Total Syntheses of Ginkgolide A, B, C

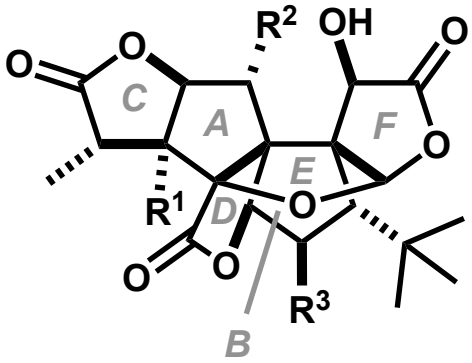
2022.11.5. Literature Seminar

B4 Shintaro Fukaya

Contents

Contents

1. Ginkgolide



Ginkgolide A : R^1 = OH, R^2 = R^3 = H
Ginkgolide B : R^1 = OH, R^2 =OH, R^3 = H
Ginkgolide C : R^1 = OH, R^2 =OH, R^3 = OH
Ginkgolide M : R^1 = OH, R^2 =H, R^3 = OH
Ginkgolide J : R^1 = H, R^2 =OH, R^3 = OH

Isolation

from the leaves and root bark of the *Ginkgo biloba* tree
Ginkgolides A, B, C, M (isolated in 1932[1)], elucidated in 1967[2)])
Ginkgolide J (1987)[3)]

Biological activity

strong antagonists to PAFR[4)]

Total synthesis of Ginkgolide

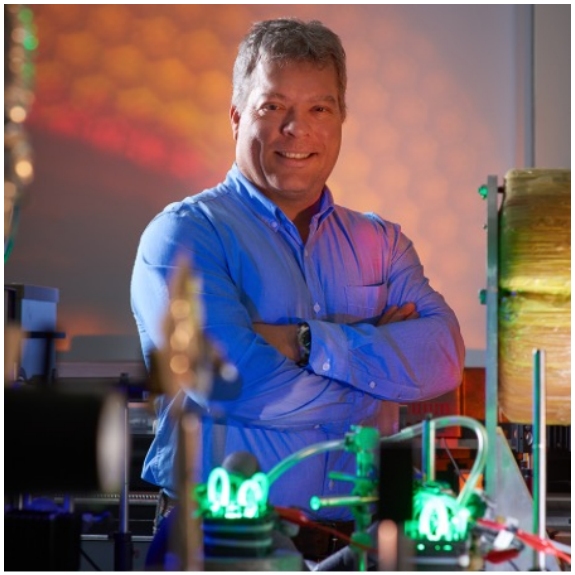
Corey (1988, (±)-Ginkgolide A, B)[5), 6)]
Crimmins (2000, (±)-Ginkgolide B)[7)]
(see also 150206_LS_Kosuke_Minagawa)
Barriault (2022,(±)-Ginkgolide A, B, C)[8)]

Structural features

six 5-membered rings, three lactones,
four quarternary carbons, *t*-butyl group

1) Furukawa, S. *Sci. Pap. Inst. Phys. Chem. Res.* **1932**, *19*, 27.
2) (a) Maruyama, M.; Terahara, A.; Itagaki, Y.; Nakanishi, K. *Tetrahedron Lett.* **1967**, *8*, 299. (b) Maruyama, M.; Terahara, A.; Itagaki, Y.; Nakanishi, K. *Tetrahedron Lett.* **1967**, *8*, 303. (c) Maruyama, M.; Terahara, A.; Nakadaira, Y.; Woods, M. C.; Nakanishi, K. *Tetrahedron Lett.* **1967**, *8*, 309. (d) Maruyama, M.; Terahara, A.; Nakadaira, Y.; Woods, M. C.; Takagi, Y.; Nakanishi, K. *Tetrahedron Lett.* **1967**, *8*, 315. (e) Woods, M. C.; Miura, I.; Nakadaira, Y.; Terahara, A.; Maruyama, M.; Nakanishi, K. *Tetrahedron Lett.* **1967**, *8*, 321.
3) Weinges, K.; Hepp, M.; Jaggy, H. *Liebigs Ann. Chem.* **1987,** *1987*, 521.
4) Liu, Y.; Shields, L. B. E.; Gao, Z.; Wang, Y.; Zhang, Y. P.; Chu, T.; Zhu, Q.; Shields, C. B.; Cai, J. *Mol. Neurobiol*. **2017**, *54*, 5563.
5) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110,* 649.
6) Corey, E. J.; Ghosh, A. K. *Tetrahedron Lett.* **1988**, *29*, 3205.
7) Crimmins, M. T.; Pace, J. M.; Nantermet, P. G.; Kim-Meade, A. S.; Thomas, J. B.; Watterson, S. H.; Wagman, A. S. *J. Am. Chem. Soc.* **2000**, *122*, 8453.
8) Hebert, M.; Bellavance, G.; Barriault, L. *J. Am. Chem. Soc.* **2022**, *144*, 17792.

Introduction of Prof. Barriault



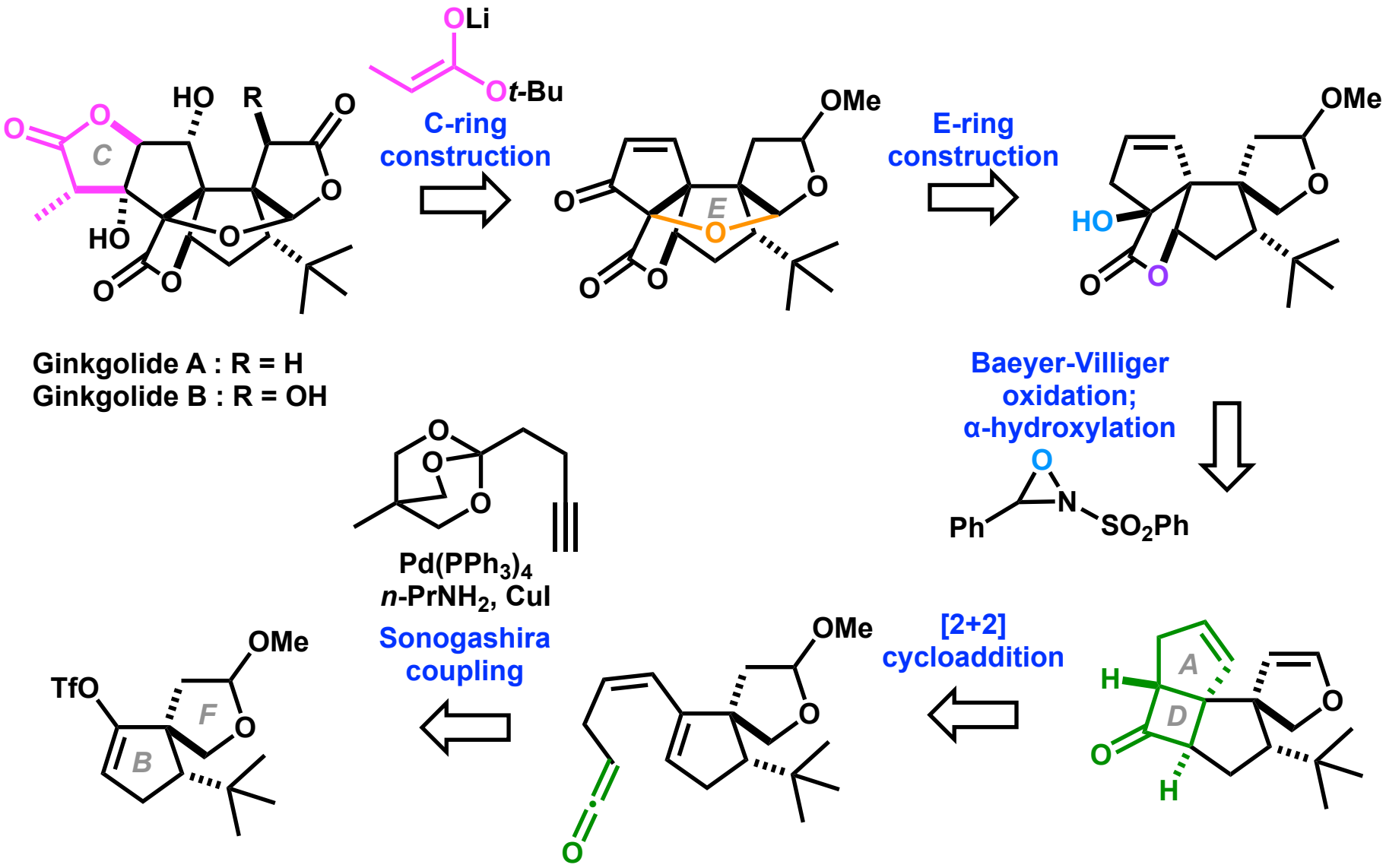
1993 B. Sc., @ University of Sherbrooke
1997 Ph.D., @ University of Sherbrooke (Prof. Deslongchamps, P.)
1997- Postdoctoral fellow @ Ohio State University (Prof. Paquette, L. A.)
1999- Assistant Professor @ University of Ottawa
2010- Full Professor @ University of Ottawa

Research topic:
asymmetric synthesis, development of new synthetic methods, total synthesis of natural products

https://thebarriaultlab.com/louis/
https://science.uottawa.ca/chemistry/people/barriault-louis

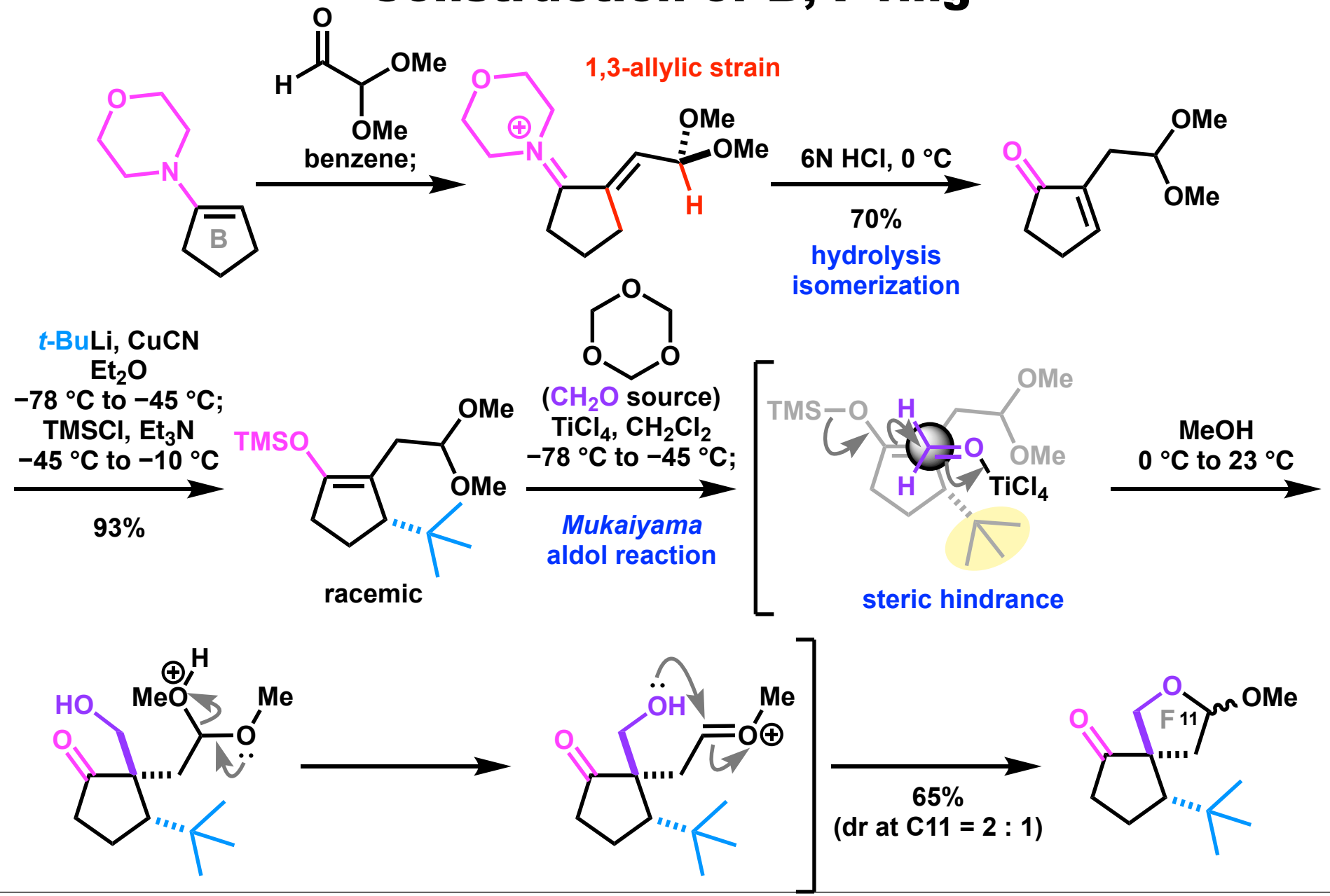
Contents

Retrosynthetic Analysis



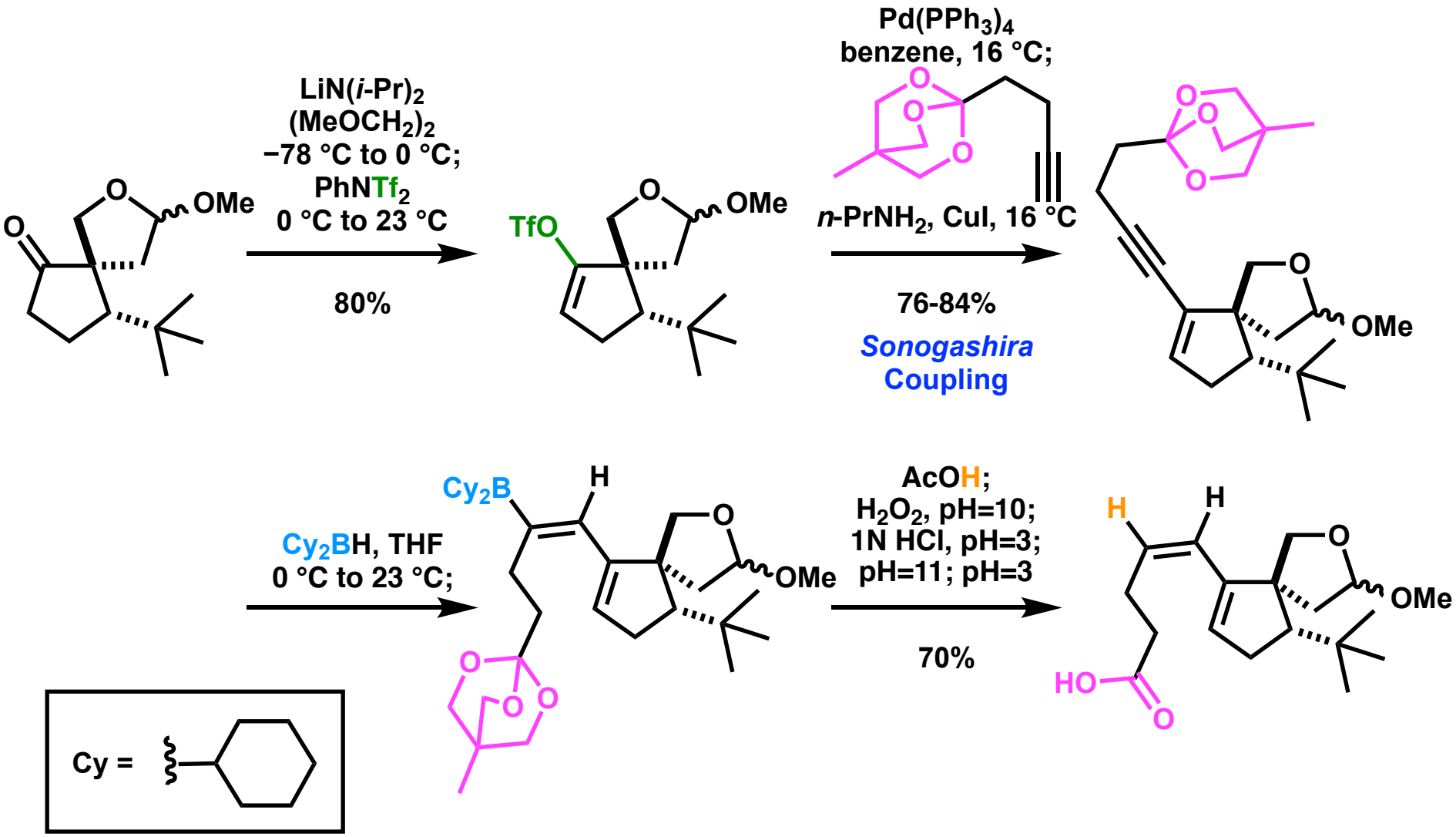
1) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110,* 649.

Construction of B, F-ring



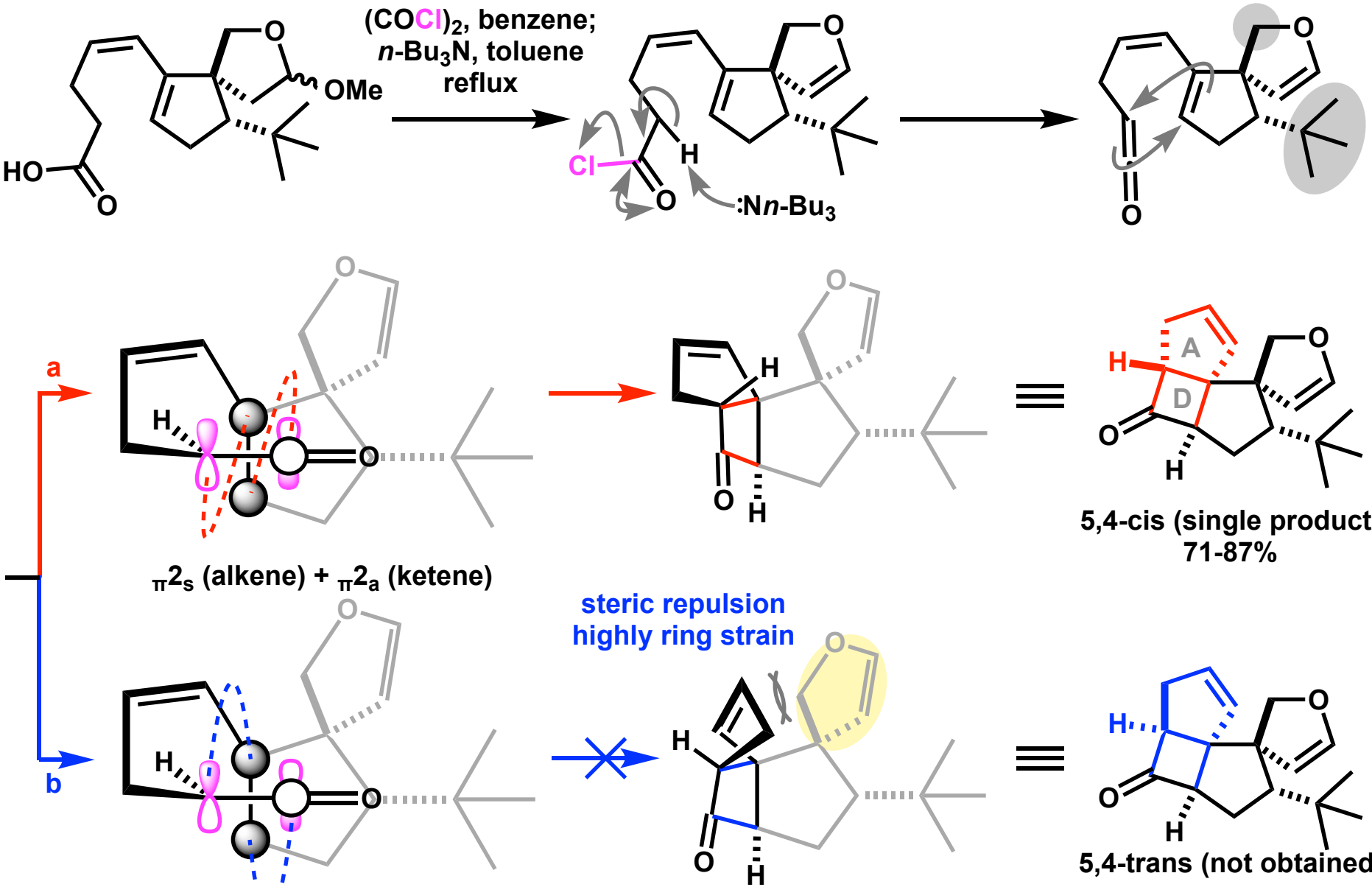
1) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110,* 649.

Formation of Carboxylic Acid



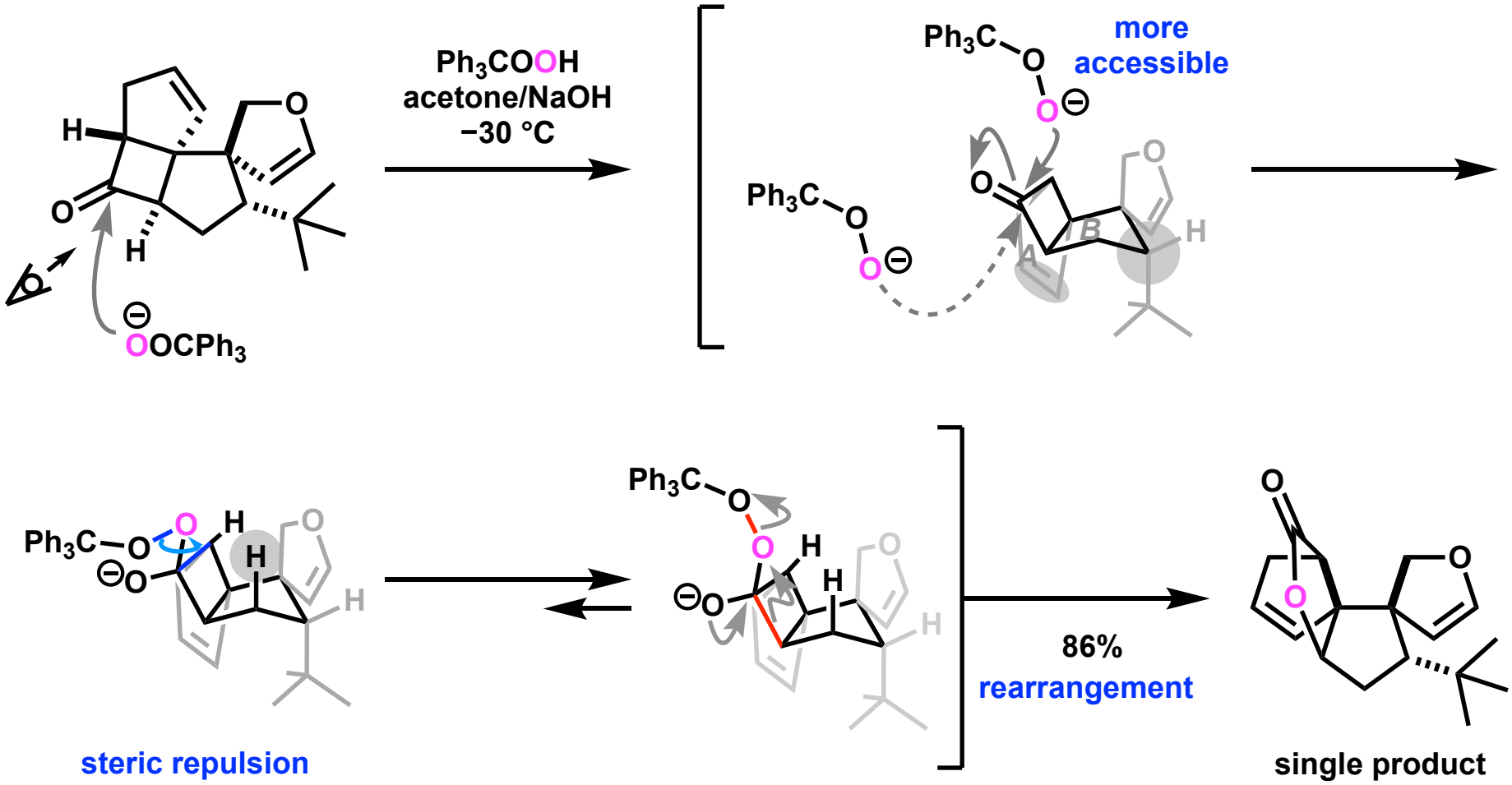
1) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110,* 649.

[2+2] Cycloaddition



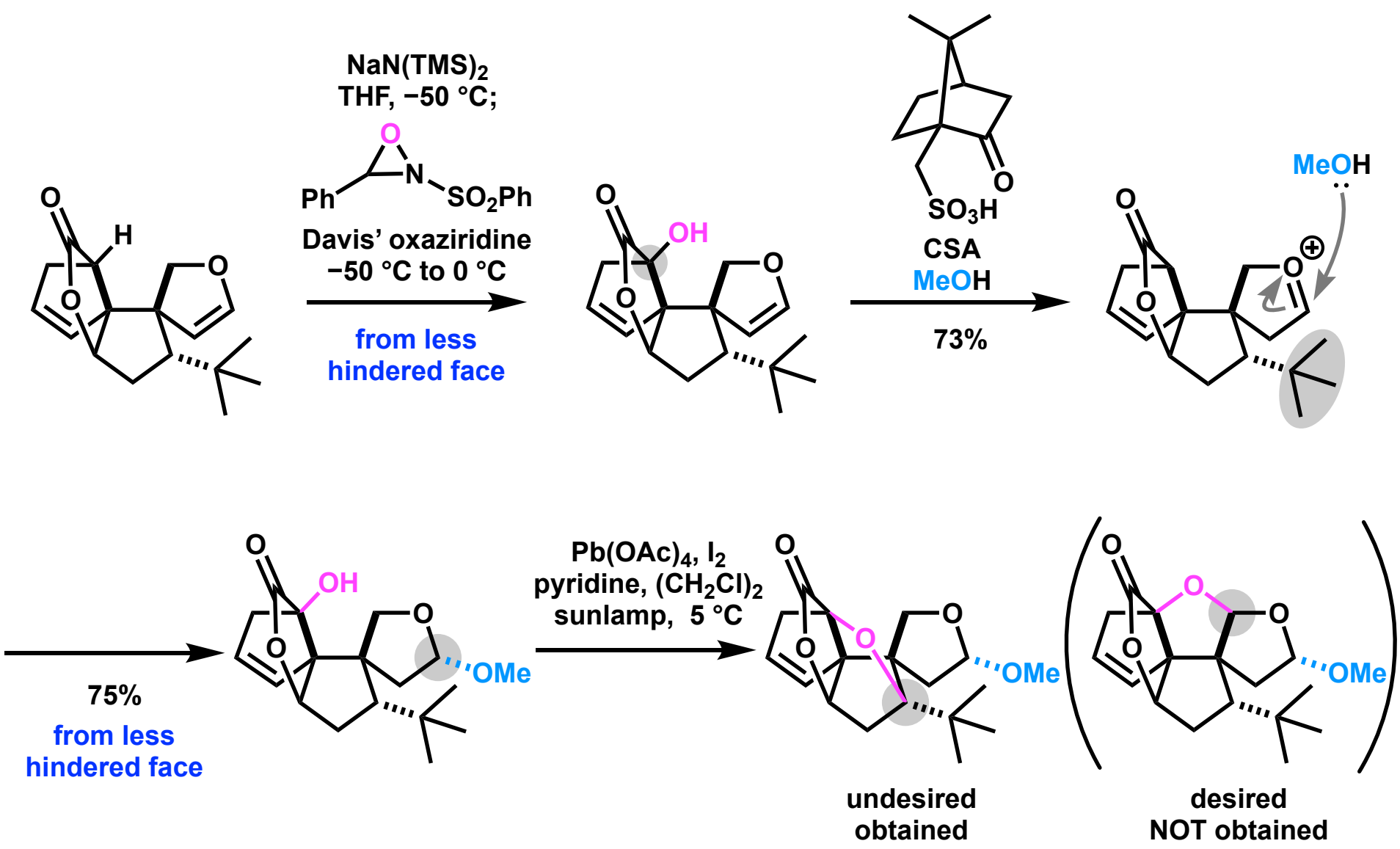
1) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110,* 649.

Baeyer-Villiger Oxidation



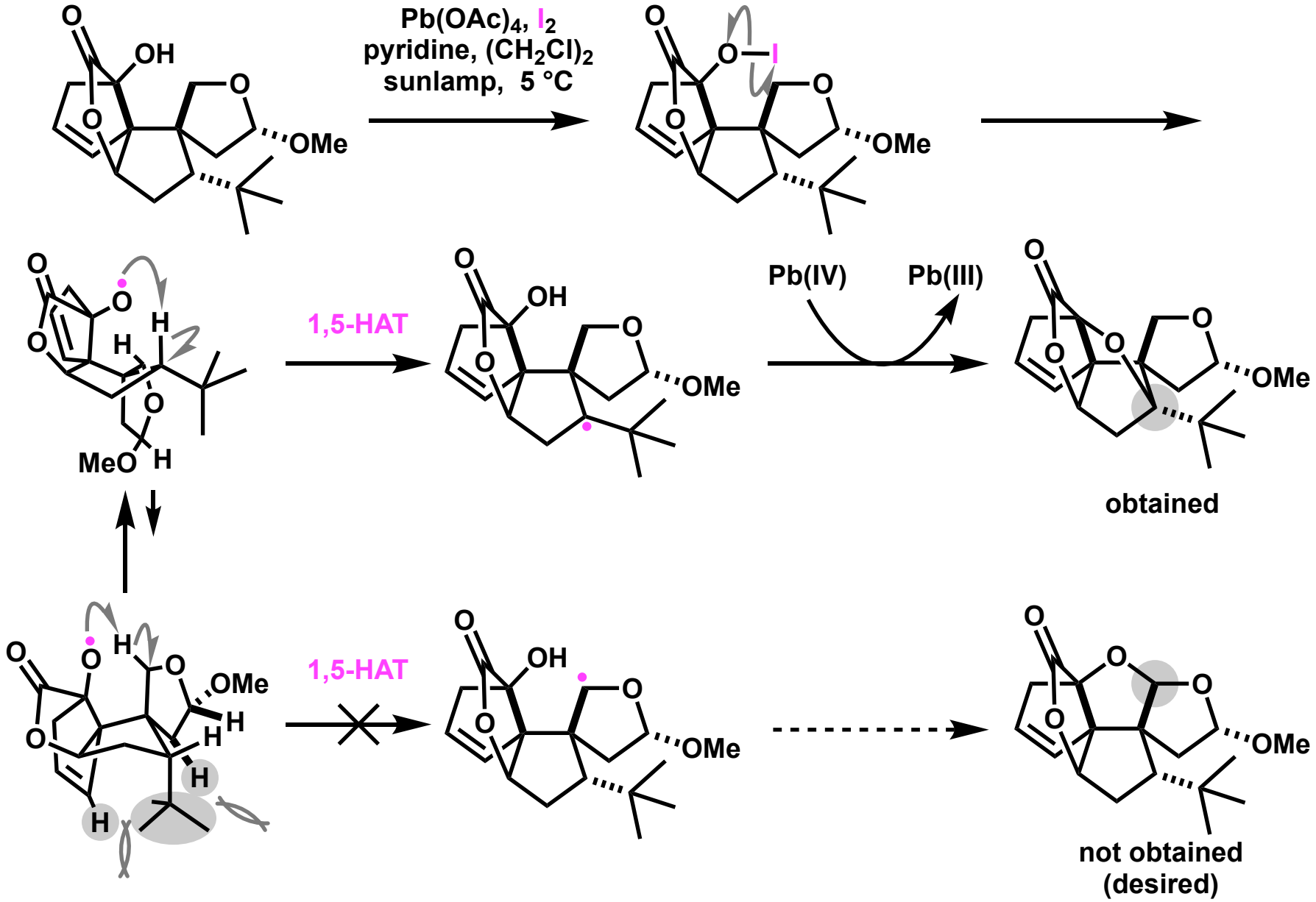
1) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110,* 649.

Attempted E-ring Formation



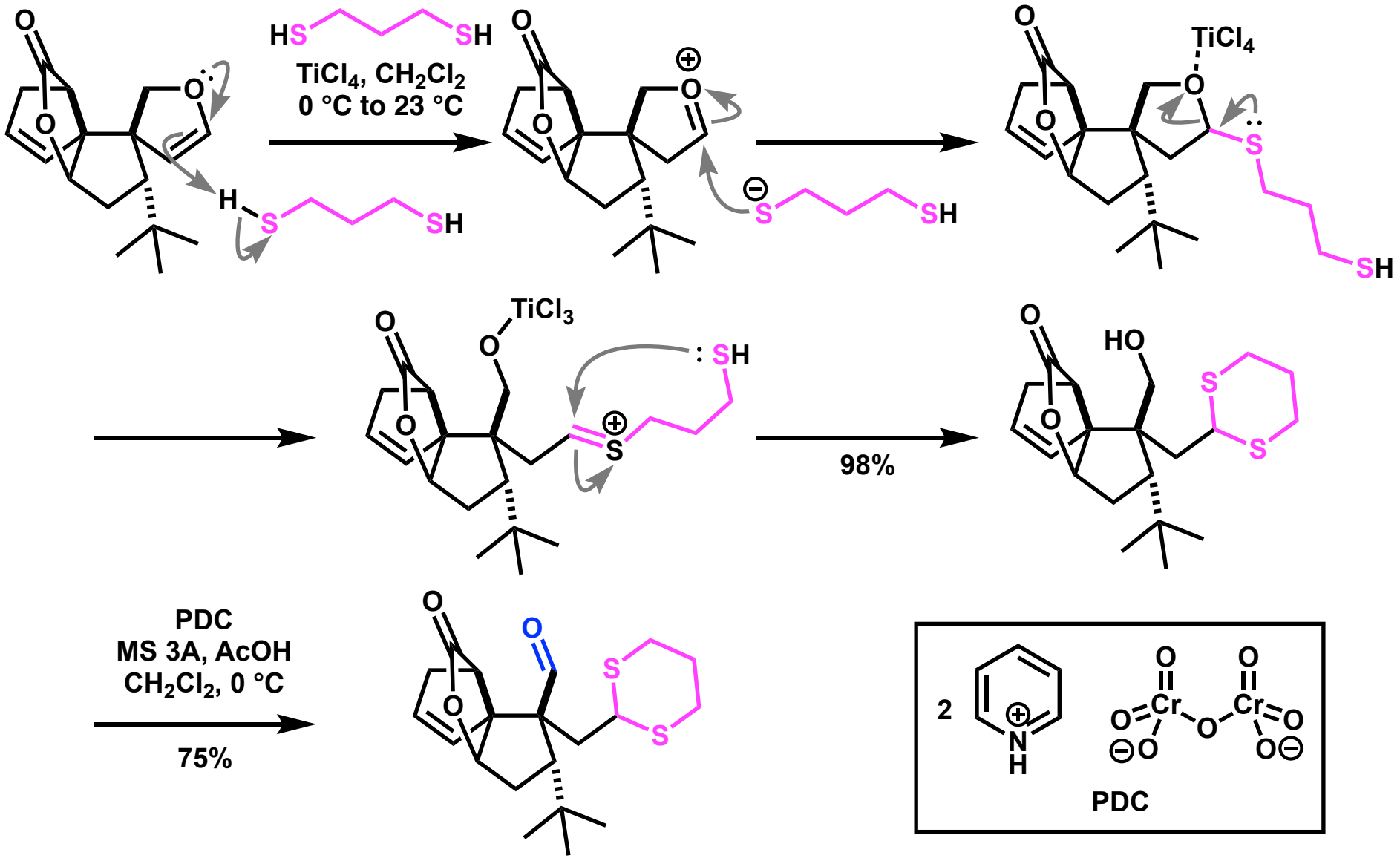
1) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110,* 649.

Rationale for Regioselectivity



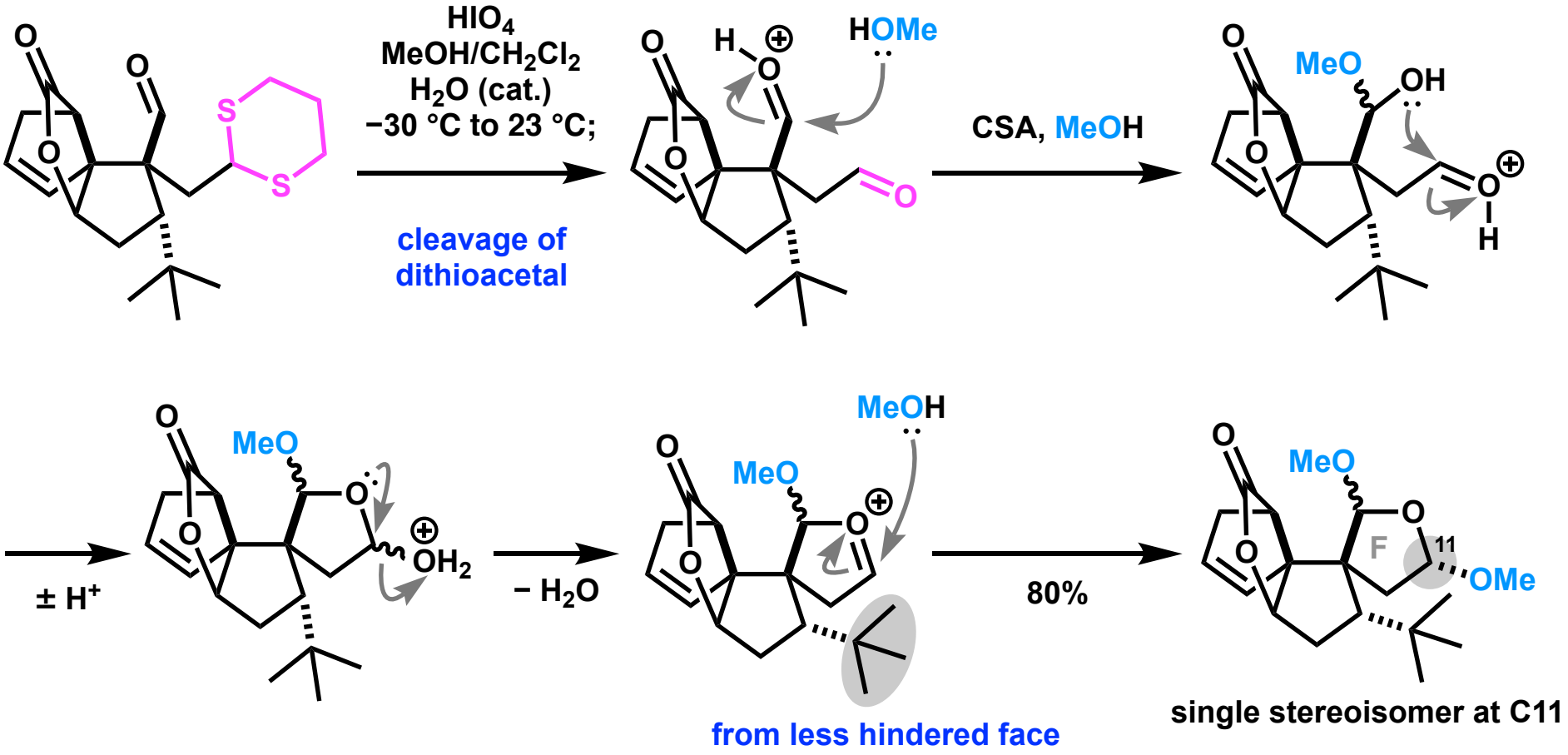
1) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110,* 649.

Alternative Route of E-ring Formation (1)



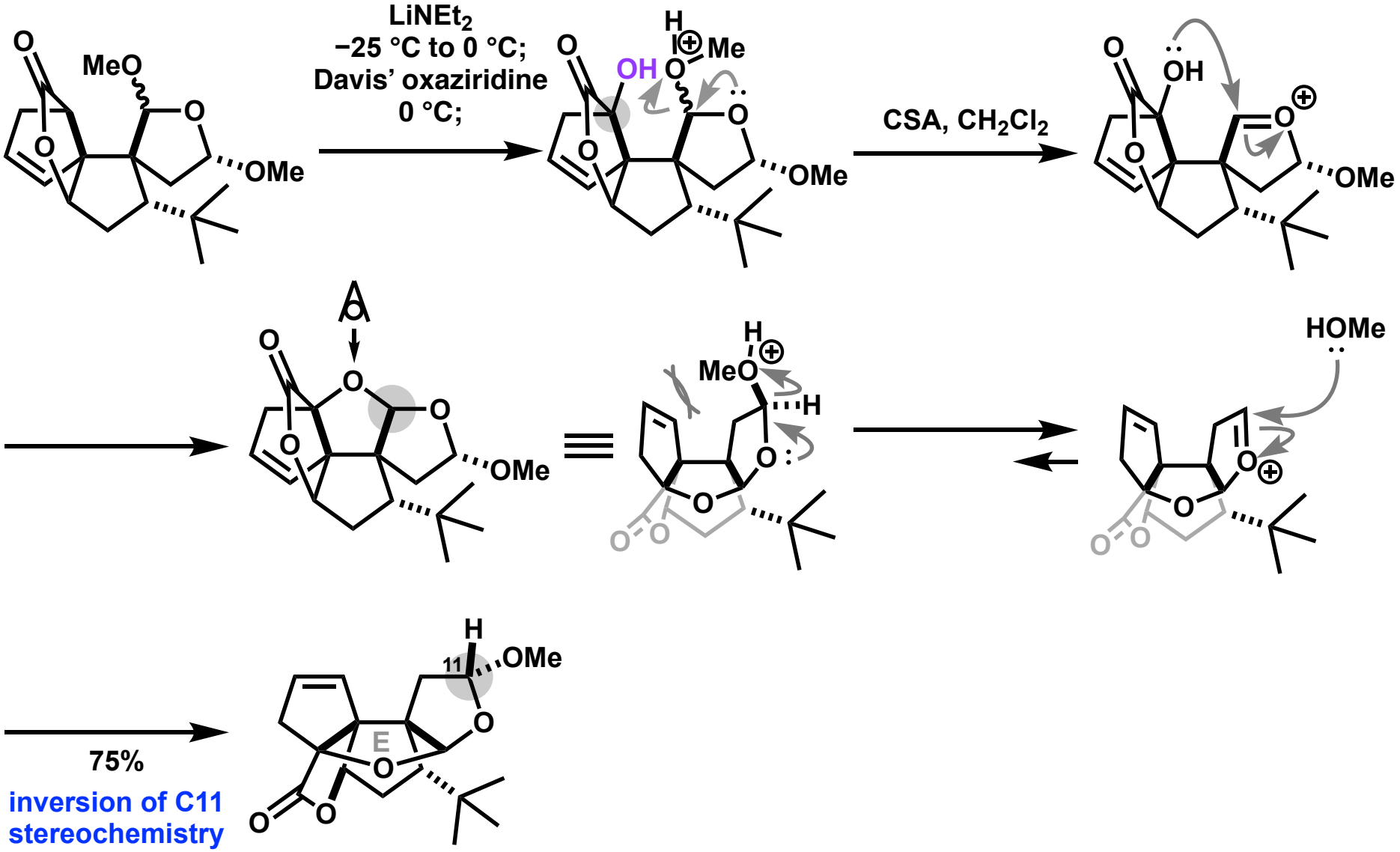
1) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110,* 649.

Alternative Route of E-ring Formation (2)



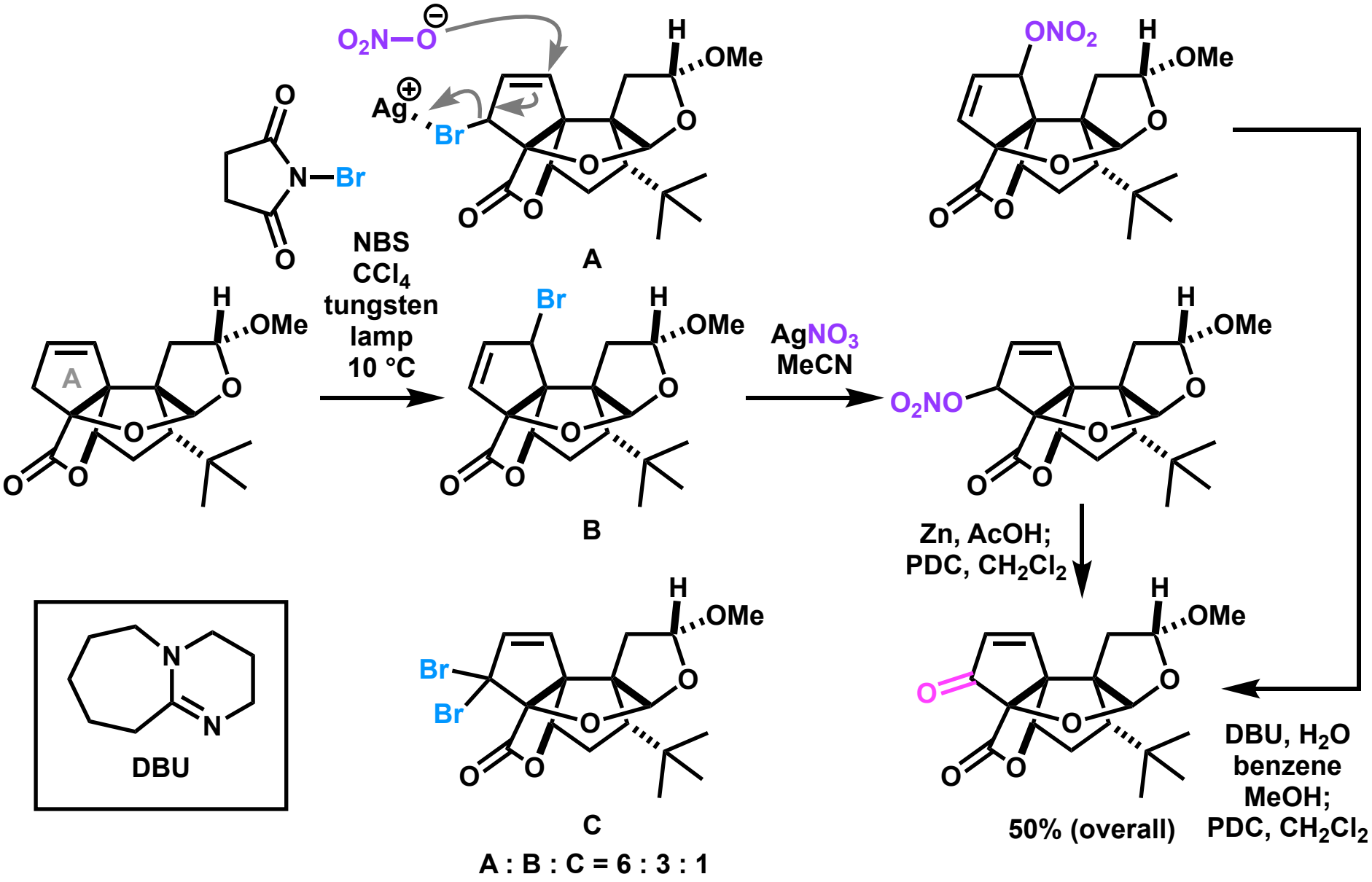
1) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110,* 649.

Alternative Route of E-ring Formation (3)



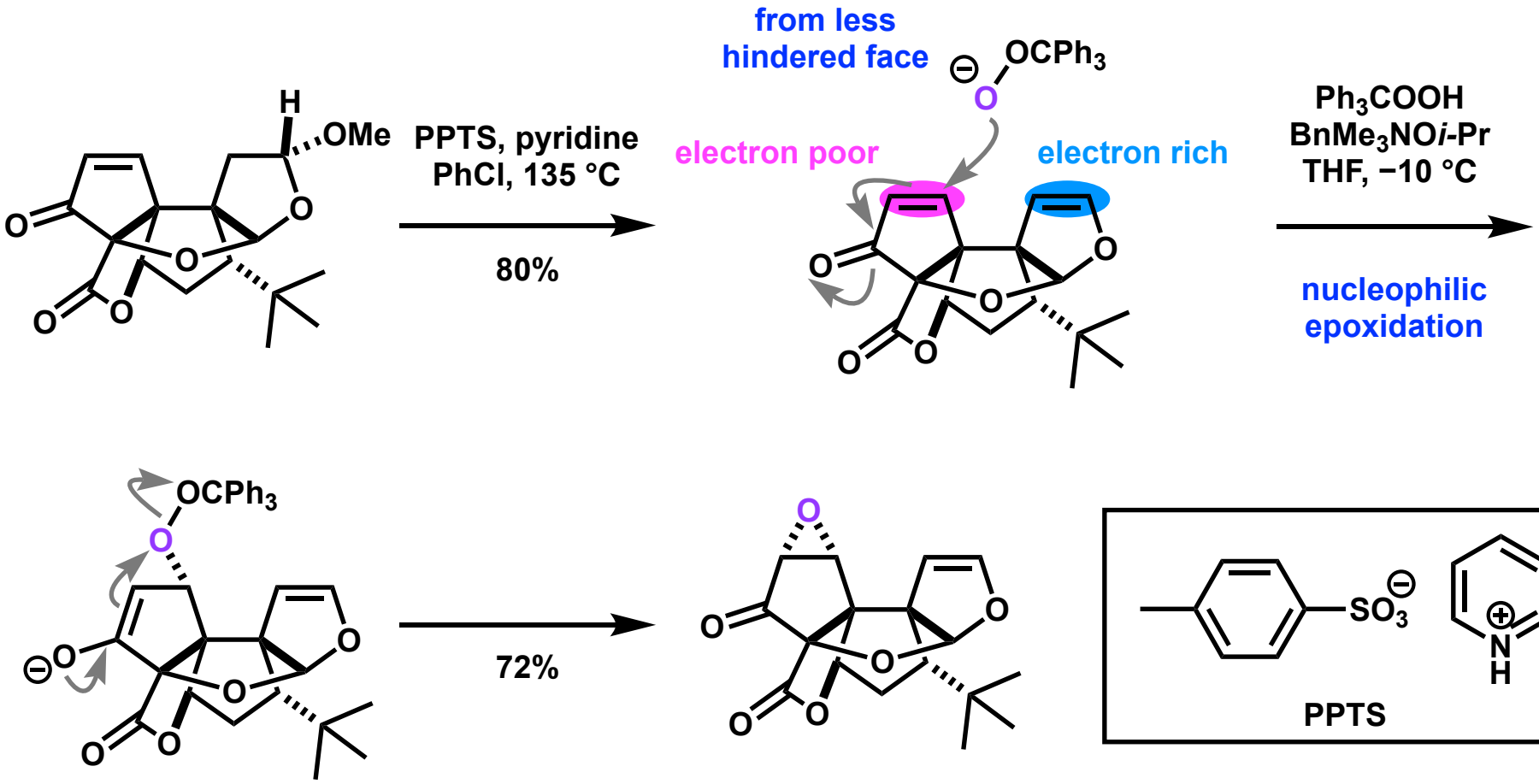
1) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110,* 649.

Enone Formation of A-ring



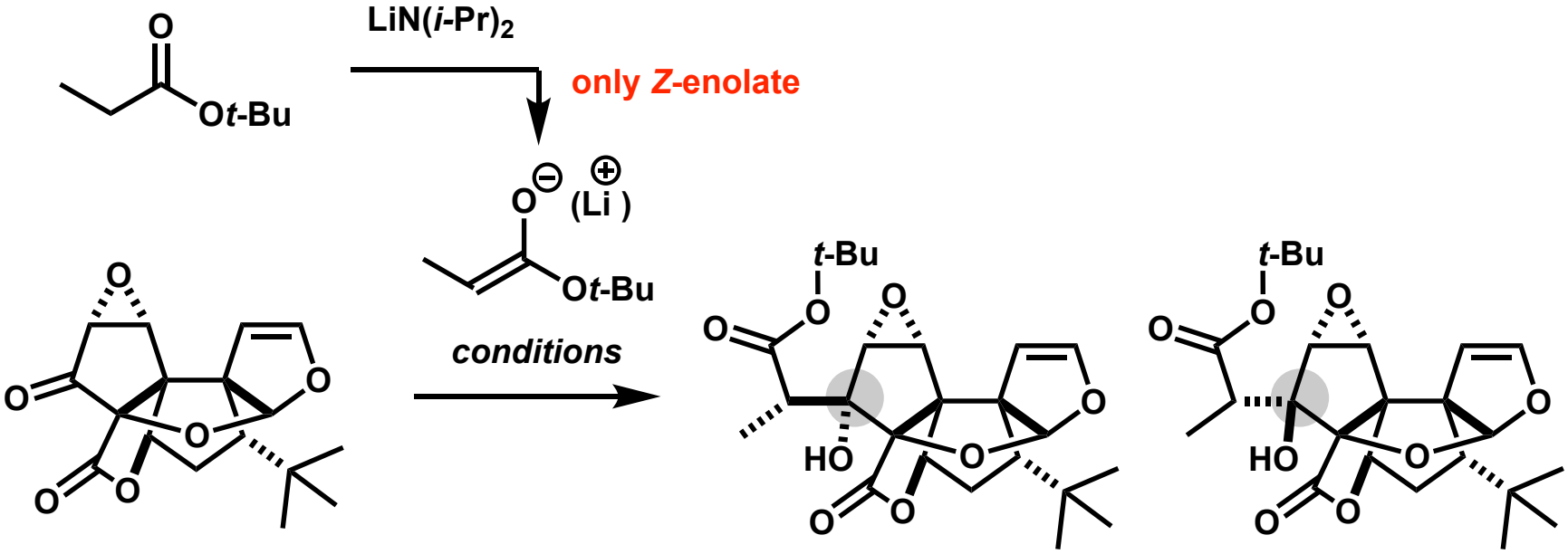
1) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110,* 649.

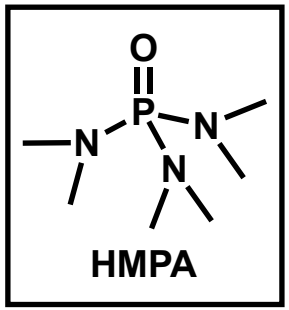
Stereoselective Aldol Reaction (1)



1) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110,* 649.

Stereoselective Aldol Reaction (2)



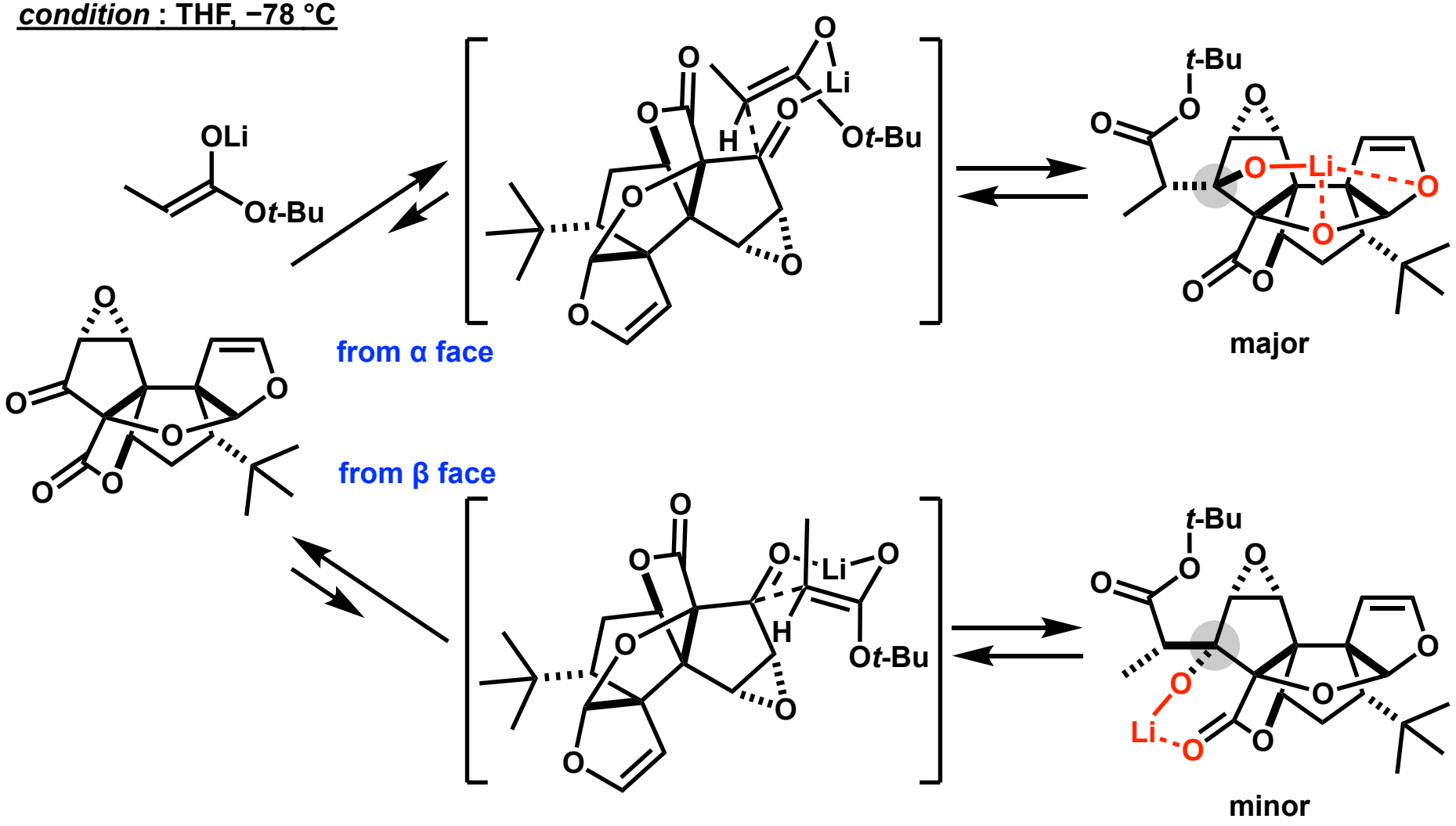


conditions	desired	undesired
THF −78 °C	minor	major
THF/HMPA = 4/1 −78 °C to −30 °C	**60%**	**calc. 7%**

1) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110,* 649.

Stereoselective Aldol Reaction (3)

condition **: THF, −78 °C**

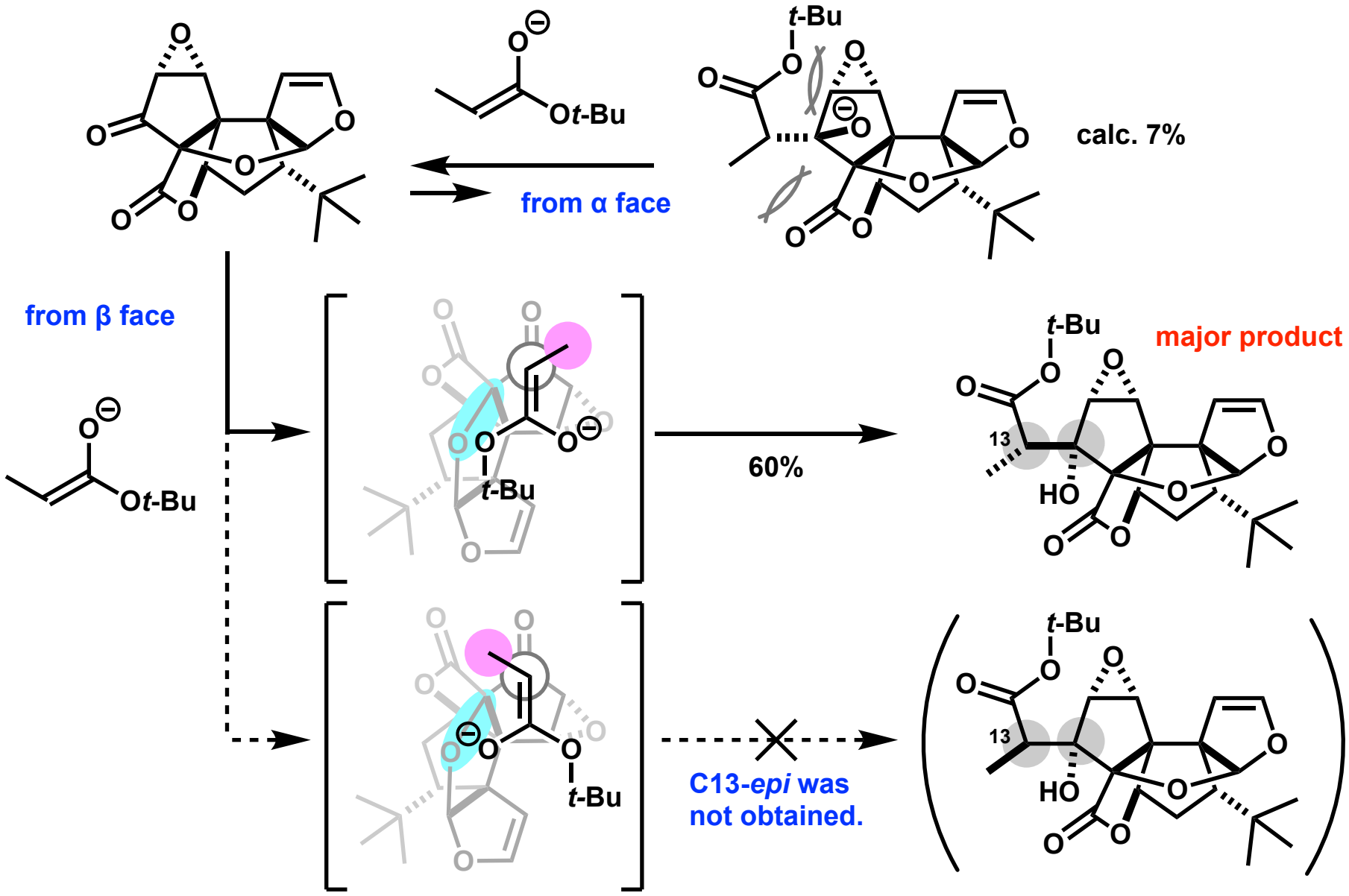


The number of oxygen atoms which can coordinate with Li^+ is different.

1) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110,* 649.

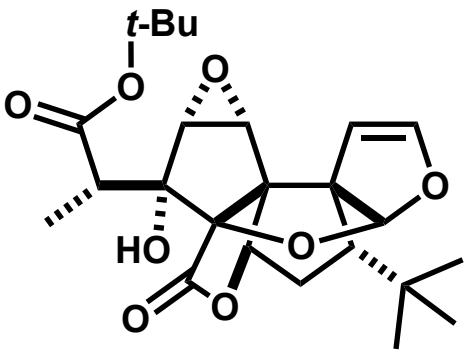
Stereoselective Aldol reaction (4)

condition **: THF/HMPA = 4/1, −78 °C to −30 °C**



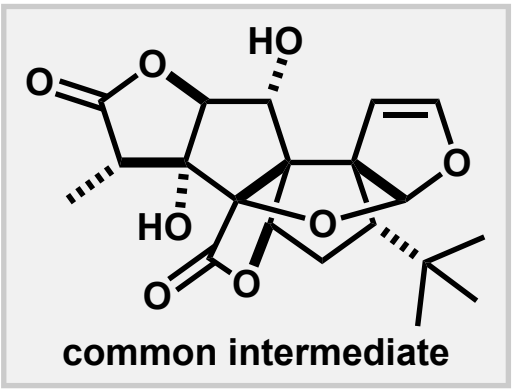
1) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110,* 649.

Stereoselective Dihydroxylation



CSA, CH_2Cl_2

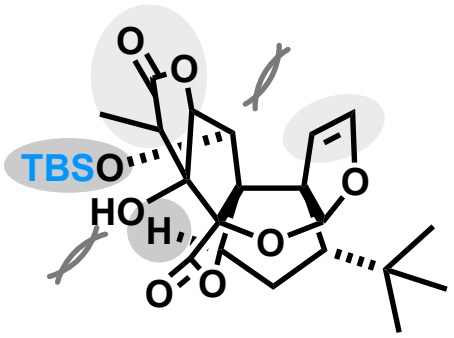
82%



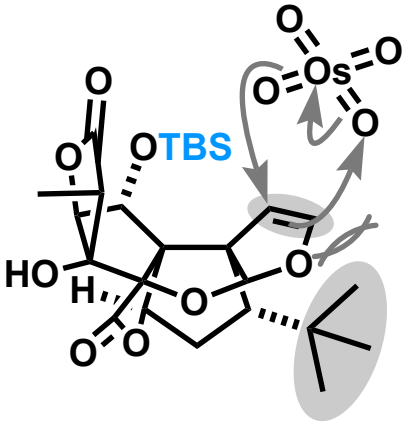
common intermediate

TBSOTf
2,6-lutidine
MeCN

89%

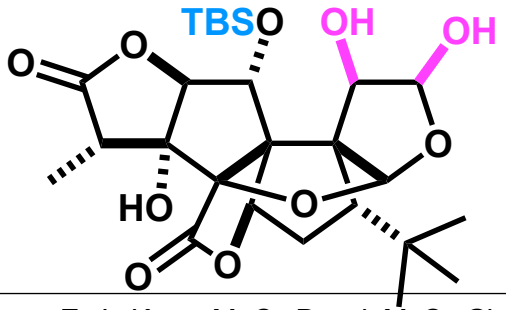


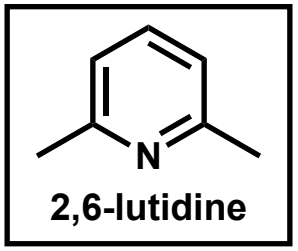
larger steric repulsion



OsO_4, pyridine;

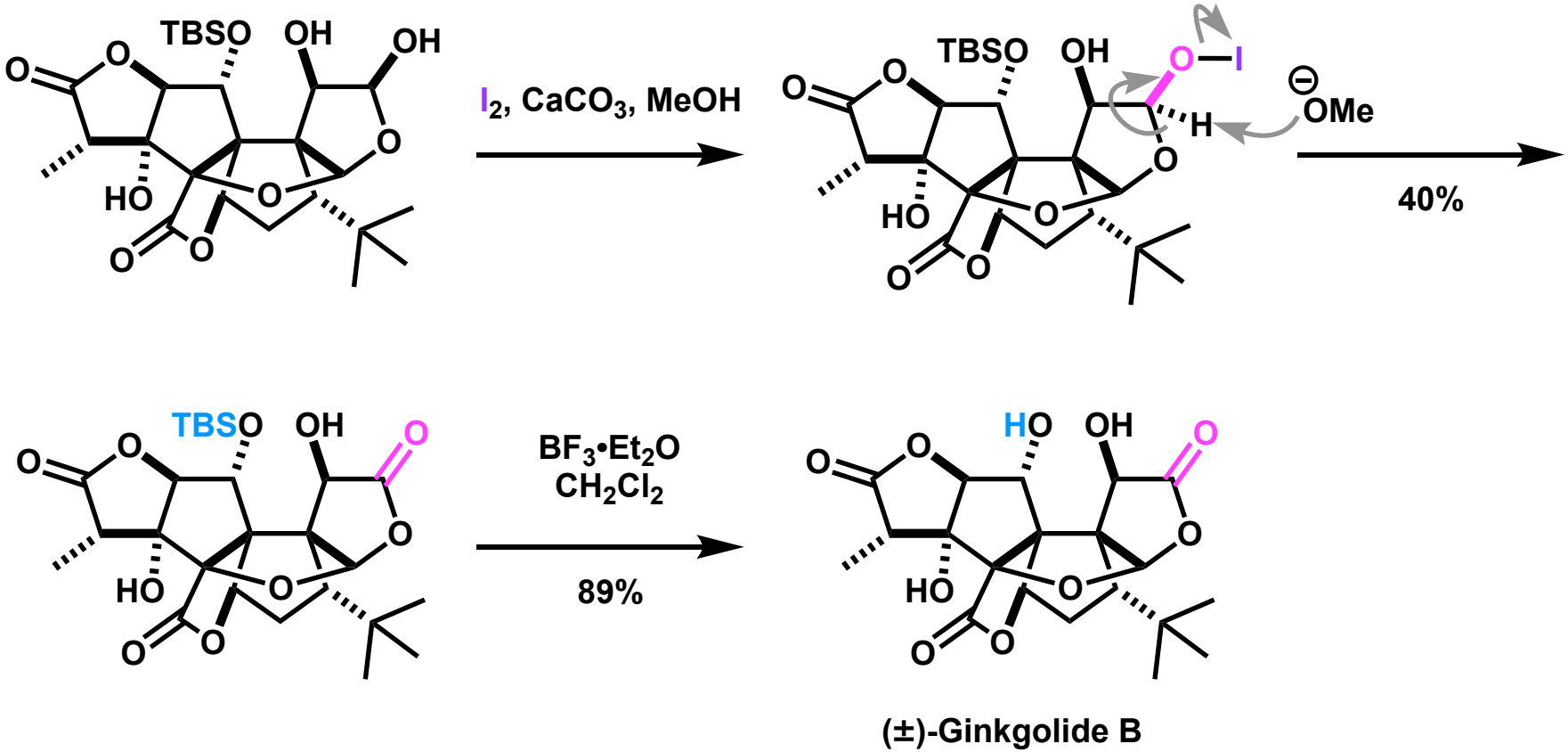
OsO_4 reacts from less hindered β face





1) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110,* 649.

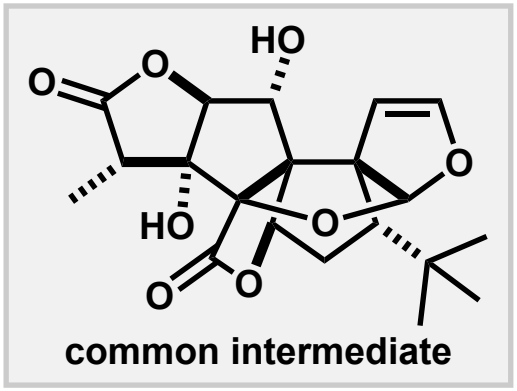
Total synthesis of Ginkgolide B



(±)-Ginkgolide B

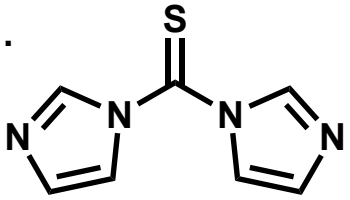
1) Corey, E. J.; Kang, M.-C.; Desai, M. C.; Ghosh, A. K.; Houpis, I. N. *J. Am. Chem. Soc.* **1988**, *110,* 649.

Total synthesis of Ginkgolide A (1)



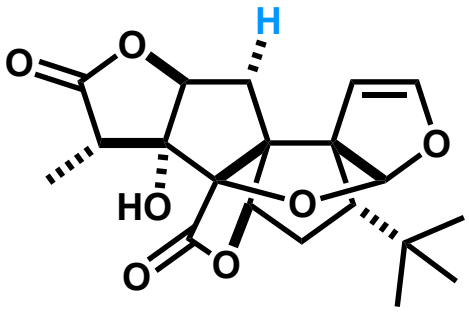
common intermediate

1.

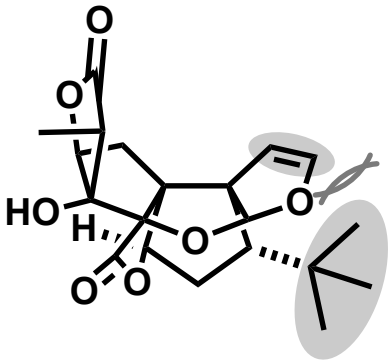


toluene, pyridine
45 °C, 84%

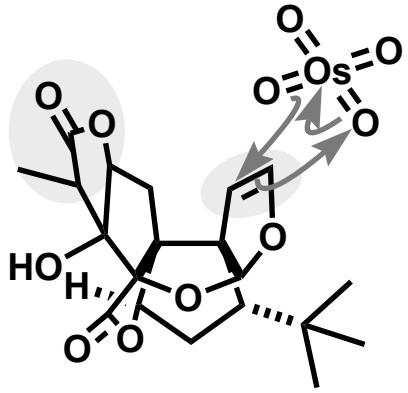
2. *n*-Bu_3SnH, dioxane
reflux, 90%



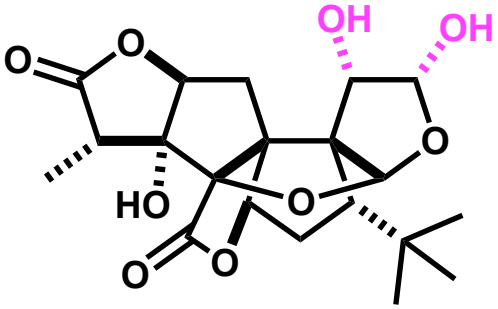
OsO_4
pyridine, 60 °C;



larger steric repulsion

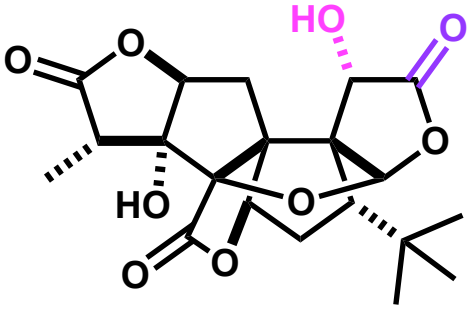


OsO_4 reacts from
less hindered α face



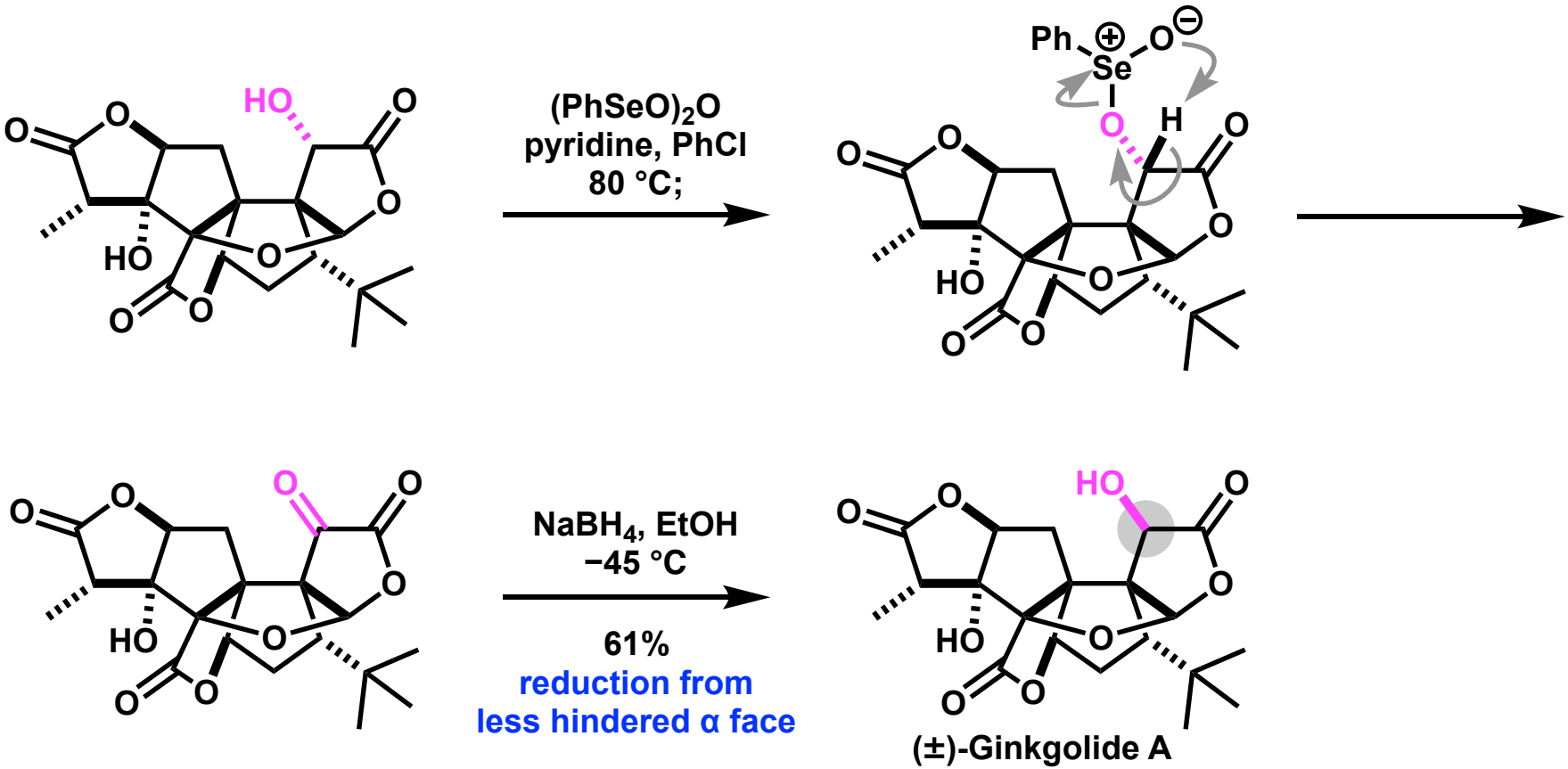
I_2, $CaCO_3$
MeOH, H_2O

48%



1) Corey, E. J.; Ghosh, A. K. *Tetrahedron Lett.* **1988**, *29*, 3205.

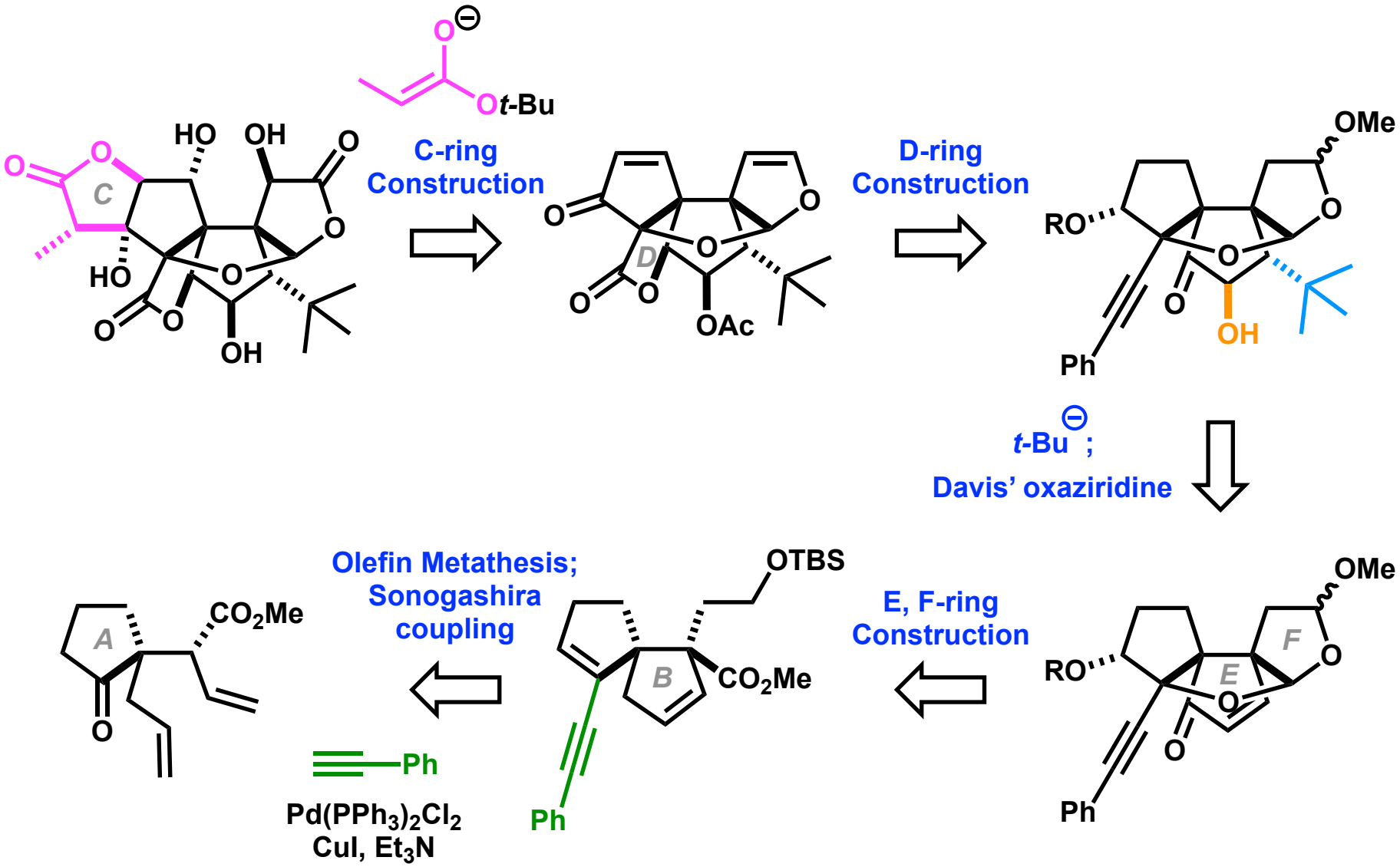
Total synthesis of Ginkgolide A (2)



1) Corey, E. J.; Ghosh, A. K. *Tetrahedron Lett.* **1988**, *29*, 3205.

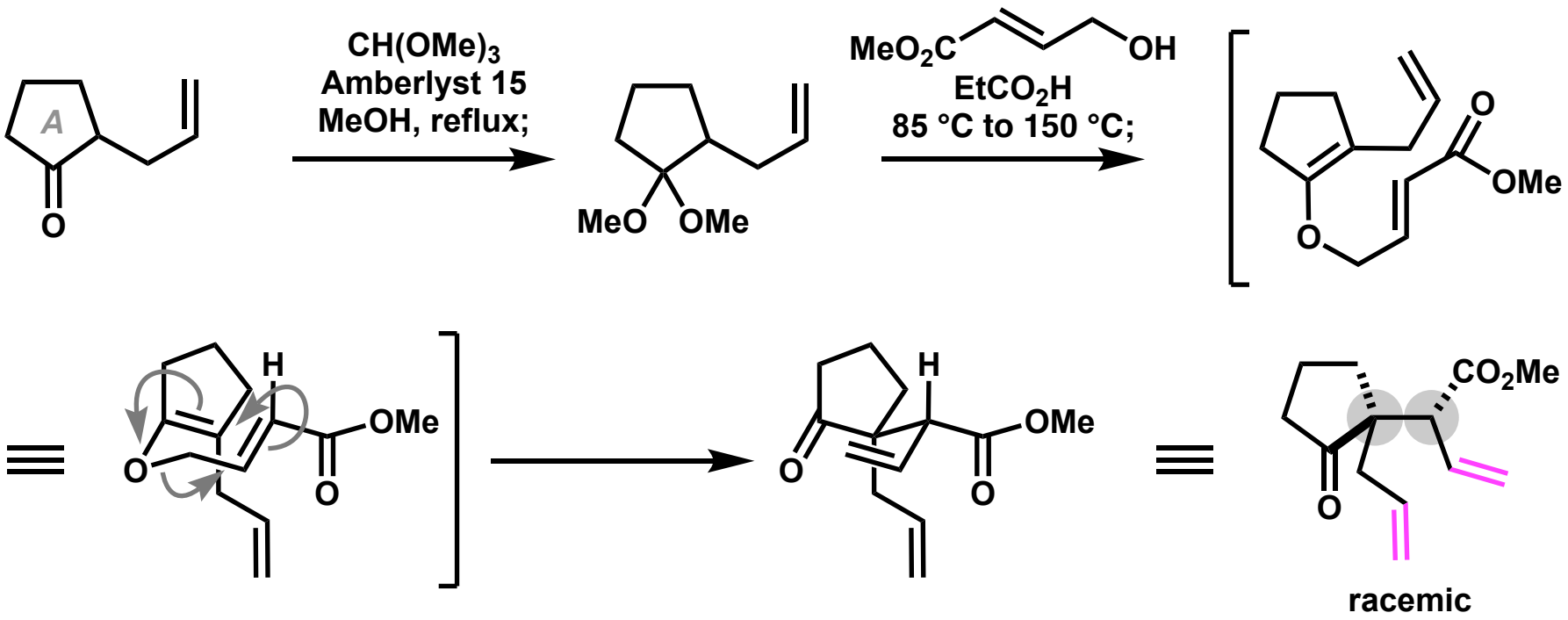
Contents

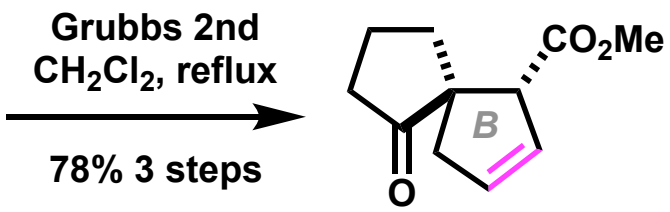
Retrosynthetic Analysis of Ginkgolide C

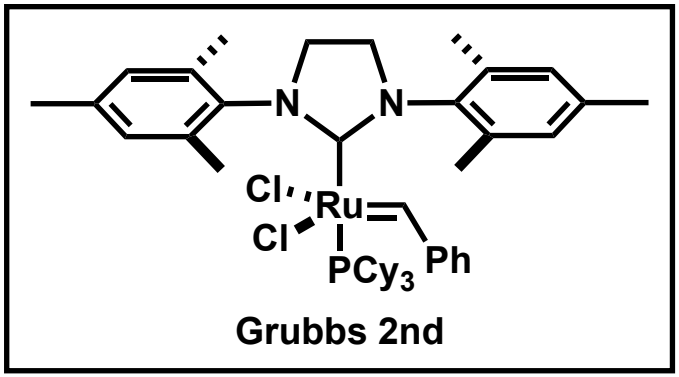


1) Hebert, M.; Bellavance, G.; Barriault, L. *J. Am. Chem. Soc.* **2022**, *144*, 17792.

Claisen Rearrangement and B-ring Construction

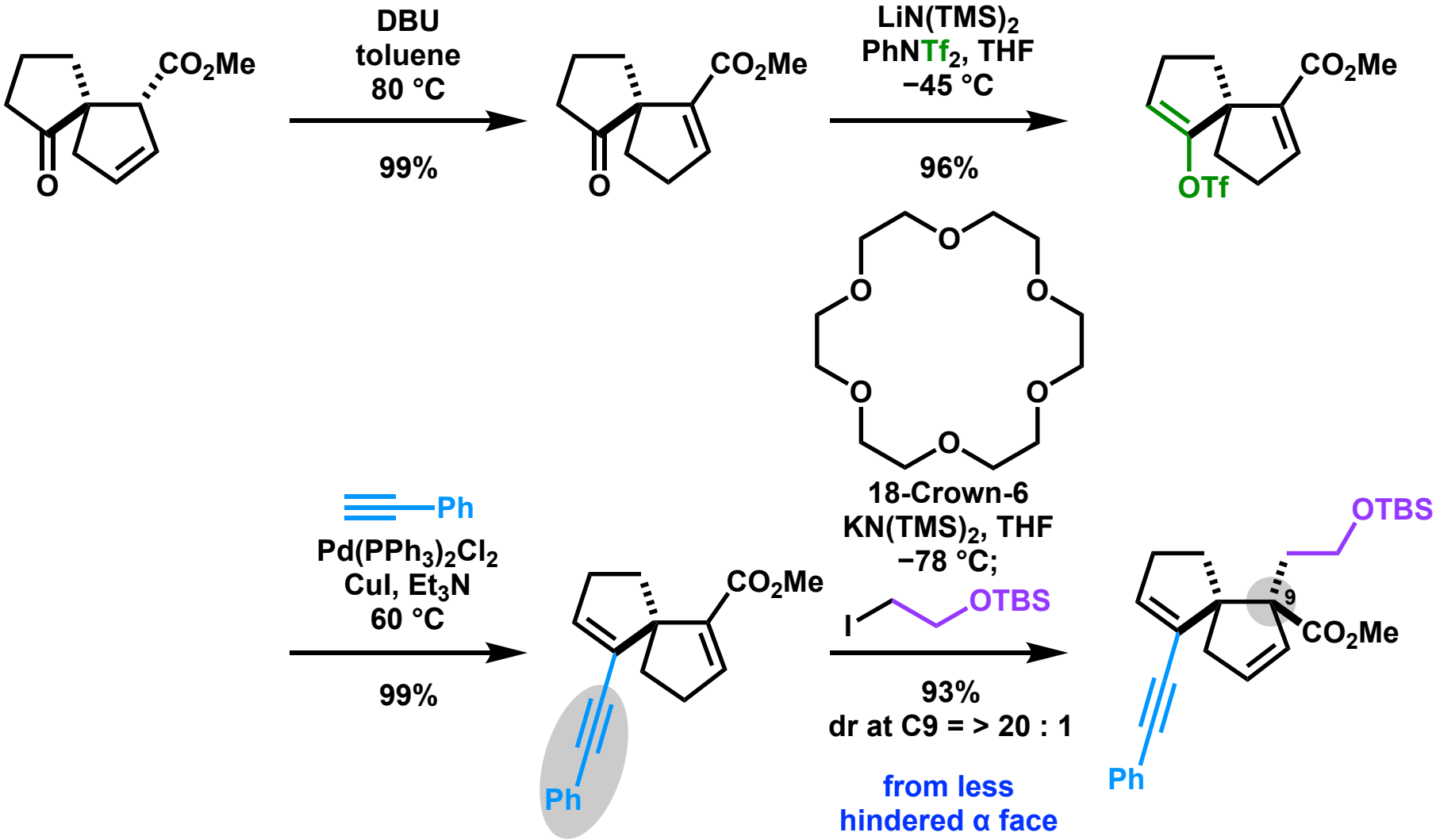






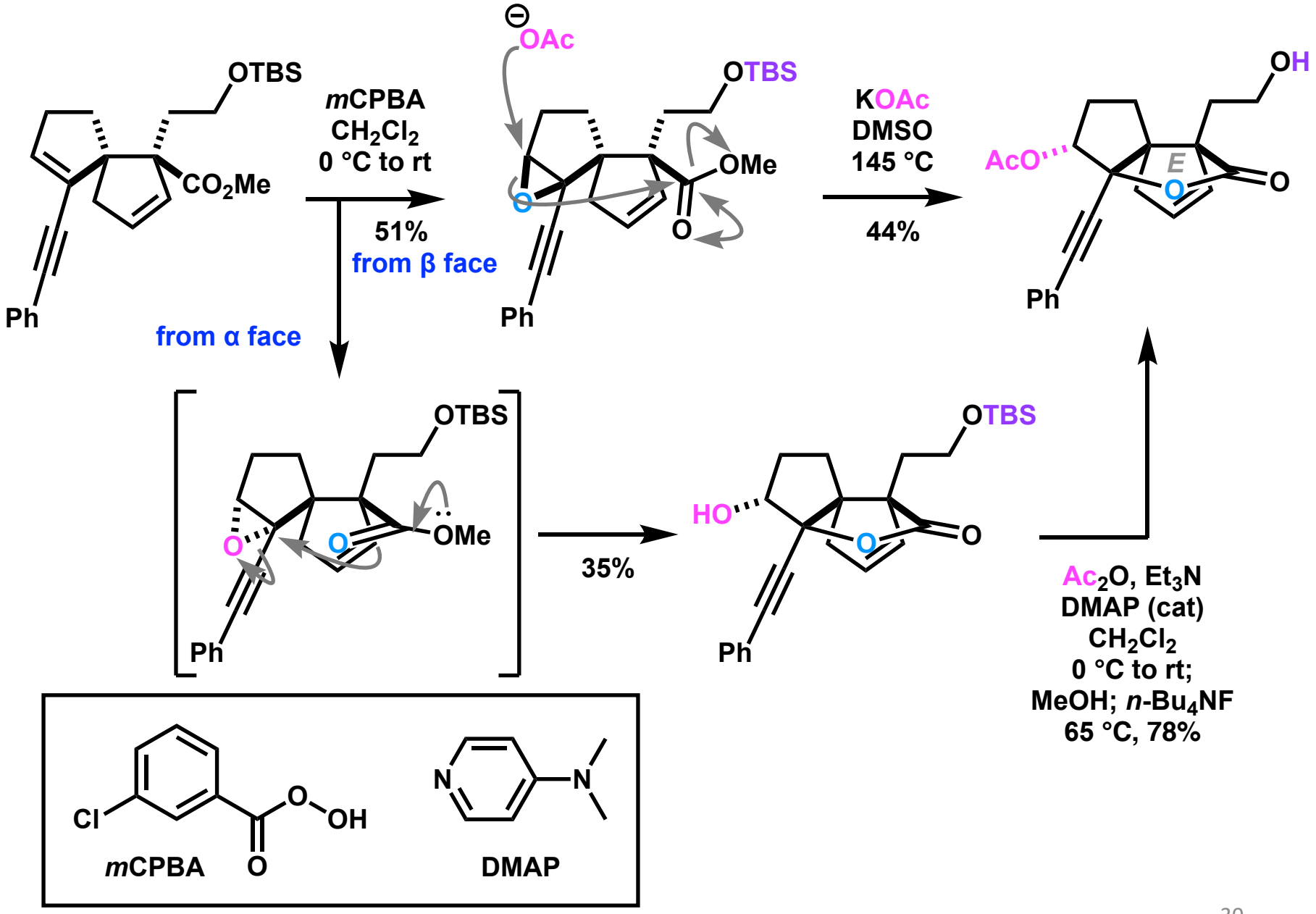
1) Hebert, M.; Bellavance, G.; Barriault, L. *J. Am. Chem. Soc.* **2022**, *144*, 17792.

E-ring Construction (1)



1) Hebert, M.; Bellavance, G.; Barriault, L. *J. Am. Chem. Soc.* **2022**, *144*, 17792.

E-ring Construction (2)



1) Hebert, M.; Bellavance, G.; Barriault, L. *J. Am. Chem. Soc.* **2022**, *144*, 17792.

F-ring Construction under Acidic Condition

1. Dess-Martin periodinane
   CH_2Cl_2, 0 °C to rt;
   $CH(OMe)_3$, Amberlyst 15
   CH_2Cl_2/MeOH, 65 °C, 75%
2. DIBAL-H, THF
   −78 °C to 0 °C
   90%, dr at C10 = 5 :1

anhydrous HCl
THF, 0 °C to rt;

too far

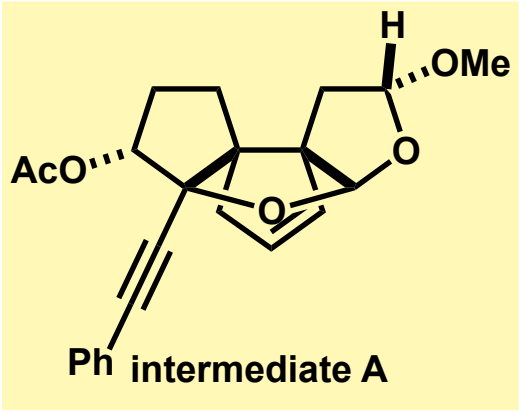
Ac_2O, Et_3N
DMAP (cat)
THF
0 °C to rt, 96%

intermediate A : X = H, Y = OMe (37%)
intermediate B : X = OMe, Y = H (59%)

Dess-Martin periodinane

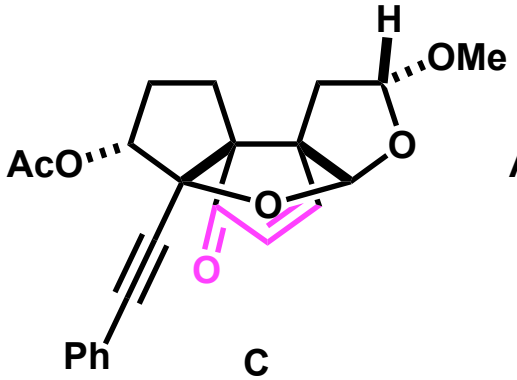
1) Hebert, M.; Bellavance, G.; Barriault, L. *J. Am. Chem. Soc.* **2022**, *144*, 17792.

Introduction of *t*-Bu Group

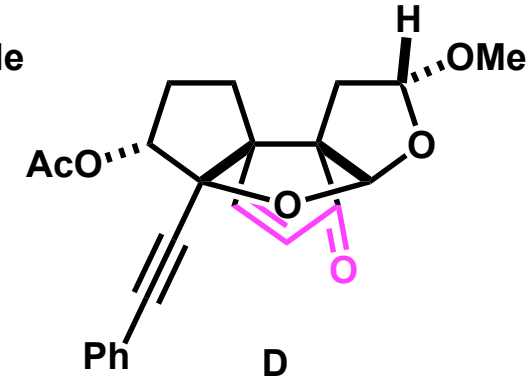


SeO_2, dioxane
110 °C;
Dess-Martin
periodinane
dioxane/CH_2Cl_2
60 °C

78%



C

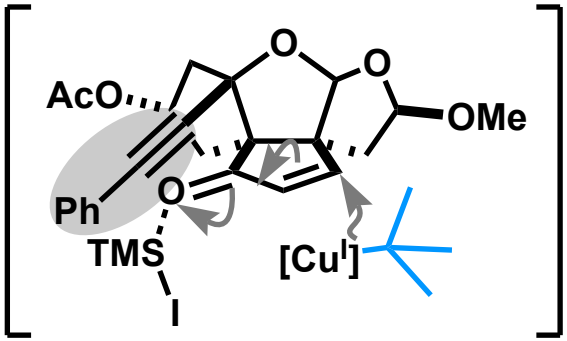


D

C : D = 6.4 : 1

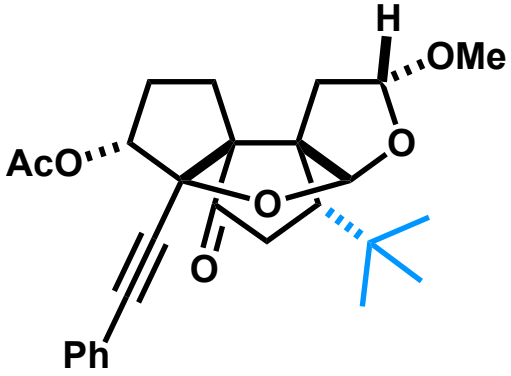
t-BuLi, CuCN
THF
−78 °C to −45 °C;
C, −78 °C;
TMSI, −78 °C;

from less hindered α face



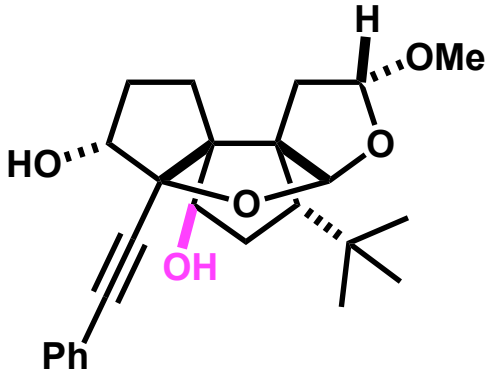
n-Bu_4NF
−78 °C to rt

81%



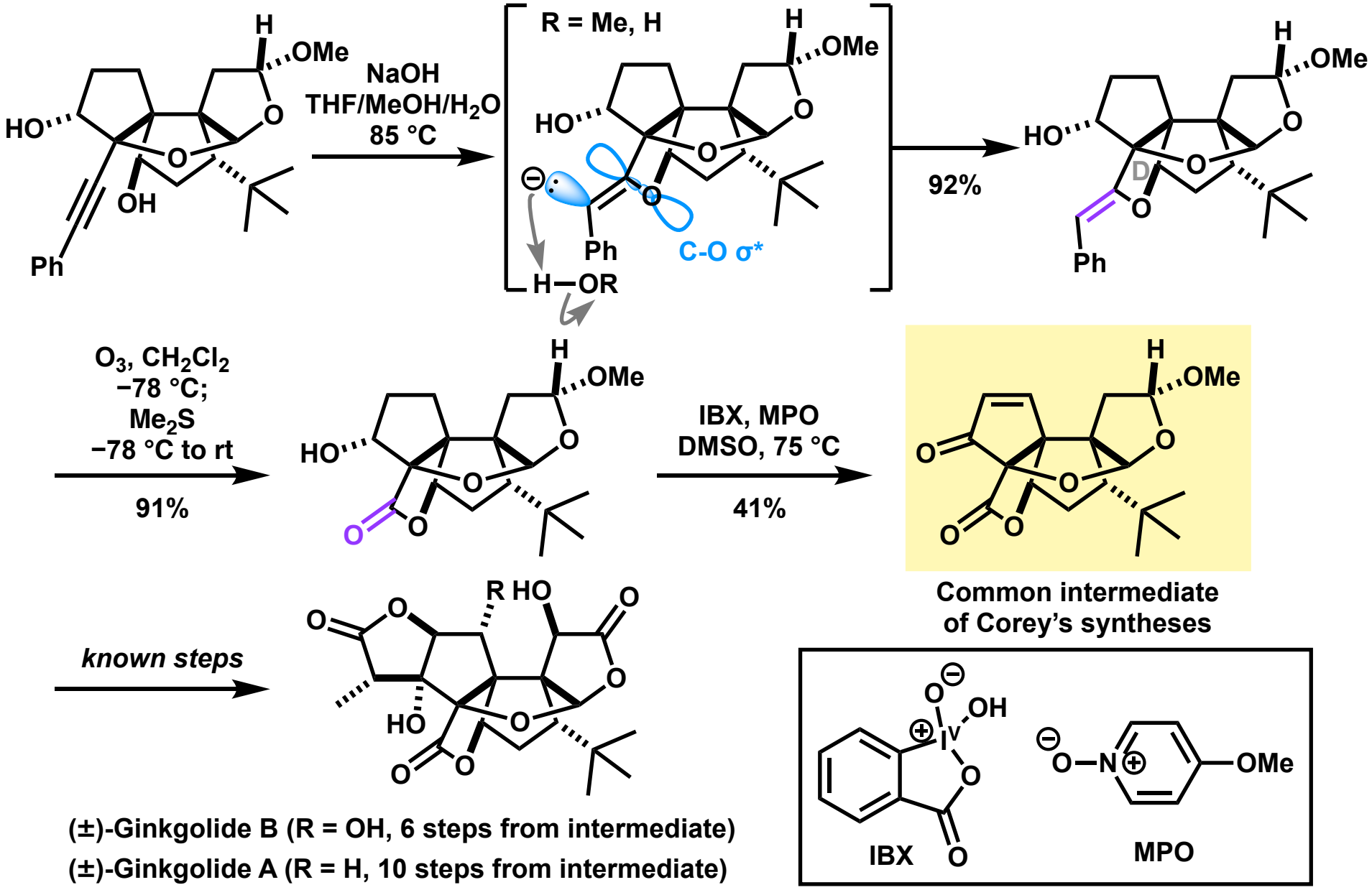
$LiBH_4$, THF
0 °C to rt;

stereoselective
reduction
deacetylation



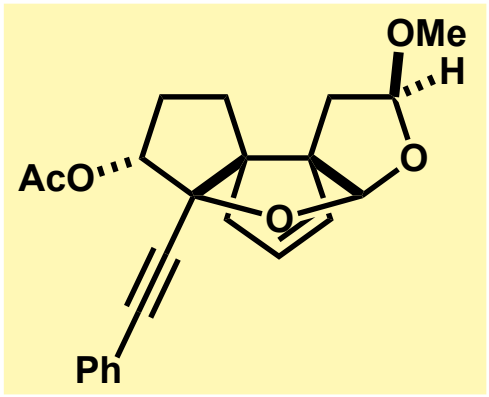
1) Hebert, M.; Bellavance, G.; Barriault, L. *J. Am. Chem. Soc.* **2022**, *144*, 17792.

Formal Synthesis of Ginkgolide A, B



1) Hebert, M.; Bellavance, G.; Barriault, L. *J. Am. Chem. Soc.* **2022**, *144*, 17792.

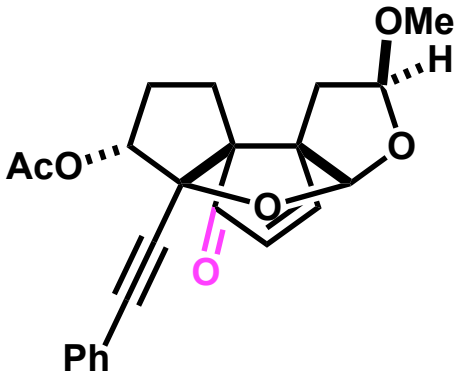
Attempted α-Hydroxylation



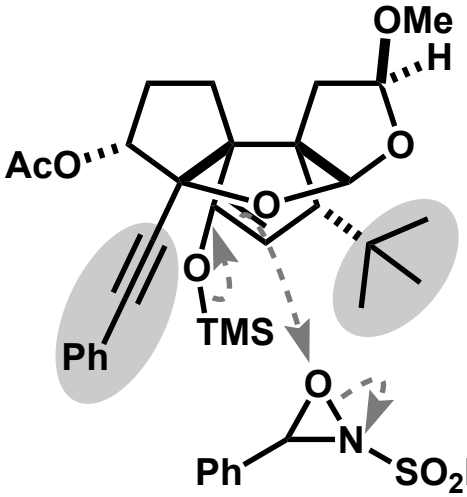
intermediate B

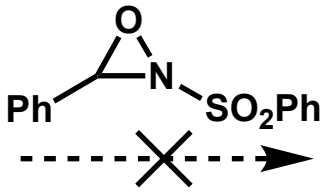
SeO_2
dioxane, 110 °C;
Dess-Martin
periodinane
dioxane/CH_2Cl_2
60 °C

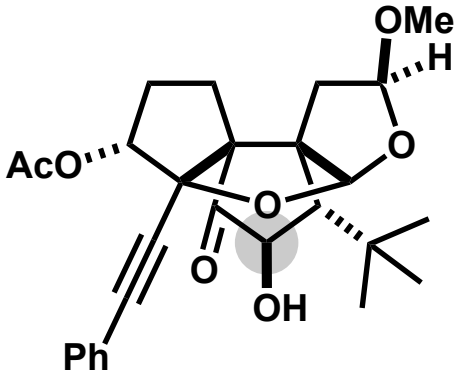
85%

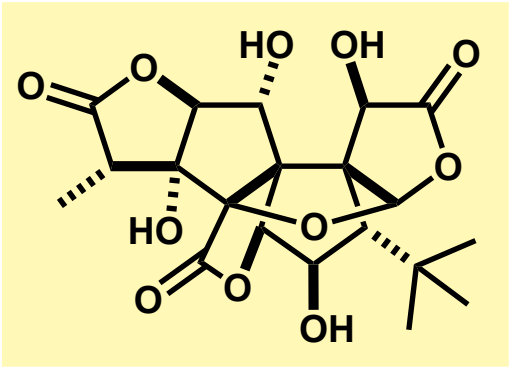


t-BuLi, CuCN;
TMSI, THF;





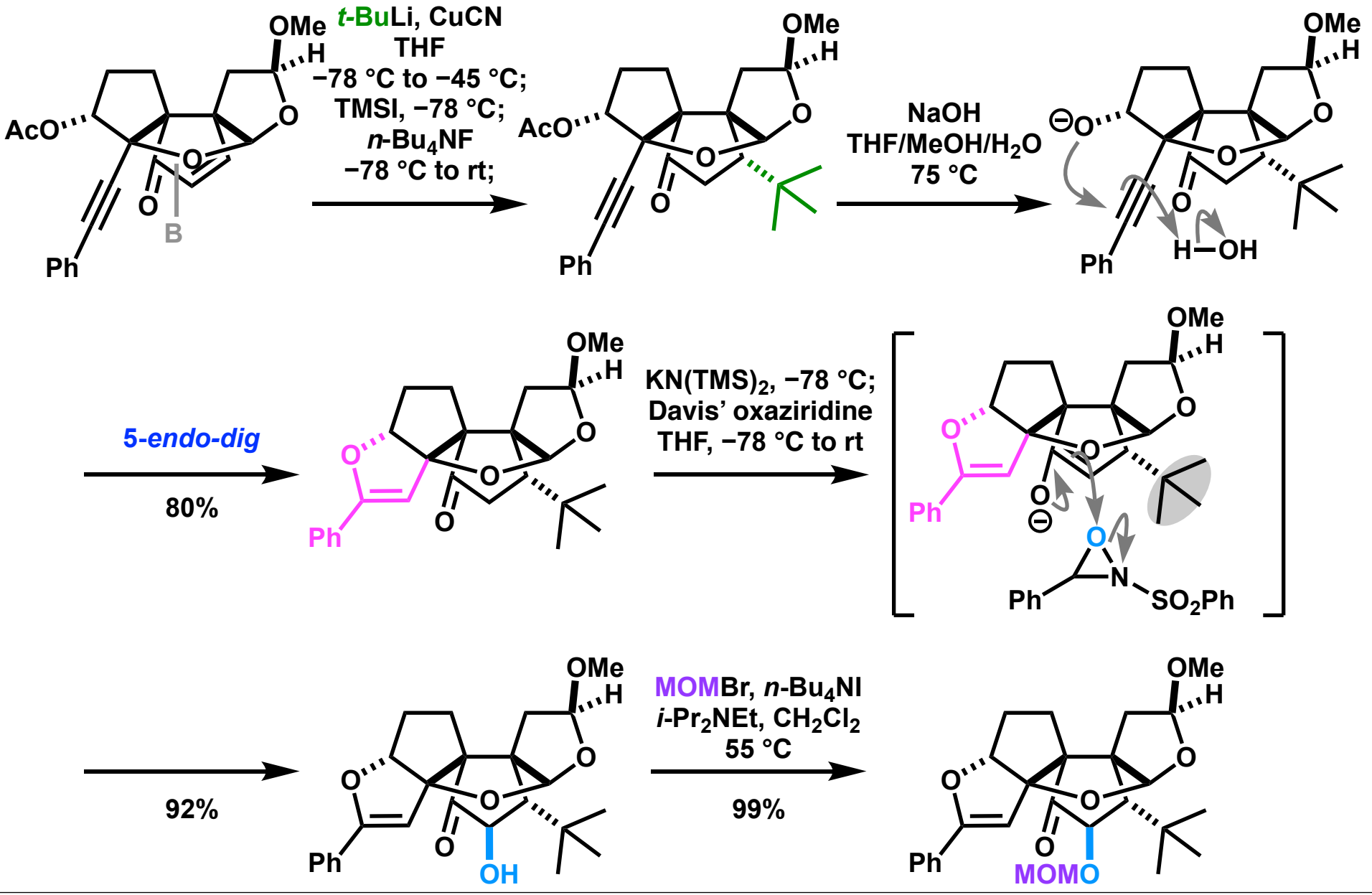




Ginkgolide C

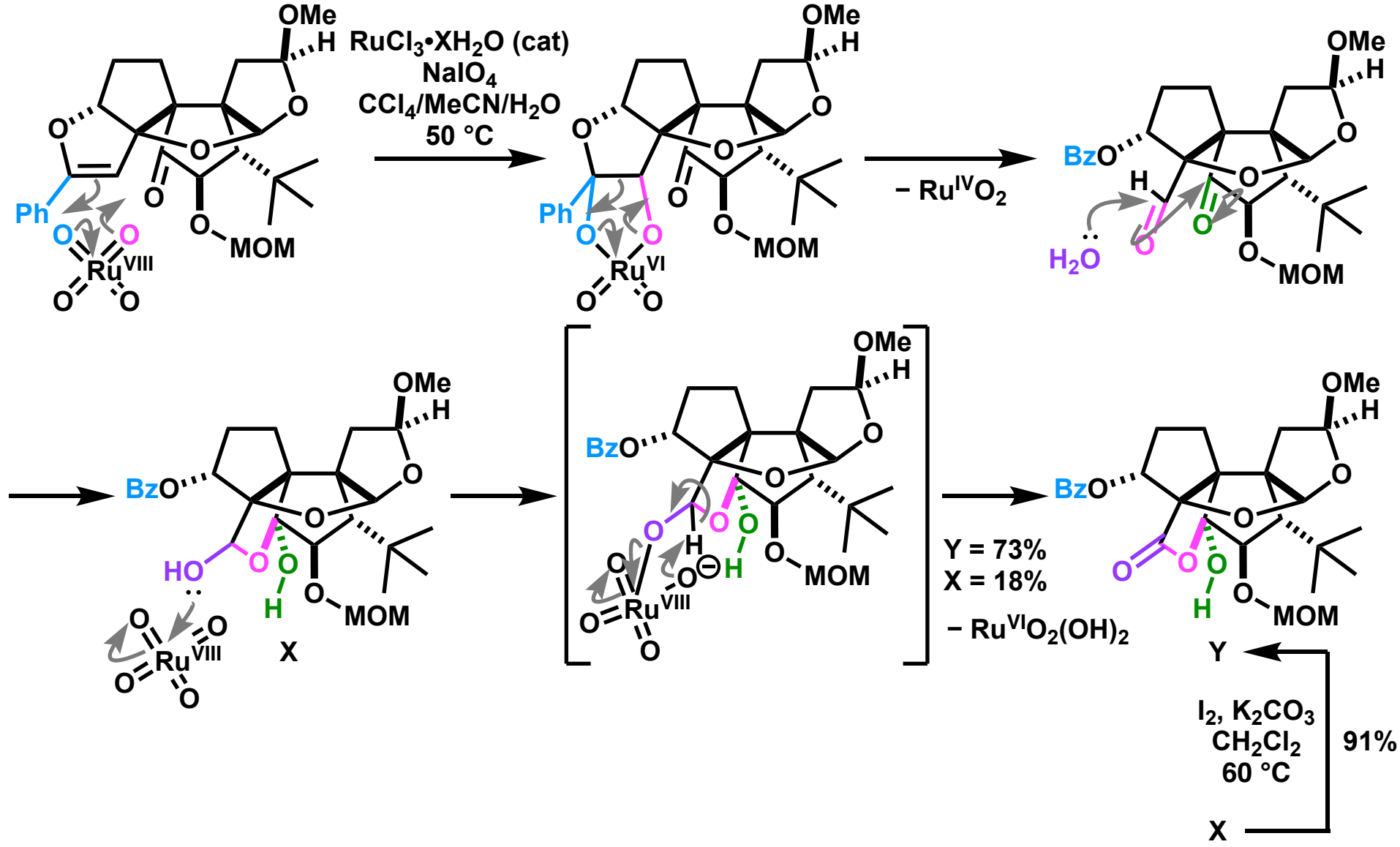
1) Hebert, M.; Bellavance, G.; Barriault, L. *J. Am. Chem. Soc.* **2022**, *144*, 17792.

Modification of Phenyl Acetylene Group



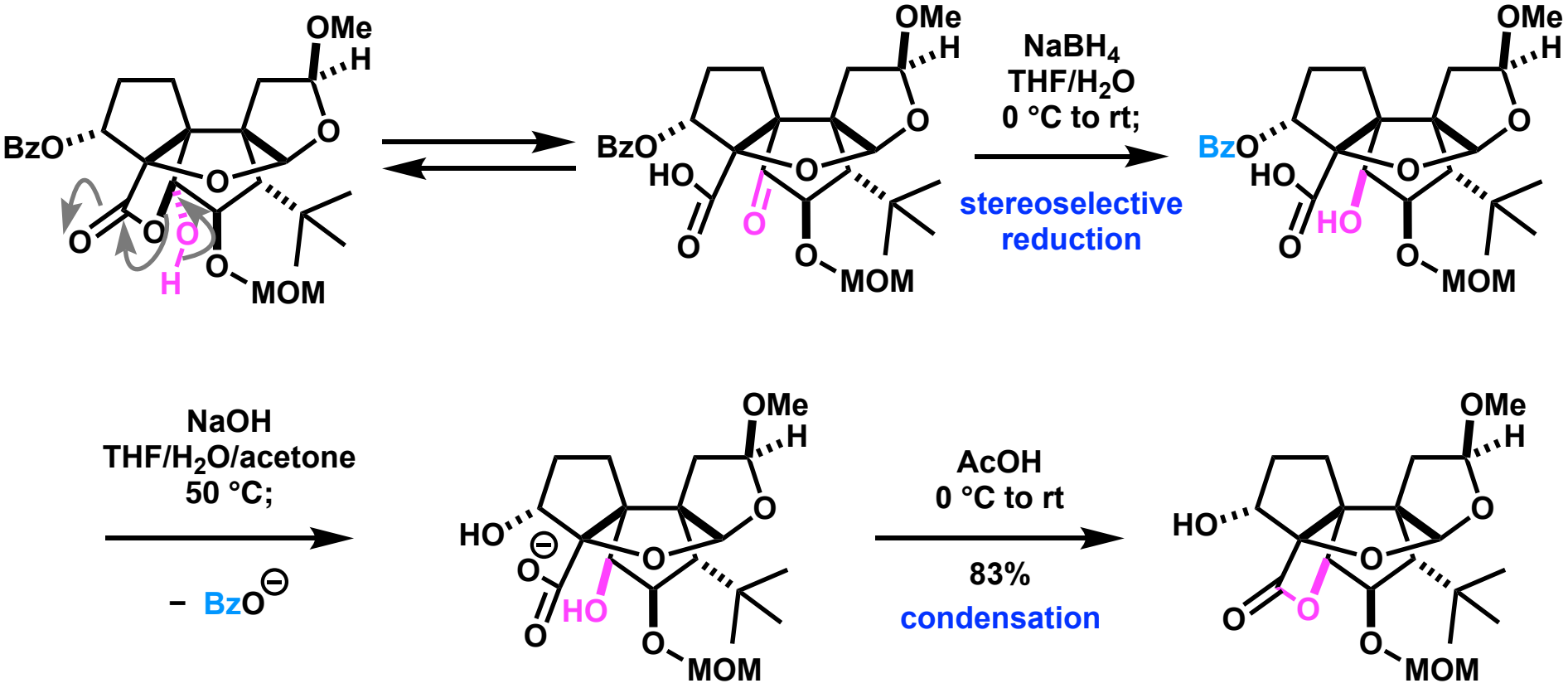
1) Hebert, M.; Bellavance, G.; Barriault, L. *J. Am. Chem. Soc.* **2022**, *144*, 17792.

Oxidative Fragmentation and D-ring Construction



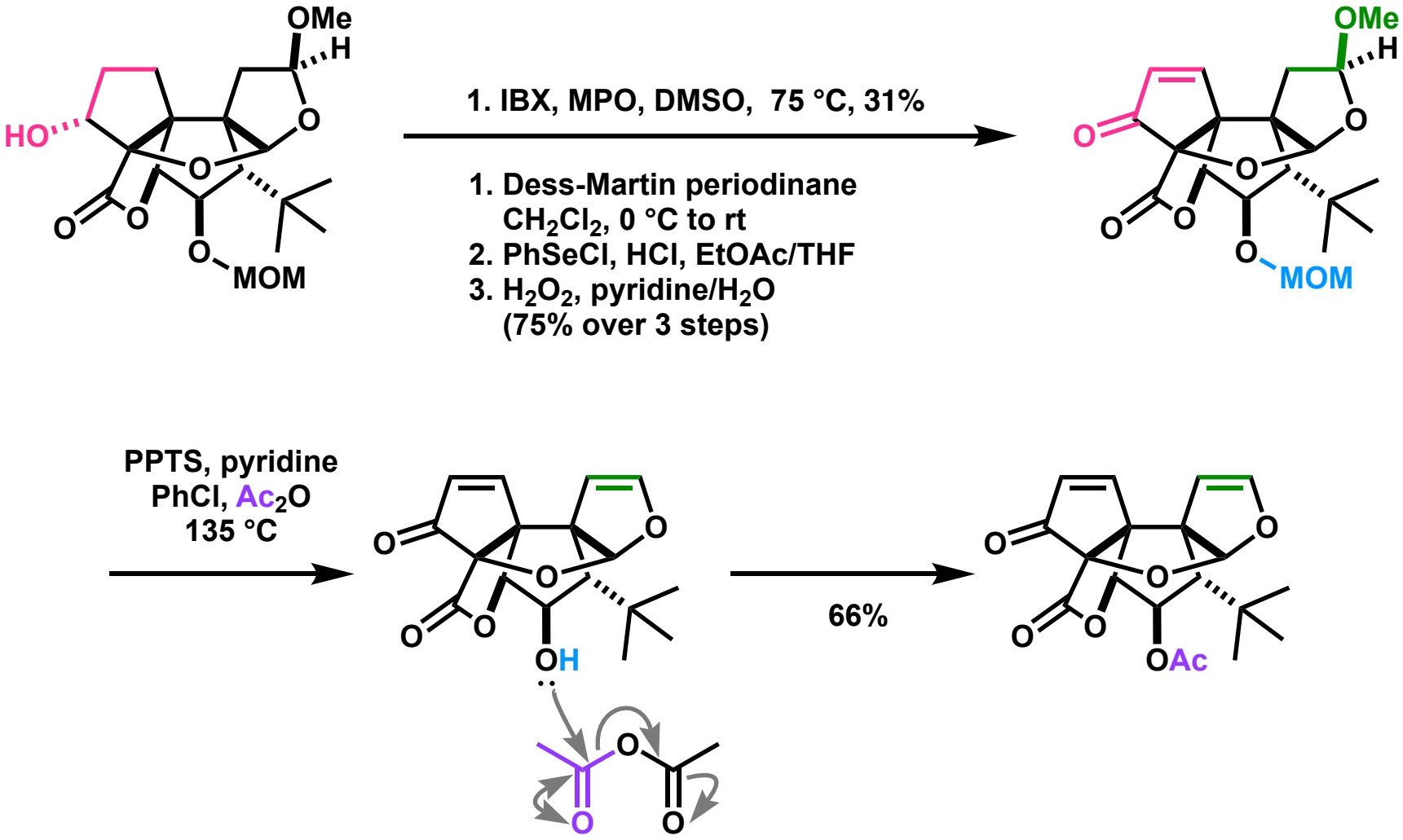
1) Hebert, M.; Bellavance, G.; Barriault, L. *J. Am. Chem. Soc.* **2022**, *144*, 17792.

Dehydroxylation



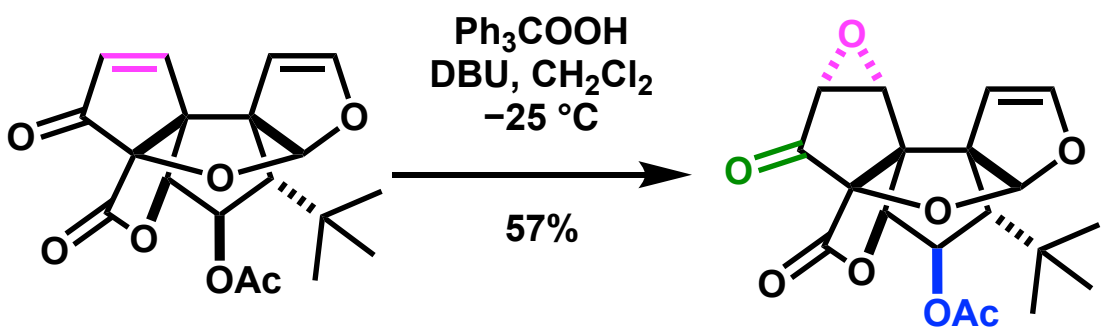
1) Hebert, M.; Bellavance, G.; Barriault, L. *J. Am. Chem. Soc.* **2022**, *144*, 17792.

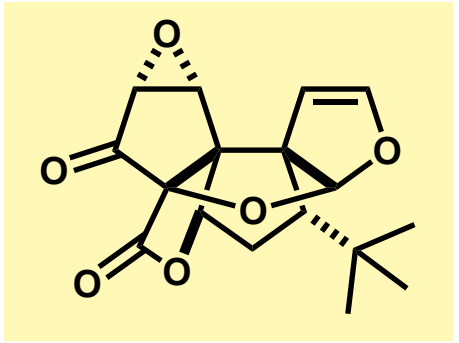
C-ring Formation (1)



1) Hebert, M.; Bellavance, G.; Barriault, L. *J. Am. Chem. Soc.* **2022**, *144*, 17792.

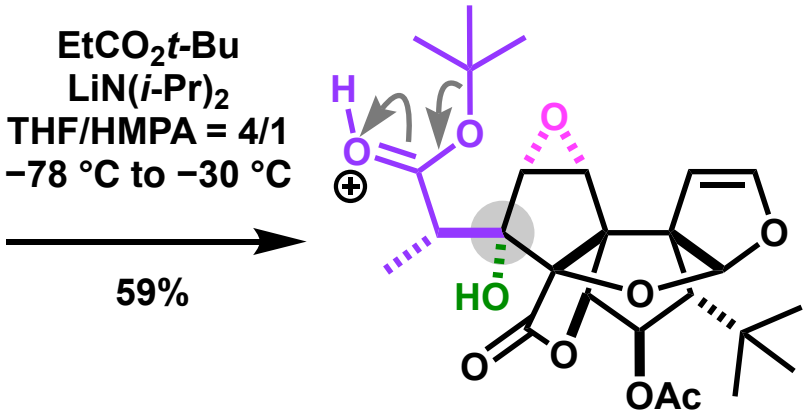
C-ring Formation (2)

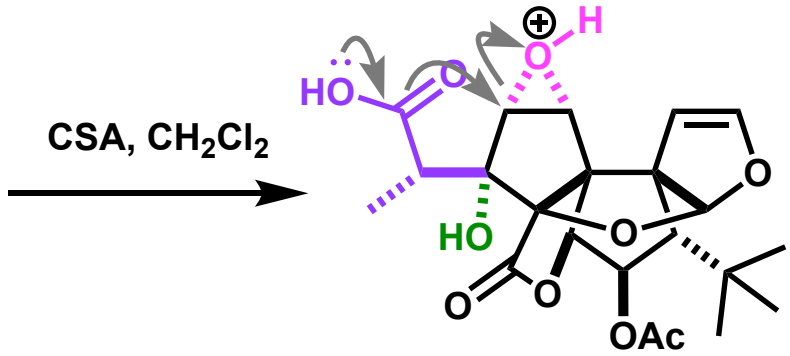


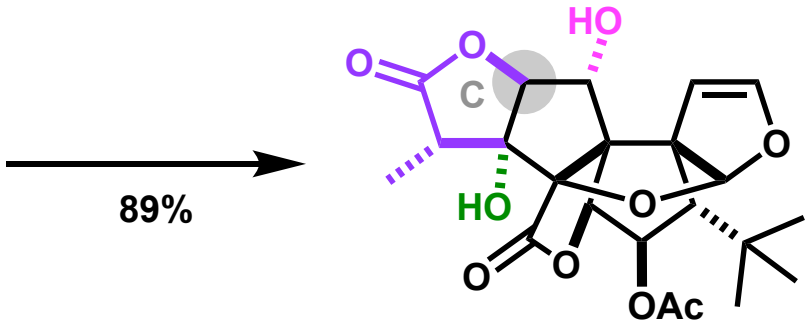


Corey's intermediate

difference : existence of OAc group
stereoselectivity : explained by the same reasons

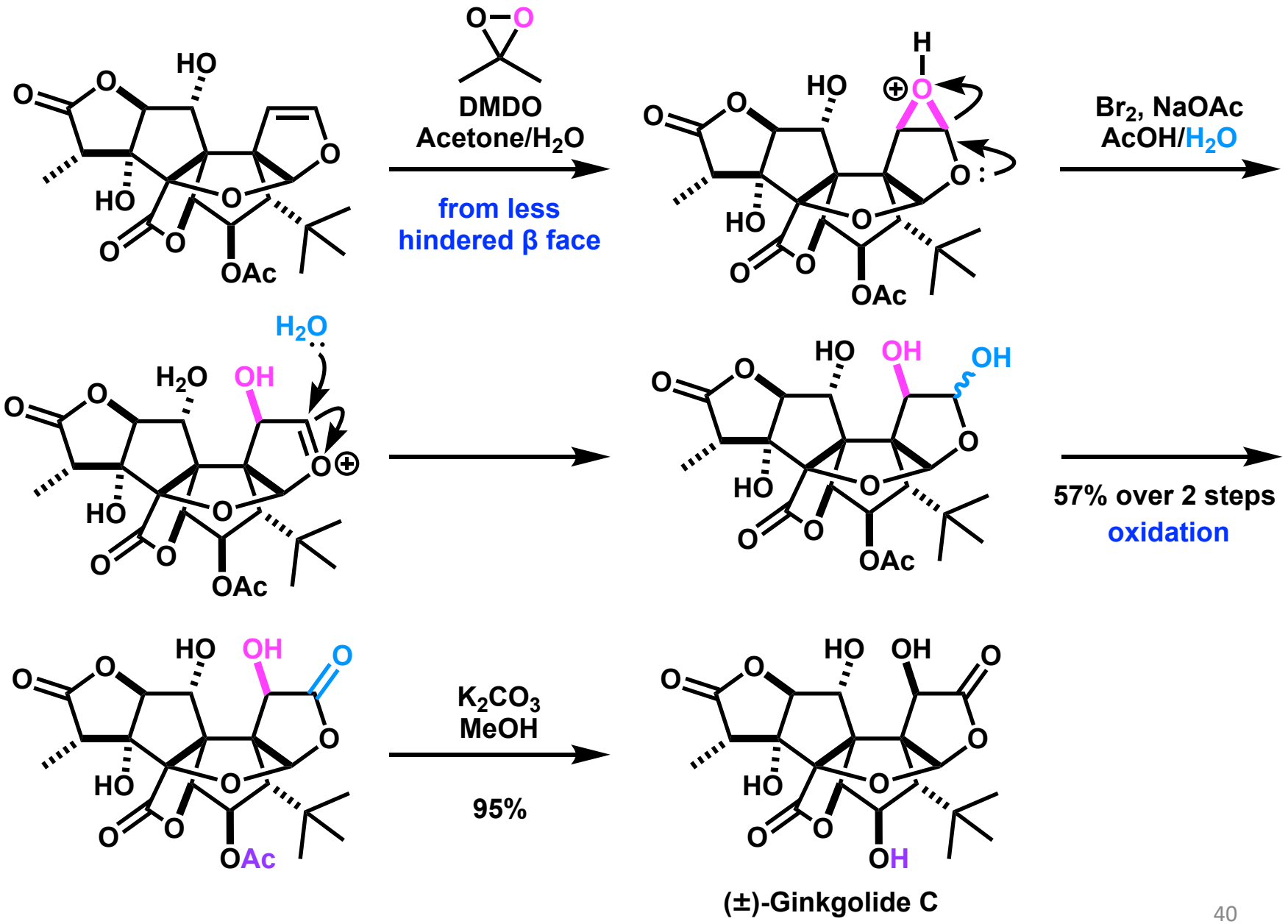






1) Hebert, M.; Bellavance, G.; Barriault, L. *J. Am. Chem. Soc.* **2022**, *144*, 17792.

Total Synthesis of Ginkgolide C

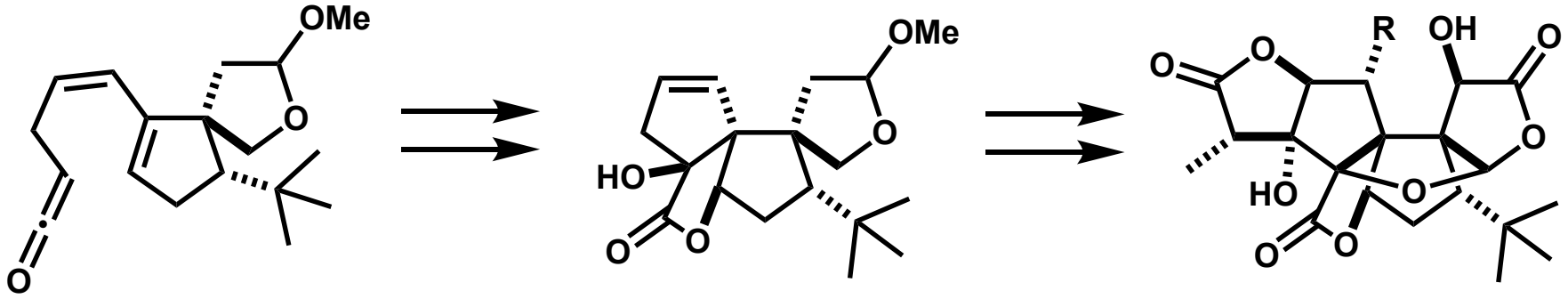


1) Hebert, M.; Bellavance, G.; Barriault, L. *J. Am. Chem. Soc.* **2022**, *144*, 17792.

Contents

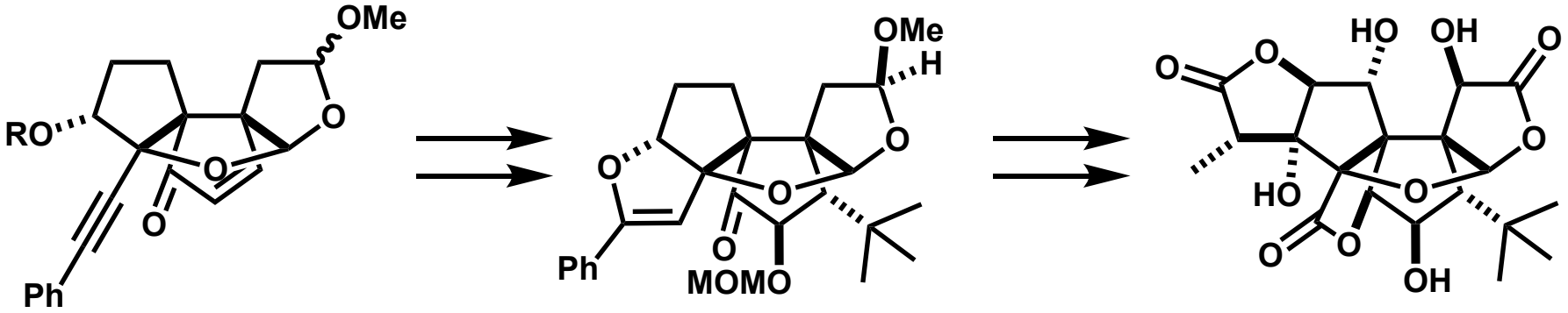
Summary

Corey's work



Ginkgolide A : R = H
Ginkgolide B : R = OH

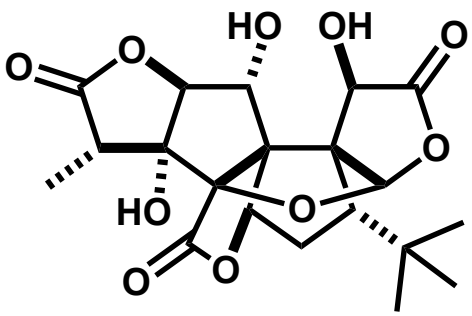
Barriault's work



Ginkgolide C

Appendix

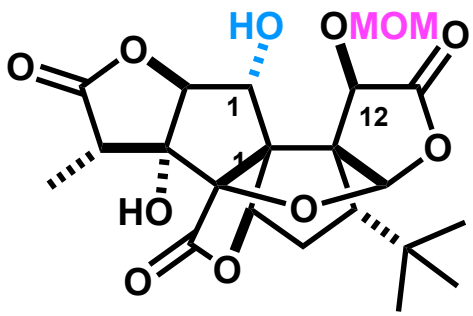
Conversion of Ginkgolide B to Ginkgolide A



(±)-Ginkgolide B

MOMCl, *i*-Pr_2NEt
MeCN

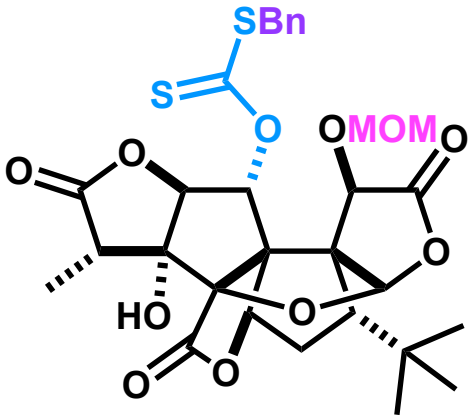
89%



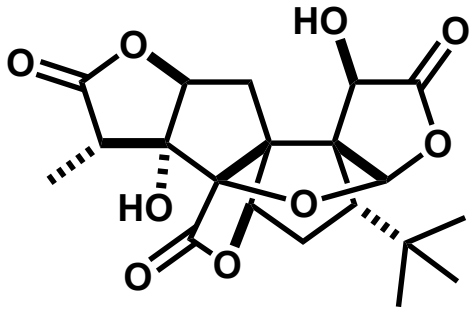
C1-OMOM : C12-OMOM = 1 : 3

KH, THF;
CS_2
23 °C to 45 °C;
BnBr

71%



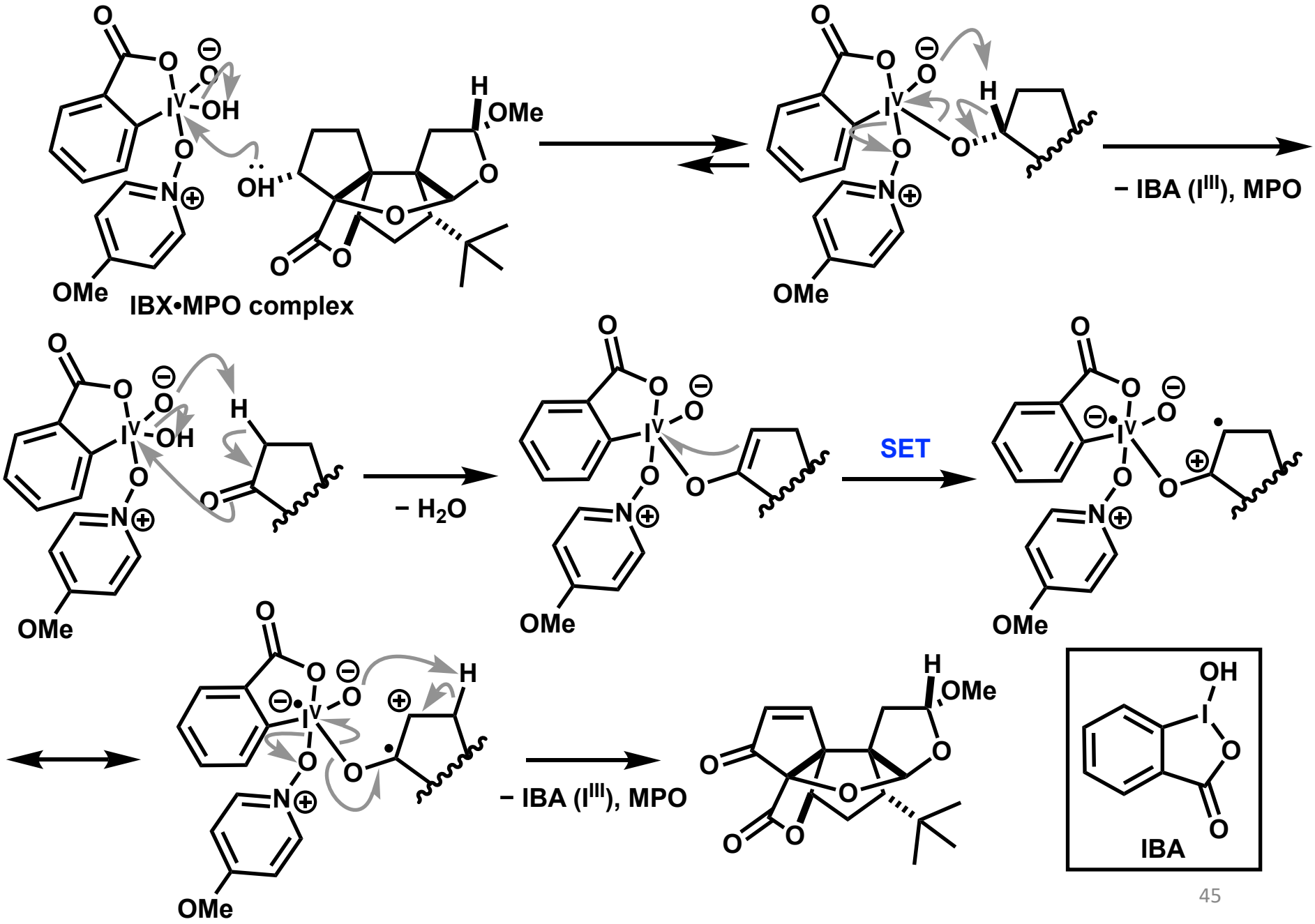
1. *n*-Bu_3SnH
   dioxane
   reflux, 71%
2. BF_3•Et_2O
   PhSH, CH_2Cl_2
   −10 °C



(±)-Ginkgolide A

1) Corey, E. J.; Ghosh, A. K. *Tetrahedron Lett.* **1988**, *29*, 3205.

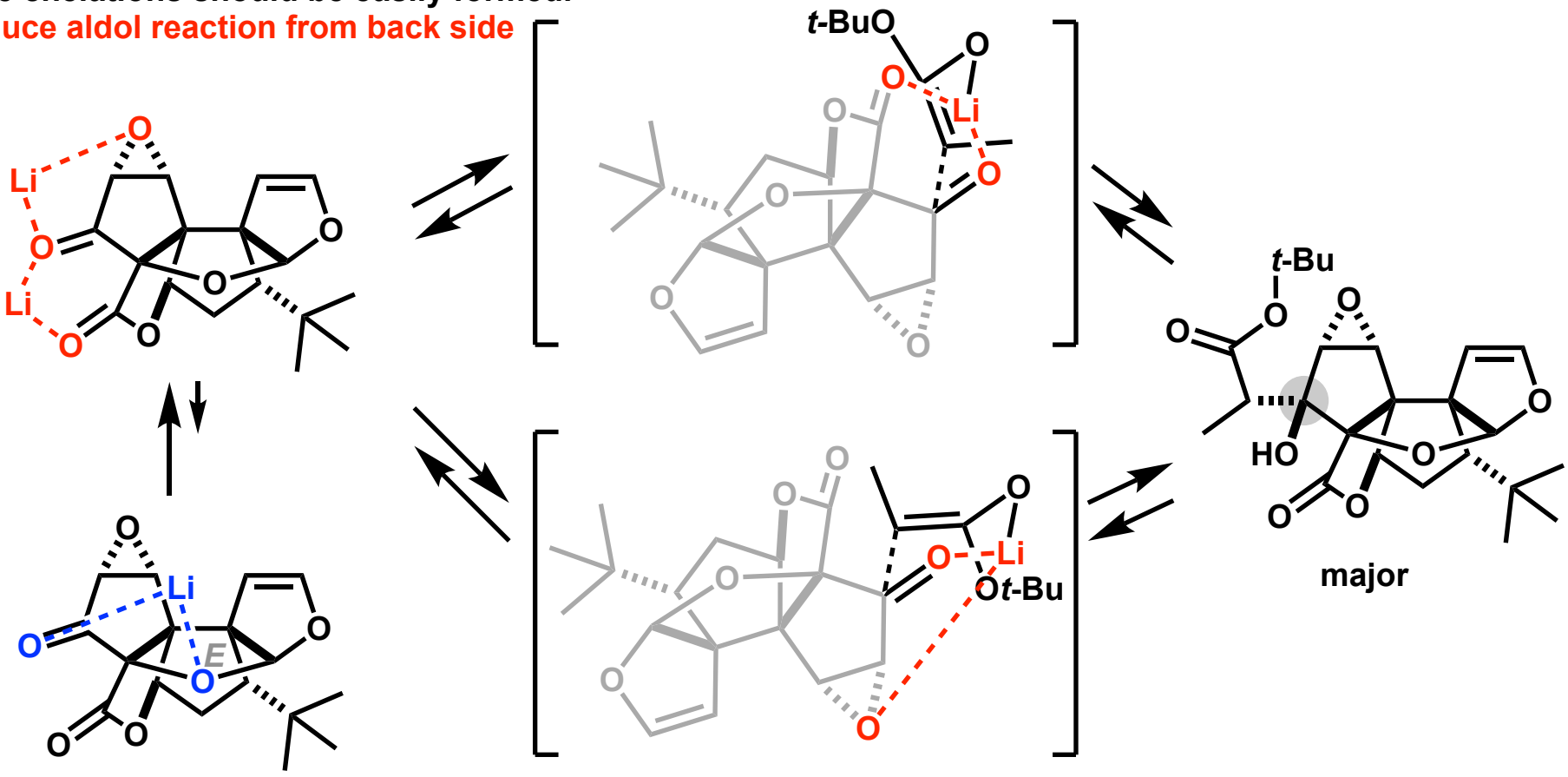
Mechanism of Enone Formation



Stereoselectivity of aldol reaction (proposed by Nakamura-san)

condition **: THF, −78 °C** **in the presense of Li^+…**

These chelations should be easily formed.
→induce aldol reaction from back side



This chelation is thought to be difficult because the direction of lone pairs of E-ring oxygen is not proper to this chelation.