Total Synthesis of Natural Products Containing Tropolone Structure

2024.1.6. Literature Seminar
B4 Kensuke Kawamura

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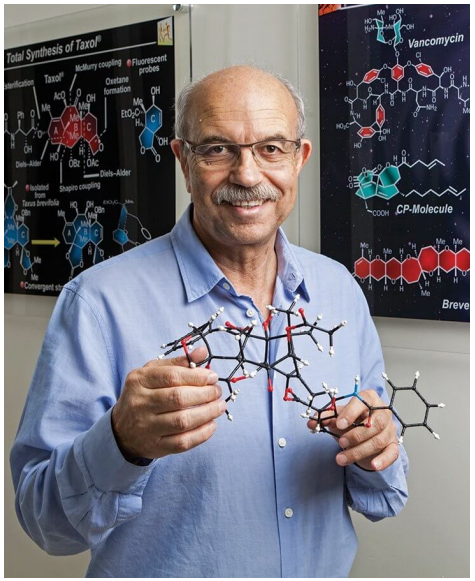
Introduction of Prof. Yokoshima and K. C. Nicolaou

Prof. Satoshi Yokoshima

1997: B.S. @ The University of Tokyo
2002: Ph. D. @ The University of Tokyo (Prof. Fukuyama)
2004~2007: Assistant @ The University of Tokyo (Prof. Fukuyama)
2007~2008: Assistant professor @ The University of Tokyo (Prof. Fukuyama)
2008~2011: Lecturer @ The University of Tokyo (Prof. Fukuyama)
2011~2012: Associate professor @ The University of Tokyo (Prof. Fukuyama)
2012~2017: Associate professor @ Nagoya University (Prof. Fukuyama)
2017~: Professor @ Nagoya University

Research topic: Total synthesis, reaction development



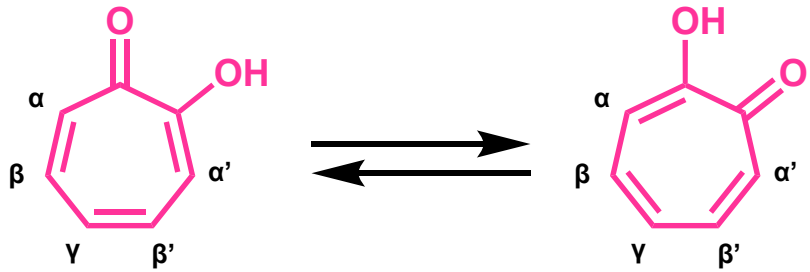
Prof. K. C. Nicolaou

1969: B.S. @ The University of London
1972: Ph. D. @ The University of London (Professors F. Sondheimer/P. J. Garratt)
1972~1973: Postdoc @ Columbia University (Prof. T. J. Katz)
1973~1976: Postdoc @ Harvard University (Prof. E. J. Corey)
1976~1989: Professor @ The University of Pennsylvania
1989~1996: Professor @ The University of California, San Diego
1996~2013: Professor @ The Scripps Research Institute
2013~: Professor @ Rice University

Research topic: Total synthesis

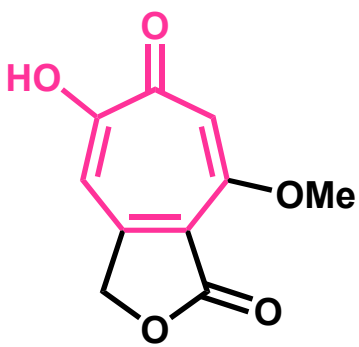
1) https://www.ps.nagoya-u.ac.jp/lab_pages/natural_products/index.html
2) https://nicolaou.rice.edu/

Tropolone as a Motif in Natural Products

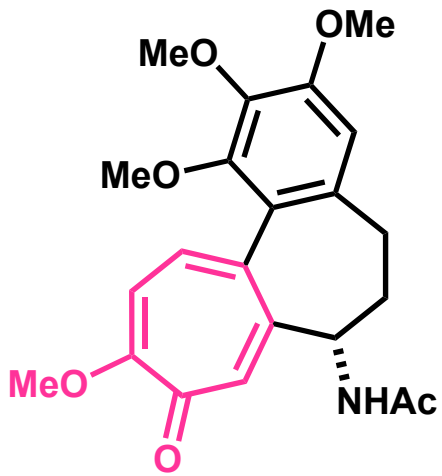


tropolone

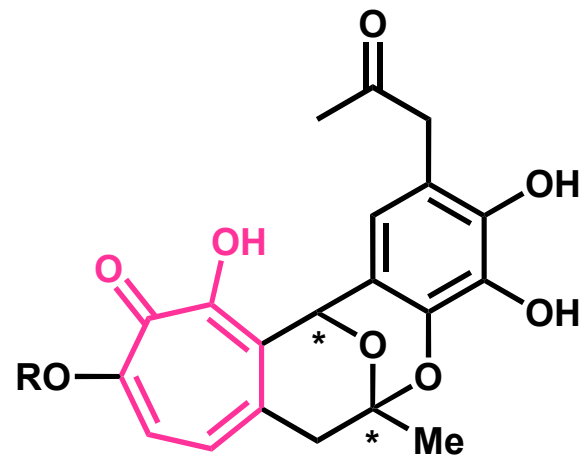
Natural Products



viticolin C



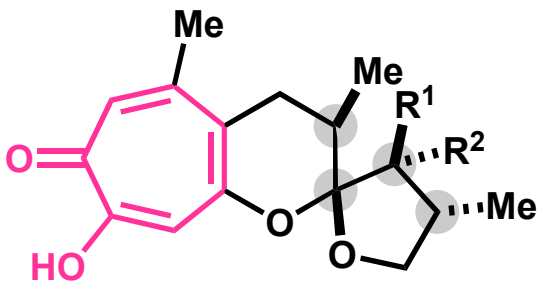
colchicine



namanolone F: R = H
namanolone G: R = Me

*Stereochemistries are not determined.

Malettinin C and E



Malettinin C: R^1 = H, R^2 = OH
Malettinin E: R^1 = OH, R^2 = H

Isolation:
from the stromata of *Hypoxylon* sp. growing on dead Aspen logs (Malettinin C)[1)]
from the fungus *Cladosporium* sp. growing in Wadden Sea (Malettinin E)[2)]

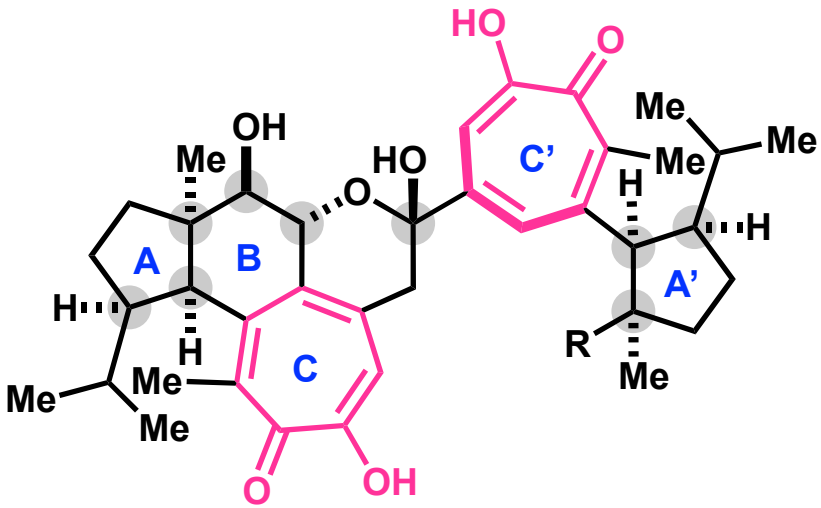
Biological activity:
antifungal activity (Malettinin C)
anticancer activity (Malettinin E)

Total synthesis:
Yokoshima[3)] (2023)

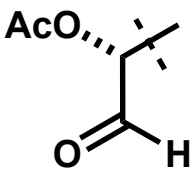
Structural features:
trisubstituted tropolone ring
4 contiguous stereocenters
spiro acetal

1) Angawi, R. F.; Swenson, D. C.; Gloer, J. B.; Wicklow, D. T. *J. Nat. Prod.* **2005**, *68*, 212
2) Silber, J.; Ohlendorf, B.; Labes, A.; Wenzel-Storjohann, A.; Näther, C.; Imhoff, J. F. *Front. Mar. Sci*. **2014**, *1,* 35
3) Umekubo, N.; Yokoshima, S. *Org. Lett.* **2023**, *25*, 4530.

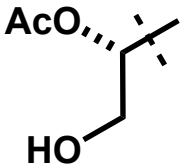
Gukulenin A and B



Gukulenin A: R =



Gukulenin B: R =



Isolation:
from the marine sponge *Phorbas gukhulensis*[1)]

Biological activity:
cytotoxicities against various human cancer cell lines

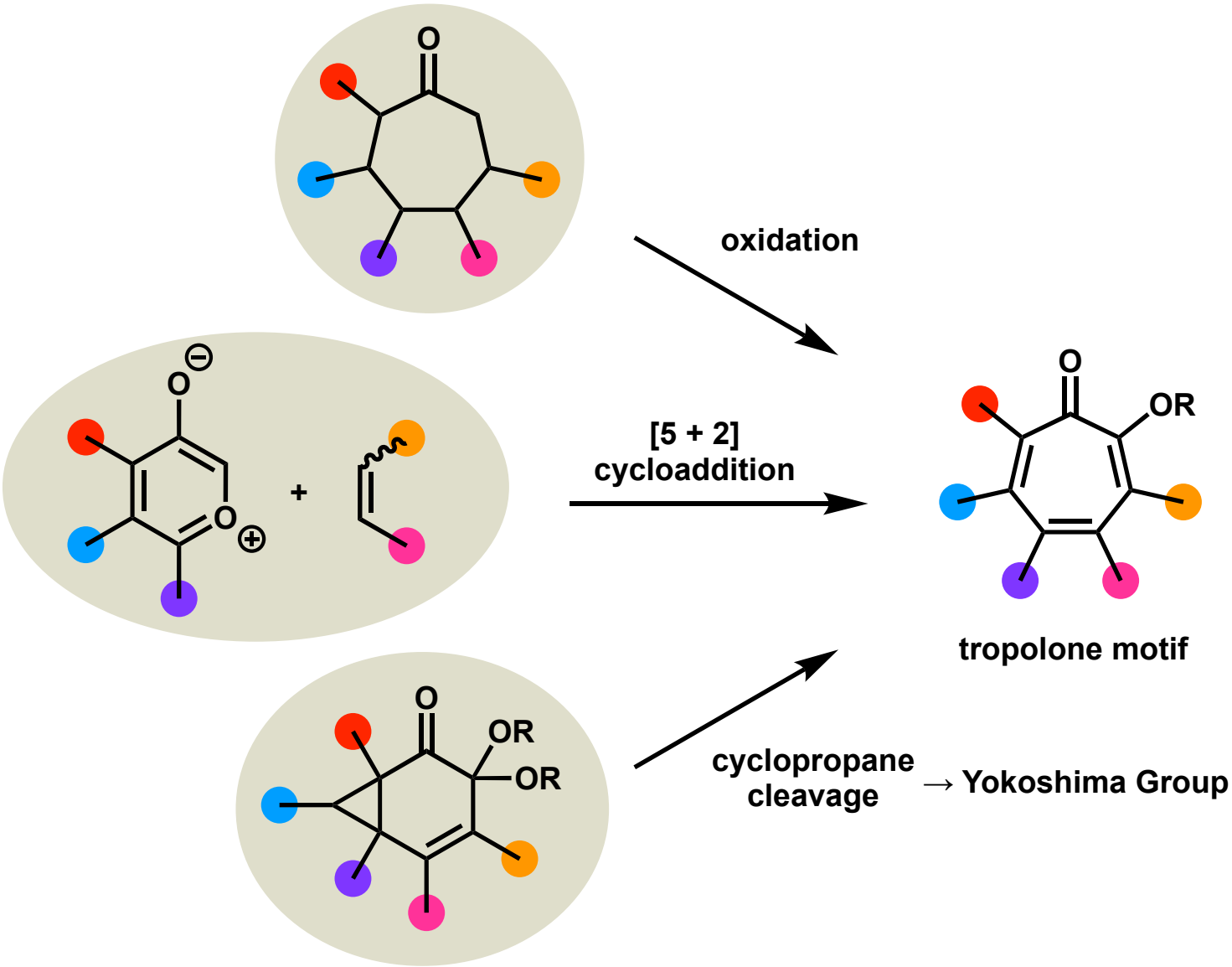
Total synthesis:
Nicolaou[2)] (GukuleninB, 2022)

Synthetic study:
Herzon[3, 4)] (2015, 2023)
Hiersemann[5)] (2018)

Structural features:
tetrasubstituted tropolone C ring and trisubstituted tropolone C' ring
pseudodimeric structure
9 stereocenters

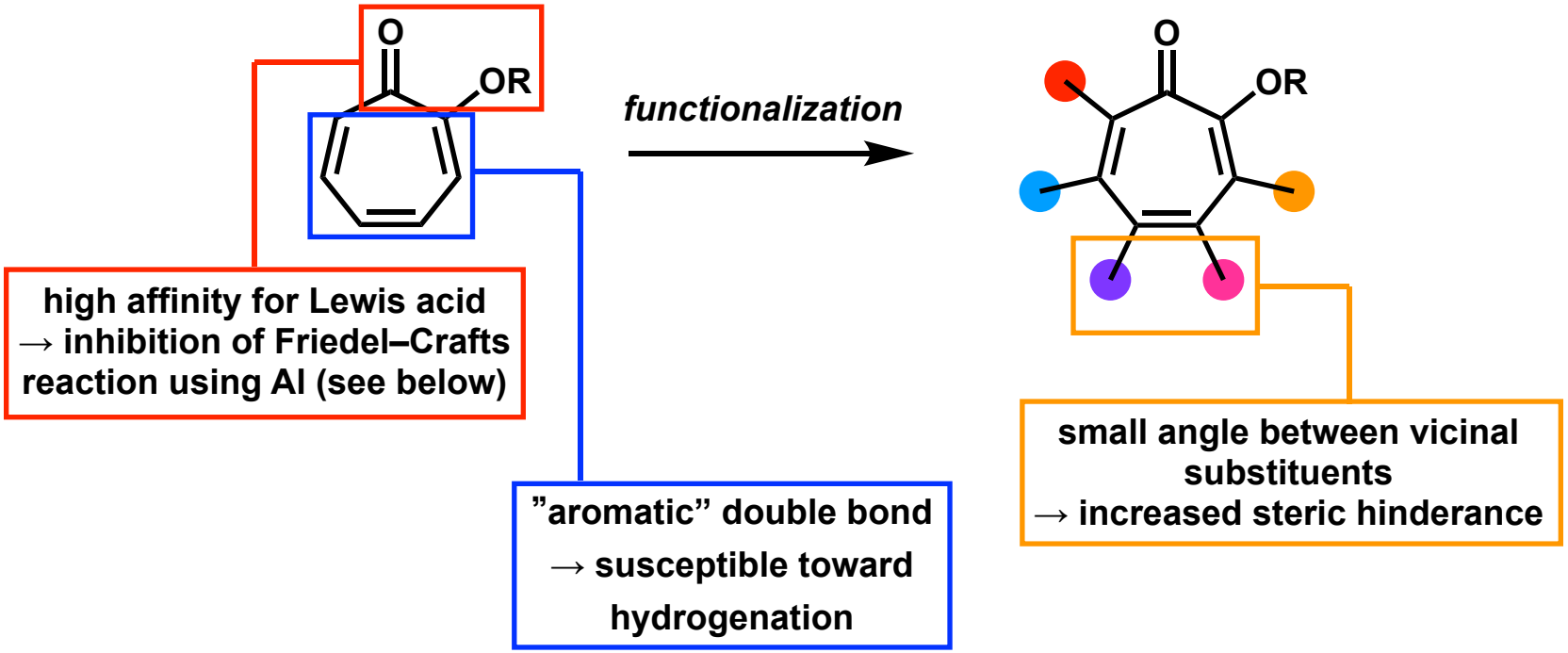
1) Park, S. Y.; Choi, H.; Hwang, H.; Kang, H.; Rho, J. R. *J. Nat. Prod.* **2010**, *73*, 734.
2) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.
3) Kats-Kagan, R.; Herzon, S. B. *Org. Lett.* **2015**, *17*, 2030.
4) Combs, J.; Wright, T.; Chen, L.; Holmes, R.; Qin, B.; Oh, J.; Crawford, J; Herzon, S. *ChemRxiv.* **2023**, 16/08/23.
5) Tymann, D.; Bednarzick, U.; Iovkova-Berends, L.; Hiersemann, M. *Org. Lett.* **2018**, *20*, 4072.

Strategy 1: Construction of Tropolone via Prefunctionalized Fragments

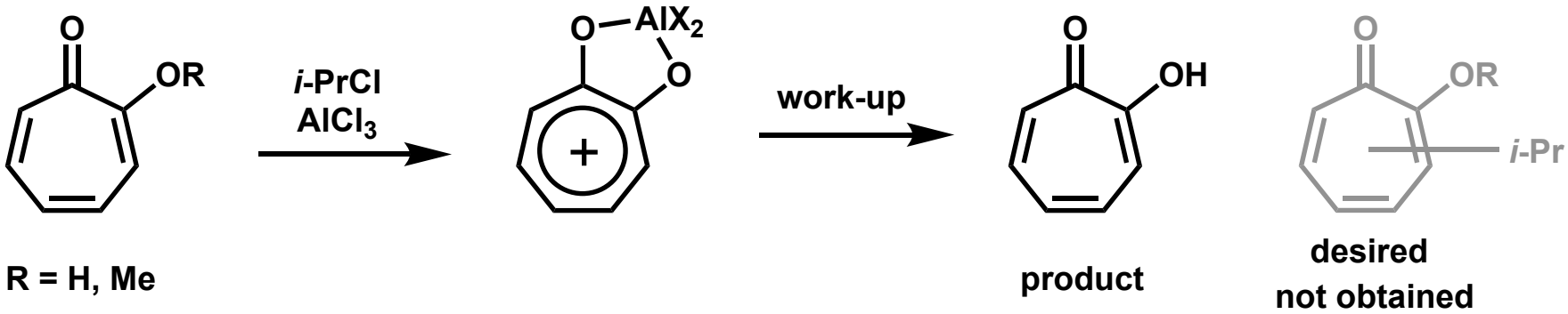


1) Liu, N.; Song, W.; Schienebeck, C. M.; Zhang, M.; Tang, W. *Tetrahedron*. **2014**, *70*, 9281.

Strategy 2: Late-Stage Functionalization



inhibiting mechanism of Friedel–Crafts reaction



1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.
2) Cook, J. W.; Raphael, R. A.; Scott, A. I. 847. *J. Chem. Soc.* **1952**, 4416.

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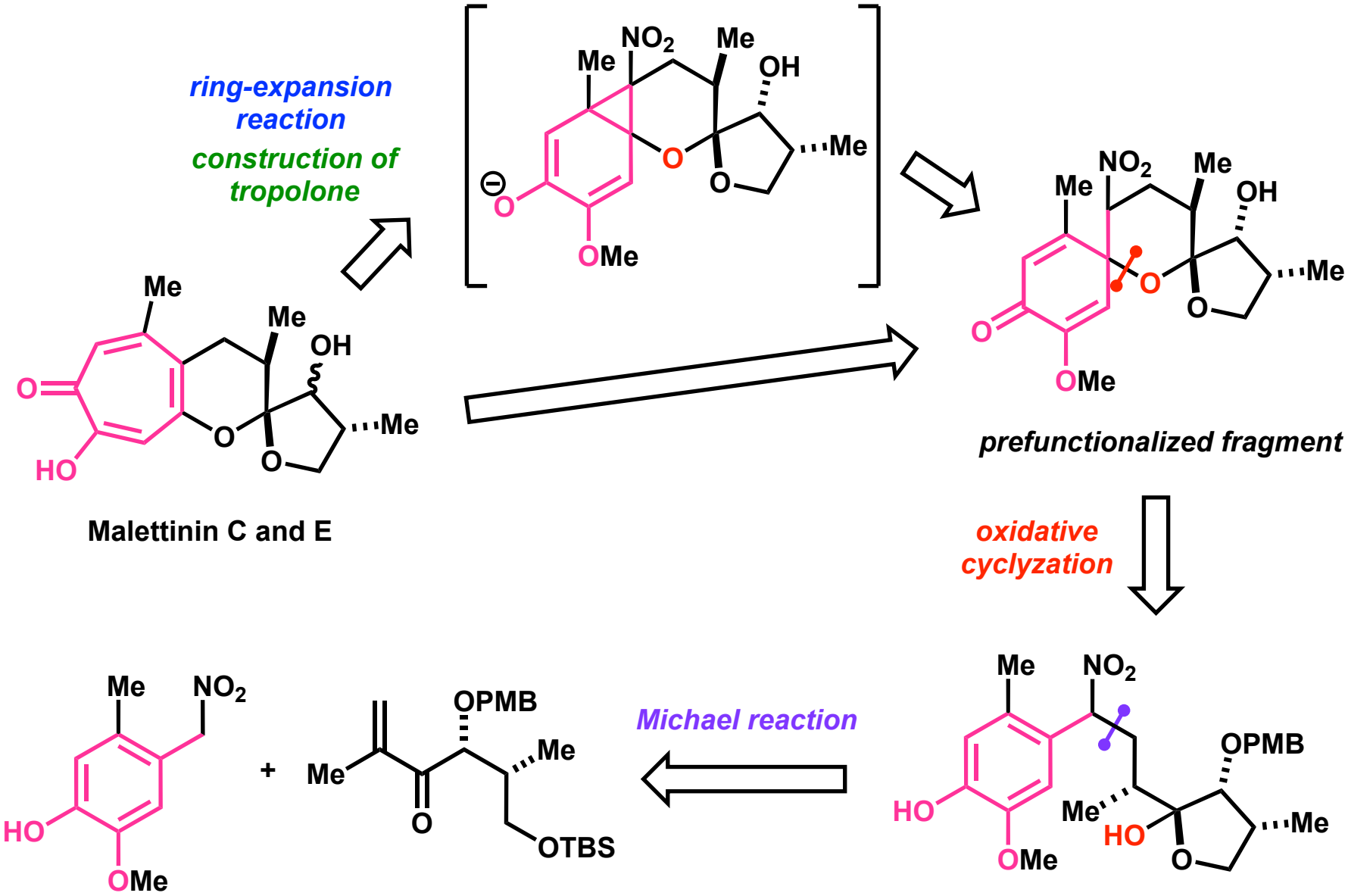
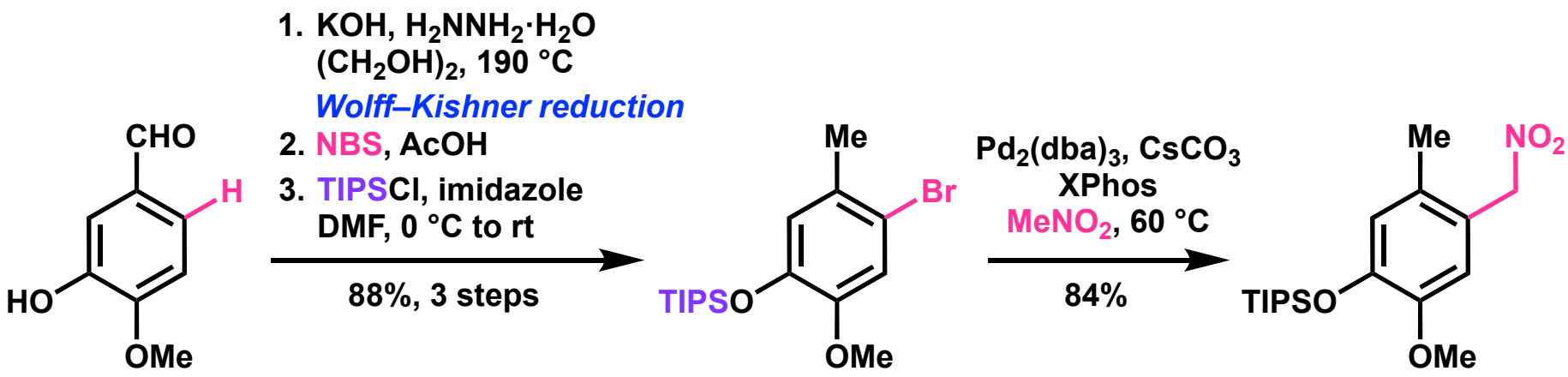
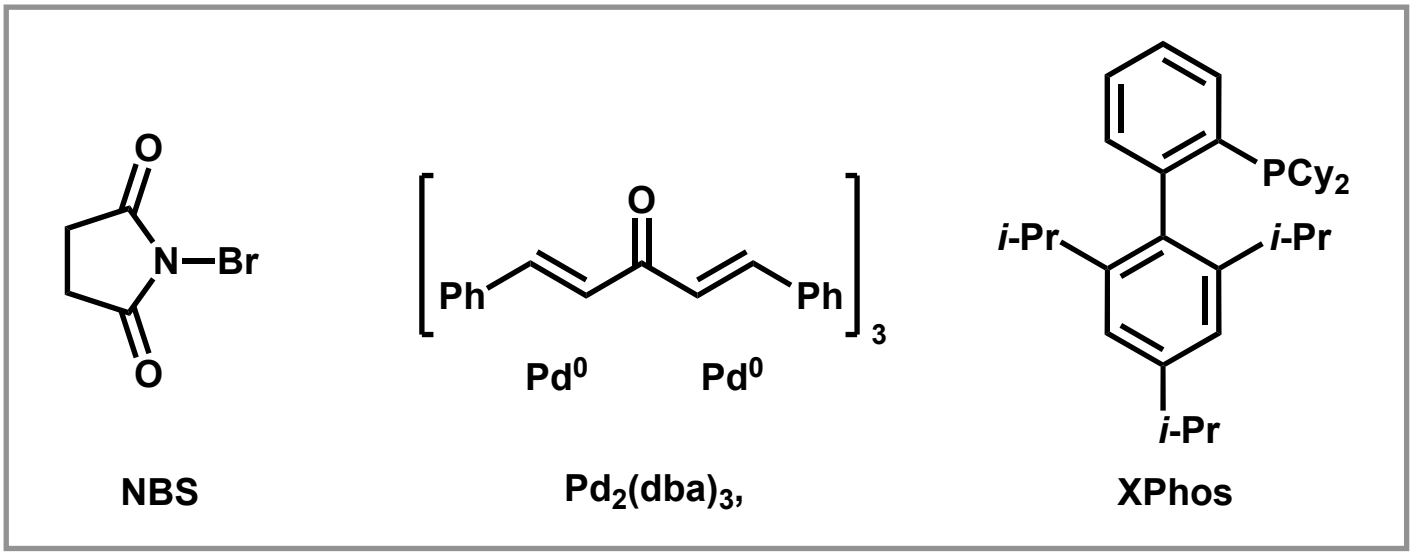
Retrosynthetic Analysis of Malettinin C and E



1) Umekubo, N.; Yokoshima, S. *Org. Lett.* **2023**, *25*, 4530.

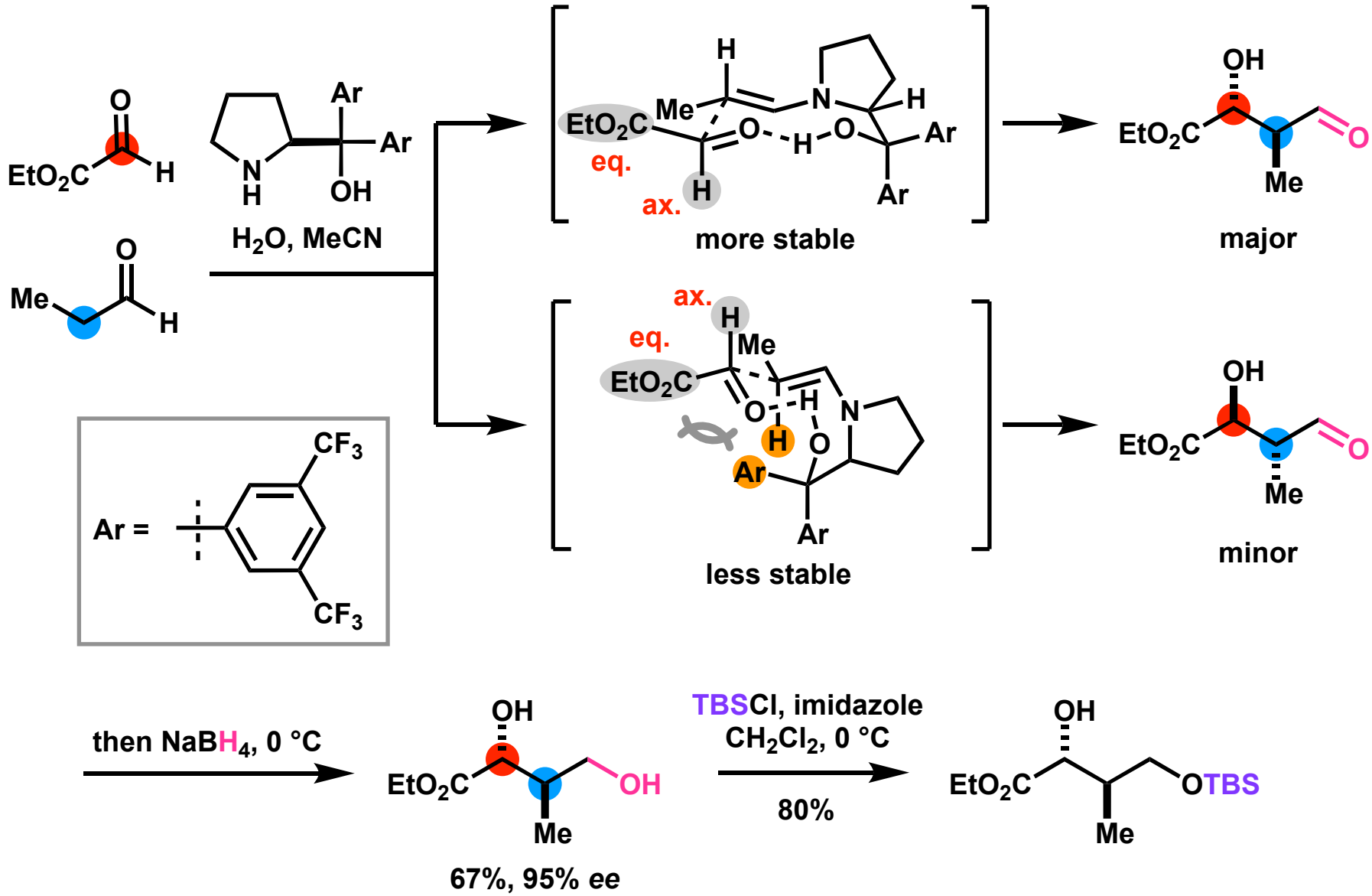
Synthesis of the Aromatic Fragment





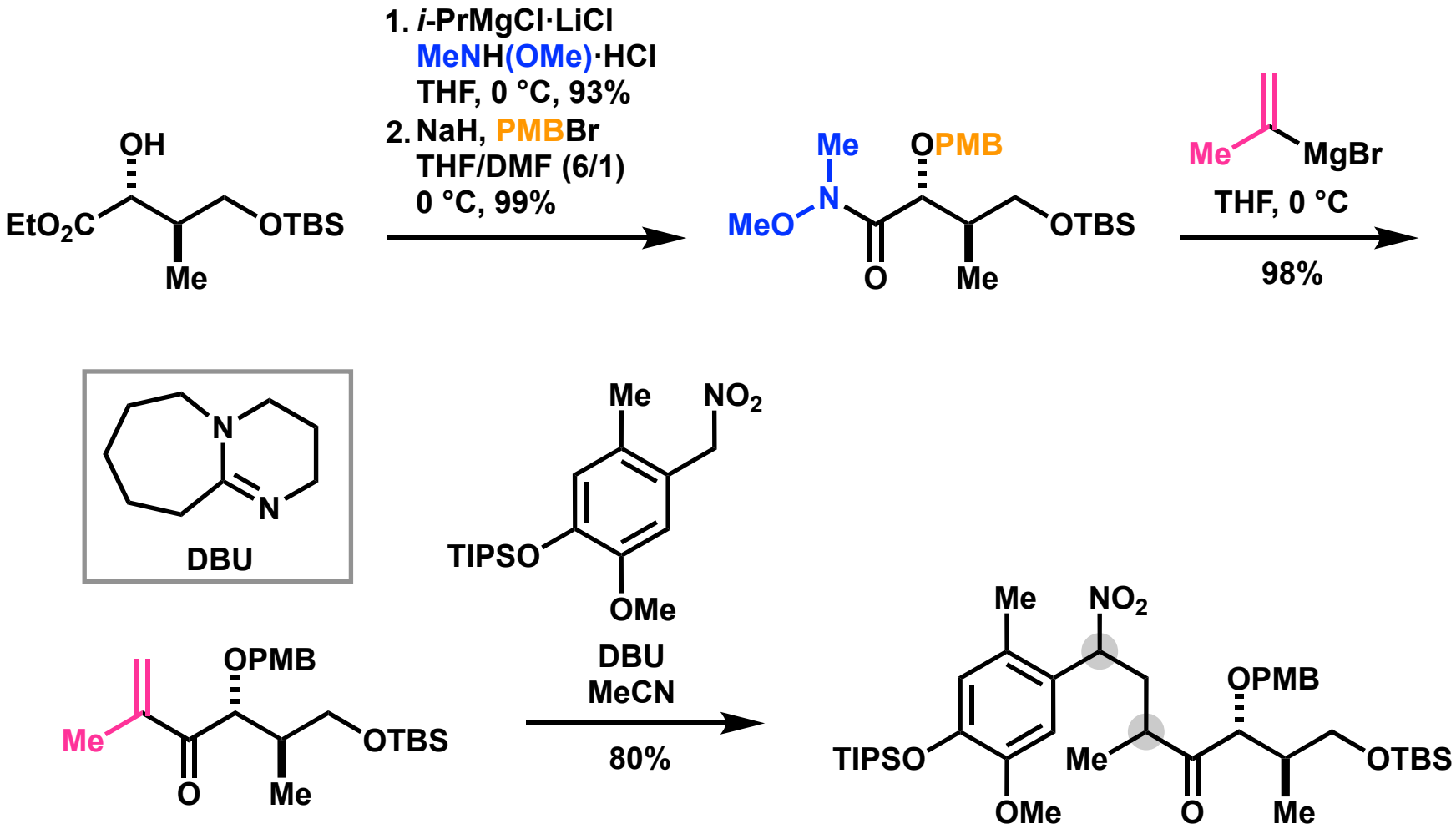
1) Umekubo, N.; Yokoshima, S. *Org. Lett.* **2023**, *25*, 4530.

Asymmetric Aldol Reaction



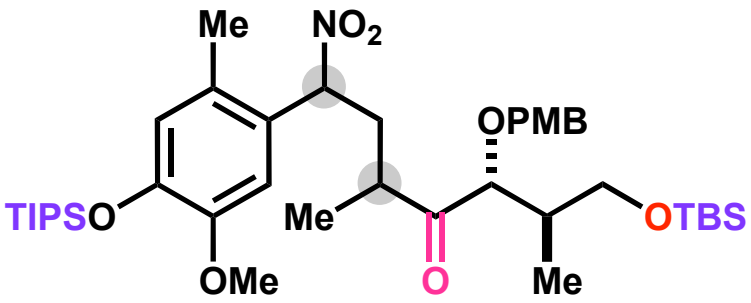
1) Umekubo, N.; Yokoshima, S. *Org. Lett.* **2023**, *25*, 4530.

Coupling of the Fragments



1) Umekubo, N.; Yokoshima, S. *Org. Lett.* **2023**, *25*, 4530.

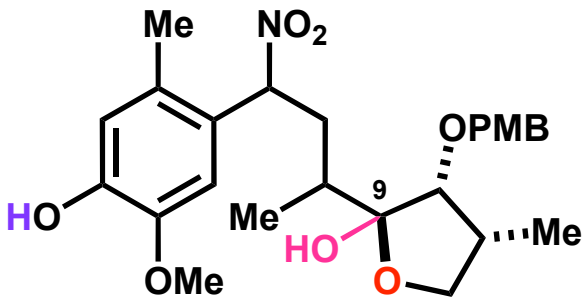
Hemiketal Formation



mixture of 4 diastereomers

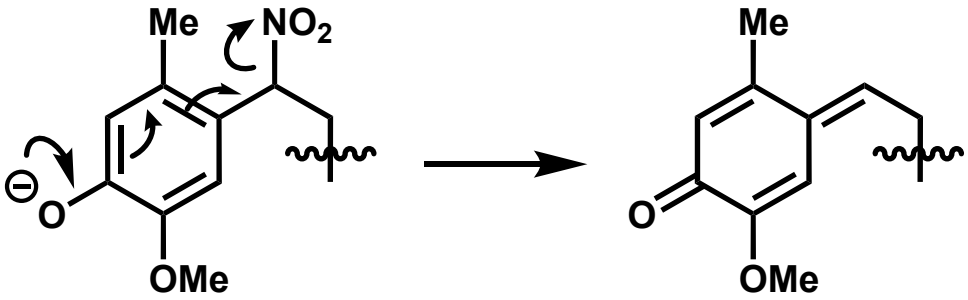
3HF·NEt$_3$
additive
THF

86%



d.r. = 4 : 1 at C9
mixture of 8 diastereomers

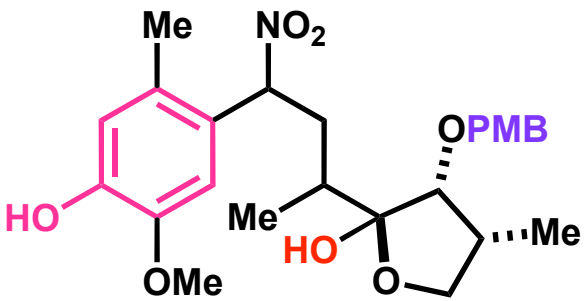
additive	yield
none	41%
NEt$_3$	0%
AcOH	86%



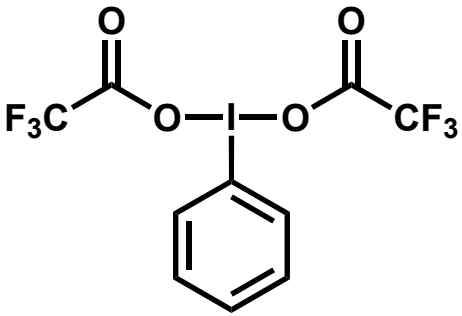
Under basic condition, NO$_2$ group was eliminated.

1) Umekubo, N.; Yokoshima, S. *Org. Lett.* **2023**, *25*, 4530.

Oxidative Cyclization

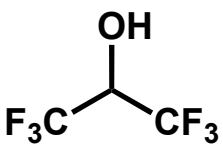


d.r. = 4 : 1 at C9
mixture of 8 diastereomers

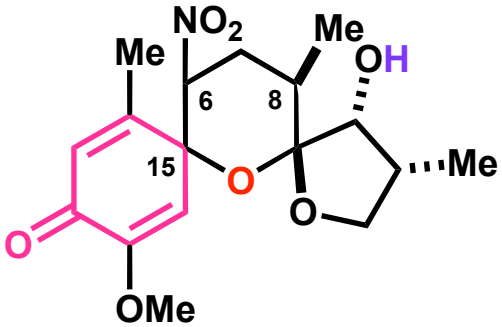


CH_2Cl_2/HFIP (1/1)
0 °C

36%



HFIP

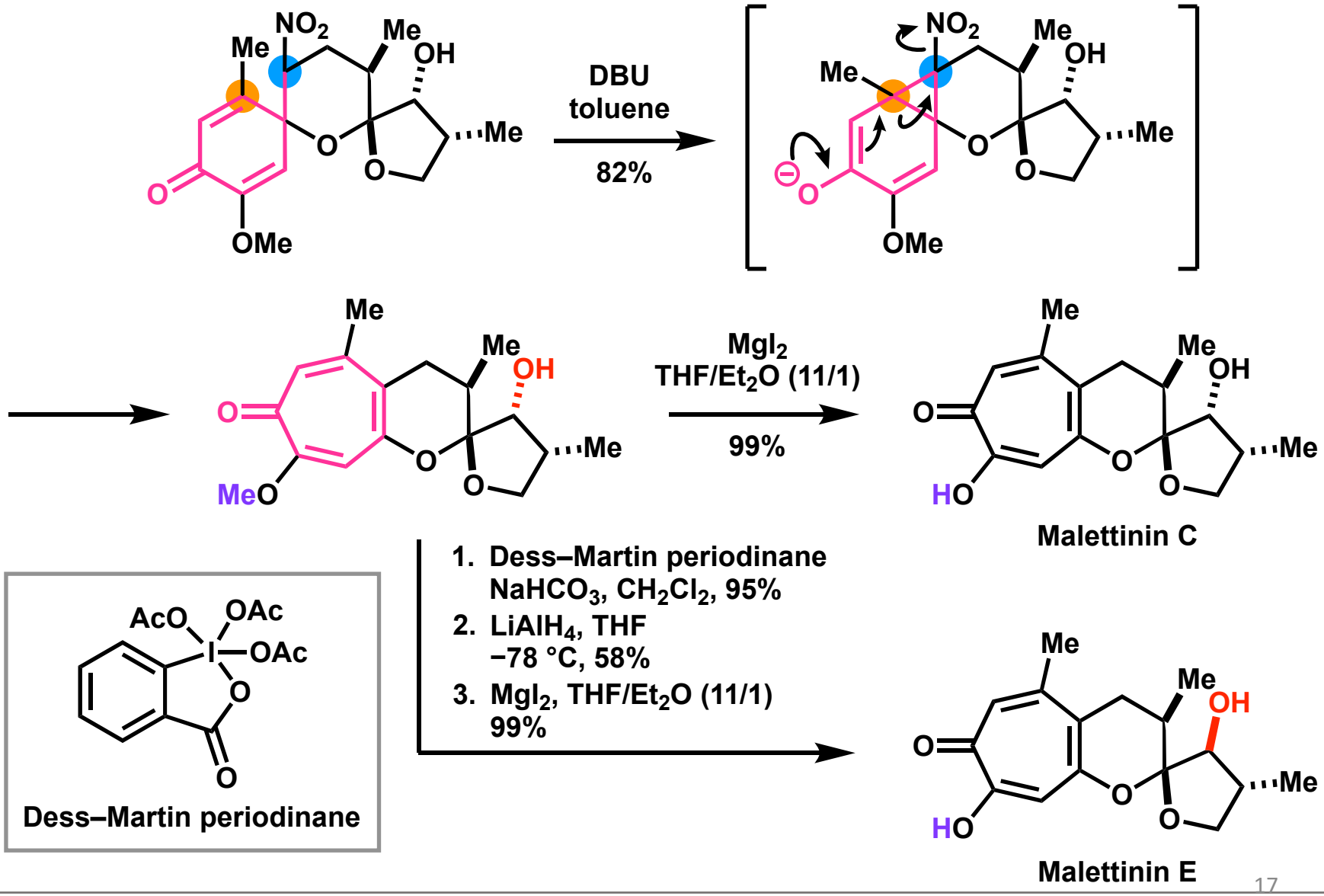


mixture of 2 diastereomers (0.59 : 0.41)

Stereocenter was not determined (C6 or C15).

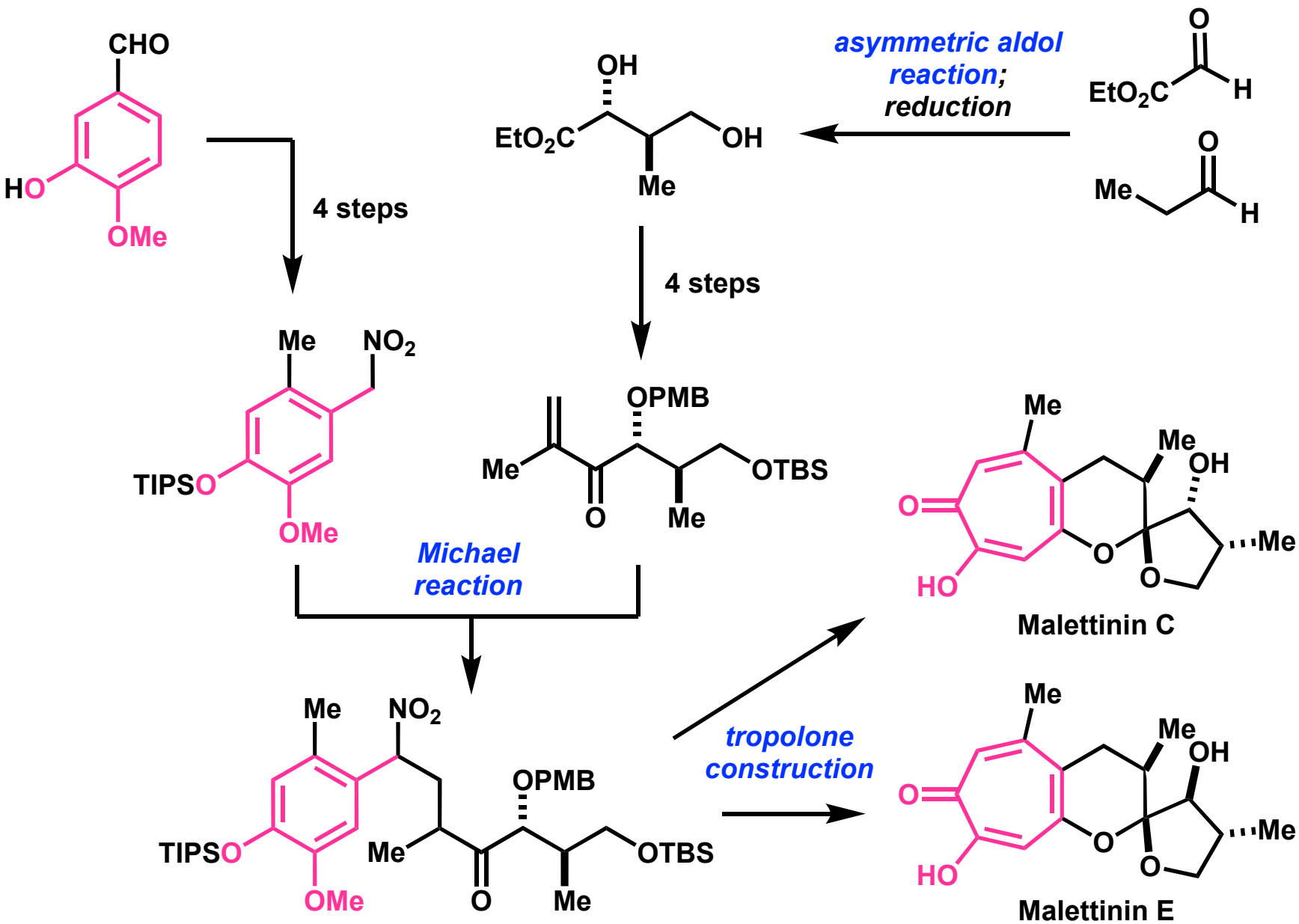
1) Umekubo, N.; Yokoshima, S. *Org. Lett.* **2023**, *25*, 4530.

Construction of Tropolone and Total Synthesis of Malettinin C and E



1) Umekubo, N.; Yokoshima, S. *Org. Lett.* **2023**, *25*, 4530.

Summary



1) Umekubo, N.; Yokoshima, S. *Org. Lett.* **2023**, *25*, 4530.

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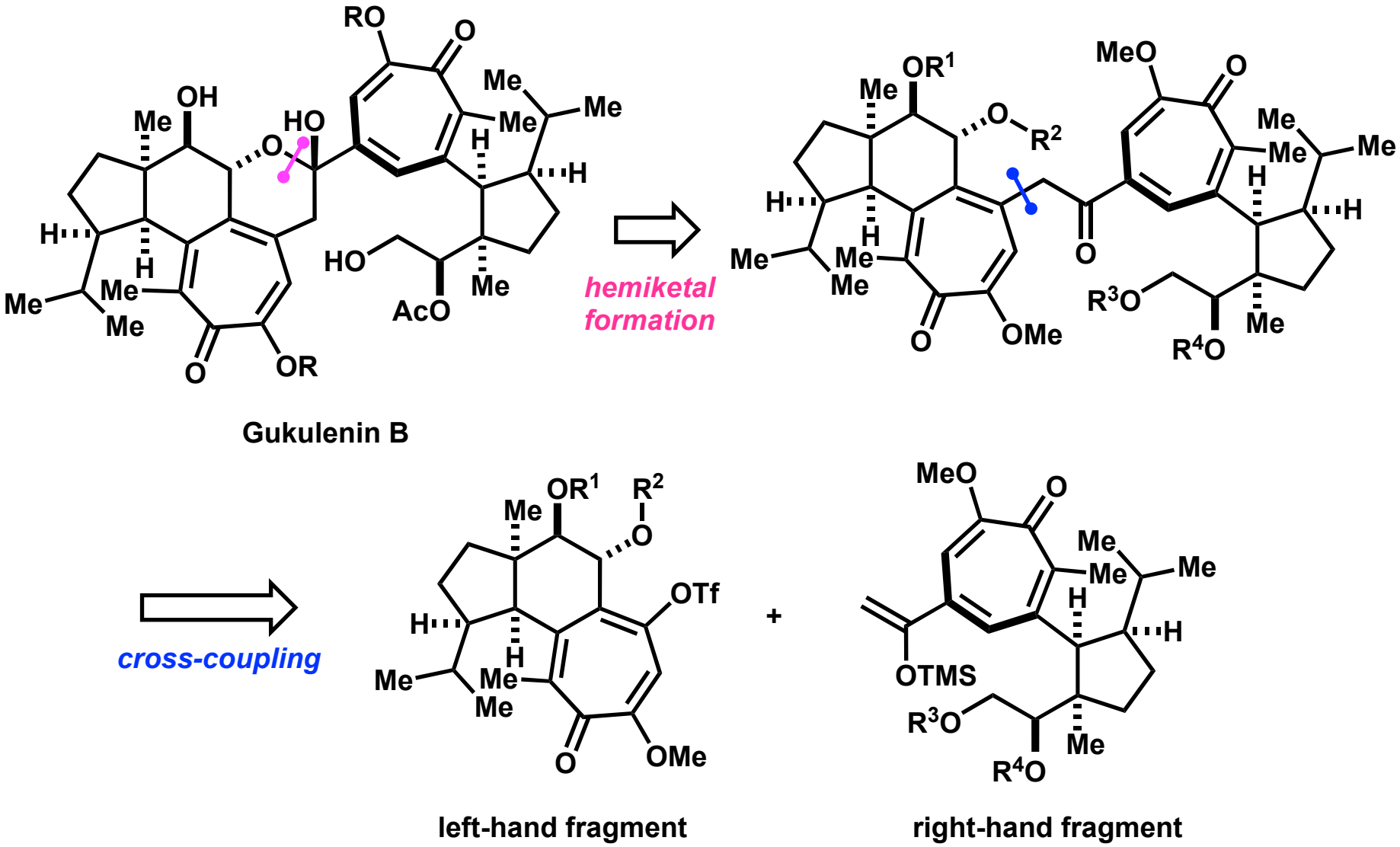
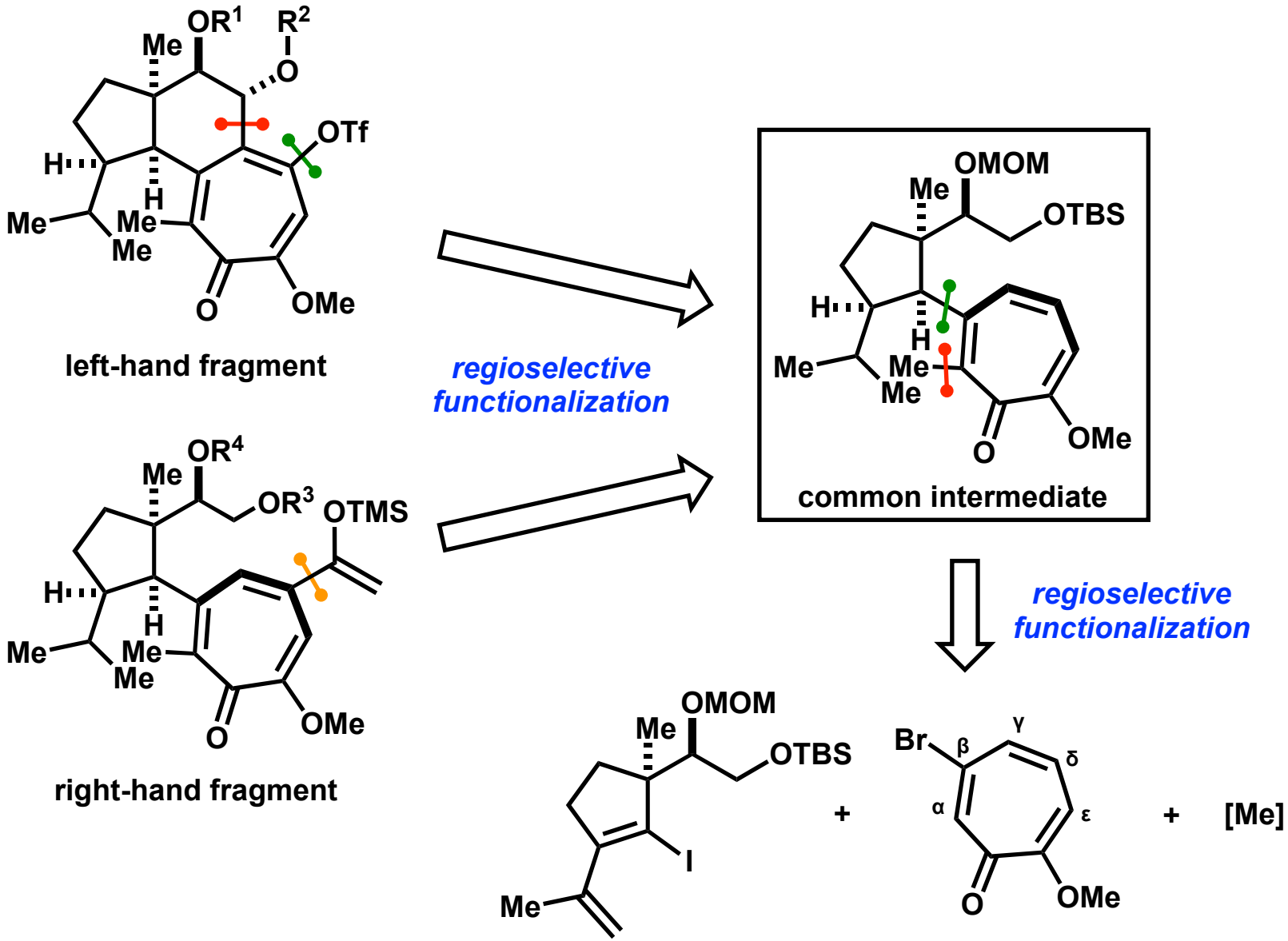
Retrosynthetic Analysis of Gukulenin B



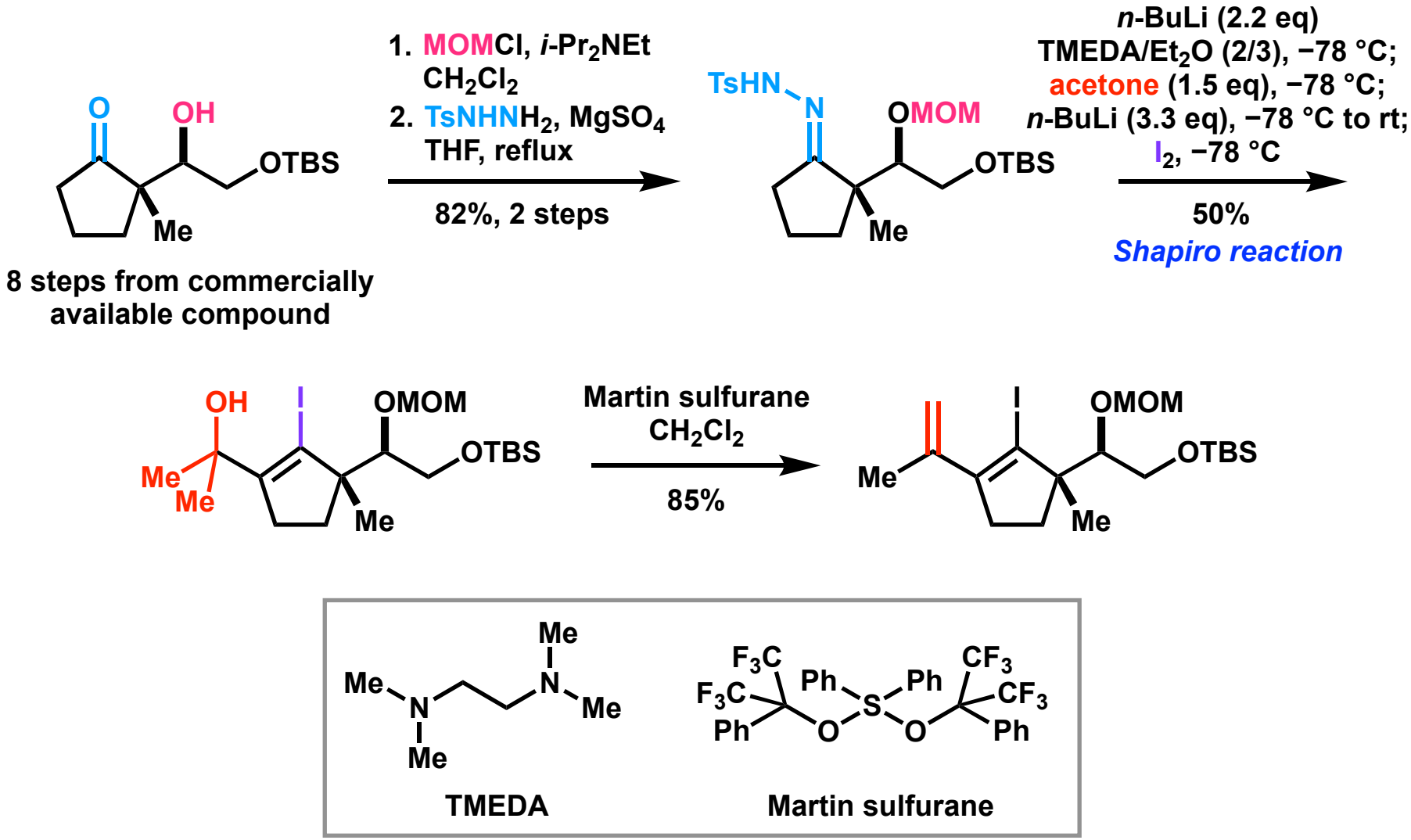
1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.

Retrosynthetic Analysis of Gukulenin B



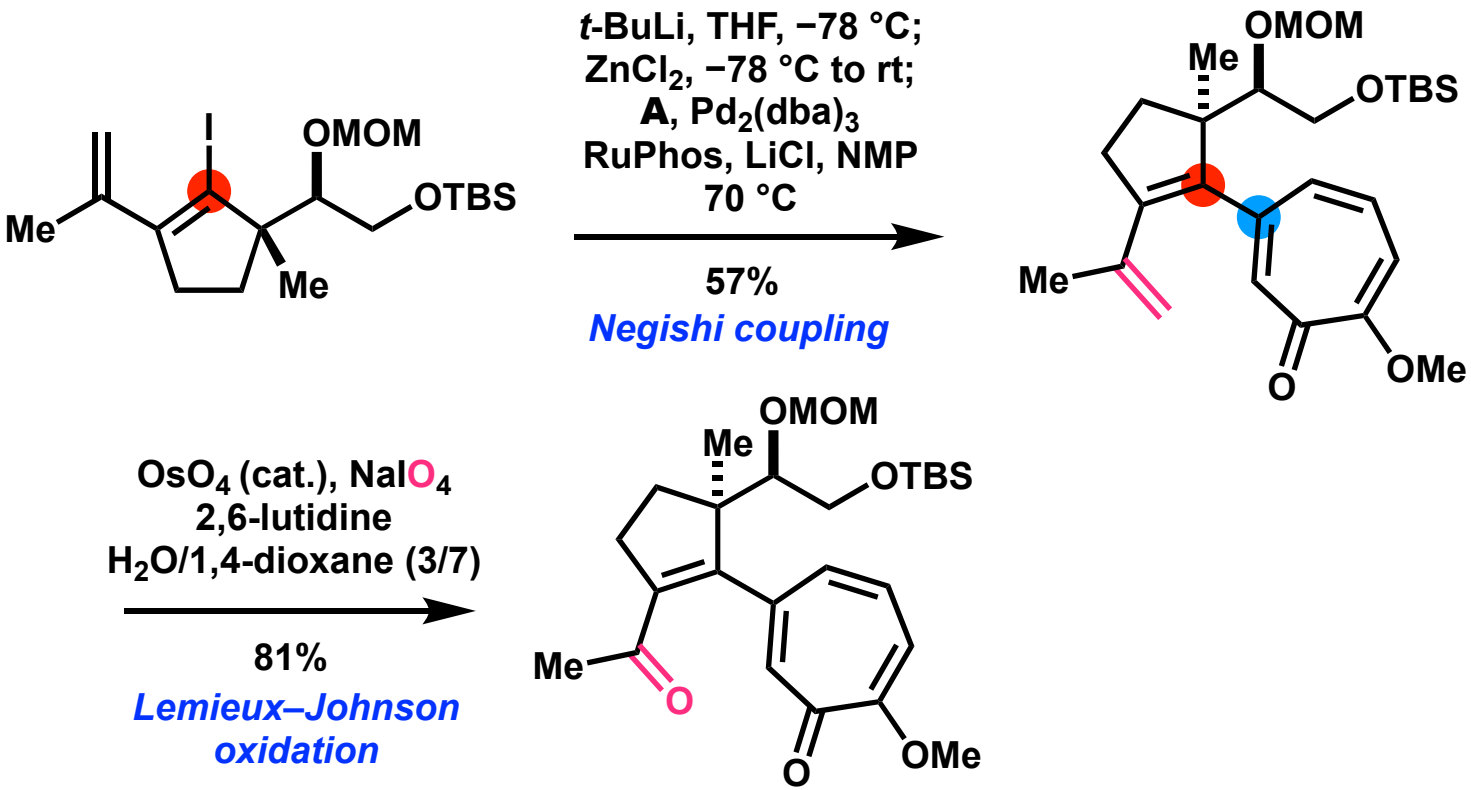
1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.

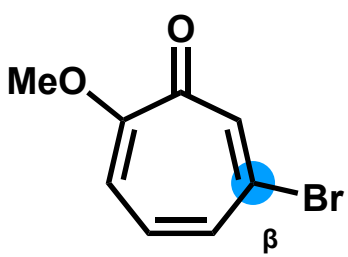
Fragment Synthesis



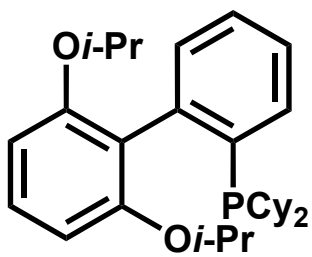
1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.

Functionalization of Tropolone at β Position





A

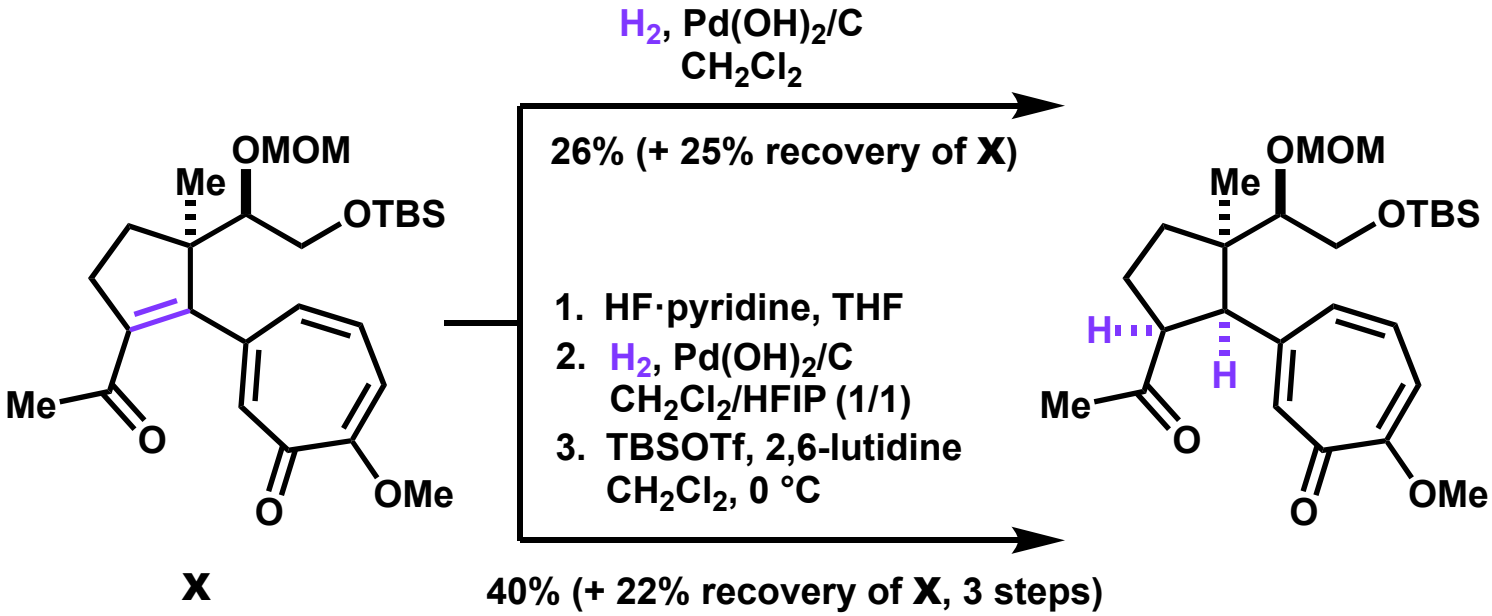


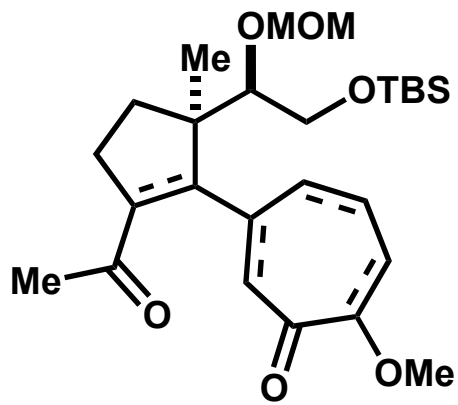
RuPhos

5 steps from 1,3-cyclohexadiene

1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.

Hydrogenation

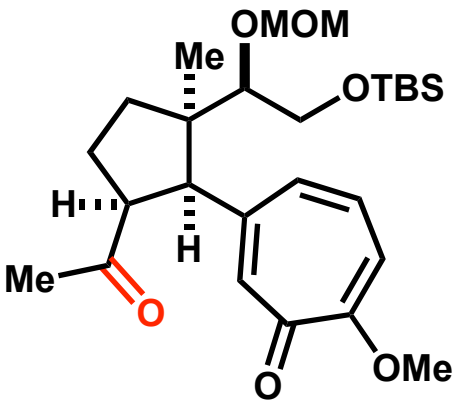




isolated byproduct

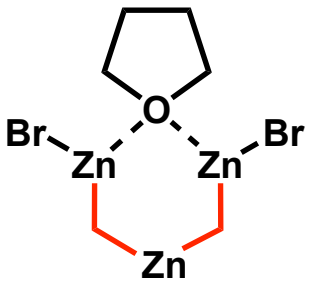
1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.

Methylation and α Functionalization

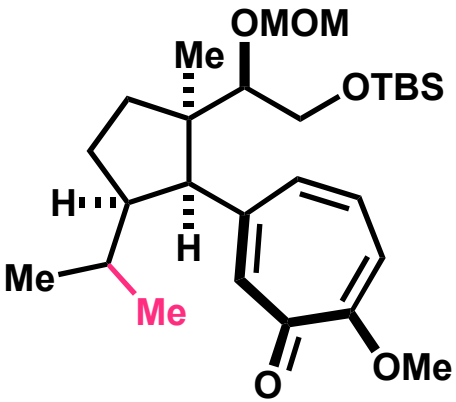


1. Nysted reagent
   $Ti(O\mathit{i}\text{-}Pr)_2Cl_2$
   THF
   −20 °C to −5 °C
   63%

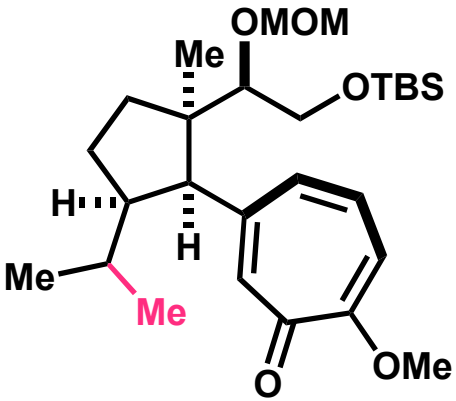
2. H_2, catalyst
   CH_2Cl_2, 92%



Nysted reagent

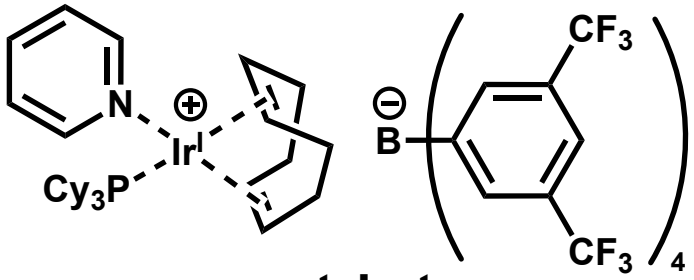


R-1

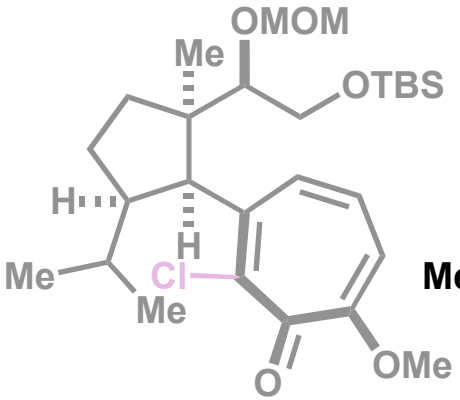


R-2

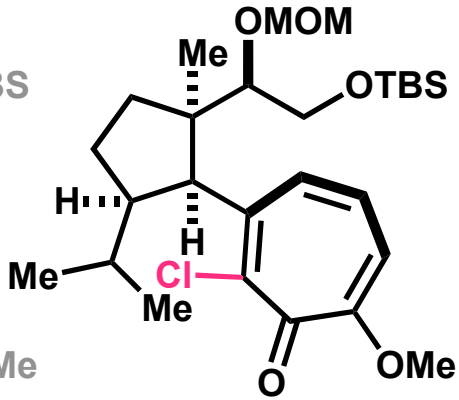
R-1 : R-2 = 1.2 : 1
rotameric mixture



catalyst

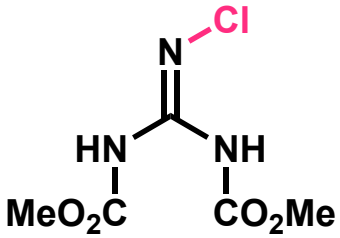


not obtained



60%

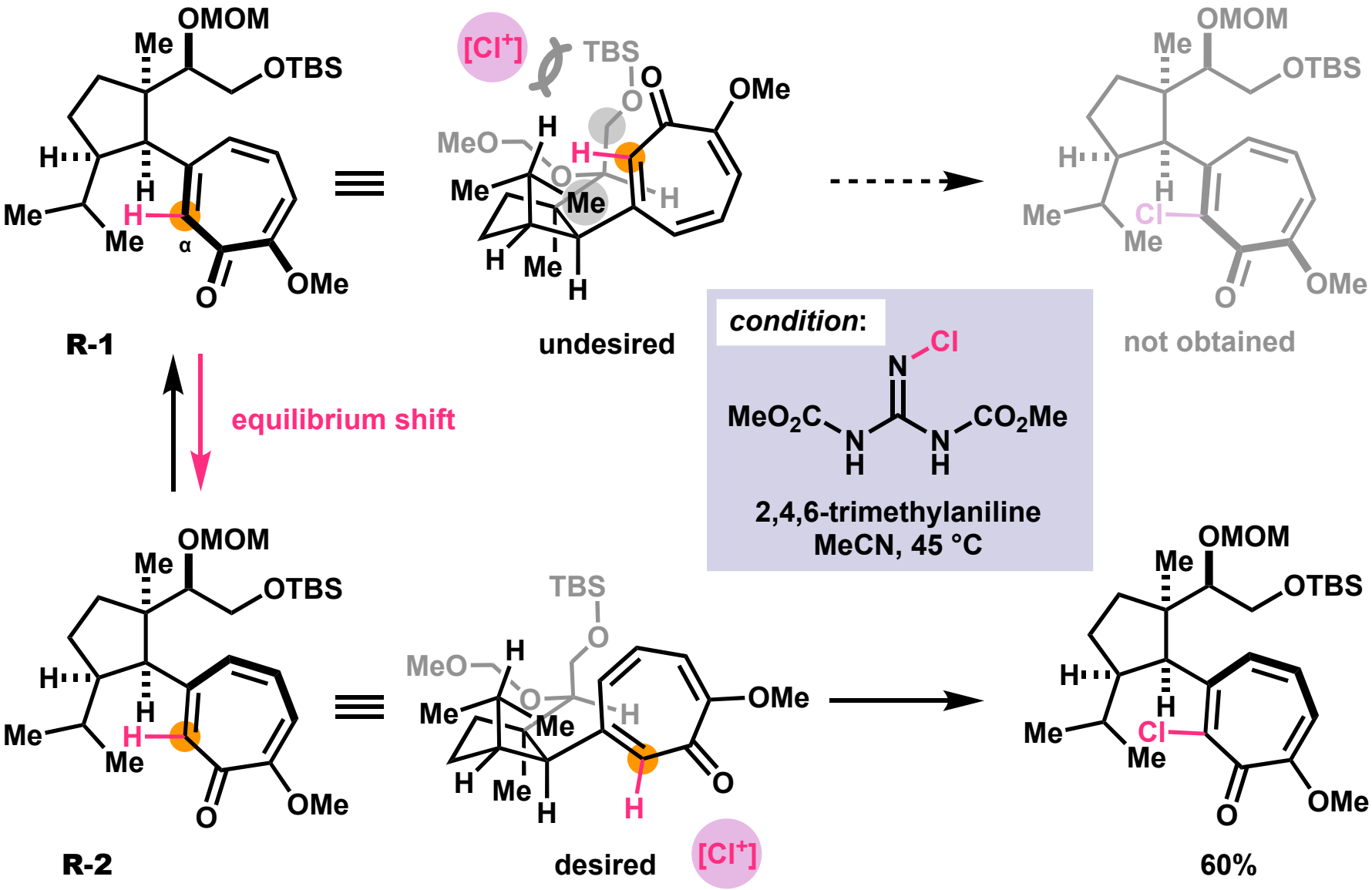
Palau'Chlor
2,4,6-trimethylaniline
MeCN, 45 °C



Palau'Chlor

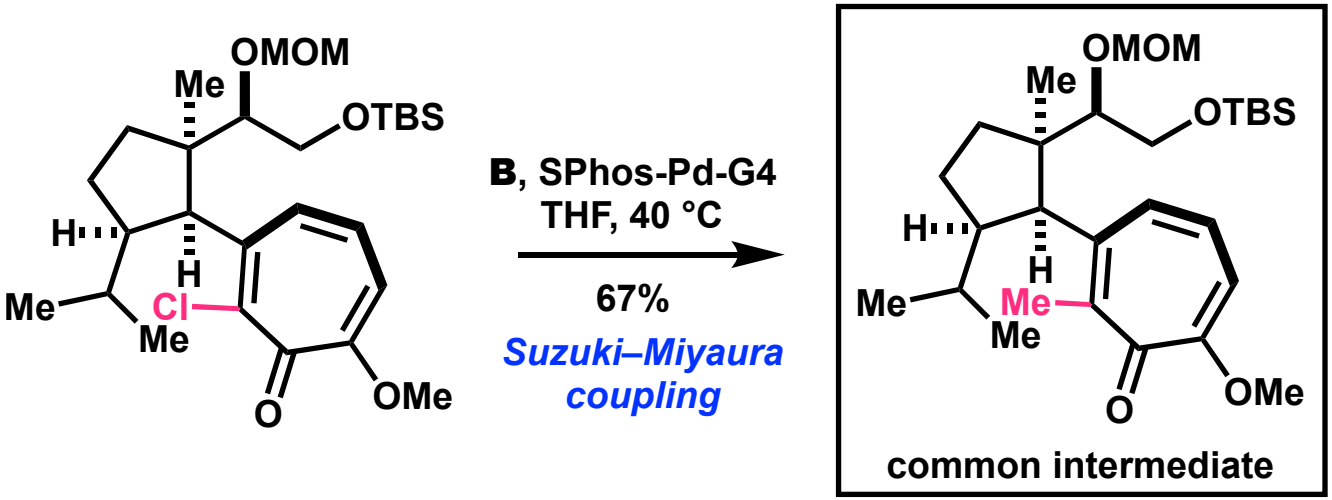
1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.

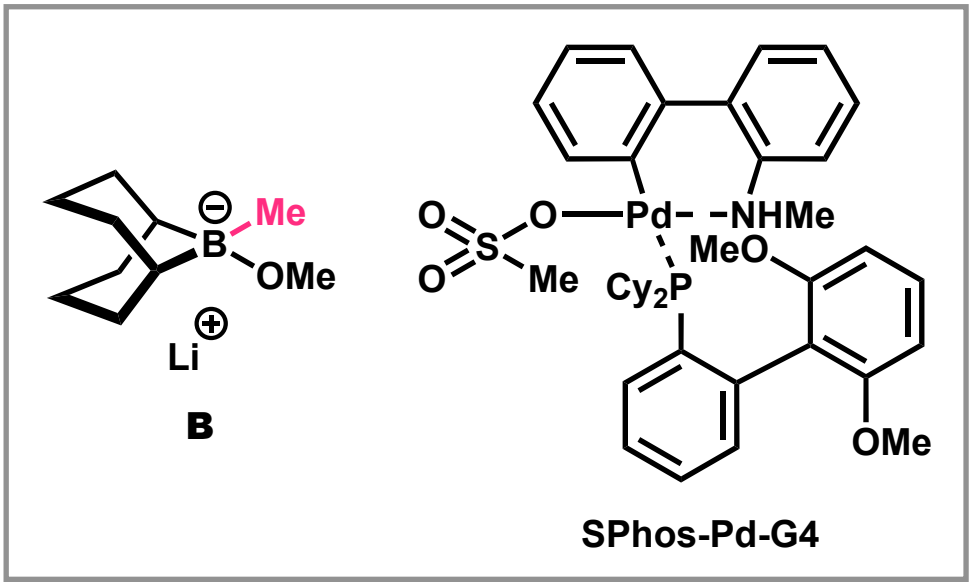
Equilibrium Shift in α Functionalization



1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.

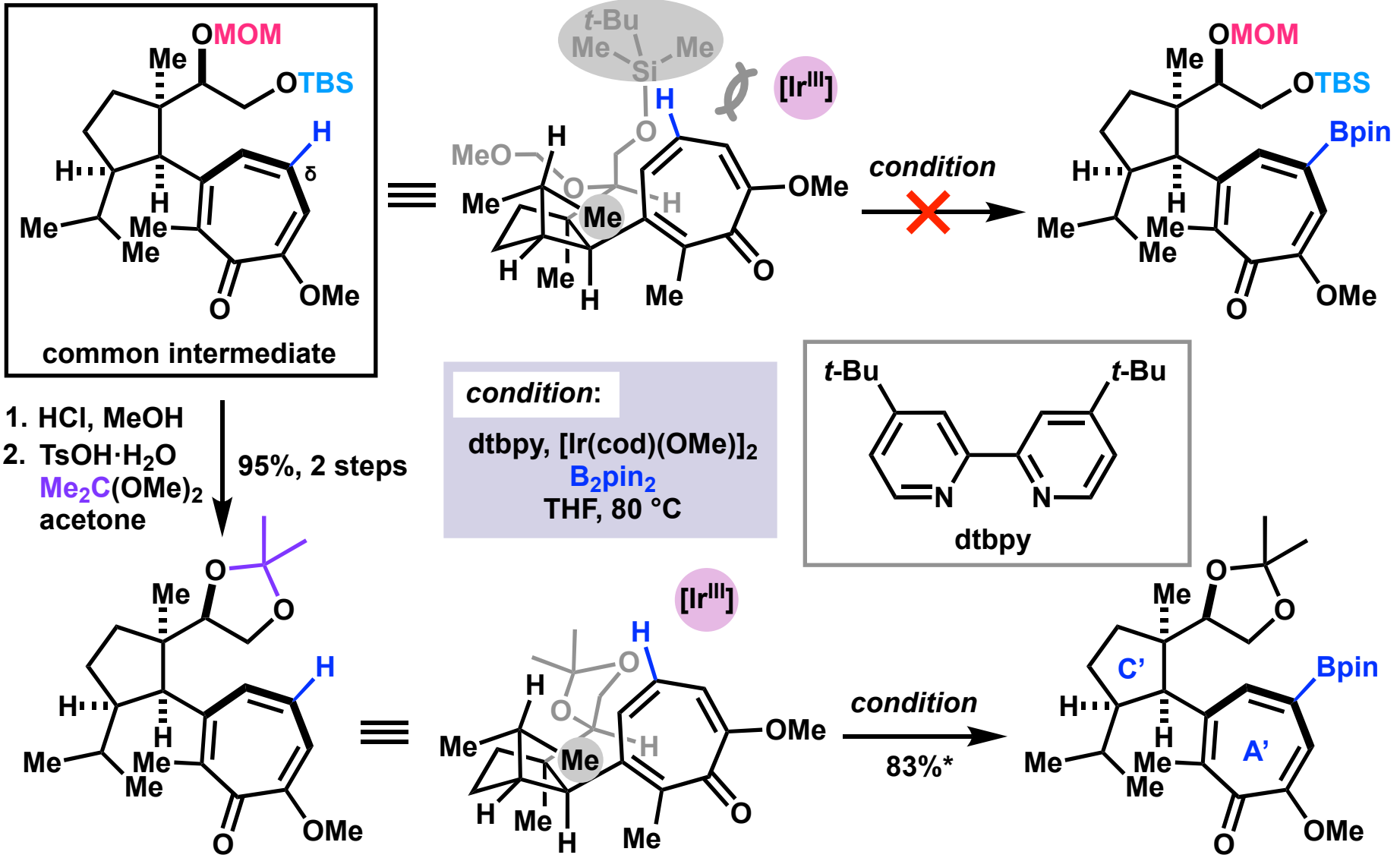
Functionalization of Tropolone at α Position





1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.

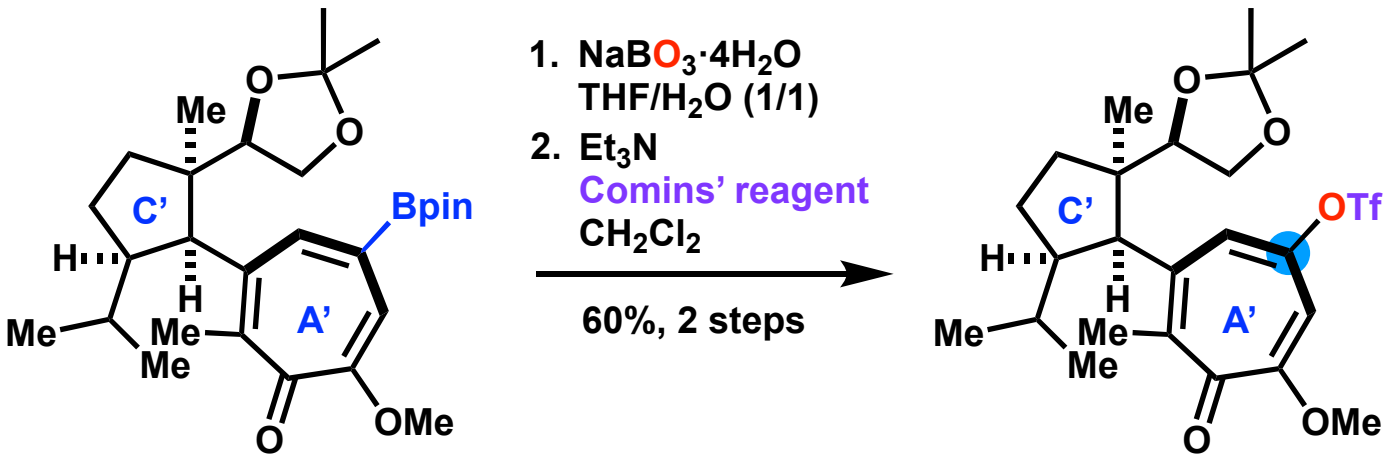
Synthesis of Right-Hand Fragment
-Functionalization of Tropolone at δ Position-

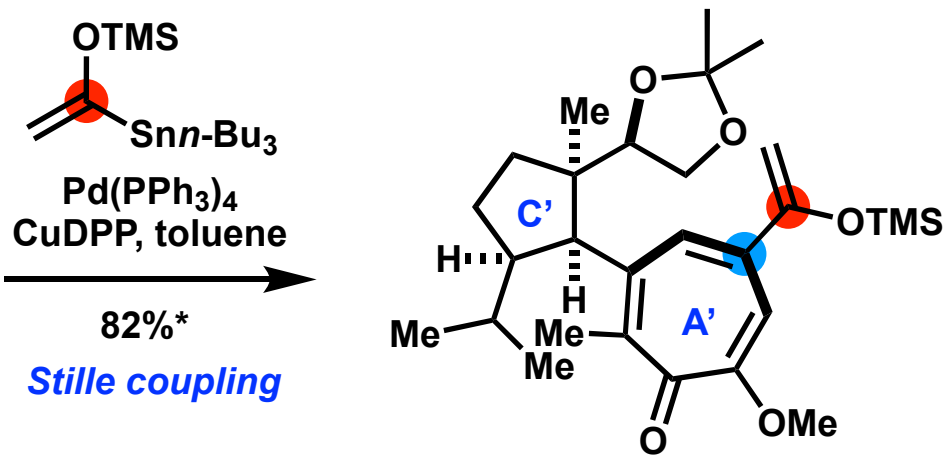


1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.

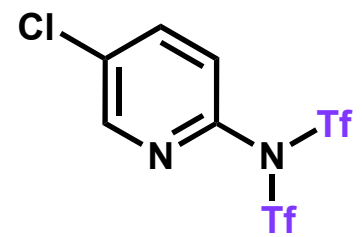
*The yield was calculated based on ^{1}H NMR using CH_2Br_2 as an internal standard due to its sensitivity to silica gel chromatography.

Synthesis of Right-Hand Fragment

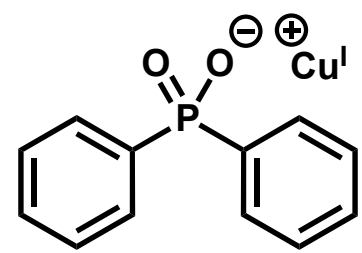




right-hand fragment



Comins' reagent

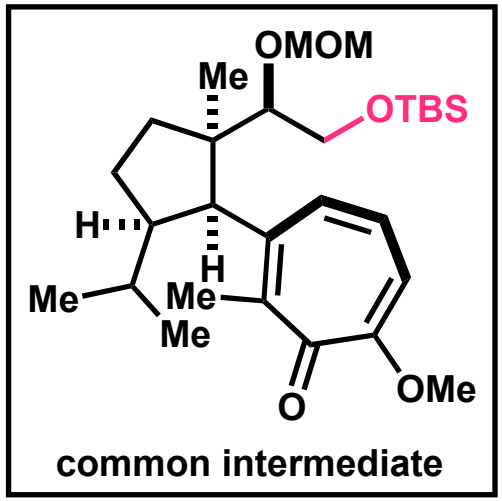


CuDPP

1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.

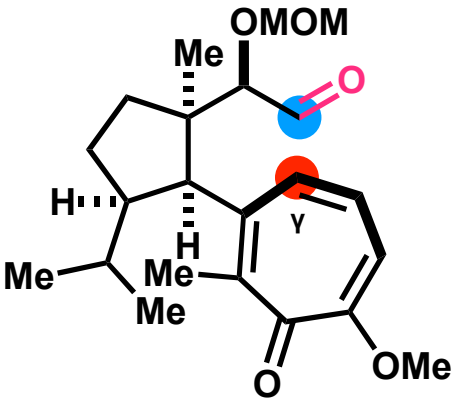
*The yield was calculated based on ^{1}H NMR using CH_2Br_2 as an internal standard due to its sensitivity to silica gel chromatography.

Synthesis of Left-Hand Fragment
-Functionalization of Tropolone at γ Position-

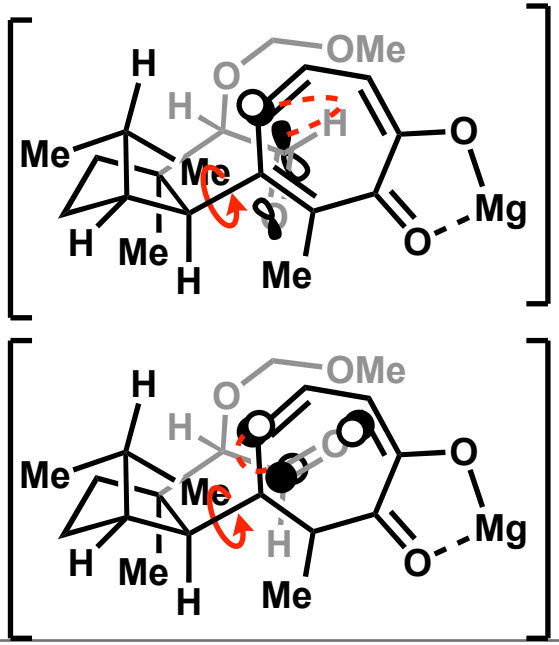


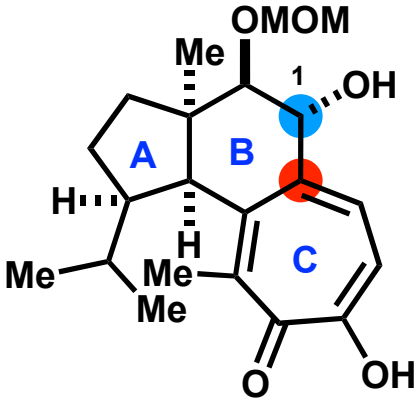
1. HCl, MeOH
   0 °C
2. Dess–Martin periodinane
   CH_2Cl_2

97%, 2 steps



$MgBr_2 \cdot OEt_2$
THF, reflux





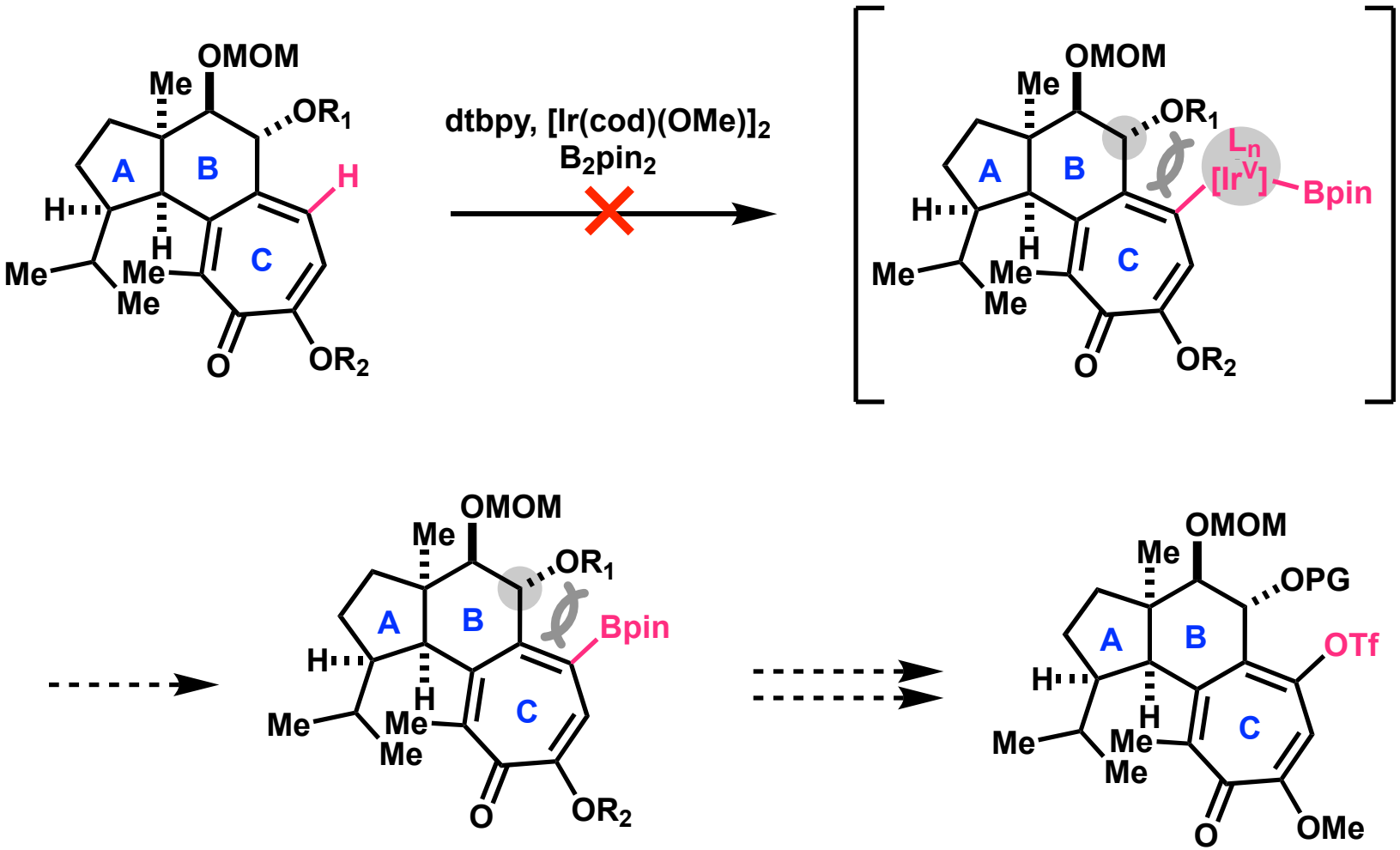
C
89%*

C1-*epi*-C
not obtained

1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.

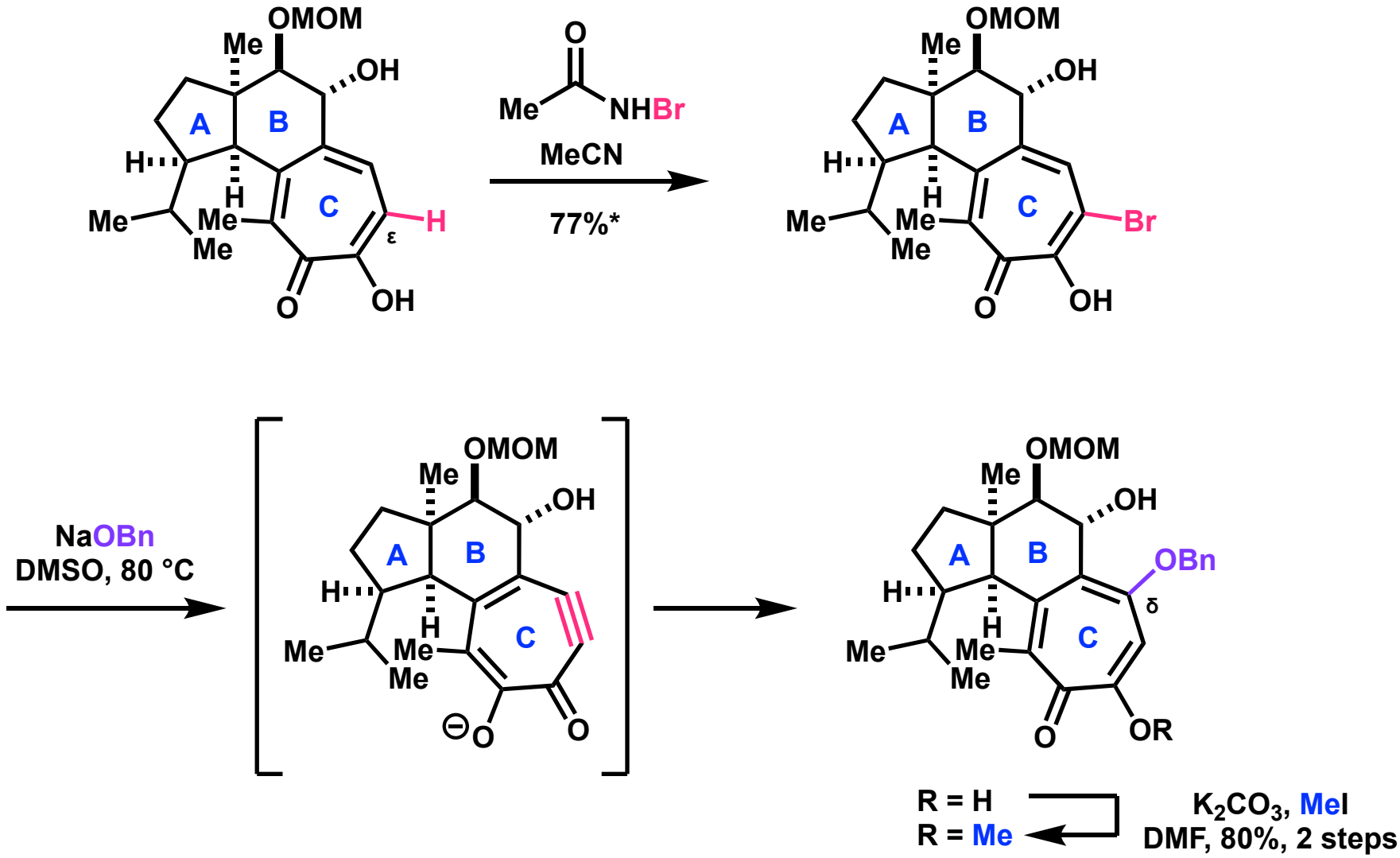
*The yield was calculated based on ^1H NMR using CH_2Br_2 as an internal standard due to its sensitivity to silica gel chromatography.

Synthesis of Left-Hand Fragment
-Attempted Functionalization at δ Position-



1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.

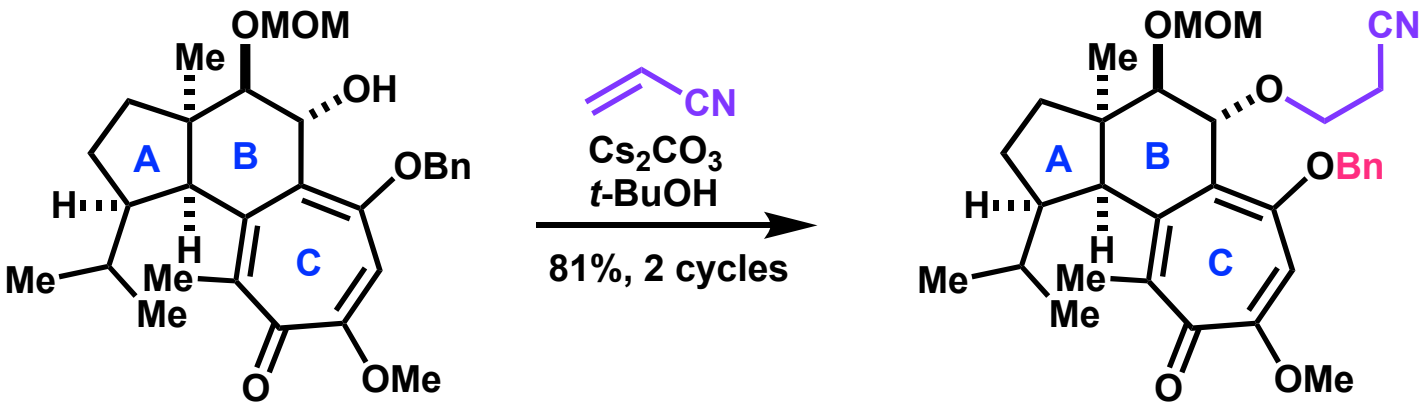
Synthesis of Left-Hand Fragment
-Functionalization via Benzyne-Type Intermediate-

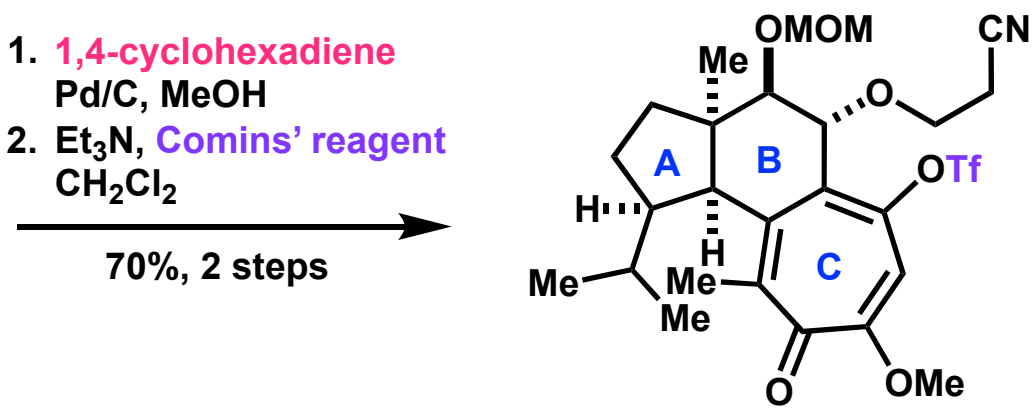


1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.

*The yield was calculated based on ^{1}H NMR using CH_2Br_2 as an internal standard due to its sensitivity to silica gel chromatography.

Synthesis of Left-Hand Fragment

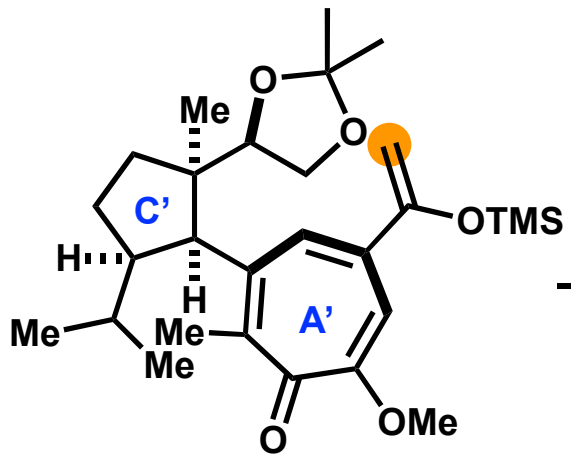




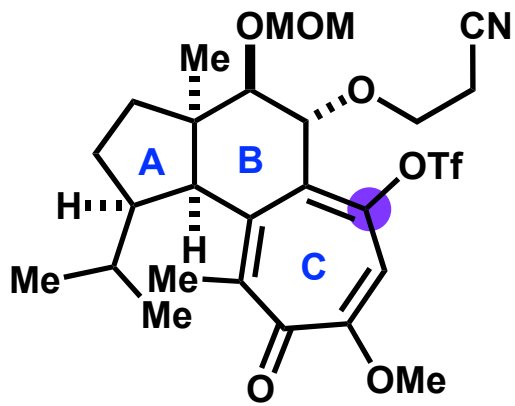
left-hand fragment

1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.

Pd-Catalyzed Cross-Coupling

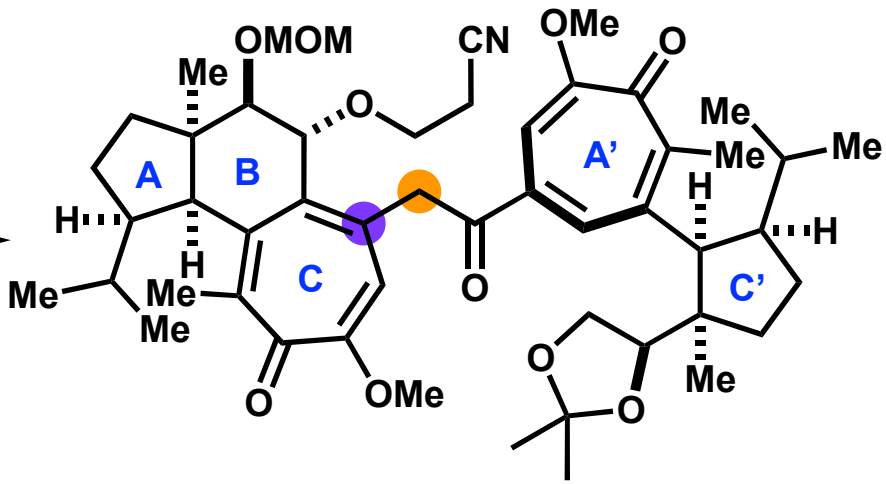


Y (= right-hand fragment, 1.7 eq)



Z (= left-hand fragment, 1.0 eq)

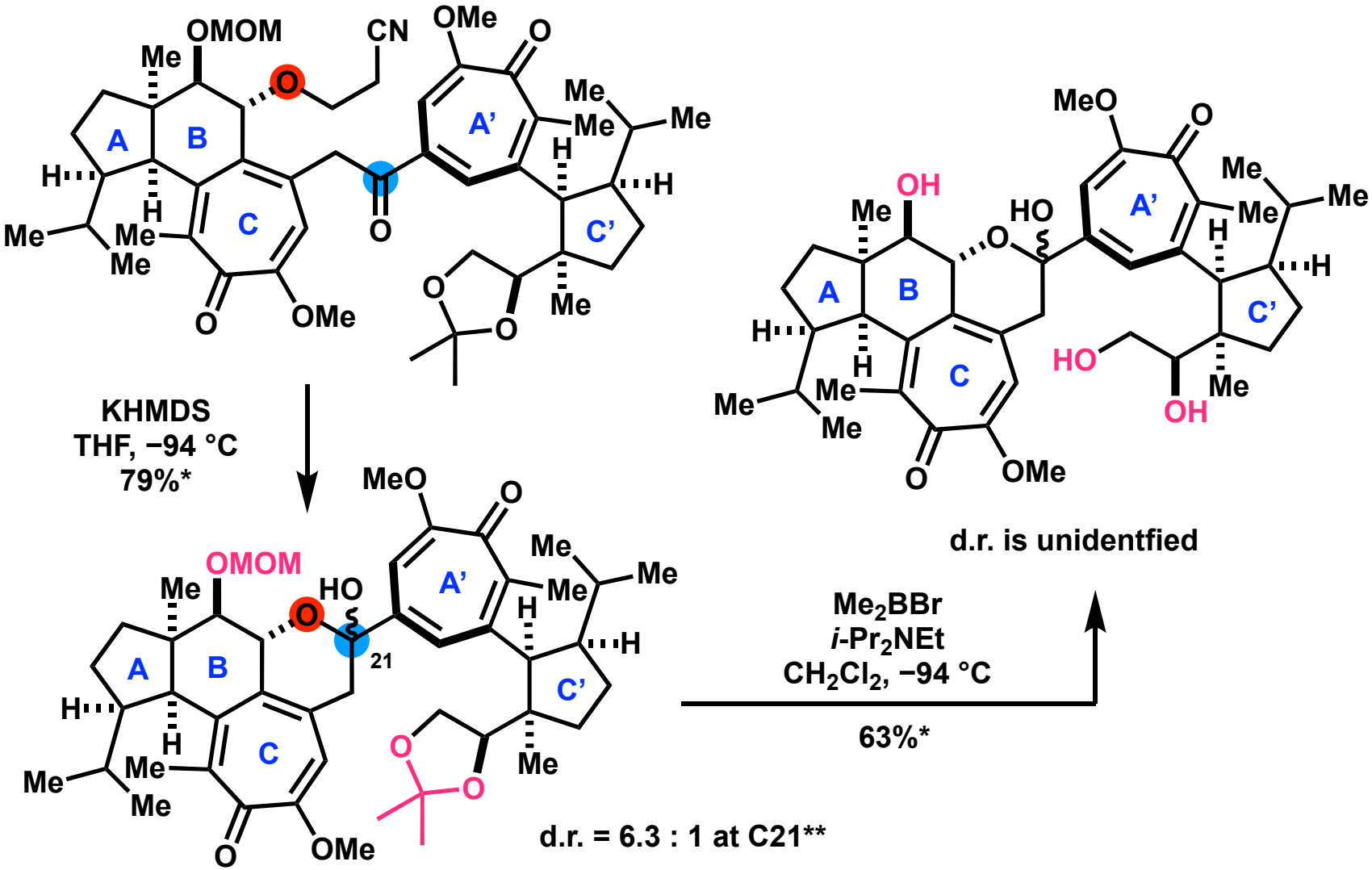
$Pd(Pt\text{-}Bu_3)_2$
$n\text{-}Bu_3SnF$
toluene, 82 °C



43% (based on **Z**)

1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.

Hemiketal Formation and Acetonide Removal

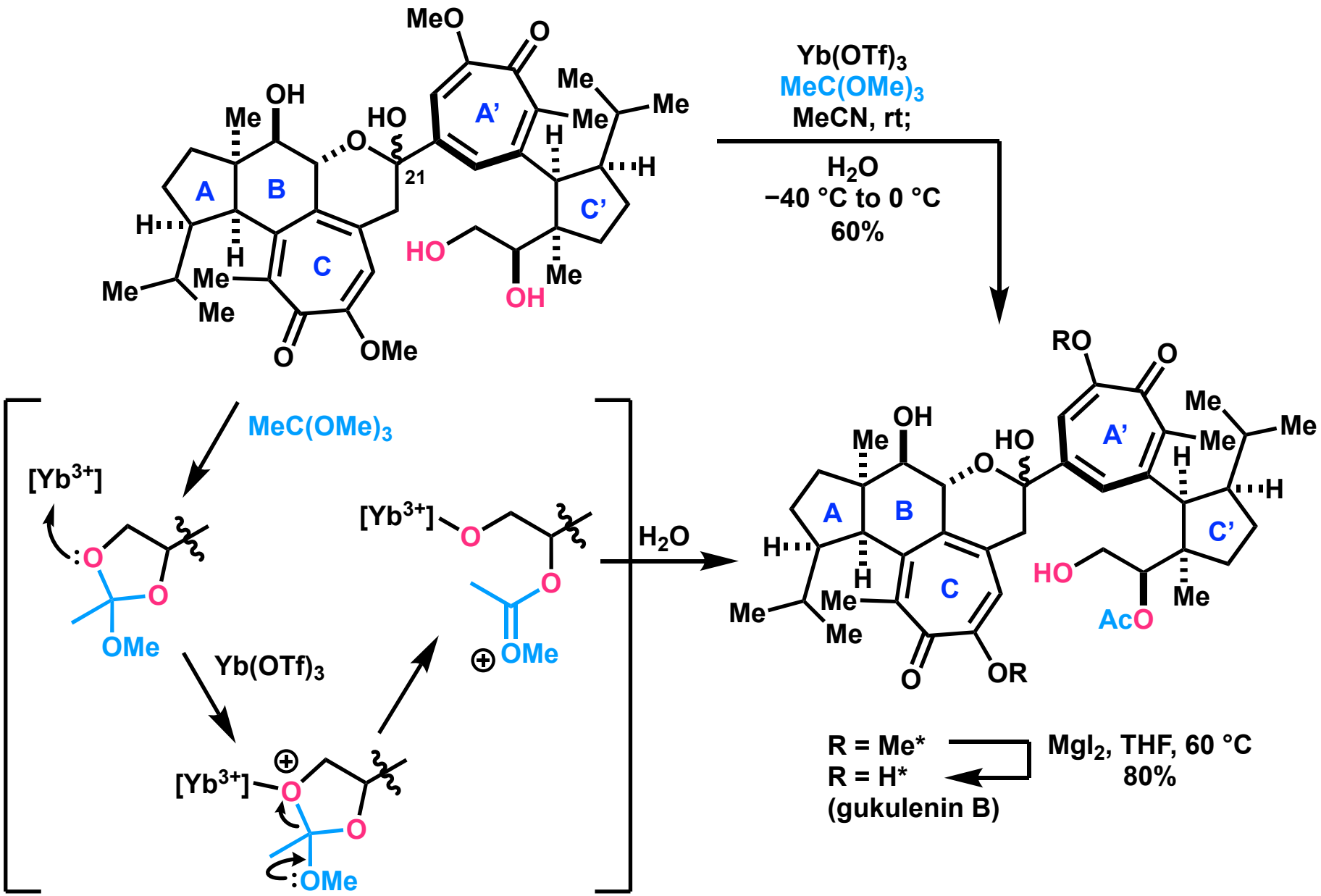


1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.

*The yield was calculated based on ^{1}H NMR using CH_2Br_2 as an internal standard due to its ability to interconvert on silica gel.

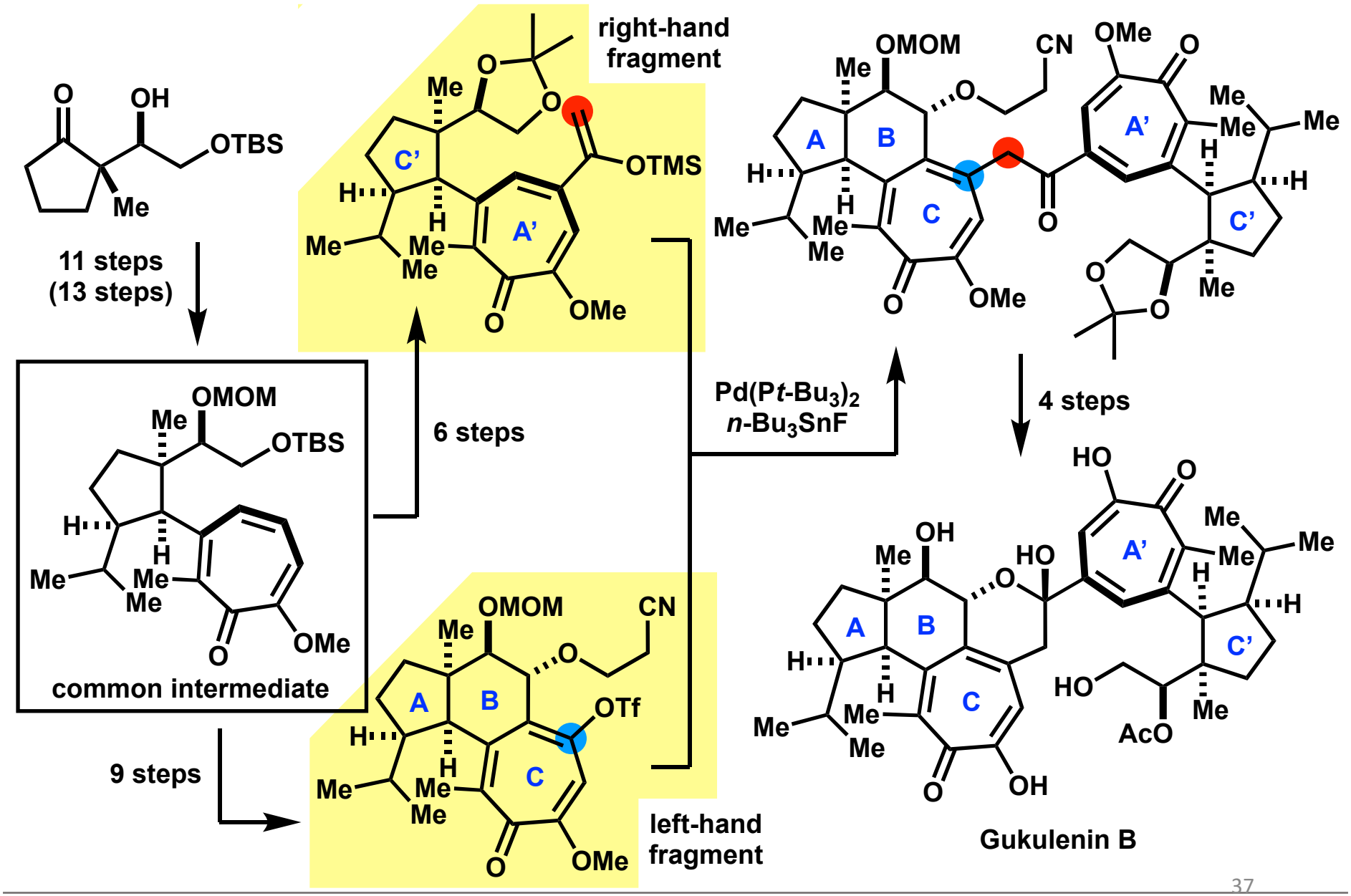
**The major product is C21-β-OH.

Total Synthesis of Gukulenin B



1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.
*d.r. at C21 = 20 : 1 (R = Me), and 1 : 0 (R = H).

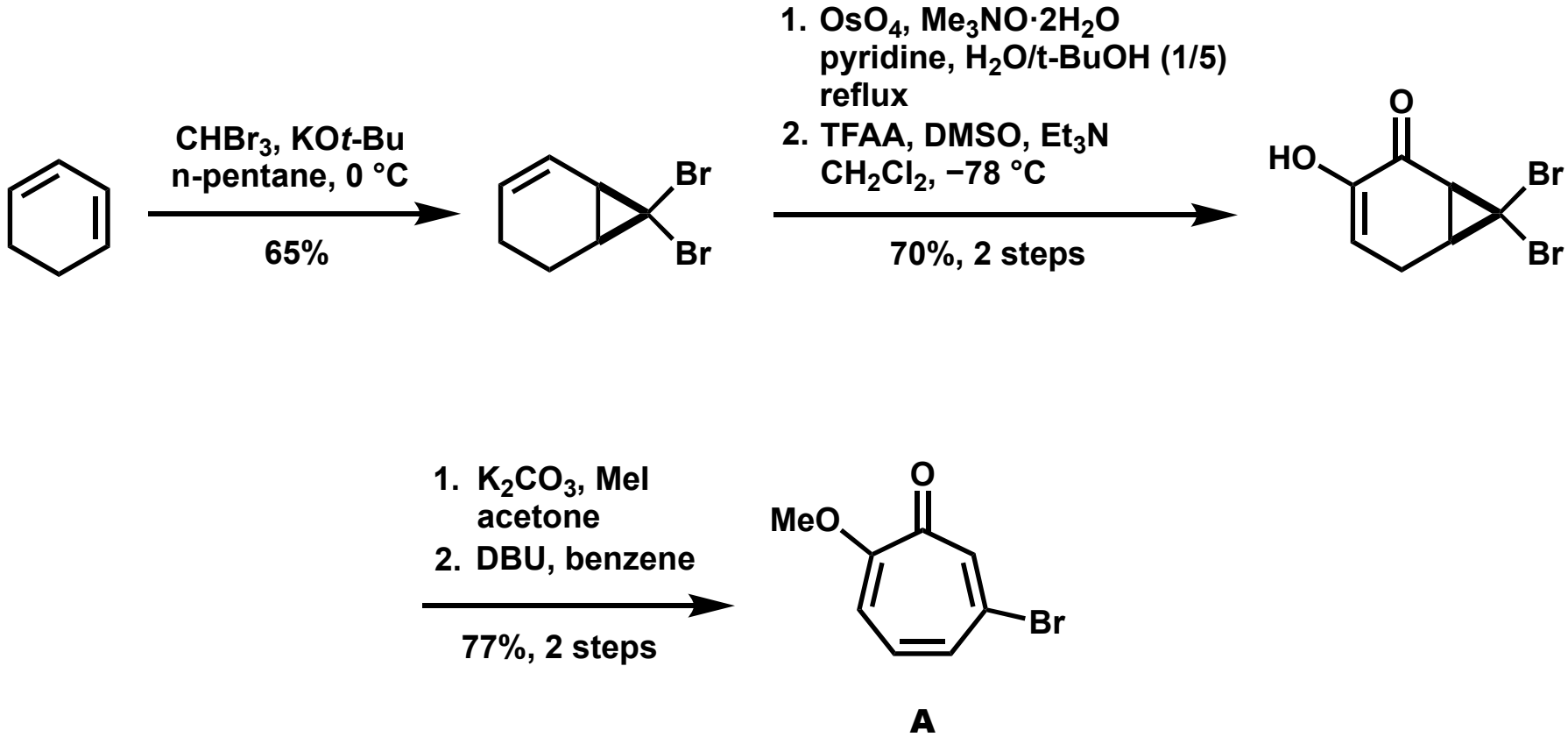
Summary



1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.

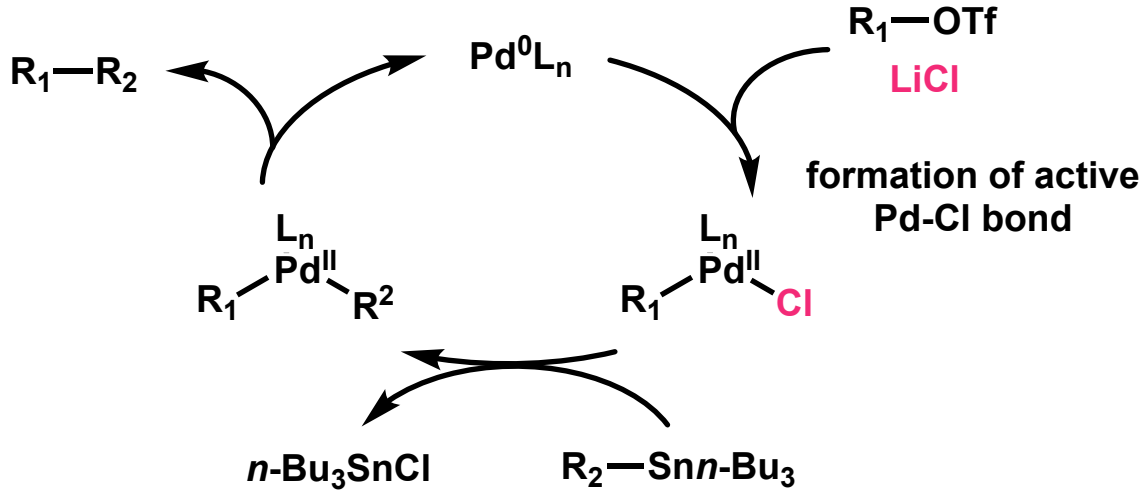
Appendix

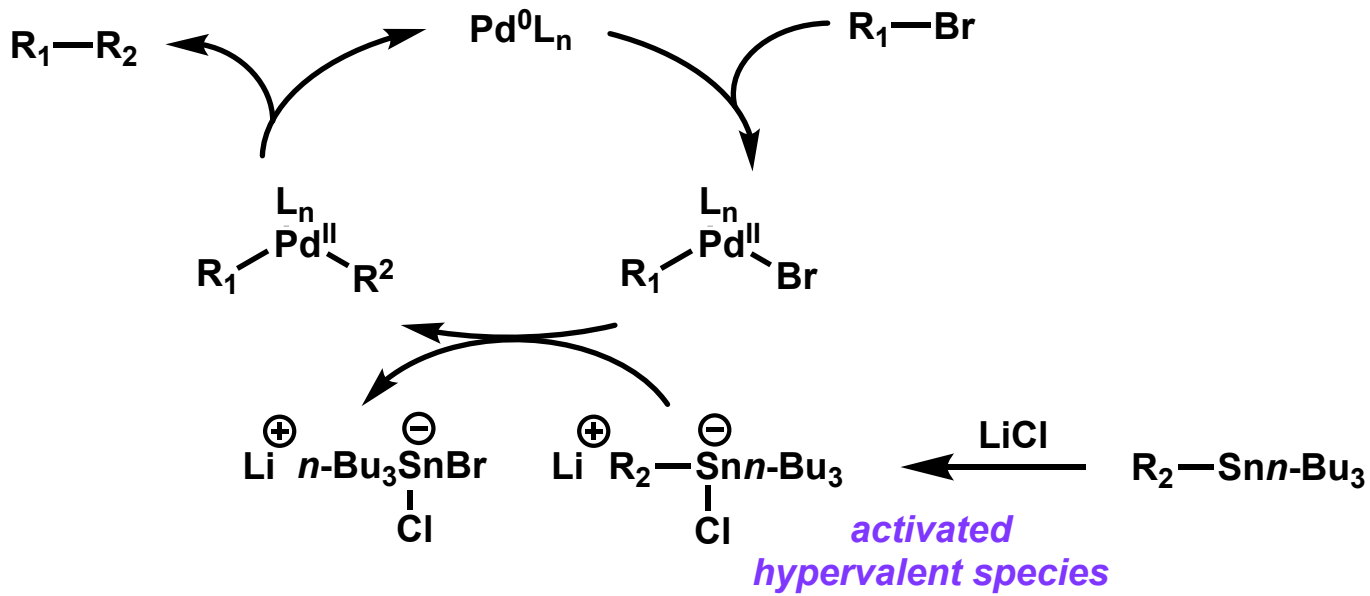
Synthesis of β-Substituted Tropolone



1) Nicolaou, K. C.; Yu, R.; Lu, Z.; Alvarez, F. G. *J. Am. Chem. Soc.* **2022**, *144*, 5190.

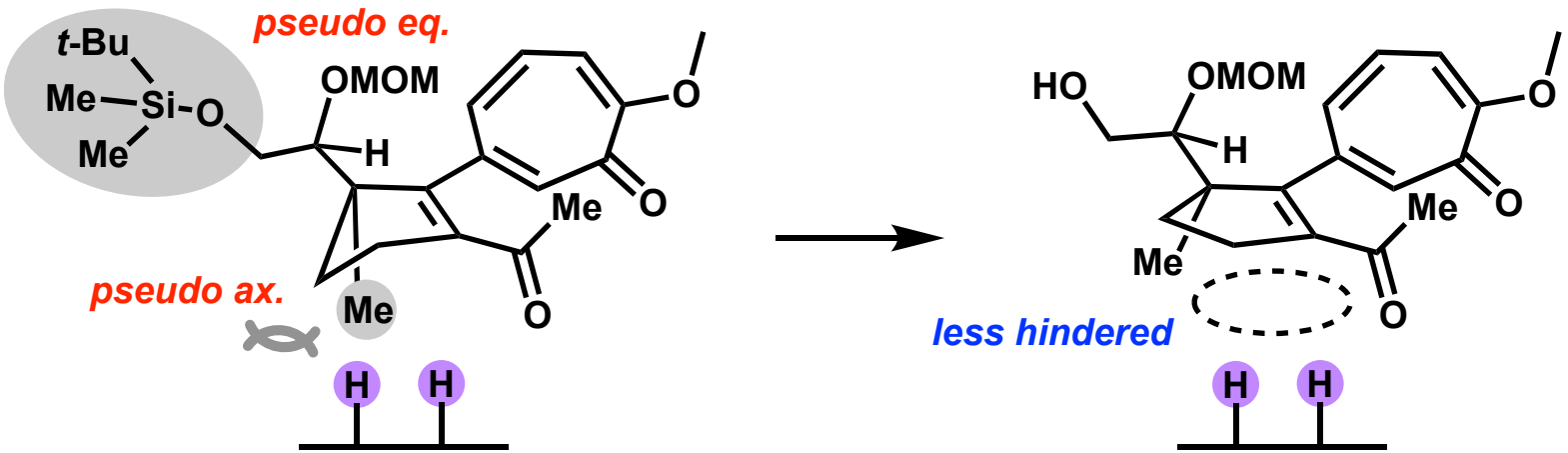
The Role of LiCl in Stille Coupling



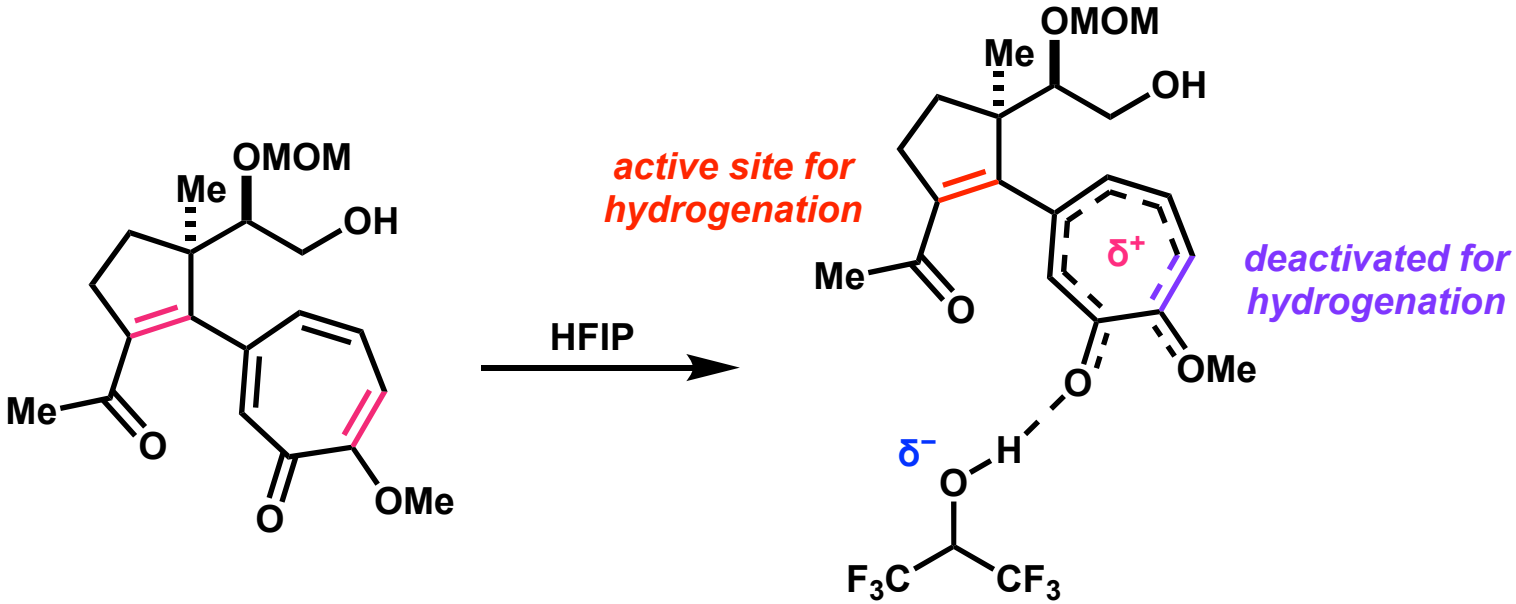


1) Scott, W. J.; McMurry, J. E. *Acc. Chem. Res.* **1988**, 21, 47.
2) Fujita, M.; Oka, H.; Ogura, K. *Tetrahedron Lett*, **1995**, *36*, 5247.

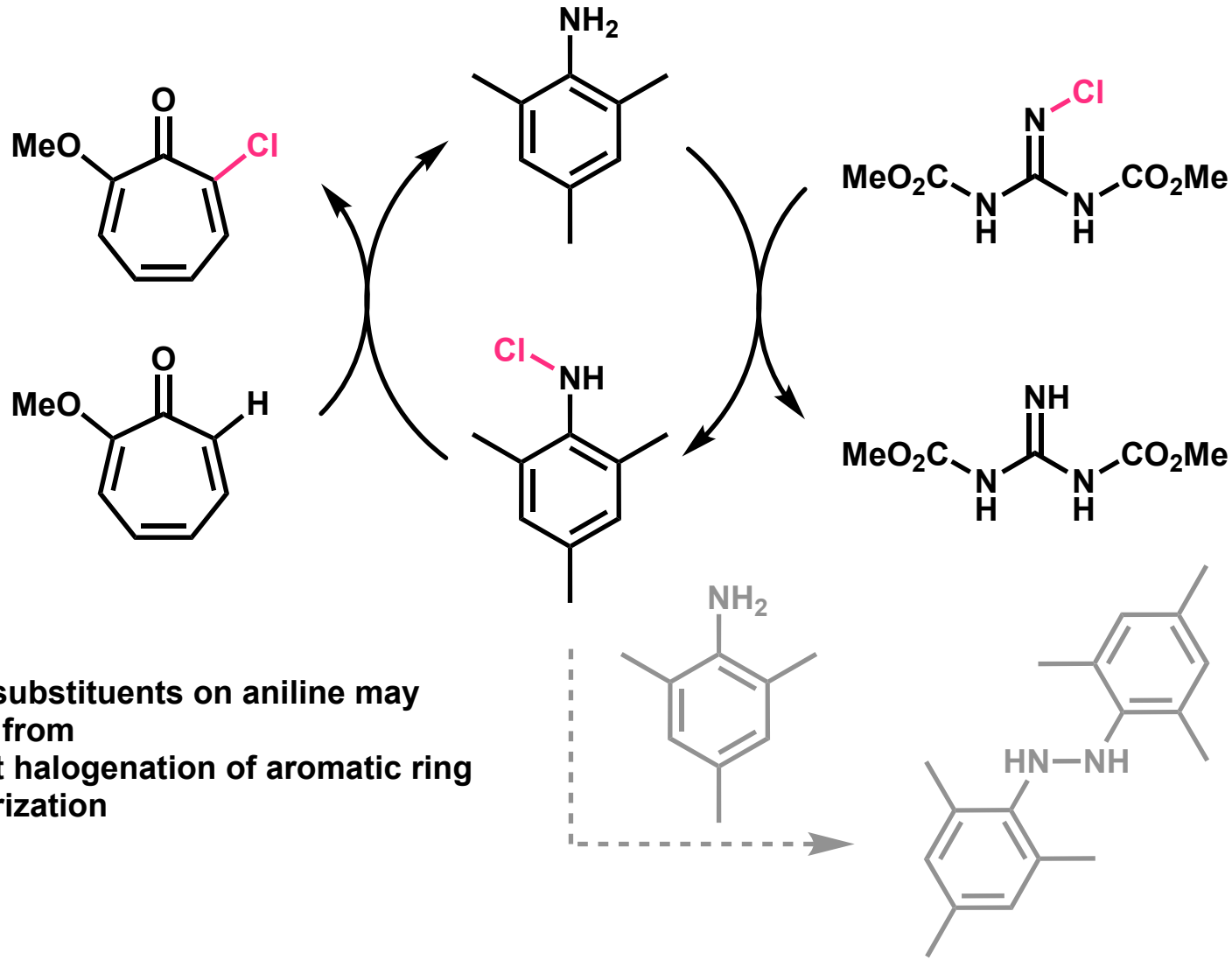
Rationale for the Result of Hydrogenation



Use of HFIP in Hydrogenation



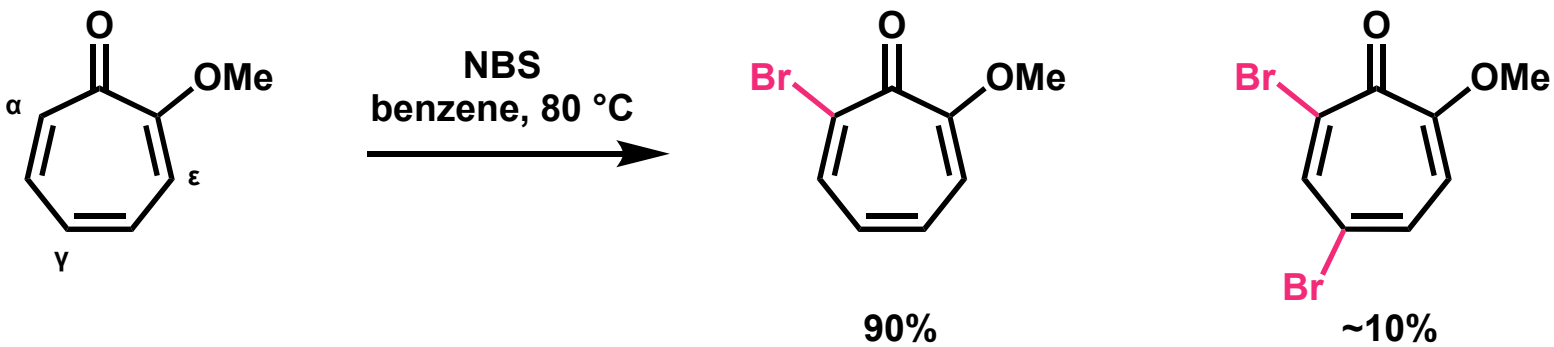
The Role of 2,4,6-trimethylaniline

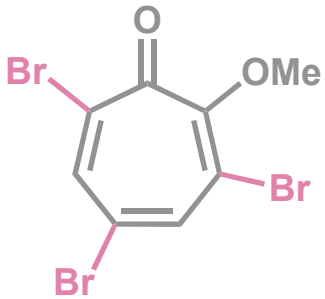


bulky substituents on aniline may inhibit from
- direct halogenation of aromatic ring
- dimerization

1) Samanta, R. C.; Yamamoto, H. *Chem. Eur. J.* **2015**, 21, 11976.

Regioselectivity of Electrophilic Addition toward Tropolone



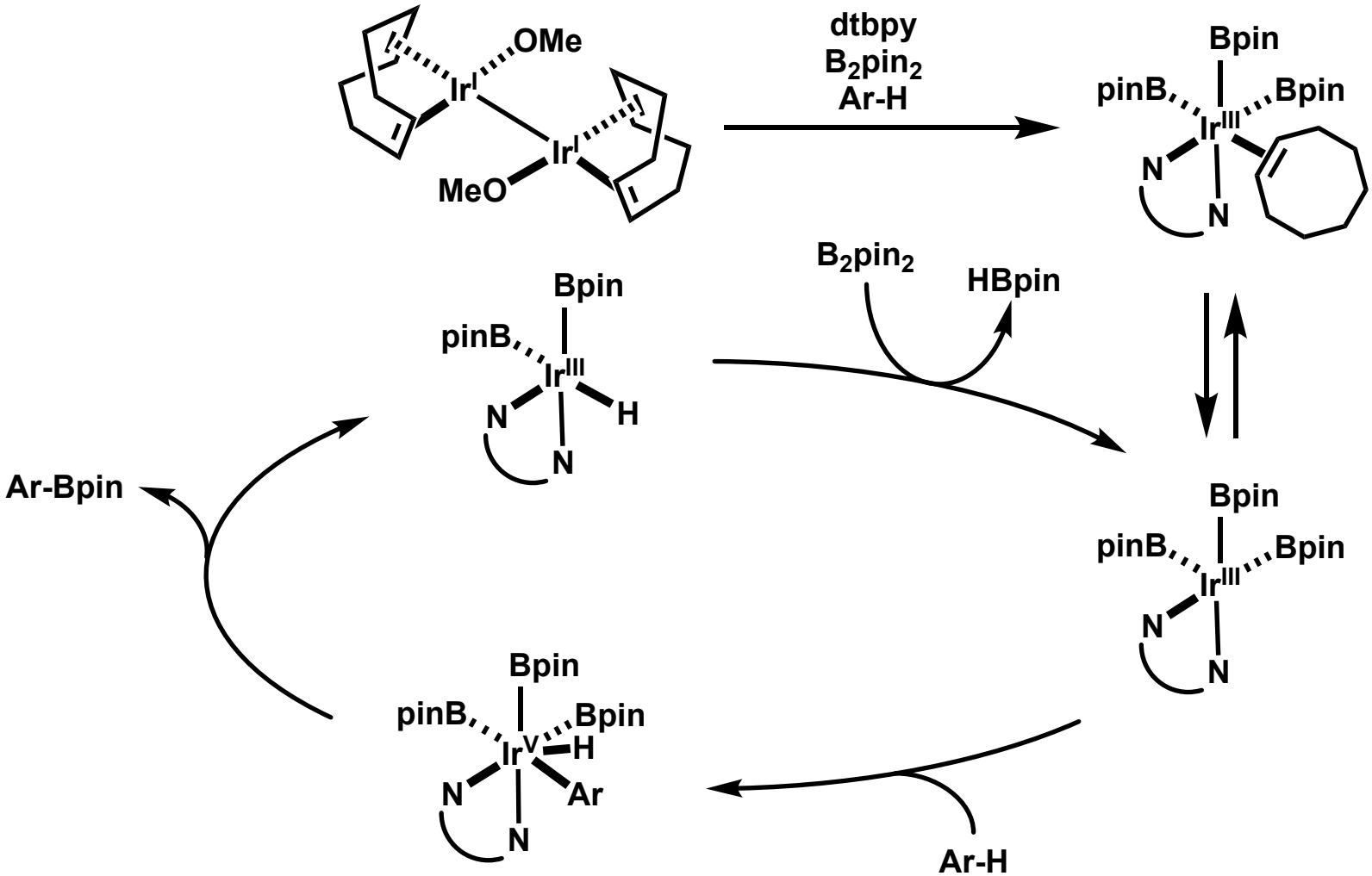


not obtained

Reactivity towrad electrophilic attack is high in the order α > γ > ε.

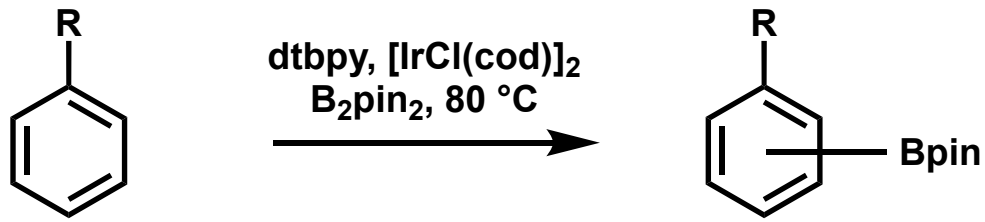
1) Takeshita, H.; Mori, A.; Kusaba, T. *Synthesis.* **1986**, 578.

Ir-Catalyzed Borylation



1) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**. *124*, 390.
2) Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura,N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**,127, 14263.

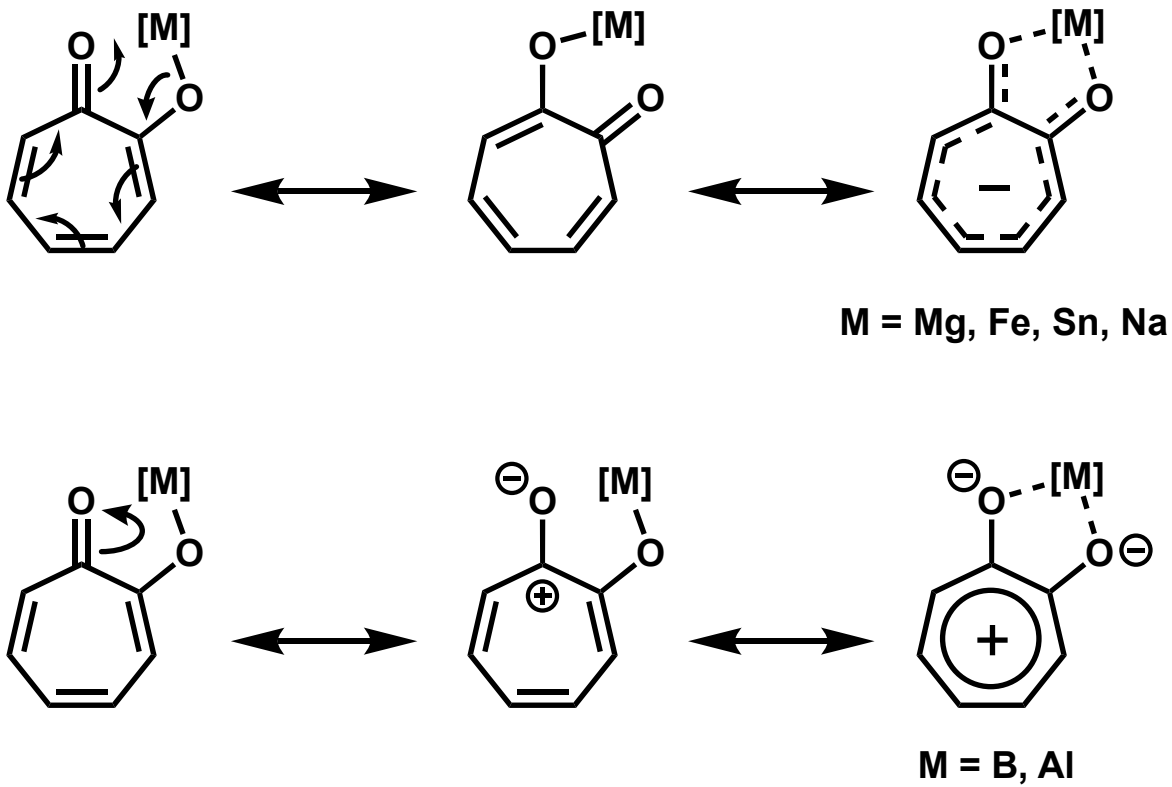
Ir-Catalyzed Borylation



R	yield	*o* / *m* / *p*
CH_3	82%	0 / 69 / 31
OMe	95%	1 / 74 / 25
CF_3	80%	0 / 70 / 30

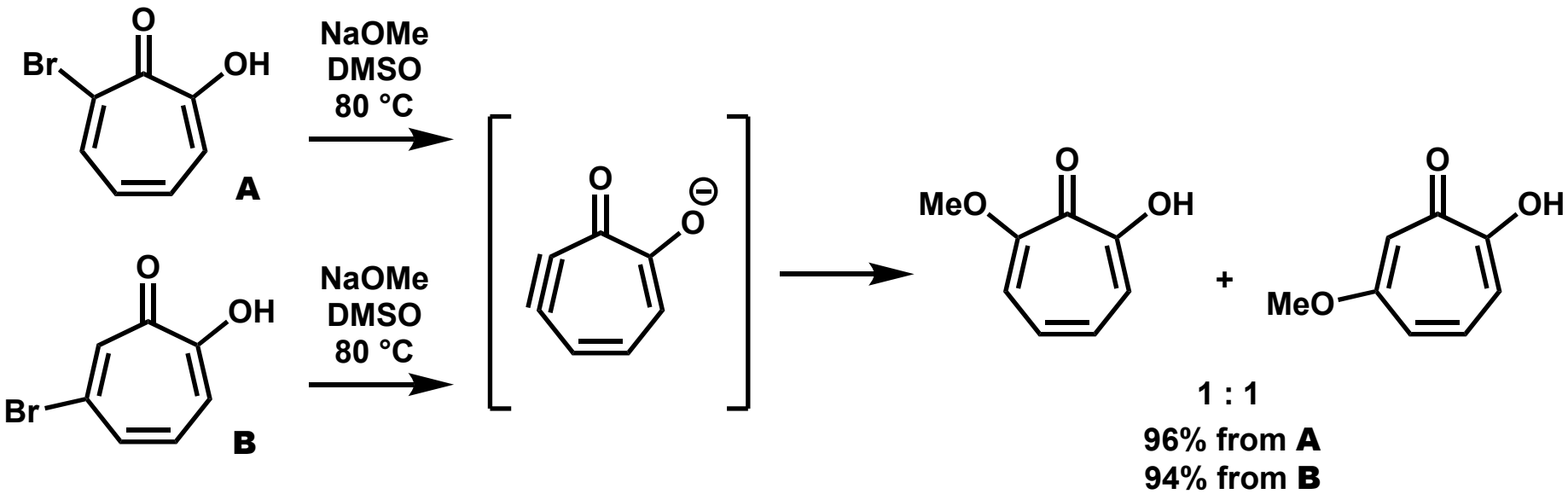
1) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**. *124*, 390.

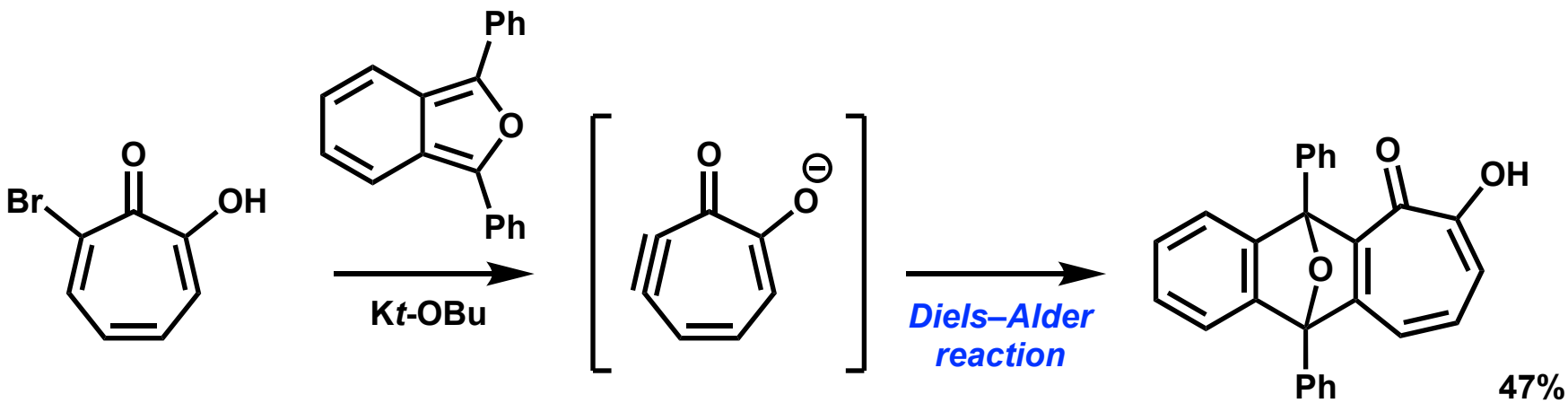
Two Modes of Troponato Ion



1) Cook, J. W.; Raphael, R. A.; Scott, A. I. 847. *J. Chem. Soc.* **1952**, 4416.
2) Karipides, A.; Graf, J. *Inorg. Nucl. Chem. Lett.* **1972**, 8, 161.

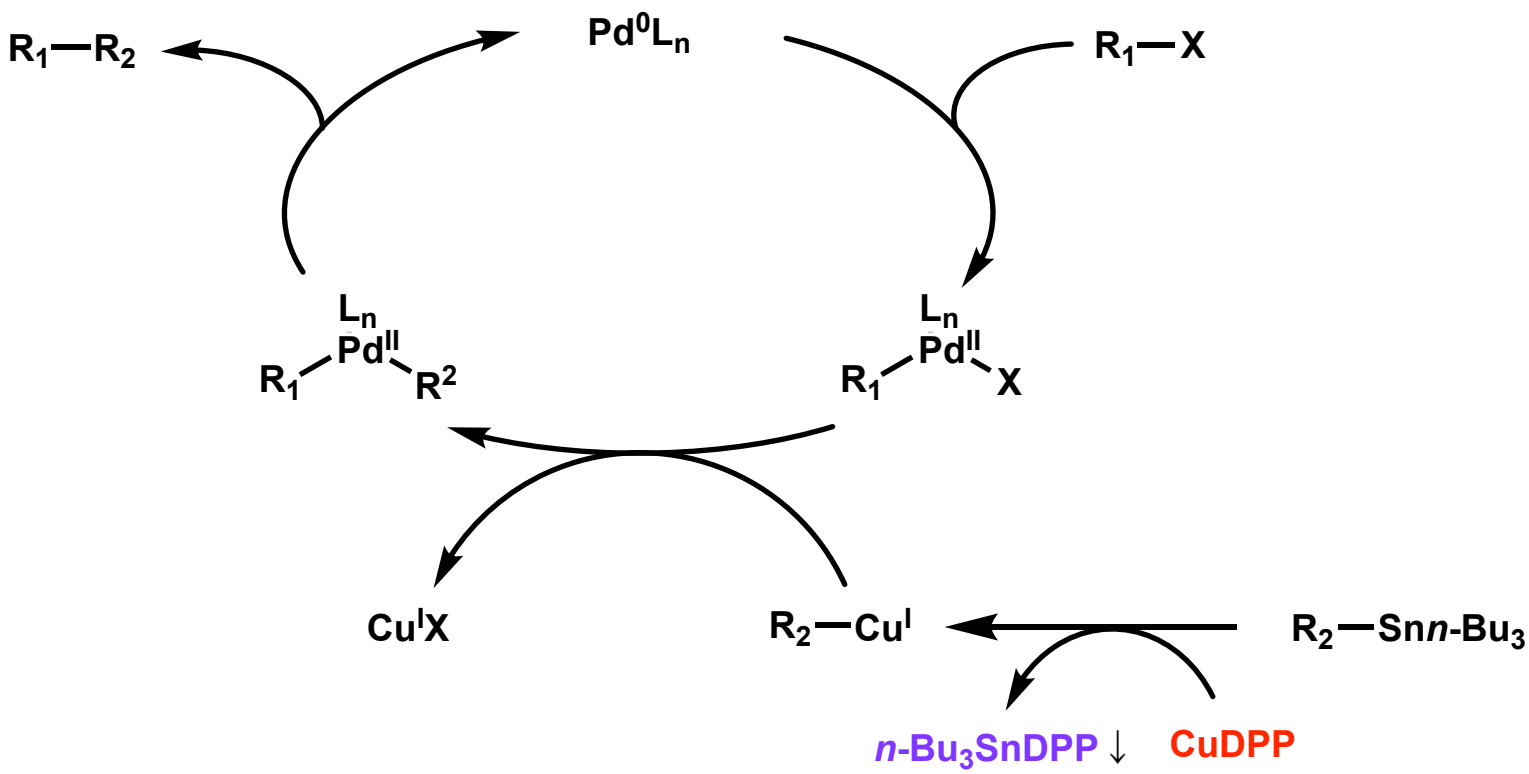
Previous Reserch on Tropolone Benzyne





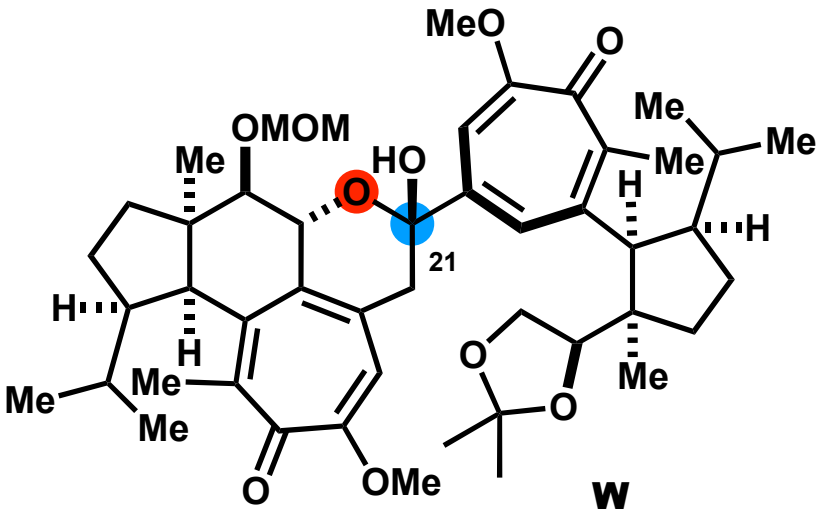
1) Yamatani, T.; Yasunami, M.; Takase, K. *Tetrahedron Lett.* **1970**, 11, 1725.

Use of CuDPP in Stille Coupling



1) Allred, G. D.; Liebeskind, L. *S. J. Am. Chem. Soc.* **1996**, 118, 2748.
2) Srogl, J.; Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1997**, 119, 12376.

Rationale for the Stereoselectivity at C21



W : C21-*epi*-W = 1 : 1 in crude NMR.
However, after standing the NMR tube at 23 °C for 16 h, the ratio changed to 6.3 : 1.
It indicates that there is a thermodynamic equilibrium between these diastereomers.