Recent Developments of the Nazarov Reaction

Banibrata Ghosh

Michigan State University

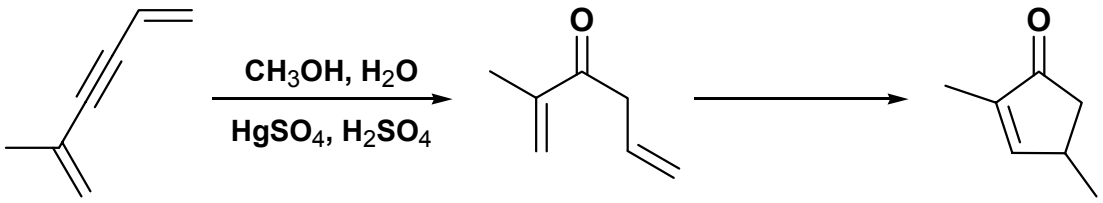
January 14, 2004

Outline

- Directed Nazarov reactions
- Asymmetric Nazarov reactions
- Other recent variants of the Nazarov reaction

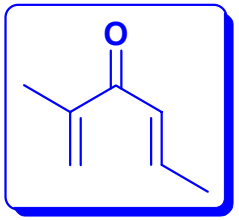
Introduction

- Named after the eminent Russian chemist **I. N. Nazarov** (1906–1957)



Discovered in 1942[a]

- Carbocation intermediate[b]
- Proceeds via α,α'-divinyl ketone[b]
- Intramolecular electrocyclization reaction[c]

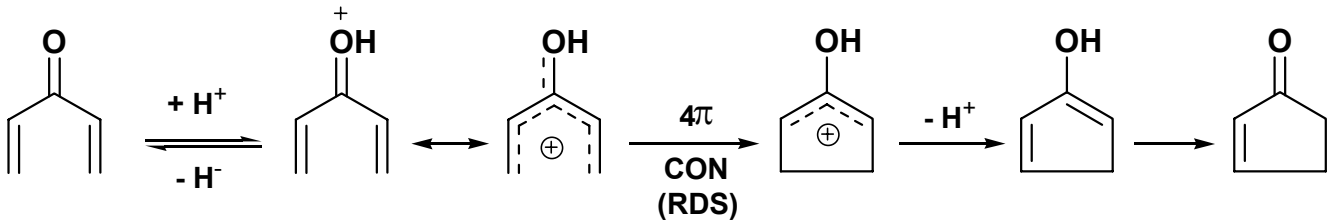


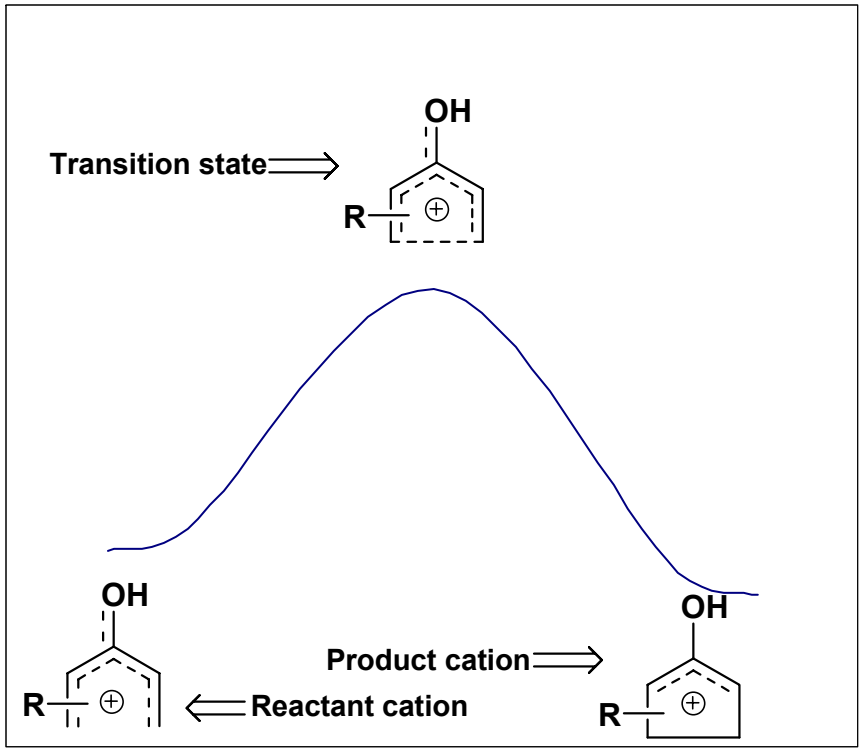
- Definition of the classical acid-catalyzed Nazarov reaction:

Acid (protic or Lewis) induced cationic 4π conrotatory electrocyclic ring closure reaction of divinyl ketone to form cyclopentenones

[a]Nazarov, I. N.; Zaretskaya, I. I. *Bull. Acad. Sci. (USSR)* **1942**, 200-209.
[b]Braude, E. A.; Coles, J. A. *J. Chem. Soc*. **1952**, 1430-1433.
[c]Shoppee, C. W.; Lack, R. E. *J. Chem. Soc*. **1969**, 1346-1348.

Mechanism of Classical Nazarov Reaction





Comments:

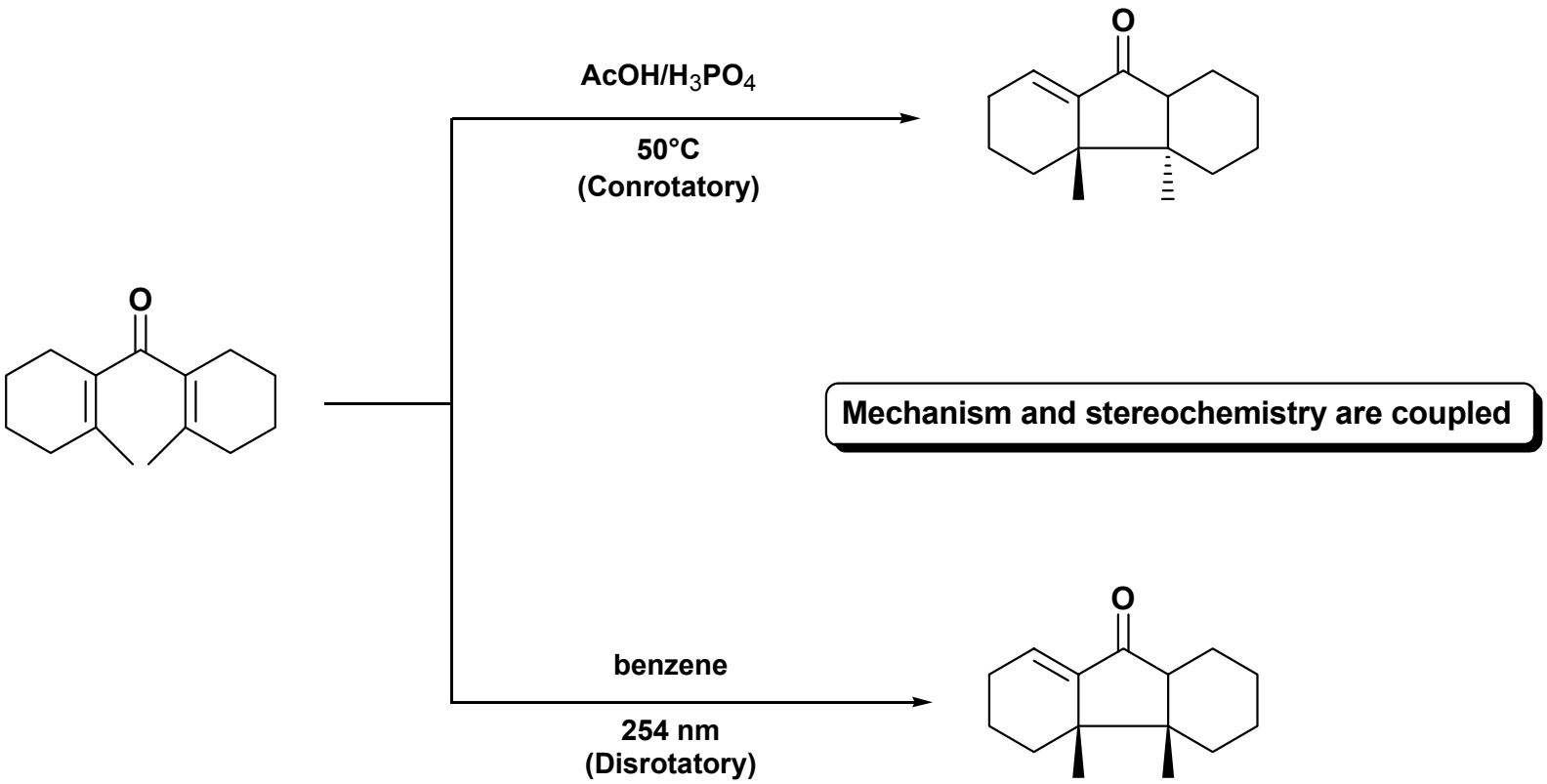
1. **Stabilization of the positive charge on the terminal carbons increases the energy of activation and lowers the heat of cyclization**

2. **Stabilization of the positive charge on the carbons β to the hydroxyl group decreases the energy of activation and increases the heat of cyclization**

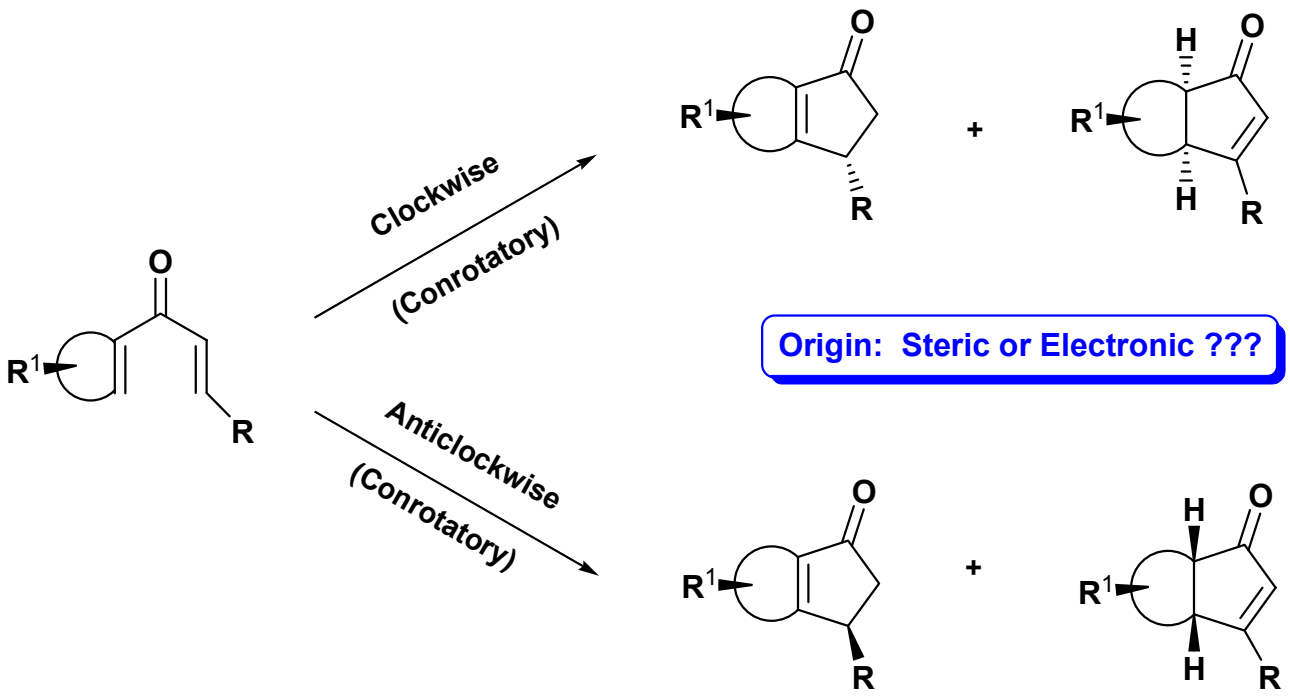
3. **Steric effects should also be considered**

Smith, D. A.; Ulmer, C. W. *J. Org. Chem*. **1991**, *56*, 4444-4447.

Stereochemistry



Duality of the Electrocyclization Pathway: *Torquoselectivity*[a]

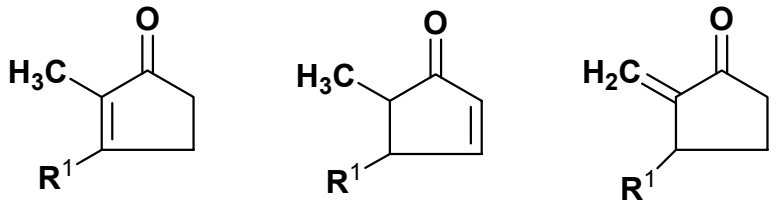


[a]**This term was coined by K. N. Houk.**

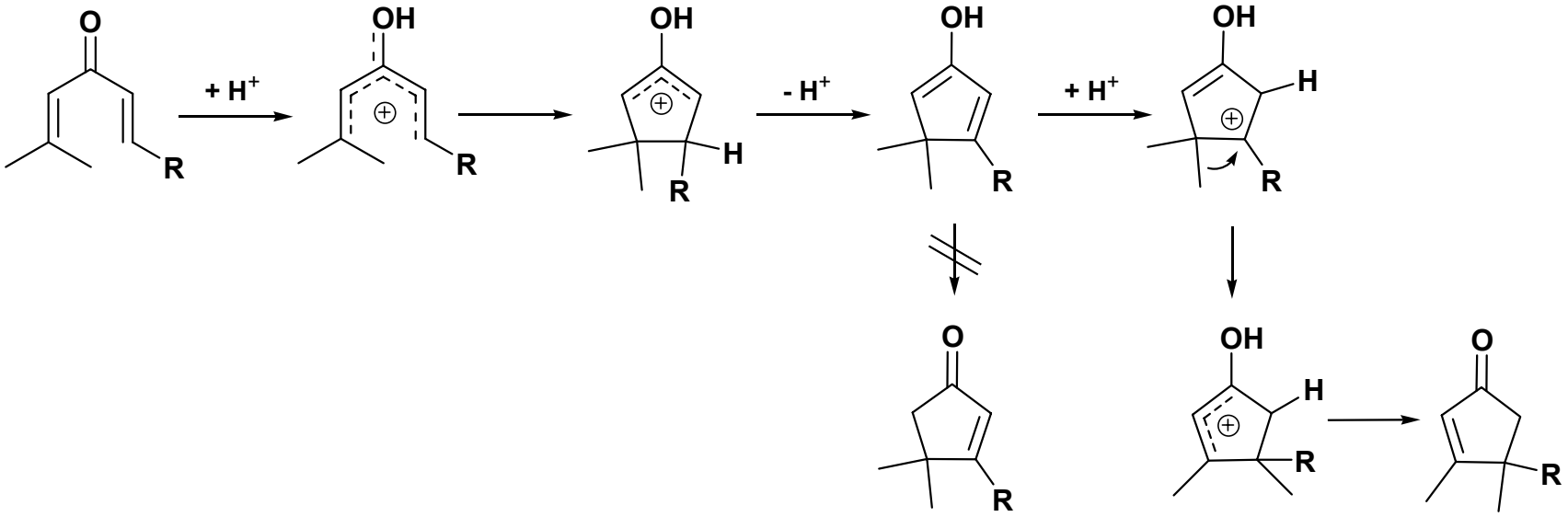
Houk, K. N. In *Strain and Its Implications in Organic Chemistry*; de Meijere, A.; Blechert, S. Ed.; Kluwer Academic: Boston, **1989**, Vol. 1, pp 25-37.

Limitations of the Classical Nazarov Reaction

1. Lack of control over torquoselectivity
2. Lack of positional control of the double bond

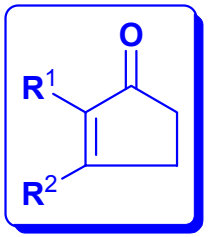


3. Strong acidic media leading to some undesirable rearrangements



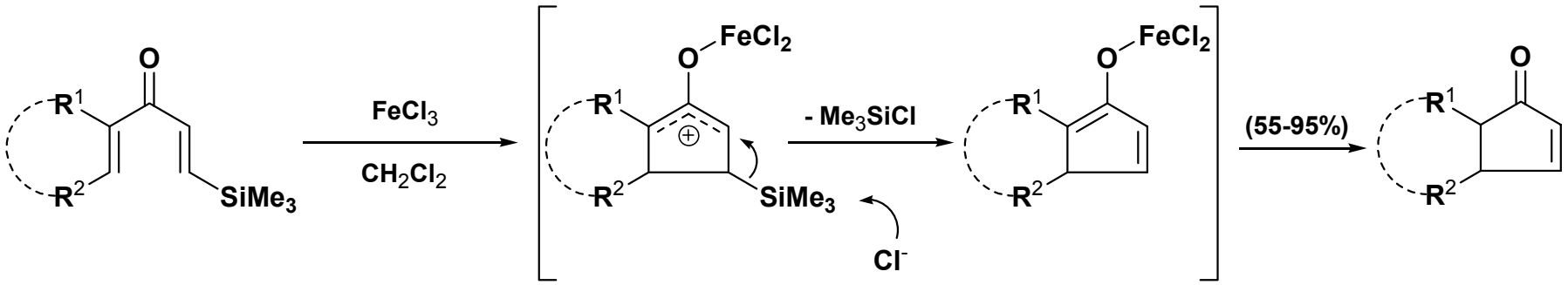
Motoyoshia, J.; Yazaki, T.; Hayashi, S. *J. Org. Chem*. **1991**, *56*, 735-740.

Directed Nazarov Reactions



- Silicon-directed Nazarov reactions
- Tin-directed Nazarov reactions
- Fluorine-directed Nazarov reactions

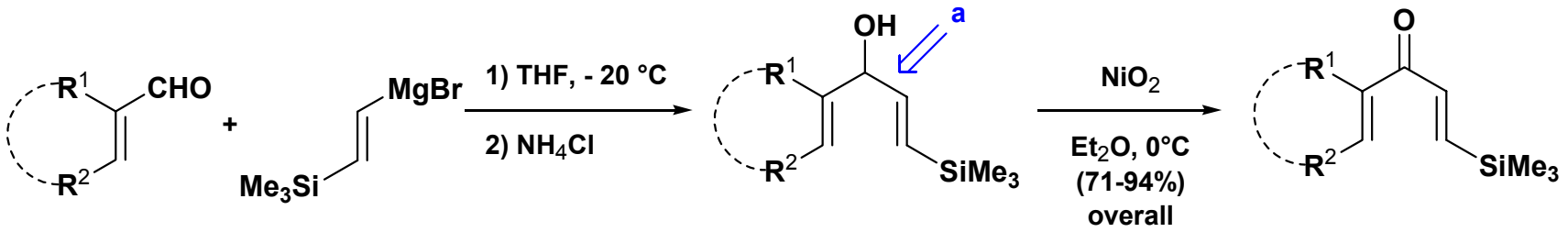
Silicon-Directed Nazarov Reactions



Advantages:

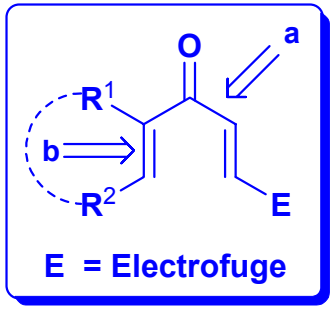
1. Controlled introduction of a double bond

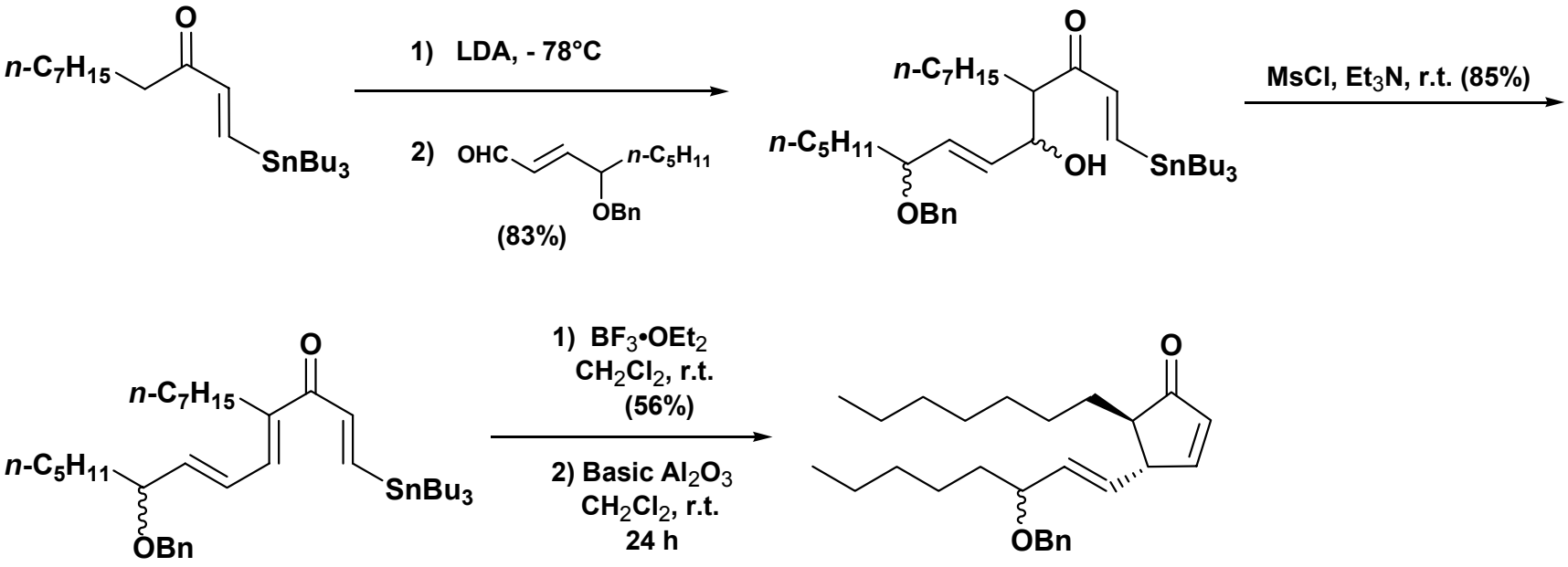
2. Ready isomerization of the double bond to the most substituted position or its transformation to other functionalities if needed



Denmark, S. E.; Jones, T. K. *J. Am. Chem. Soc*. **1982**, *104*, 2642-2645.

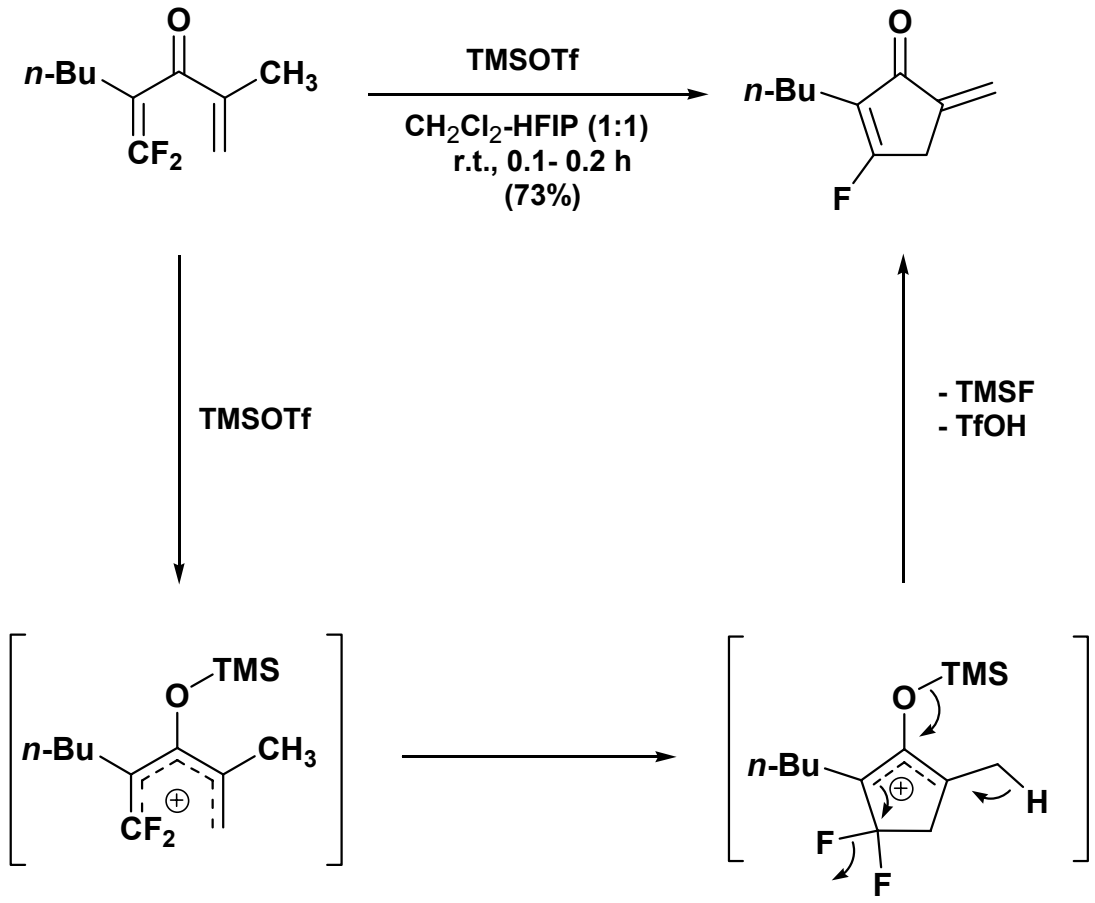
Tin-Directed Nazarov Cyclization





Peel, M. R.; Johnson, C. R. *Tetrahedron Lett*. **1986**, *27*, 5947-5950.

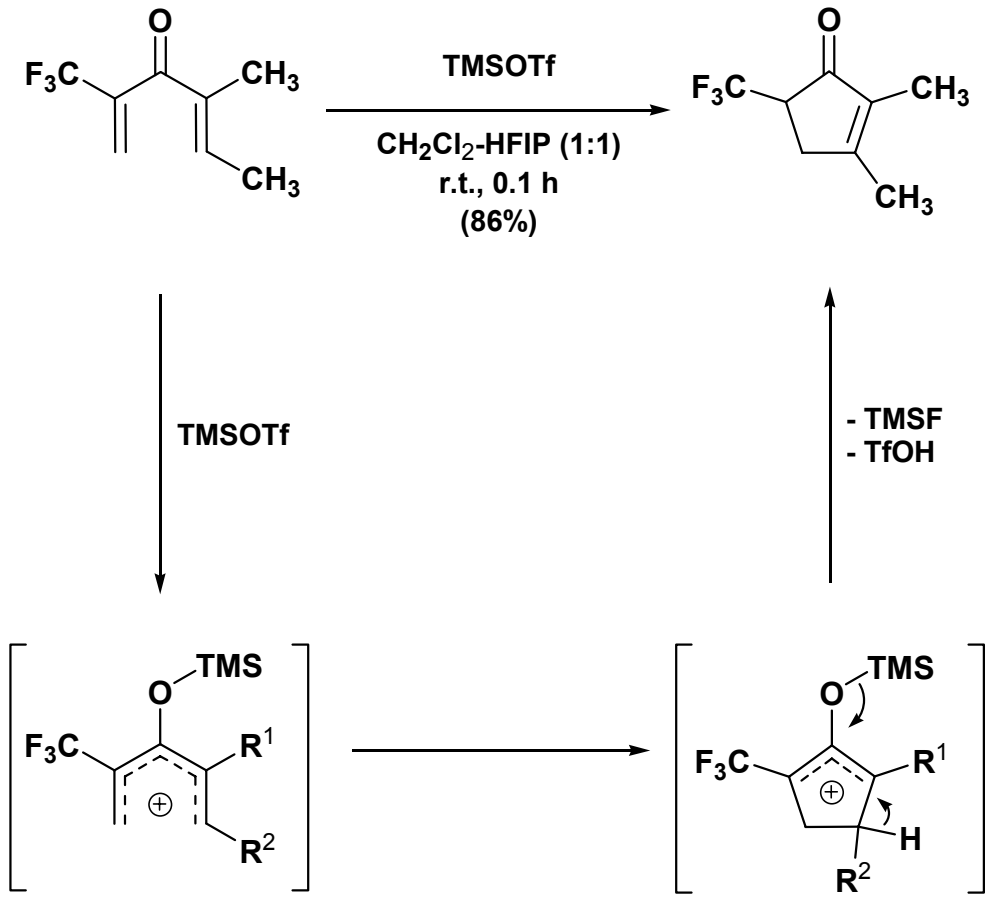
Fluorine-Directed Nazarov Reaction



Note: HFIP = Hexafluoroisopropanol

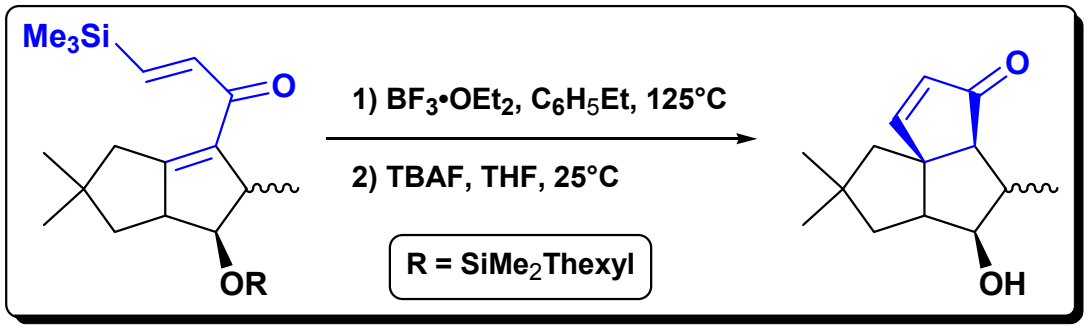
Ichikawa, J.; Miyazaki, S.; Fujiwara, M.; Minami, T. *J. Org. Chem*. **1995**, *60*, 2320-2321.

Another Variant of Fluorine-Directed Nazarov Reaction



Ichikawa, J.; Fujiwara, M.; Okauchi, T.; Minami, T. *Synlett* **1998**, 927-929.

Conclusions on Directed-Nazarov Reactions

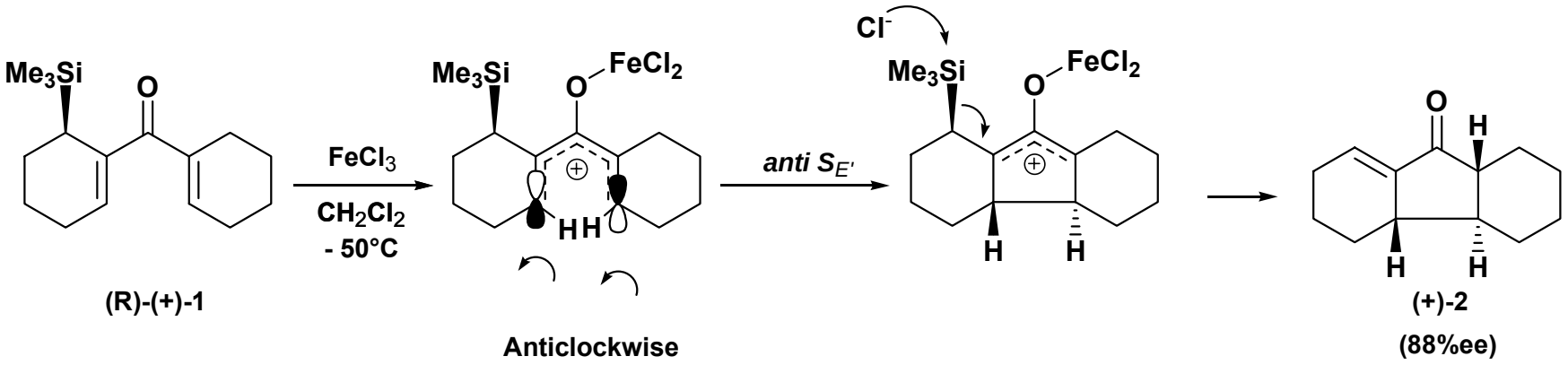
- Regiocontrol is possible through directed-Nazarov reactions
- Silicon and tin can function as a β-cation stabilizer and also as electrofuge to control the introduction of the double bond of the cyclopentenone product in a position depending on the placement of silicon or tin
- Fluorine can function as a β-cation destabilizer and as a nucleofuge to control the introduction of a double bond away from fluorine in the cyclopentenone product
- 

Miesch, M.; Gross, L. M.; Neumann, M. F. *Tetrahedron* **1997**, *53*, 2111-2118.

Asymmetric Nazarov Reactions

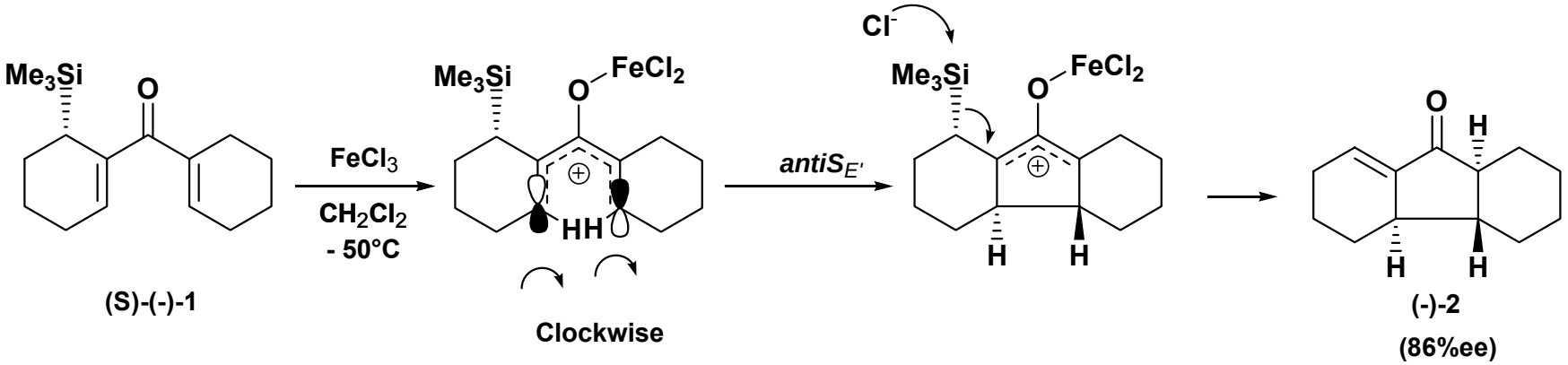
- Substrate control
- Reagent control

Electronic Control of Torquoselectivity



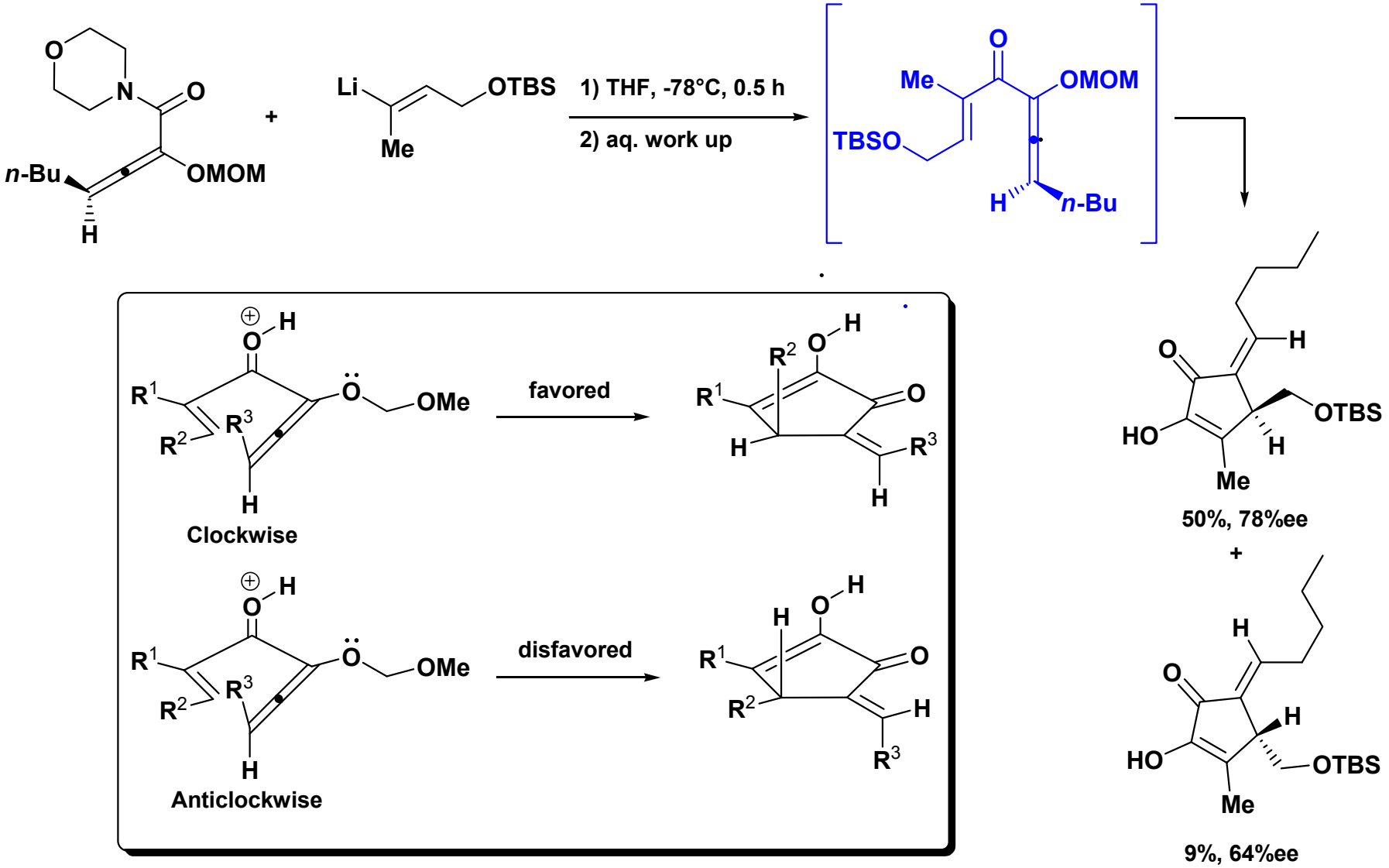
Anti-$S_{E'}$ pathway in the electrocyclization

Stereospecific reaction



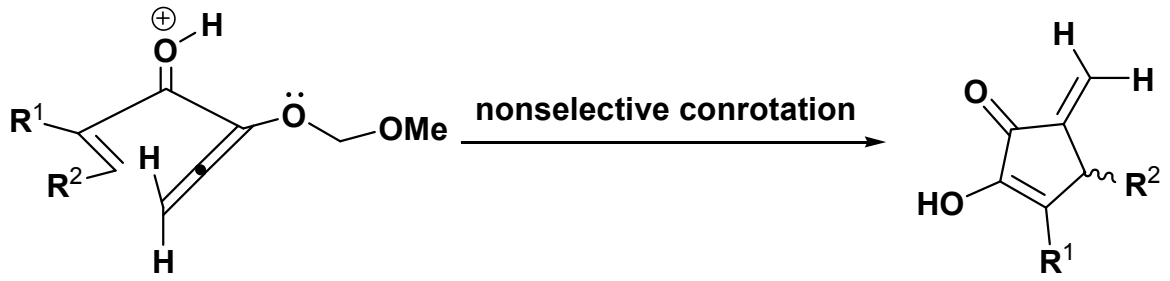
Denmark, S. E.; Wallace, M. A.; Walker, C. B. *J. Org. Chem.* **1990**, *55*, 5543-5545.

Asymmetric Nazarov: *Axial to Tetrahedral Chirality Transfer*



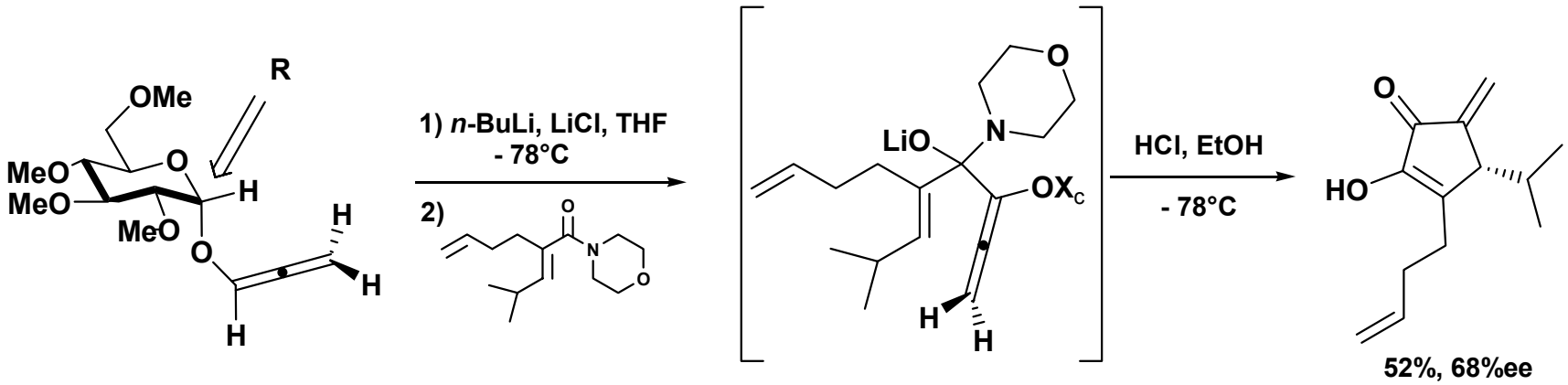
: Hu, H.; Smith, D.; Cramer, R. E.; Tius, M. A. *J. Am.Chem. Soc*. **1999**, *121*, 9895-9896.

Chiral Auxiliary on Non-Stereogenic Allenes

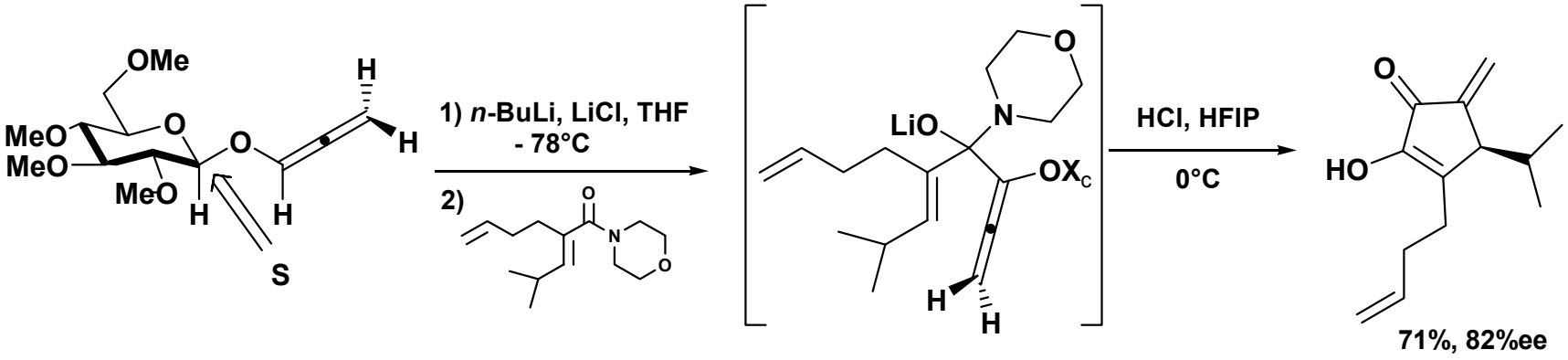


For synthesis of chiral cyclopentenone here we need an asymmetric environment!

Carbohydrate-Derived Auxiliaries

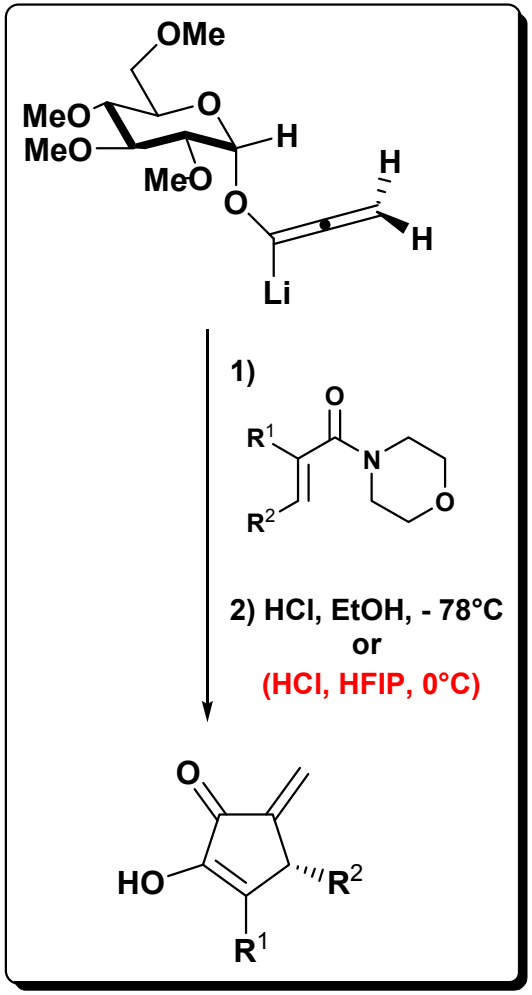


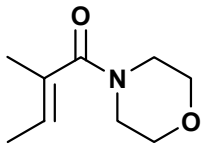
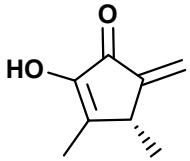
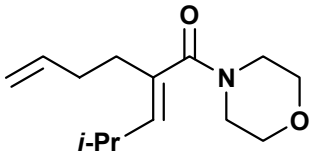
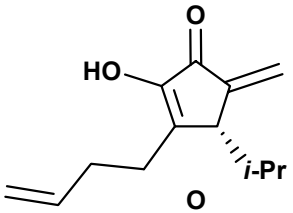
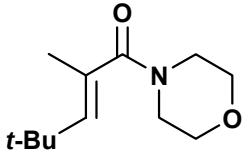
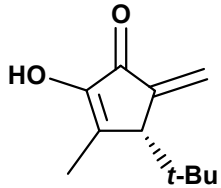
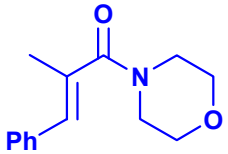
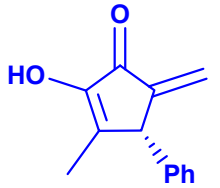
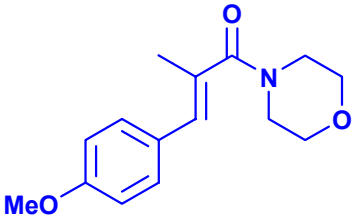
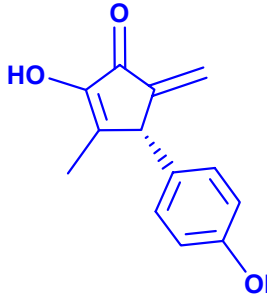
Stereospecific reaction



Harrington, P. E.; Tius, M. A. *Org. Lett*. **2000**, *2*, 2447-2450.

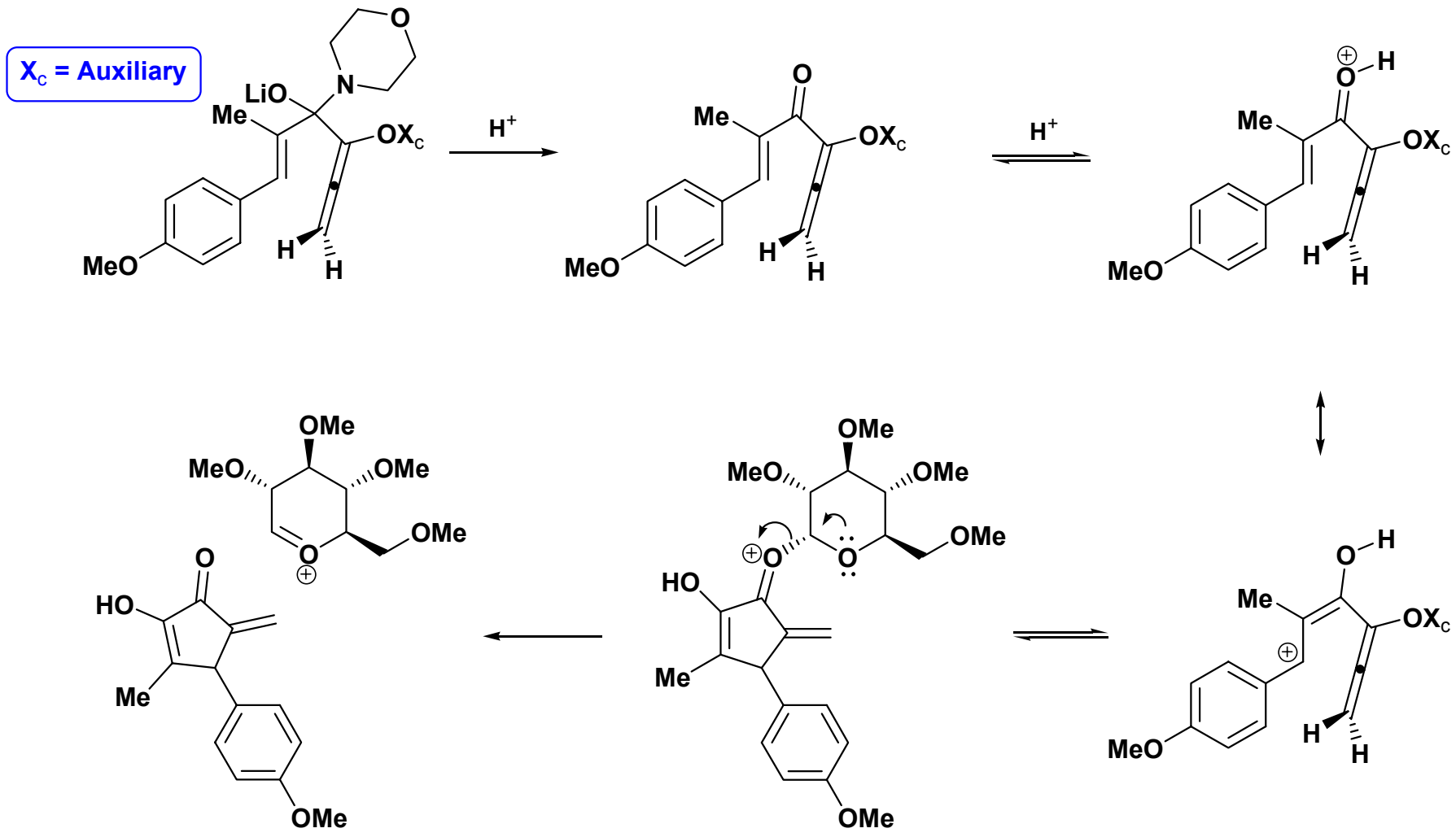
Summary of the Results



Entry	Amide	Product	Yield (%)	ee (%)
1			45 (61)	41 (66)
2			67 (52)	67 (68)
3			71 (61)	57 (73)
4			65 (58)	42 (67)
5			56 (69)	<5 (63)

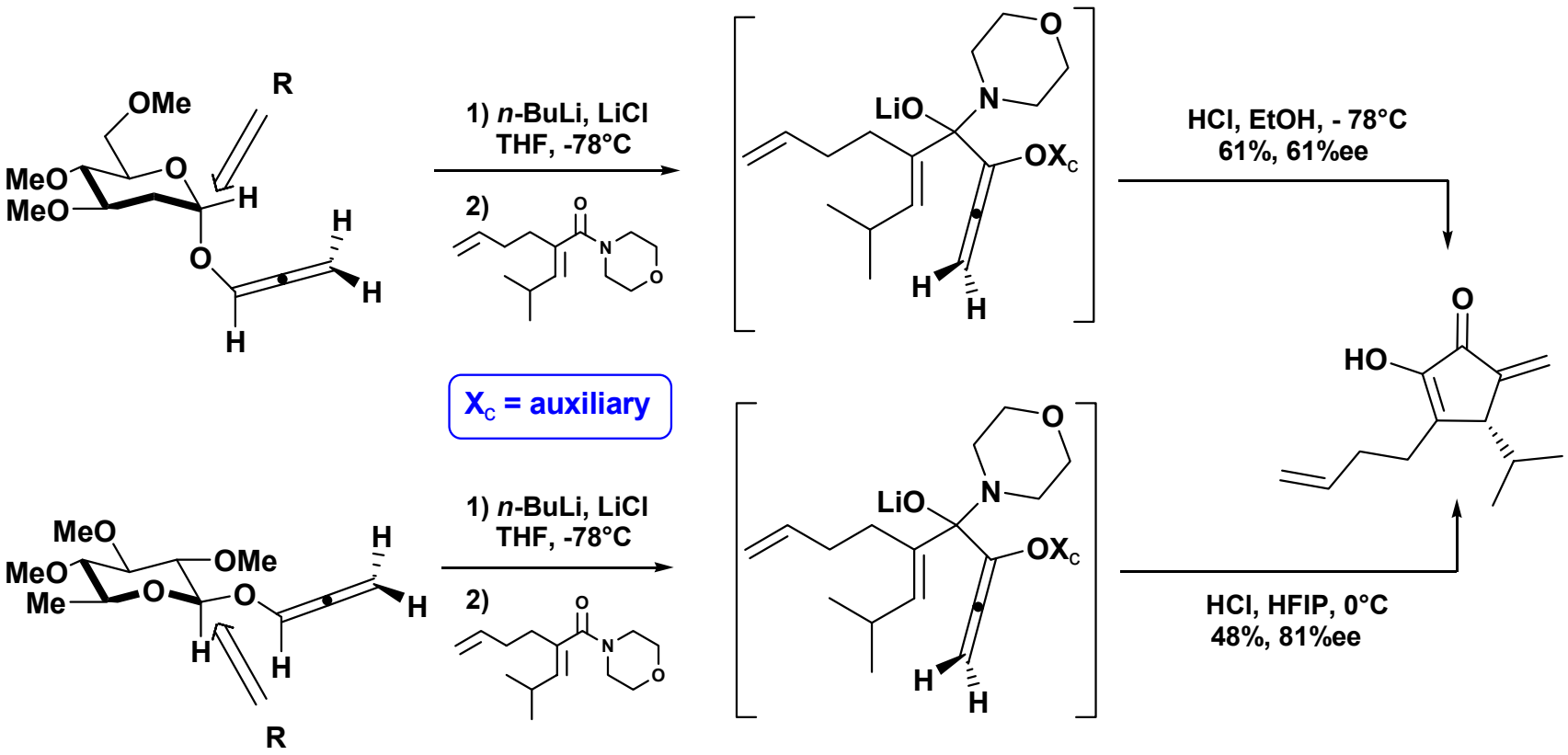
Harrington, P. E.; Tius, M. A. *Org. Lett*. **2000**, *2*, 2447-2450.

Possible Reason: *Mechanistic Insight*



Harrington, P. E.; Tius, M. A. *Org. Lett*. **2000**, *2*, 2447-2450.

Origin of Stereoselection!!!



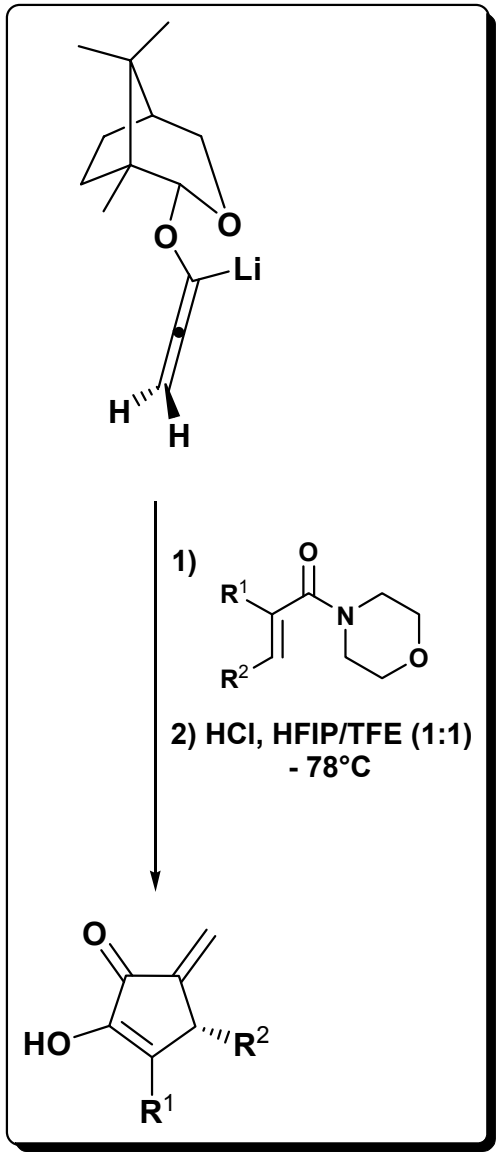
Direction of conrotation is governed by the anomeric carbon atom and that might involve the interaction of pyran oxygen atom

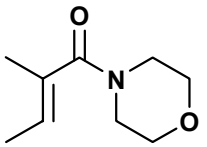
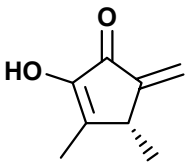
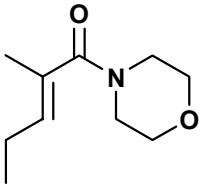
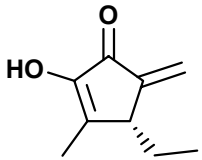
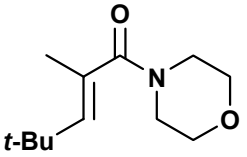
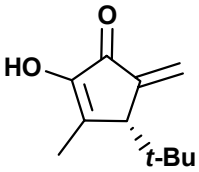
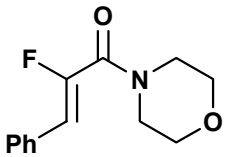
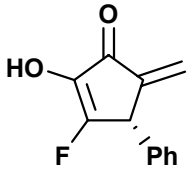
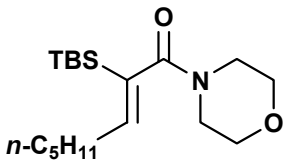
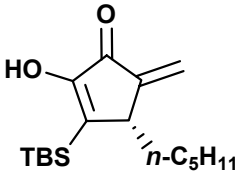
Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc*. **2001**, *123*, 8509-8514.

Limitations of the Carbohydrate-Derived Auxiliary Approach

- Nucleophilicity of the lithiated allenes was unsatisfactory
- Erosion of the %ee took place upon scale up of the reaction
- Preparation of carbohydrate-derived auxiliary was tedious on large scale

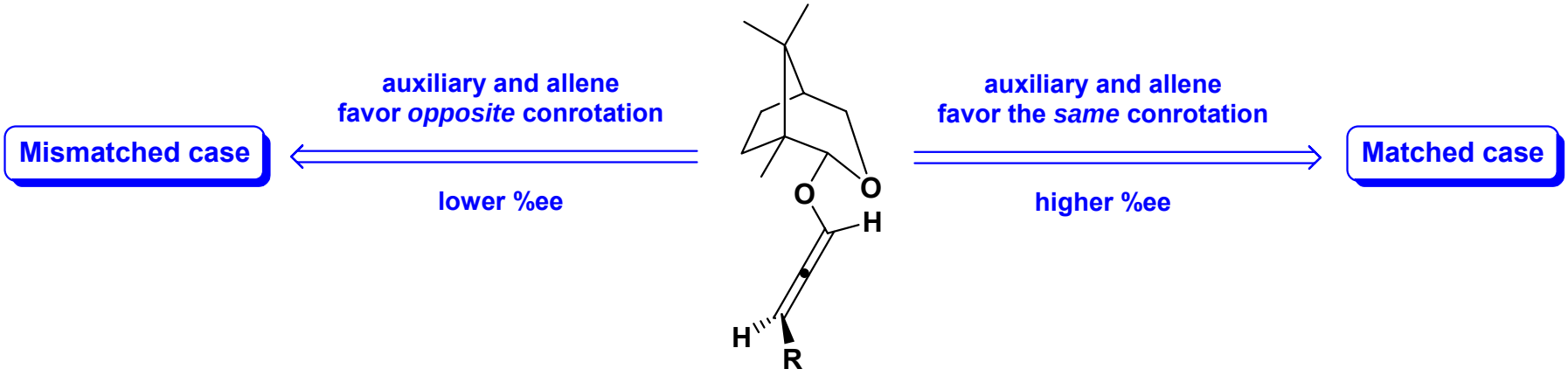
Camphor-Derived Auxiliary



Entry	Amide	Product	Yield (%)	ee (%)
1			67	65
2			69	74
3			84	87
4			55	58
5			62	76

Harrington, P. E.; Murai, T.; Chu, C.; Tius, M. A. *J. Am. Chem. Soc*. **2002**, *124*, 10091-10100.

Auxiliary on Stereogenic Allenes: *Matched and Mismatched Cases!!!*

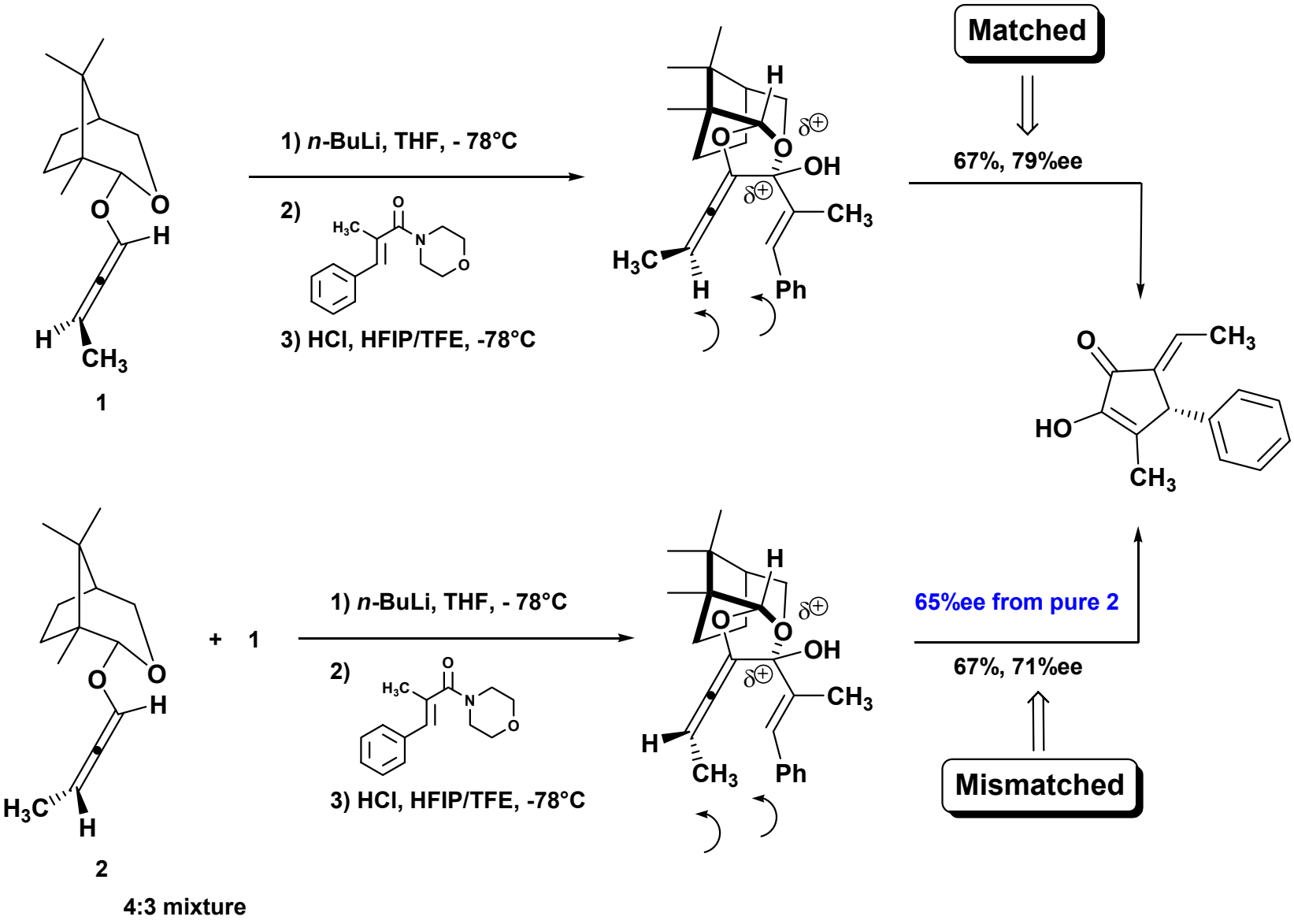


Outcome:

1. If auxiliary directs the conrotation, two allene enantiomers would give products with same stereogenic center β to the carbonyl group

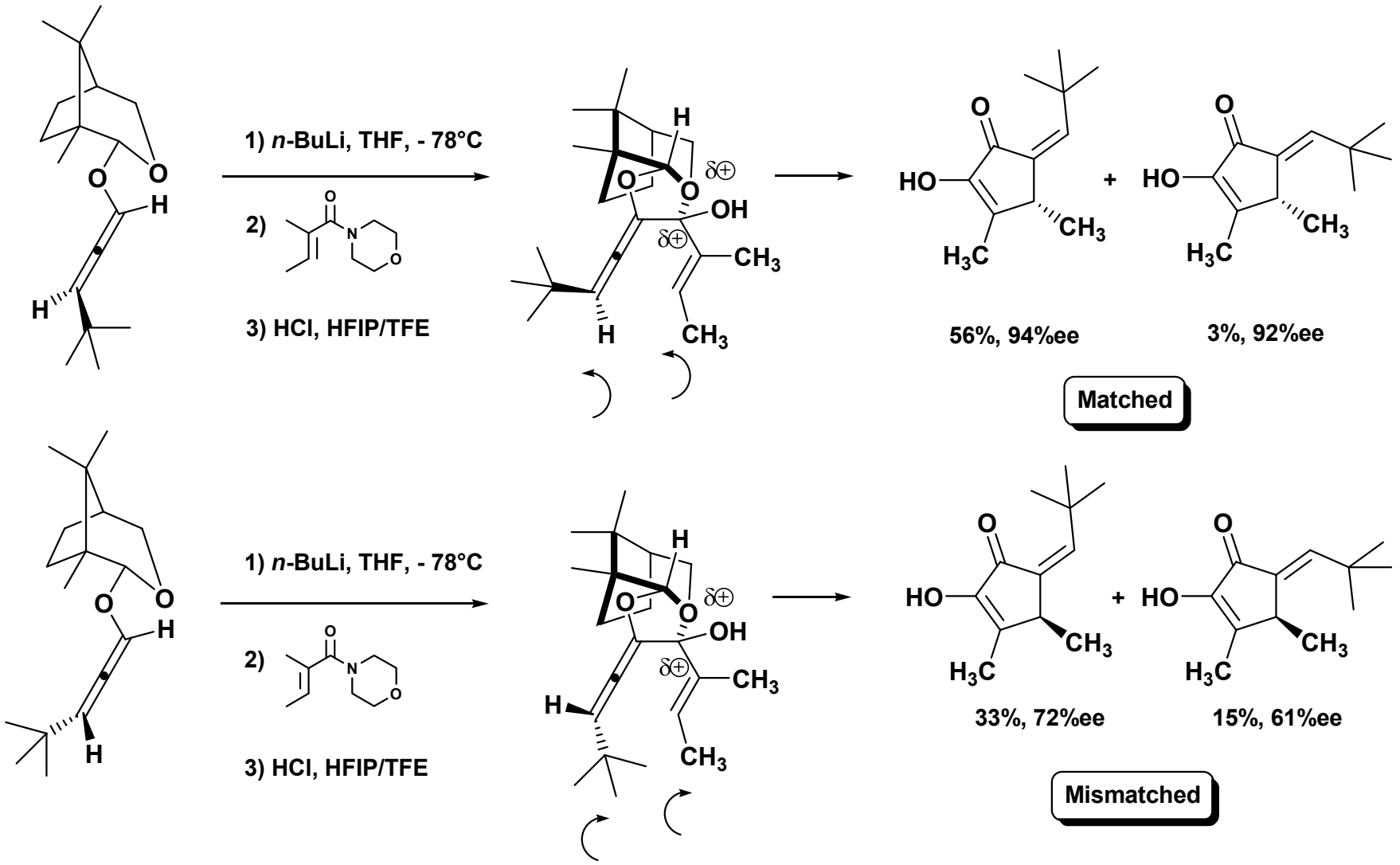
2. If allene directs the conrotation, different allene enantiomers would give enantiomerically different products

An Example Where Auxiliary Controls the Conrotation



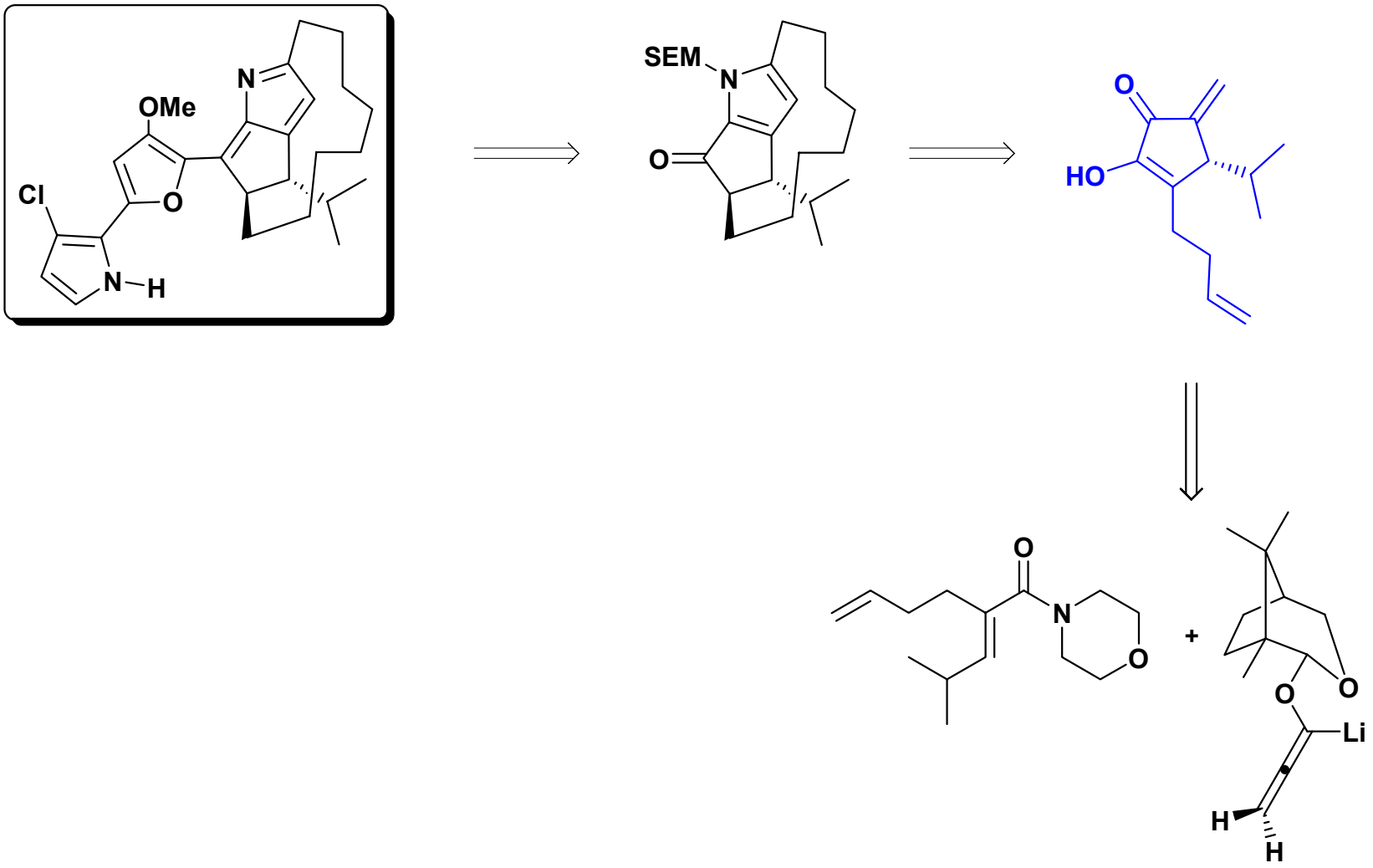
Harrington, P. E.; Murai, T.; Chu, C.; Tius, M. A. *J. Am. Chem. Soc*. **2002**, *124*, 10091-10100.

An Example Where Allene Controls the Conrotation



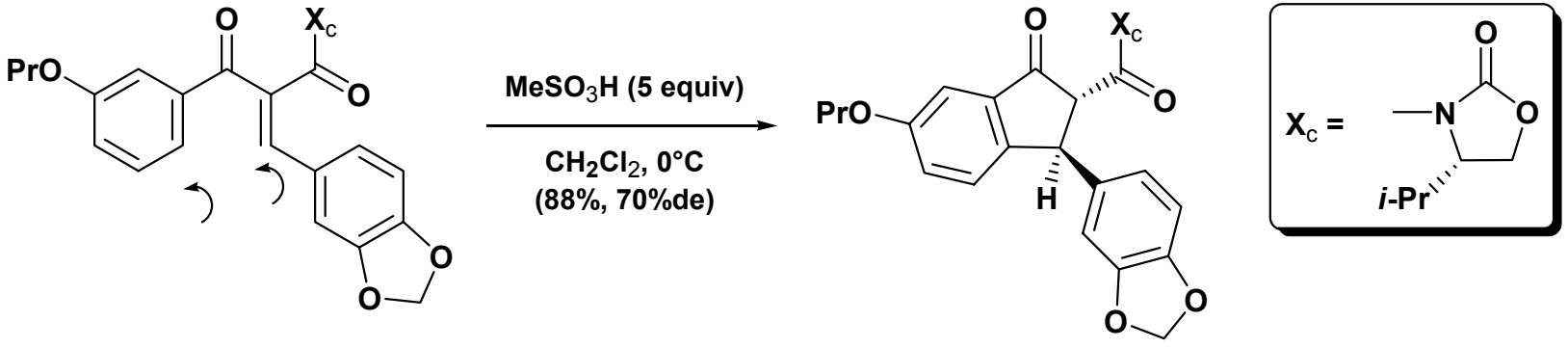
Harrington, P. E.; Murai, T.; Chu, C.; Tius, M. A. *J. Am. Chem. Soc*. **2002**, *124*, 10091-10100.

Application of Chiral Auxiliary Approach: *Synthesis of Roseophilin*

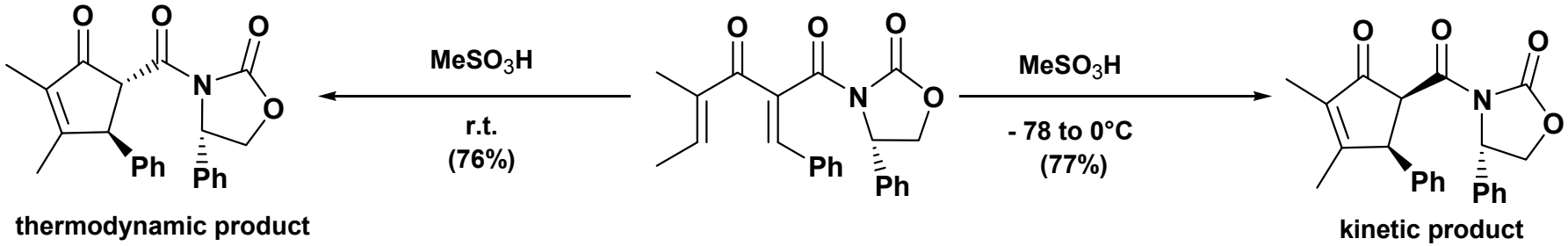


Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc*. **2001**, *123*, 8509-8514.

Some Other Auxiliaries

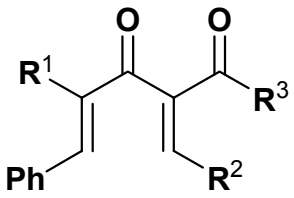


Pridgen, L. N. *et al*. *Synlett* **1999**, 1612-1614.



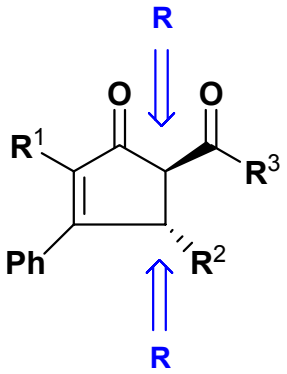
Kerr, D. J.; Metje, C.; Flynn, B. L. *Chem. Commun*. **2003**, 1380-1381.

Reagent Controlled Nazarov: *Catalytic Asymmetric Nazarov Cyclization*

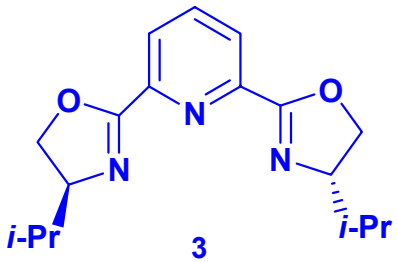


Ligand *, $CuBr_2$
$AgSbF_6$, CH_2Cl_2, r.t.

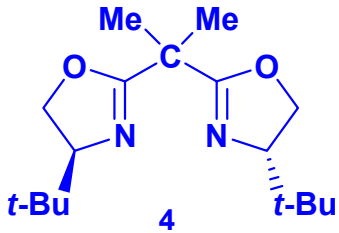
* Ligand = 3 when R_3 = OEt
= 4 when R_3 = NEt_2



Ligands



3

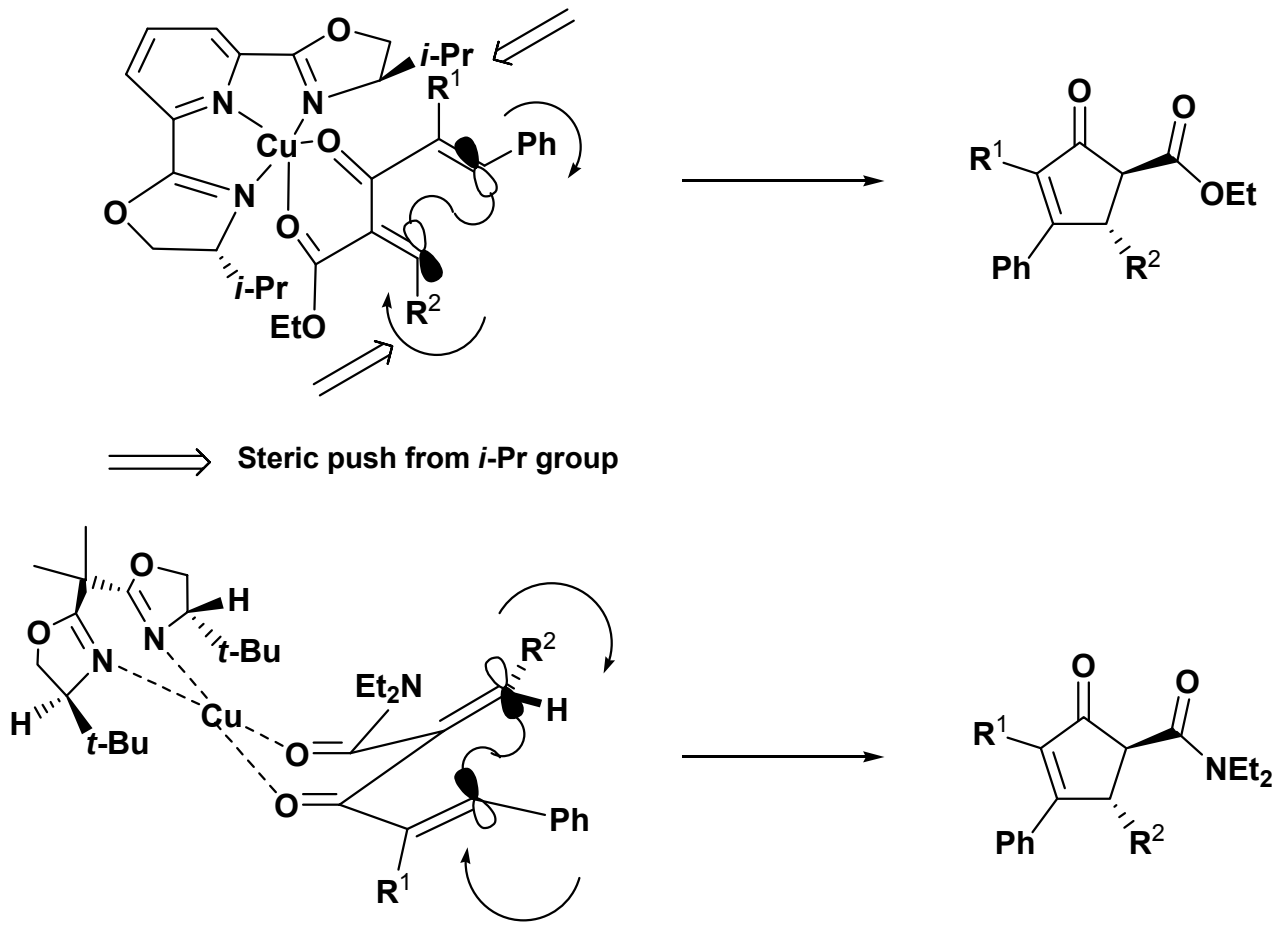


4

Entry	Substrate	R^1	R^2	R^3	Yield (%)	ee (%)
1	1a	Me	Ph	OEt	42	78
2	1b	Ph	Ph	OEt	96	86
3	1c	Me	Me	OEt	27	01
4	1d	Ph	Me	OEt	86	35
5	1e	Me	Ph	NEt_2	56	87
6	1f	Ph	Ph	NEt_2	56	85

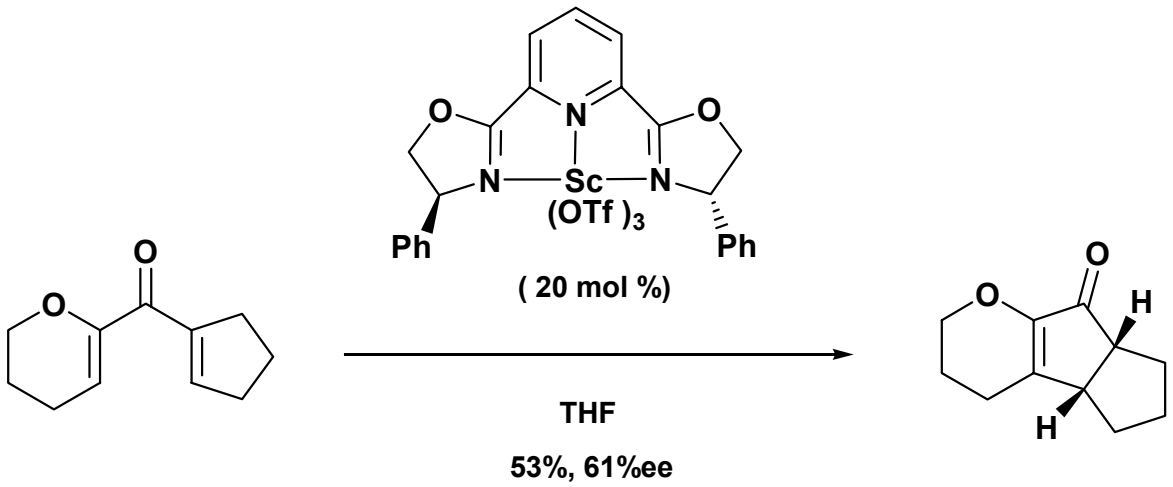
Aggarwal, V. K.; Belfield, A. J. *Org. Lett*. **2003**, *5*, 5075-5078.

Origin of the Stereoselection: *Stereochemical Model*



Aggarwal, V. K.; Belfield. A. J. *Org. Lett*. **2003**, *5*, 5075-5078.

Catalytic Asymmetric Nazarov Cyclization: *Another Example*



Probably Sc is binding to both oxygens forming a distorted complex structure and predisposing the orbital lobes to favor clockwise conrotation

Liang, G.; Gradl, S. N.; Trauner, D. *Org. Lett*, **2003**, *5*, 4931-4934.

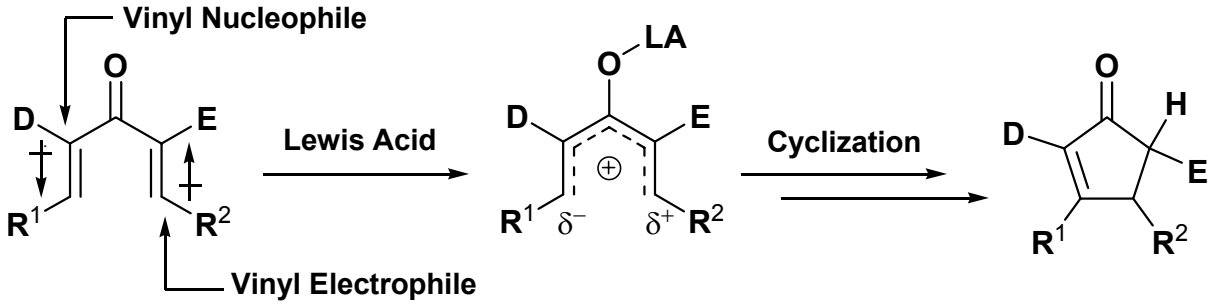
Conclusions on Asymmetric Nazarov Reaction

- Both substrate and reagent controlled asymmetric induction is possible
- Chiral auxiliaries induce asymmetry by favoring one mode of conrotation
- Chiral catalysts distort the divinyl ketone to favor one conrotation over the other

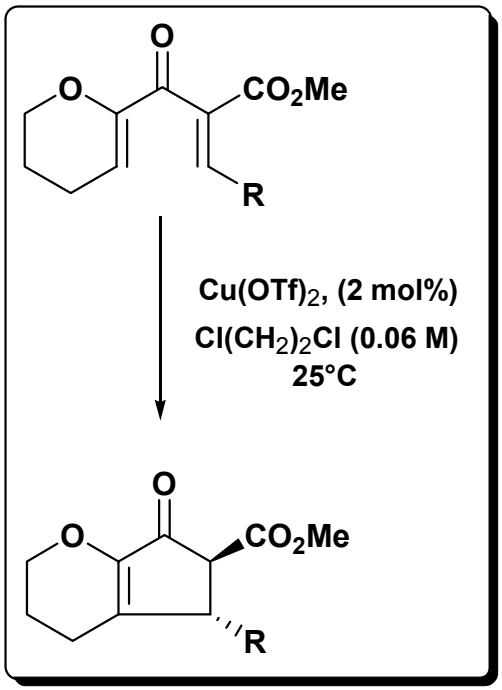
Other Recent Variants of the Nazarov Reaction

- Polarized Nazarov reactions
- Pd(II)-catalyzed Nazarov reactions
- Intercepted Nazarov reactions
- Retro-Nazarov reactions

Polarized Nazarov Reaction



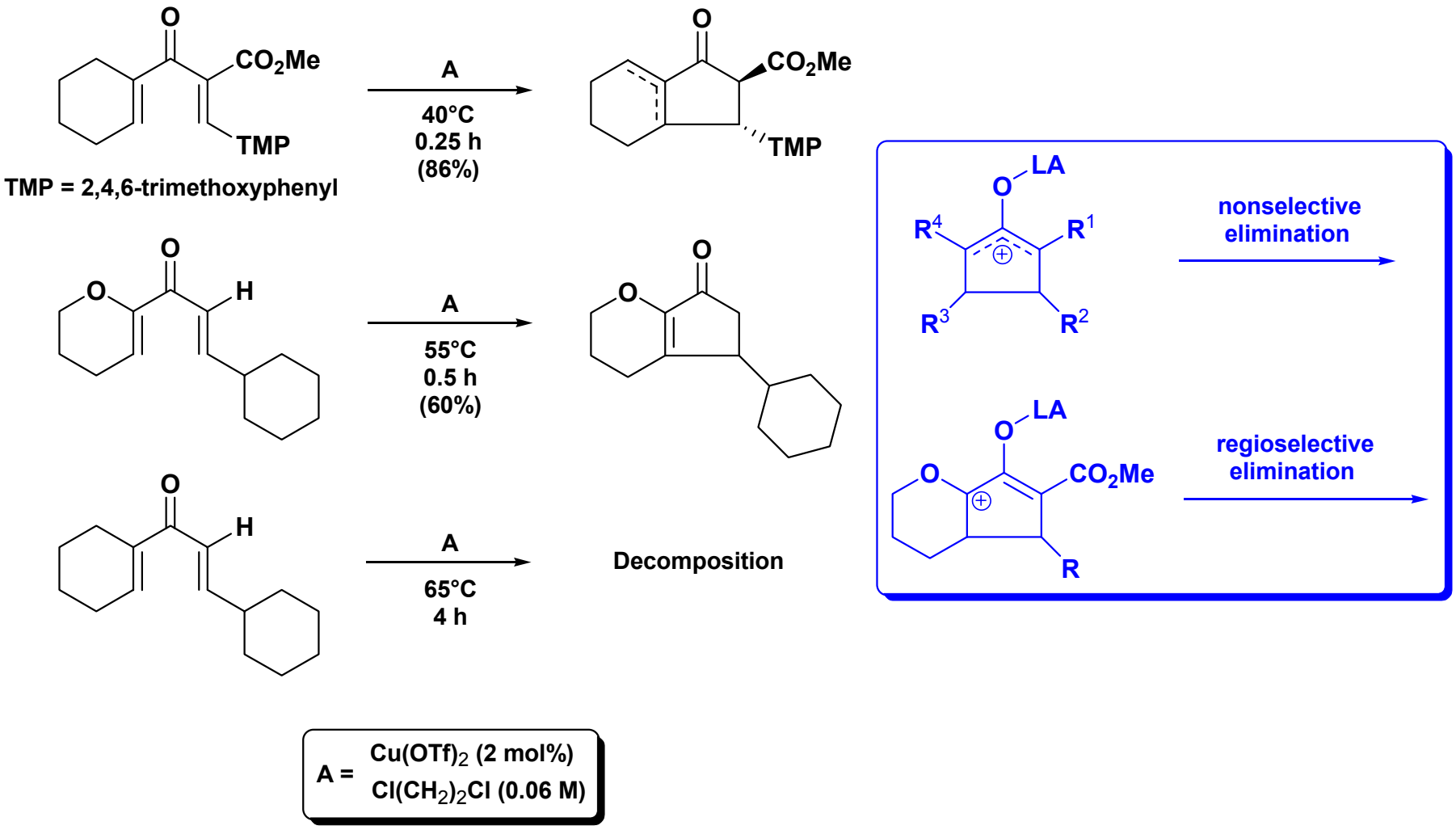
D = Electron donating group
E = Electron withdrawing group



Entry	Ketone	R	Time	Yield (%)
1	3a	2,4,6-trimethoxyphenyl	5 min	> 99
2	3b	4-methoxyphenyl	3.5 h	99
3	3c	3-methoxyphenyl	48 h	96
4	3d	phenyl	108 h	99
5	3e	cyclohexyl	240 h	< 50

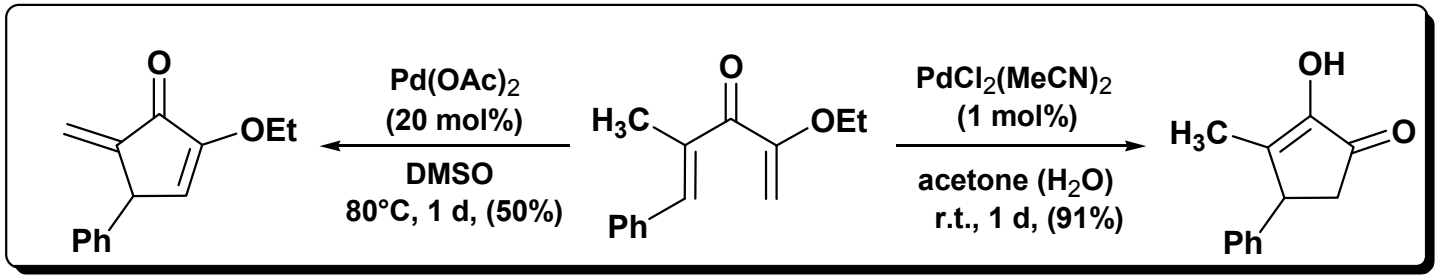
He, W.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc*. **2003**, *125*, 14278-14279.

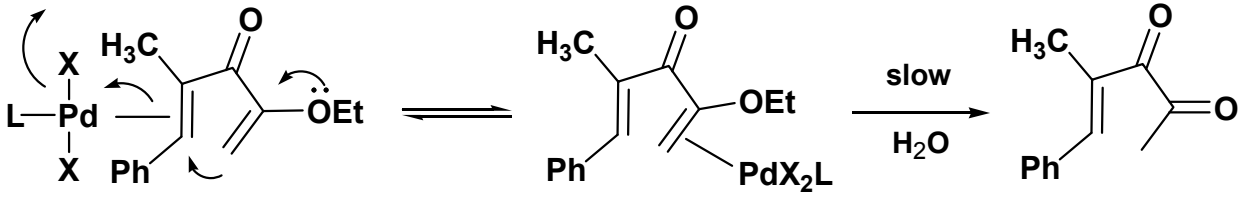
Role of Vinyl Nucleophile and Vinyl Electrophile

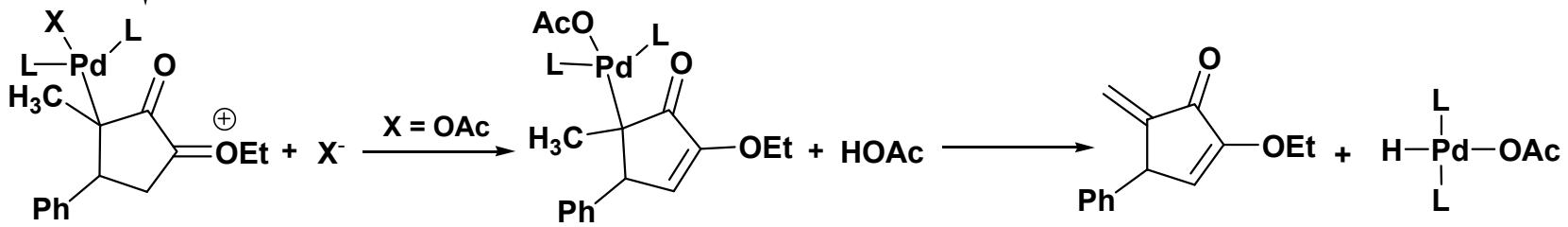


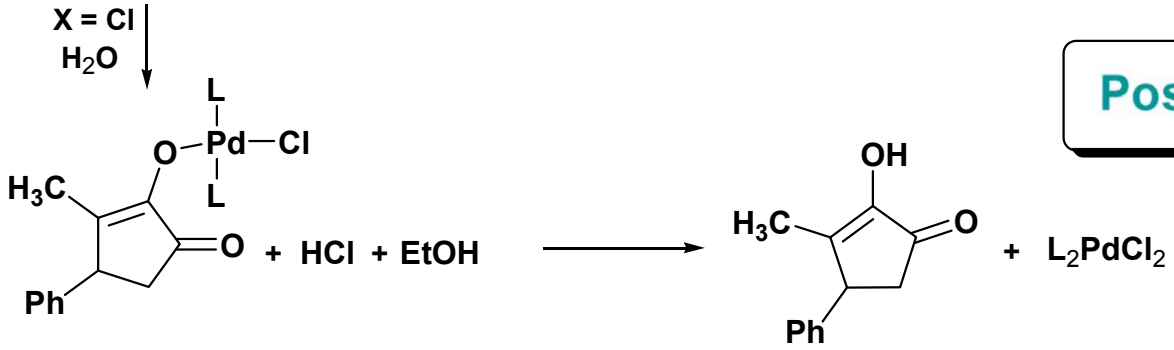
He, W.; Sun, X.; Frontier, A. J. *J. Am. Chem. Soc*. **2003**, *125*, 14278-14279.

Palladium(II) Catalyzed Nazarov Reaction





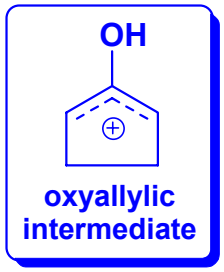


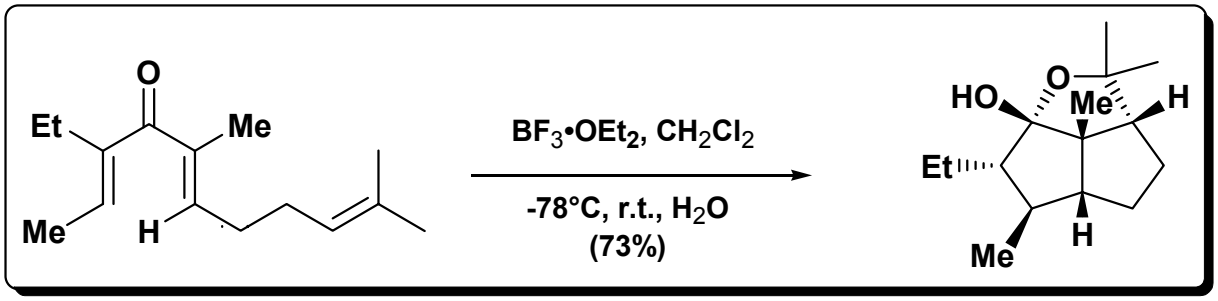


Possible Mechanism !!!

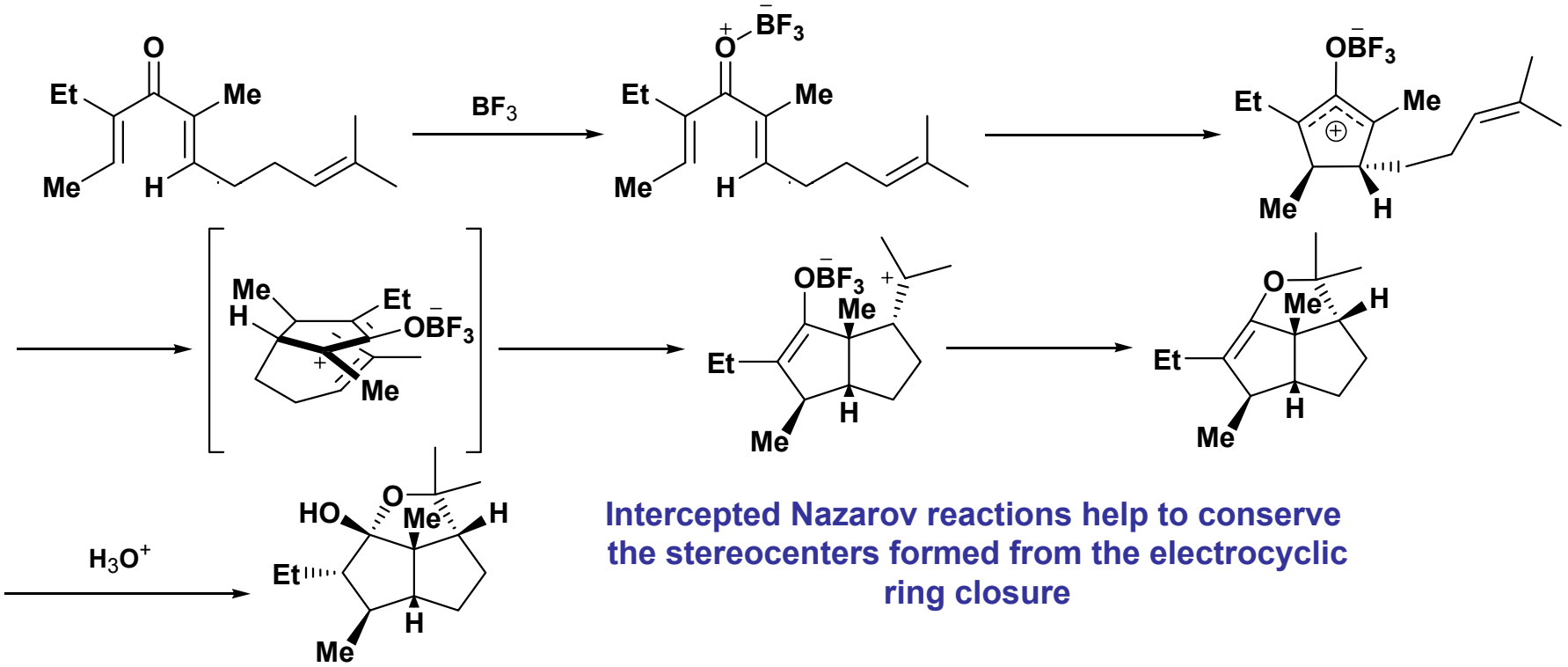
Bee, C.; Leclerc, E.; Tius, M. A. *Org. Lett*. **2003**, *5*, 4927-4930.

Intercepted Nazarov Reactions: *Intramolecular*





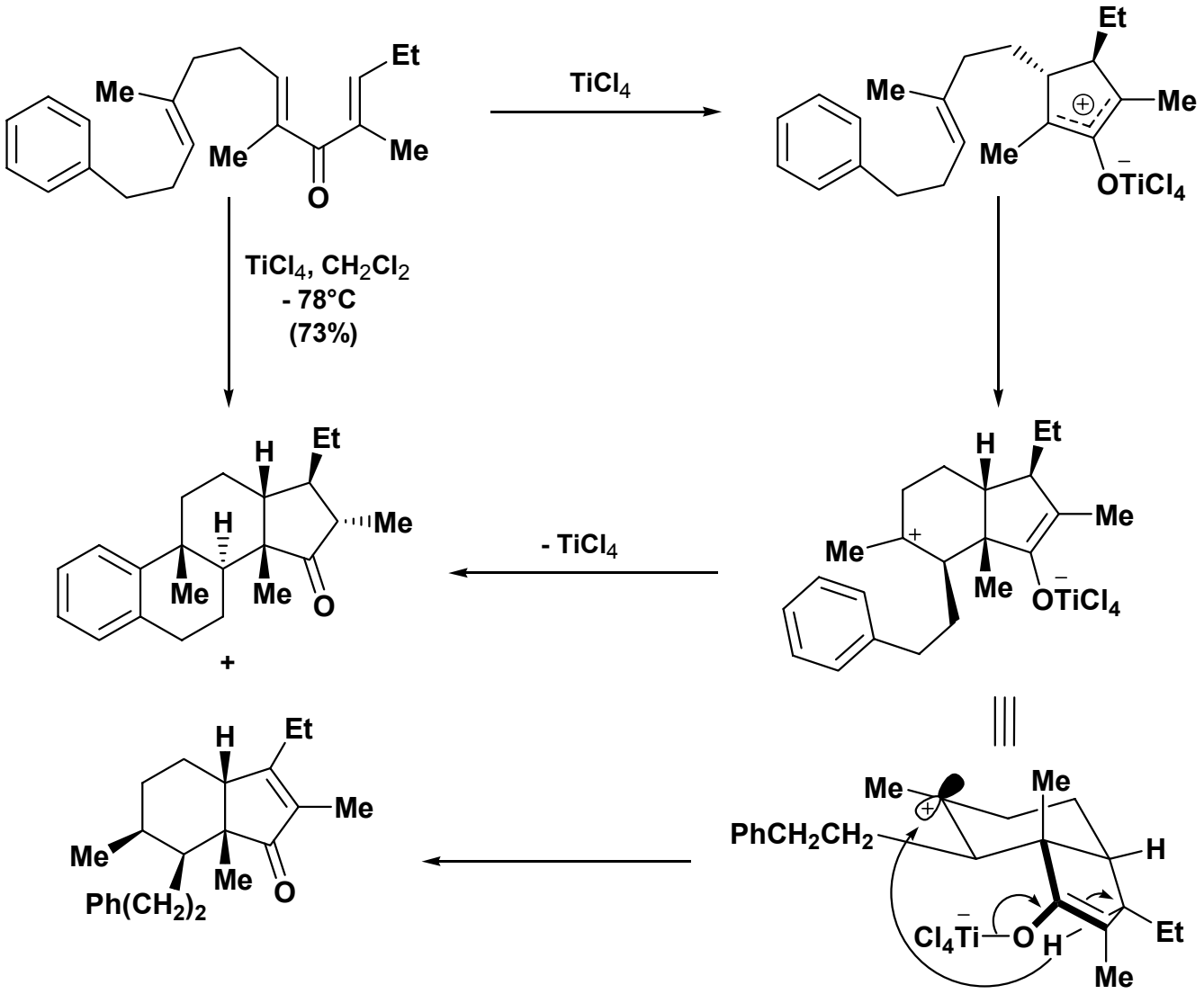
Mechanistic Rationale:



Intercepted Nazarov reactions help to conserve the stereocenters formed from the electrocyclic ring closure

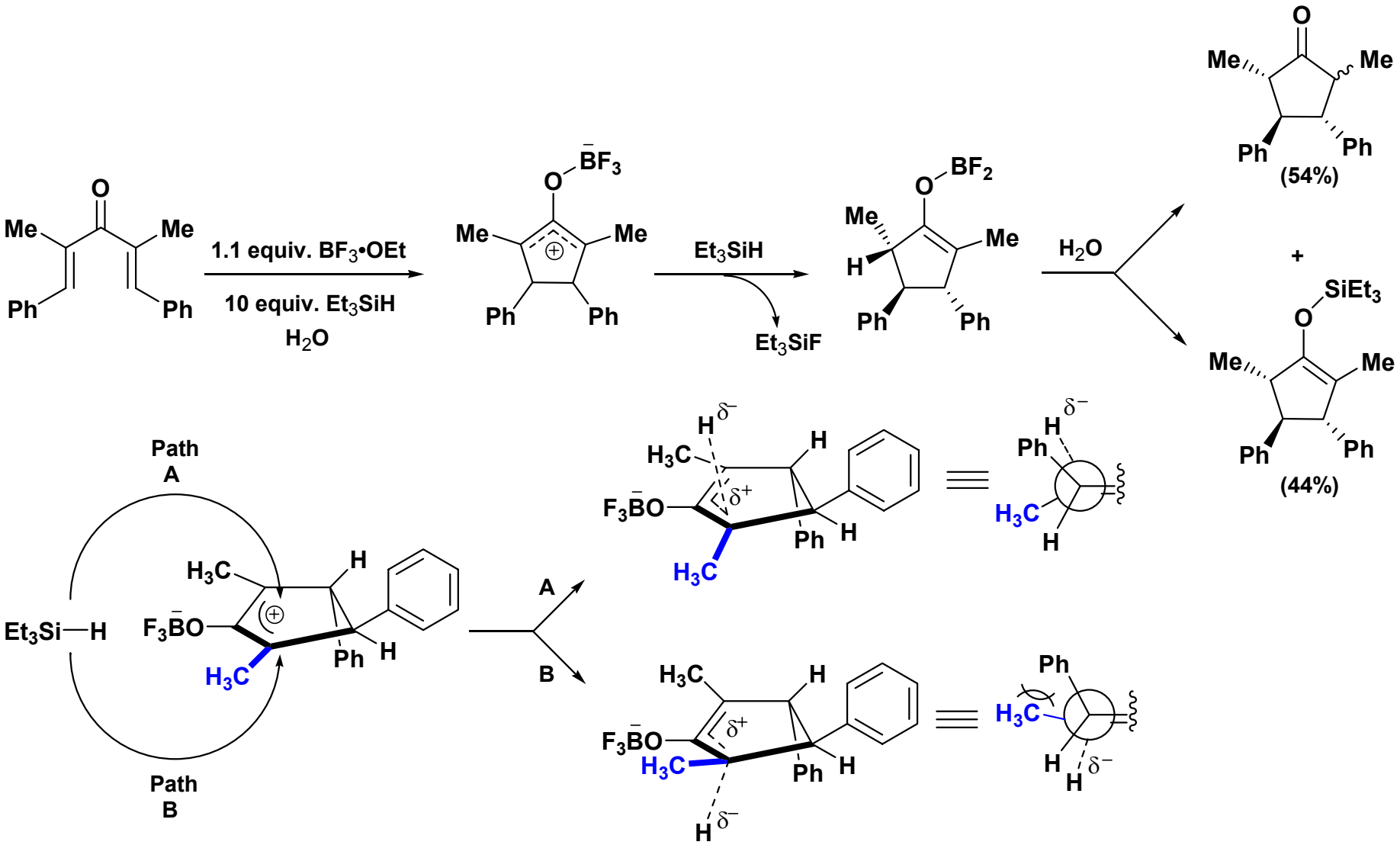
Bender, J. A.; Blize, A. E.; Browder, C. C.; Giese, S.; West, F. G. *J. Org. Chem*. **1998**, *63*, 2430-2431.

Domino-Nazarov Reaction



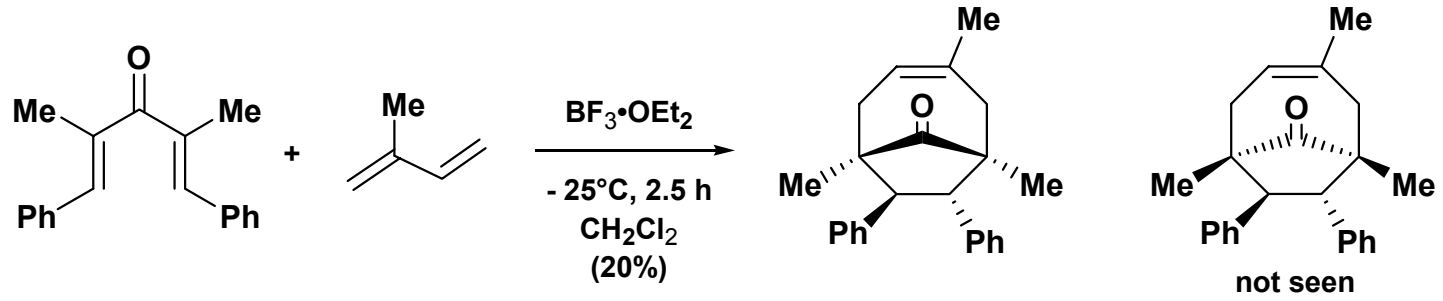
Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc*. **1999**, *121*, 7443-7444.

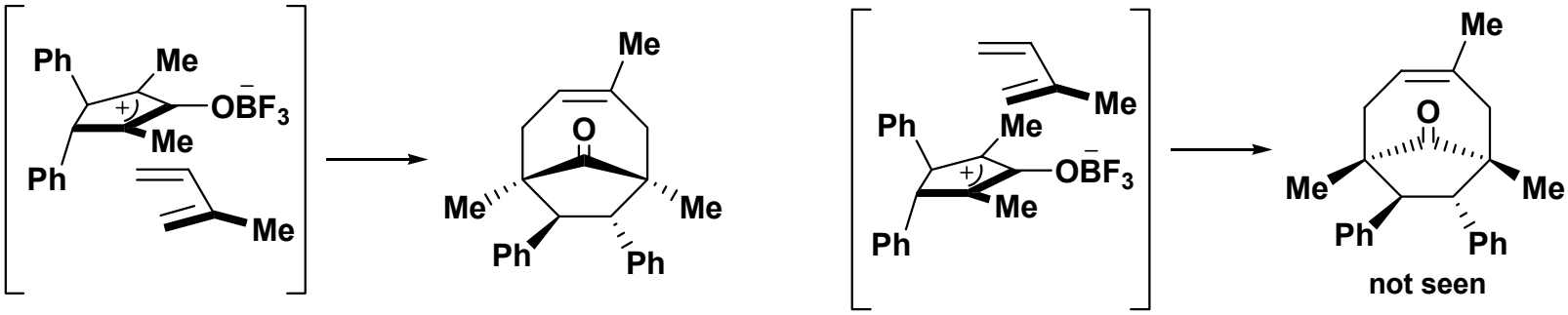
Intermolecular Trapping of Nazarov Intermediate: *Reductive Nazarov Cyclization*



Giese, S.; West, F. G.; *Tetrahedron* **2000**, *56*, 10221-10228.

[4+3] Capture of Oxyallyl Intermediate: *Another Intermolecular Case*

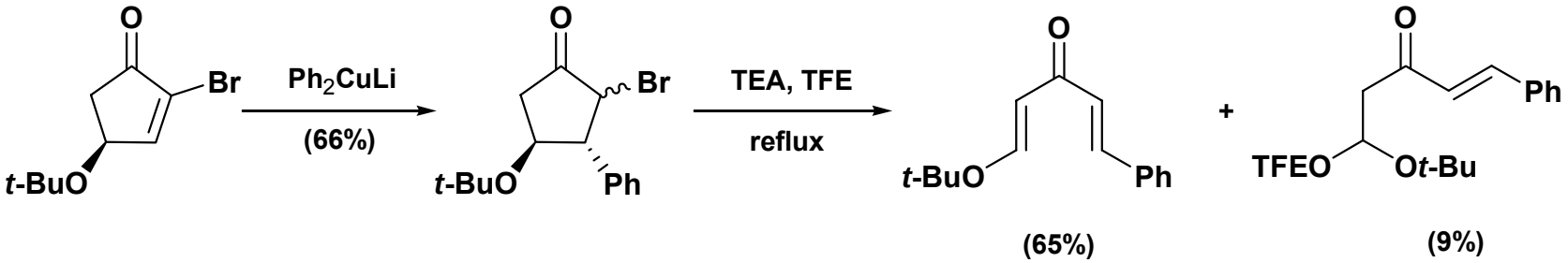




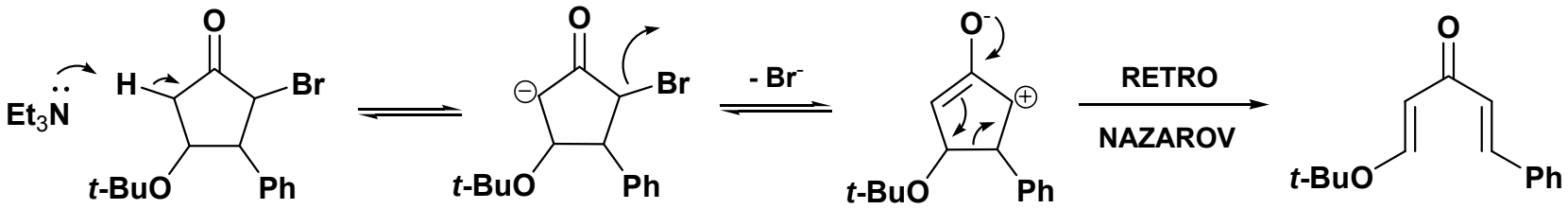
Stepwise cycloaddition?

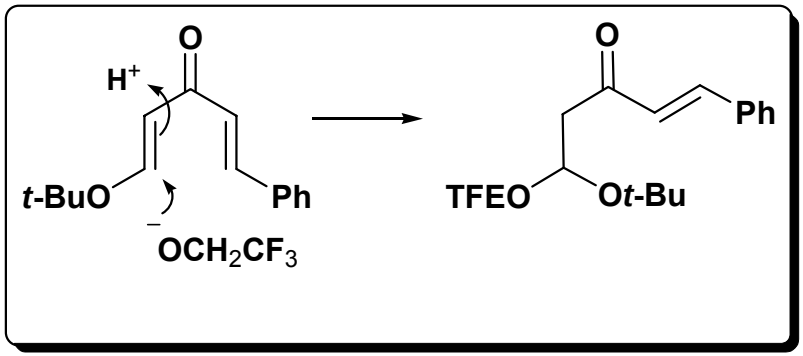
Wang, Y.; Schill, B. D.; Arif, A. M.; West, F. G. *Org. Lett*, **2003**, *5*, 2747-2750.

Retro-Nazarov Reaction



Probable Mechanism !!!





Retro-Nazarov: ***misnomer?***

Harmata, M.; Lee, D. R. *J. Am. Chem. Soc*. **2002**, *124*, 14328-14329.

Conclusions

- Classical acid catalyzed Nazarov cyclization reaction is a 4π conrotatory electrocyclic ring closure reaction of divinyl ketones
- Directed Nazarov reactions attempt to overcome the problems related to regiocontrol of the double bond in the product
- Asymmetric Nazarov reactions provide a means to selectively favor one mode of conrotation in the electrocyclic ring closure
- Polarization of the precursor divinyl ketone gives the Nazarov product with regiocontrol under milder conditions
- Trapping of the oxyallylic intermediate of the reaction can be done both intra and intermolecularly and that helps to conserve the stereocenters created by the electrocyclic ring closure

Acknowledgements

Dr. Robert Maleczka

Edith

Jill

Ron

Andrea

Feng

Kyoungsoo

Kim

Sanjit

Jill

Dr. Wagner

Dr. Tepe

Dr. Jackson

Dr. Reusch

Manish

Vijay

Manasi

Mahesh

All other friends!