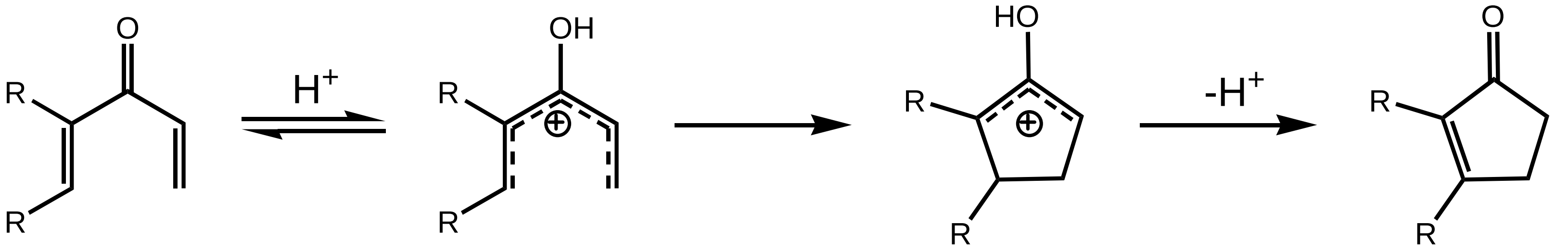
The Nazarov Cyclization



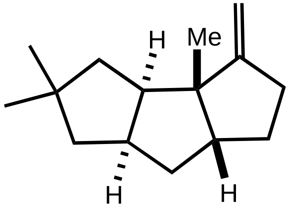
Jeffrey D. Frein

Third Year Seminar

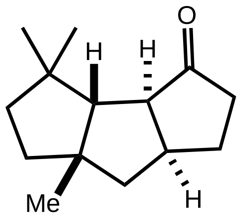
April 9, 2004

Why the Nazarov?

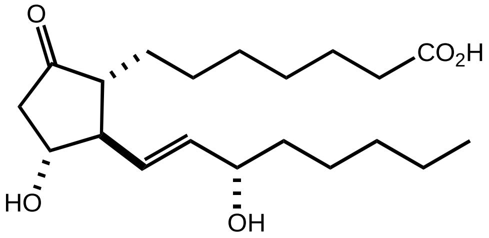
- Ease of substrate synthesis
- Ability to set 2 or more stereocenters in a single step
- Occurrence of cyclopentanoids in natural products



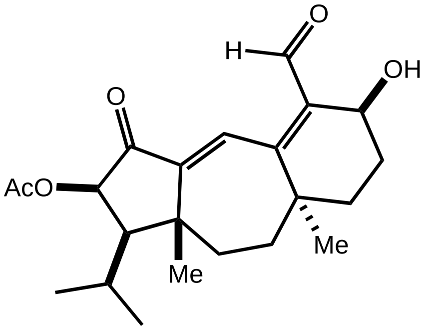
Hirsulene



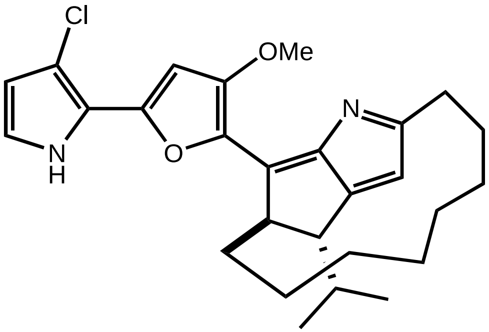
Capnellene



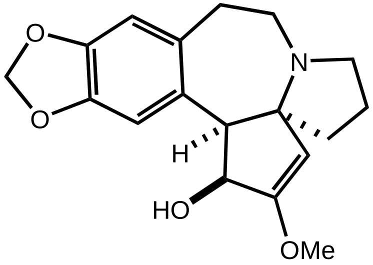
Prostaglandins (PGE_1)



Guanacastepene A



Roseophilin



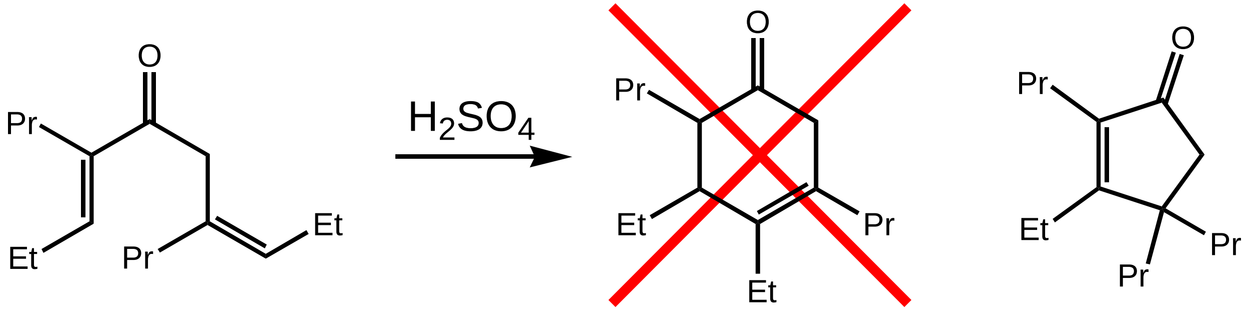
Cephalotaxine

Overview

- Historical Background
- Mechanism and Computational Studies
- Nazarov Cyclizations
  - Divinyl Ketone
  - Silicon Directed
  - Reductive/Interrupted
  - Asymmetric
- Applications in Total Synthesis

First Report and Thorough Investigation

- Reported by Vorlander in 1903
- Investigated by Marvel (1933-1939)

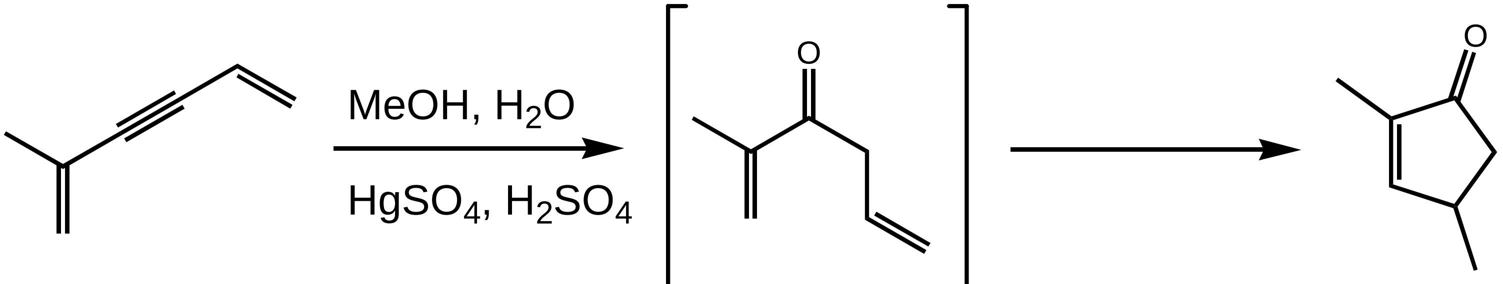


- Carbocation intermediate proposed by Braude & Coles in 1952

Denmark, S. E.; “Nazarov and Related Cyclizations” In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Vol. 5; Pergamon Press: Oxford, 1991; pp. 751-784.

Acid-Catalyzed Hydration Cyclization of Dienynes

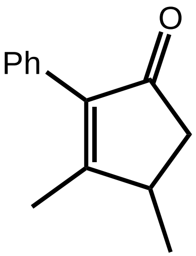
- Extensively studied in 1940's and 1950's by Nazarov and coworkers



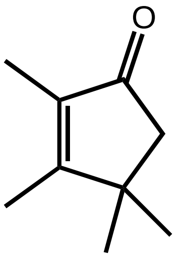
MeOH, H_2O

$HgSO_4$, H_2SO_4

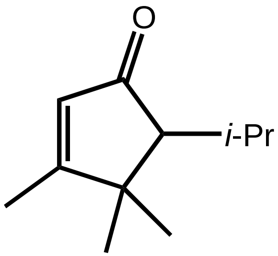
75%



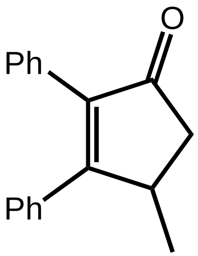
95%



60%



81%

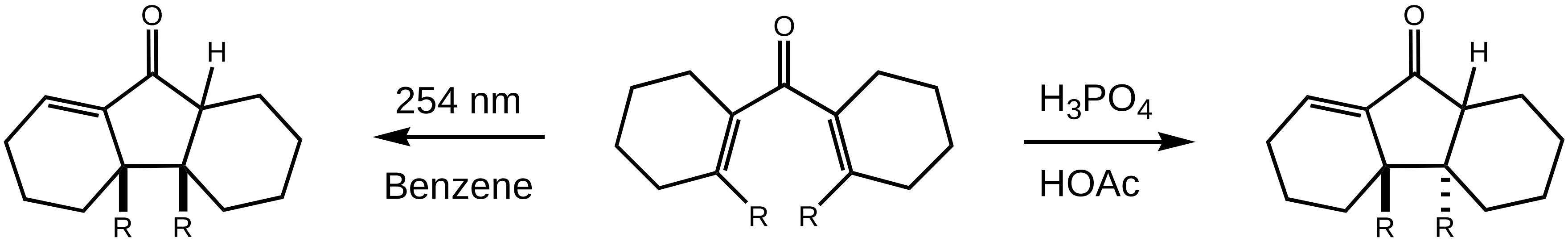


95%

Nagibina, T. D.; Nazarov, I. N. *J. Gen. Chem. USSR (Engl. Transl.)* **1953**, *23*, 839.

General Mechanism

- 4π-electrocyclic closure of a oxypentadienyl cation
  - Rotation Pathways
    - Thermal (conrotatory)
    - Photochemical (disrotatory)

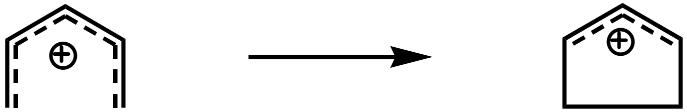


disrotatory

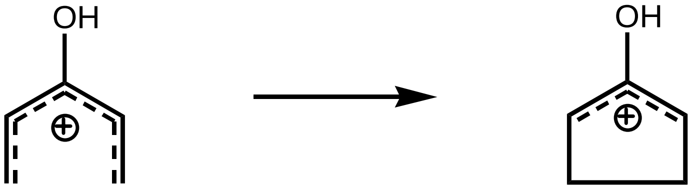
conrotatory

Pentadienyl Cation vs. Protonated Divinyl Ketones

A



B

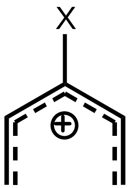


	A	B
E_a (kcal/mol) =	19.9	20.4
Heat of Cyclization (kcal/mol) =	-33.6	-19.9
Transition State =	early	late

All calculations at the MP3/6-31G**//RHF/3-21G level

Smith, D. A.; Ulmer, II, C. W. *Tet. Lett.* **1991**, *32*, 725.

Substitution at the 3-Position



X = AlH_2, BH_2, PH_2, H, SH, OH, NH_2

- E_a : $AlH_2 < BH_2 < PH_2 < H < SH < OH < NH_2$

- T. S.: $AlH_2 < BH_2 < H < PH_2 < SH < OH < NH_2$

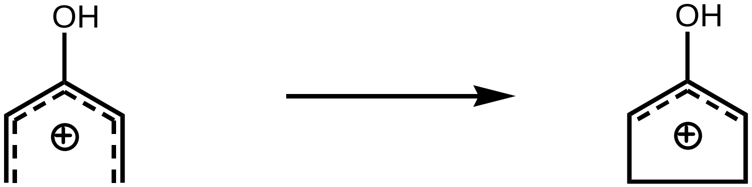
  Early - - - - - - - - - - - - - - - - - - Late

All calculations at the MP3/6-31G**//RHF/3-21G level

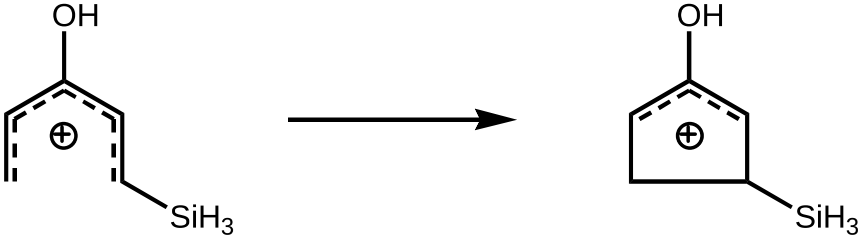
Smith, D. A.; Ulmer, II, C. W. *J. Org. Chem.* **1997**, *62*, 5110.

β-Silyl and β-Methyl Substituents

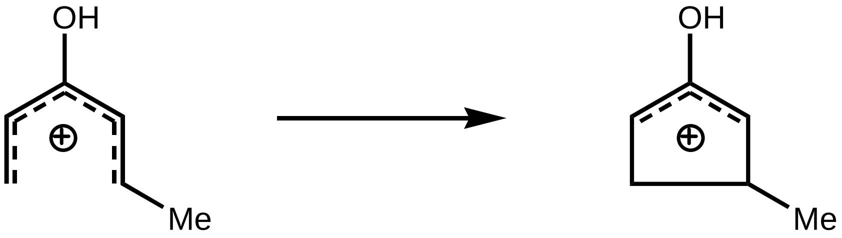
E_a (kcal/mol)



20.4



21.7

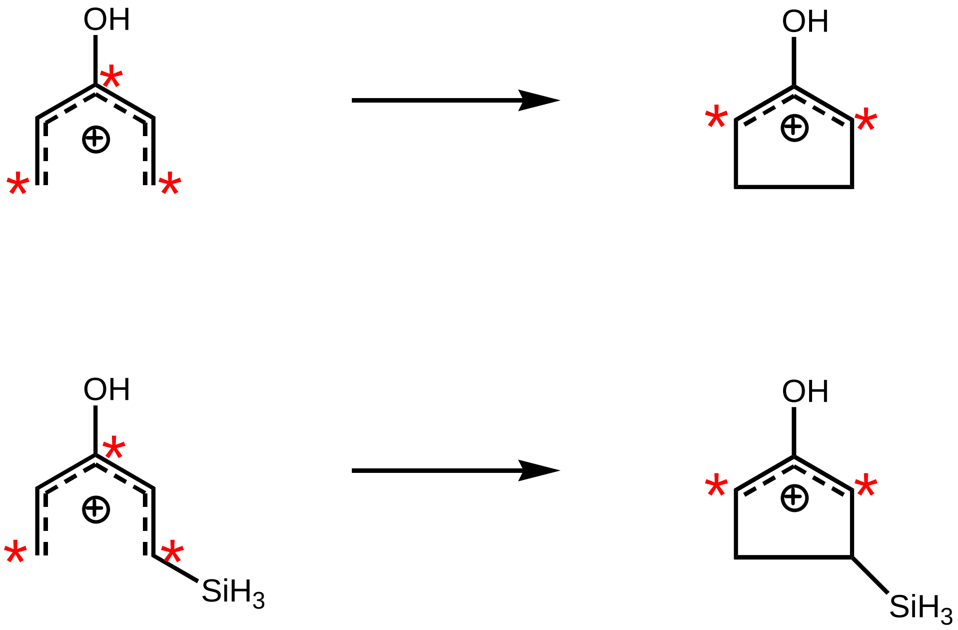


21.9

All calculations at the MP3/6-31G**//RHF/3-21G level

Smith, D. A.; Ulmer, II, C. W. *J. Org. Chem.* **1991**, *56*, 4444.

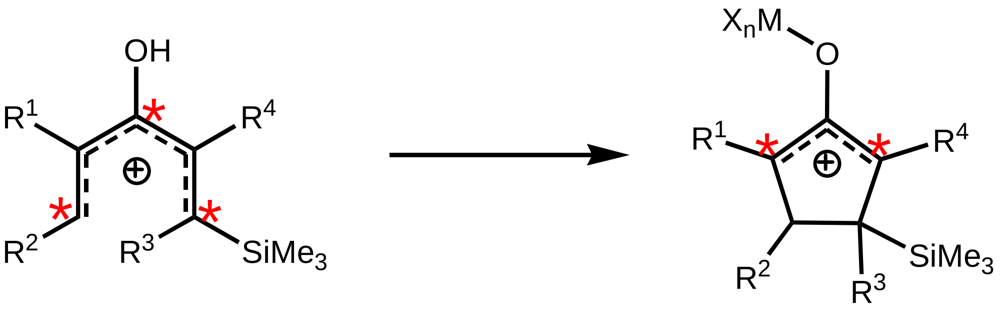
Activation Energy



All calculations at the MP3/6-31G**//RHF/3-21G level

Smith, D. A.; Ulmer, II, C. W. *J. Org. Chem.* **1991**, *56*, 4444.

Energy of Activation and Rate

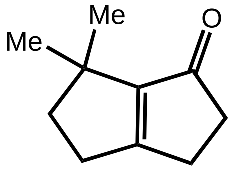


- E_a increased if: R^2 and R^3 are cation stabilizing
- E_a decreased if: R^1 and R^4 are cation stabilizing
- R^1 and R^4 impact rate more than R^2 and R^3

Denmark, S. E.; Habermas, K. L.; Hite, G. A. *Helv. Chim. Acta* **1988**, *71*, 168.

Nazarov Cyclization Products

- All cyclizations performed with Brønsted acids



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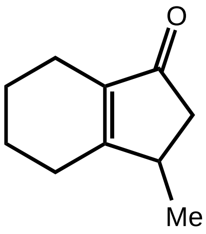

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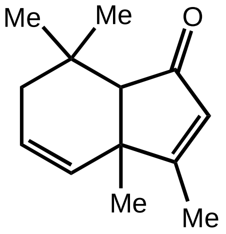
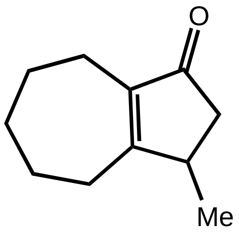
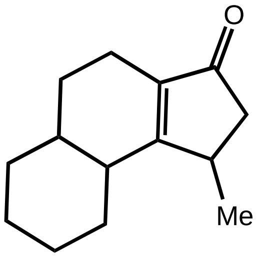


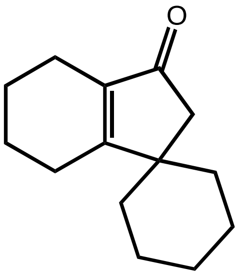
80%



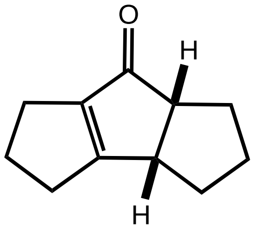
75%



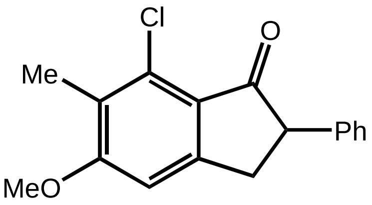
73%



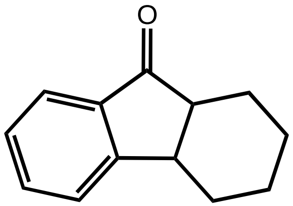
76%



62%



100%



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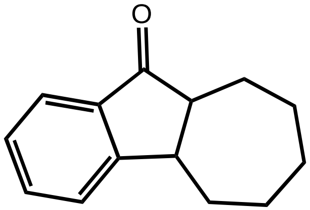

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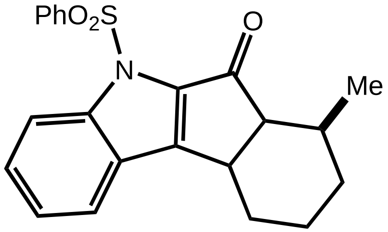
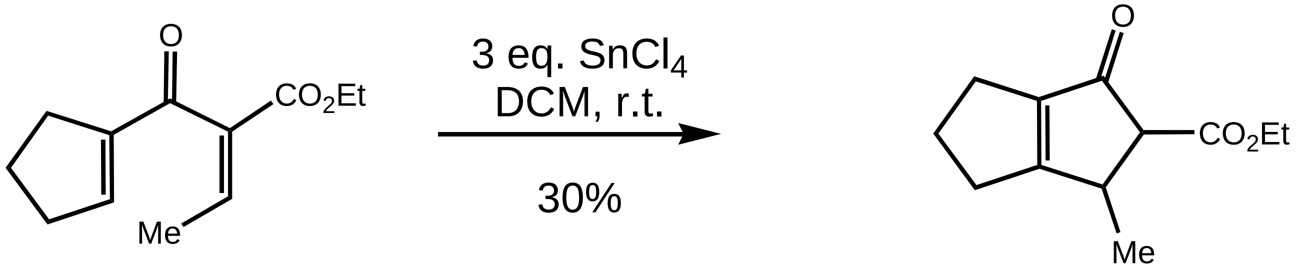
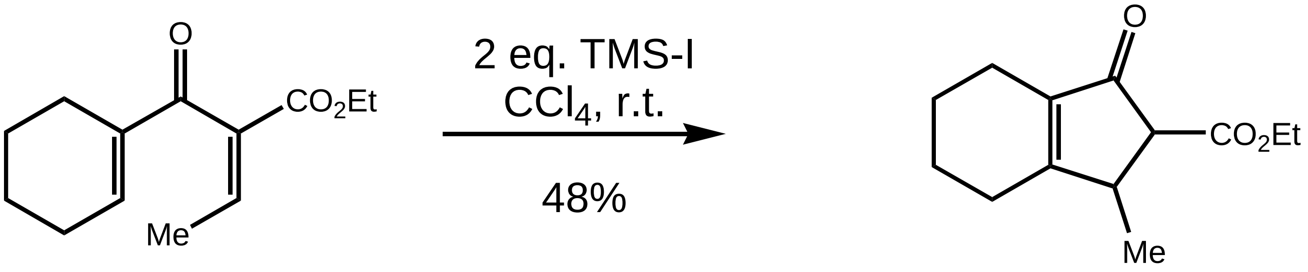


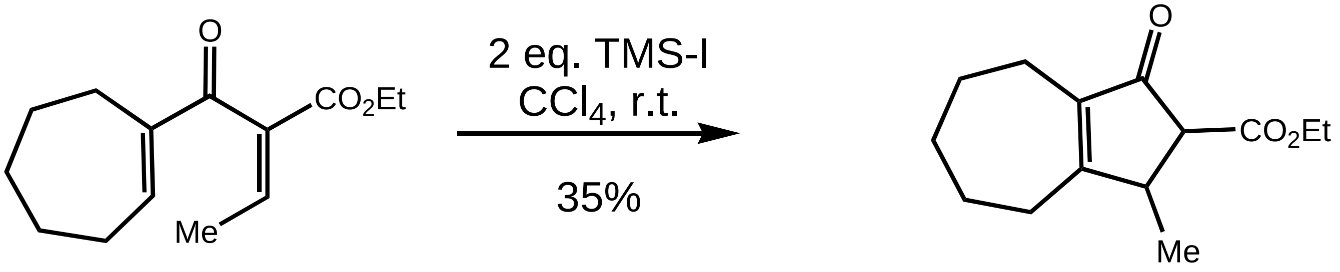
49% *syn:anti*
24% *syn:syn*

Denmark, S. E.; Haberman, K. L. *Organic Reactions*, v. 45, **1994**, 1-158.

Lewis Acid Mediated

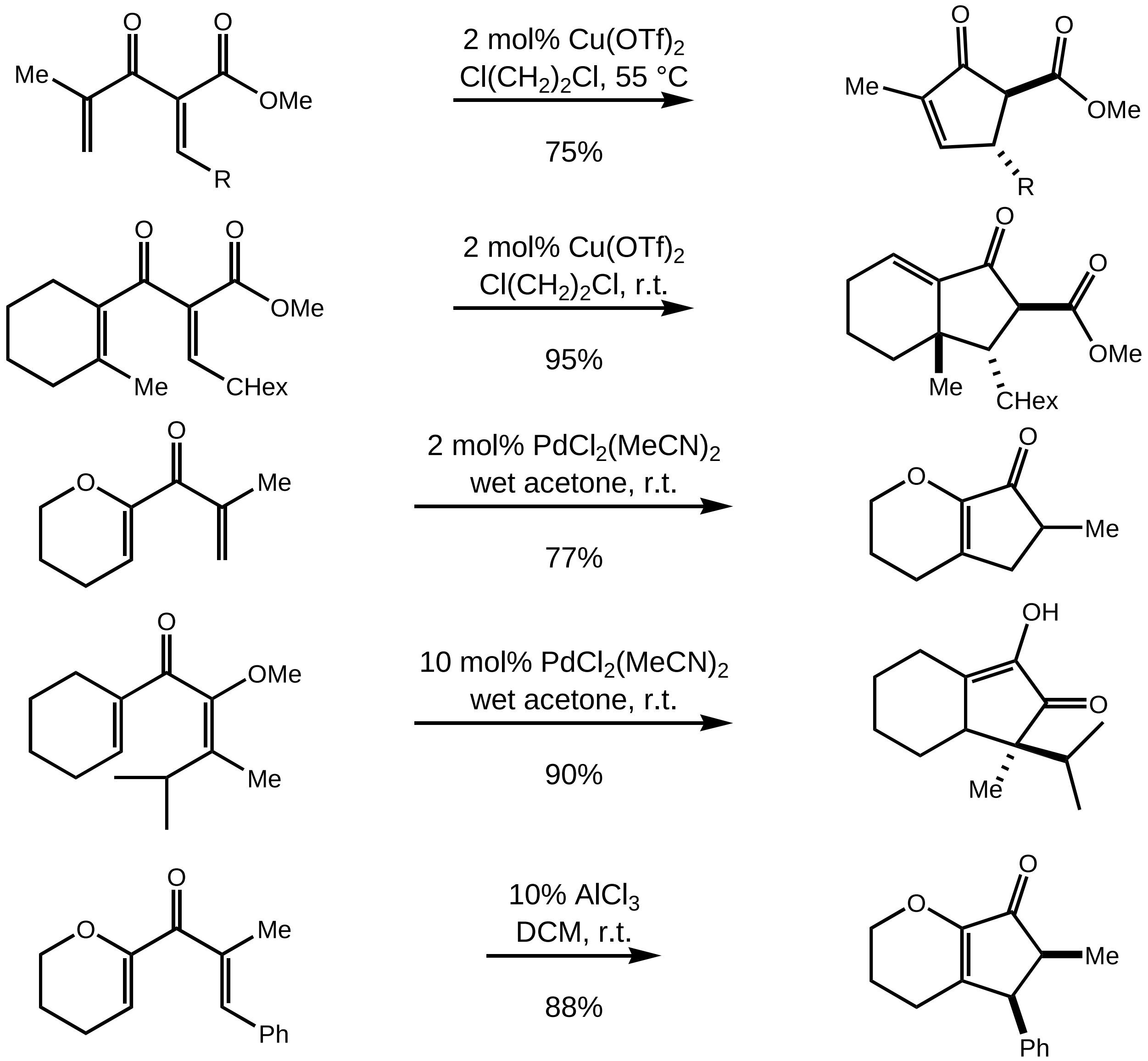






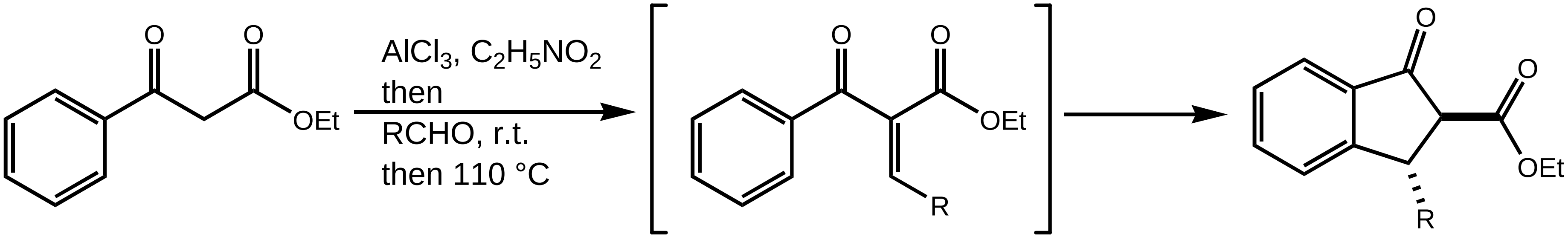
Marino, J. P.; Linderman, R. J. *J. Org. Chem.* **1981**, *46*, 3696.

Lewis Acid Catalyzed



Frontier, A. J.; Sun, X.; He, W. *J. Am. Chem. Soc.* **2003**, *125*, 14278.
Tius, M. A.; Leclerc, E.; Bee, C. *Org. Lett.* **2003**, *5*, 4927.
Trauner, D.; Liang, G.; Gradl, S. N. *Org. Lett.* **2003**, *5*, 4931.

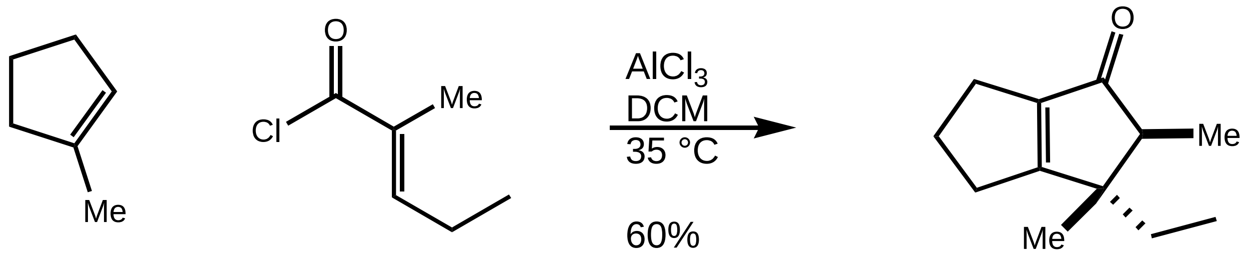
Tandem Knoevenagel/Nazarov



R	**Yield(%)**	***anti:syn***
Ph	72	88:12
4-Cl-Ph	58	87:13
4-OMe-Ph	70	89:11
PhCH=CH	63	78:22

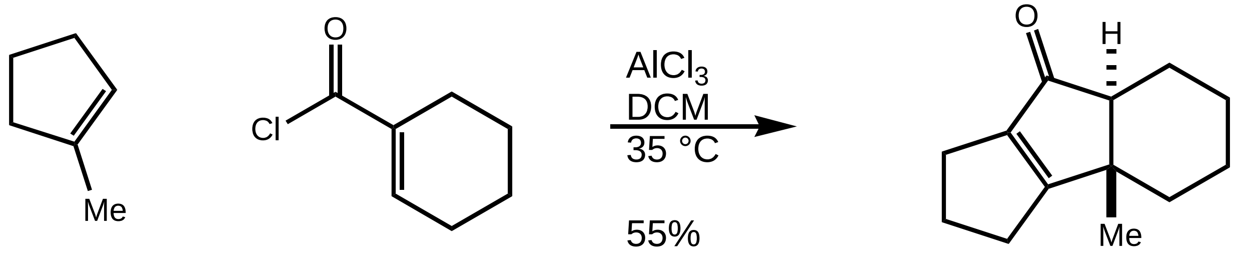
Sartori, G.; Maggi, R.; Bigi, F.; Porta, C.; Tan, X.; Bernardi, G. L.; Ianelli, S.; Nardelli, M. *Tetrahedron* **1995**, *51*, 12179.

In Situ Oxypentadienyl Cation Generation



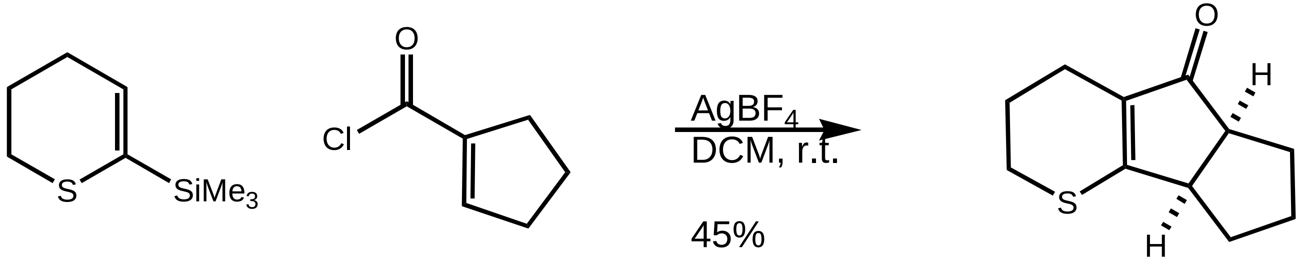
$AlCl_3$
DCM
35 °C

60%



$AlCl_3$
DCM
35 °C

55%

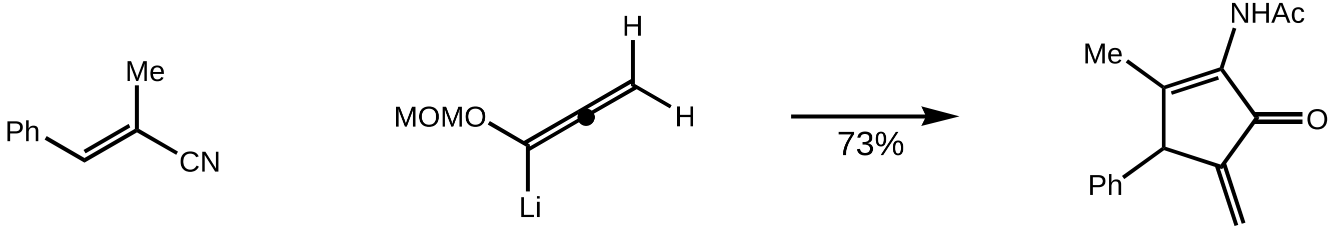


$AgBF_4$
DCM, r.t.

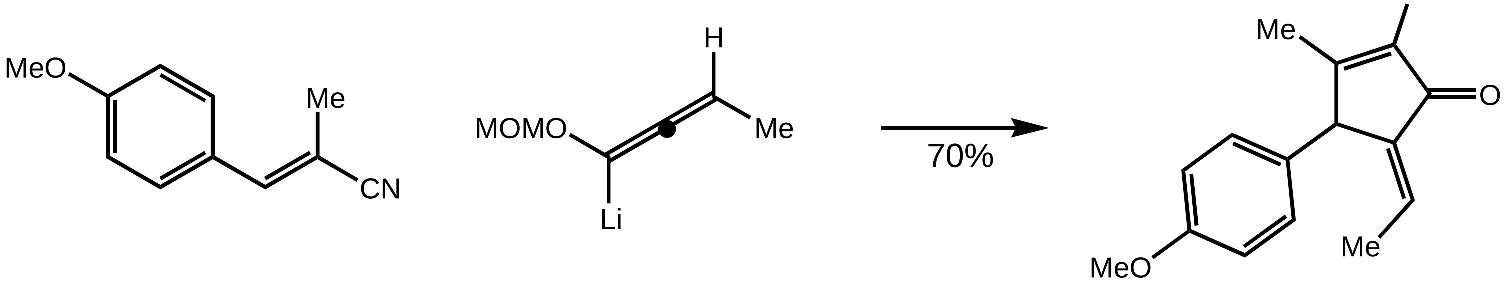
45%

Santelli, M.; Morel-Fourrier, C.; Dukere, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 8062.
Bonini, B. F.; Franchini, M. C.; Fochi, M.; Mazzanti, G.; Ricci, A. *Tetrahedron* **1997**, *53*, 7897.

Imino Nazarov

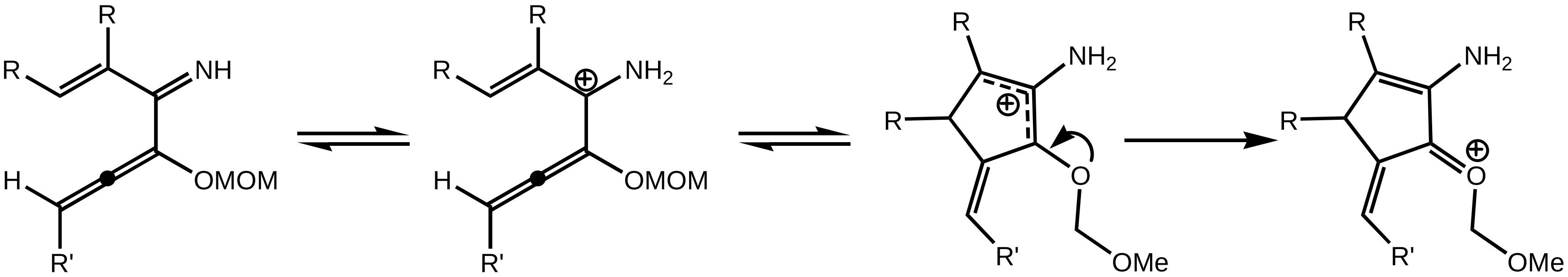


1. THF, -78 °C
2. sat. aq. $(NH_4)H_2PO_4$
   -78 °C - r.t.
3. Ac_2O, pyr.
   cat. DMAP, r.t.



E : Z
>95:5

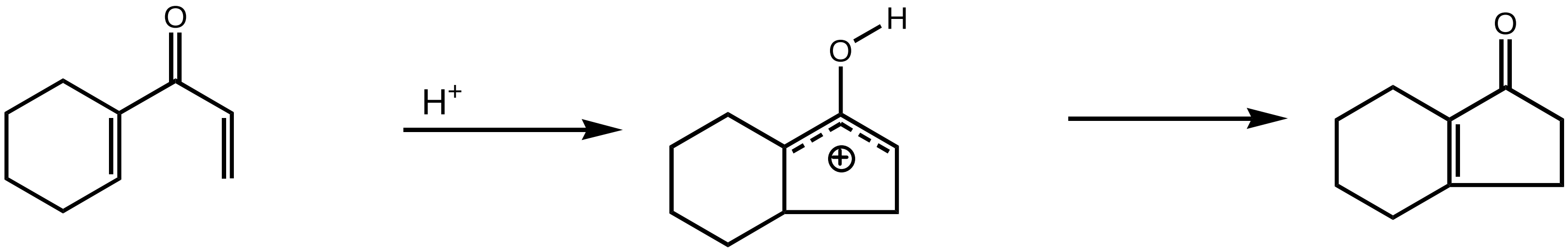
Via:



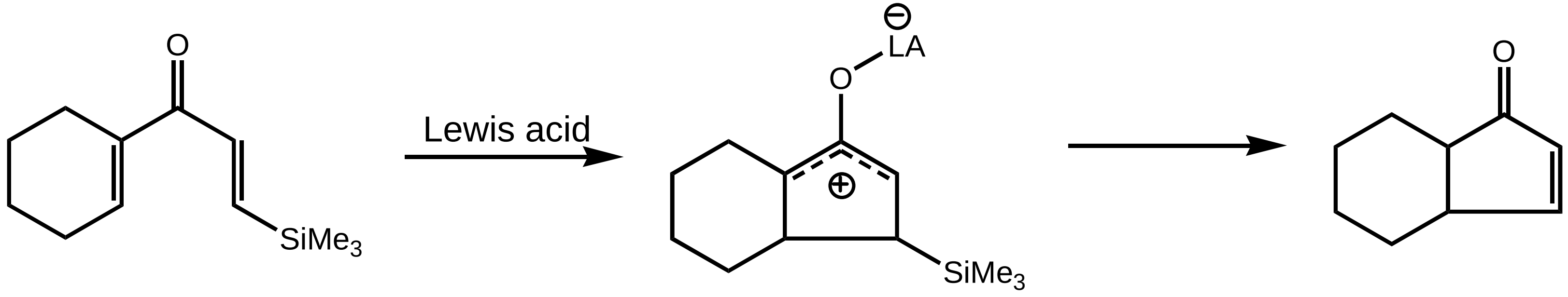
Tius, M. A.; Chu, C. C.; Nieves-Colberg, R. *Tet. Lett.* **2001**, *42*, 2419.

Silicon-Directed Nazarov Cyclization

- Standard Nazarov Product

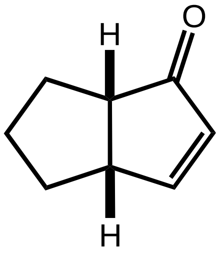


- Silicon Directed Nazarov

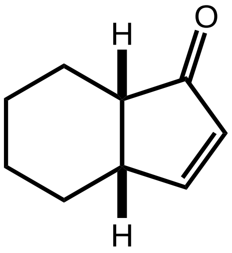


SDNC Products

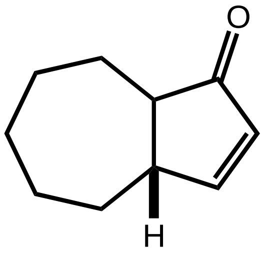
- All cyclizations performed with $FeCl_3$



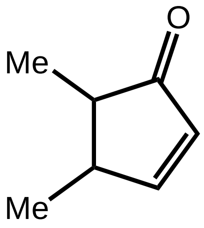
55%
single isomer



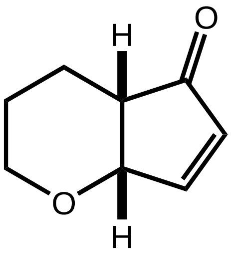
84%
single isomer



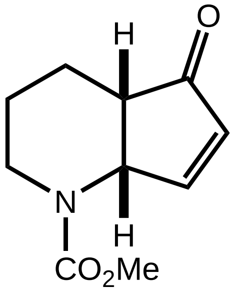
74%
85:15 *cis:trans*



95%
59:41 *cis:trans*



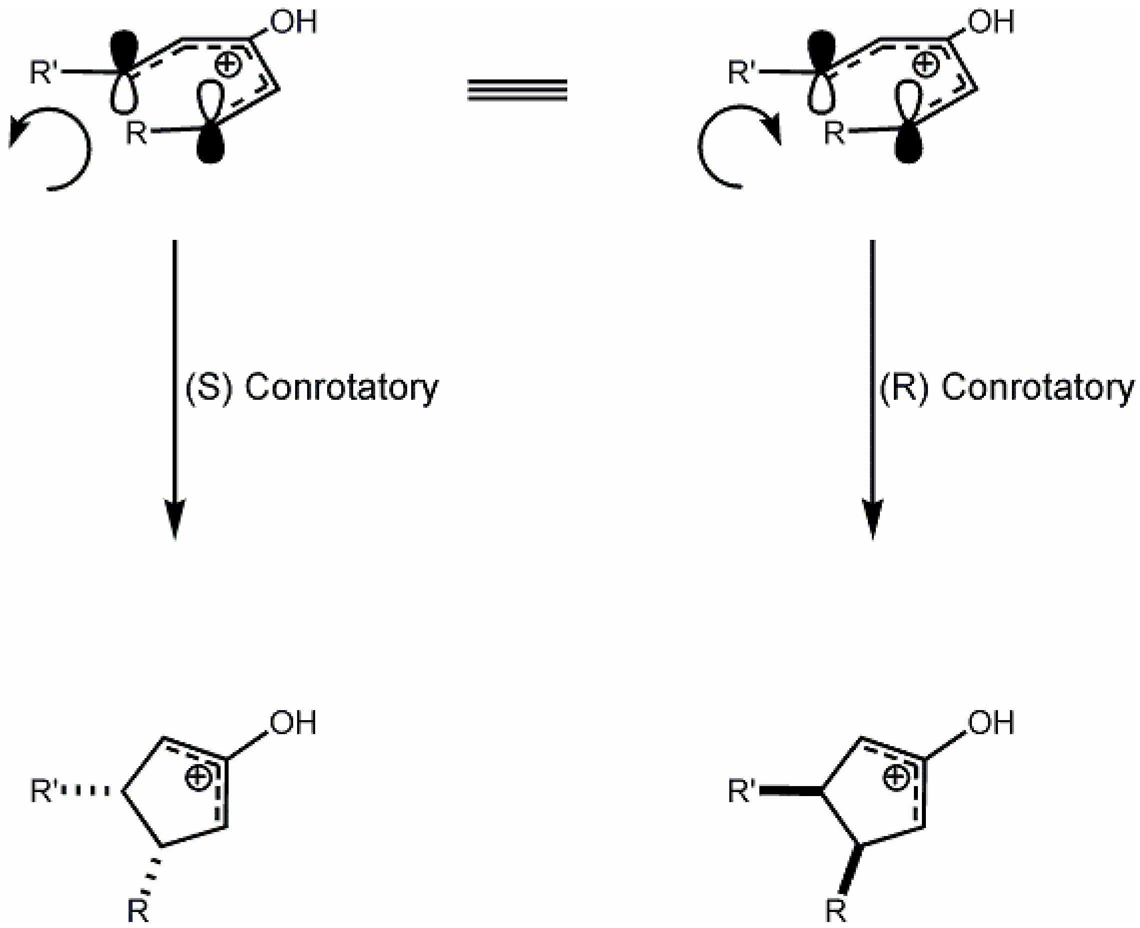
60%
single isomer



76%
single isomer

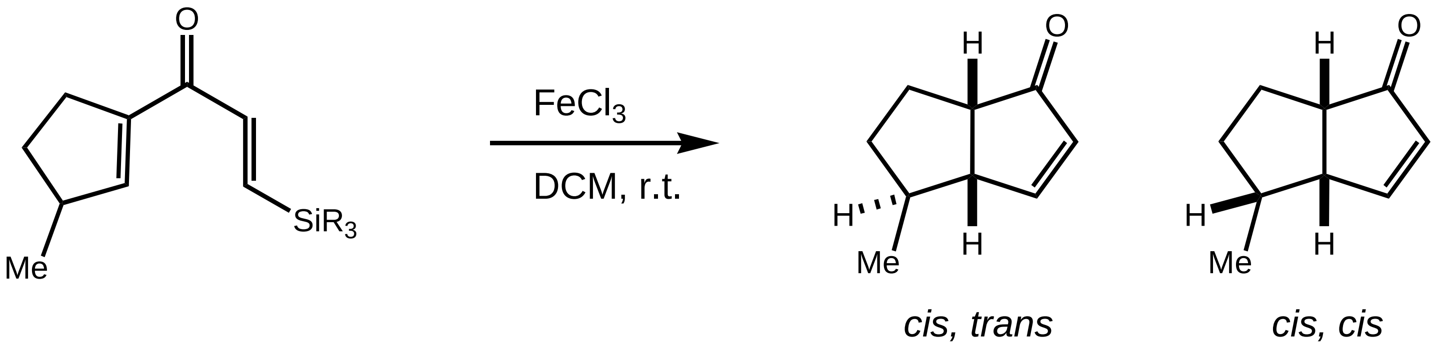
Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc.* **1982**, *104*, 2642.
Denmark, S. E.; Haberman, K. L.; Hite, G. A. *Helv. Chim. Acta* **1988**, *71*, 168.

Torquoselectivity


(S) Conrotatory

(R) Conrotatory

Silicon Substituents & Torquoselectivity

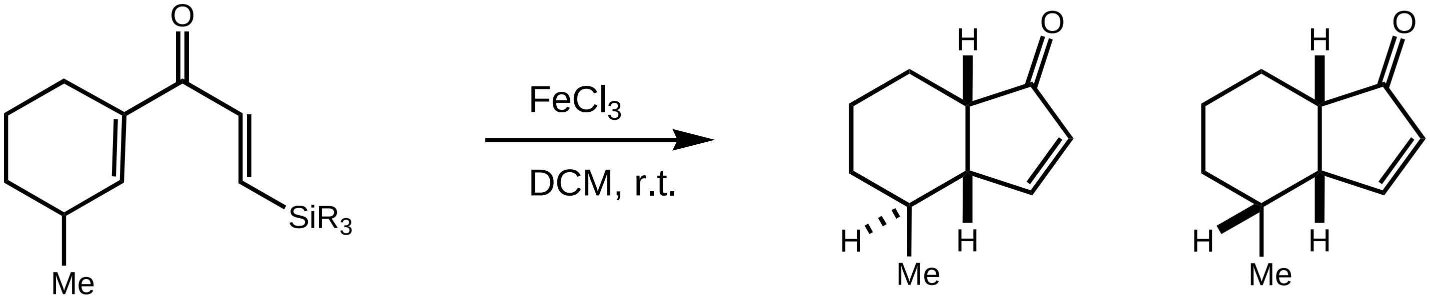


A **B**

R	**A**	**B**	**Yield(%)**
Me_3	54	46	50
Me_2Ph	59	41	46
$MePh_2$	62	38	41
Ph_3	76	24	13
i-Pr_3	79	21	13

Denmark, S. E.; Haberman, K. L.; Hite, G. A.; Jones, T. K. *Tetrahedron* **1986**, *42*, 2821.

Silicon Substituents & Torquoselectivity



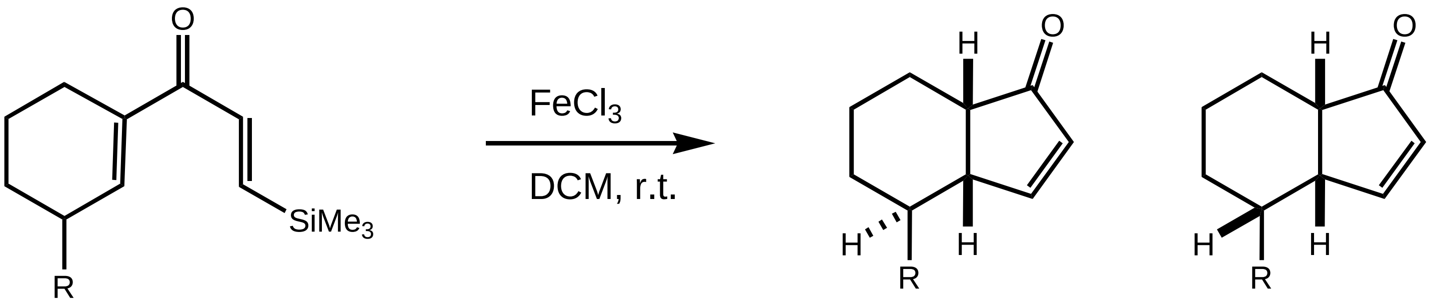
cis, trans *cis, cis*

A **B**

R	A	B	Yield(%)
Me_3	78	22	99
Me_2Ph	84	16	63
$MePh_2$	86	14	83
Ph_3	87	13	15
i-Pr_3	90	10	70

Denmark, S. E.; Haberman, K. L.; Hite, G. A.; Jones, T. K. *Tetrahedron* **1986**, *42*, 2821.

γ-Substitution & Torquoselectivity



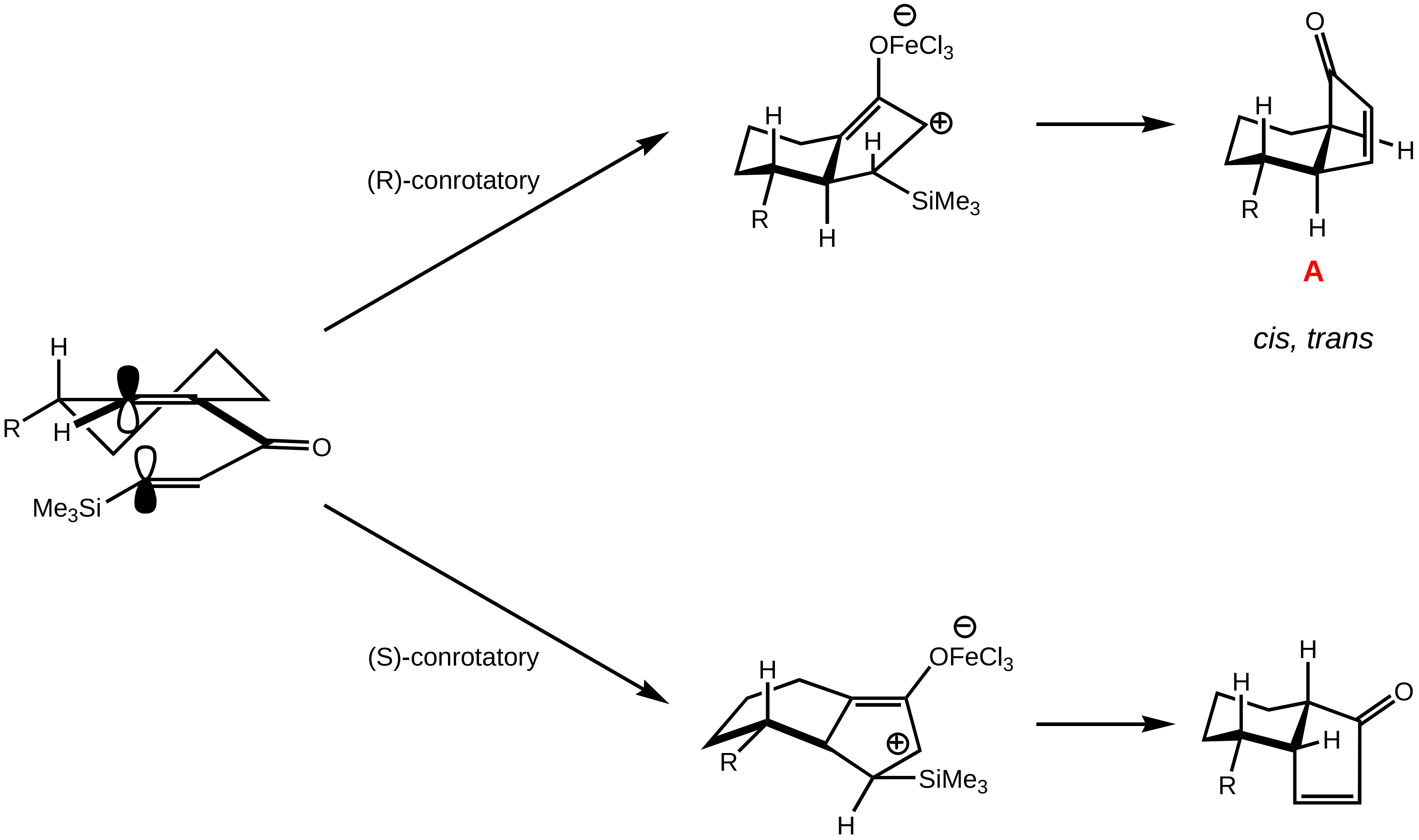
cis, trans *cis, cis*

A **B**

R	**A**	**B**	**Yield(%)**
Me	78	22	99
vinyl	70	30	66
Ph	94	6	76
t-Bu	94	6	63
OBn	90	10	76

Denmark, S. E.; Haberman, K. L.; Hite, G. A.; Jones, T. K. *Tetrahedron* **1986**, *42*, 2821.

Two Modes of Electrocyclization



A

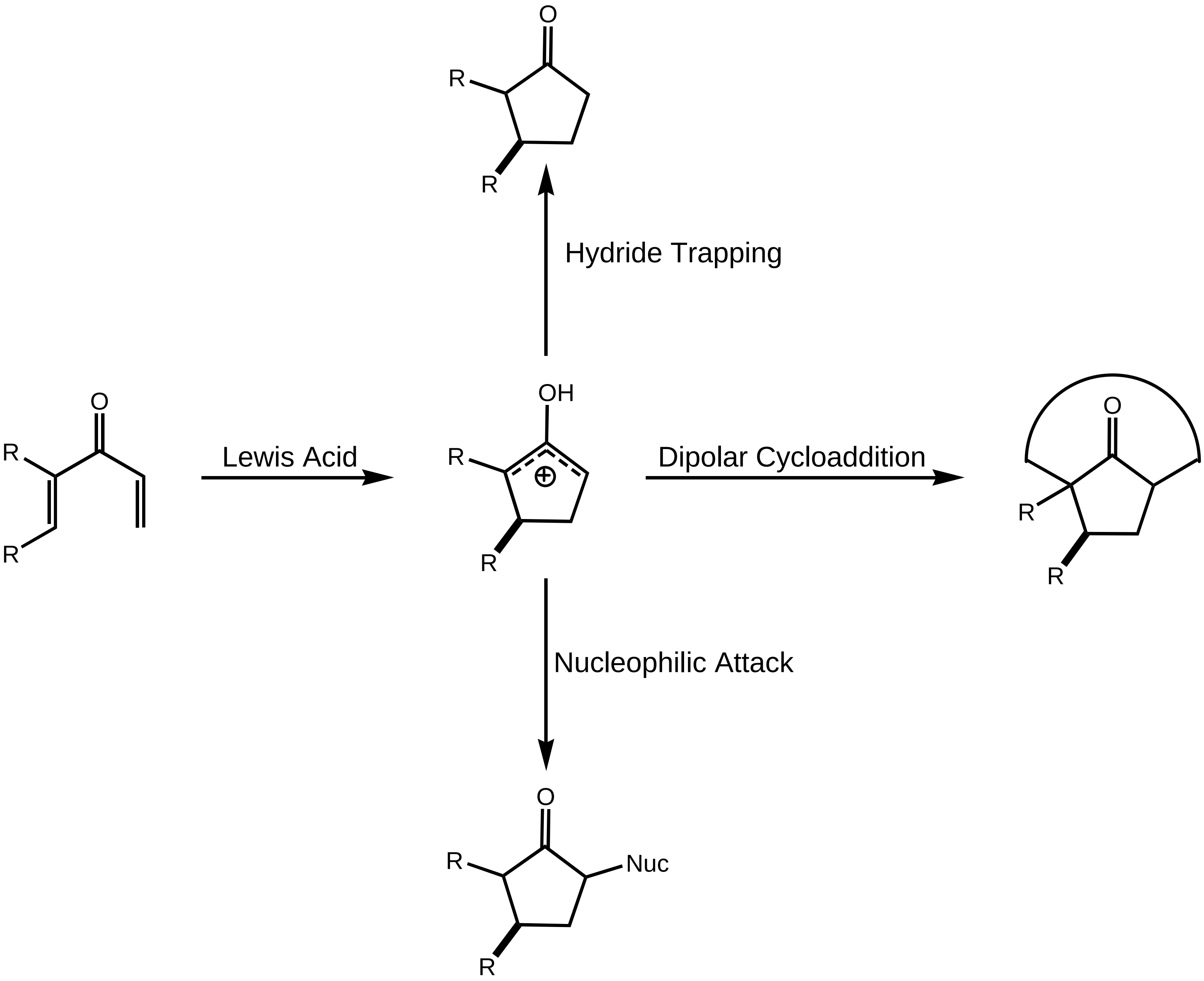
cis, trans

B

cis, cis

Denmark, S. E.; Jones, T. K. *Helv. Chim. Acta* **1983**, *66*, 2397.

Utilizing the Oxyallyl Cation



Lewis Acid

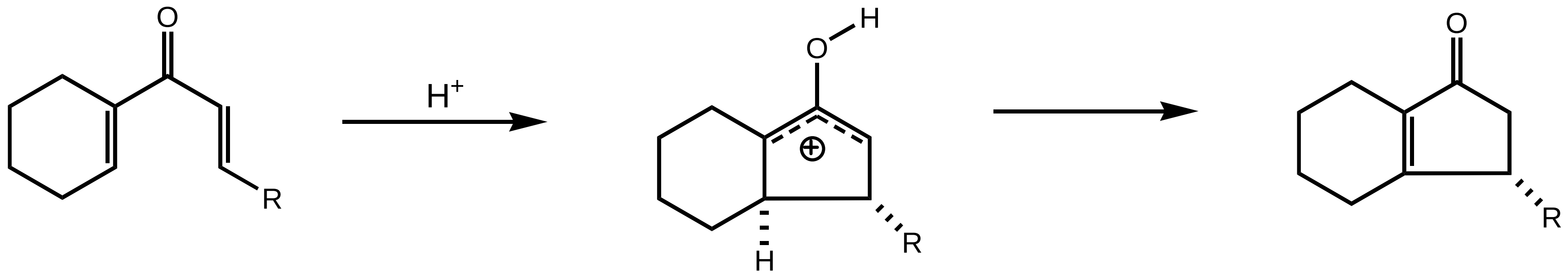
Hydride Trapping

Dipolar Cycloaddition

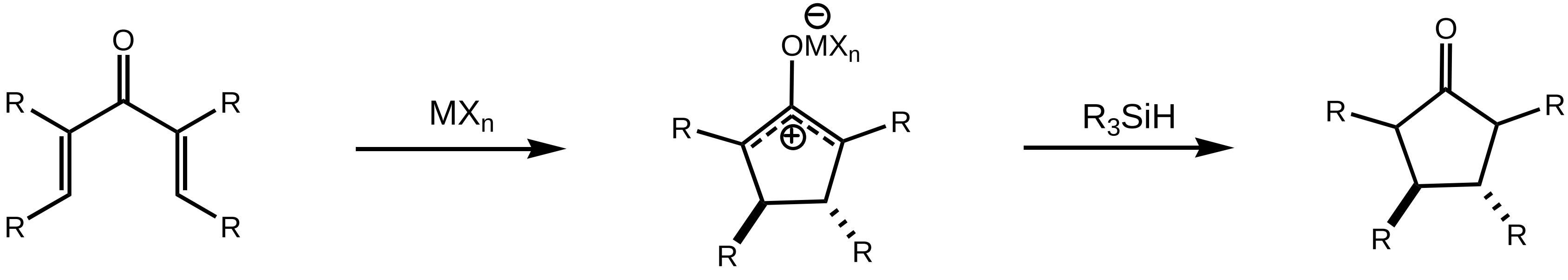
Nucleophilic Attack

Reductive Nazarov

- Standard Nazarov Product

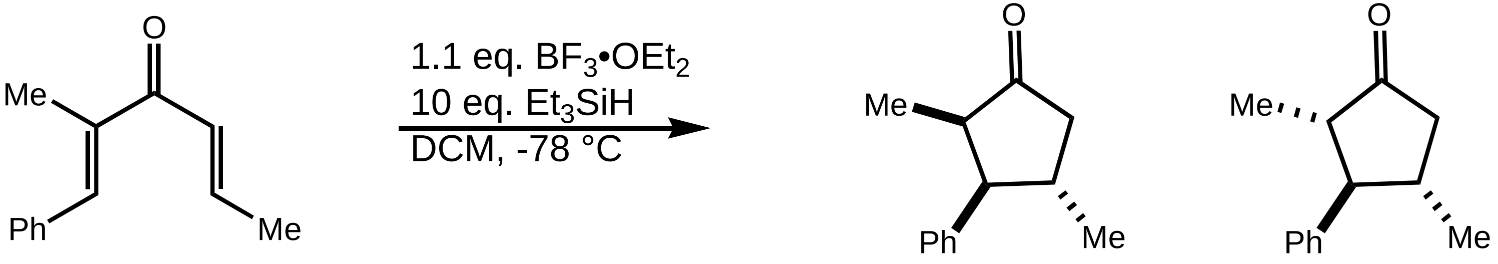


- Reductive Nazarov Product



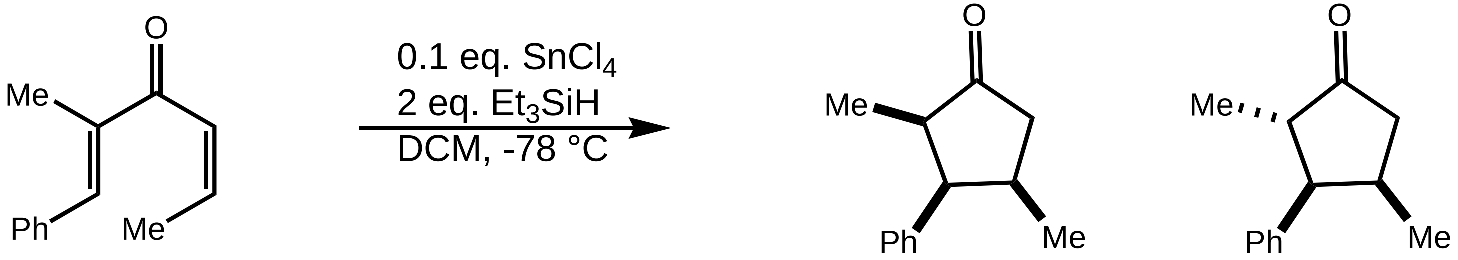
West, F. G.; Giese, S. *Tet. Lett.* **1998**, *39*, 8393.
West, F. G.; Giese, S. *Tetrahedron* **2000**, *56*, 10221.

Reductive Nazarov Products



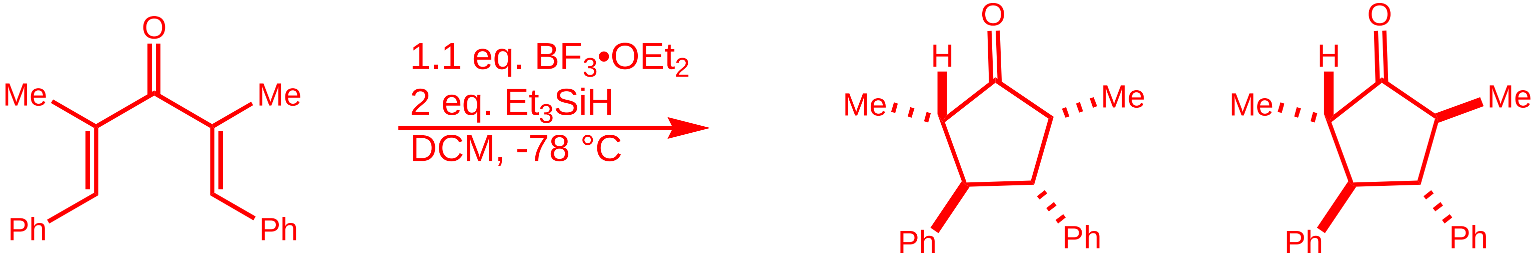
1.1 eq. $BF_3 \bullet OEt_2$
10 eq. Et_3SiH
DCM, -78 °C

1:3.3 (77%)



0.1 eq. $SnCl_4$
2 eq. Et_3SiH
DCM, -78 °C

1:5.6 (63%)



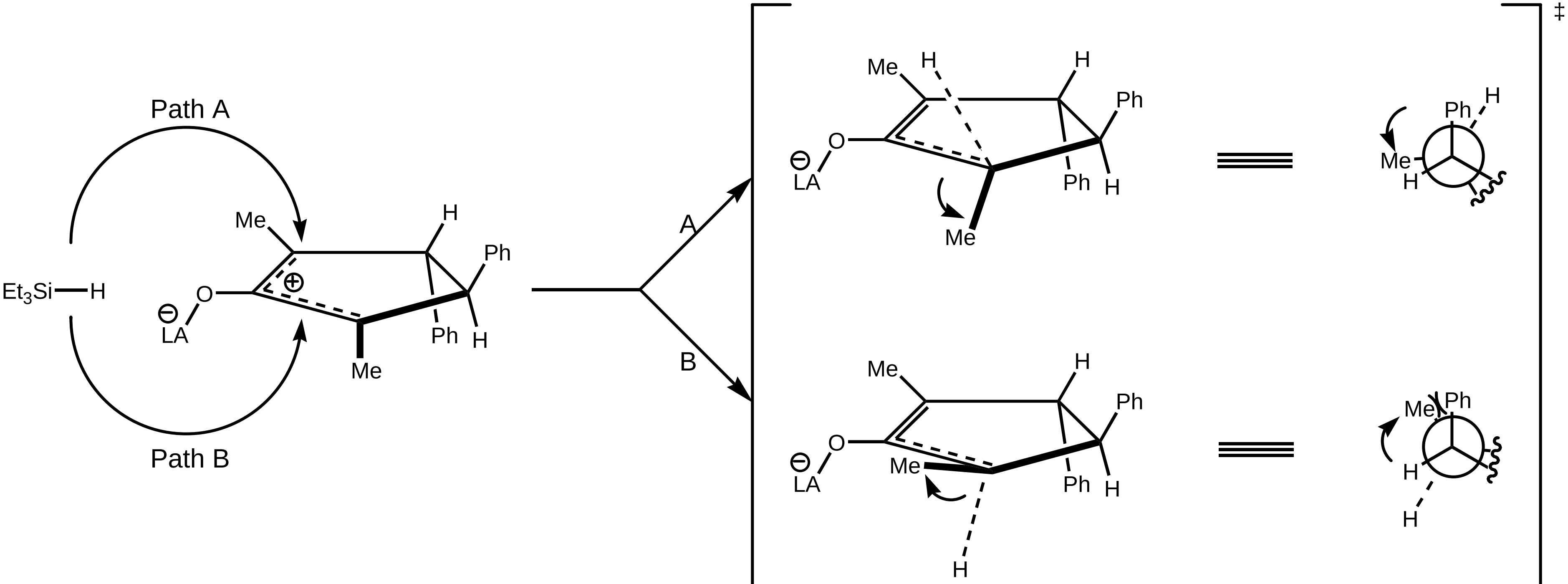
1.1 eq. $BF_3 \bullet OEt_2$
2 eq. Et_3SiH
DCM, -78 °C

1:8.8 (98%)

West, F. G.; Giese, S. *Tet. Lett.* **1998**, *39*, 8393.

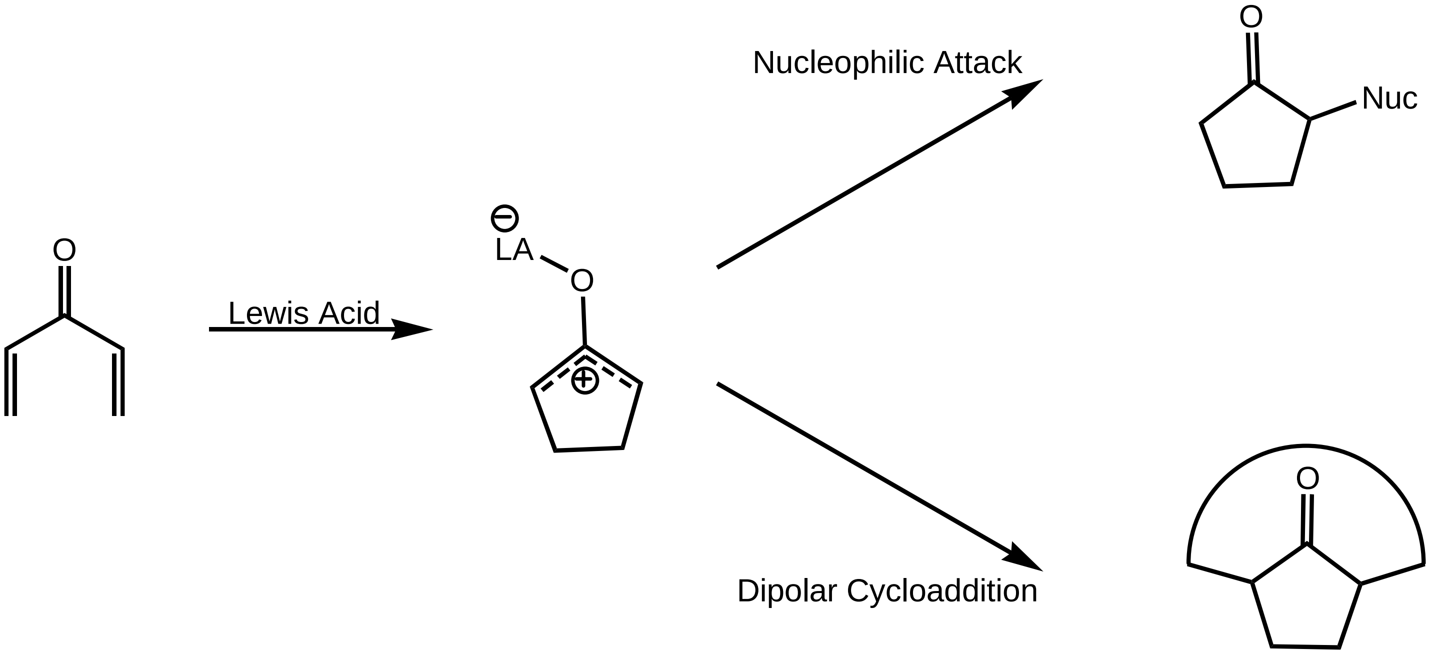
West, F. G.; Giese, S. *Tetrahedron* **2000**, *56*, 10221.

Model for Reduction



West, F. G.; Giese, S. *Tet. Lett.* **1998**, *39*, 8393.
West, F. G.; Giese, S. *Tetrahedron* **2000**, *56*, 10221.

Interrupted Nazarov

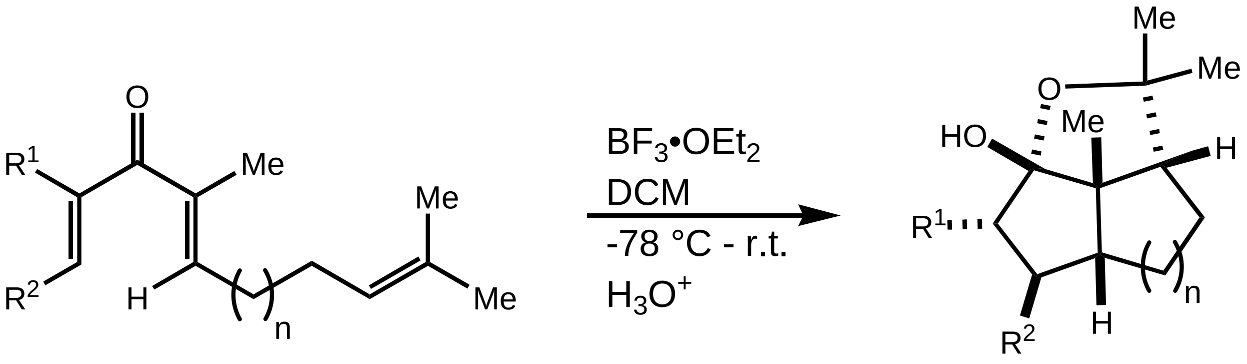


Lewis Acid

Nucleophilic Attack

Dipolar Cycloaddition

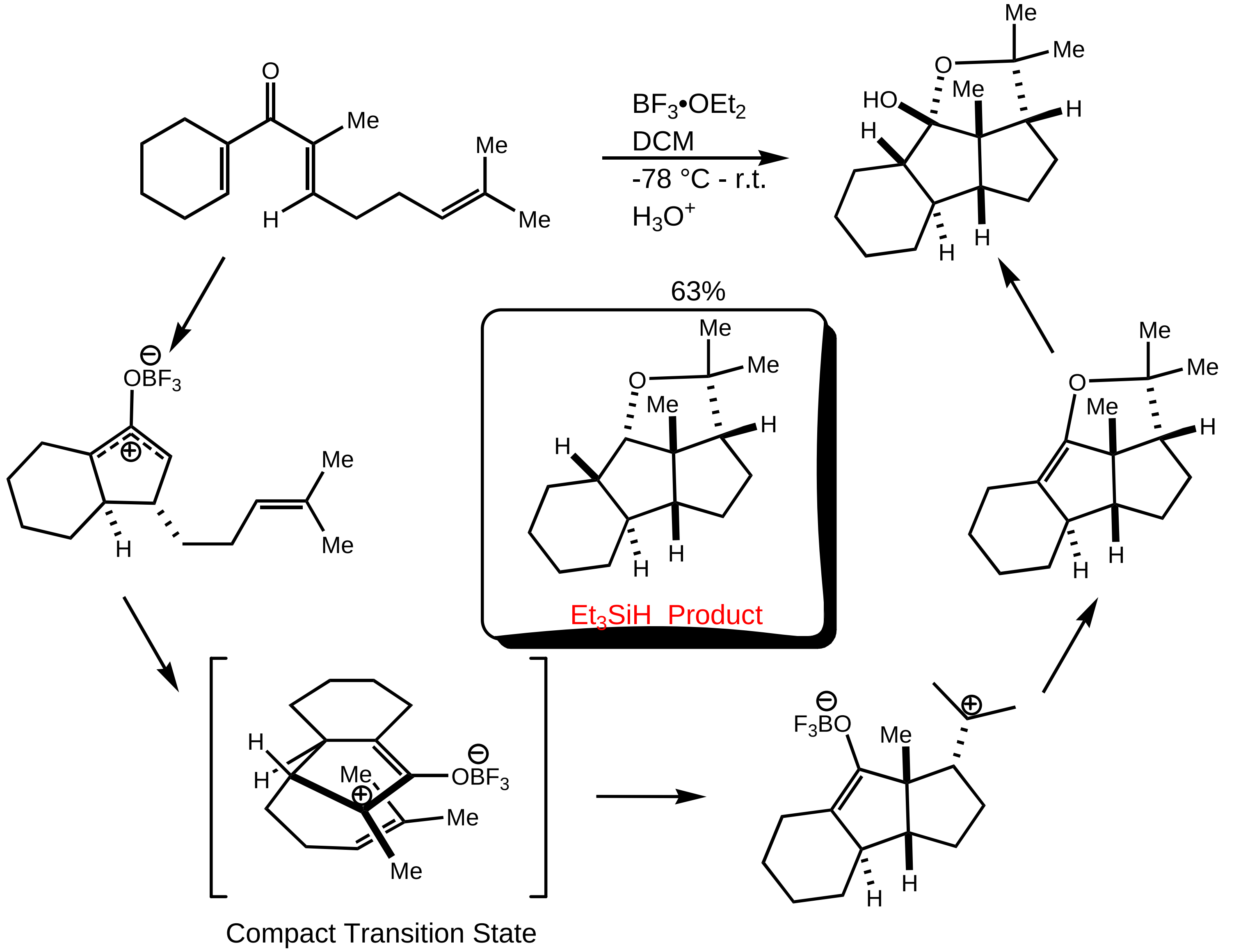
Exo-Trapping of Oxyallyl Intermediate



R^1	**R^2**	**n**	**Yield(%)**
Me	H	1	75
t-Bu	H	1	89
Et	Me	1	73
-(CH$_2$)$_4$-		1	62
Me	H	2	42

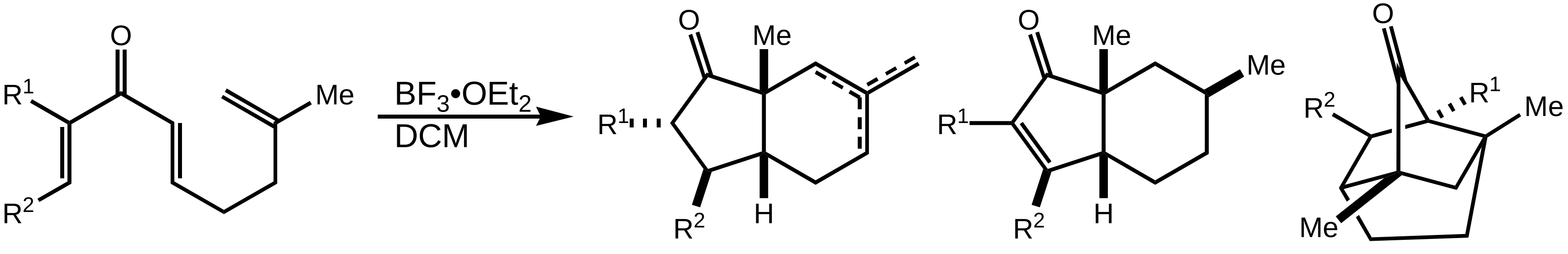
West, F. G.; Bender, J. A.; Blitze, A. E.; Browder, C. C.; Giese, S. *J. Org. Chem.* **1998**, *63*, 2430.

Mechanism of Exo-Trapping



West, F. G.; Bender, J. A.; Blitze, A. E.; Browder, C. C.; Giese, S. *J. Org. Chem.* **1998**, *63*, 2430.

Endo-Trapping of Oxyallyl Intermediate



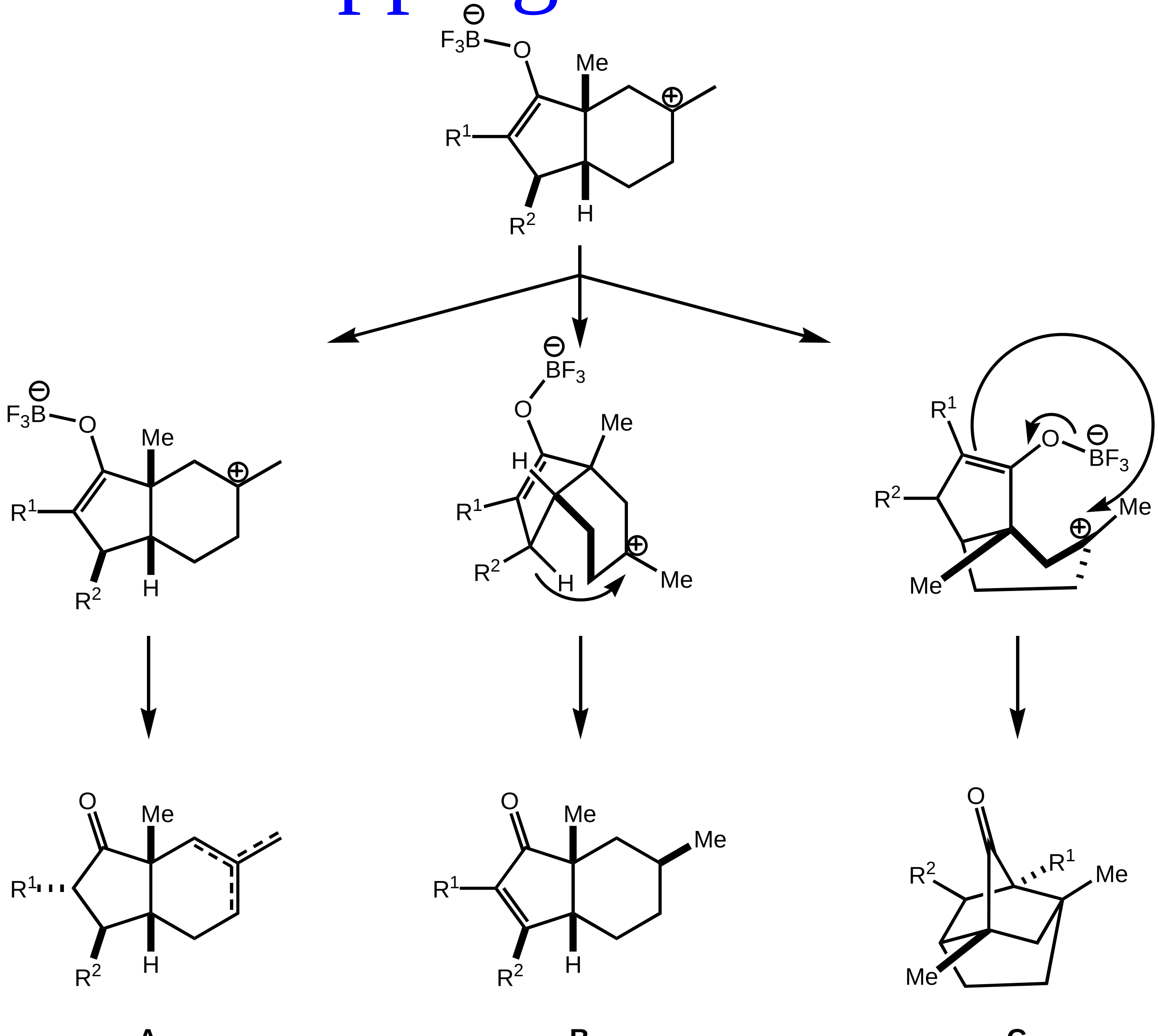
A **B** **C**

R^1	**R^2**	**Yield(%)**	**Ratio (A*:B:C)**
H	H	63	3.5 : 0 : 1
-$(CH_2)_4$-		88	1.6 : 1.2 : 1
-$(CH_2)_5$-		93	1 : 4.1 : 1.5
t-Bu	H	70	0 : 1 : 0

* Mixture of regioisomers

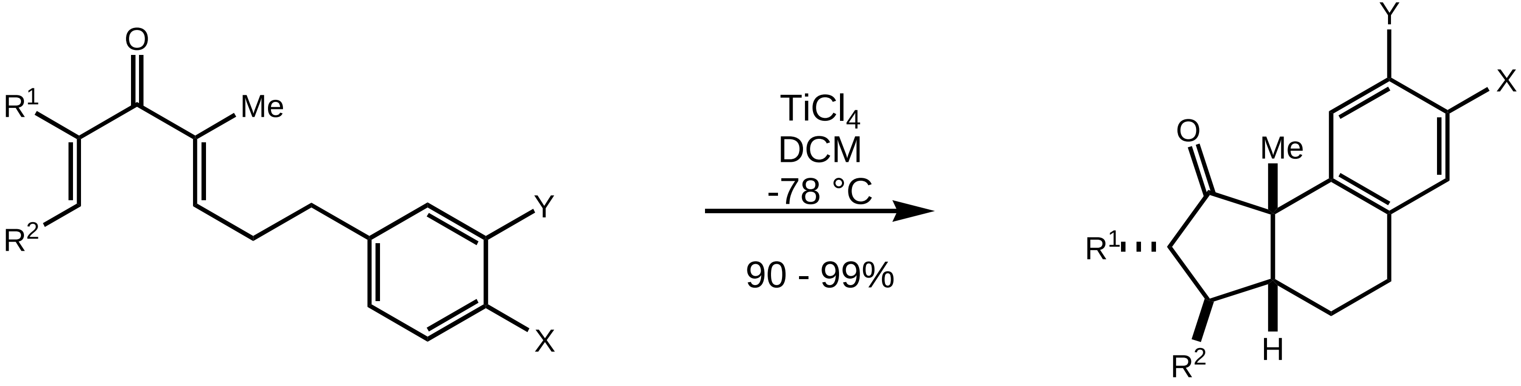
West, F. G.; Browder, C. C. *Synlett* **1999**, 1363.

Endo-Trapping Stereochemistry

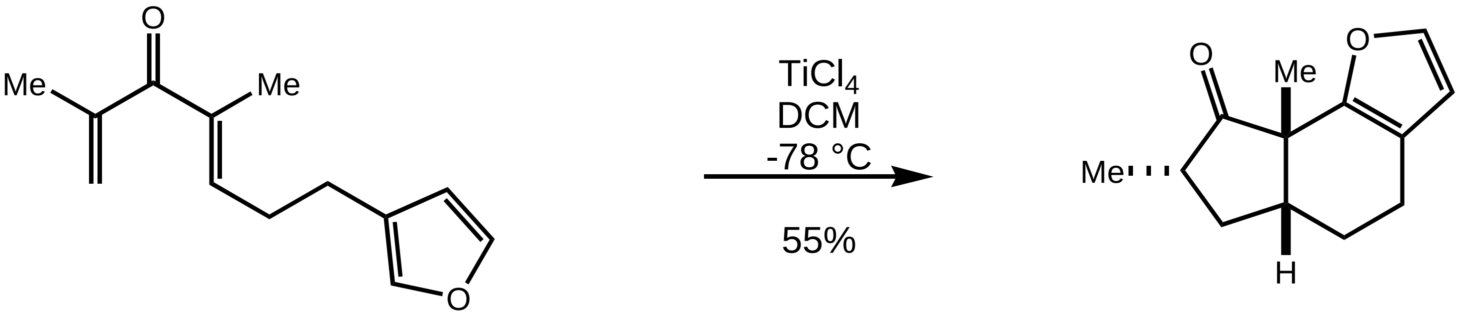


West, F. G.; Browder, C. C. *Synlett* **1999**, 1363.

Trapping with Substituted Arenes



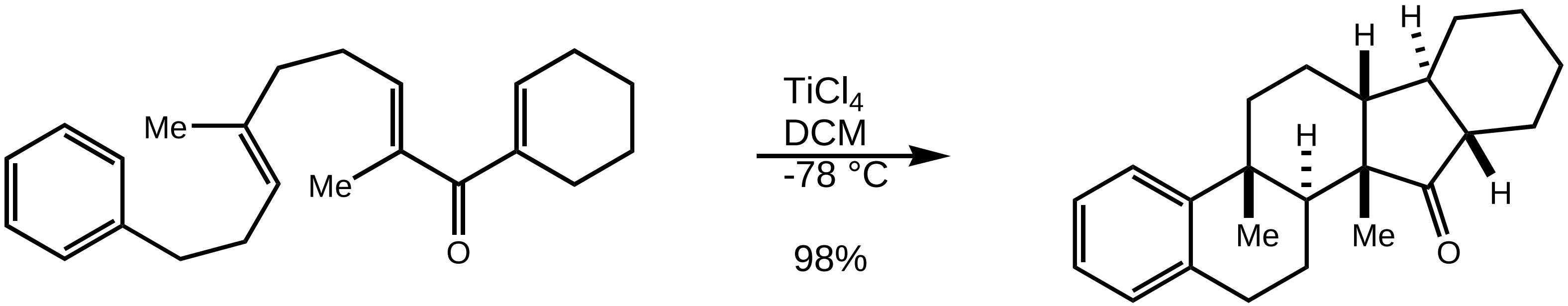
$\underline{\textbf{X}}$	$\underline{\textbf{Y}}$	$\underline{\textbf{R}^1}$	$\underline{\textbf{R}^2}$
OMe	H	Me	H
OMe	H	$-(CH_2)_4^-$	
$-OCH_2O^-$		Et	Me
$-OCH_2O^-$		$-(CH_2)_4^-$	

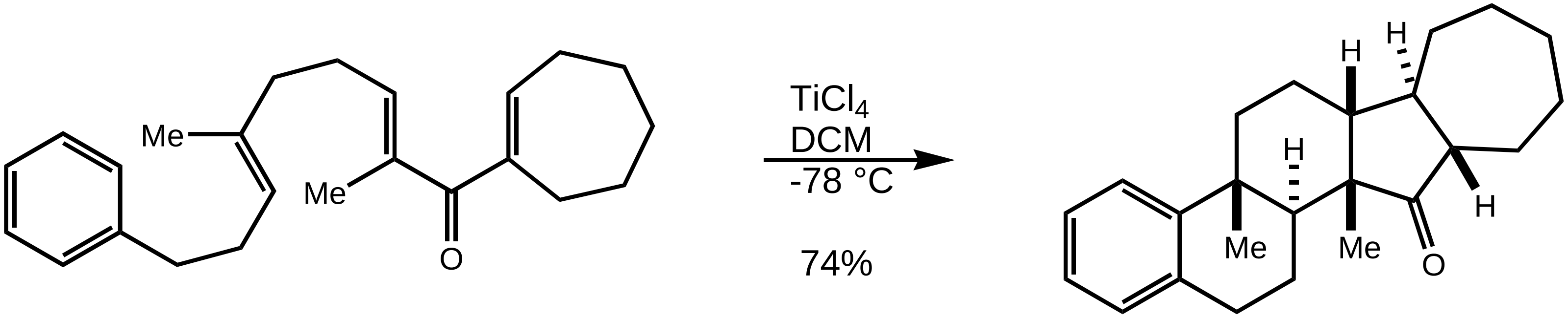


West, F. G.; Browder, C. C.; Marmstater, F. P *Org. Lett.* **2001**, *3*, 3033.

Nazarov Initiated Cascade Polycyclization

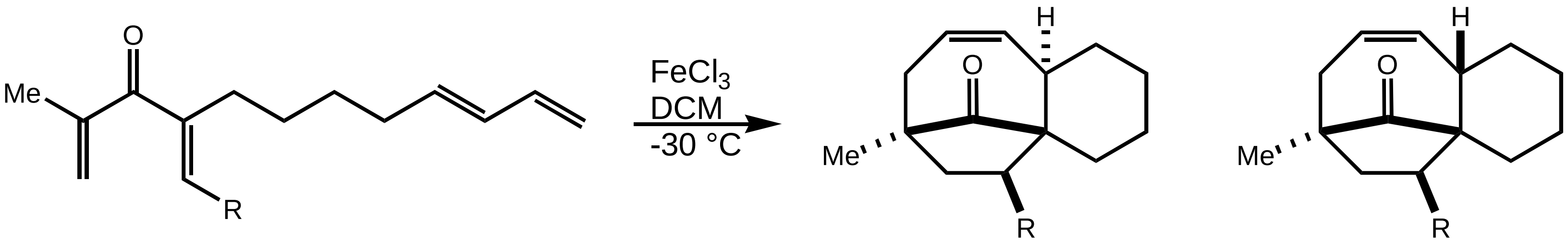
- Single Diastereomers Formed



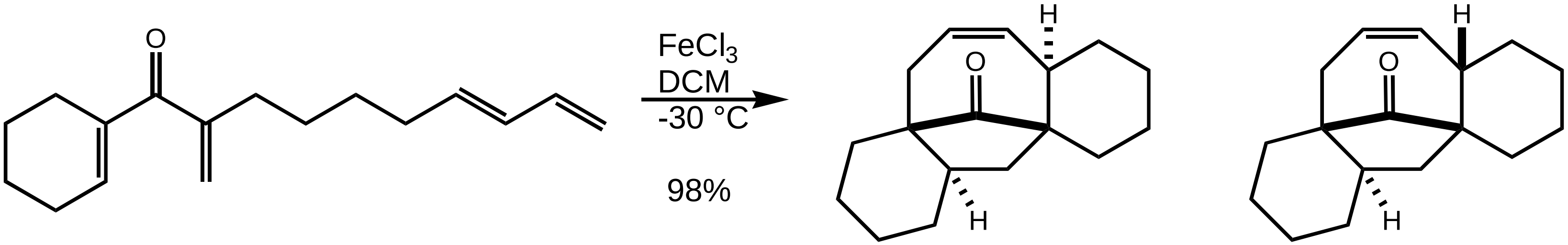


West, F. G.; Bender, J. A.; Arif, A. M. *J. Am. Chem. Soc.* **1999**, *121*, 7443.

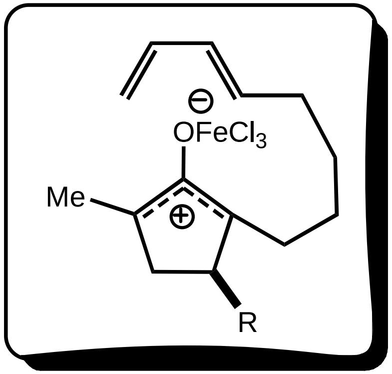
[4 + 3] Trapping



R = Me	1.3 : 1	65%
Ph	1.3 : 1	72%

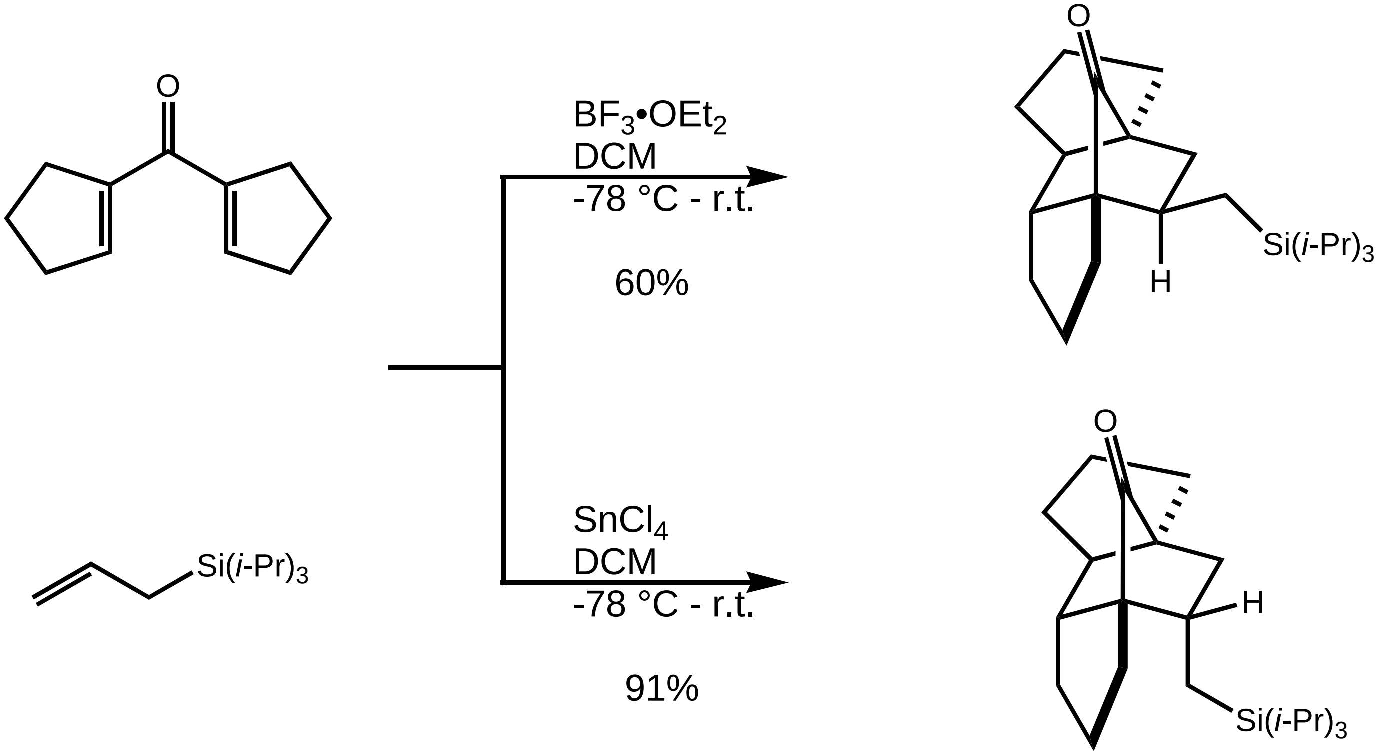


1.4:1



West, F. G.; Wang, Y.; Arif, A. M. *J. Am. Chem. Soc.* **1999**, *121*, 876.

[3 + 2] Cycloadditions with Allylsilanes

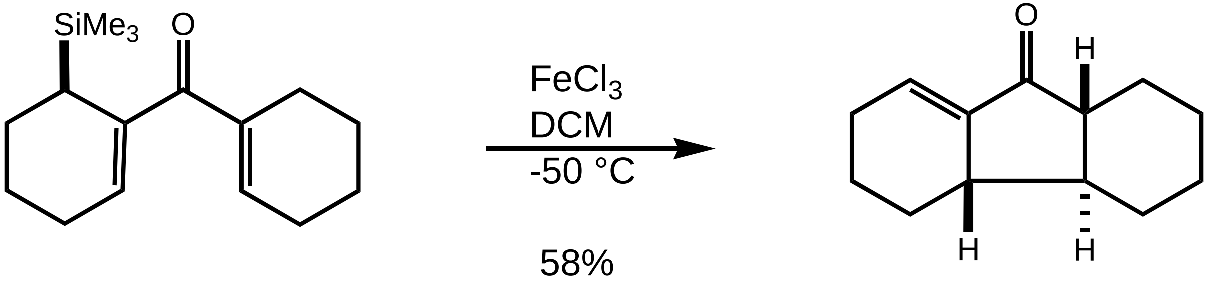


West, F. G.; Giese, S.; Kastrup, L.; Stiens, D. *Angew. Chem. Int. Ed. Eng.* **2000**, *39*, 1970.

Asymmetric Nazarov

- Normal Nazarov Cyclization
  - Most thermodynamically stable olefin
- SDNC
  - Complete control of olefin
- Diastereoselective Nazarov
  - Torquoselectivity
- Asymmetric Nazarov

Application of Torquoselectivity

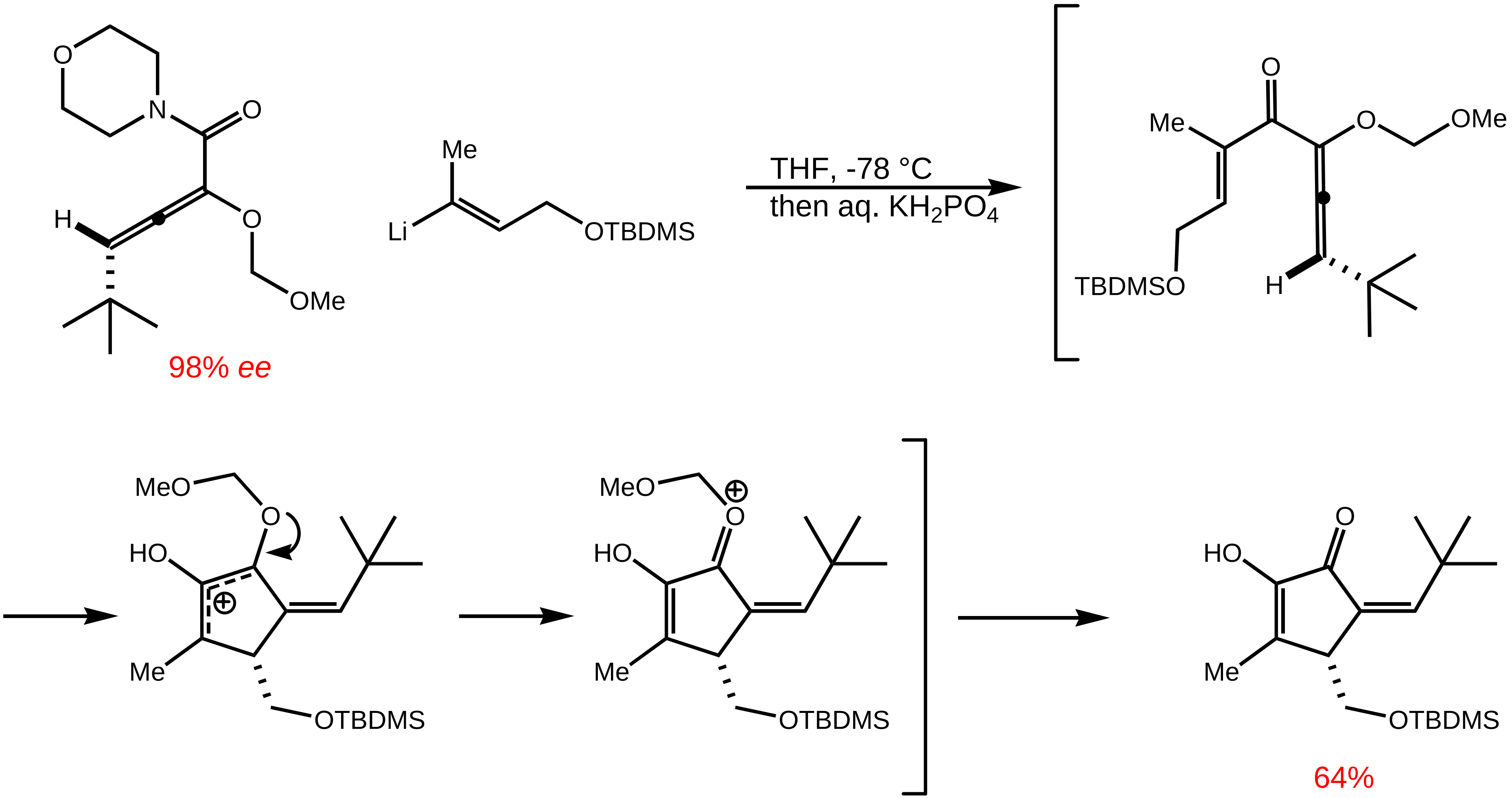


88% *ee*

88% *ee*
>99% Chirality Transfer

Denmark, S. E.; Wallace, M. A.; Walker, Jr., C. B. *J. Org. Chem.* **1990**, *55*, 5543.

Axial to Tetrahedral Chirality Transfer



98% *ee*

THF, -78 °C

then aq. KH_2PO_4

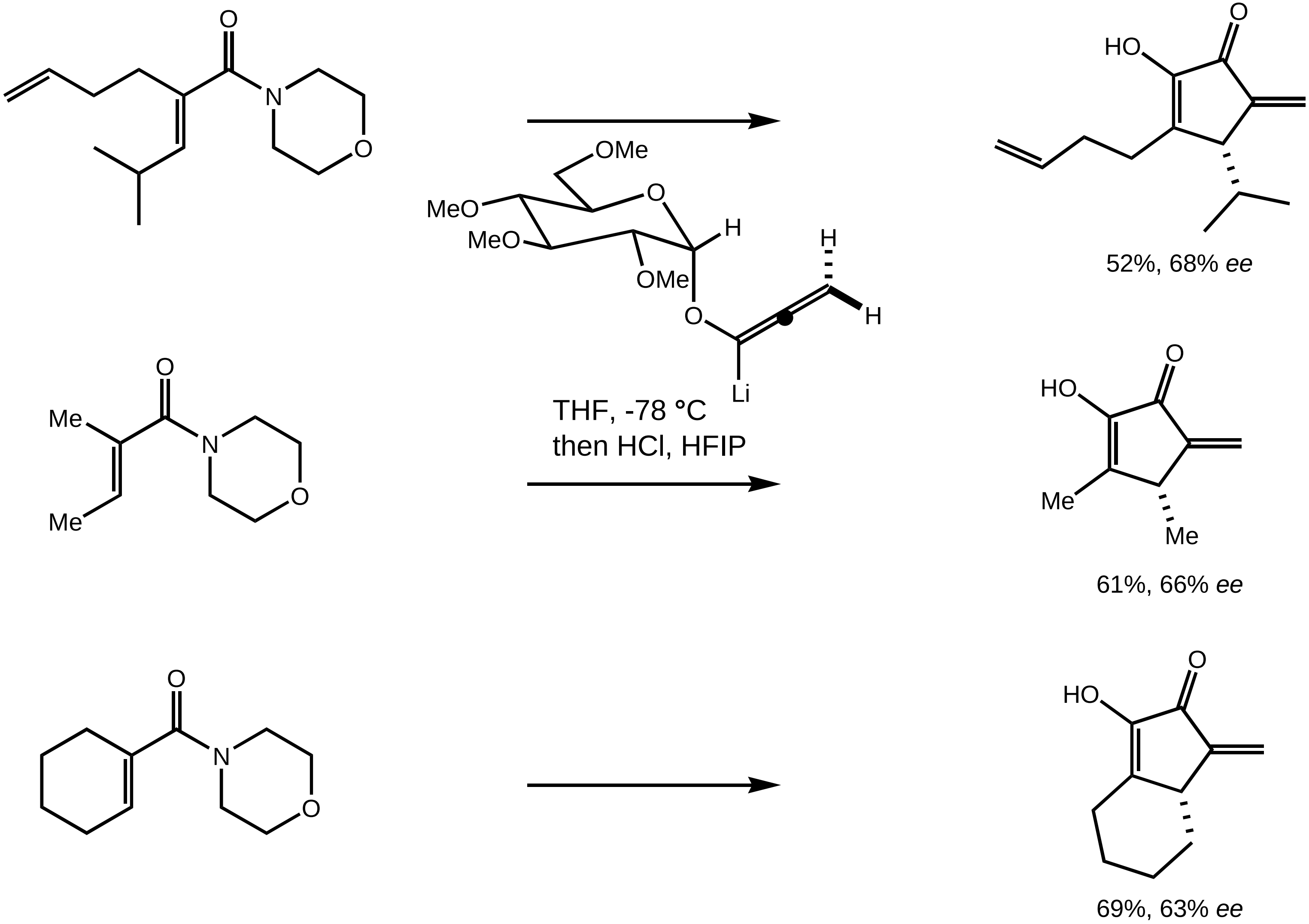
64%

95% *ee*

>95% chirality transfer

Tius, M. A. *Acc. Chem. Res.* **2000**, *36*, 284.

Sugar-Derived Auxiliary



THF, -78 °C
then HCl, HFIP

52%, 68% *ee*

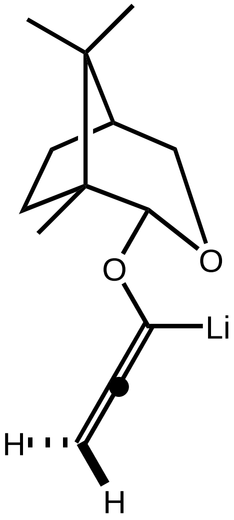
61%, 66% *ee*

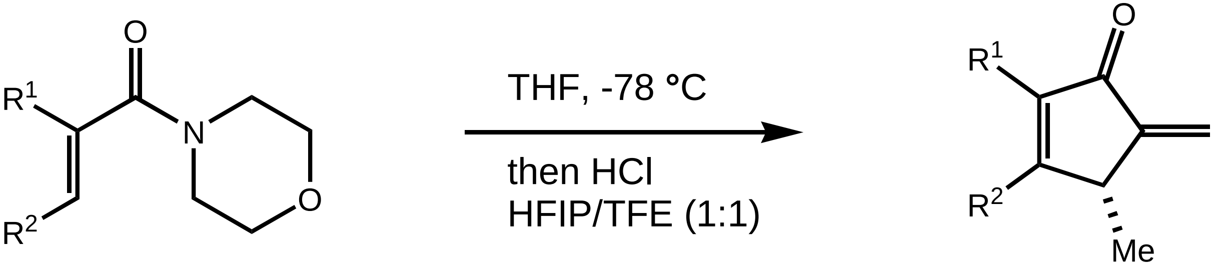
69%, 63% *ee*

HFIP = 1, 1, 1, 3, 3, 3-hexafluoro-2-propanol

Tius, M. A. *Acc. Chem. Res.* **2000**, *36*, 284.

Camphor-Derived Auxiliary

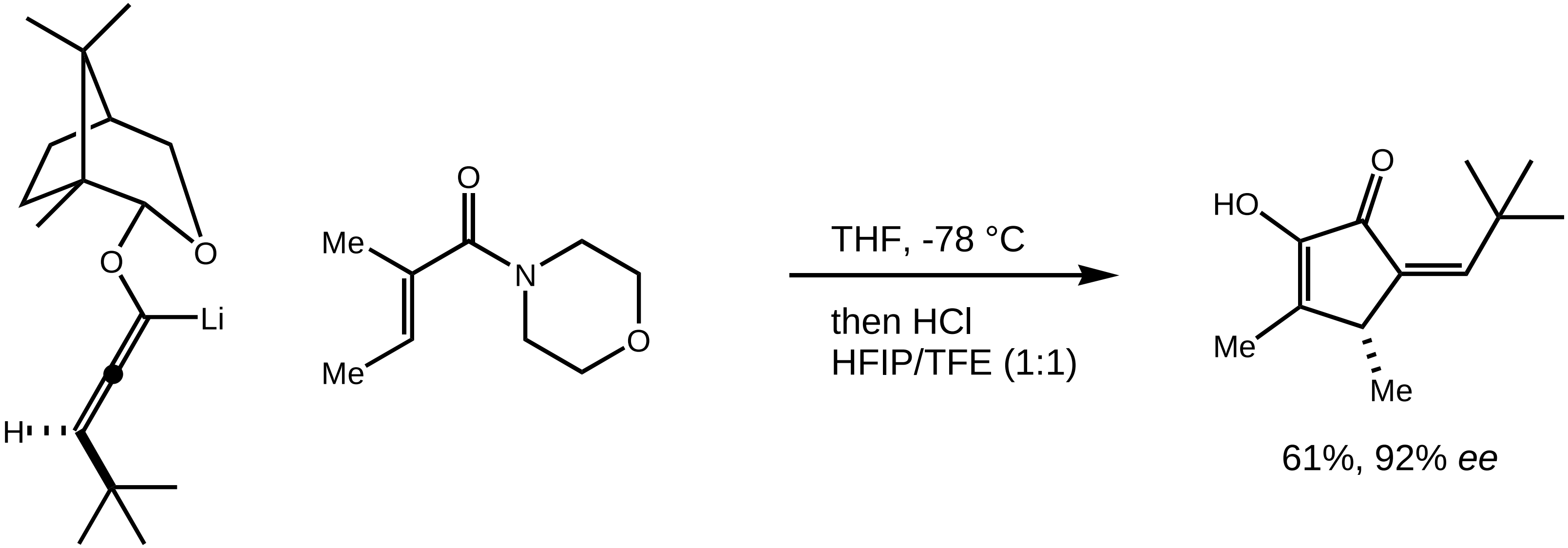




THF, -78 °C

then HCl
HFIP/TFE (1:1)

R^1	**R^2**	**Yield(%)**	***ee* (%)**
Br	Me	62	86
n-Bu	*i*-Pr	74	85



THF, -78 °C

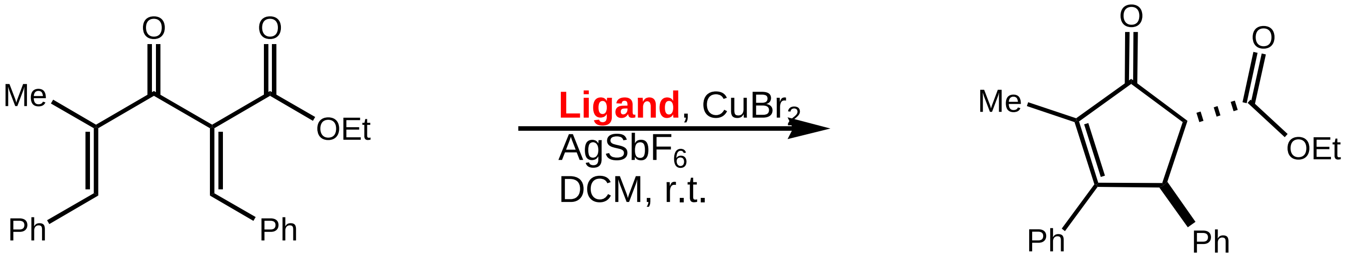
then HCl
HFIP/TFE (1:1)

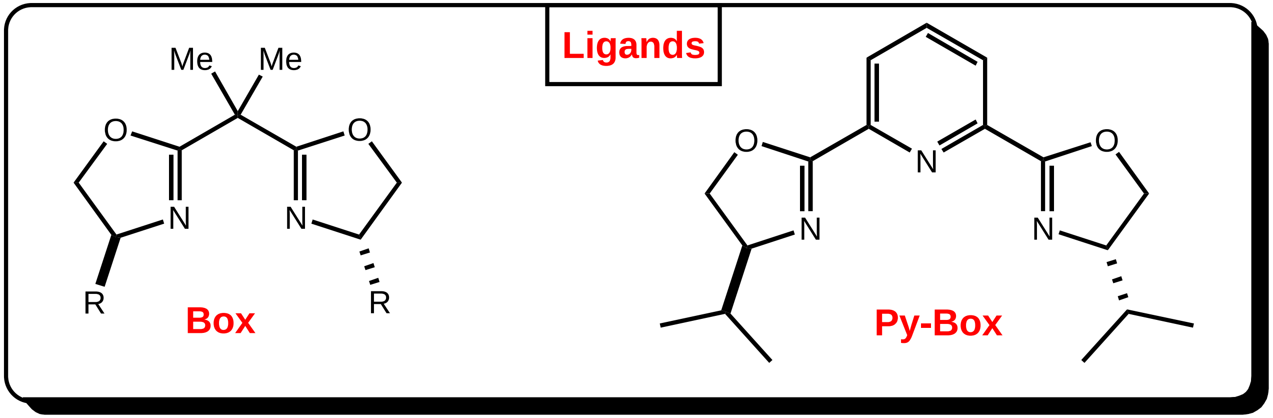
61%, 92% *ee*

TFE = trifluoroethanol

Tius, M. A.; Harrington, P. E.; Muari, T.; Chu, C. *J. Am. Chem. Soc.* **2002**, *124*, 10091.

Initial Asymmetric Results

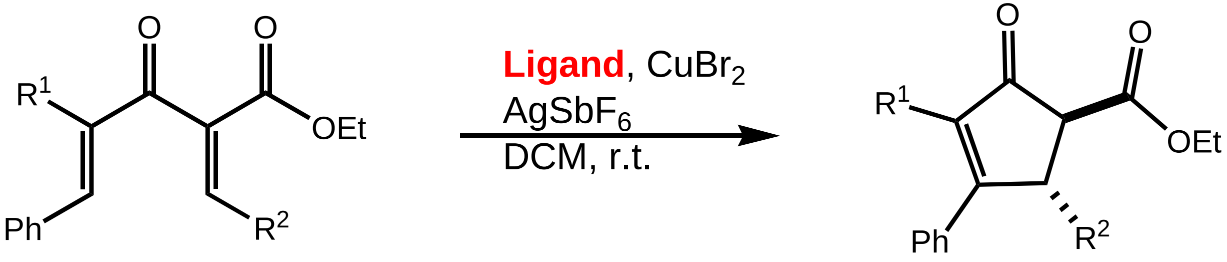


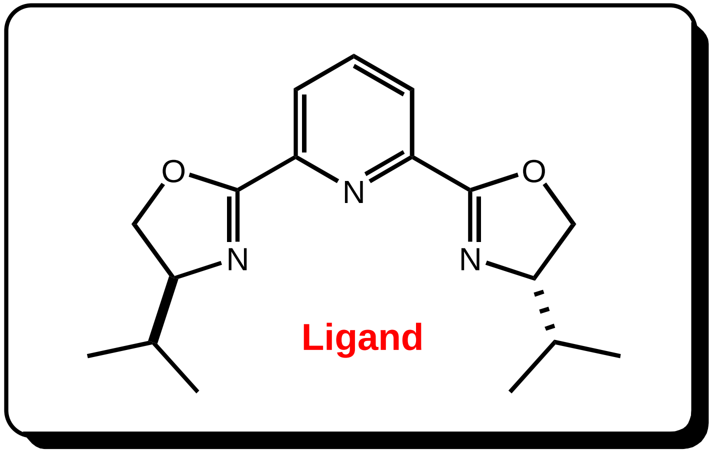


Ligand Type	**R**	**Yield(%)**	***ee* (%)**
Box	Ph	85	5
Box	*t*-Bu	70	44
Box	Bn	37	5
Py-Box	-----	35	71

Aggarwal, V. K.; Belfield, A. J. *Org.Lett.* **2003**, *5*, 5075.

Improved Conditions for Keto-Esters

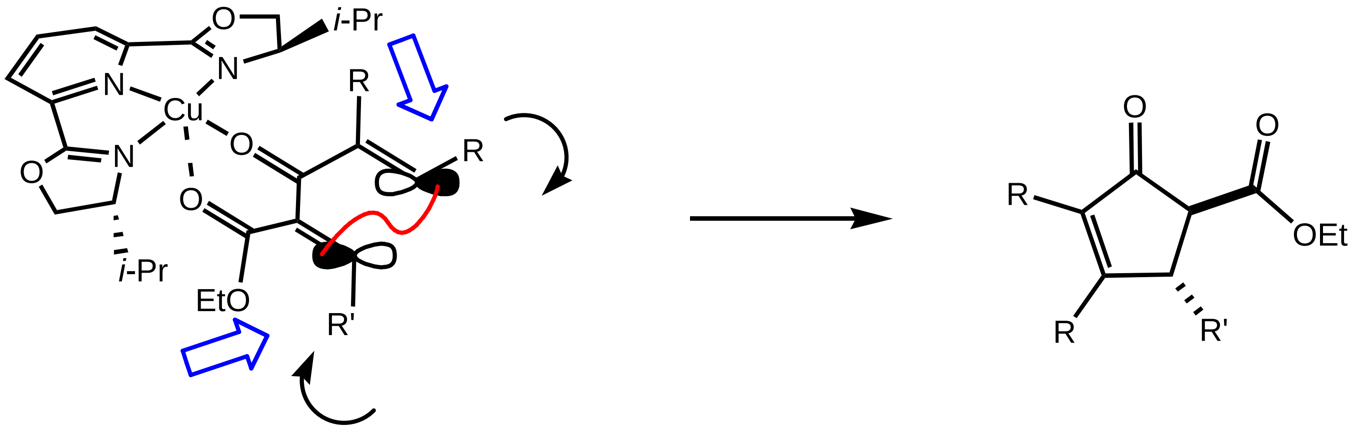




R1	**R2**	**Yield(%)**	***ee* (%)**
Me	Ph	73	76
Ph	Ph	98	86
Me	Me	35	3

Aggarwal, V. K.; Belfield, A. J. *Org.Lett.* **2003**, *5*, 5075.

Stereochemical Model for Divinyl Keto-Esters



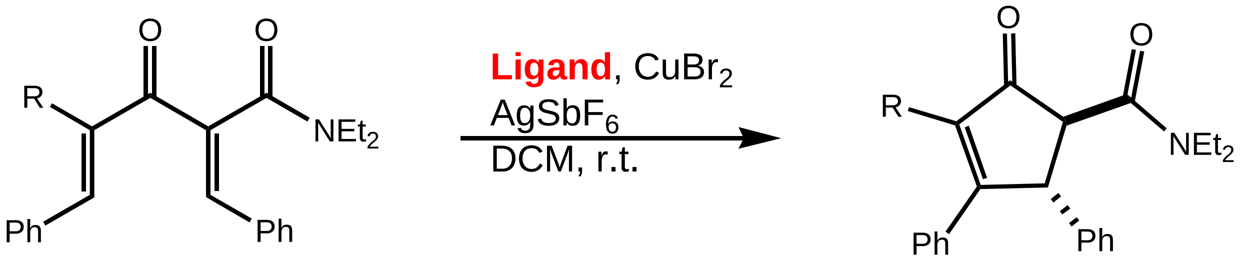
⇨ Steric Push From *i*-Pr Groups

Aggarwal, V. K.; Belfield, A. J. *Org.Lett.* **2003**, *5*, 5075.

Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686.

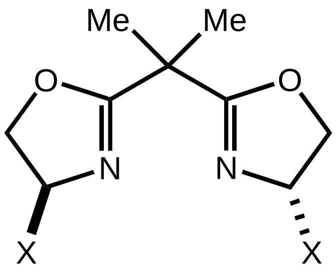
Evans, D. A.; Rovis, T.; Kozlowski, M. C., Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134.

Keto-Amides



Ligand, $CuBr_2$
$AgSbF_6$
DCM, r.t.

Ligand

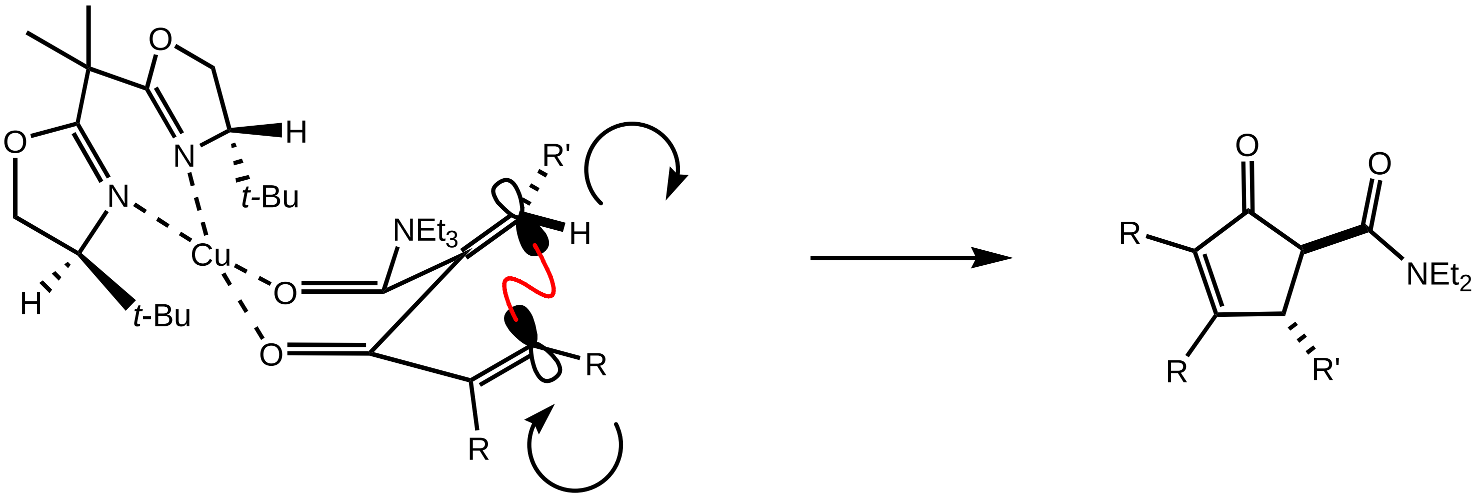


A - X = Ph
B - X = *t*-Bu

R	**Ligand**	**Yield(%)**	***ee* (%)**
Me	B	80	88
Me	A	92	86
Ph	A	72	84
Ph	B	21	75

Aggarwal, V. K.; Belfield, A. J. *Org.Lett.* **2003**, *5*, 5075.

Stereochemical Model for Divinyl Keto-Amides

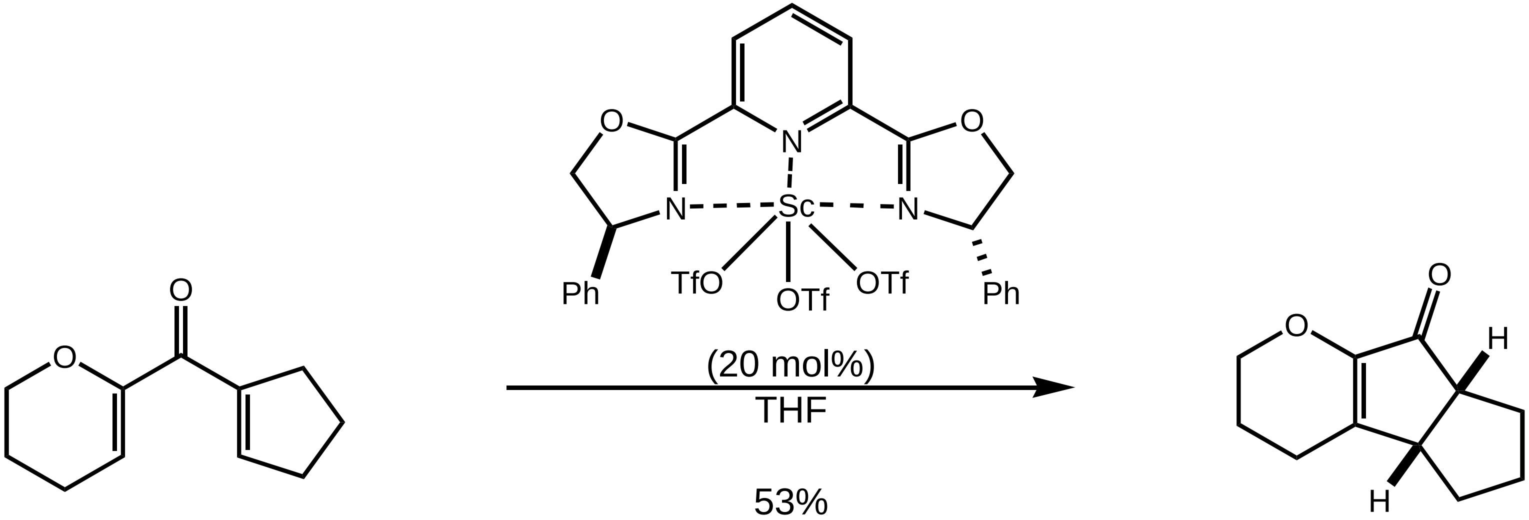


Aggarwal, V. K.; Belfield, A. J. *Org.Lett.* **2003**, *5*, 5075.

Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686.

Evans, D. A.; Rovis, T.; Kozlowski, M. C., Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134.

Asymmetric Nazarov



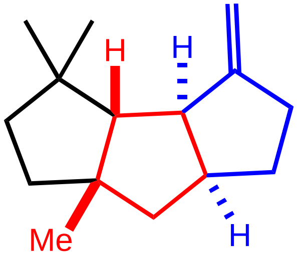
(20 mol%)
THF

53%

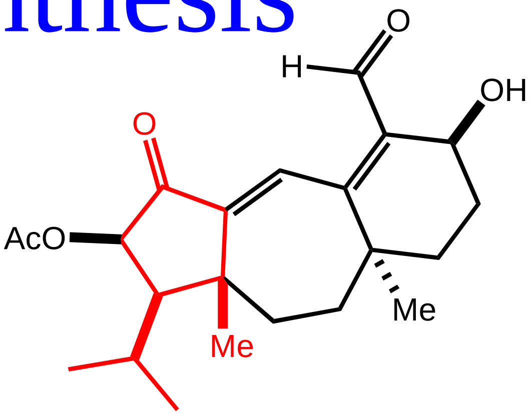
61% *ee*

Trauner, D.; Liang, G.; Gradl, S. N. *Org. Lett.* **2003**, *5*, 4931.

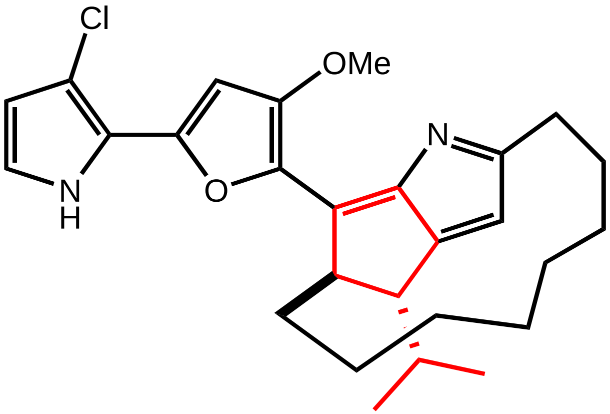
Nazarov Application to Natural Product Synthesis



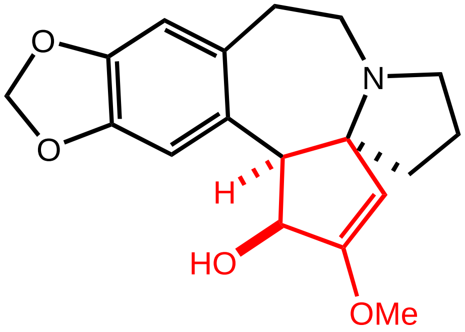
Capnellene



Guanacastepene A

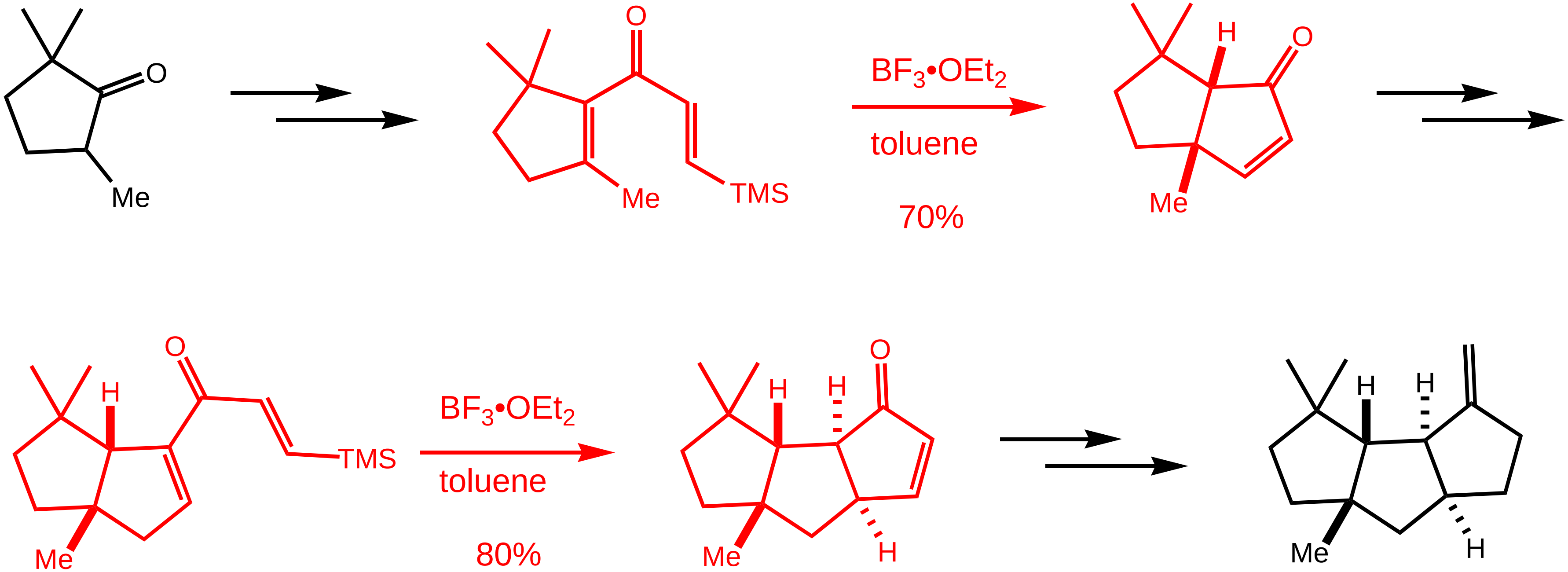


Roseophilin



Cephalotaxine

Stille's Synthesis of (±)–Capnellene

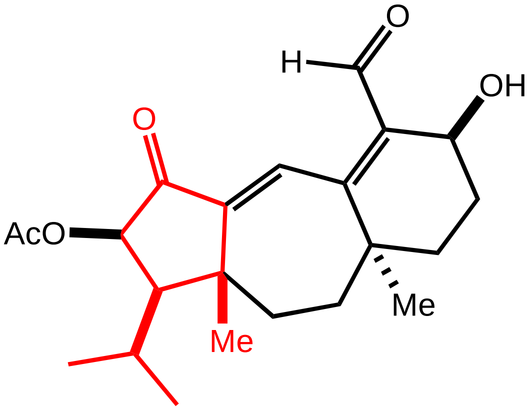


(±)$\Delta^{9(12)}$-Capnellene

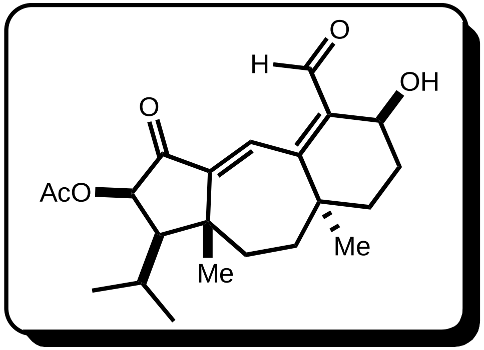
Stille, J. K.; Crisp, G. T.; Scott, W. J. *J. Am. Chem. Soc.* **1984**, *106*, 7500.

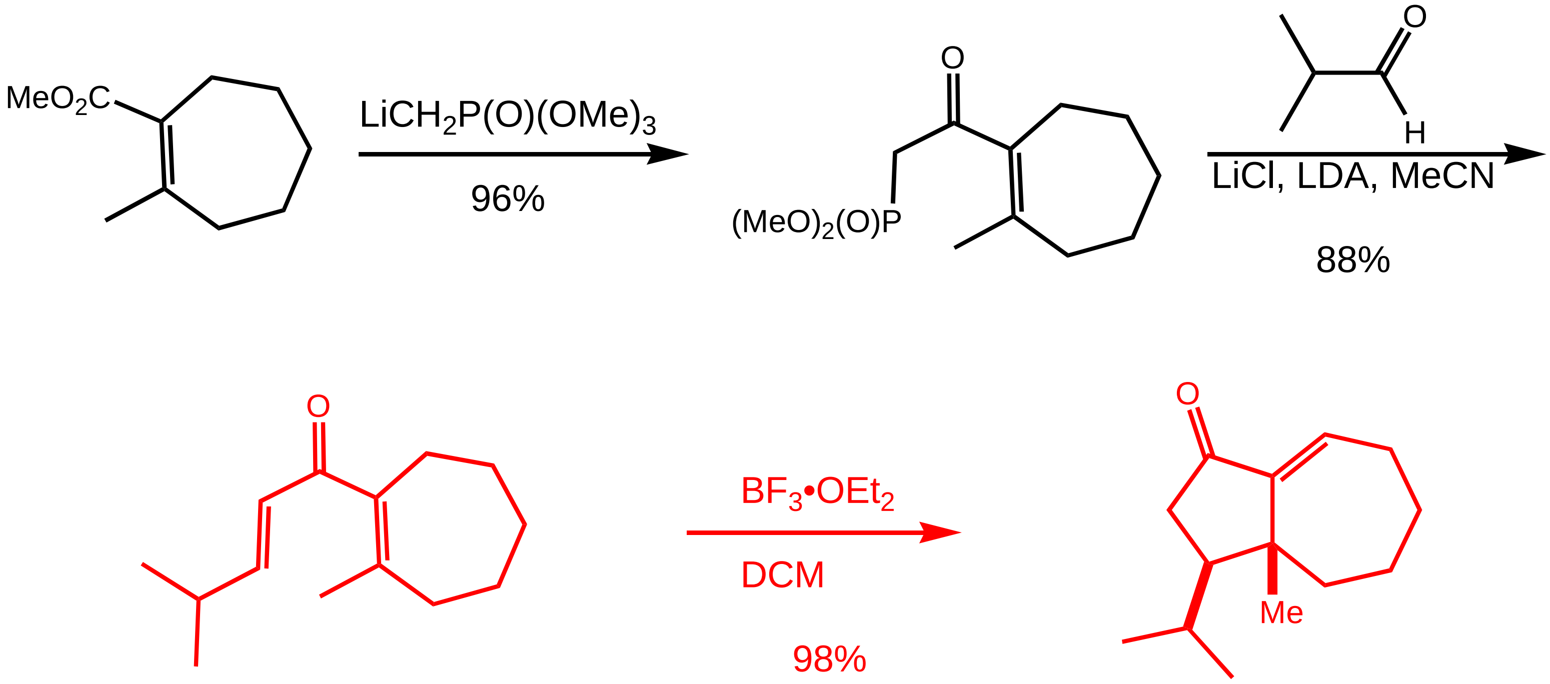
Guanacastepene A

- Chiu’s Synthesis of Hydroazulene Core



Hydroazulene Core of Guanacastepene A

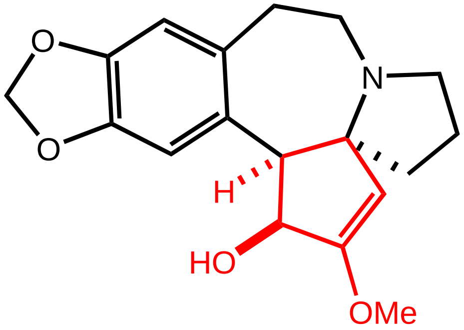




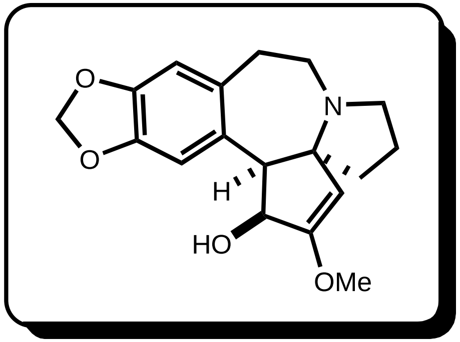
Chiu, P.; Li, S. *Org. Lett.* **2004**, *6*, 613.

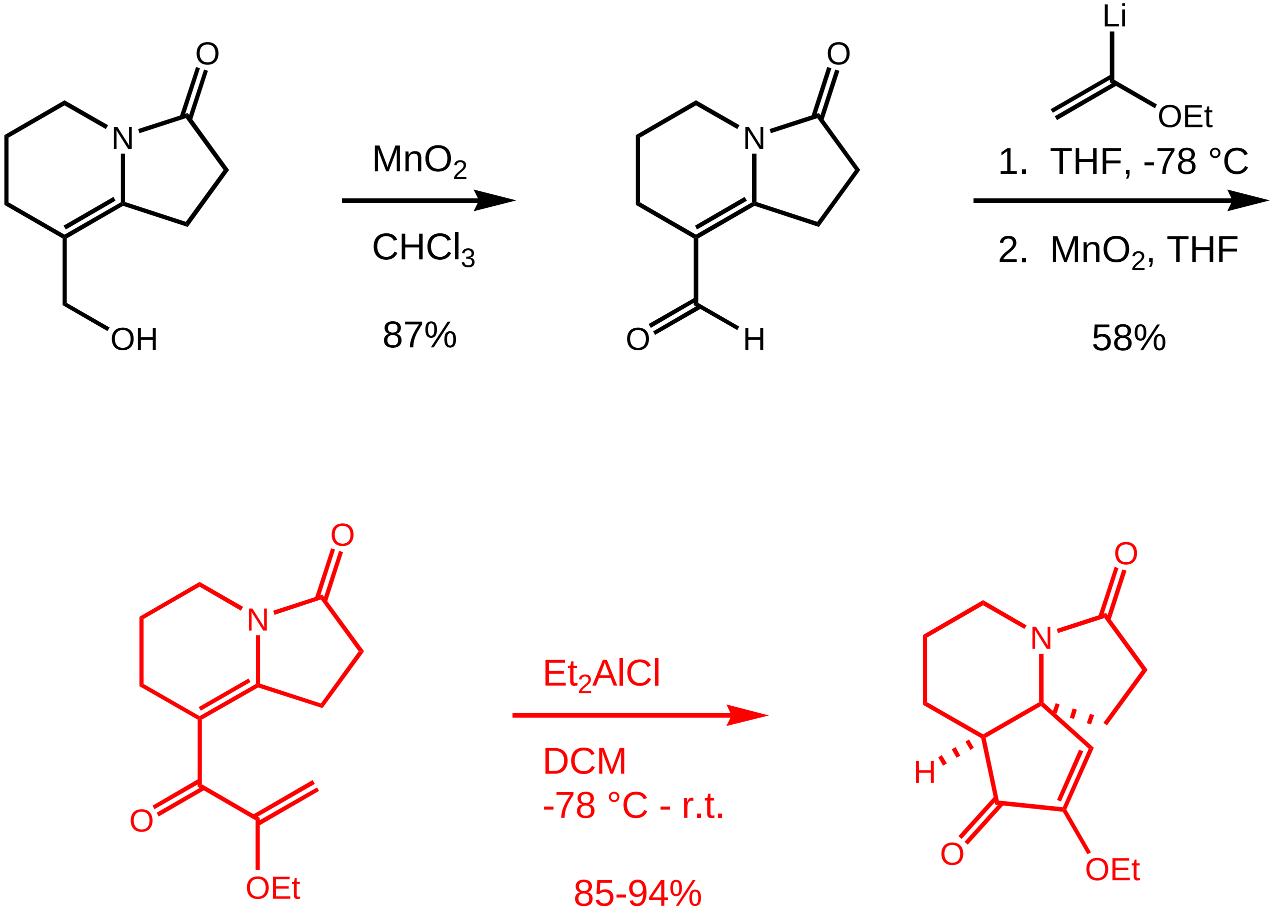
Cephalotaxine

- Cha’s Studies Towards Cephalotaxine



Studies Towards Cephalotaxine

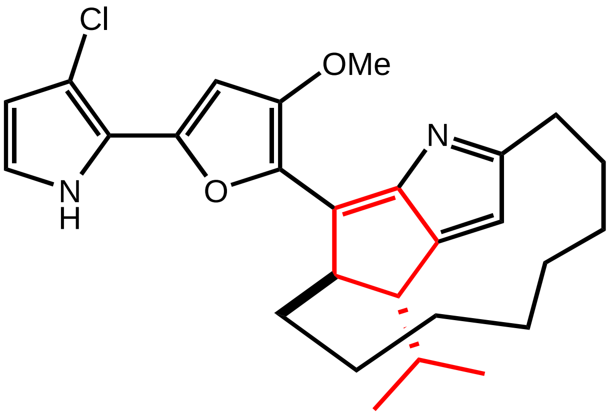




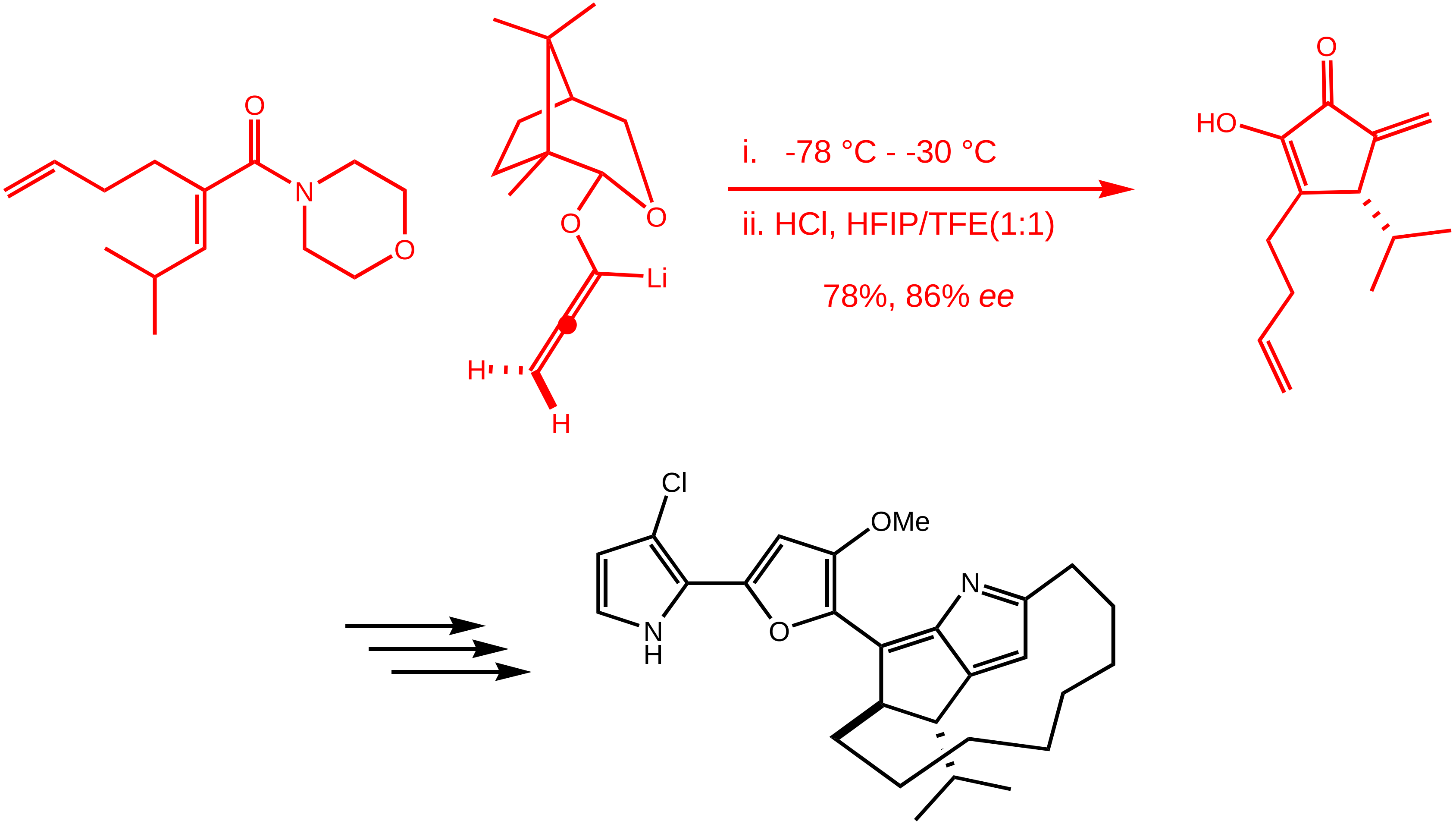
Cha, J. K.; Kim, S. H. *Synthesis* **2000**, 2113.

Roseophilin

- Tius Synthesis



Tius Synthesis of Roseophilin



i. -78 °C - -30 °C

ii. HCl, HFIP/TFE(1:1)

78%, 86% *ee*

Roseophilin

Tius, M. A.; Harrington, P. E. *J. Am. Chem. Soc.* **2001**, *123*, 8509.

Conclusion

- Selective formation of kinetic and thermodynamic cyclopentanoids
- Stereoselective formation of multiple stereocenters in a single step
- Formation of enantioselective cyclopentanoids
- The need for cyclopentanoids in natural products synthesis
- The drive for improvements in classical reactions