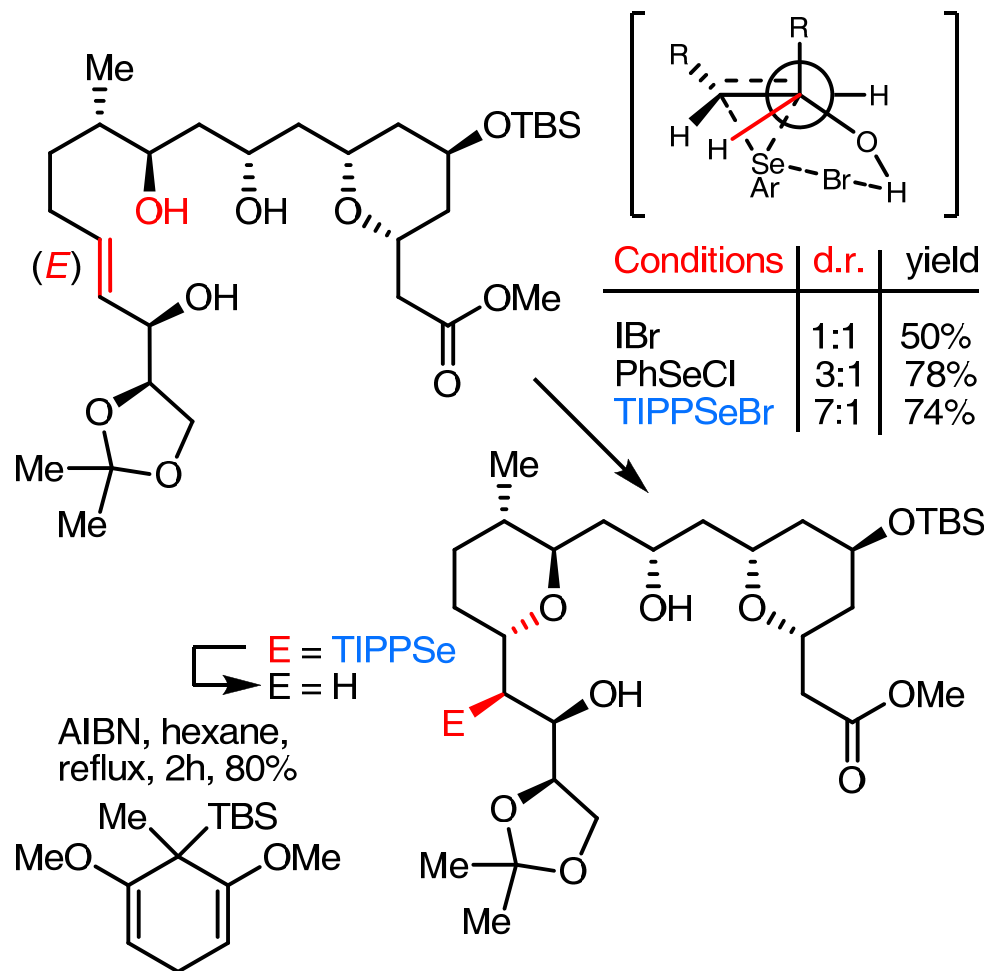
Reaction of Electrophilic Selenium with Olefins II

"Partial reagent control":



Lipshutz, B.H. *J. Org. Chem.* **1995**, *60*, 3572.

Application:



Carreira, E.M. *Angew. Chem. Int. Ed.* **2002**, *41*, 4098;
J. Org. Chem. **2003**, 9274. (Leucascandrolide A)
 Review on Sn-free reduction: Studer, A. *Synthesis* **2002**, 835.