

Sarah Elizabeth Reisman

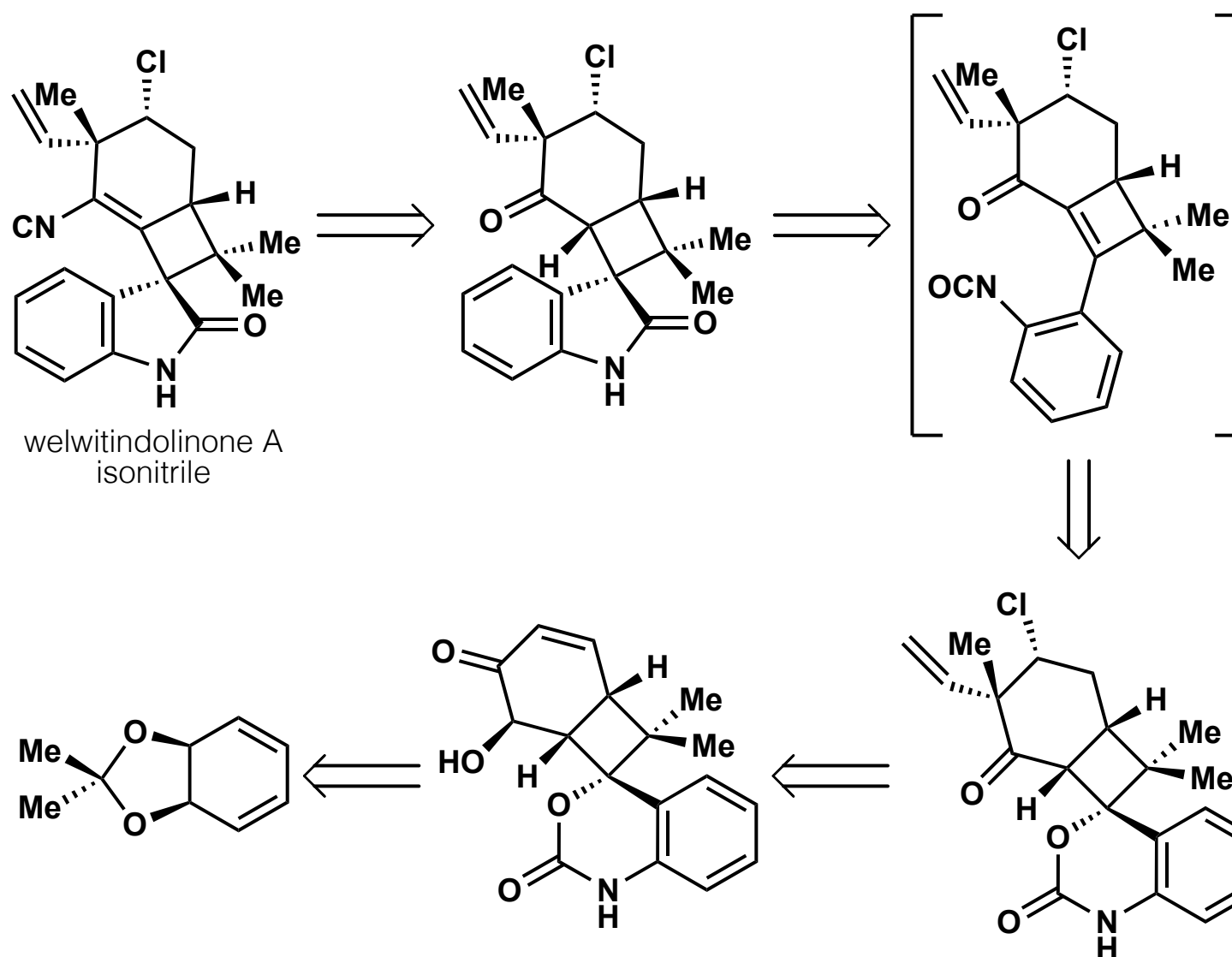
Larisa P. Pop
Group Meeting
December 13th, 2025

Shenvi Laboratory 

About Sarah



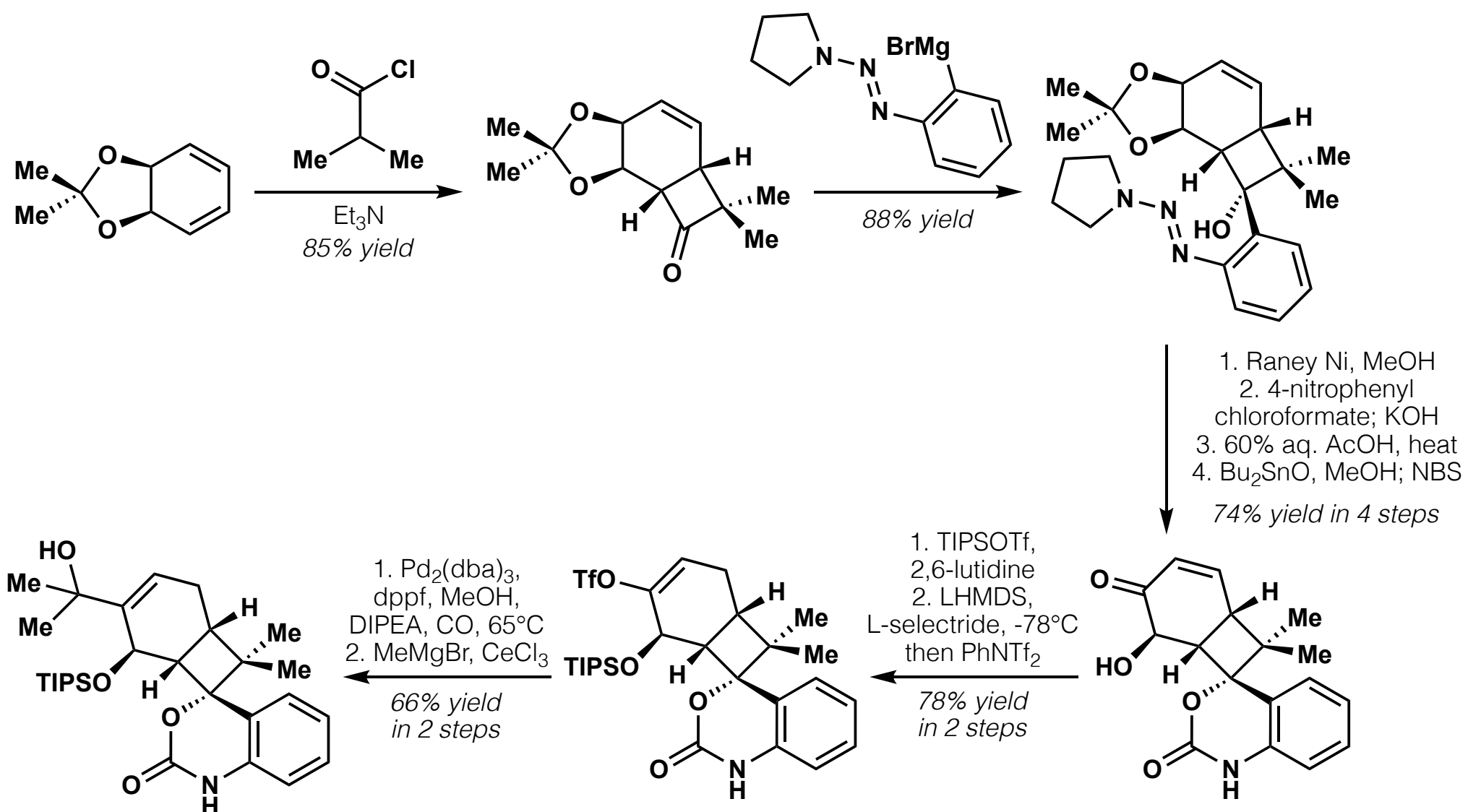
- 2001 B.A. in Chemistry at Connecticut College (T. V. Ovaska)
- 2006 Ph.D. at Yale University, (J. L. Wood)
 - *Total Synthesis of ($\pm$) Welwitindolinone A Isonitrile*



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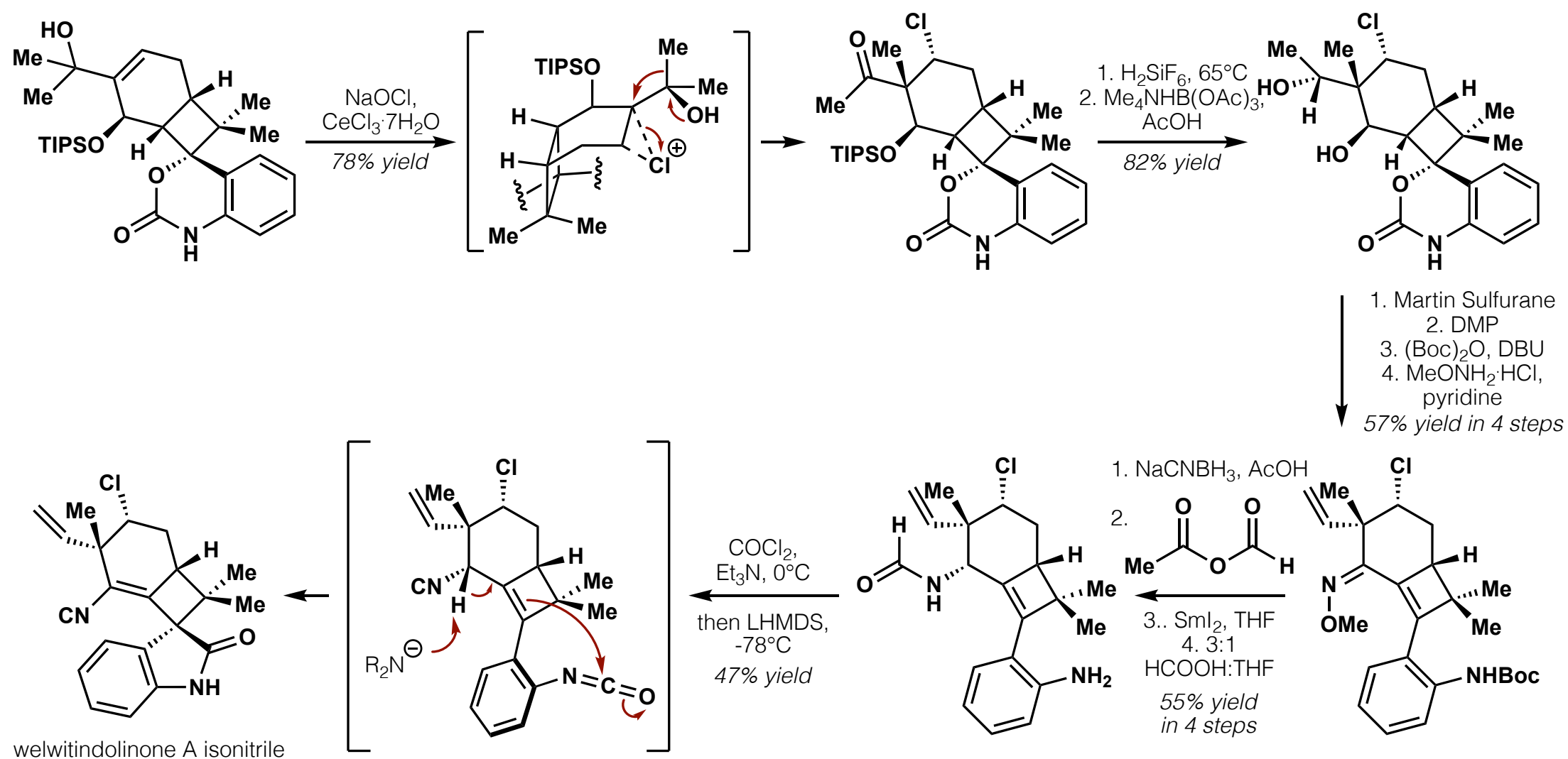
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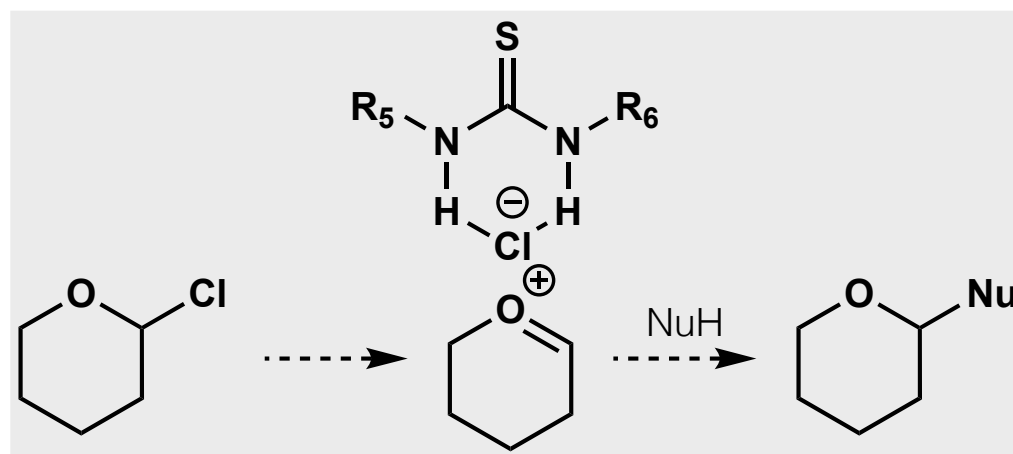
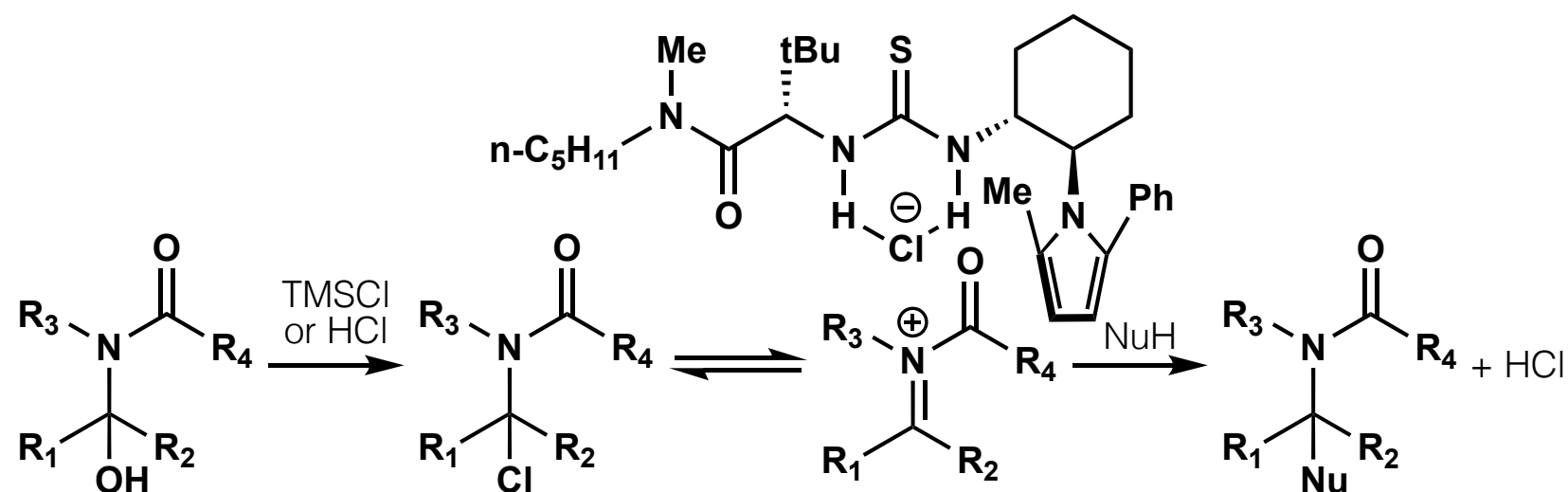
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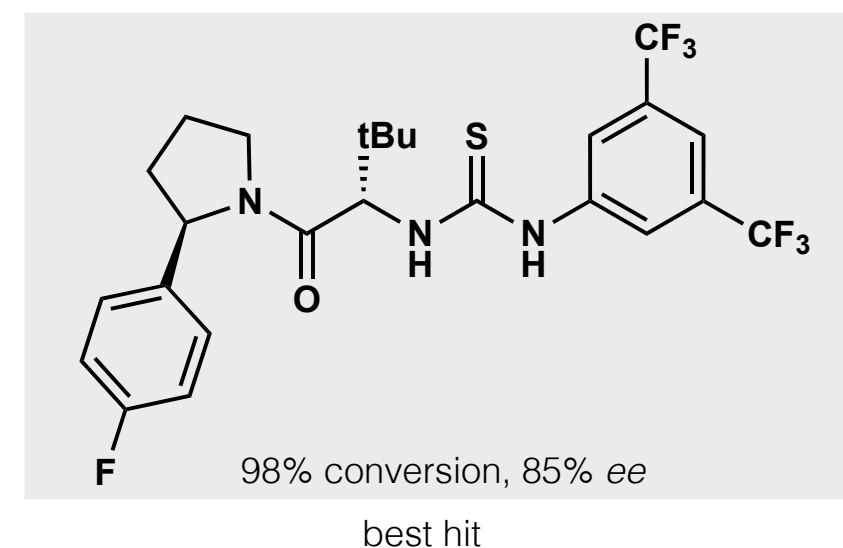
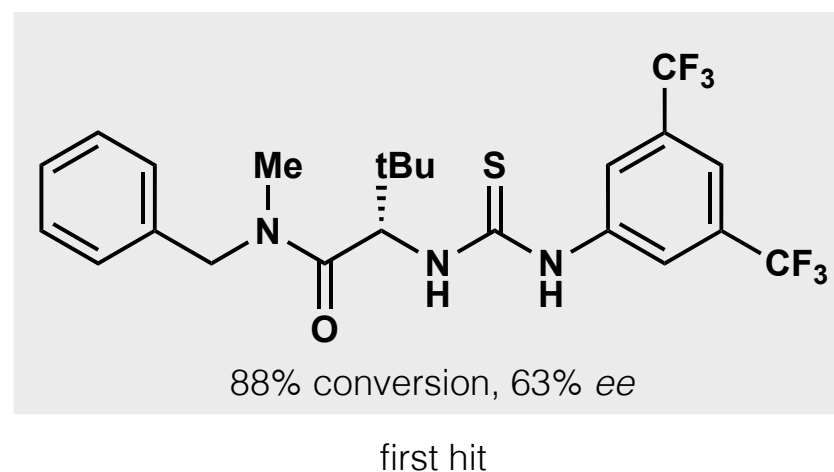
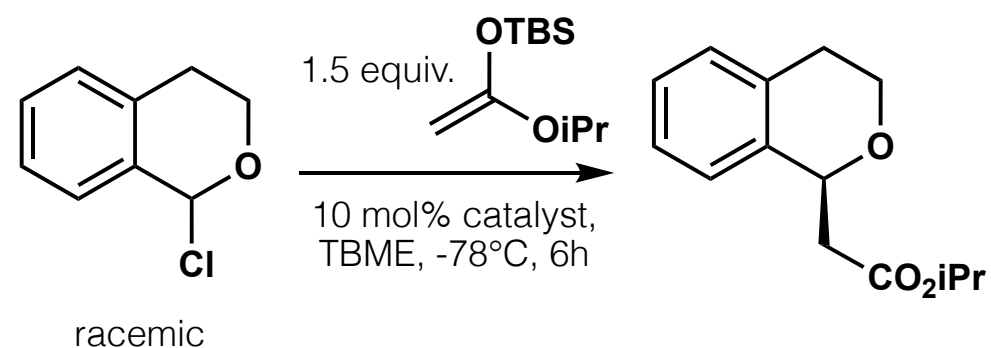
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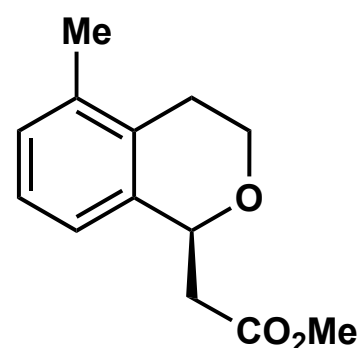
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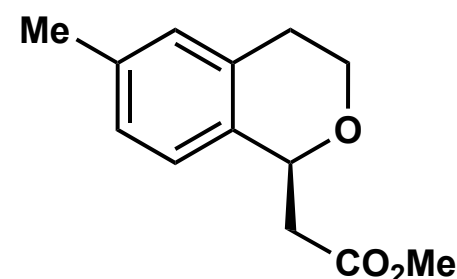
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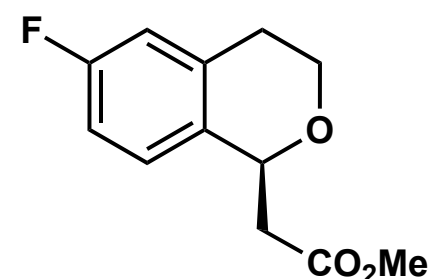
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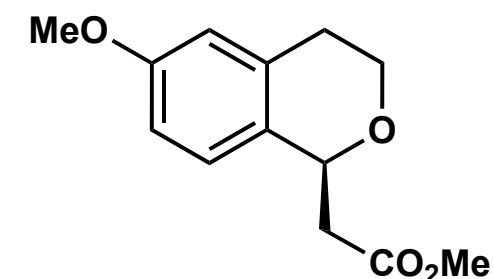
71% yield, 90% ee



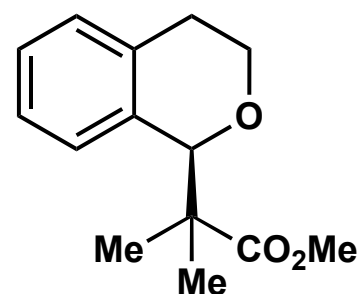
82% yield, 84% ee



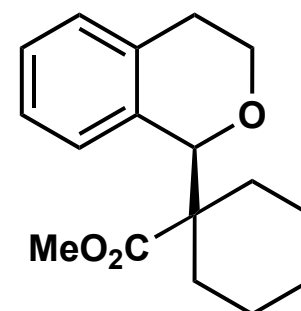
70% yield, 90% ee



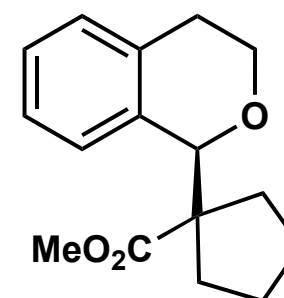
96% yield, 74% ee



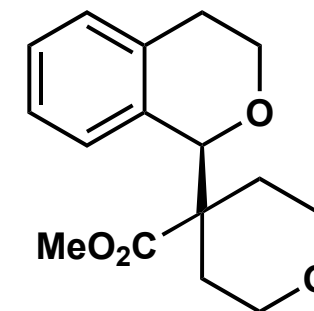
92% yield, 92% ee



84% yield, 94% ee



85% yield, 92% ee



87% yield, 93% ee

About Sarah

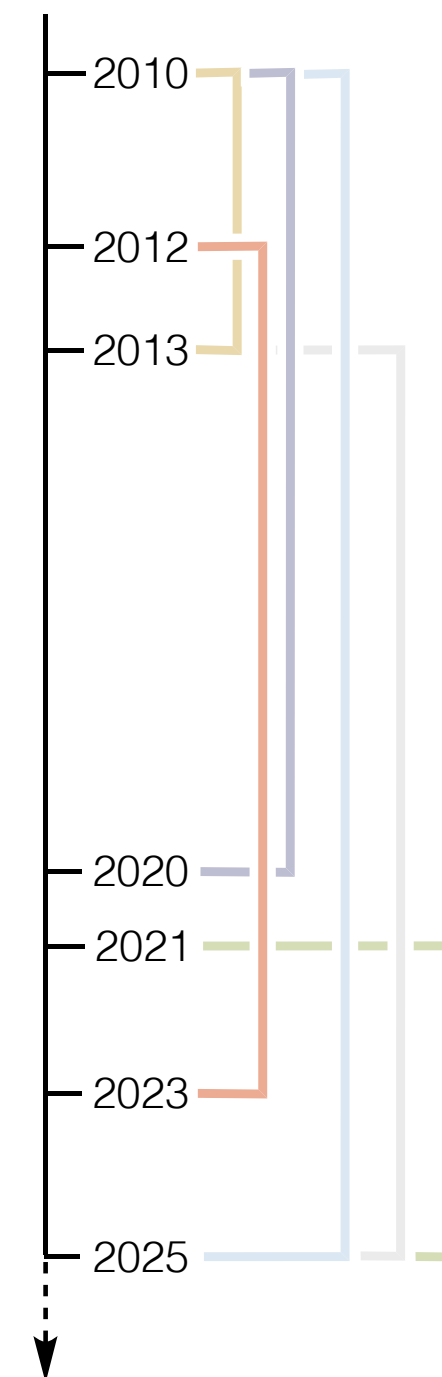
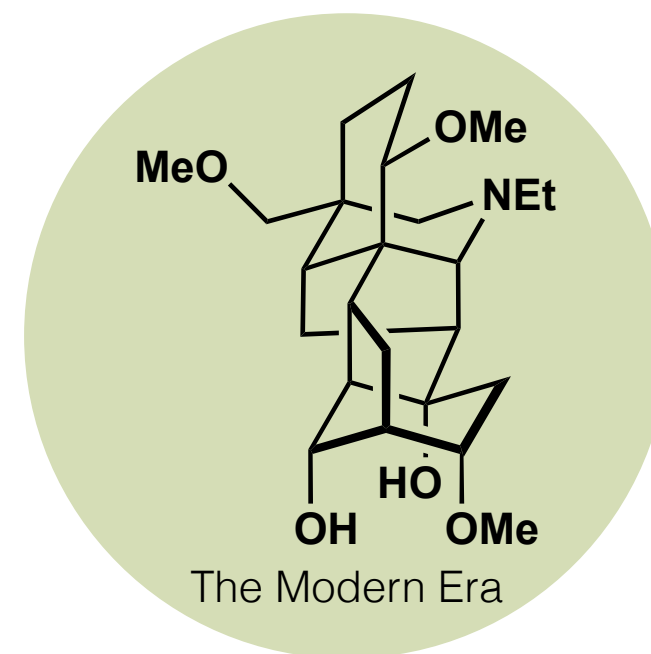
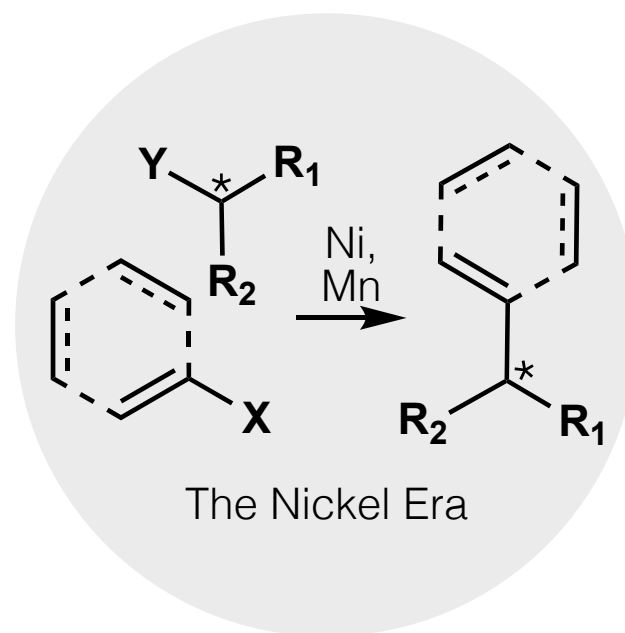
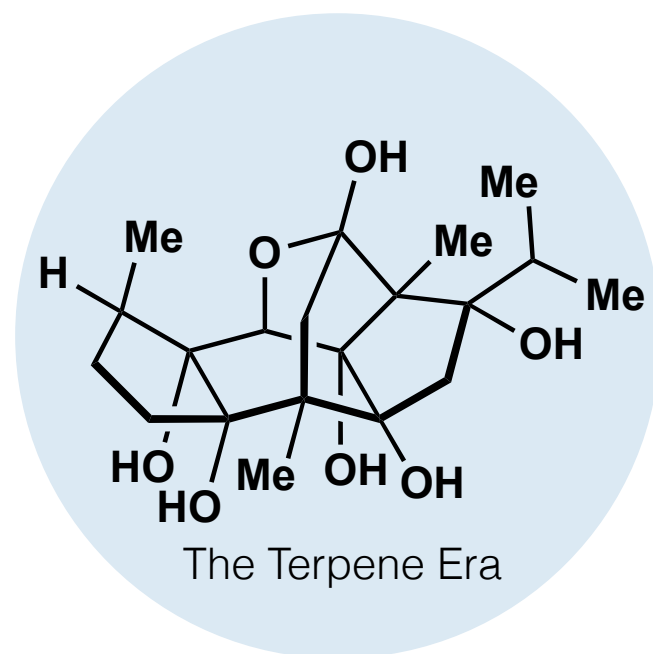
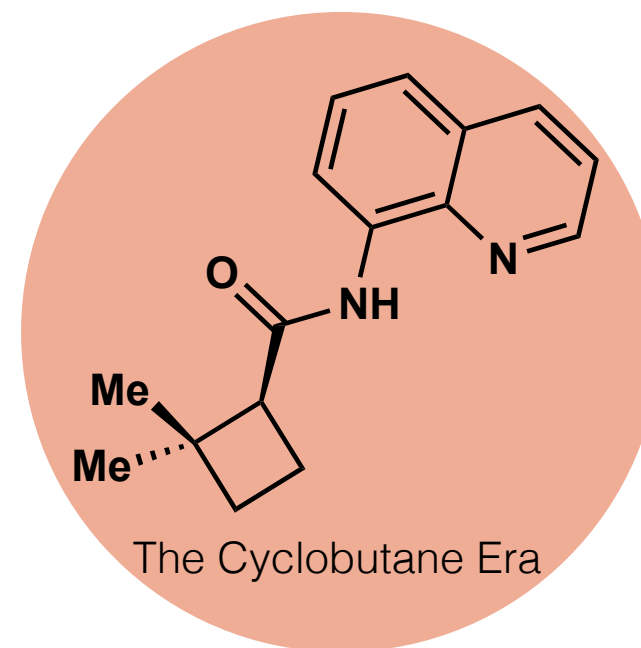
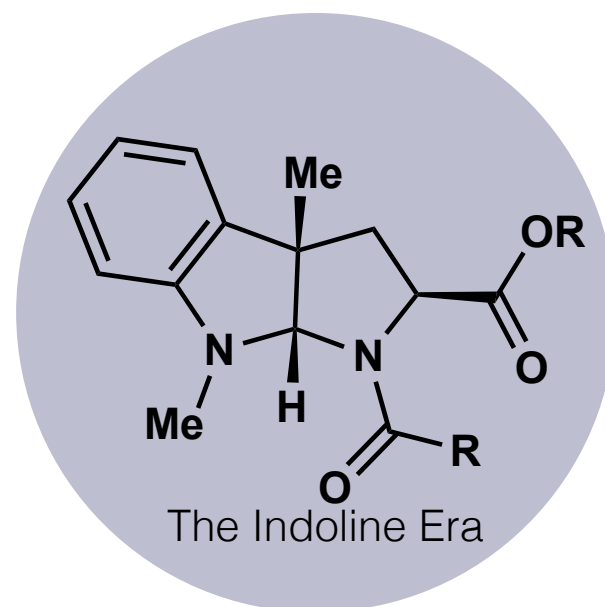
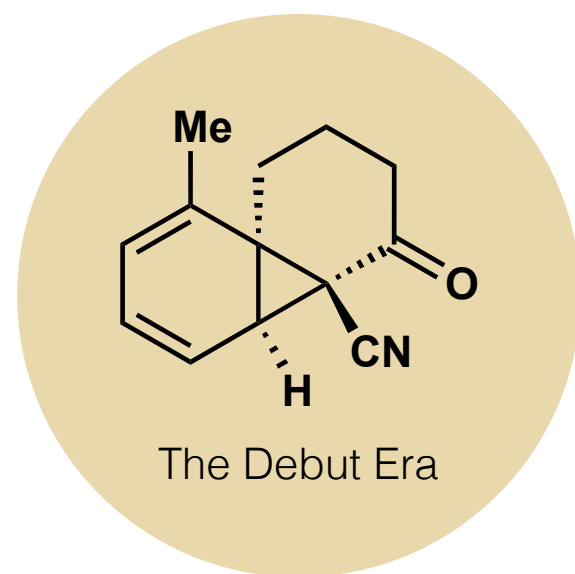


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- 2008 – 2014 Assistant Professor, Caltech
- 2014 – 2020 Professor, Caltech
- 2020 – present Bren Professor of Chemistry, Caltech



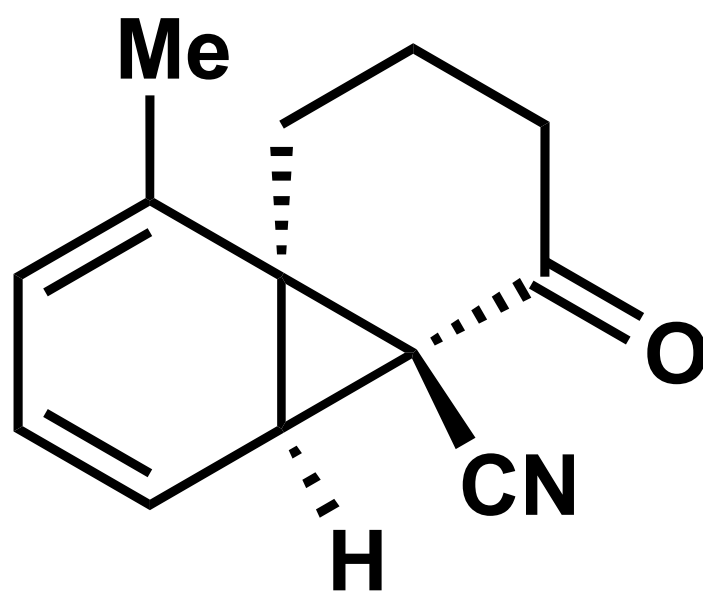
The Eras Tour: Sarah's Version

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Not Covered

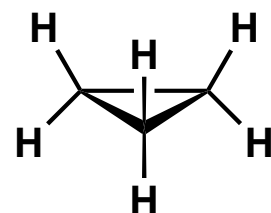
1. disulfur-containing natural products
2. pyridine dearomatization strategies
3. electrochemical applications
4. computation and data science



The Debut Era

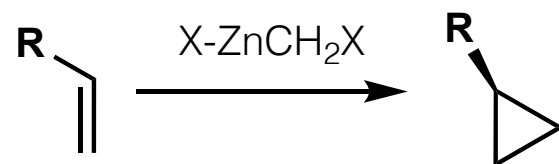
The Debut Era: Cyclopropanation

12

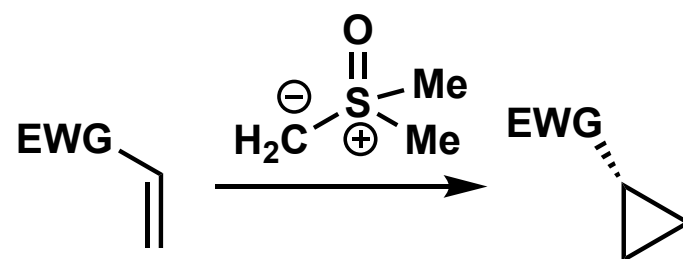


- Important structural motifs in natural products and drugs
- Strain energy ~ 28 kcal/mol
- Versatile intermediates in synthesis

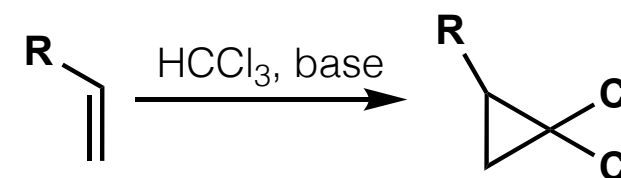
General methods for cyclopropane synthesis



Simmons-Smith carbenoids



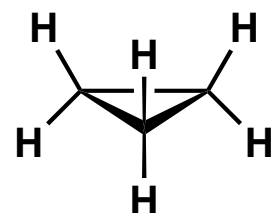
Michael initiated ring closures



dihalocarbene

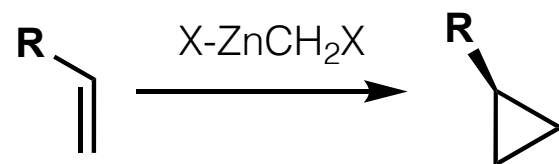
The Debut Era: Cyclopropanation

13

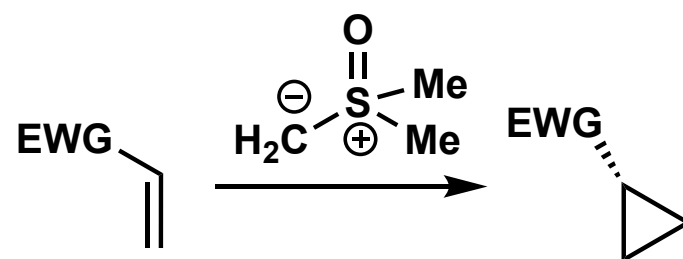


- Important structural motifs in natural products and drugs
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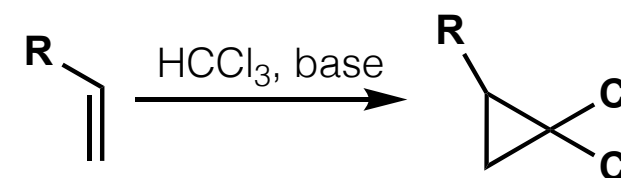
General methods for cyclopropane synthesis



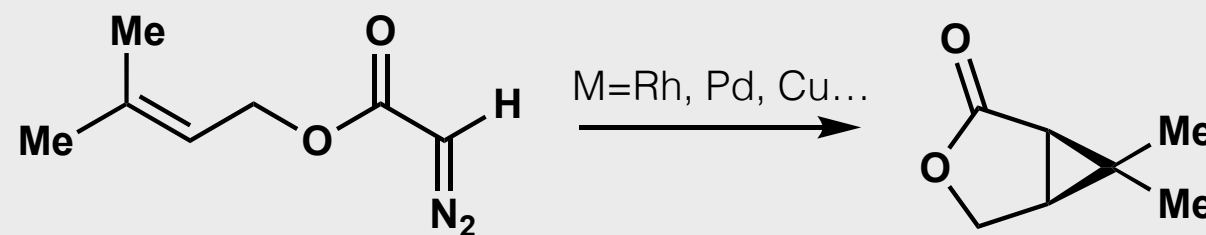
Simmons-Smith carbenoids



Michael initiated ring closures



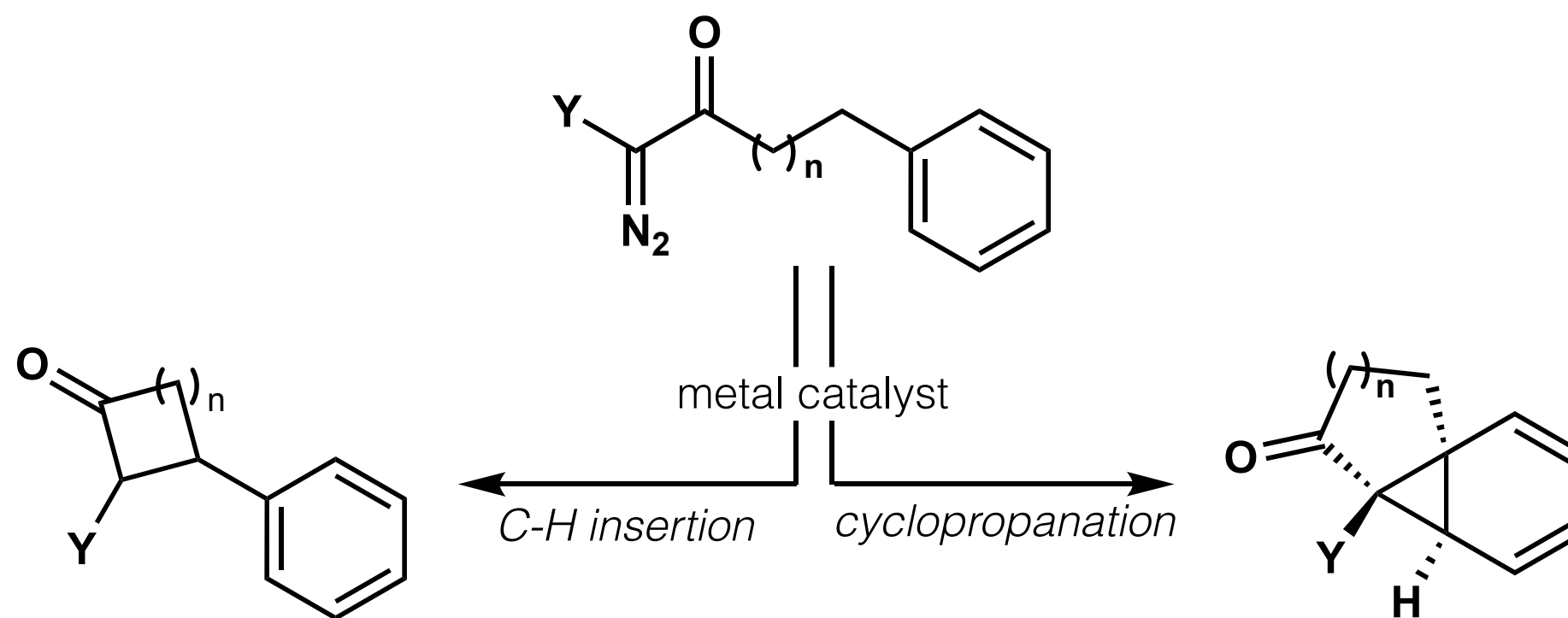
dihalocarbene



metal carbenoids

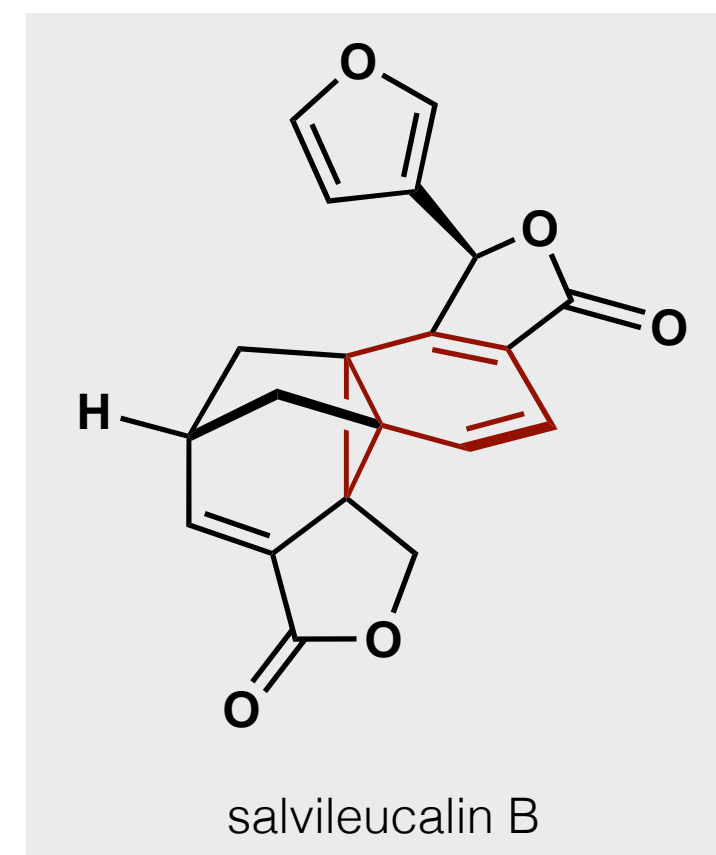
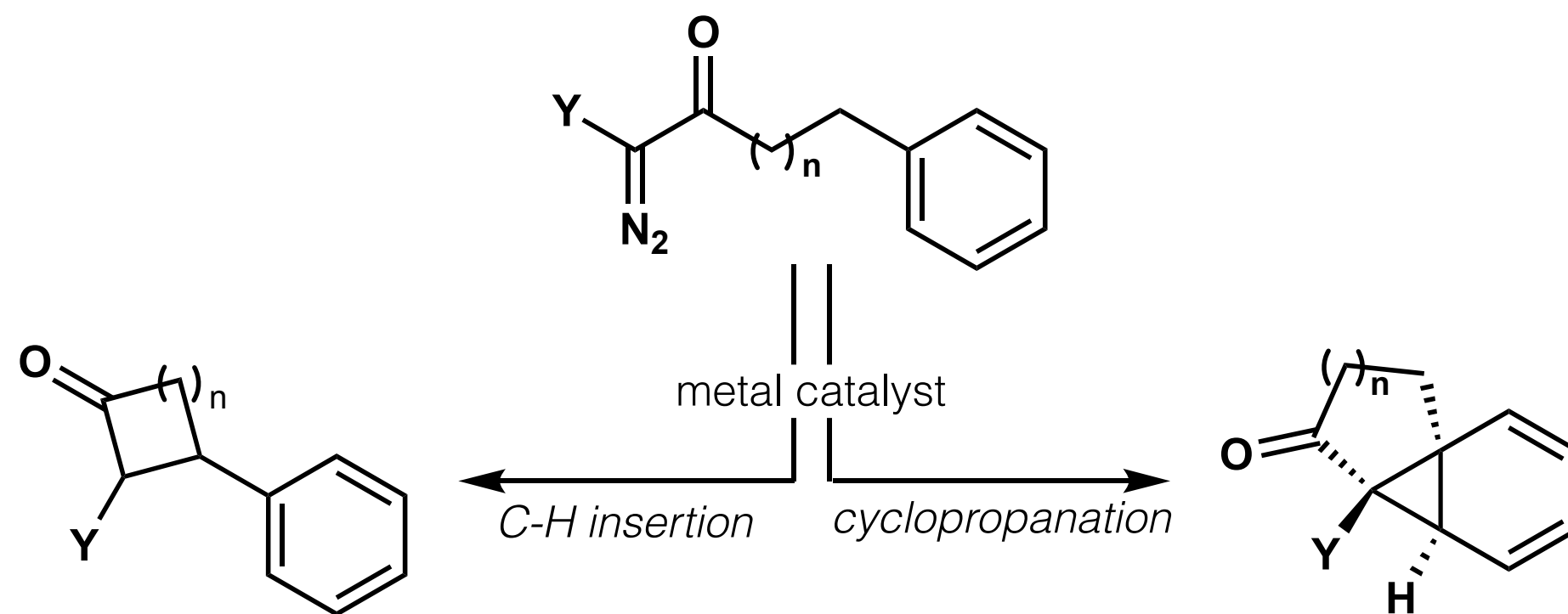
Arene Cyclopropanation

14



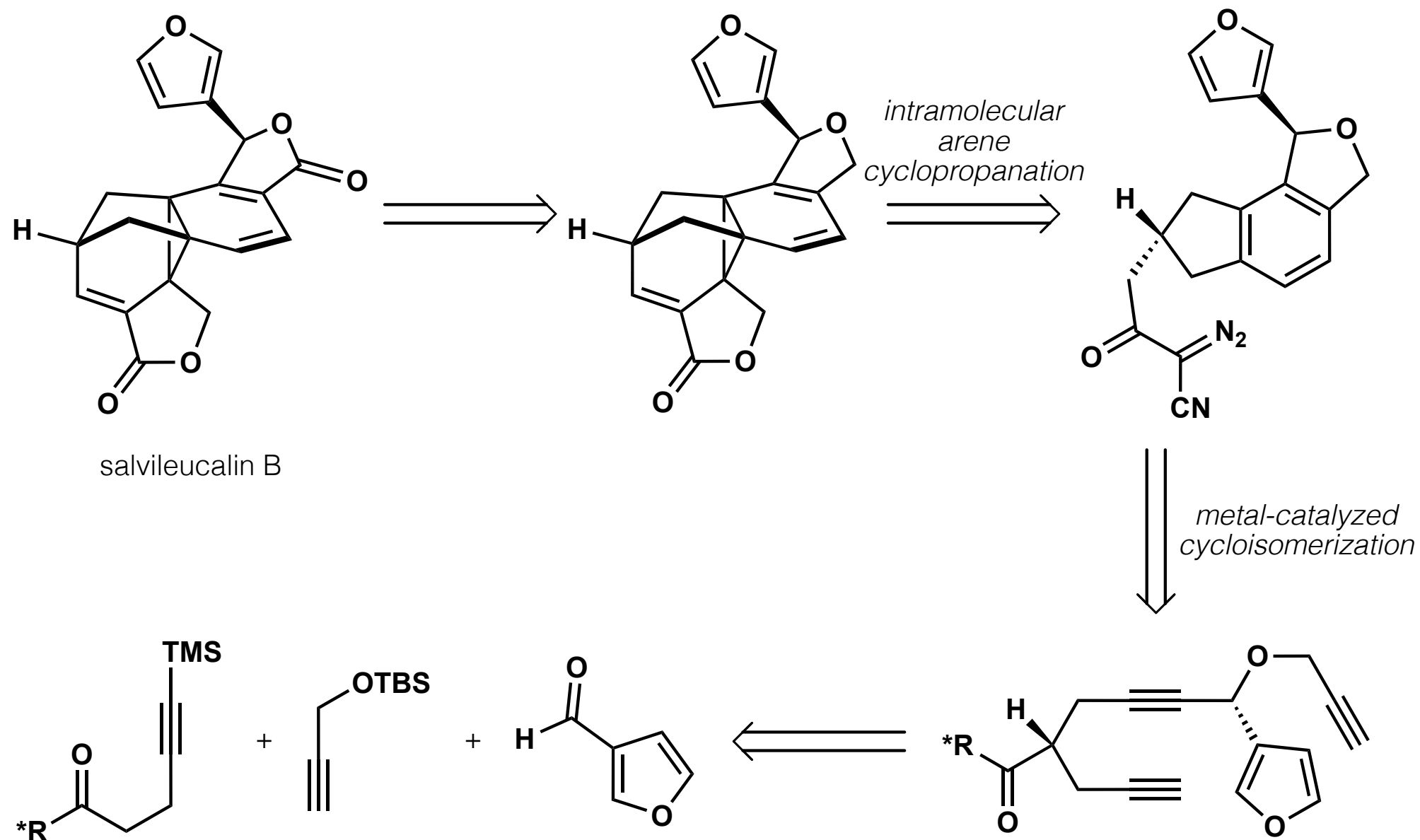
Arene Cyclopropanation

15



Total Synthesis of salvileucalin B

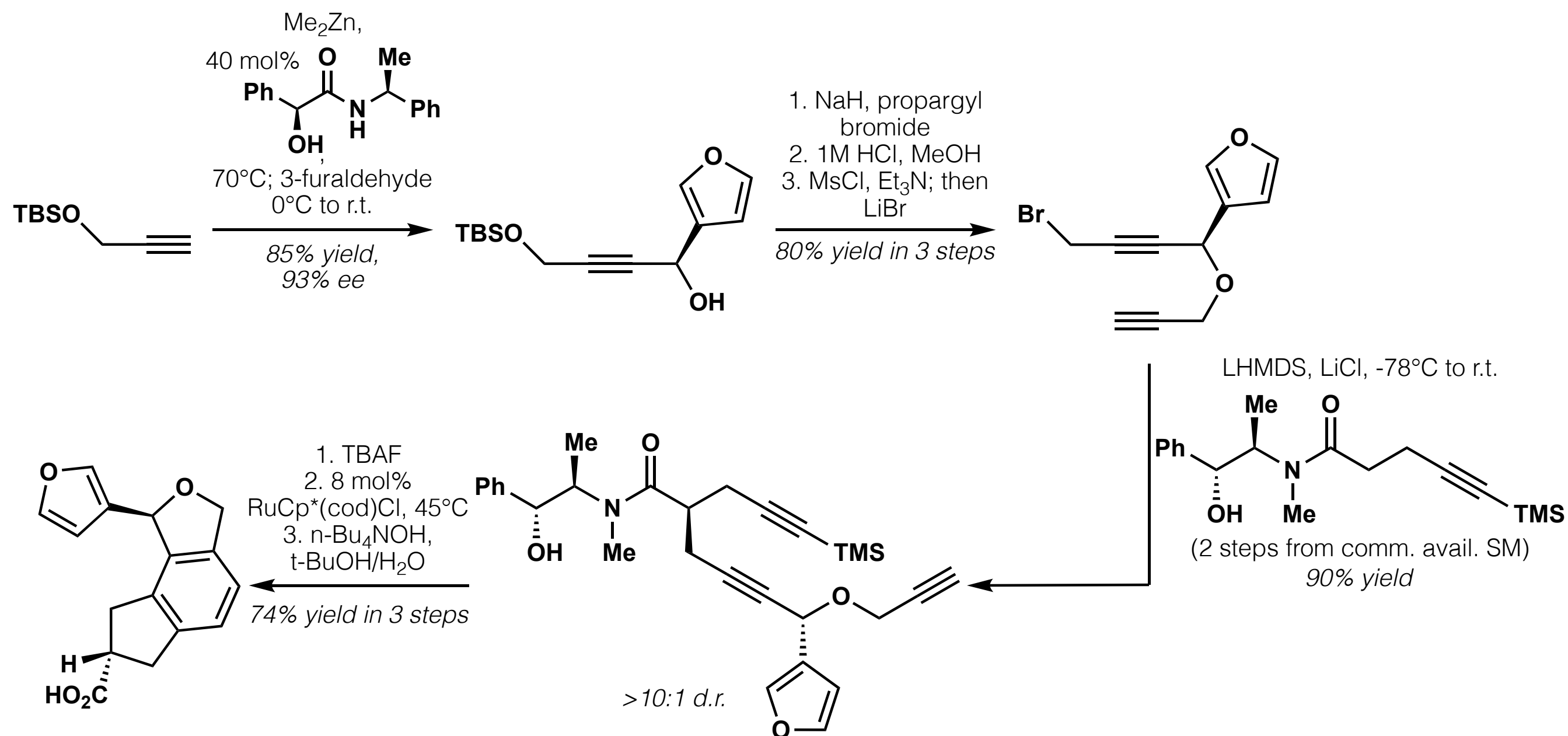
16



- Isolated in 2008 from *Salvia leucantha*
- Cytotoxic against A549 and HT-29
- Unusual norcaradiene core

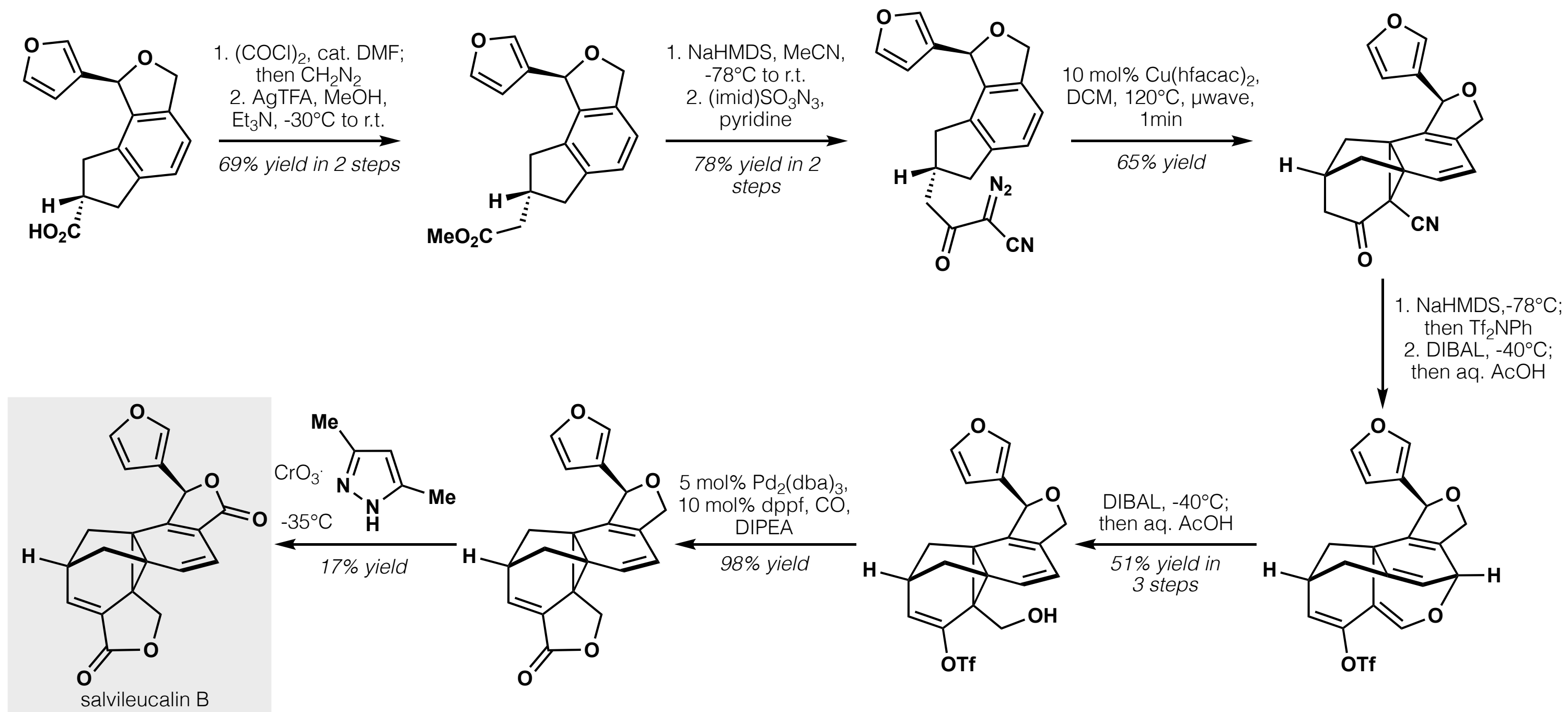
Total Synthesis of salvileucalin B

17



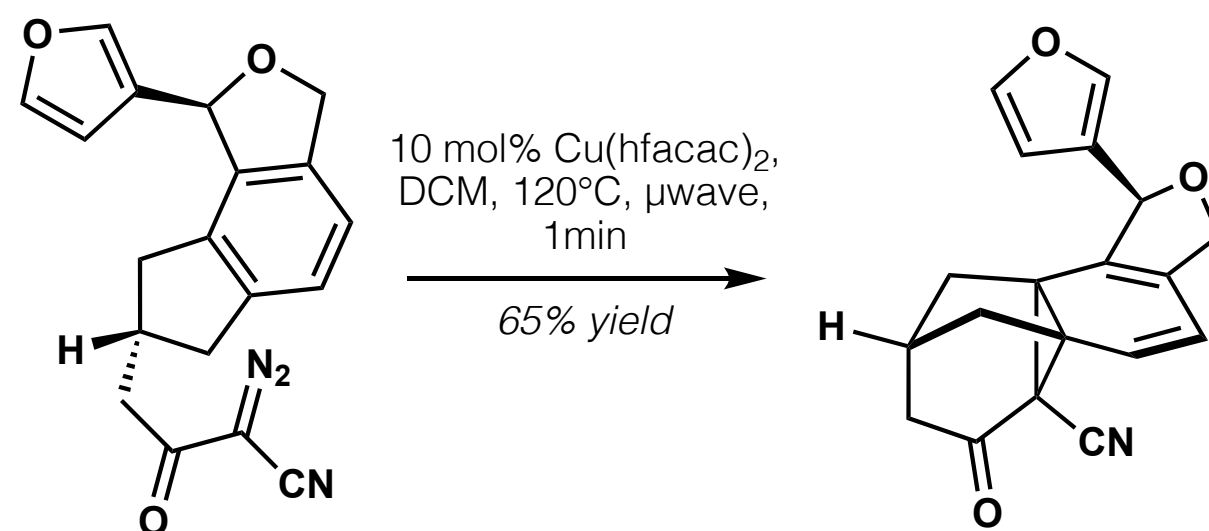
Total Synthesis of salvileucalin B

18



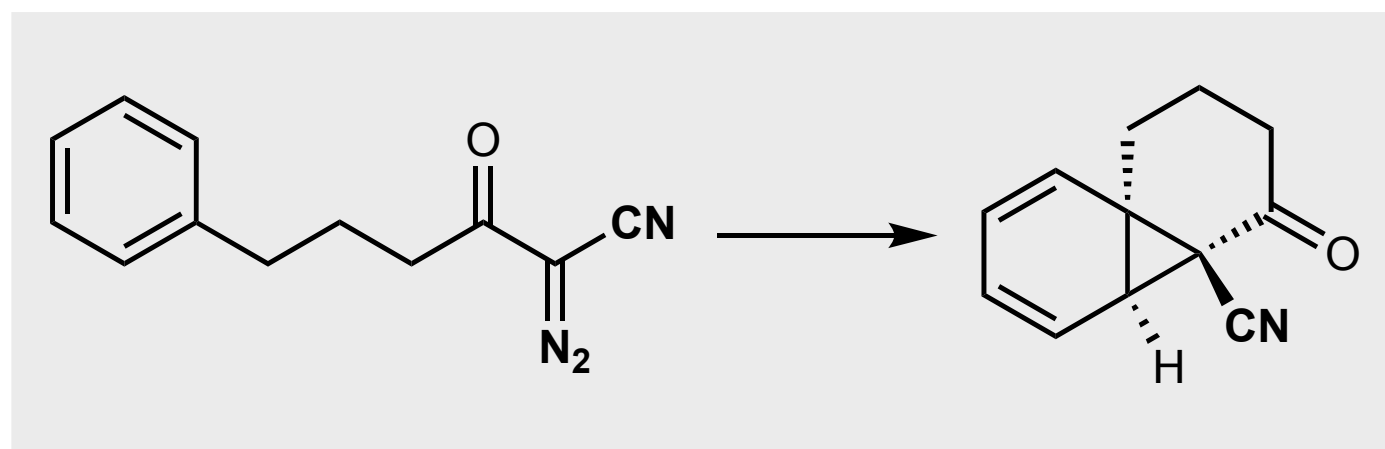
Beyond salvileucalin B

19

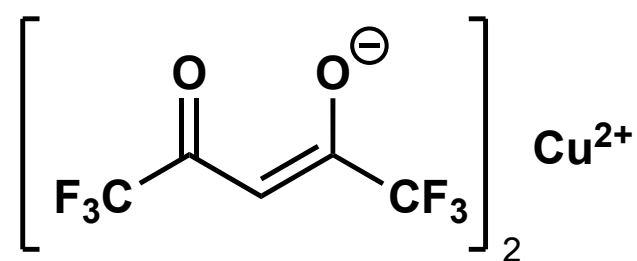


Rhodium vs Copper

20

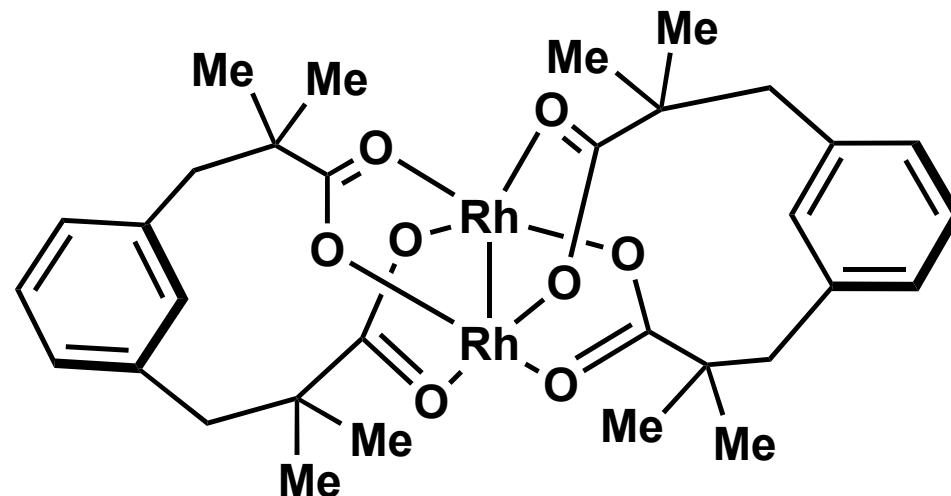


- Electron-deficient catalysts performed the best
- Copper better for hindered substrates (salvileucalin B)
- Rhodium better for unencumbered arenes



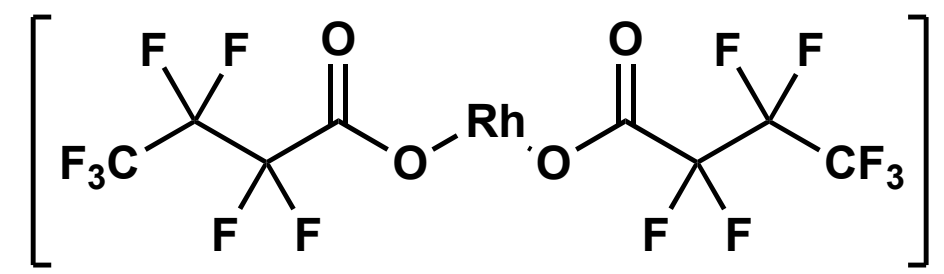
5 mol% $\text{Cu}(\text{hfacac})_2$

54% yield



2 mol% $\text{Rh}_2(\text{esp})_2$

70% yield

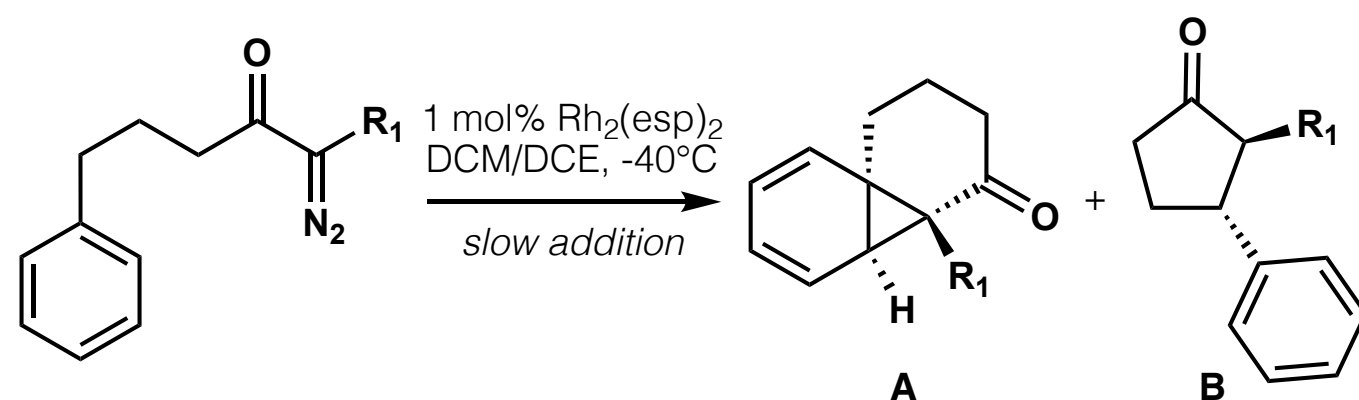


2 mol% $\text{Rh}_2(\text{pfb})_4$

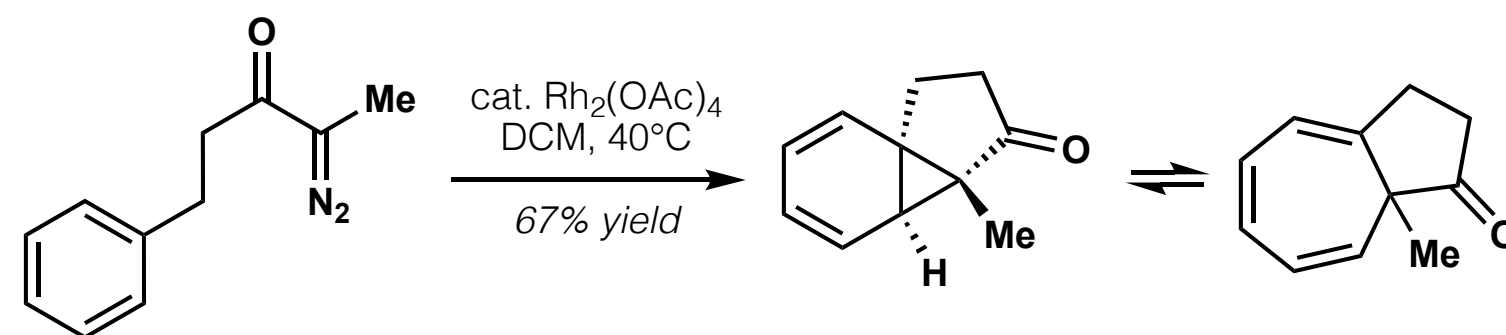
70% yield

Influence of Substitution

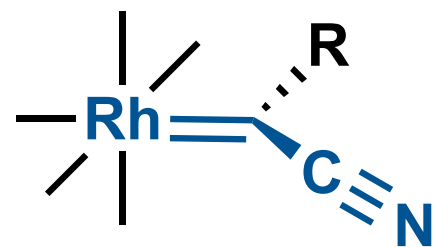
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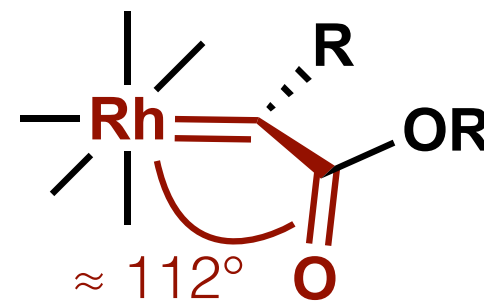
entry	R1	yield A (%)	yield B (%)
1	H	>95	n.d.
2	Me	n.d.	43
3	COMe	n.d.	32
4	CO ₂ Me	n.d.	45
5	NO ₂	n.d.	28
6	CN	70	n.d.



Kennedy and co-workers *J. Chem. Soc., Perkin Trans. 1* **1990**, 12, 1047.



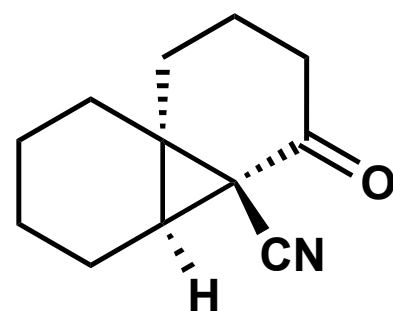
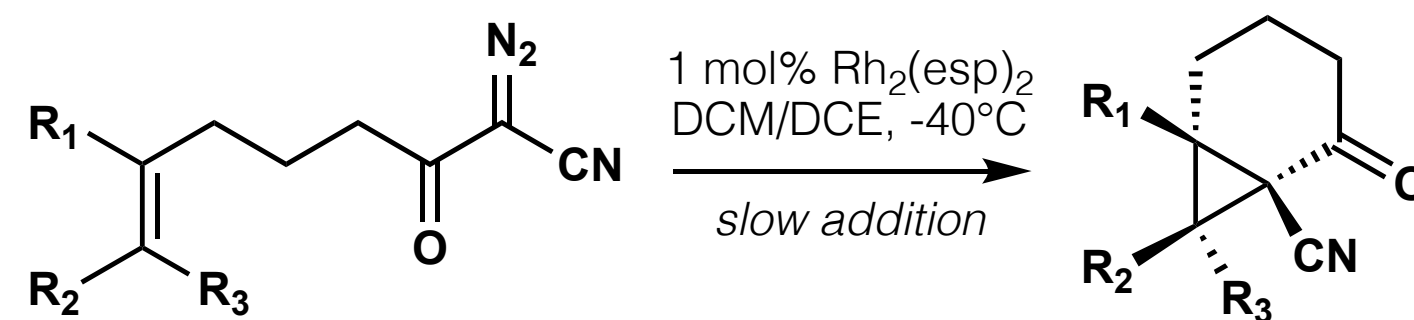
nitrile and carbenoid
are coplanar



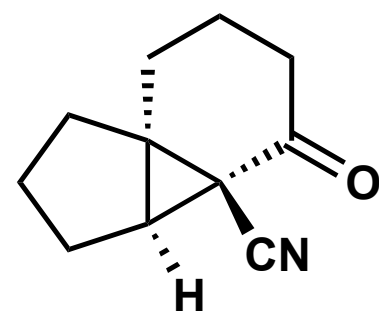
ester and carbenoid
are out-of-plane

Cyclopropanation of Alkenes

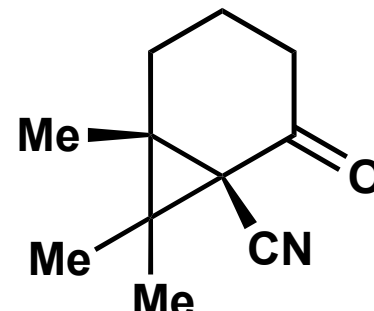
23



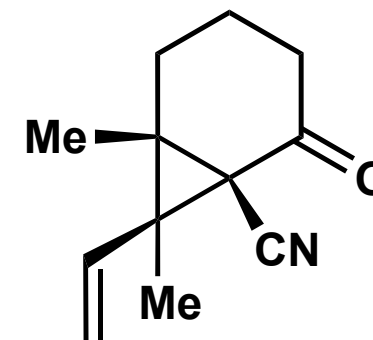
82% yield



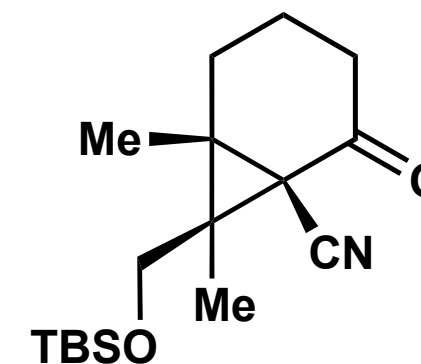
93% yield



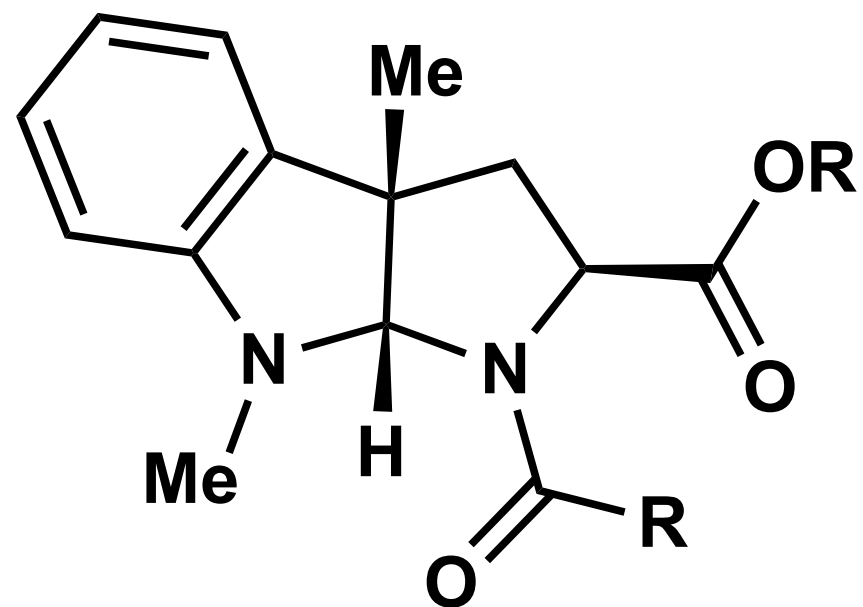
90% yield



79% yield



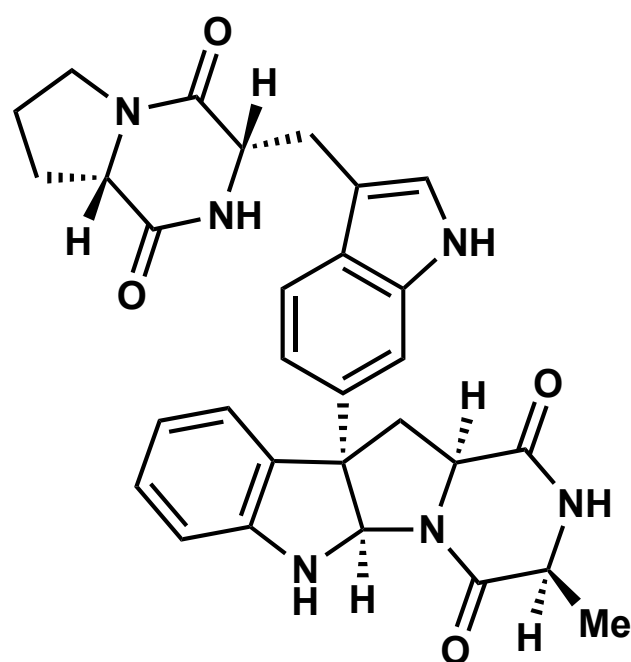
93% yield



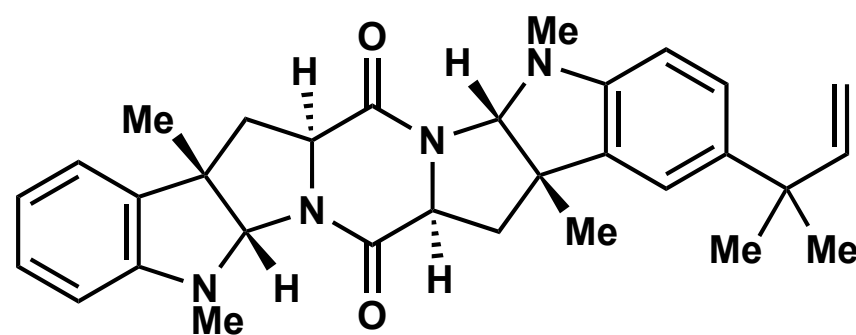
The Indoline Era

The Indoline Era

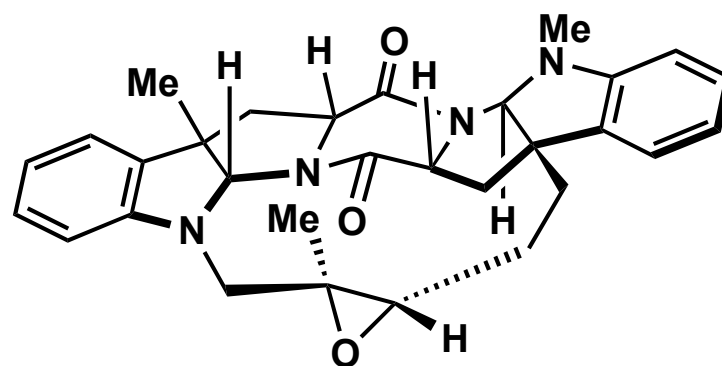
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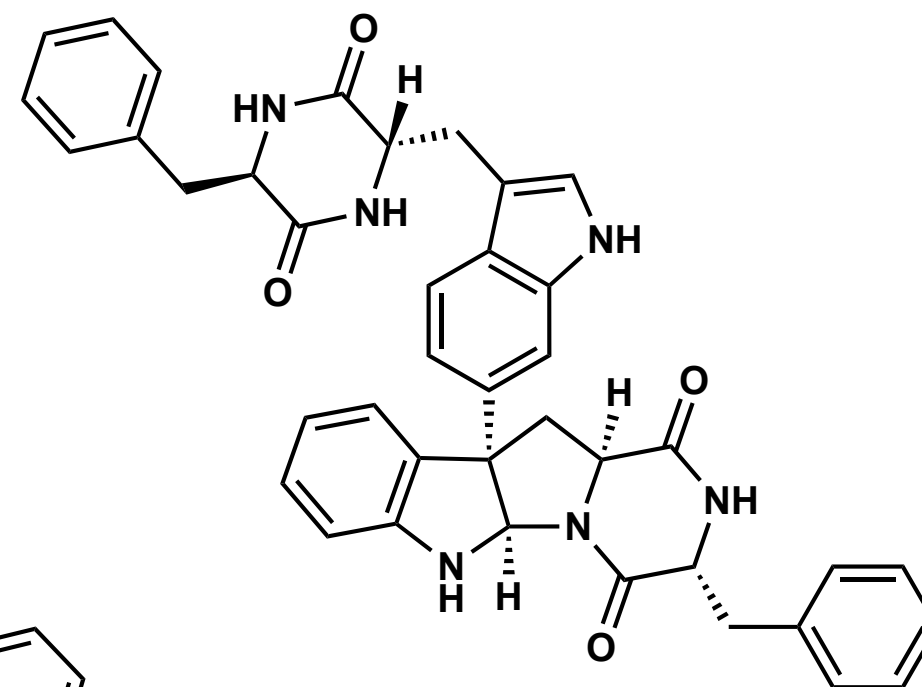
(+)-naseaezine A



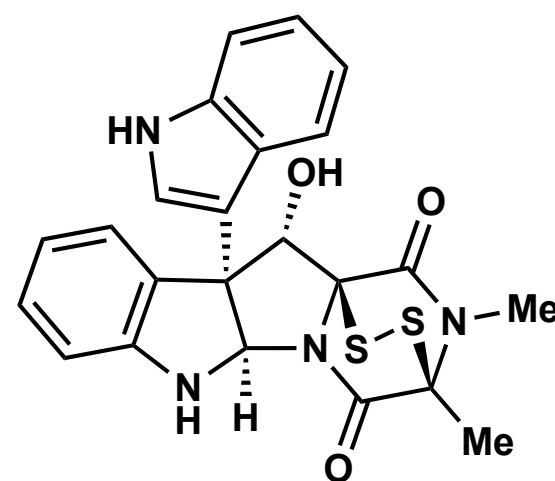
(-)-lansai B



(+)-nocardiozine A



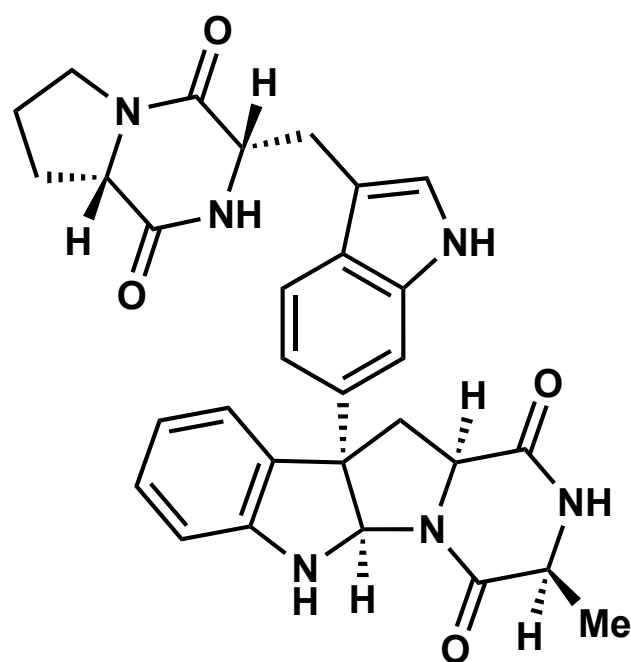
asperazine



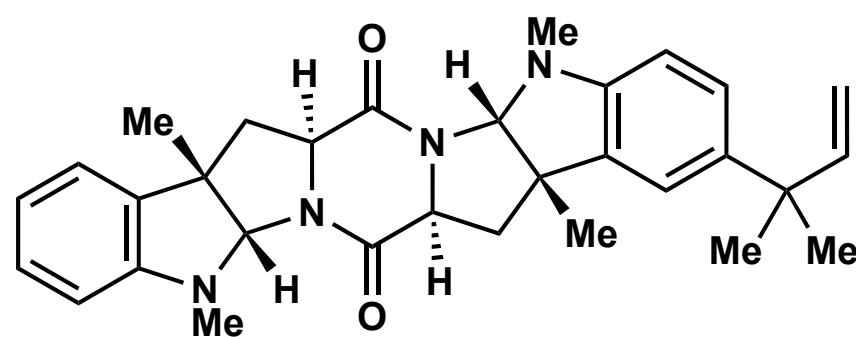
gliocladiine C

The Indoline Era

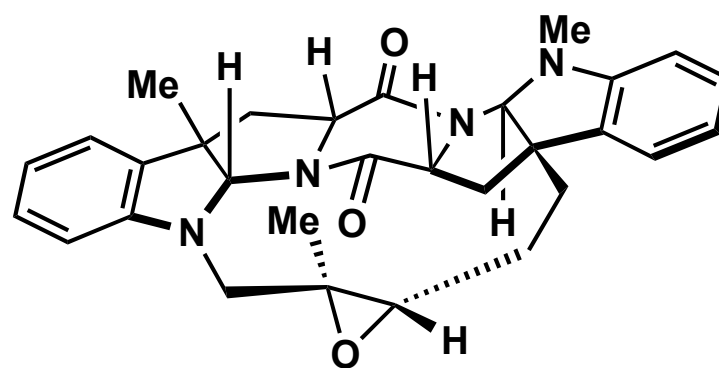
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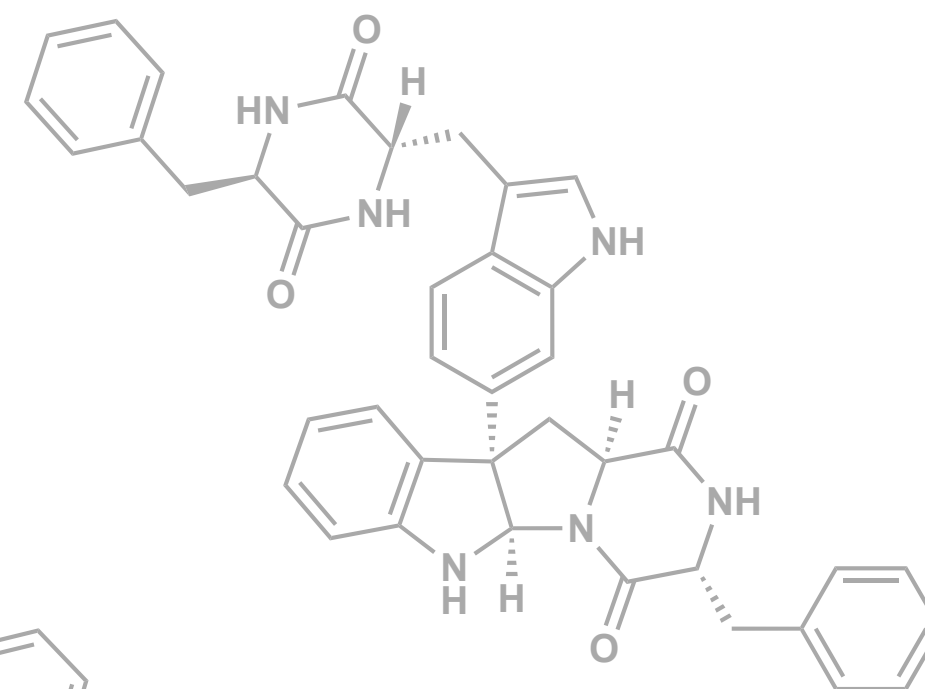
(+)-naseaezine A



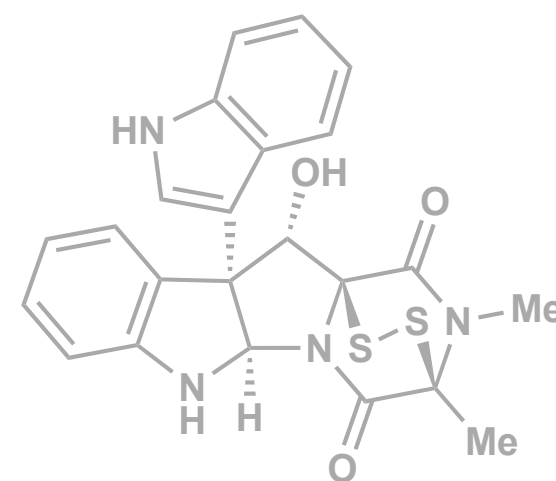
(-)-lansai B



(+)-nocardiozine A



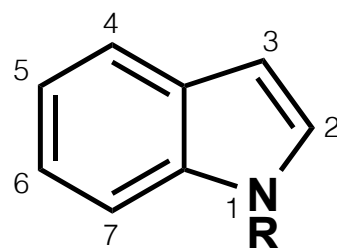
asperazine



gliocladiine C

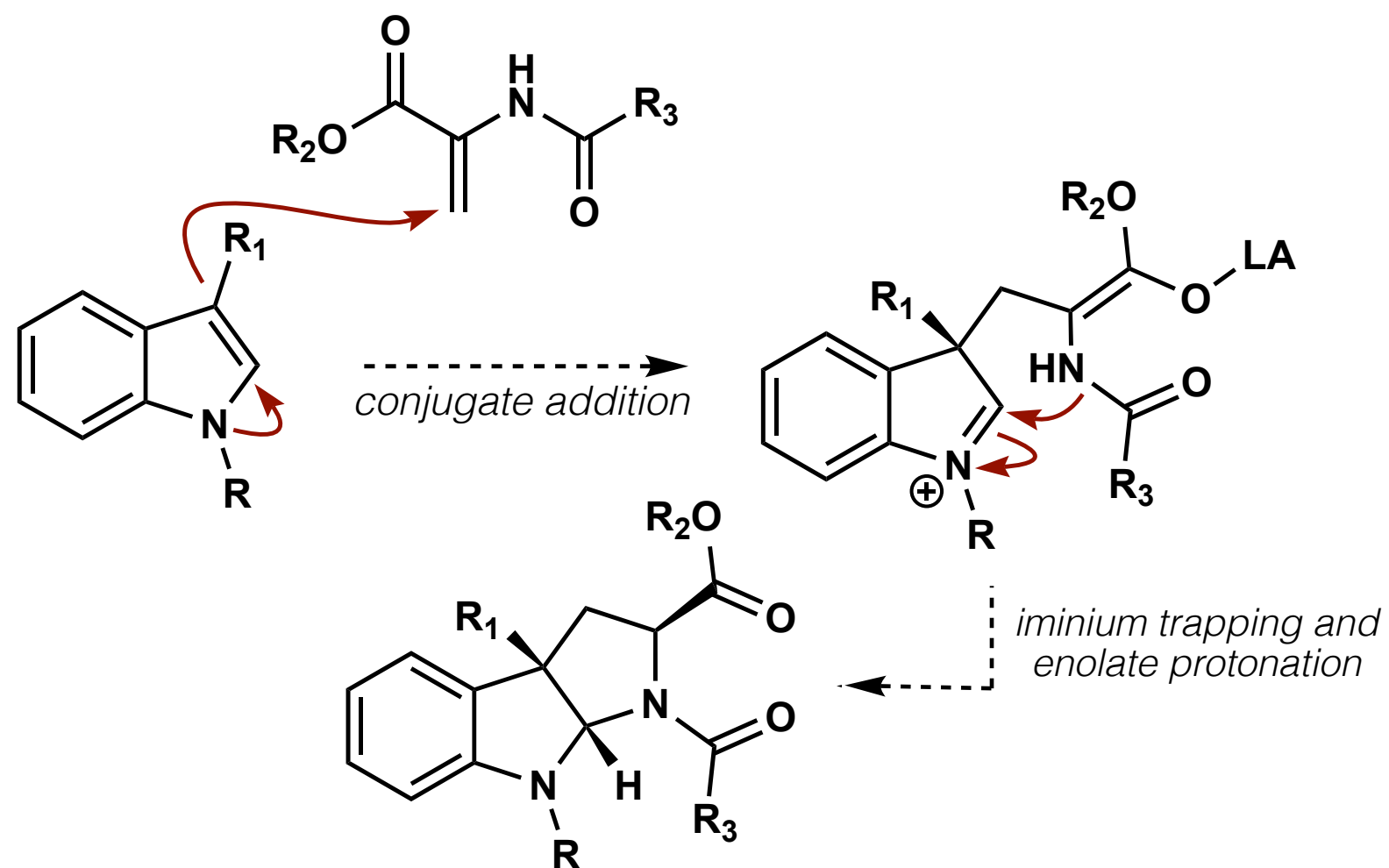
Indoles and Pyrroloindolines

27



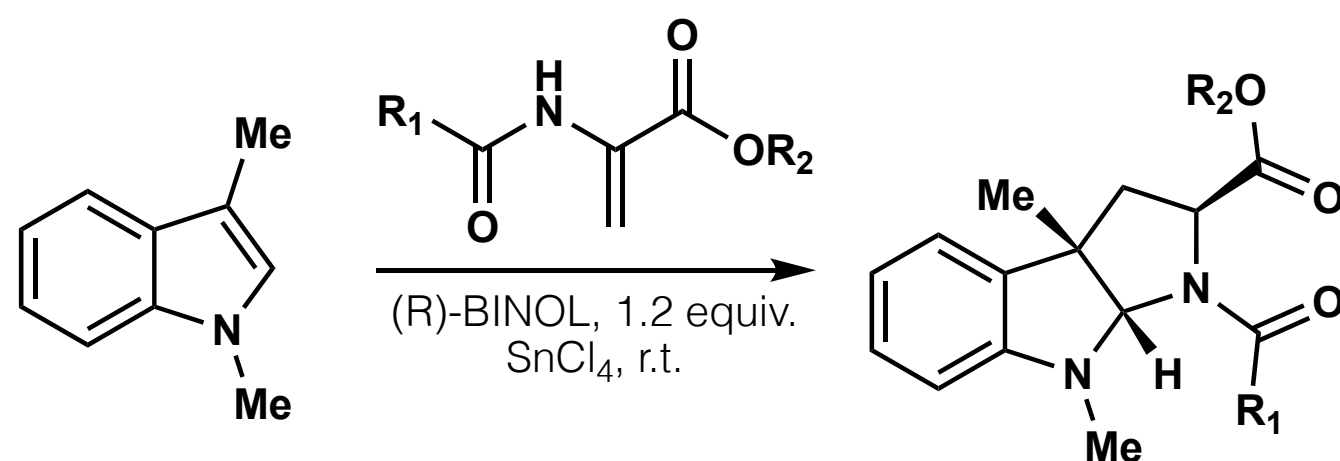
- Very weak bases (pKa protonated indole ~ -3.5)
- C-2 functionalization possible through lithiation
- Electron-rich at C-3

proposed reaction to prepare pyrroloindolines

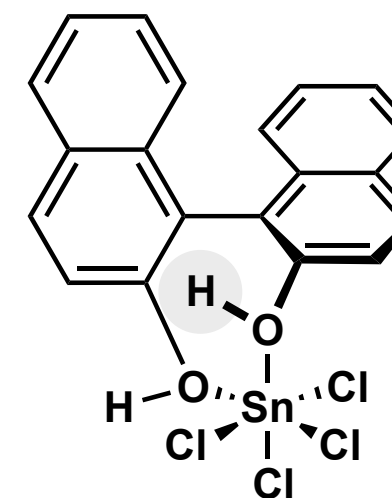


Pyrroloindolines through a Formal [3+2]

28



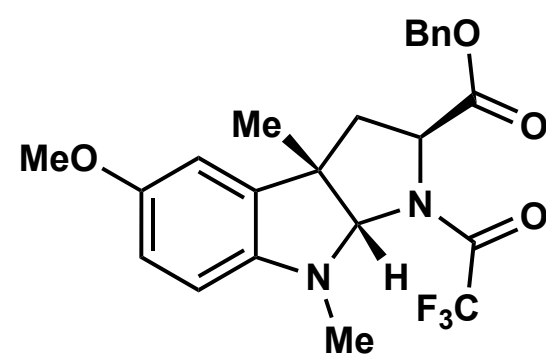
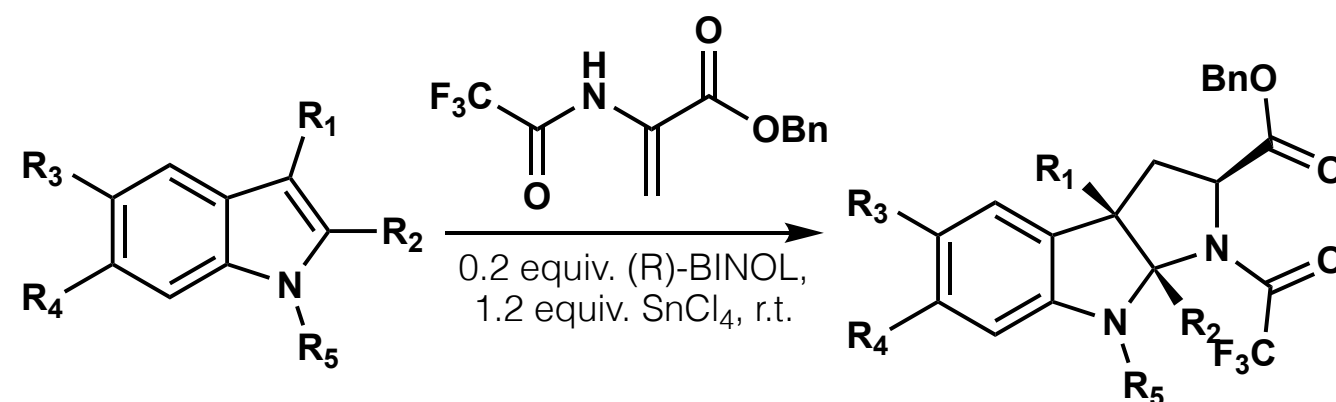
- Chlorinated solvents gave best results
- Catalytic quantities of BINOL provide the product in high yield
- Reaction yield improves when acrylate substituents are electron-deficient



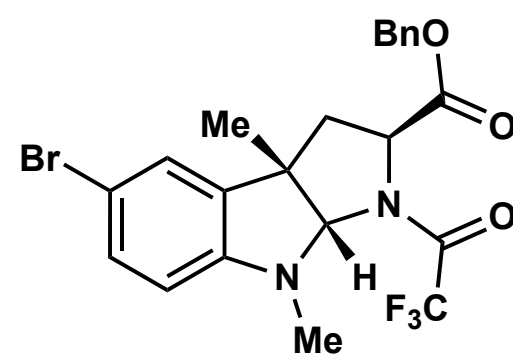
Lewis acid-assisted Brønsted acid

Pyrroloindolines through a Formal [3+2]

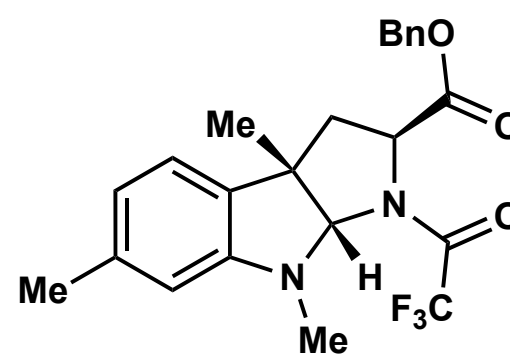
29



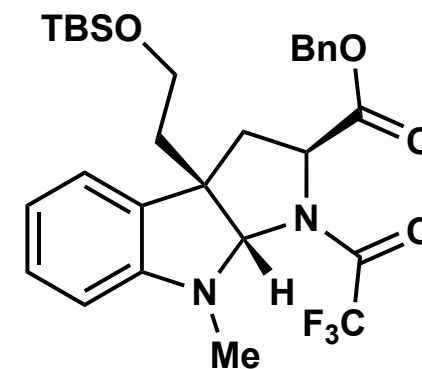
93% yield
3:1 d.r.
93/92 %ee (exo/endo)



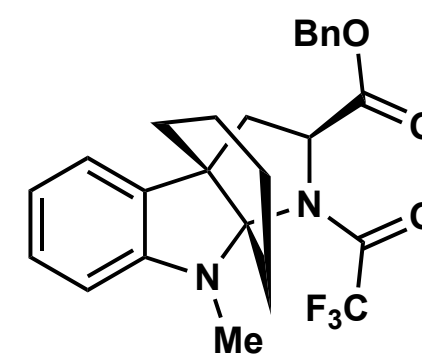
51% yield
3:1 d.r.
87/85 %ee (exo/endo)



91% yield
4:1 d.r.
94/90 %ee (exo/endo)



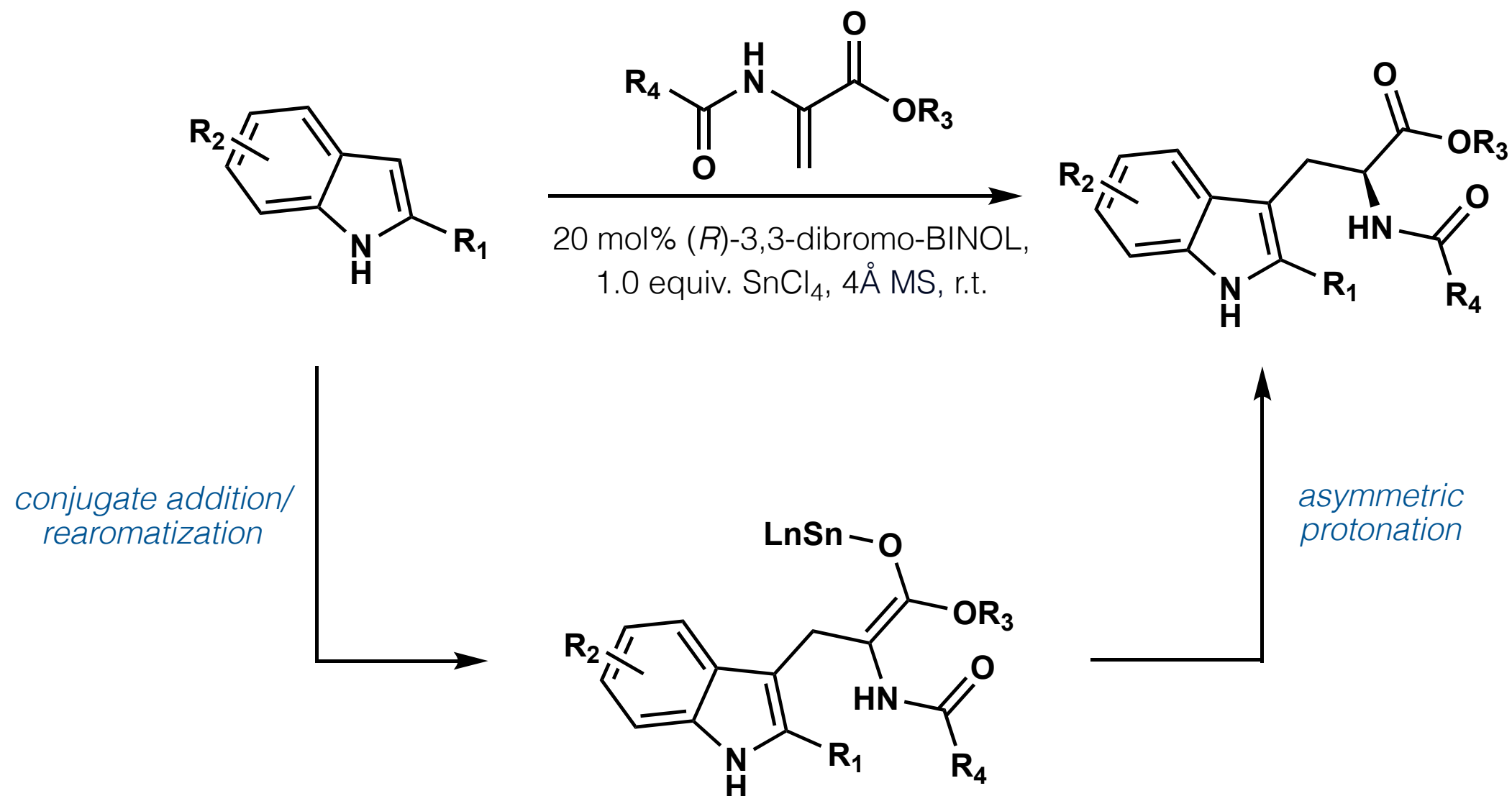
54% yield
6:1 d.r.
92/90 %ee (exo/endo)



65% yield
>18:1 d.r.
86 %ee (exo/endo)

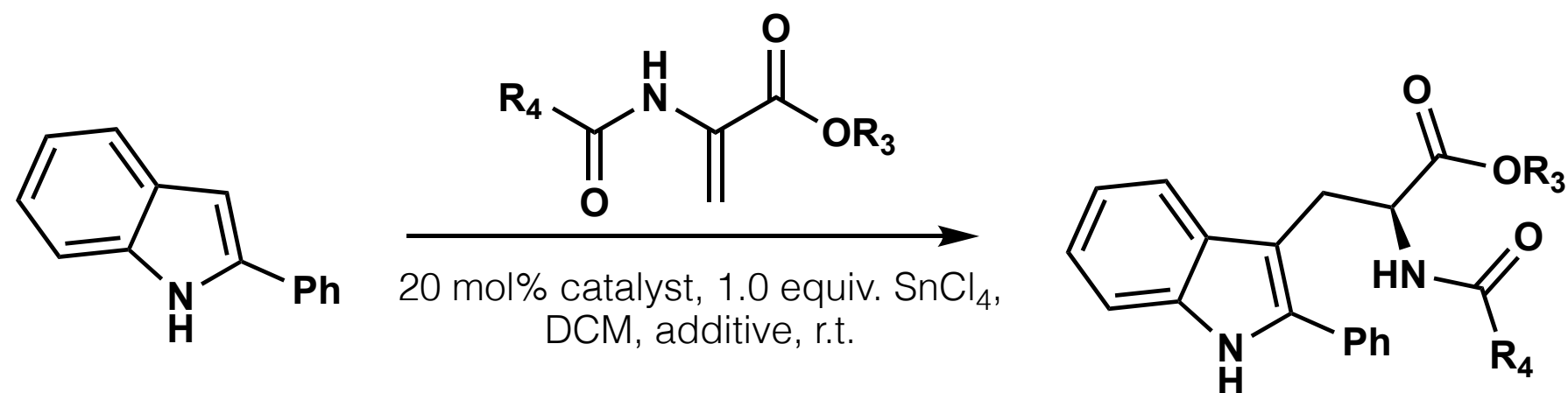
Expanding (R)-BINOL·SnCl₄ Catalysis

30

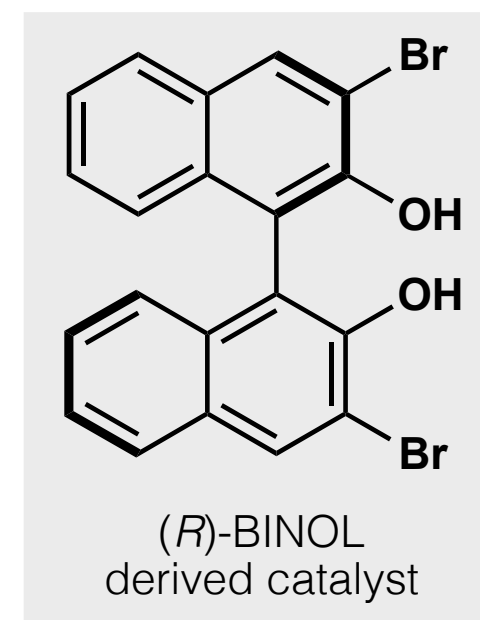


Expanding (R)-BINOL·SnCl₄ Catalysis

31

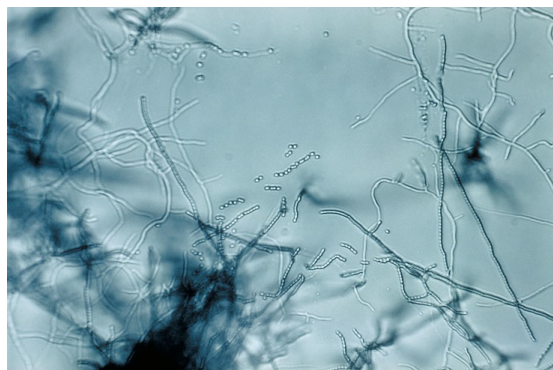


- The use of methyl 2-acetamidoacrylate improves yield drastically
- Water scavengers were tested and 4Å MS was the best performing one
- Dibromo substitution on BINOL gives highest of 93% ee

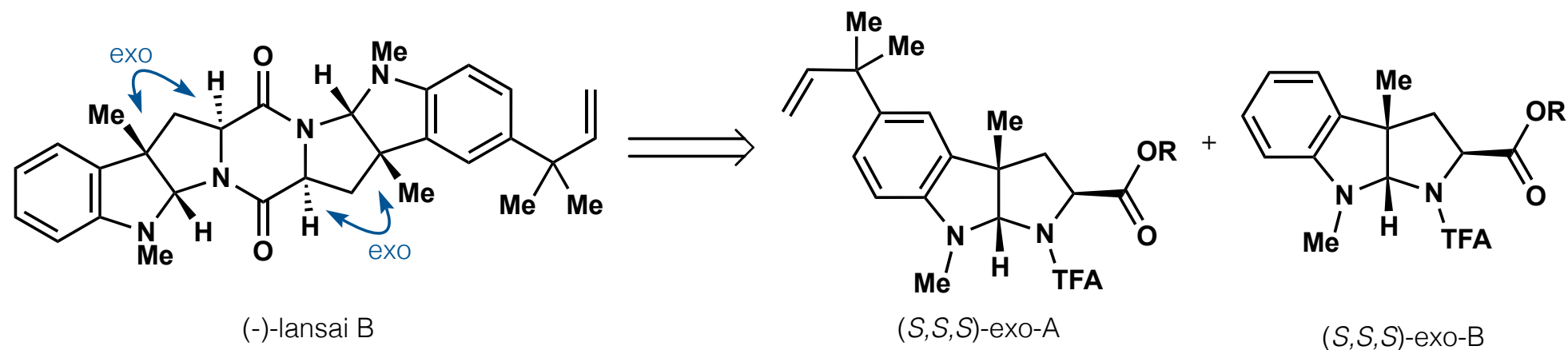


Bis(pyrroloindolines) Total Synthesis

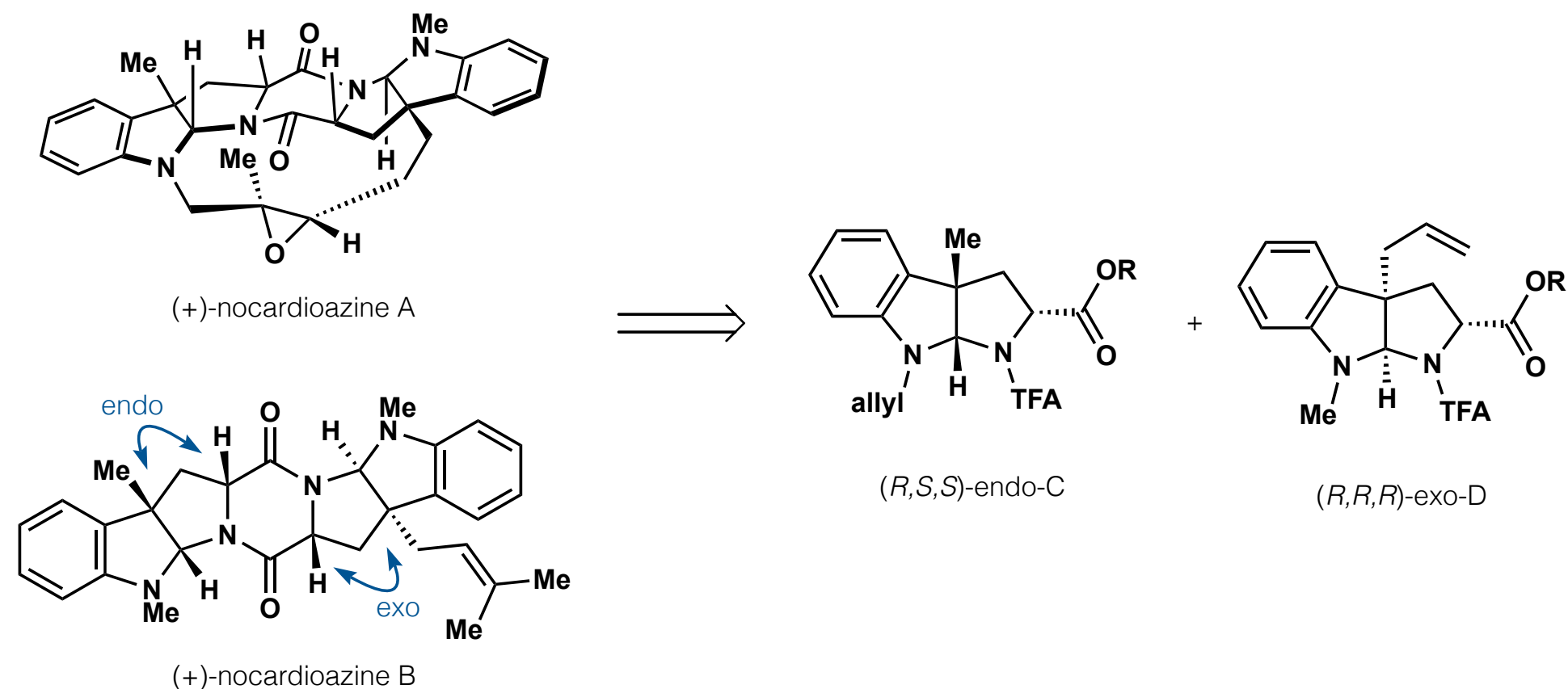
32



- Isolated from *Streptomyces* sp. SUC1
- Anticancer activity against lymphoma

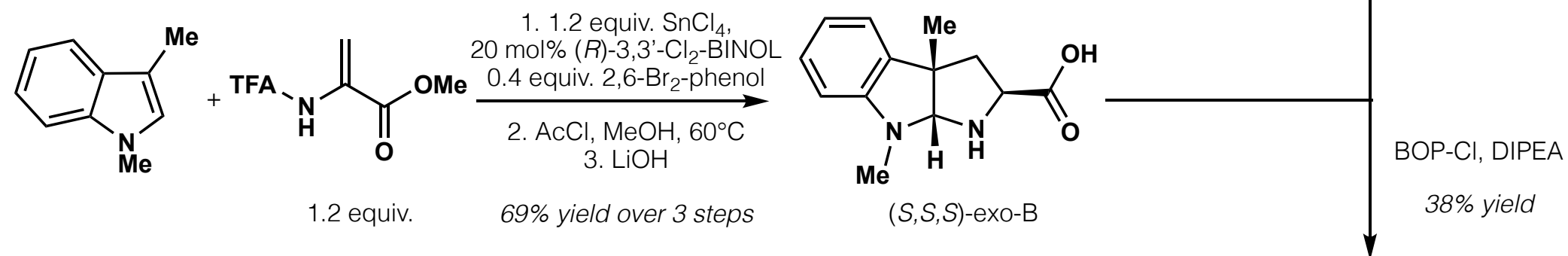
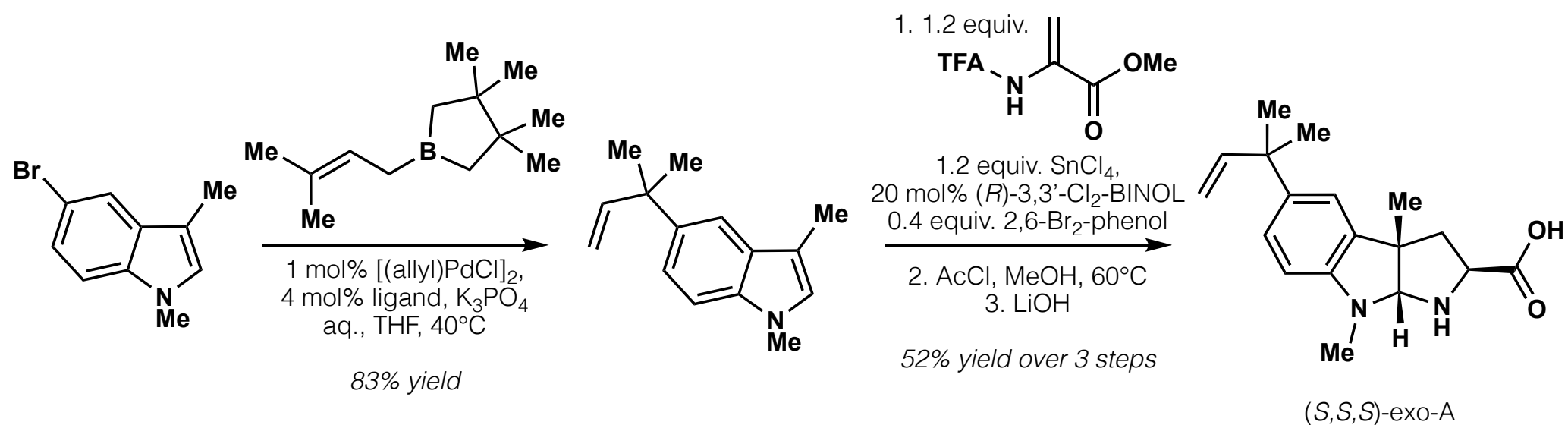


- Isolated from the bacteria genus *Nocardioopsis*
- Nocardioazine A is an inhibitor of P-glycoprotein, a transmembrane protein overexpressed in many tumors



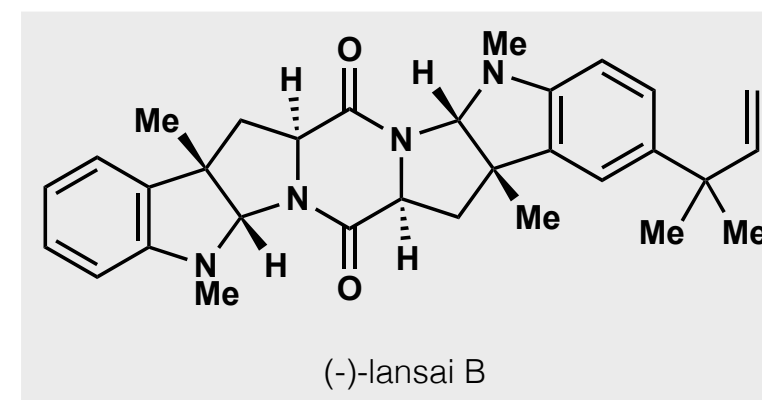
Total Synthesis of (-)-lansai B

33



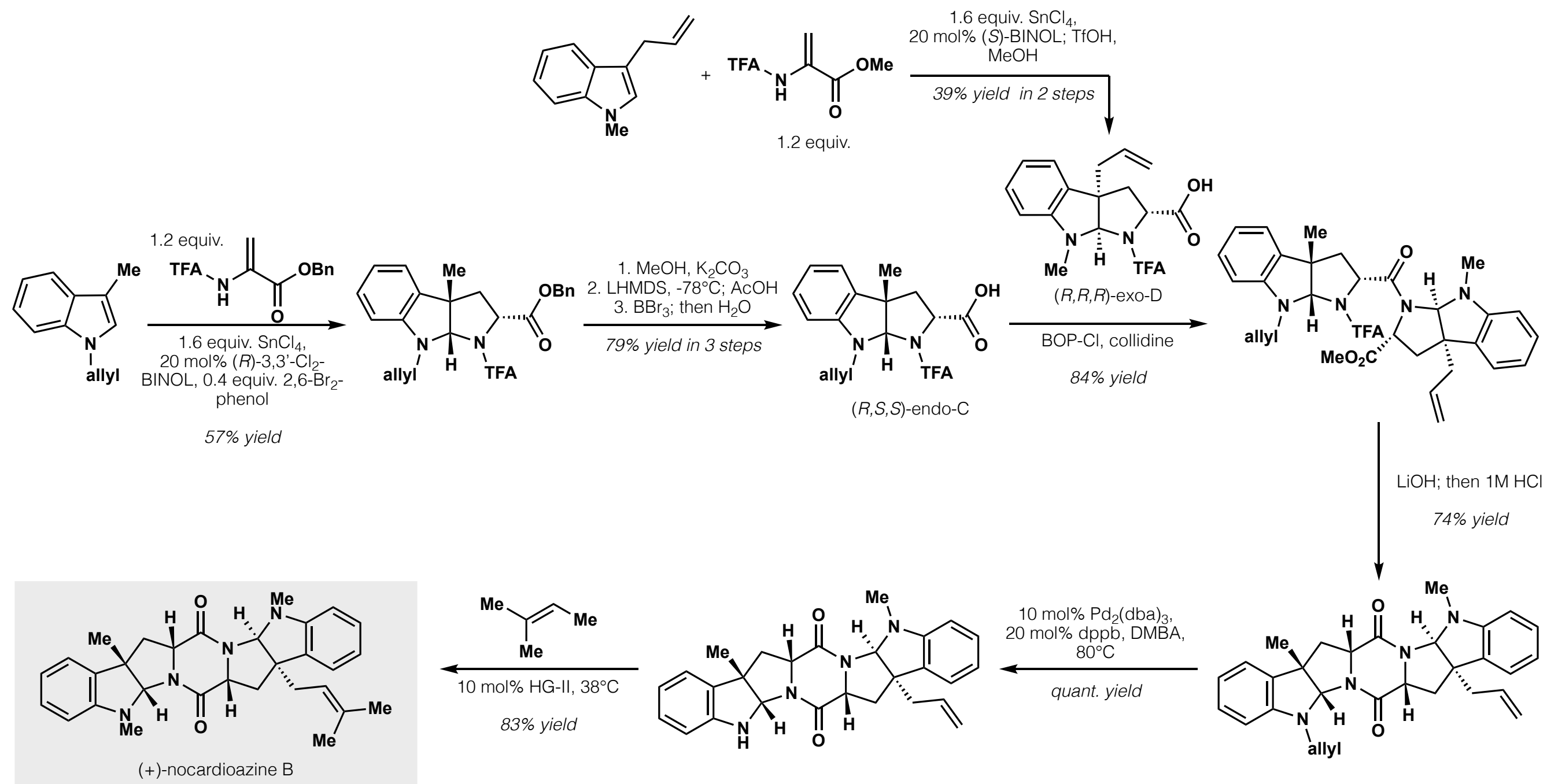
• Six steps enantioselective synthesis (LLS)

• 20% overall yield



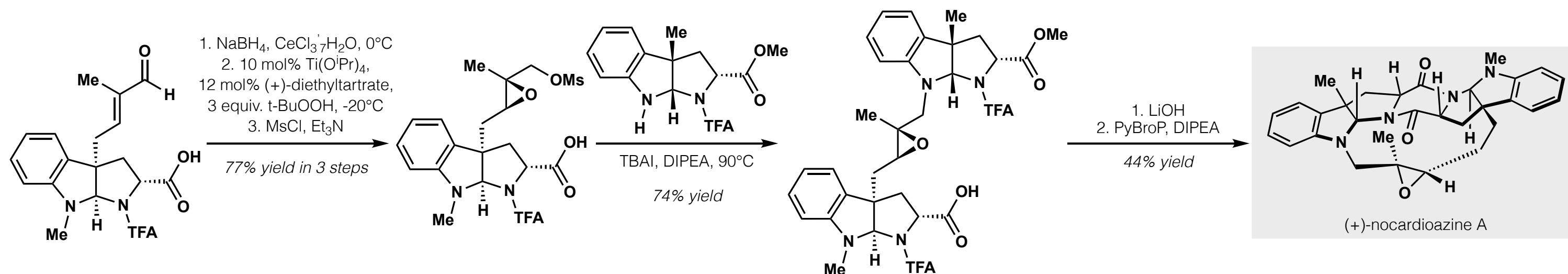
Total Synthesis of (+)-nocardioazine B

34



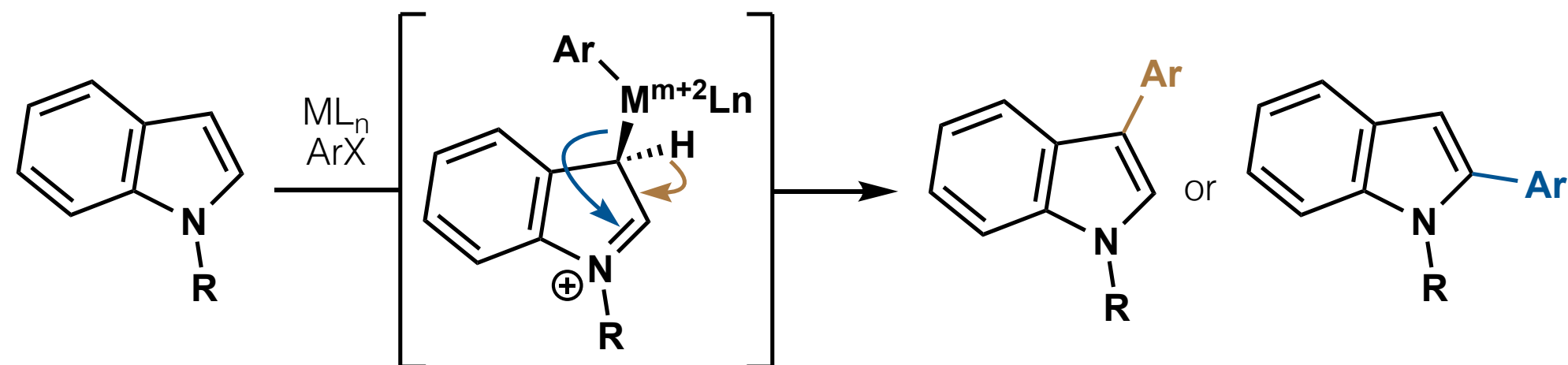
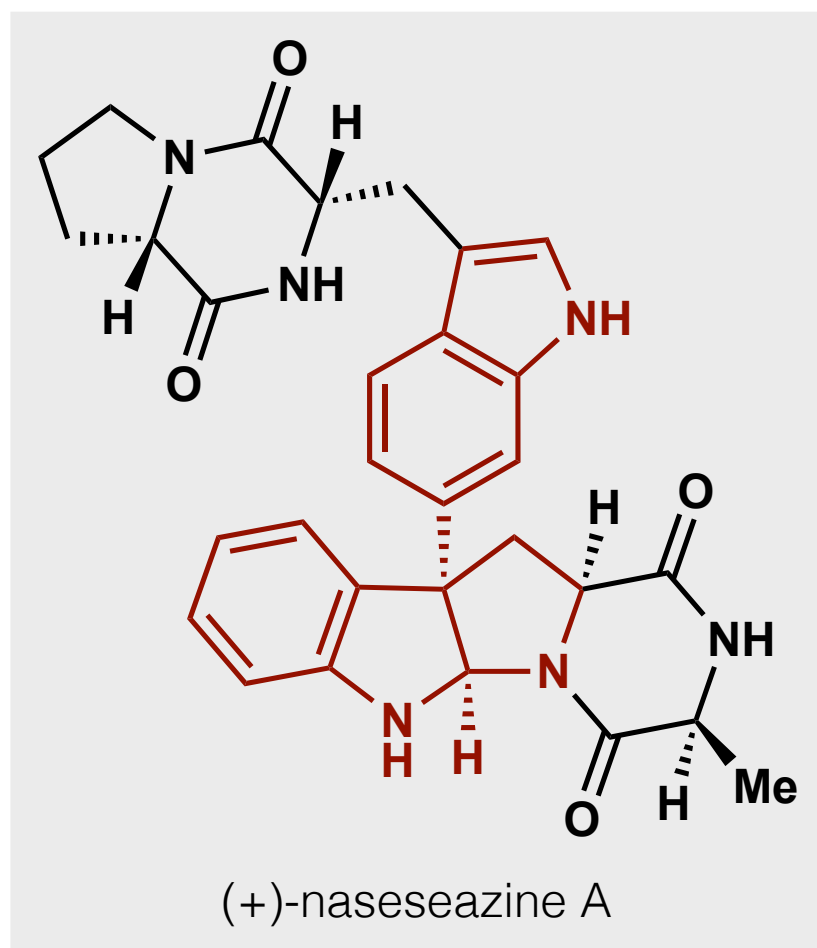
Total Synthesis of (+)-nocardioazine A

35

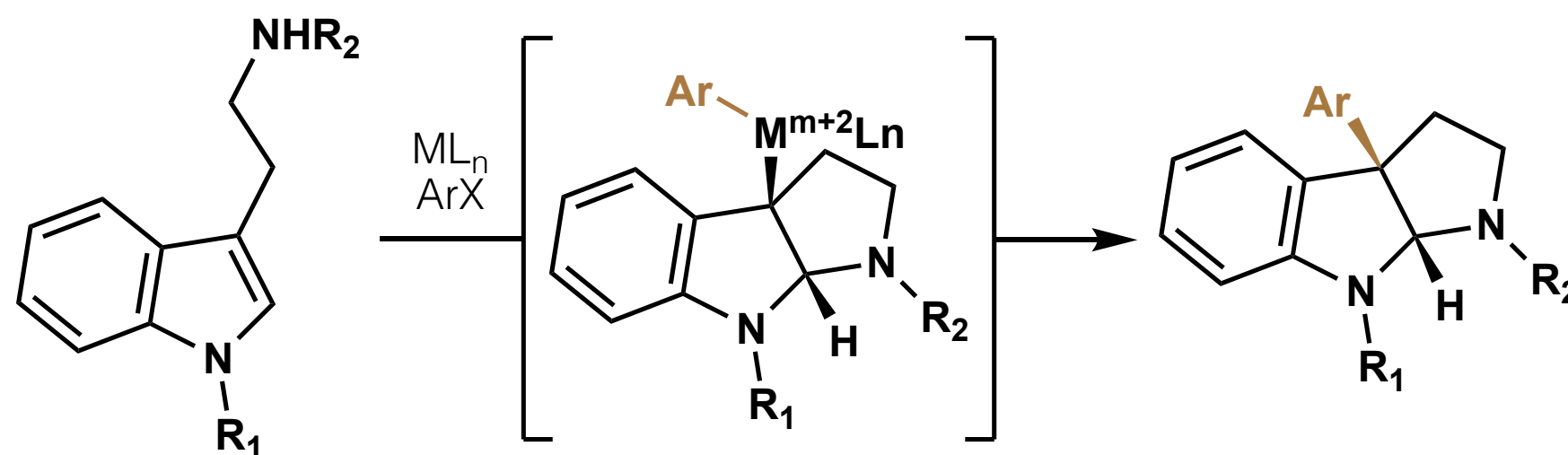


Copper-Catalyzed Arylation of Tryptophan Derivatives

36

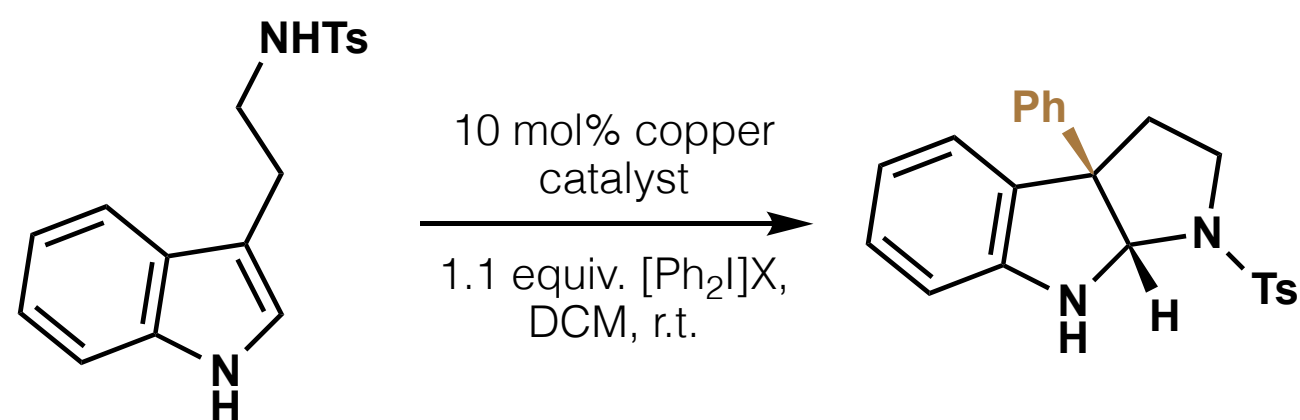


from indoles to tryptamines

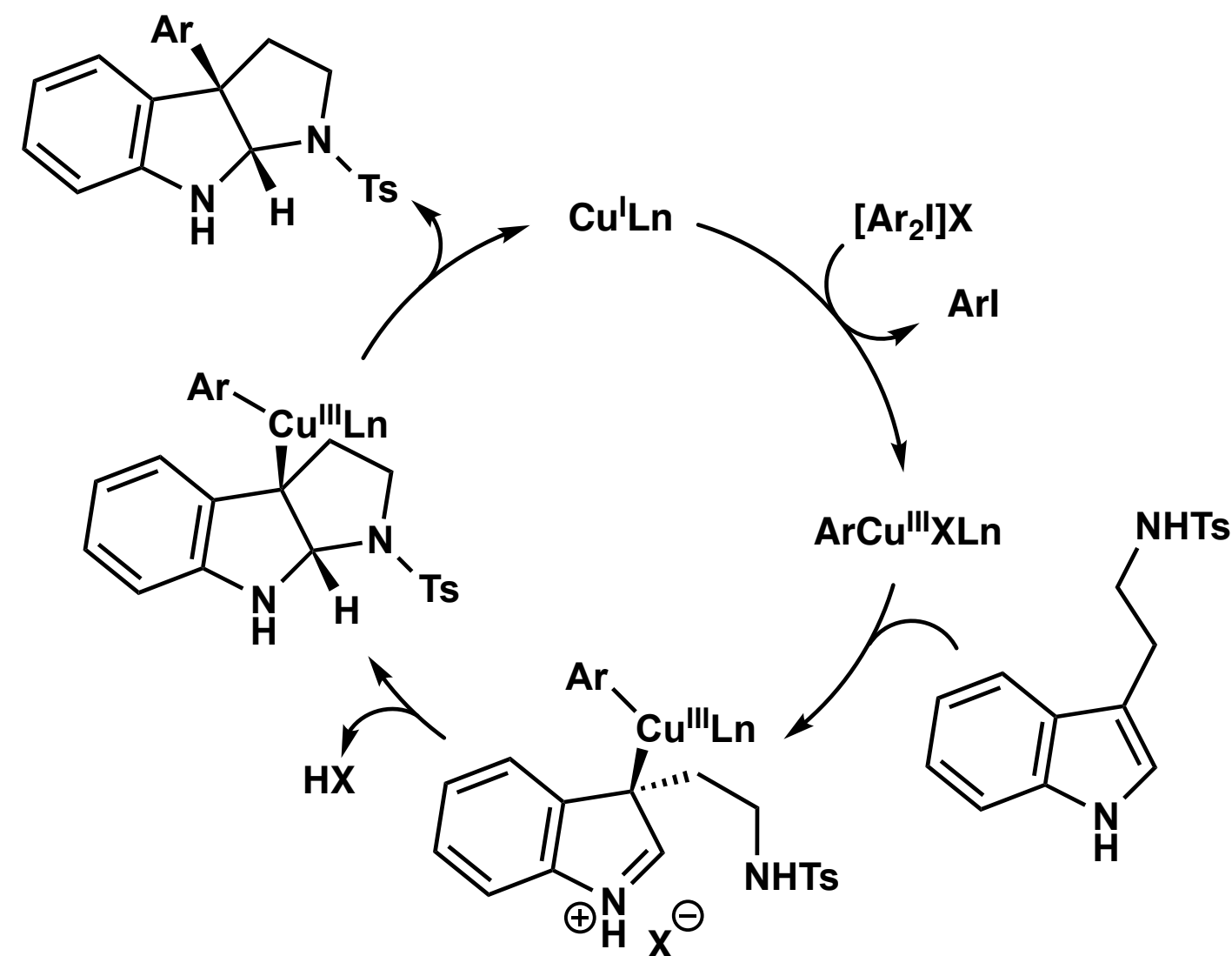


Copper-Catalyzed Arylation of Tryptophan Derivatives

37

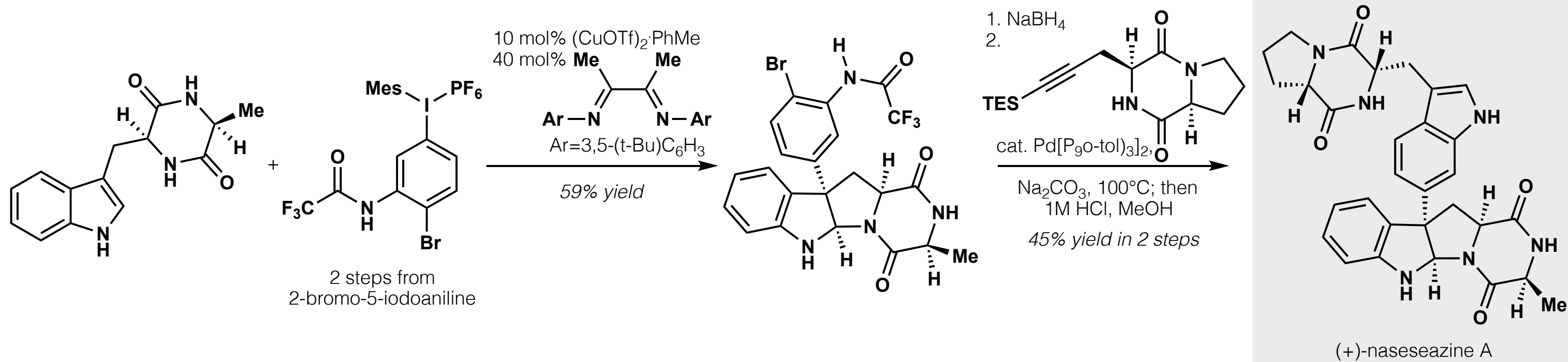


- Both Cu(I) and Cu(II) work
- **$\text{Cu}(\text{OAc})_2$** best for arylation with $[\text{Ph}_2\text{I}]\text{BF}_4$ or other symmetric iodonium salts (**64% yield, 2.9:1 C3:C2**)
- **$\text{Cu}(\text{OTf})_2$** better for arylation with less reactive, mesityl-substituted iodonium salts (**65% yield, 2.6:1 C3:C2**)

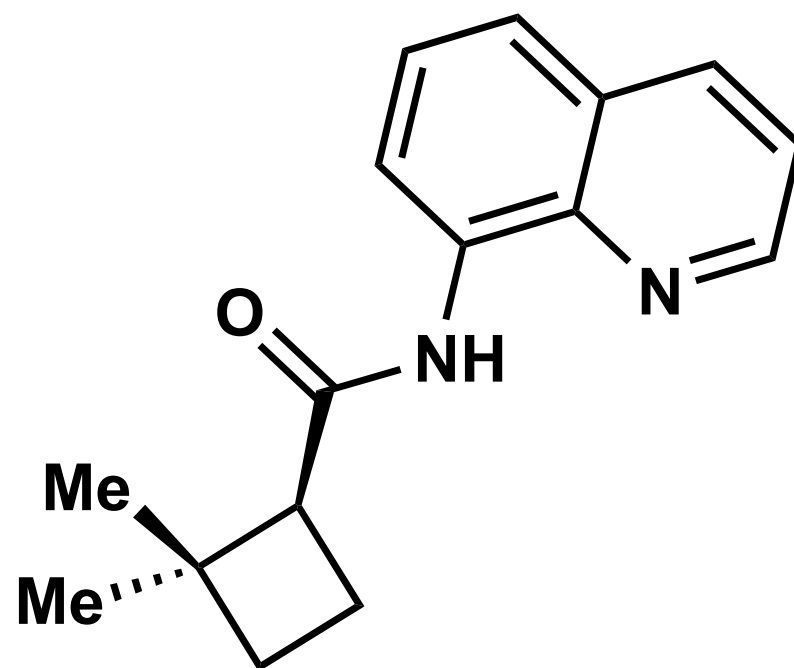


Total Synthesis of (+)-naseeseazine A

38



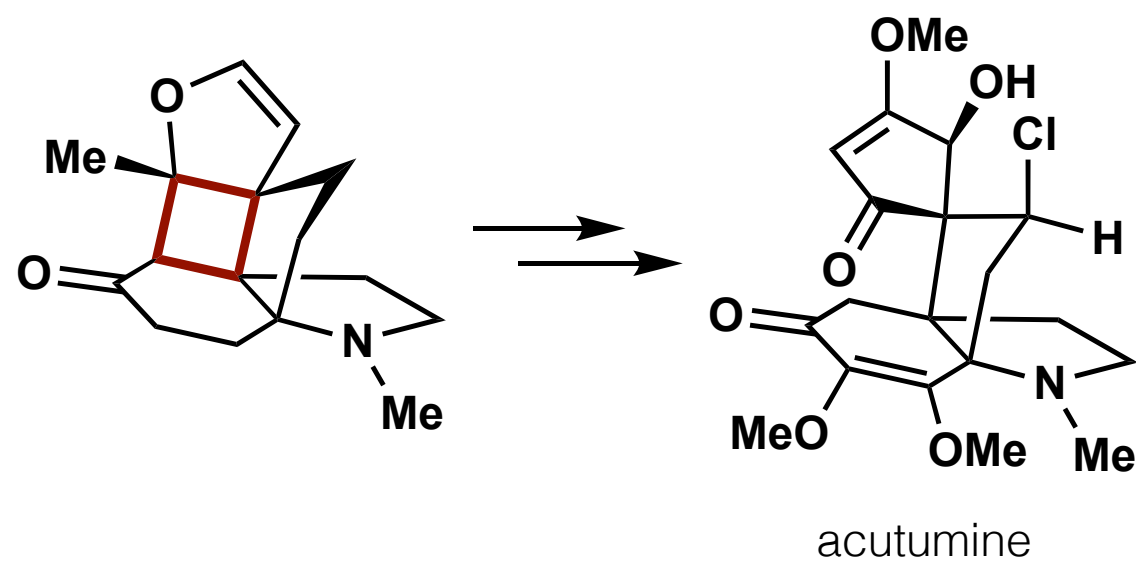
- Bidentate ligands which permit transmission of the stereochemical information (di-imine ligands are best)
 - Reaction yield is limited by C2 competitive arylation
- 5 steps sequence (LLS) from comm. avail. starting materials



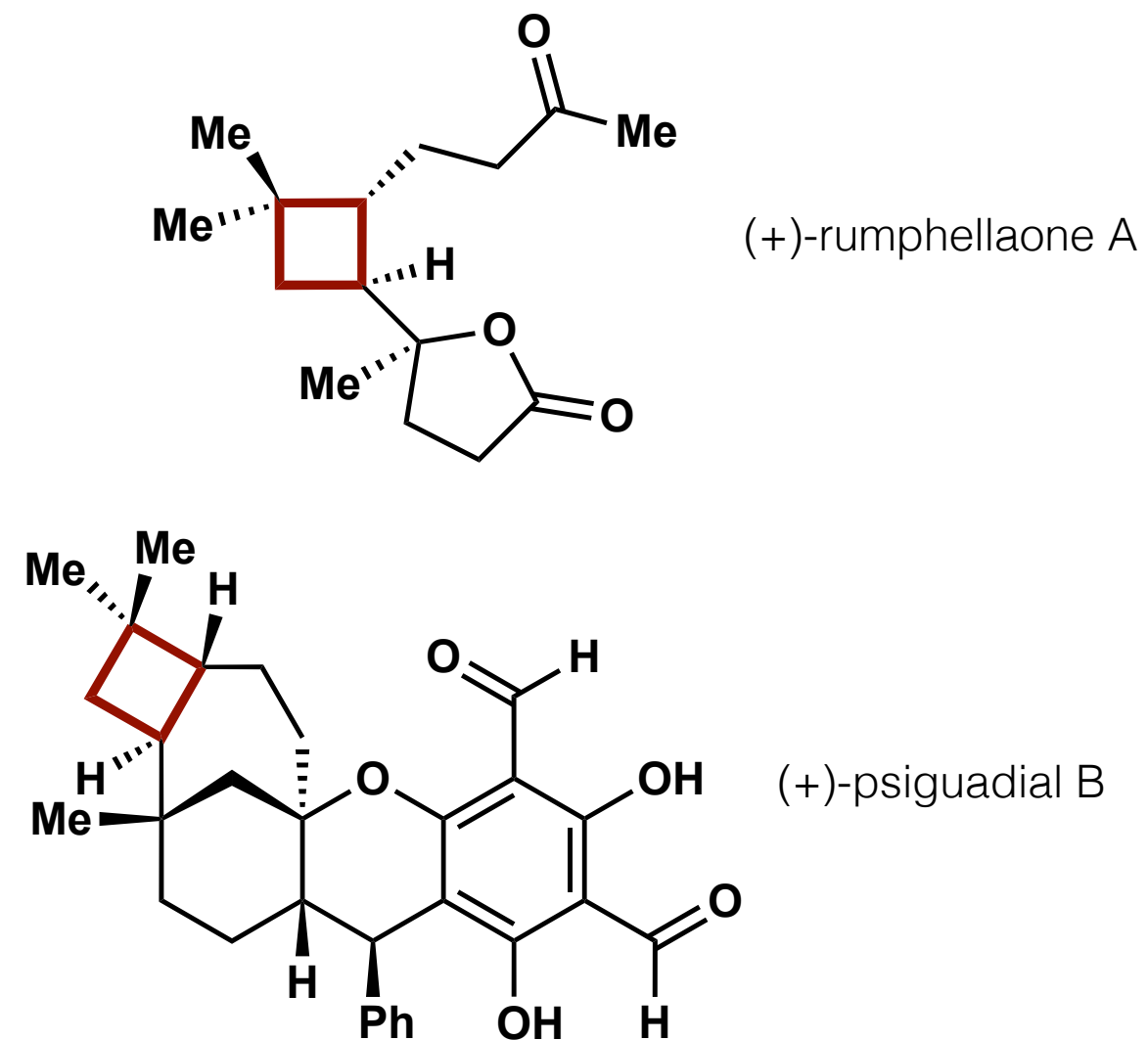
The Cyclobutane Era

The Cyclobutane Era

40



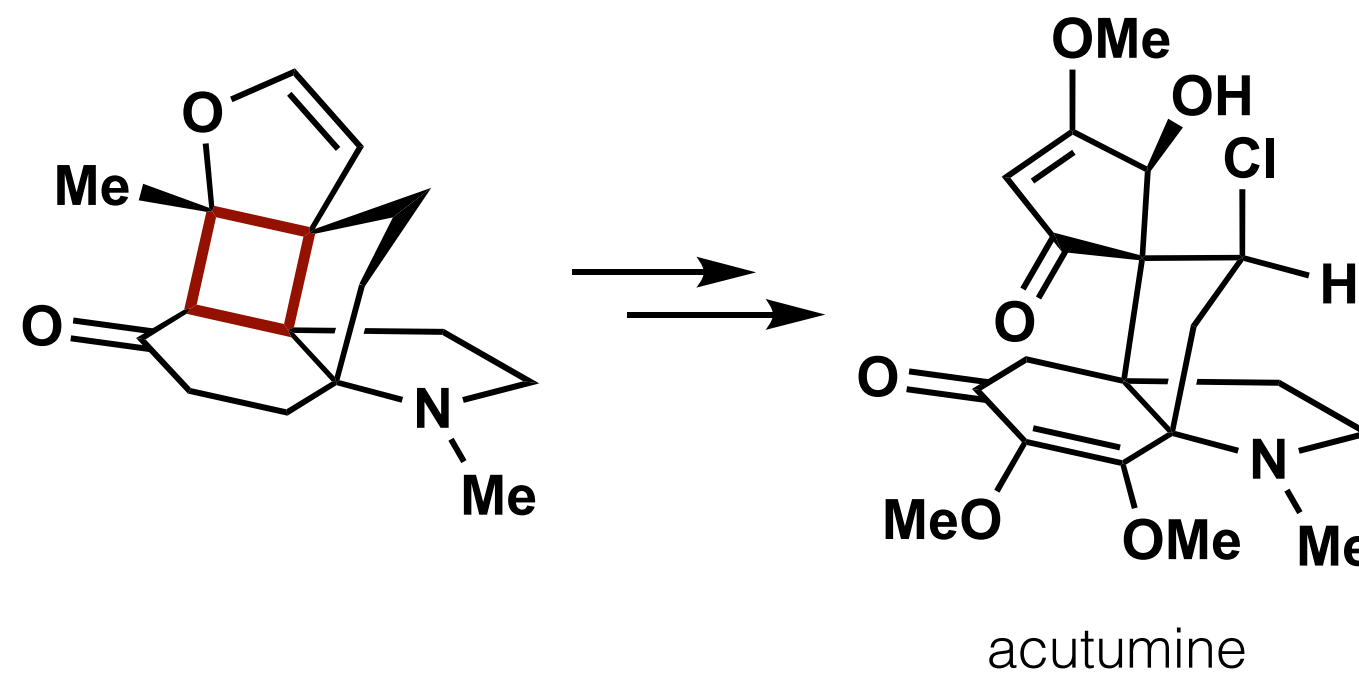
Cyclobutanes as “storage devices”



Cyclobutanes as built-in natural product motifs

The Cyclobutane Era

41



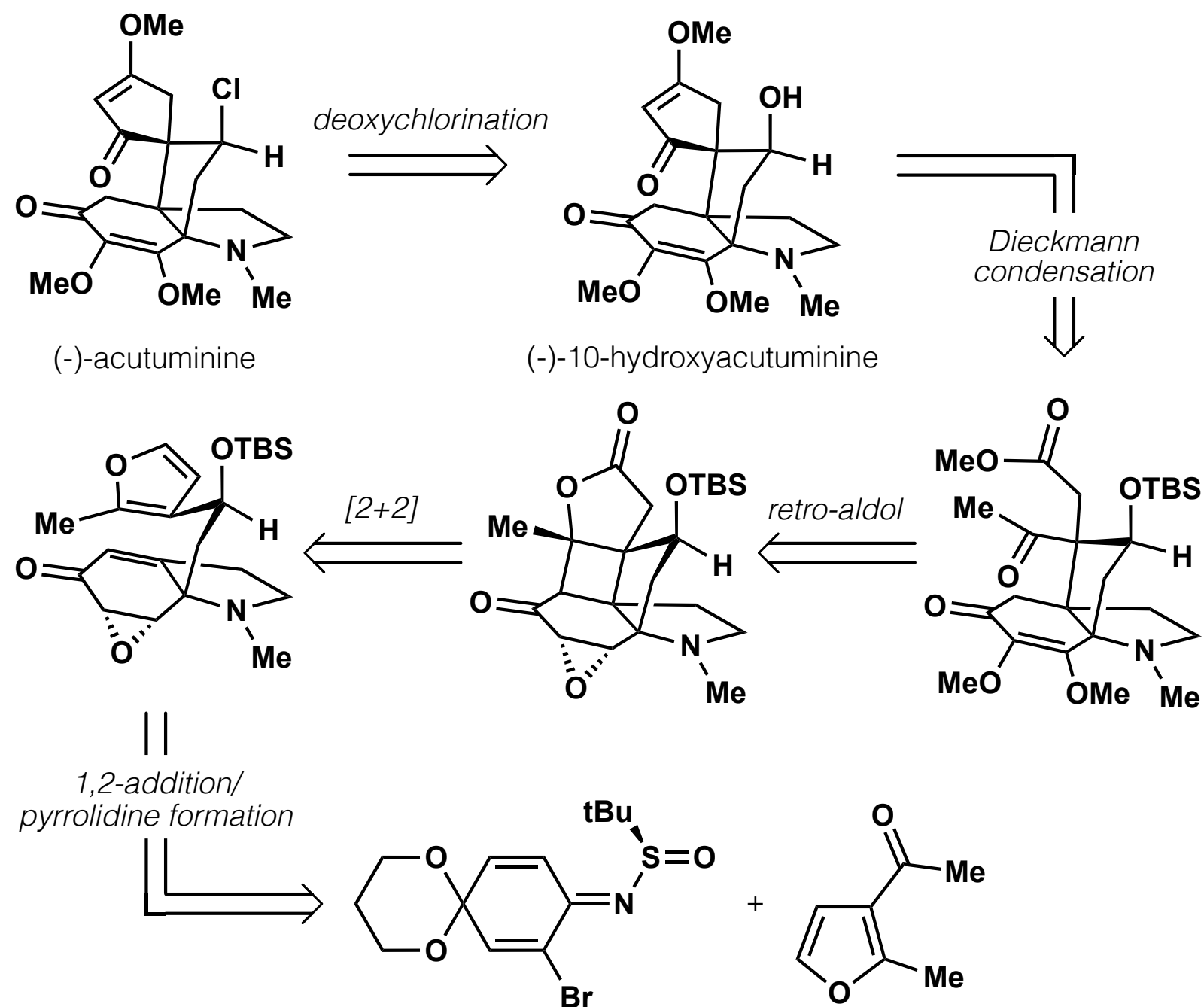
Cyclobutanes as “storage devices”

Total Synthesis of (-)-10-hydroxyacutuminine

42

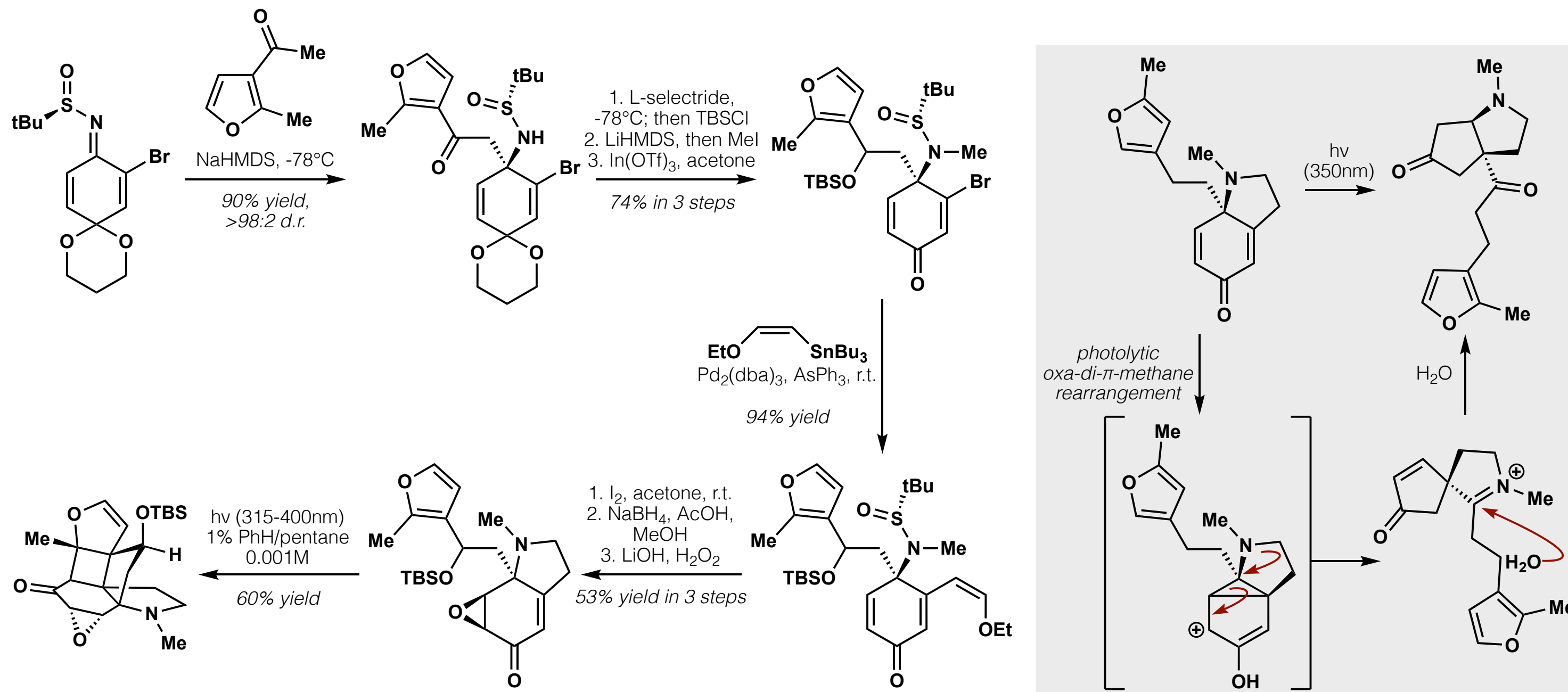


- Isolated from the Chinese moonseed plant *Sinomenium acutum*
- Member of the same family, (-)-acutumine, selectively T cell cytotoxic and anti-amnesic



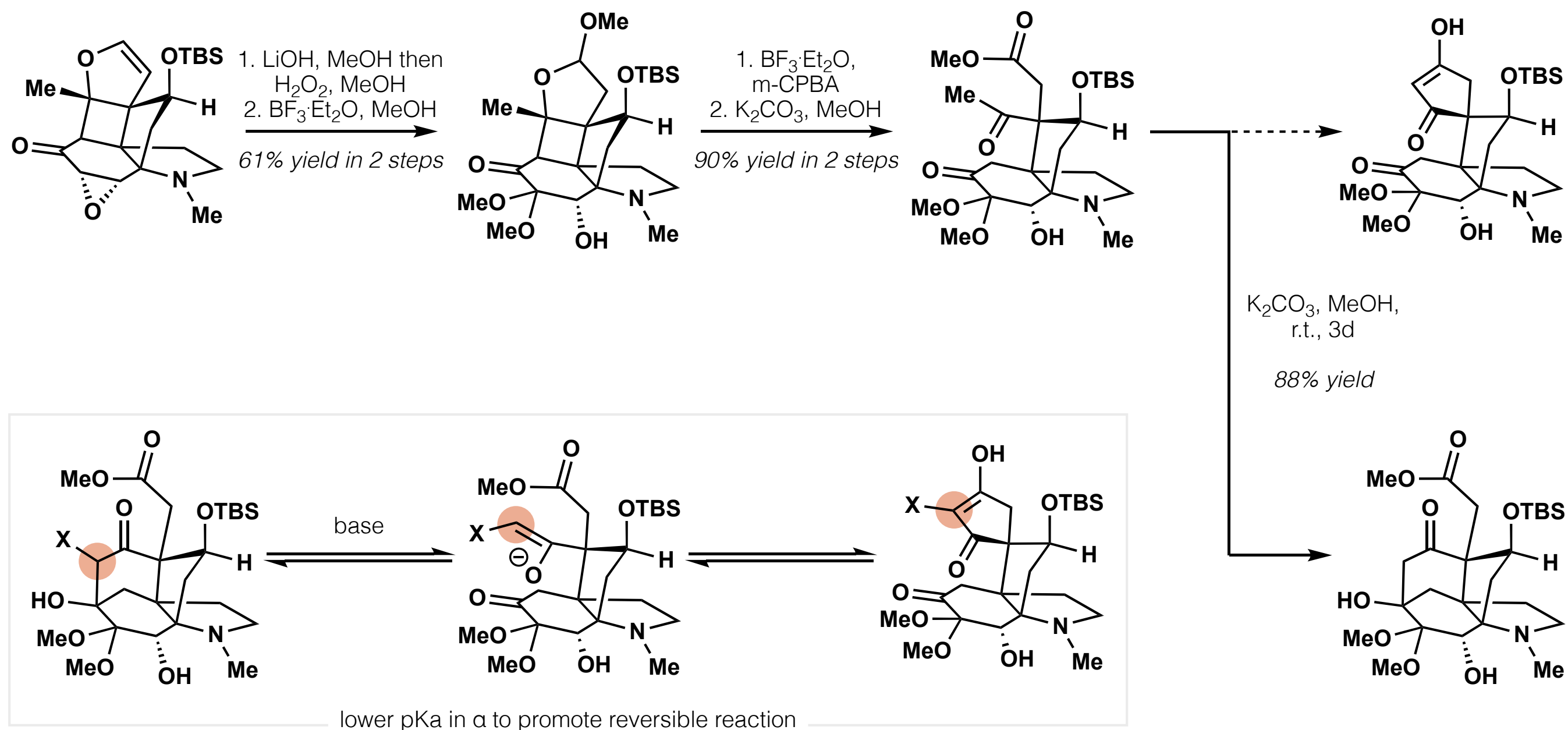
Total Synthesis of (-)-10-hydroxyacutuminine

43



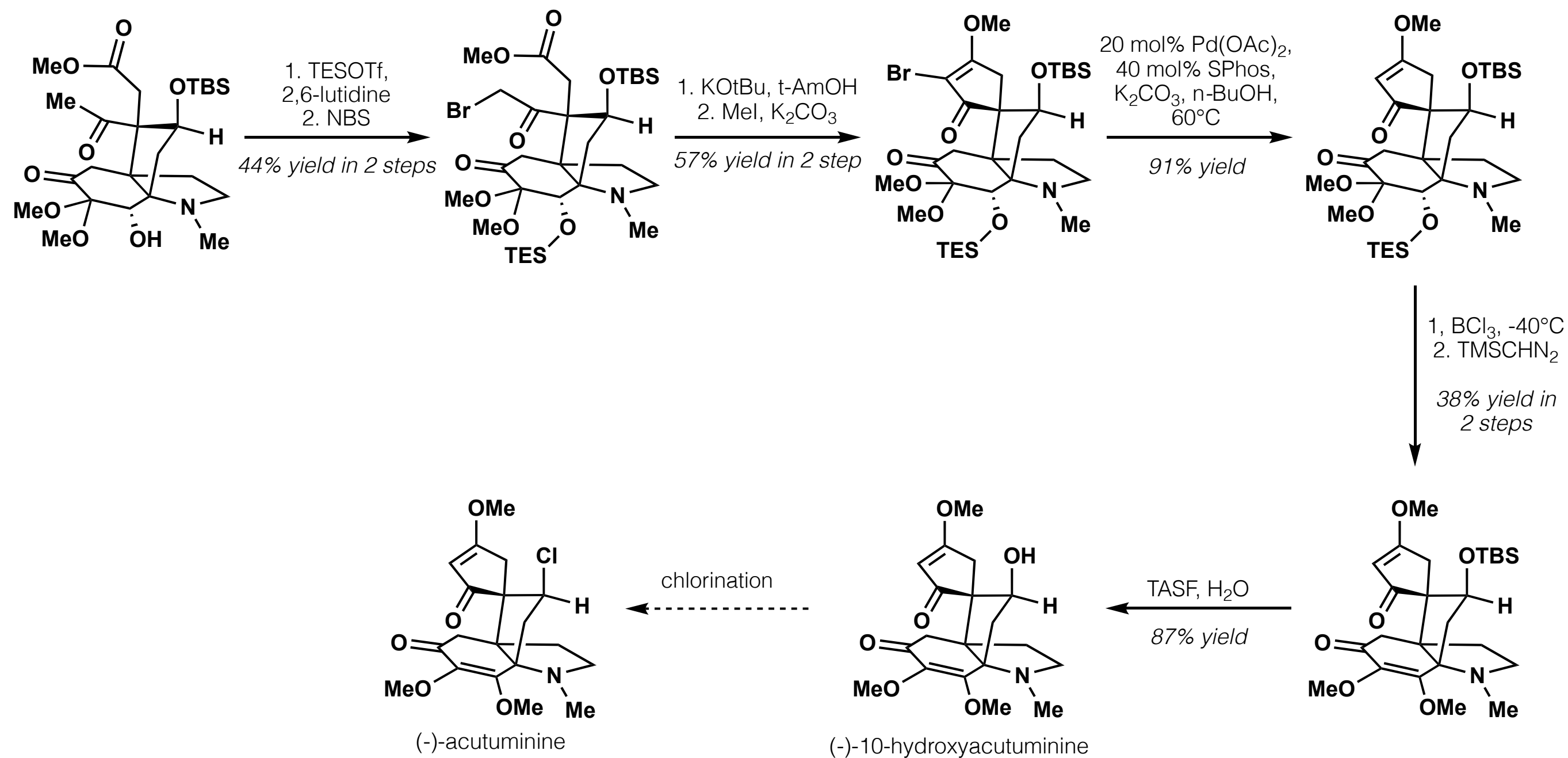
Total Synthesis of (-)-10-hydroxyacutuminine

44



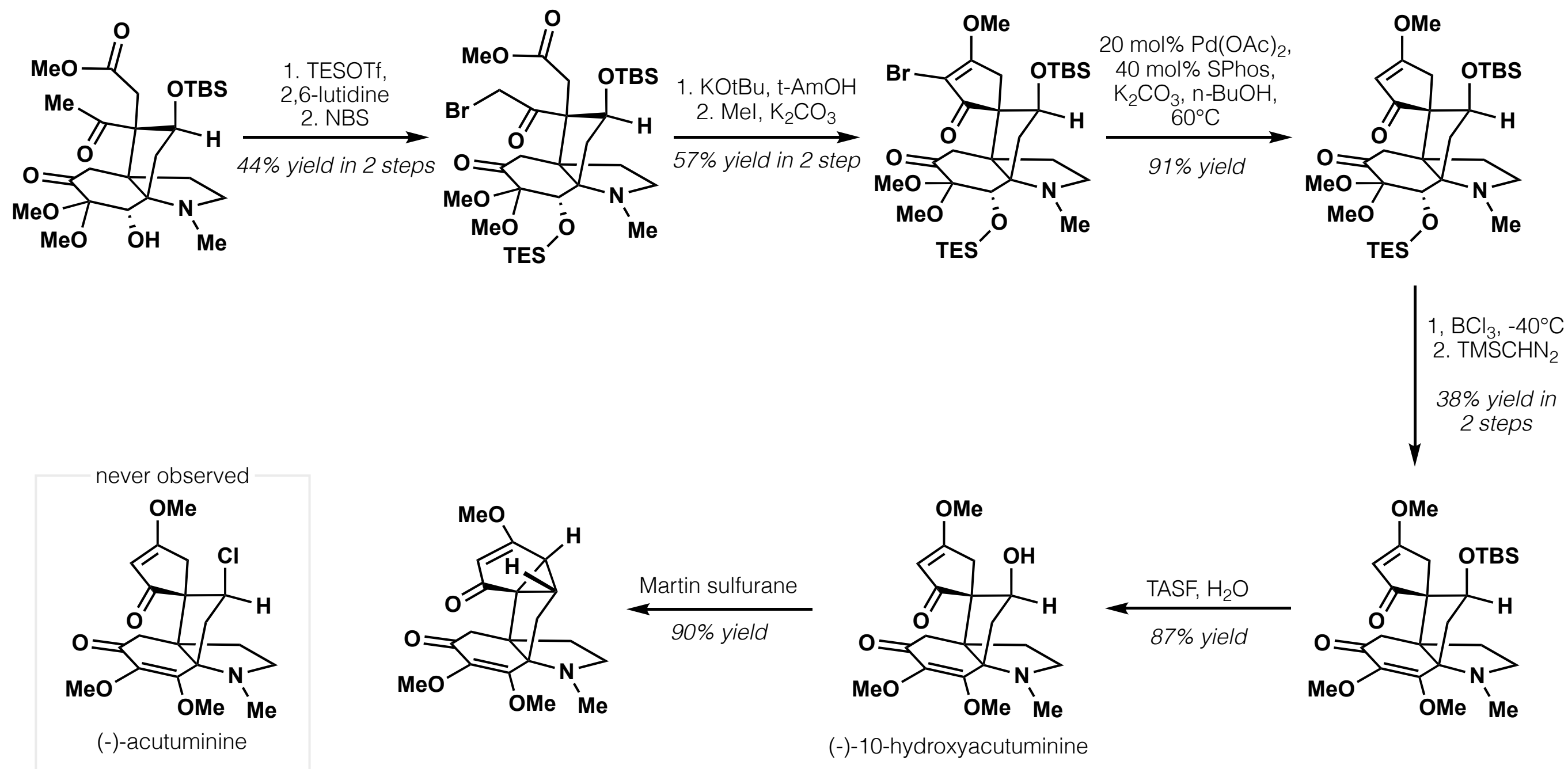
Total Synthesis of (-)-10-hydroxyacutuminine

45



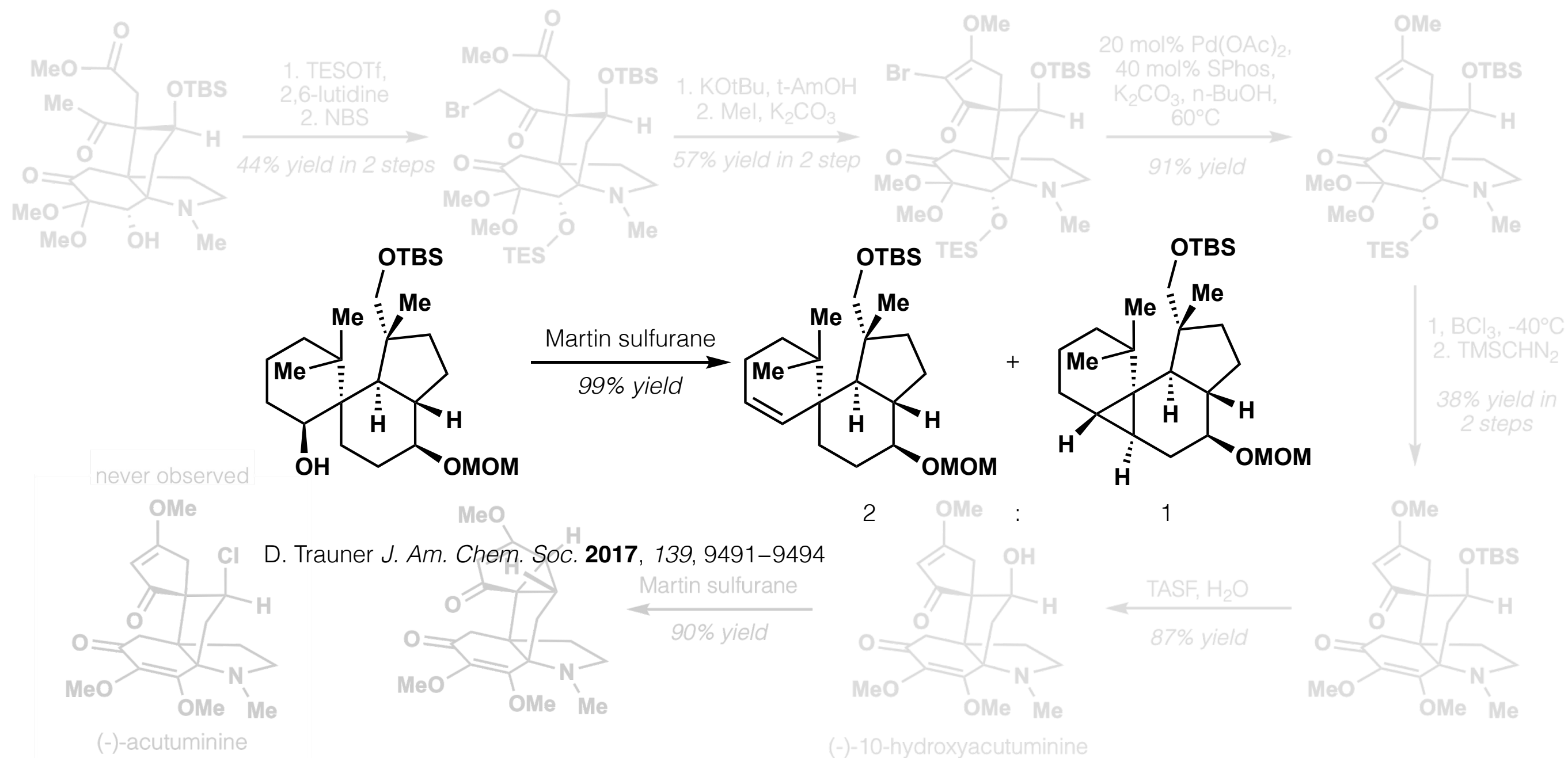
Total Synthesis of (-)-10-hydroxyacutuminine

46



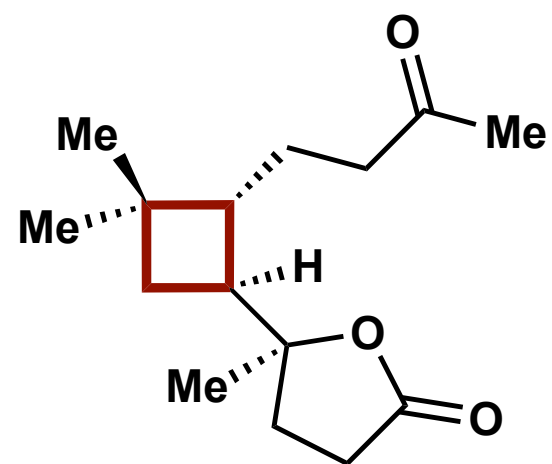
Total Synthesis of (-)-10-hydroxyacutuminine

47

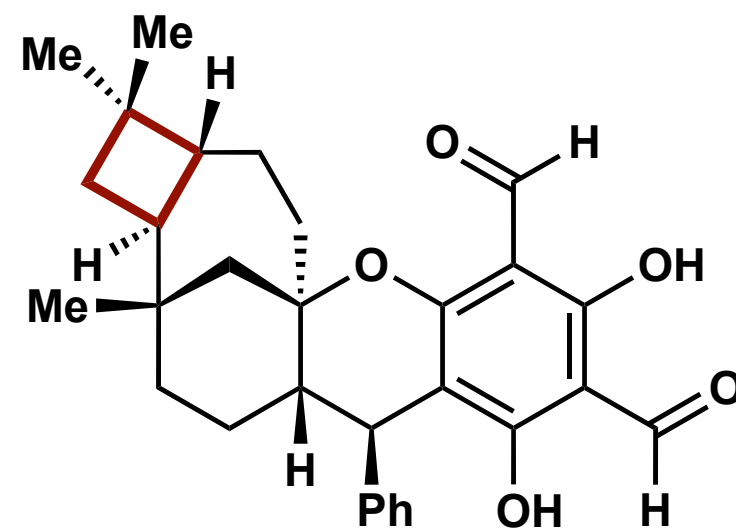


The Cyclobutane Era

48



(+)-rumphellaone A



(+)-psiguadial B

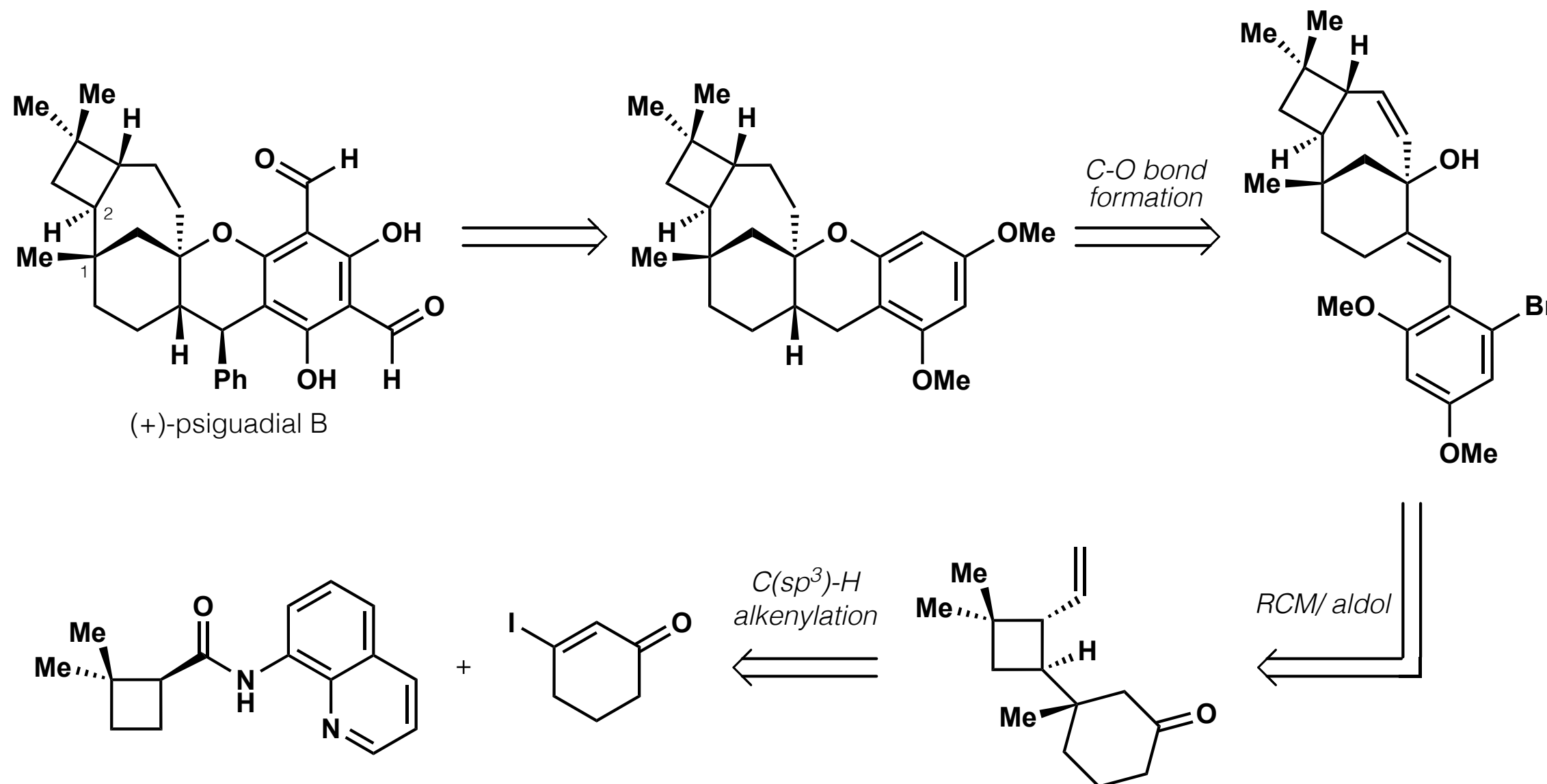
Cyclobutanes as built-in natural product motifs

Total Synthesis of (+)-psiguadial B

49



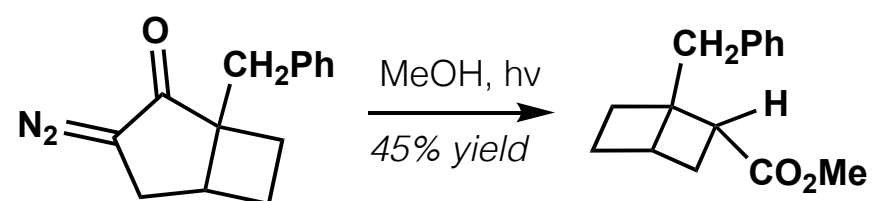
- Isolated from the leaves of *Psidium guajava*
- Potent antiproliferative activity against human hepatoma cells (HepG2 IC₅₀=46 nM)
- Mechanism of action unknown



Total Synthesis of (+)-psiguadial B

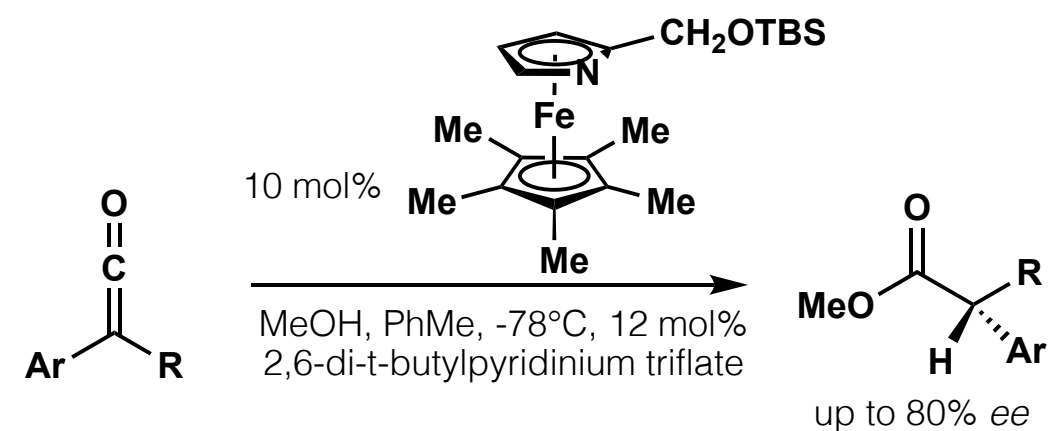
50

K. Wiberg *J. Am. Chem. Soc.* **1979**, *101*, 7675-7679

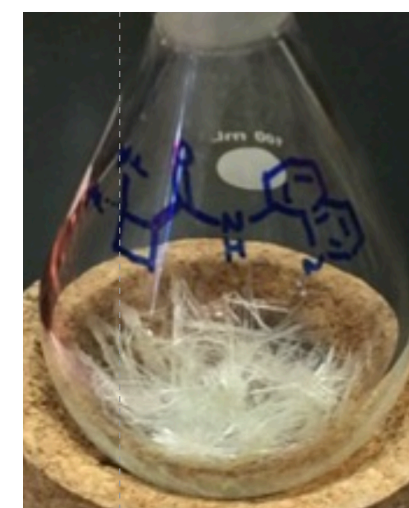
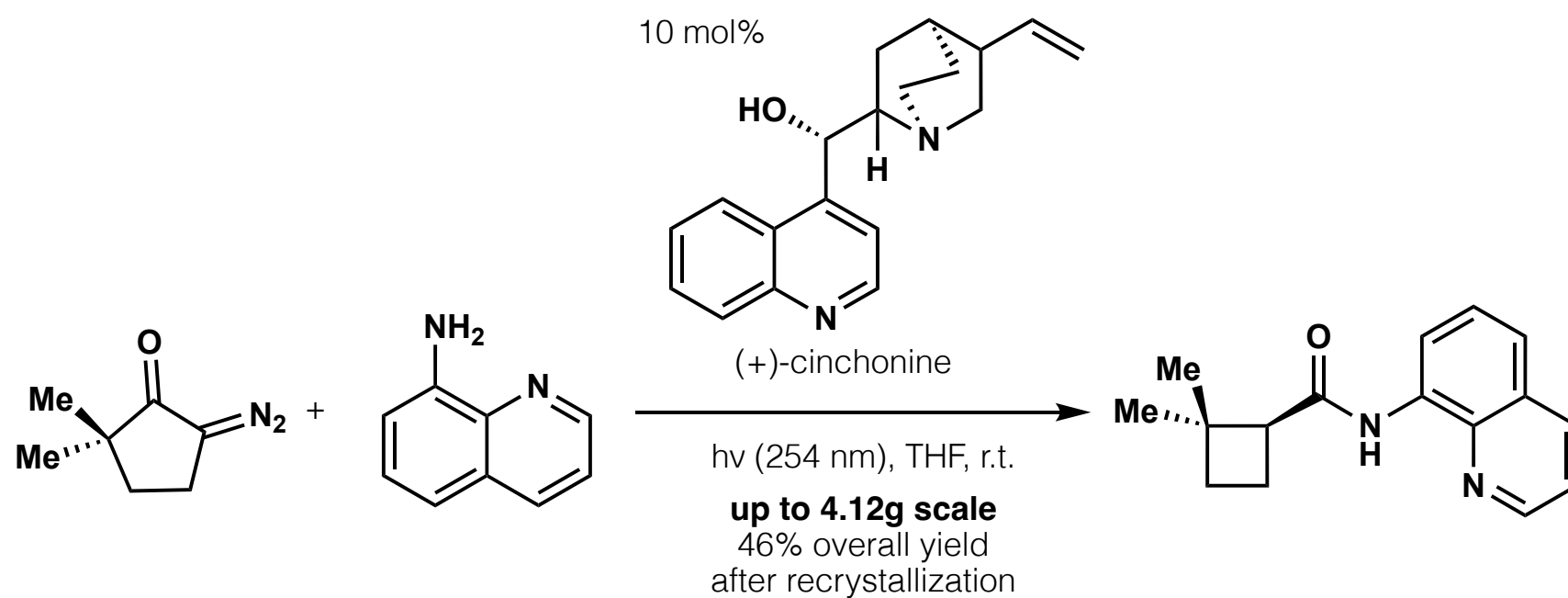


• Synthesis of racemate by Wolff rearrangement

G. Fu *J. Am. Chem. Soc.* **2005**, *127*, 6176-6177

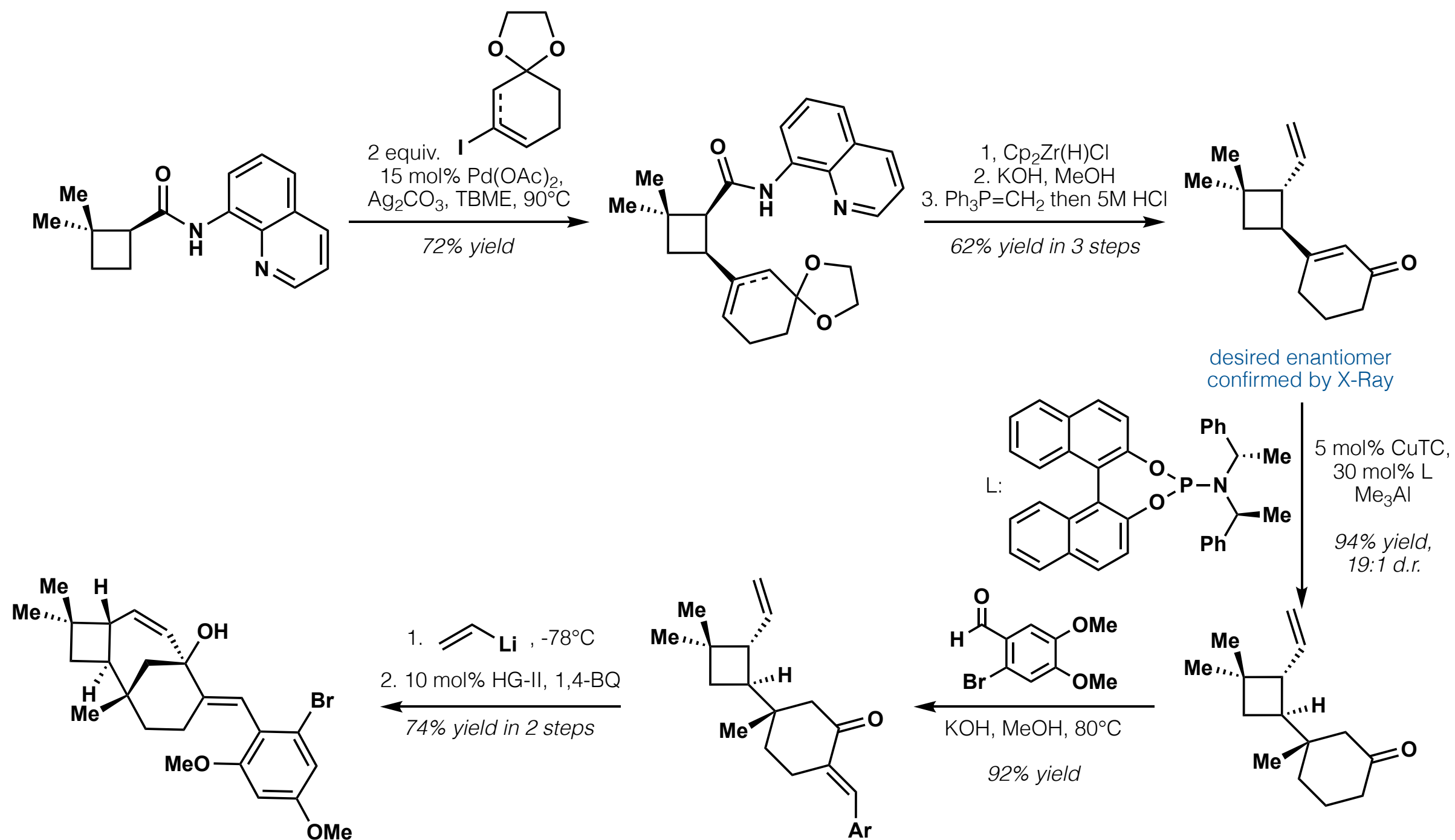


• Catalytic asymmetric nucleophilic addition to ketenes



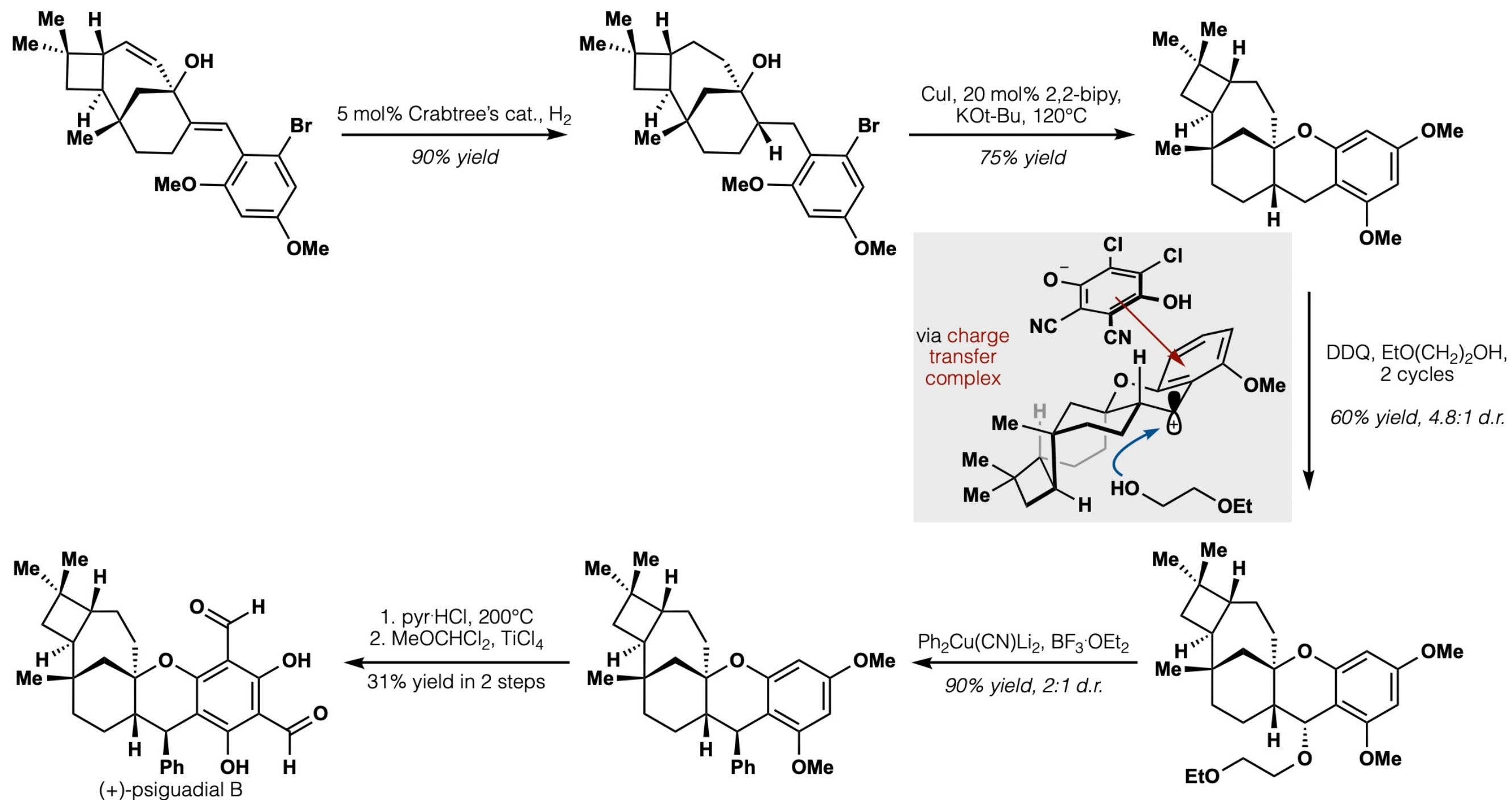
Total Synthesis of (+)-psiguadial B

51



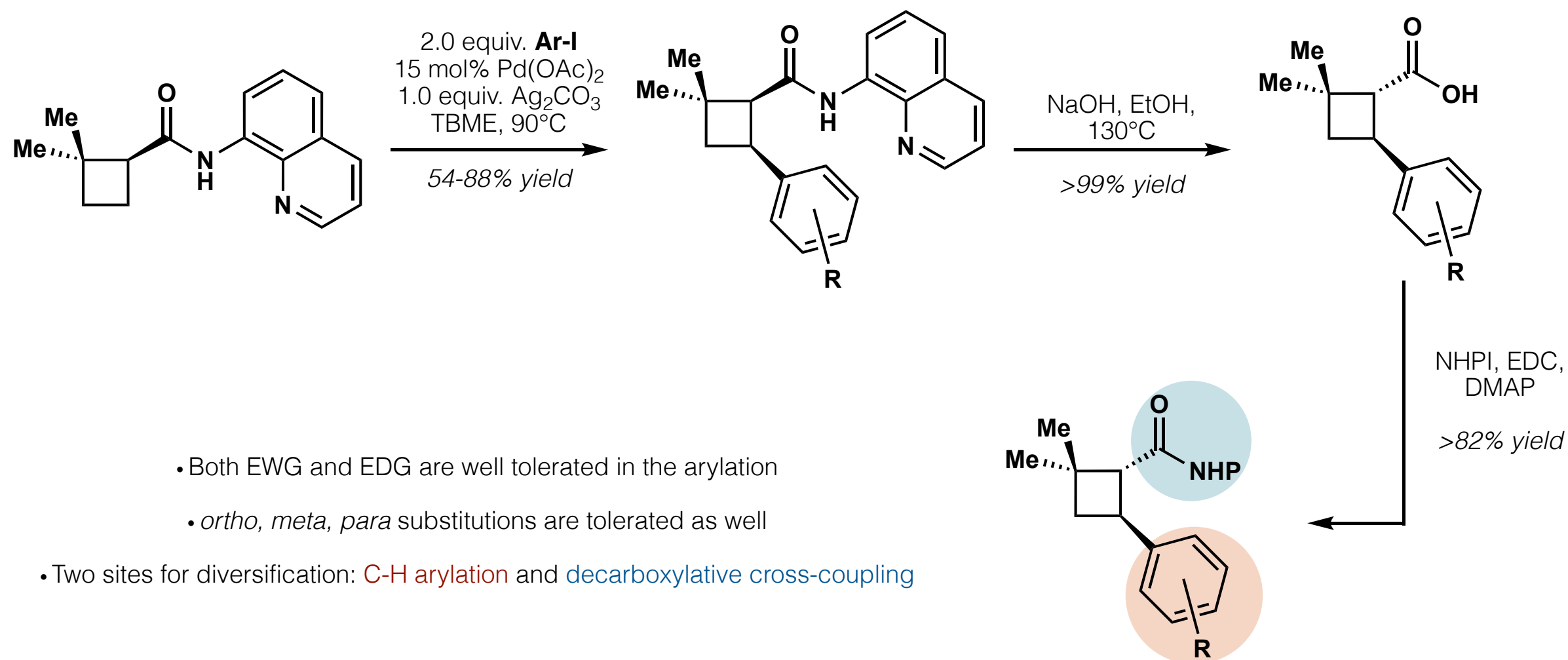
Total Synthesis of (+)-psiguadial B

52



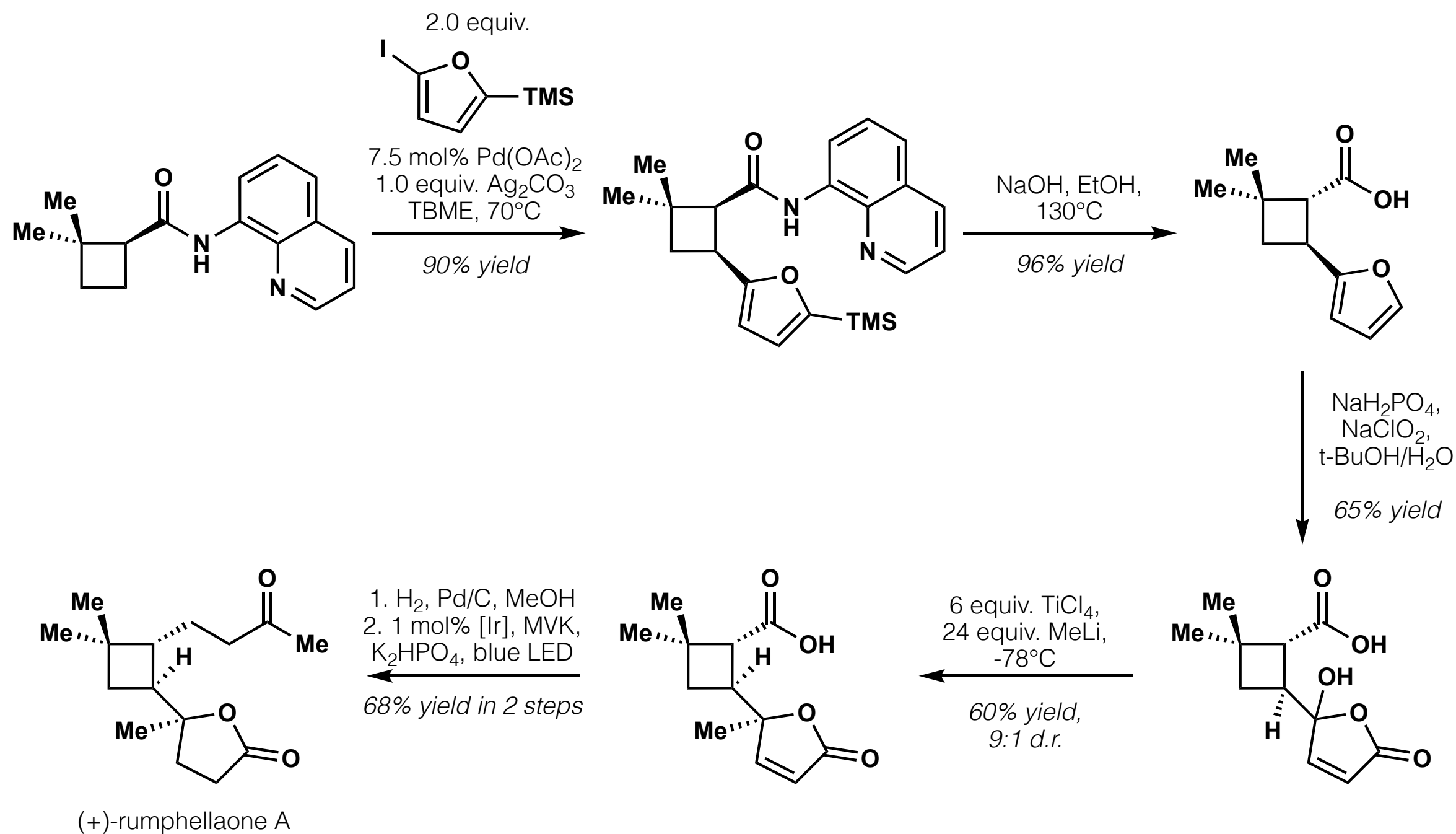
Beyond (+)-psiguadial B

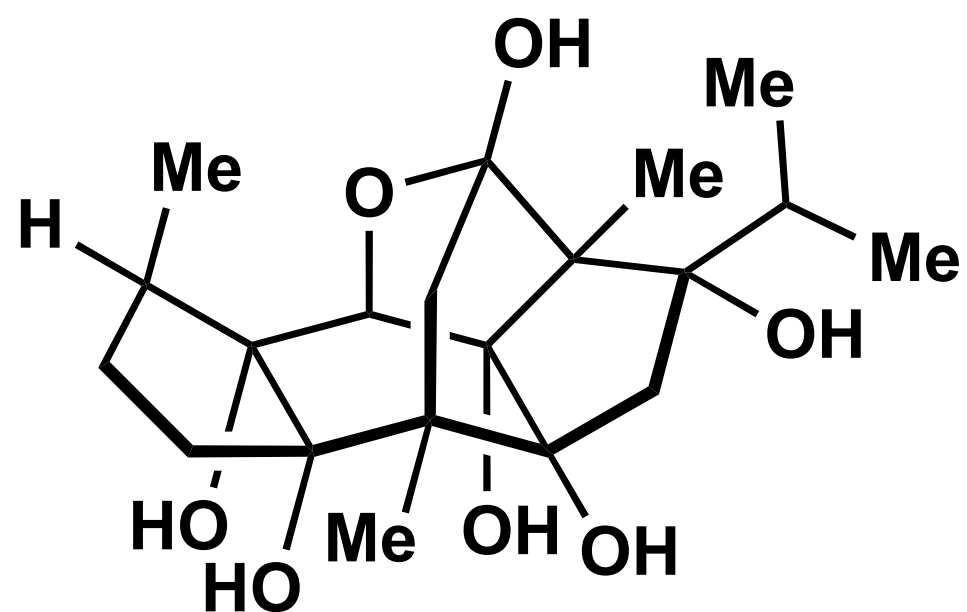
53



Total Synthesis of (+)-rumpbellaone A

54

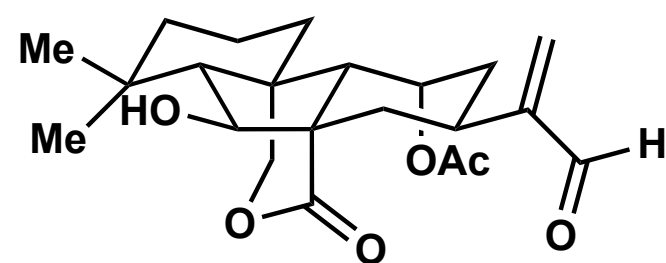




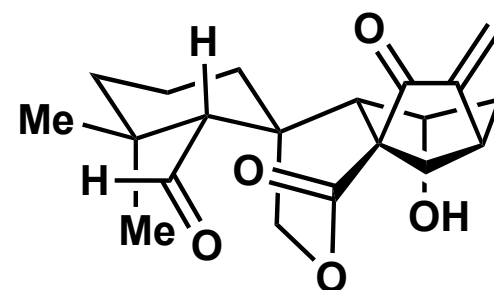
The Terpene Era

The Terpene Era

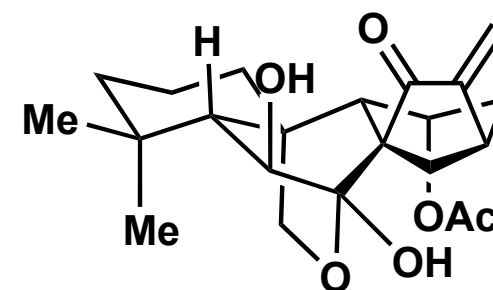
56



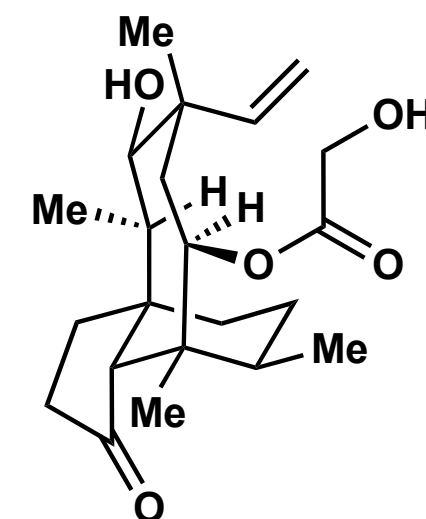
(-)-maoecrystal Z



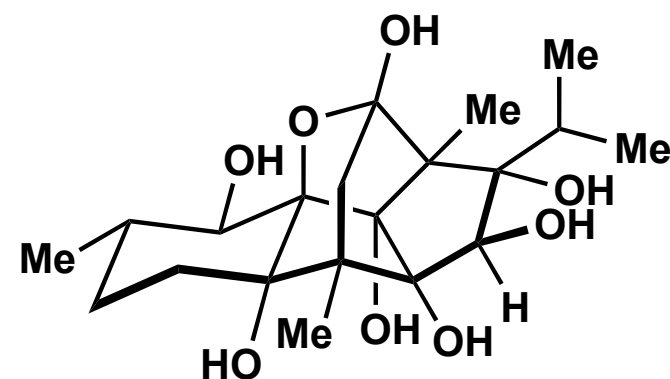
(-)-trichorabdal A



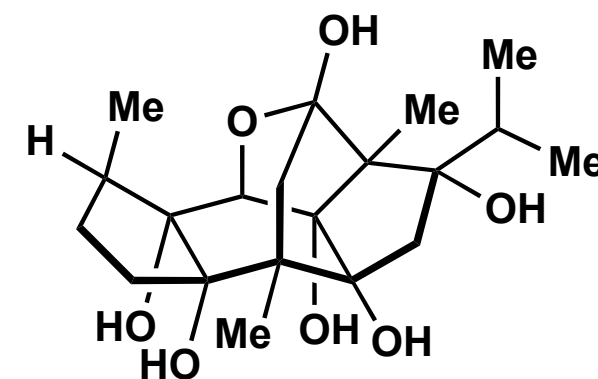
(-)-longikaurin E



(+)-pleuromutilin



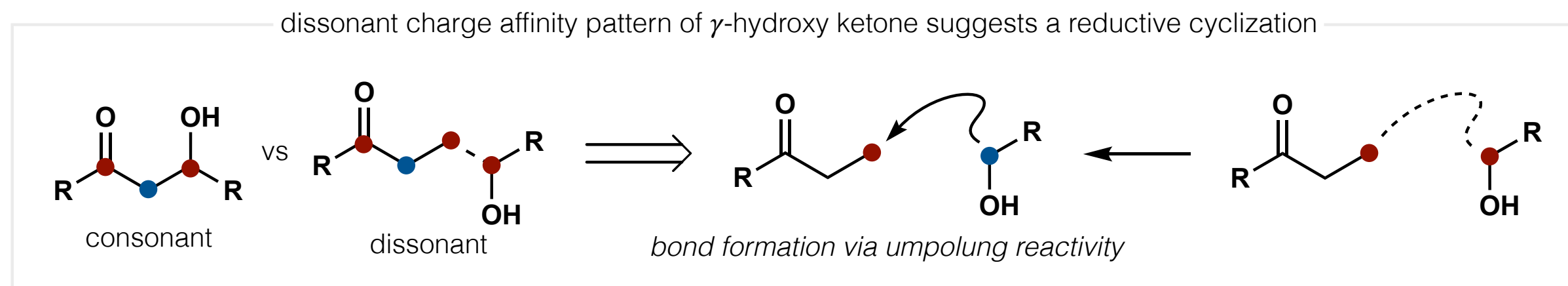
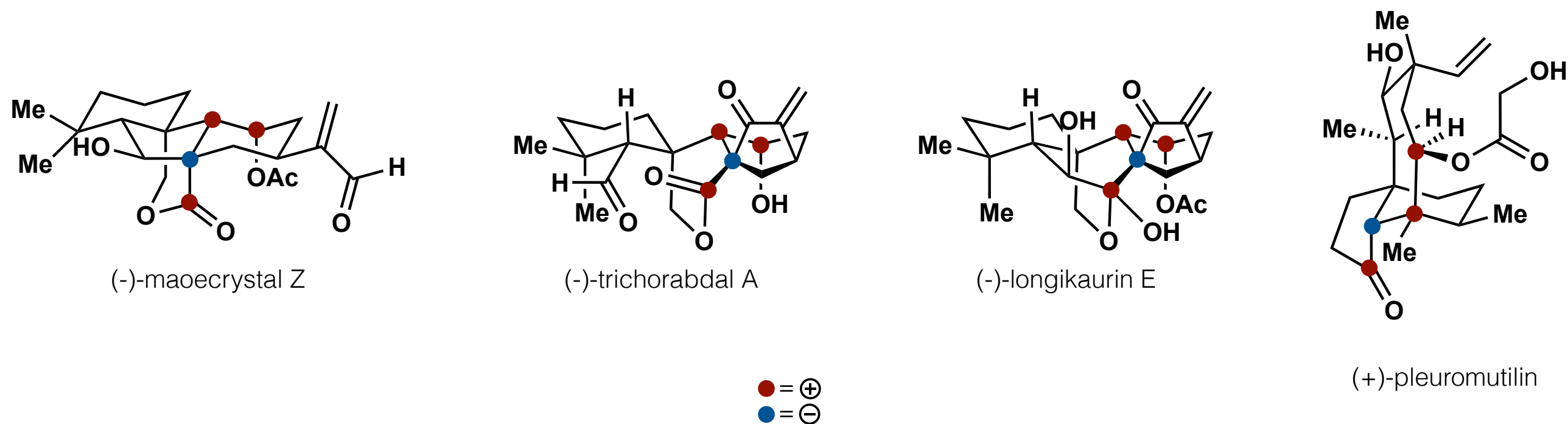
(+)-ryanodol



(+)-perseanol

Dissonant Charge Affinity Patterns

57



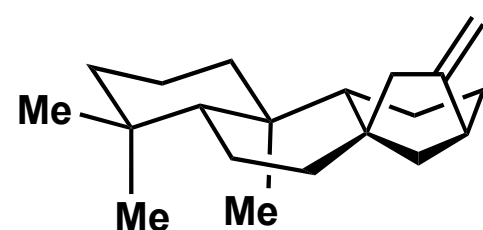
ent-kauranoid Diterpenes

58

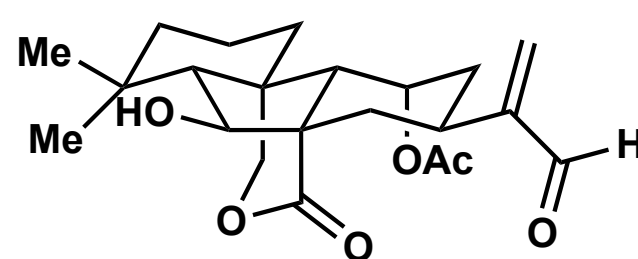
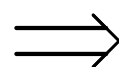


Isodon eriocalyx, source of (-)-maoecrystal Z

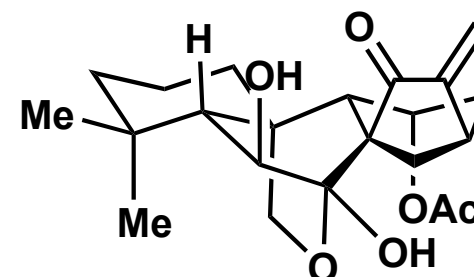
- Over 600 of *ent*-kauranoid diterpenes isolated from *Isodon* genus plants
- (-)-trichorabdal A has potent inhibitory activity of tumor growth *in vivo*
- (-)-longikaurin E and (-)-maoecrystal Z exhibit *in vitro* cytotoxicity against several human cancer cell lines



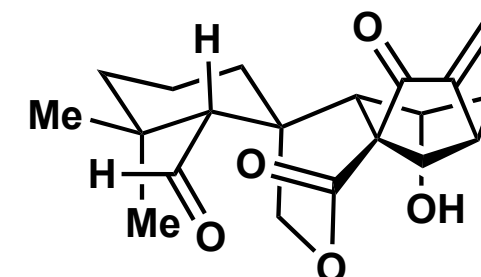
ent-kaurene



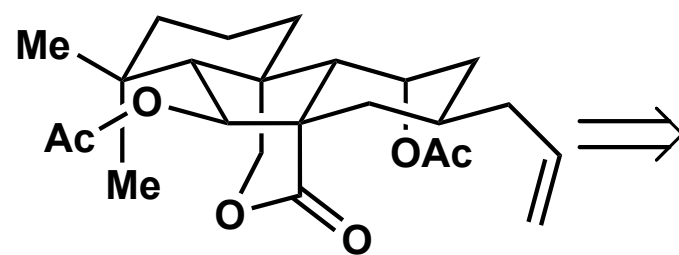
(-)-maoecrystal Z
rearranged
6,7-seco-*ent*-kauranoid



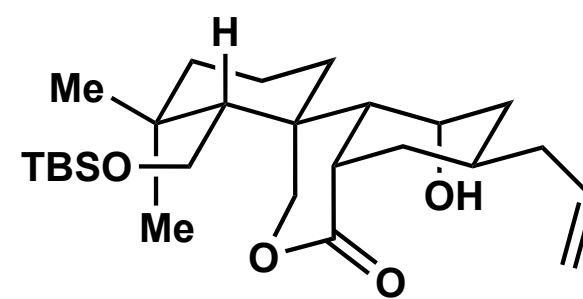
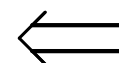
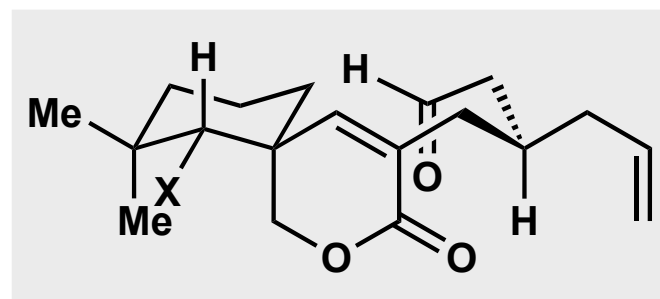
(-)-longikaurin E
C20-oxidized
ent-kauranoid



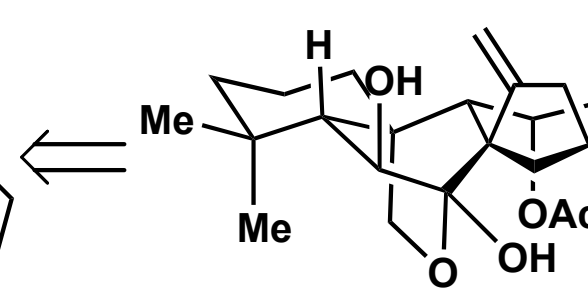
(-)-trichorabdal A
6,7-seco-*ent*-kauranoid



(-)-maoecrystal Z



(-)-trichorabdal A

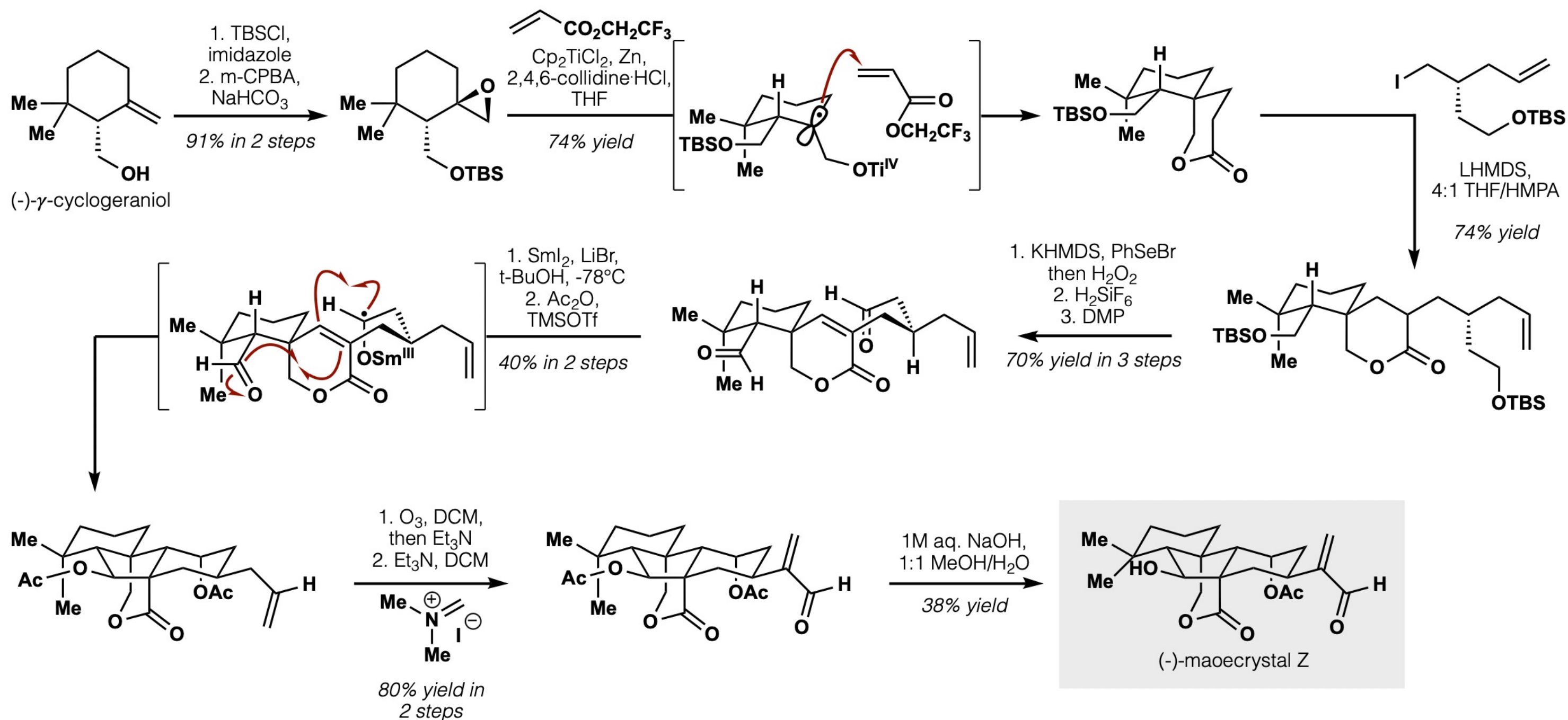


(-)-longikaurin E



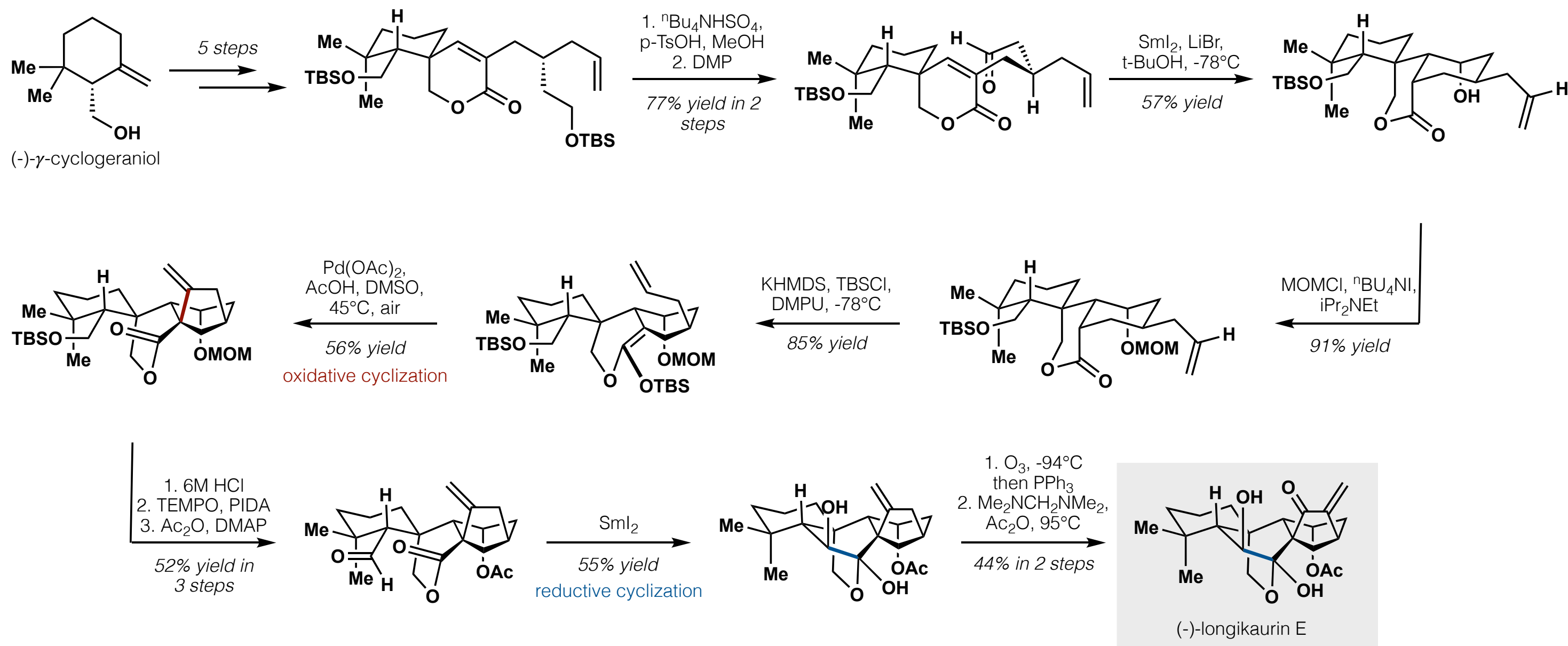
Total Synthesis of (-)-maoecrystal Z

59



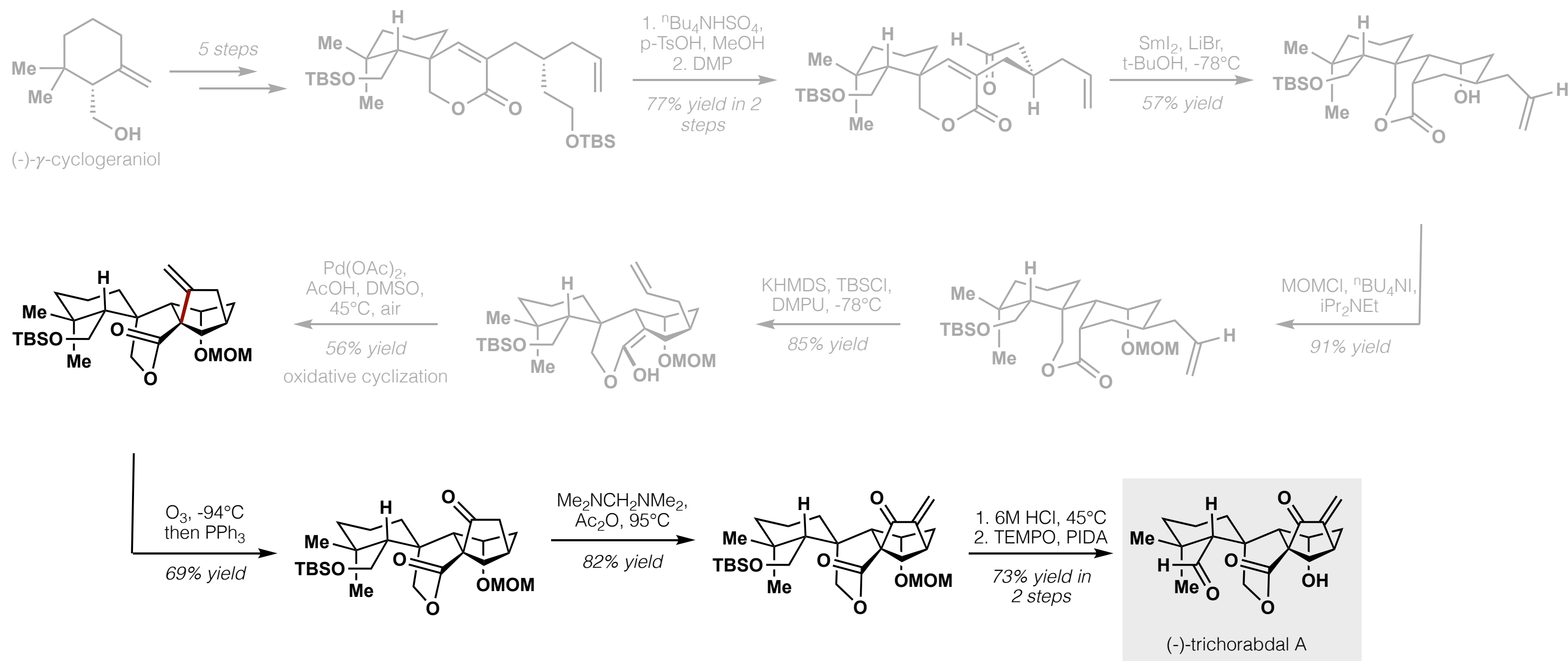
Total Synthesis of (-)-longikaurin E

60



Total Synthesis of (-)-trichorabdal A

61

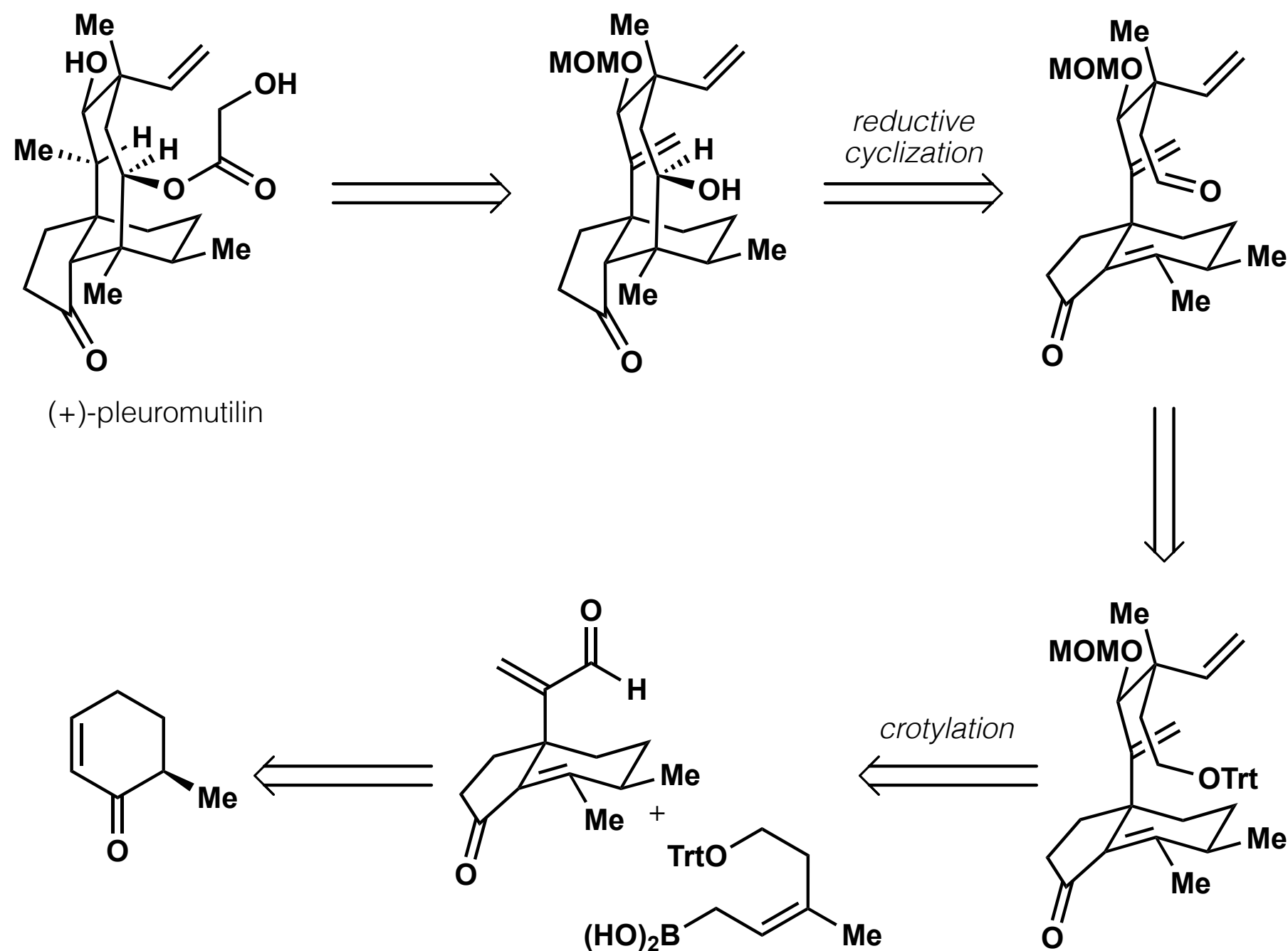


Total Synthesis of (+)-pleuromutilin

62

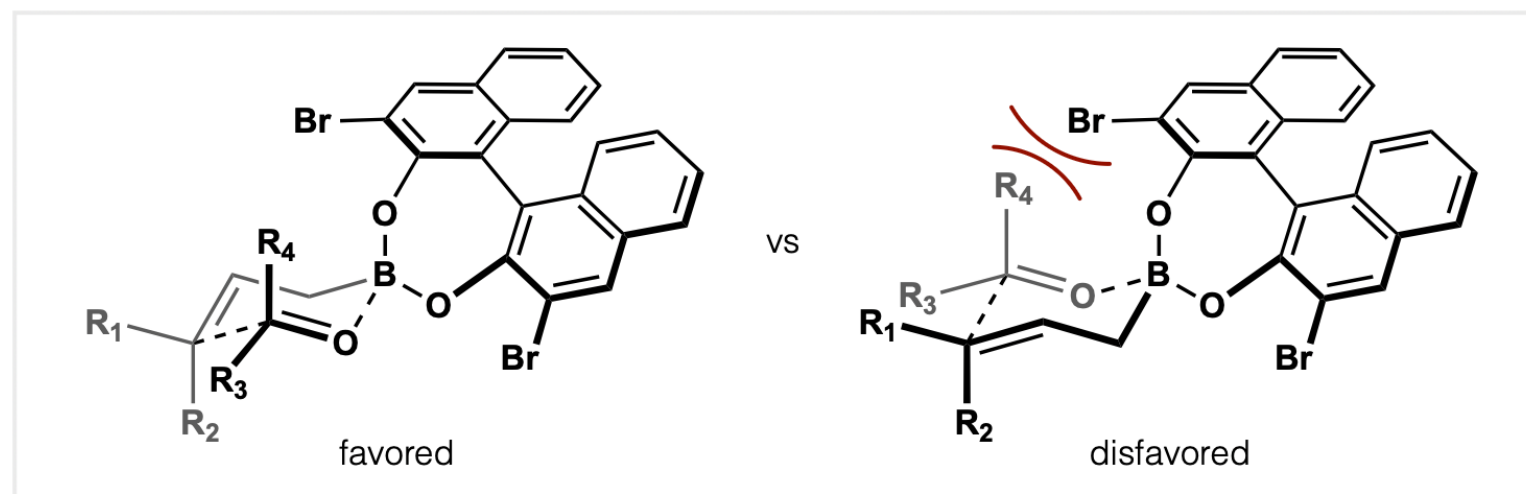
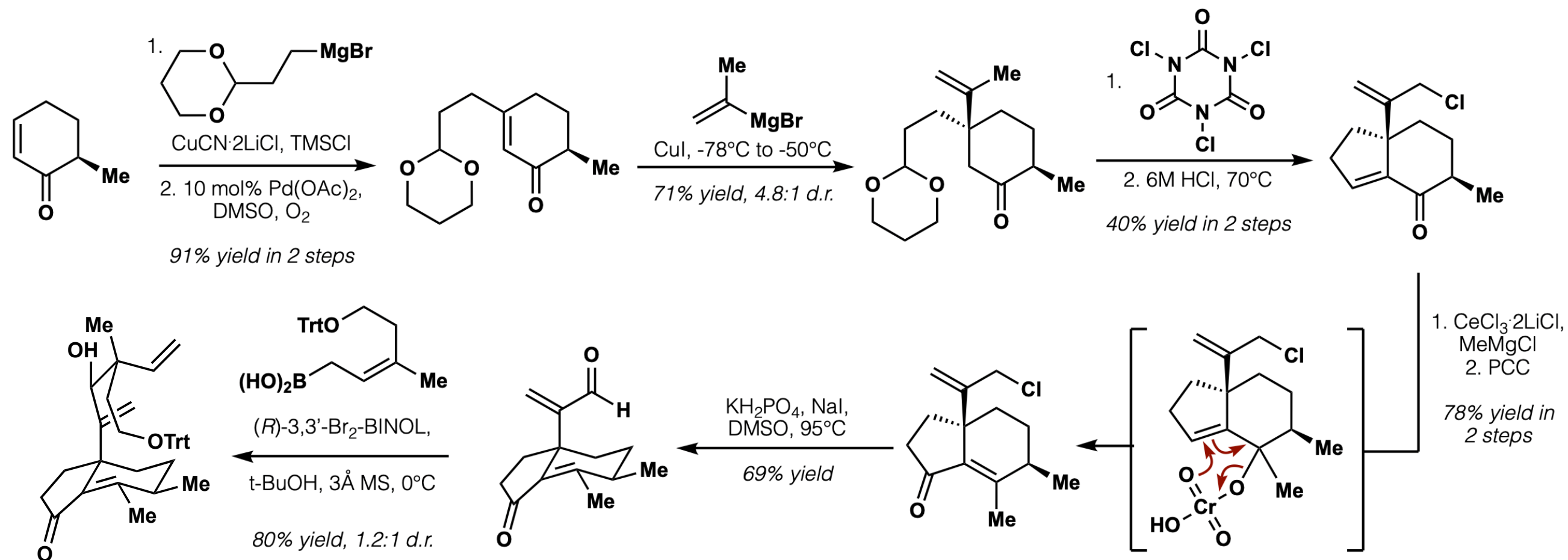


- Isolated in 1951 from the fungus *Clitopilus passeckerianus*
- Derivatives of pleuromutilin have been developed as broad-spectrum antibiotics
- Retapamulin, FDA approved for bacterial skin infections



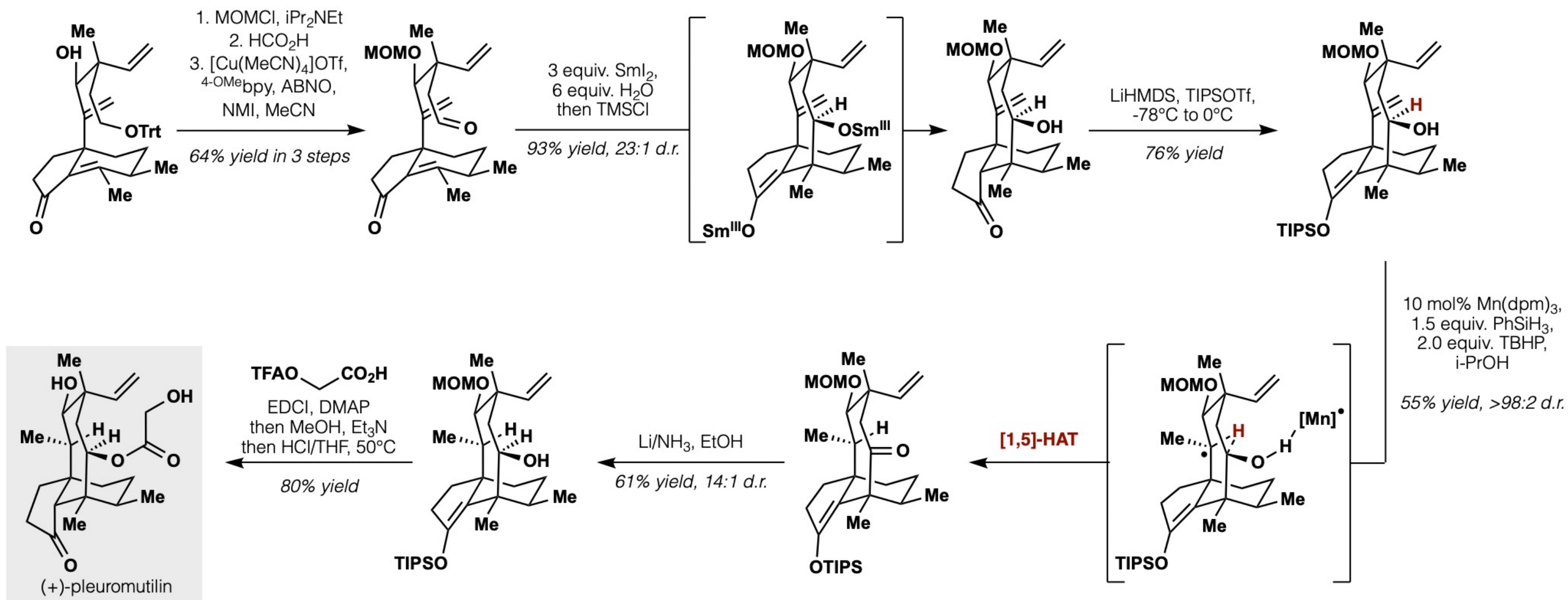
Total Synthesis of (+)-pleuromutilin

63



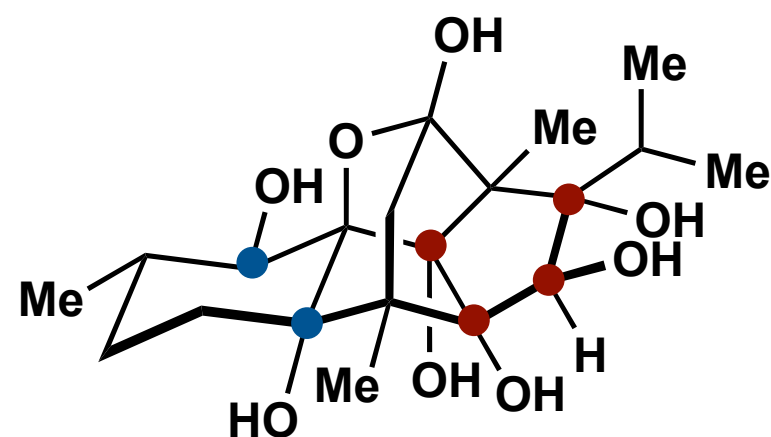
Total Synthesis of (+)-pleuromutilin

64

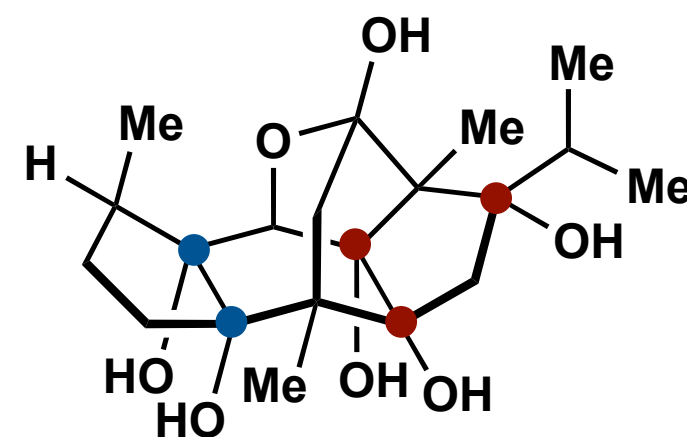


Complex Oxidation Topology

65



(+)-ryanodol



(+)-perseanol

● oxidation at early stage

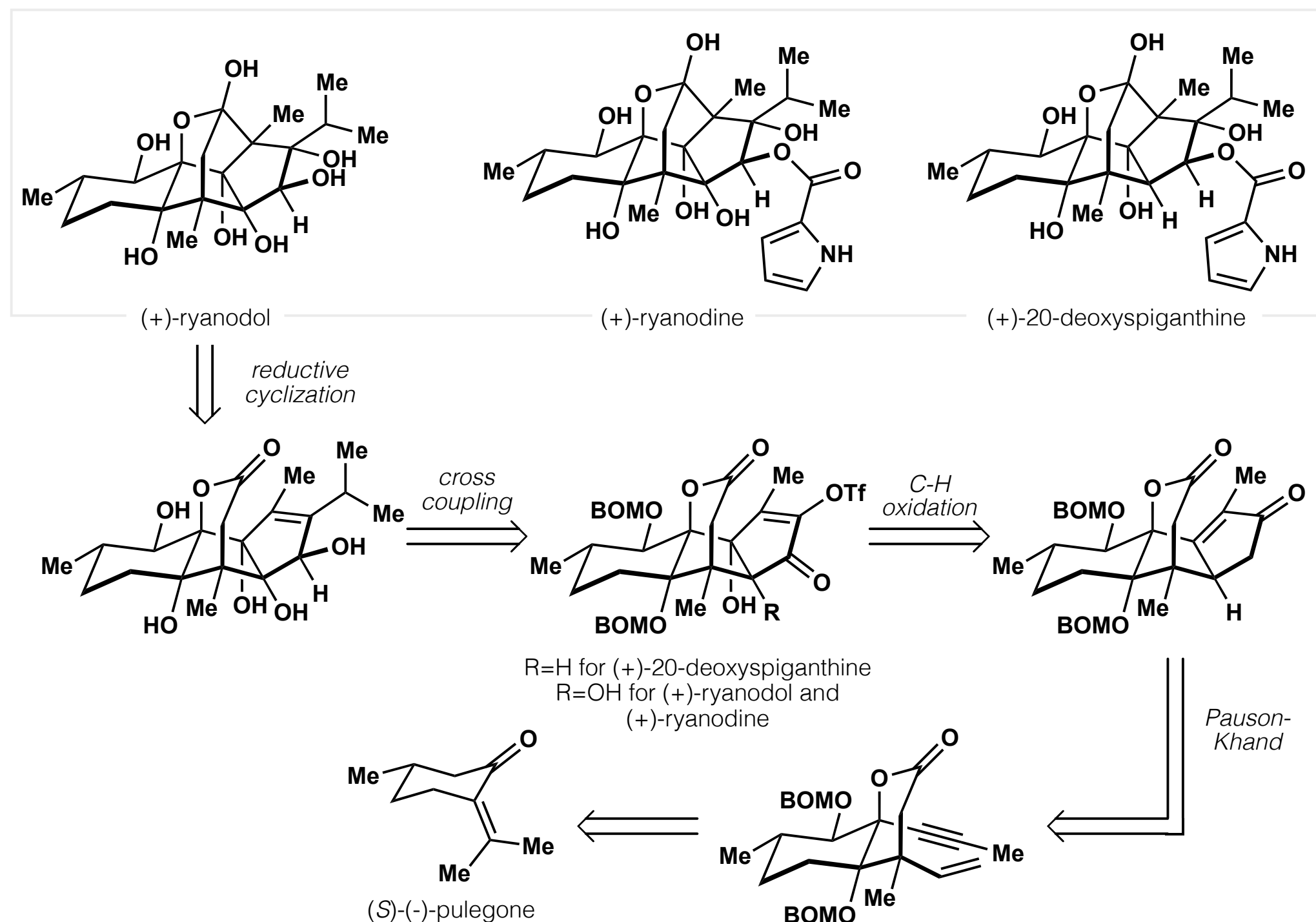
● oxidation at late stage

Ryanodane Diterpenes

66

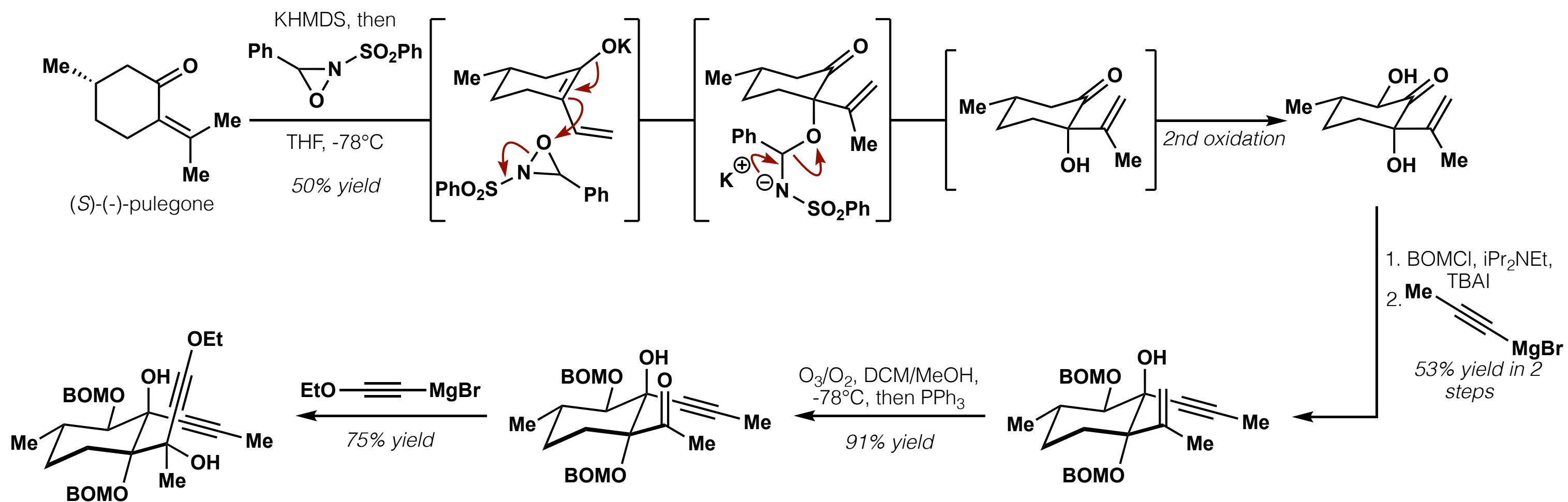


- Isolated from the tropical shrub *Ryania speciosa* Vahl
- Ryanodine studied for its insecticidal properties
- Helped in the characterization of intracellular Ca^{2+} ion channels known now as ryanodine receptors (RyRs)



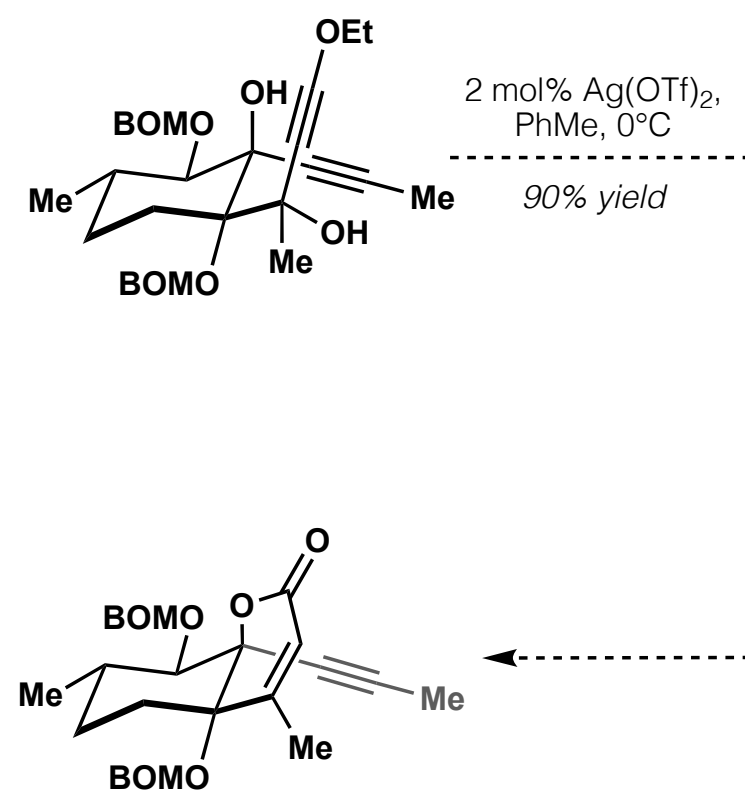
Total Synthesis of (+)-ryanodol

67



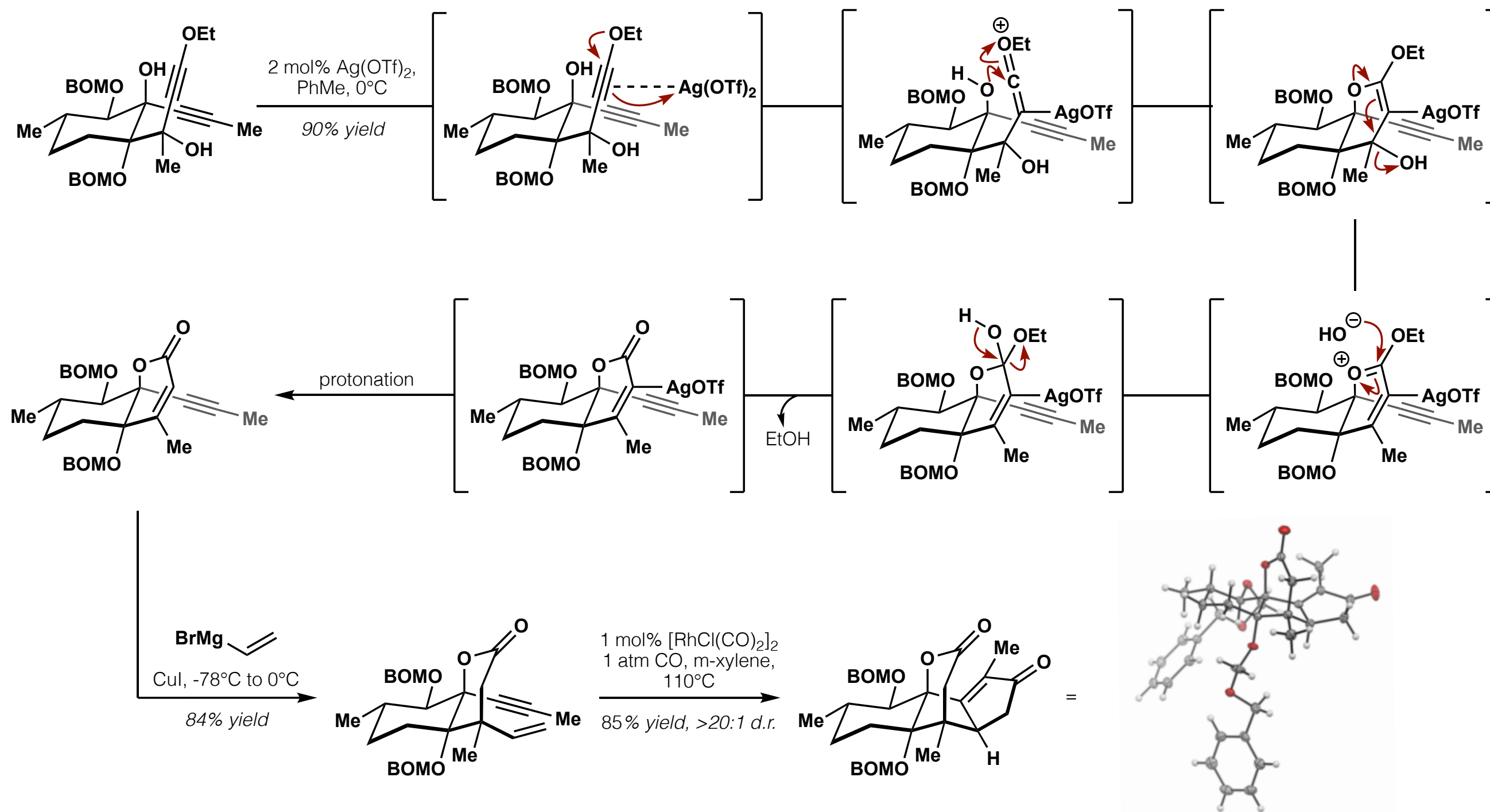
Total Synthesis of (+)-ryanodol

68



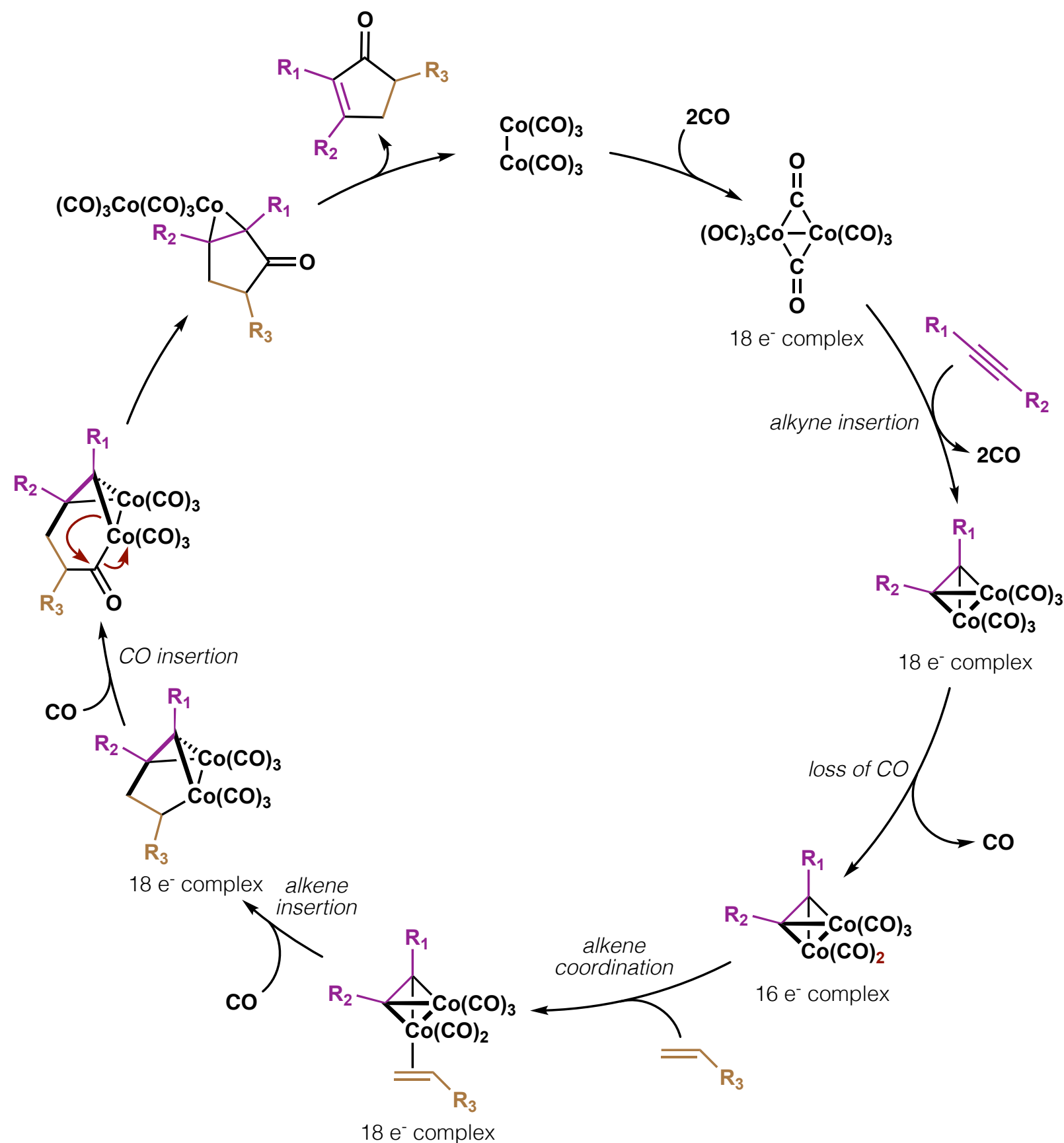
Total Synthesis of (+)-ryanodol

69



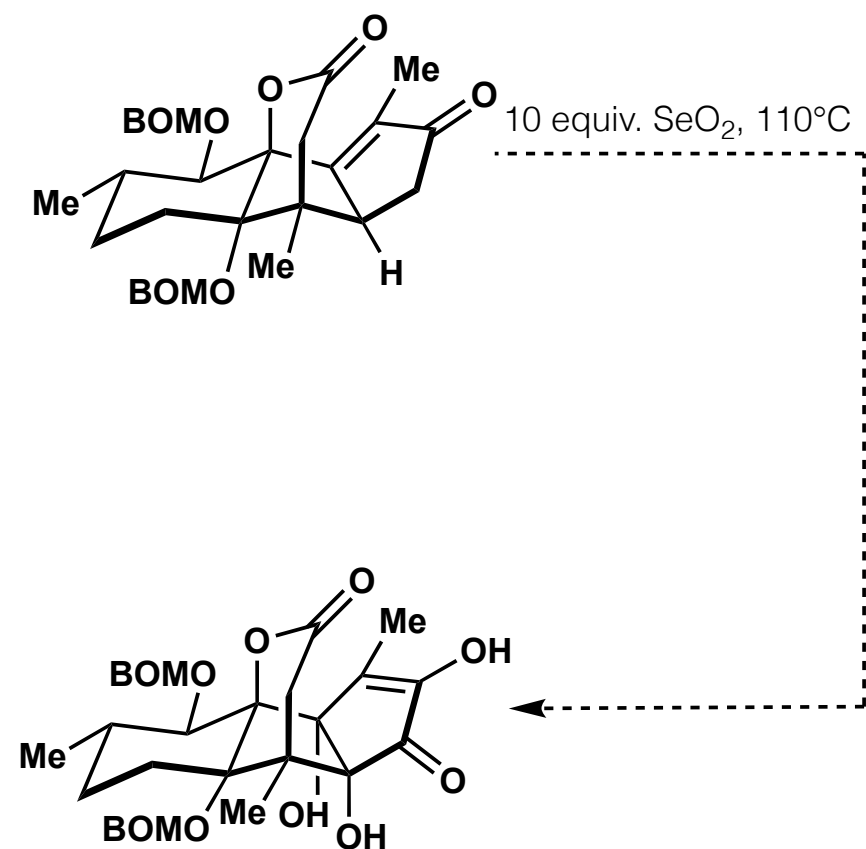
Pauson-Khand Reaction

- Reported by Pauson and Khand in 1973
- Reactions can be accelerated by additives such as NMO and Lewis bases
- Intramolecular reactions proceed with excellent regio- and stereoselectivity
- It is possible to run the reaction catalytically under high pressure of CO
- Other TM that catalyze the reaction are $\text{Fe}(\text{CO})_5$, $\text{Ru}_2(\text{CO})_{12}$, $\text{W}(\text{CO})_6$, $\text{Mo}(\text{CO})_6$, Cp_2ZrCl_2 ...



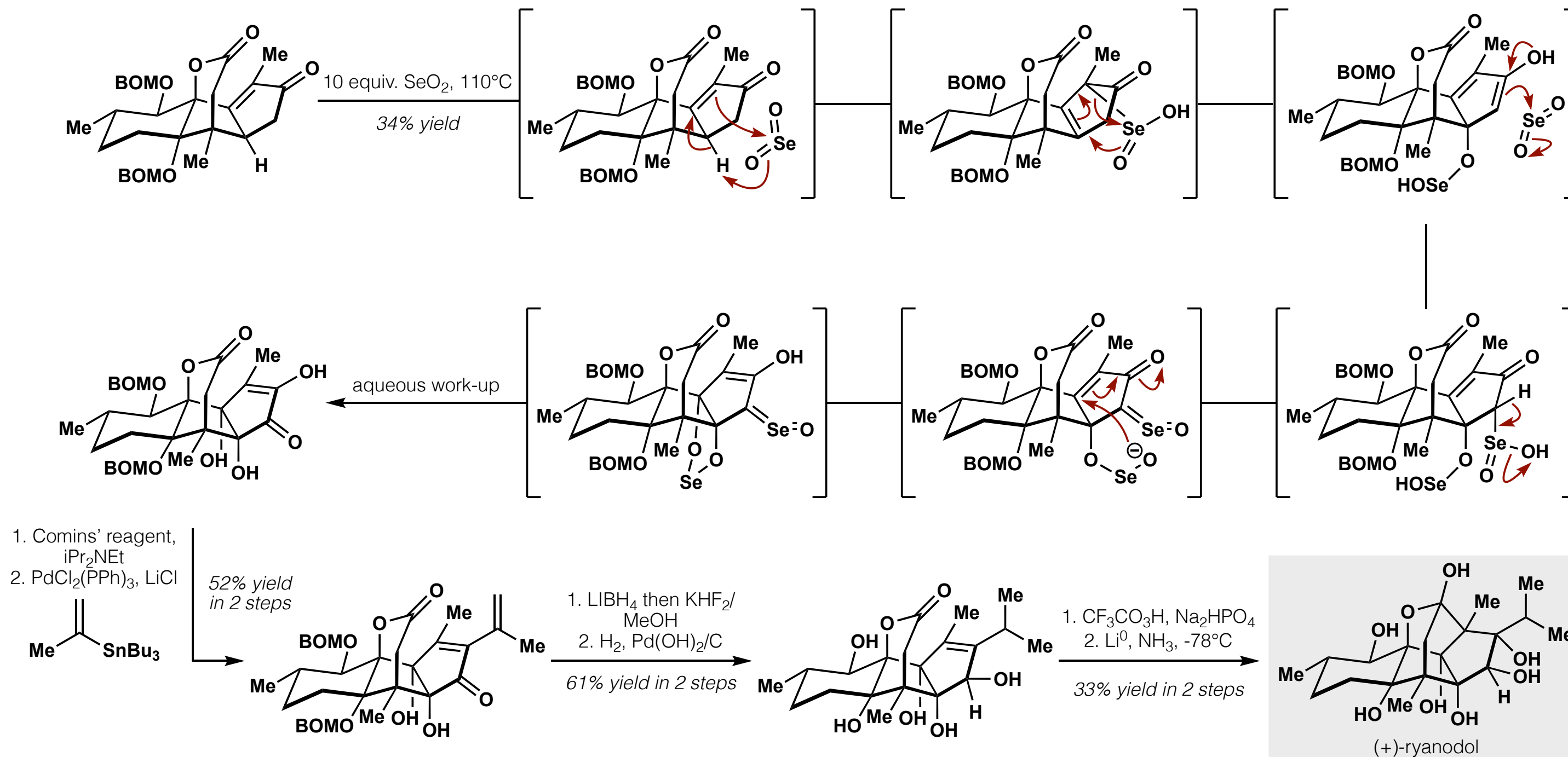
Total Synthesis of (+)-ryanodol

71



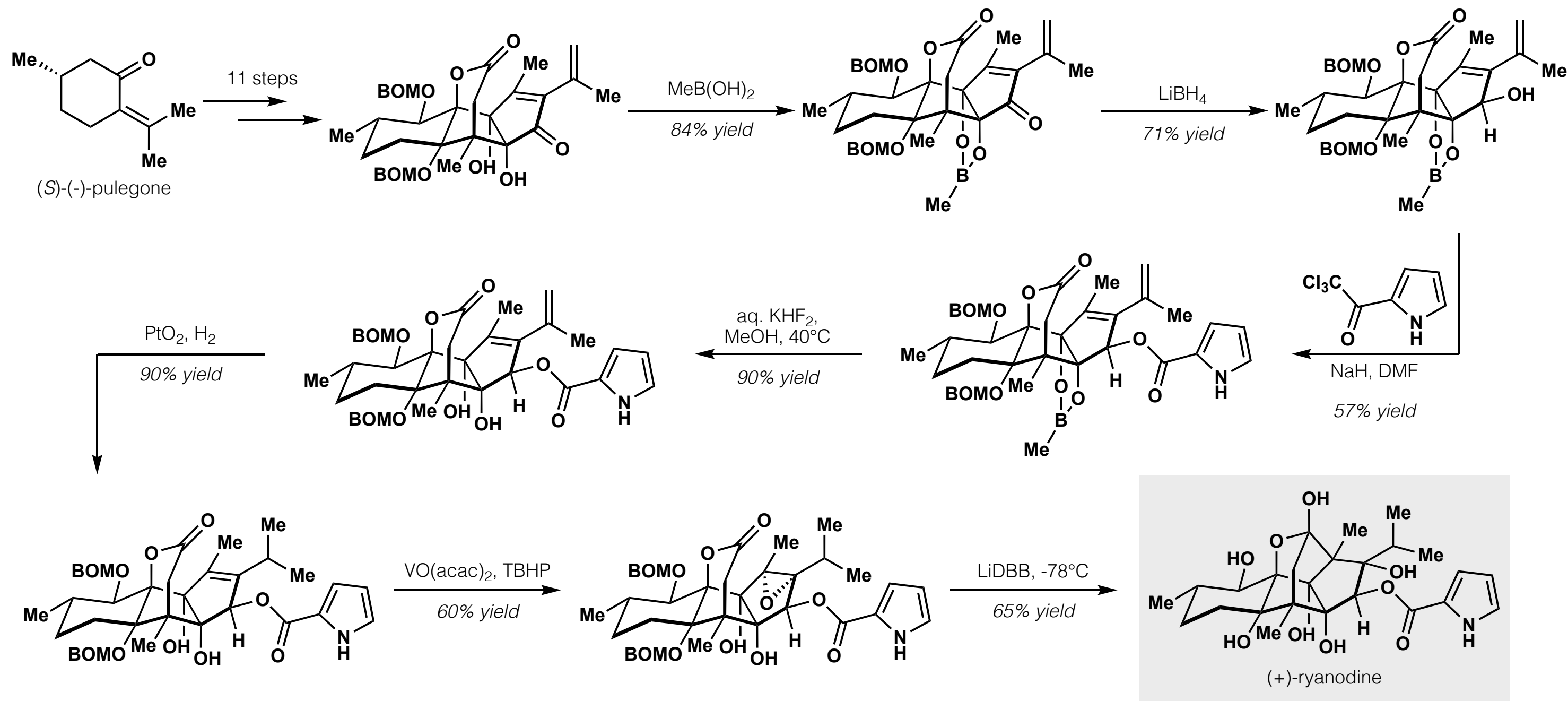
Total Synthesis of (+)-ryanodol

72



Total Synthesis of (+)-ryanodine

73



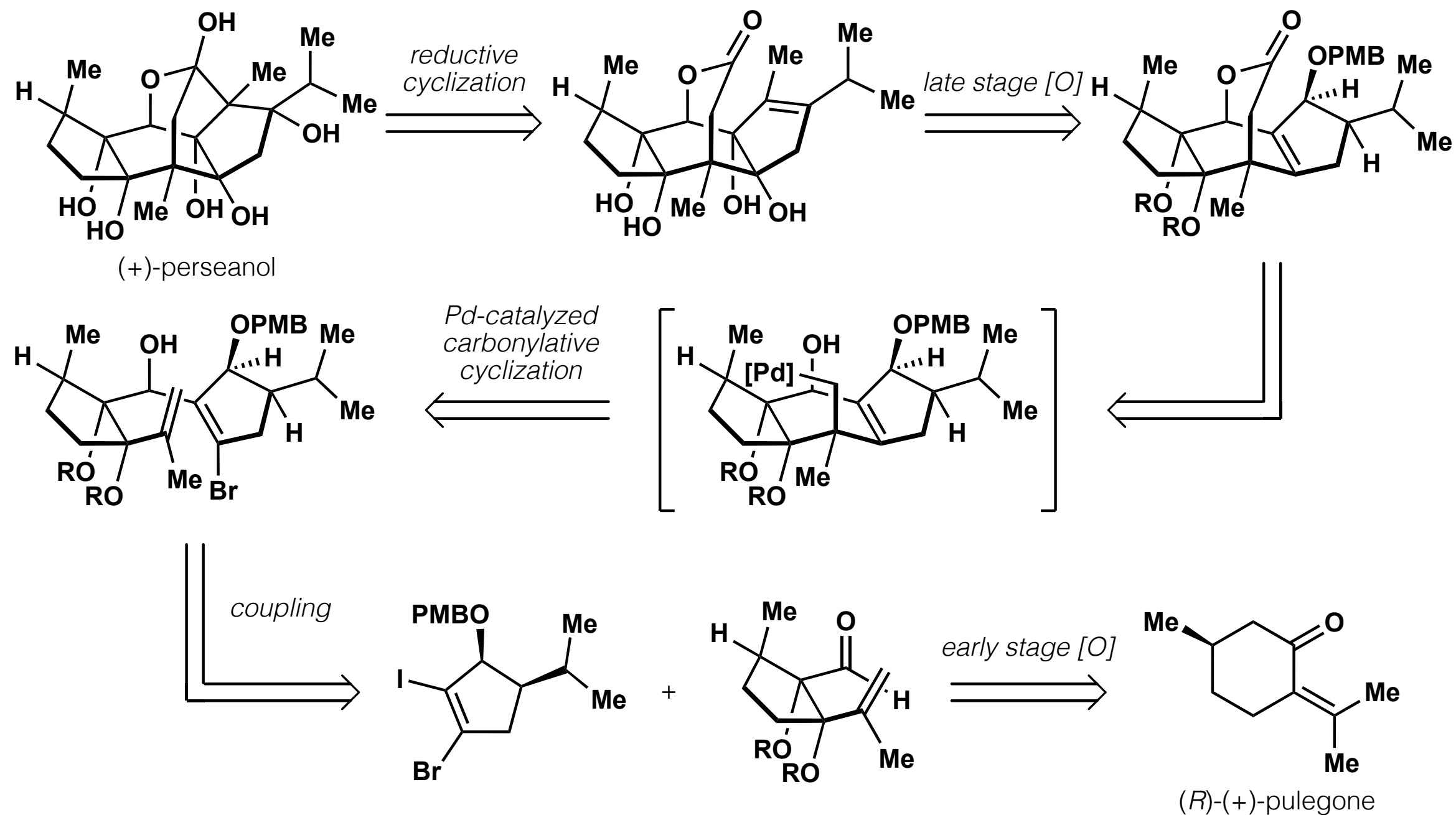
same strategy for (+)-20-deoxyspiganthine (check out their paper for details)

Total Synthesis of (+)-perseanol

74

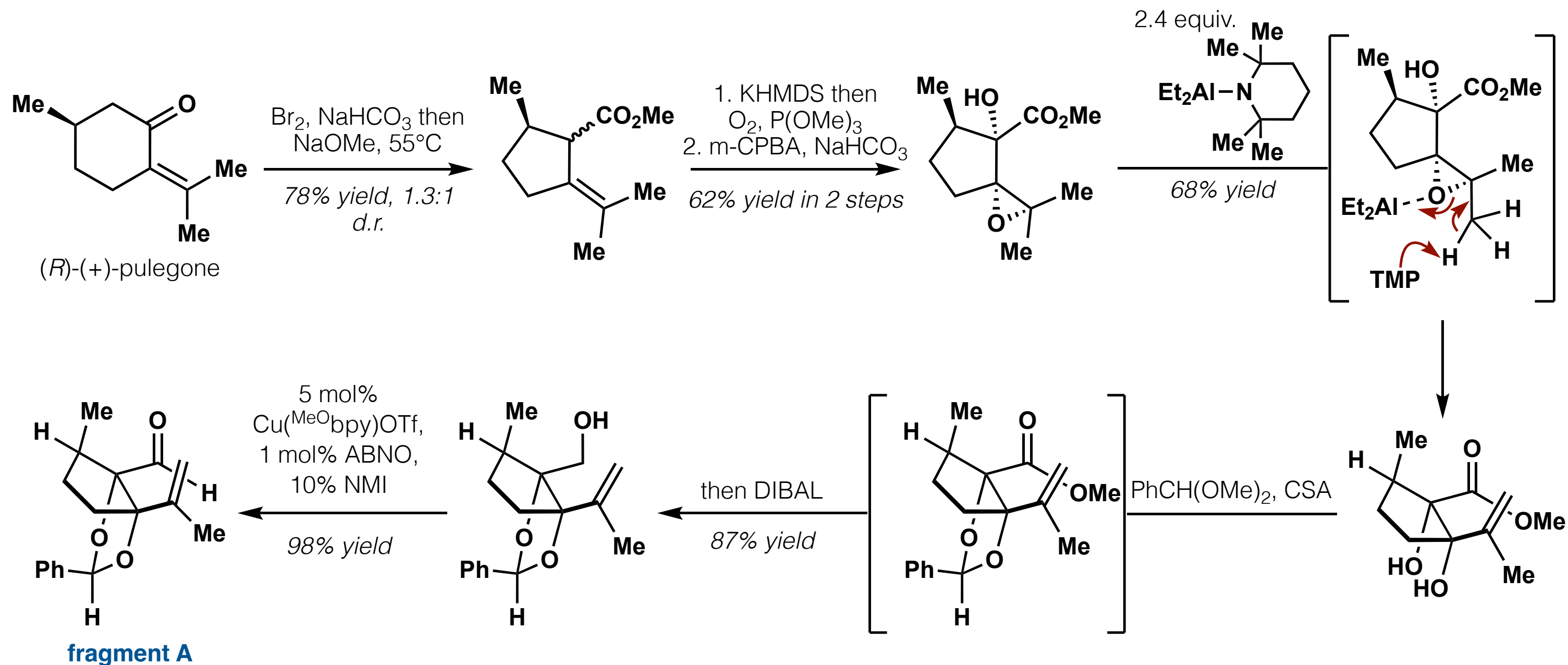


- Isolated from the tropical shrub *Persea indica*
- Potent antifeedant and insecticidal properties
- Structurally related to ryanodine
- Mechanism of action unknown but related to ryanodine receptors (RyRs)



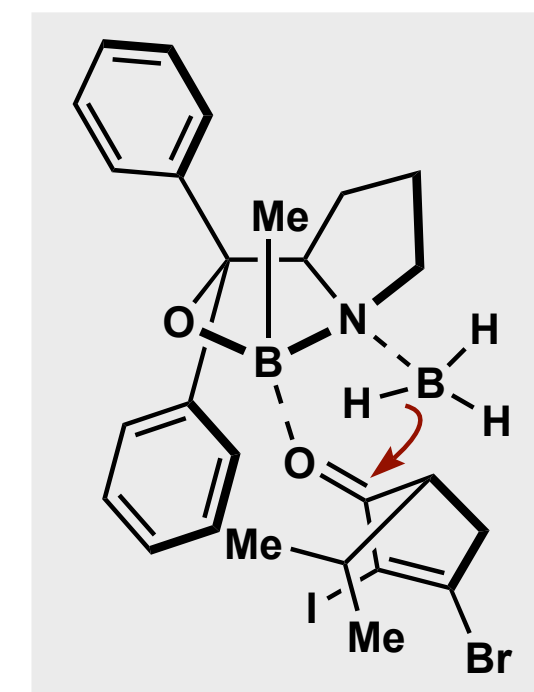
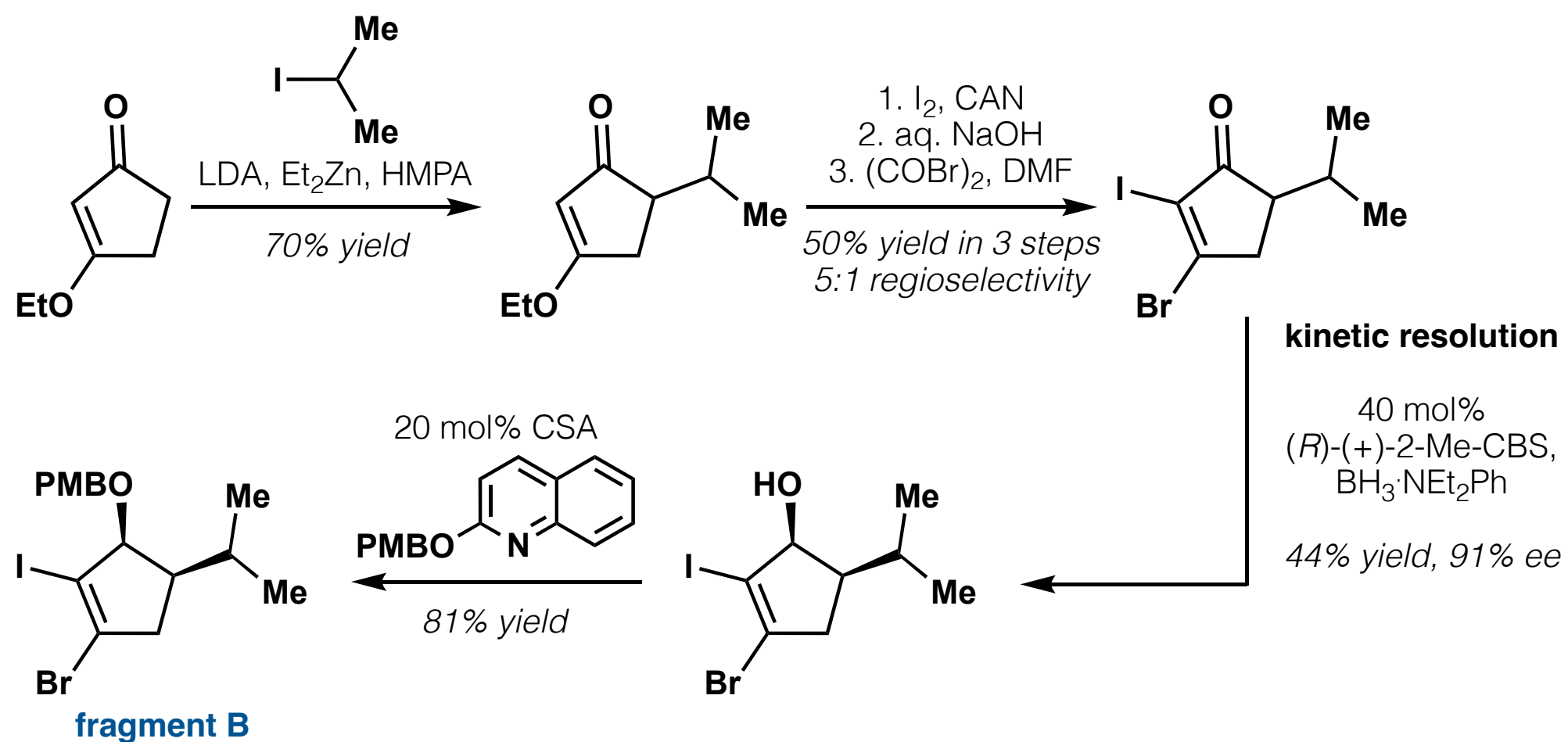
Total Synthesis of (+)-perseanol

75



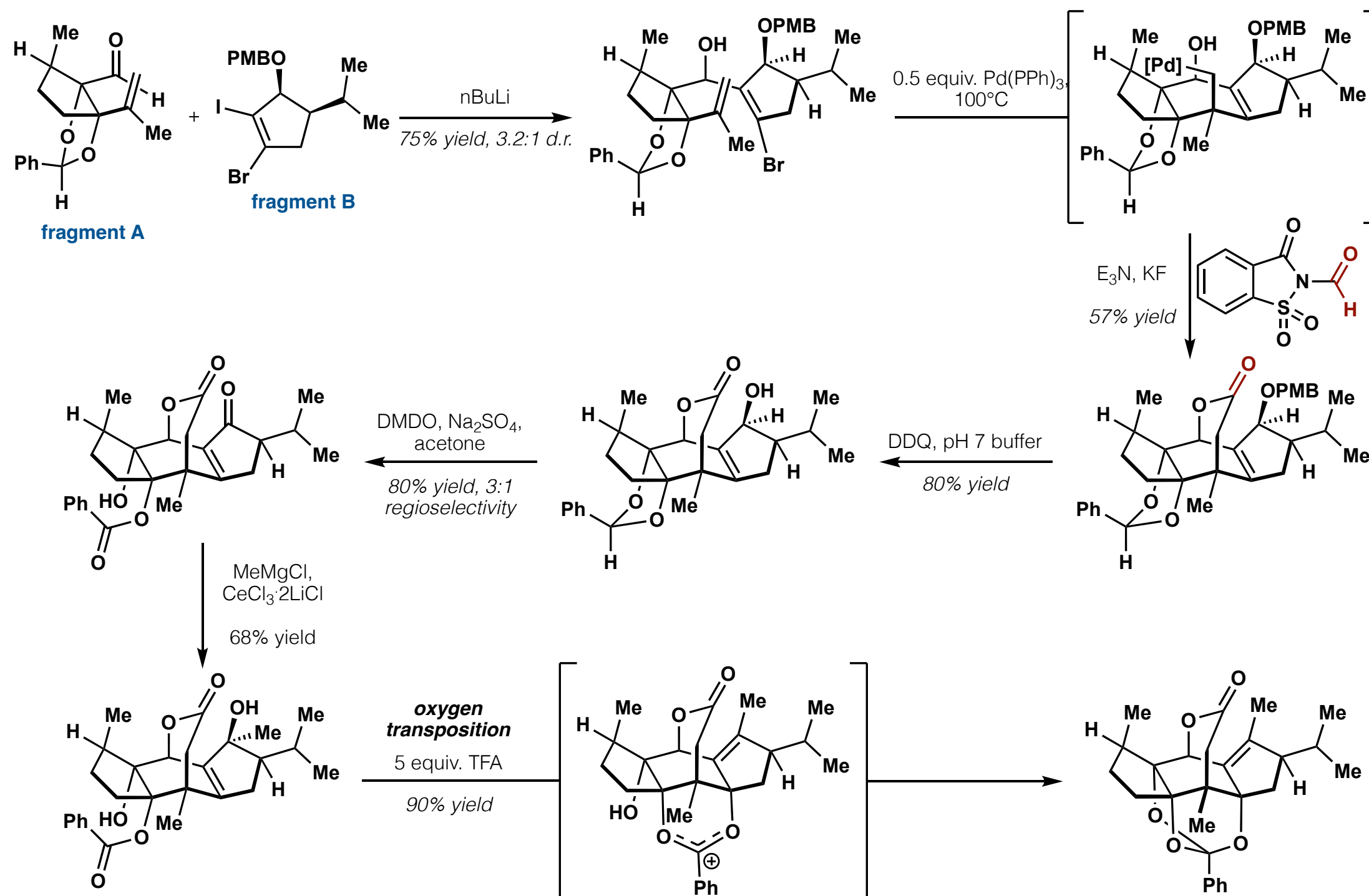
Total Synthesis of (+)-perseanol

76



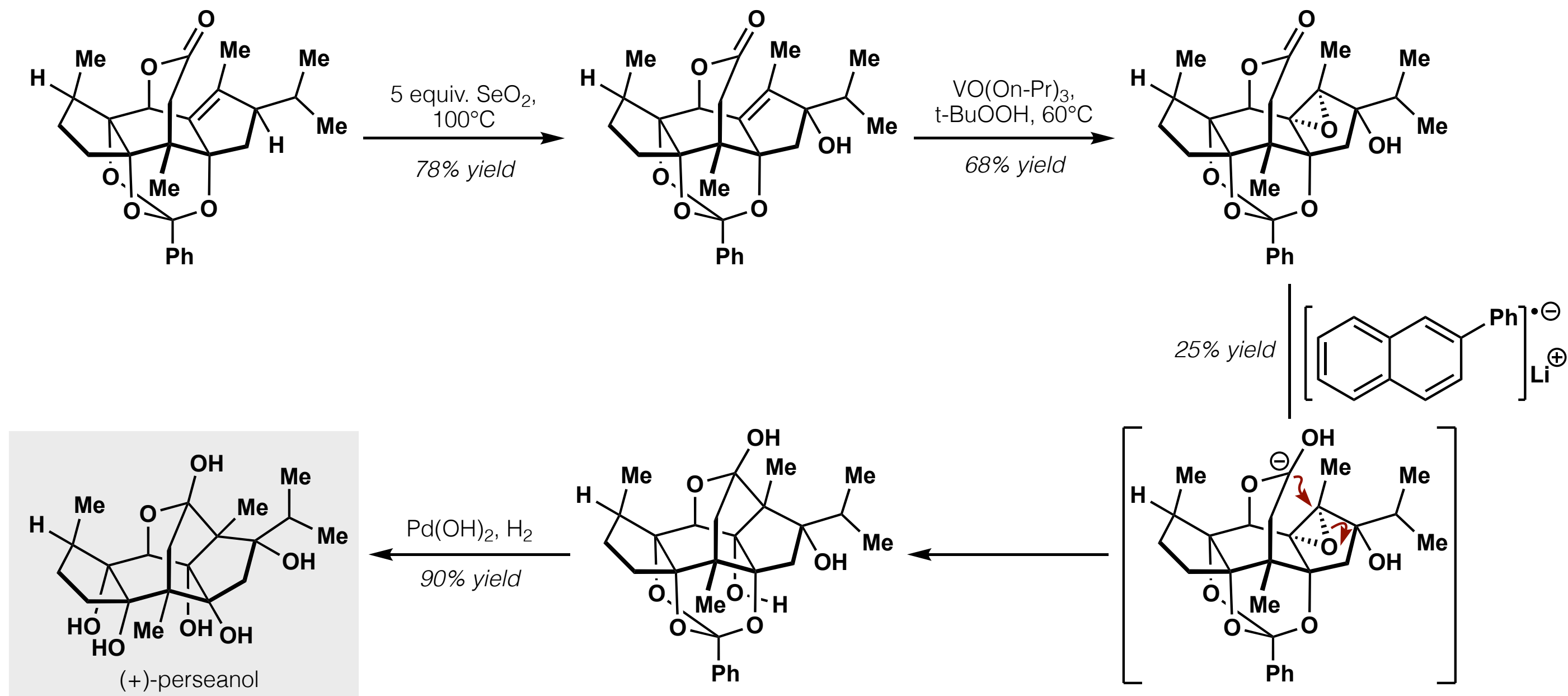
Total Synthesis of (+)-perseanol

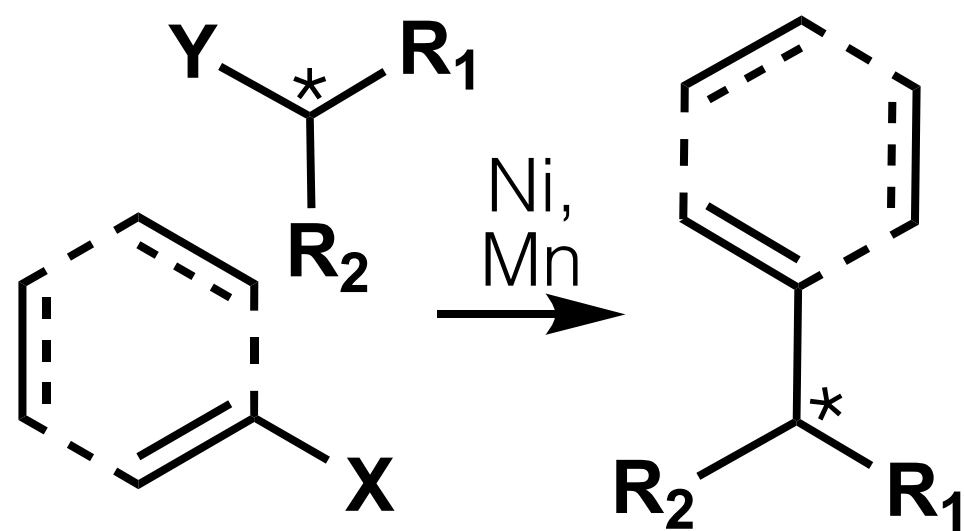
77



Total Synthesis of (+)-perseanol

78

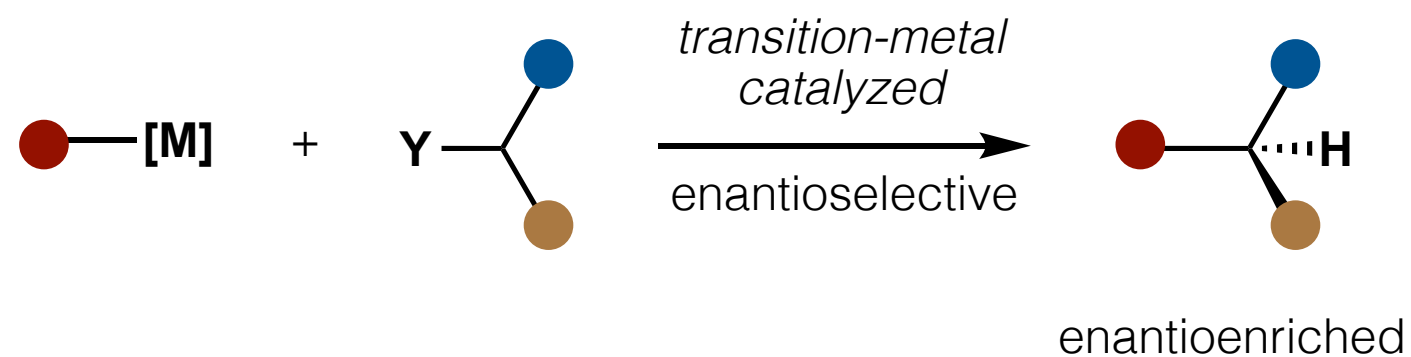




The Nickel Era

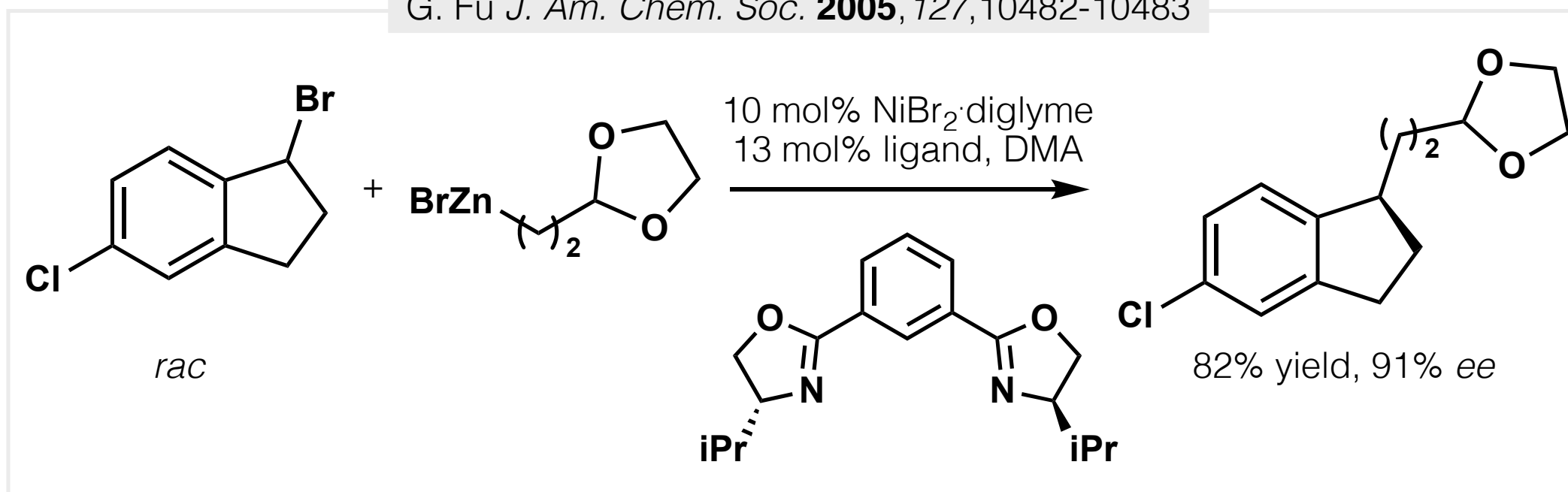
The Nickel Era

80



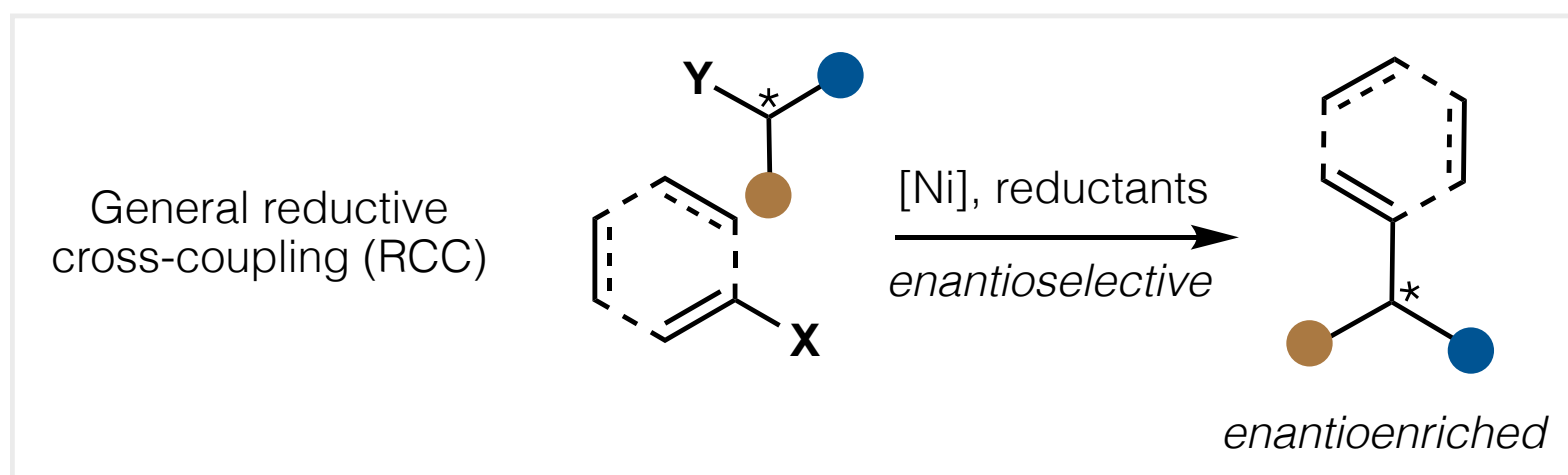
- Ni ($\text{Ni}^{0/\text{II}}$, $E_0 = -0.26 \text{ V}$ vs SHE) offers **facile oxidative addition** compared to Pd ($\text{Pd}^{0/\text{II}}$, $E_0 = 0.95 \text{ V}$ vs SHE)
 - Ni has access to a **wide range of oxidation states** ($\text{Ni}^{0, \text{I}, \text{II}, \text{III}, \text{IV}}$)

G. Fu *J. Am. Chem. Soc.* **2005**, 127, 10482-10483



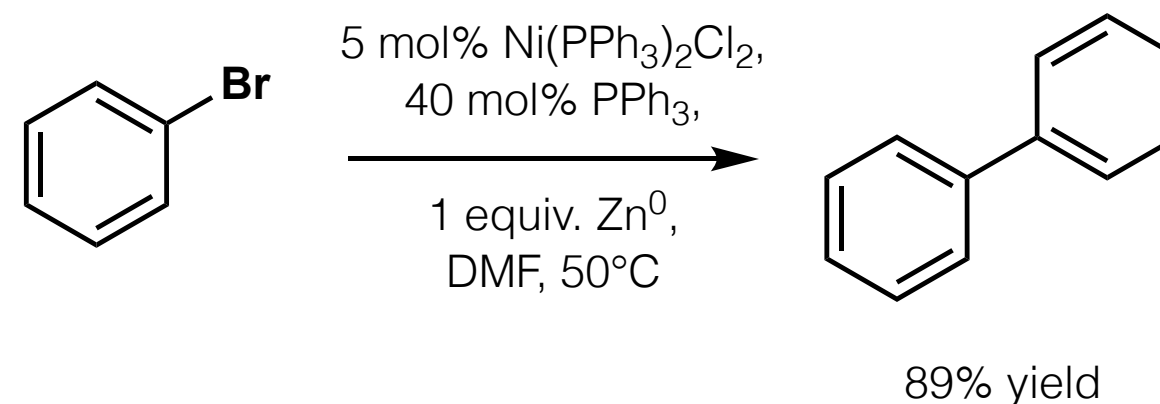
The Nickel Era

81



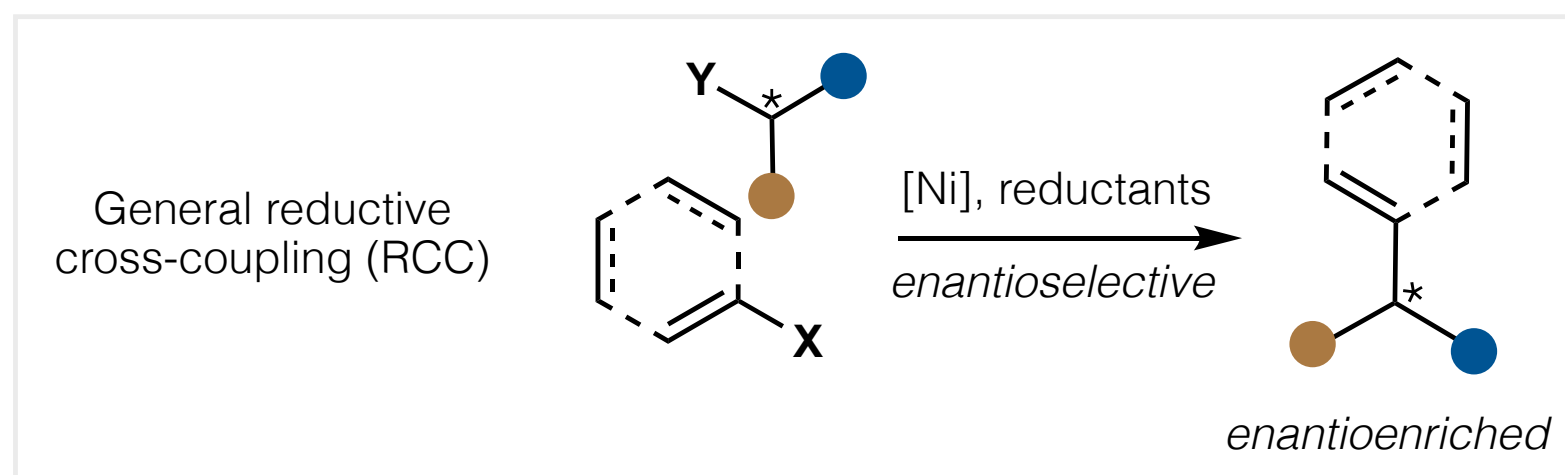
M. Kumada *Tetrahedron Lett.* **1977**, 18, 4089-4091

- First Ni-catalyzed homodimerization
- Zn powder as stoichiometric reductant

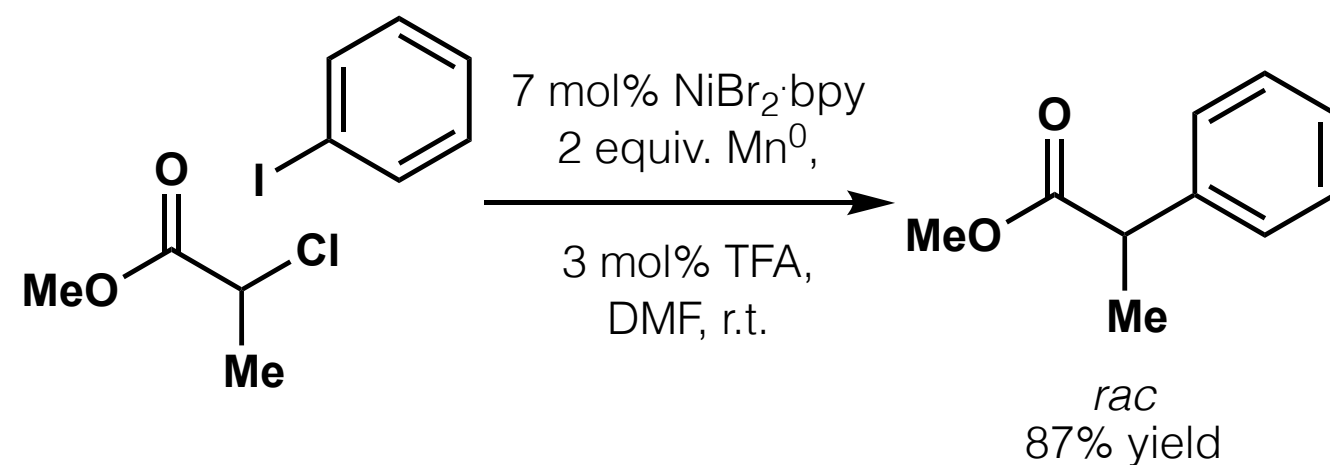


The Nickel Era

82

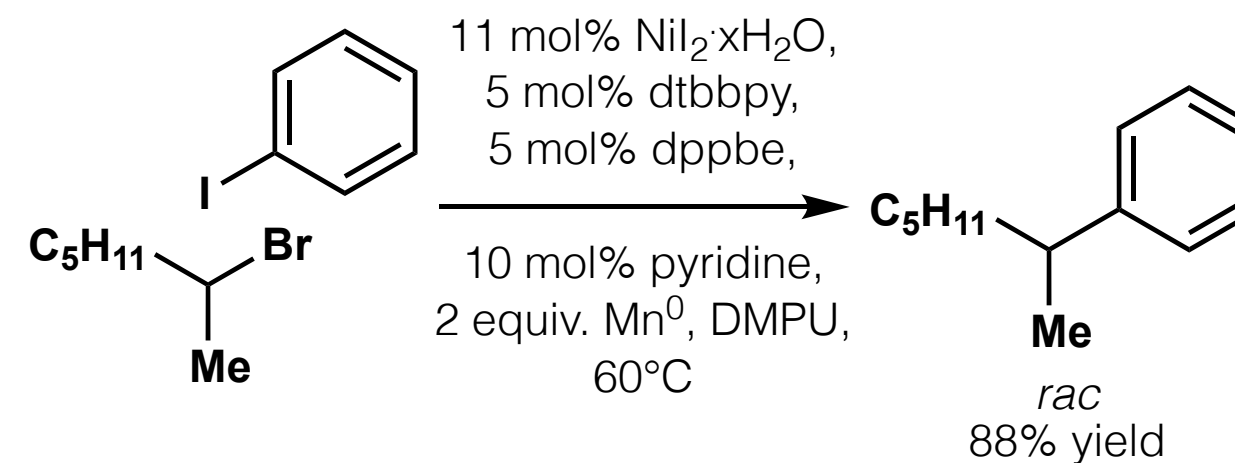


M. Durandetti *Tetrahedron* **2007**, 63, 1146-1153



- Mn^0 can also work as reductant

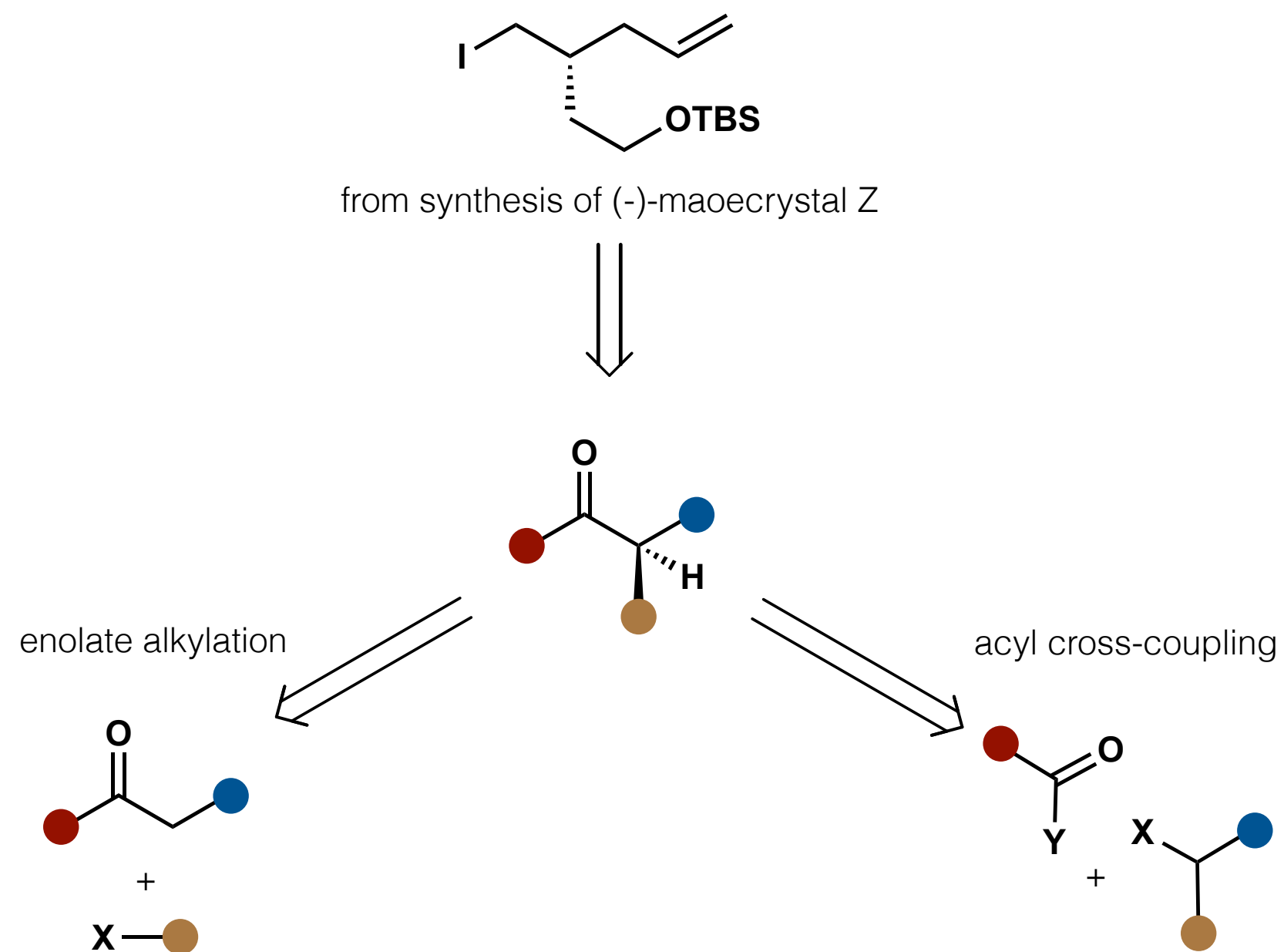
D. Weix *J. Am. Chem. Soc.* **2010**, 132, 920-921



- First Ni-catalyzed RCC of unactivated $C(sp^3)$ electrophiles

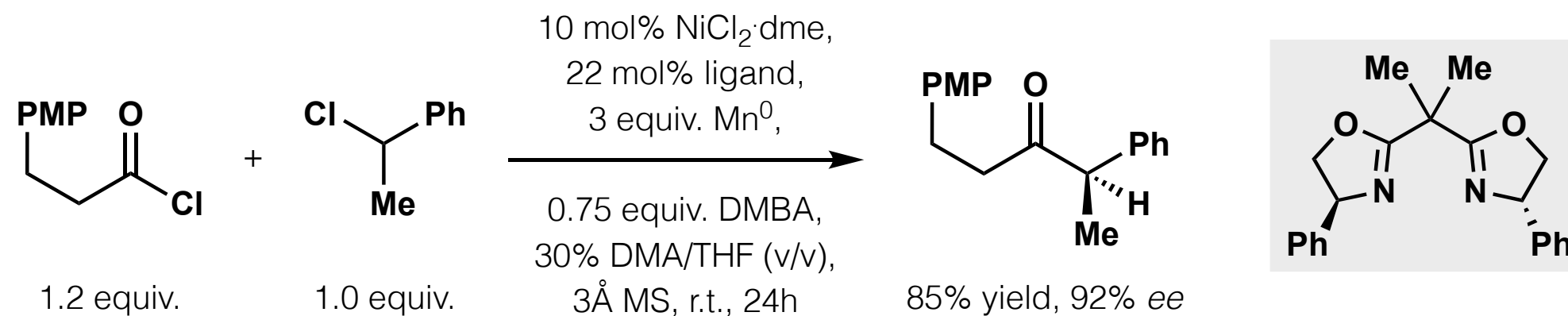
Enantioselective Reductive Cross-Coupling

83

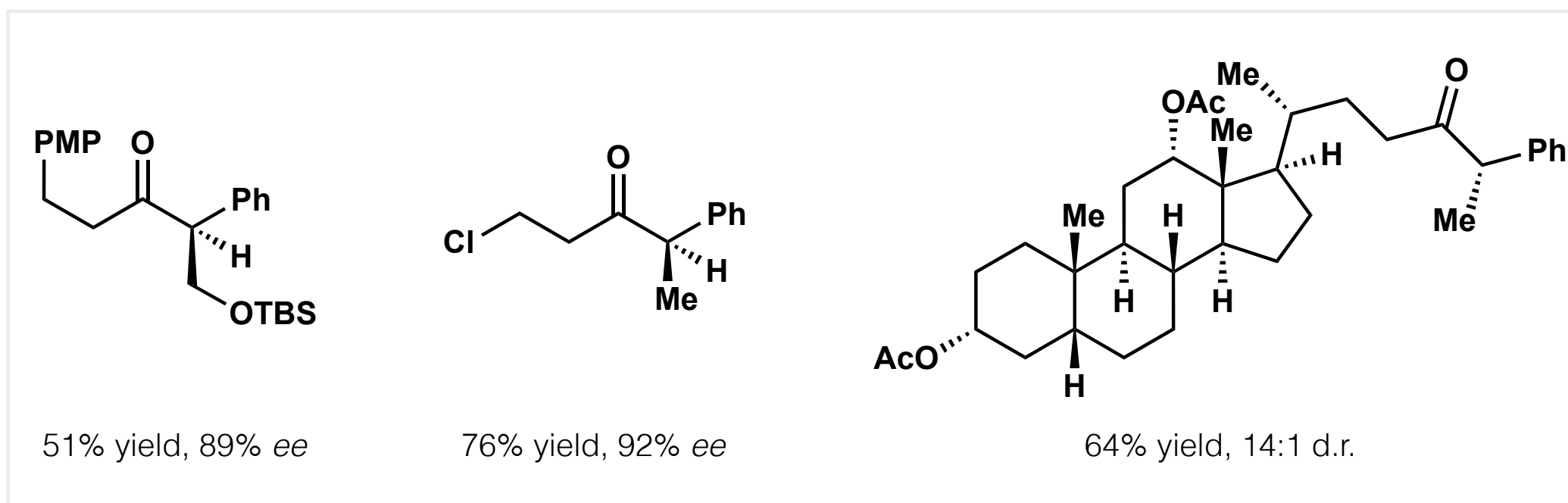


Enantioselective Reductive Cross-Coupling

84

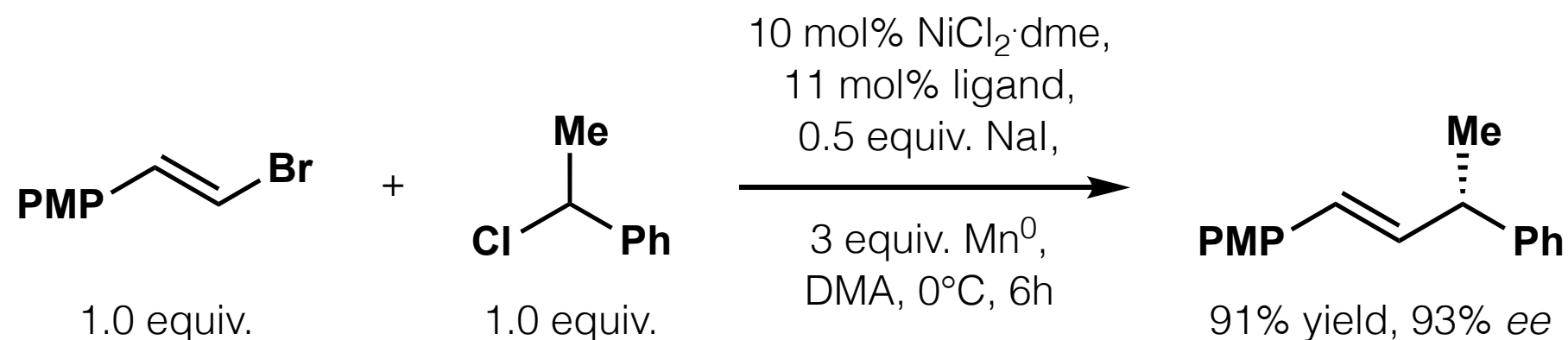


- Mild conditions avoid racemization of the α-aryl ketone product
- Wide functional group tolerance

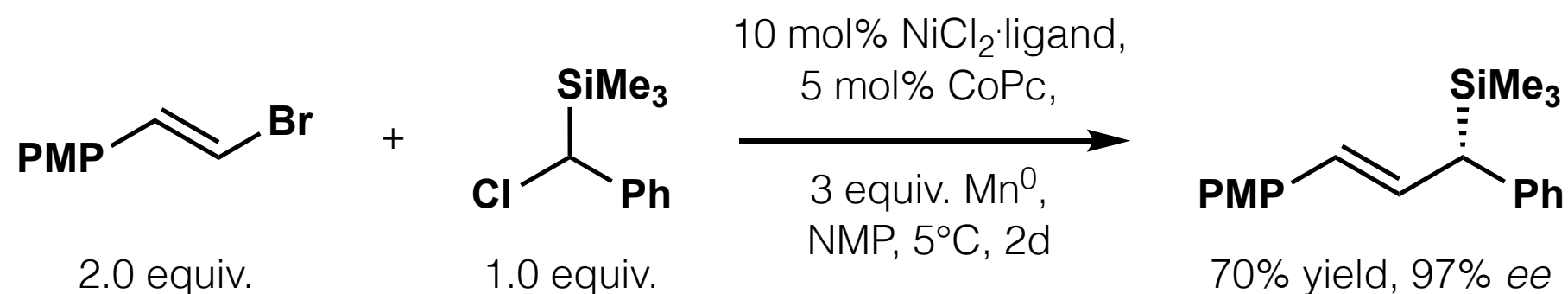
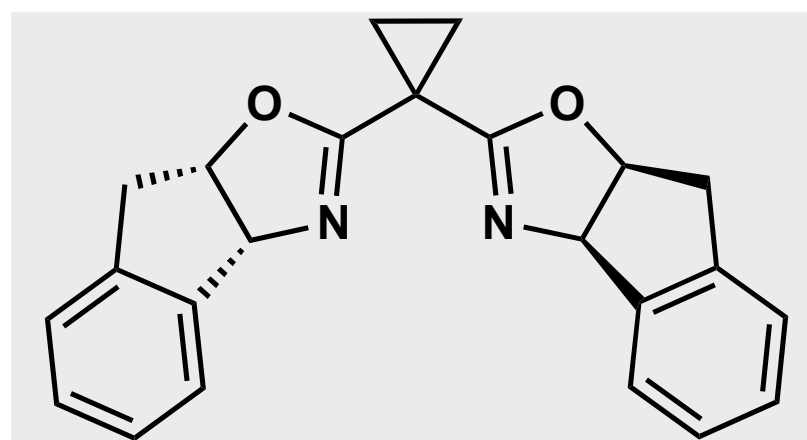


Ni-Catalyzed Asymmetric Reductive Alkenylation

85



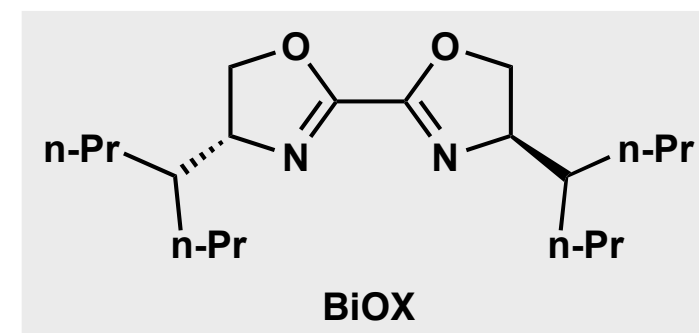
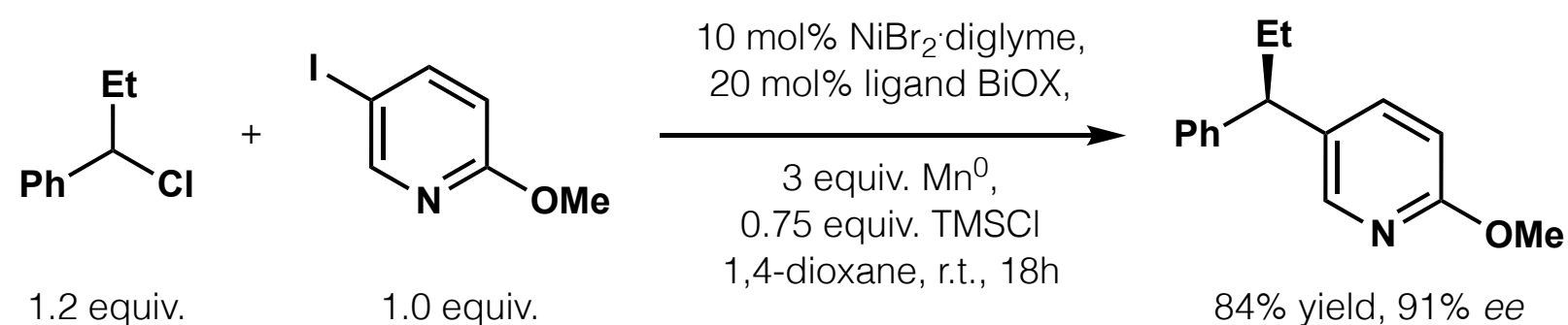
- NaI empirically found to increase yield
- Broad scope but trisubstituted olefins are still a limitation



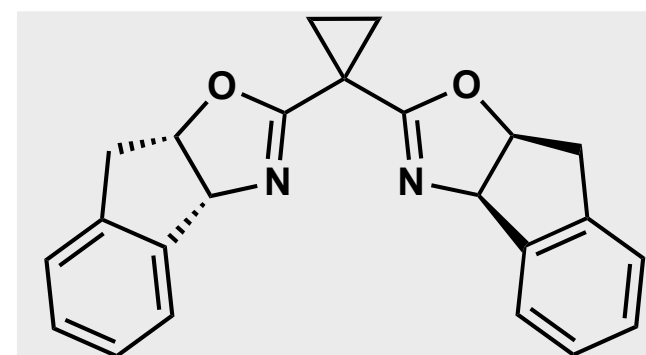
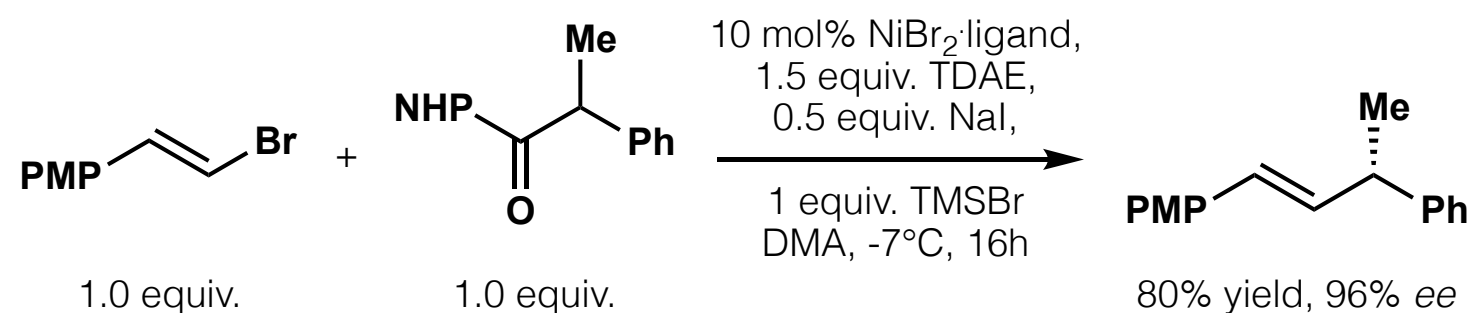
- Use of CoPc as co-catalyst increases the yield though facile radical generation

Ni-Catalyzed Asymmetric Reductive Alkenylation

86



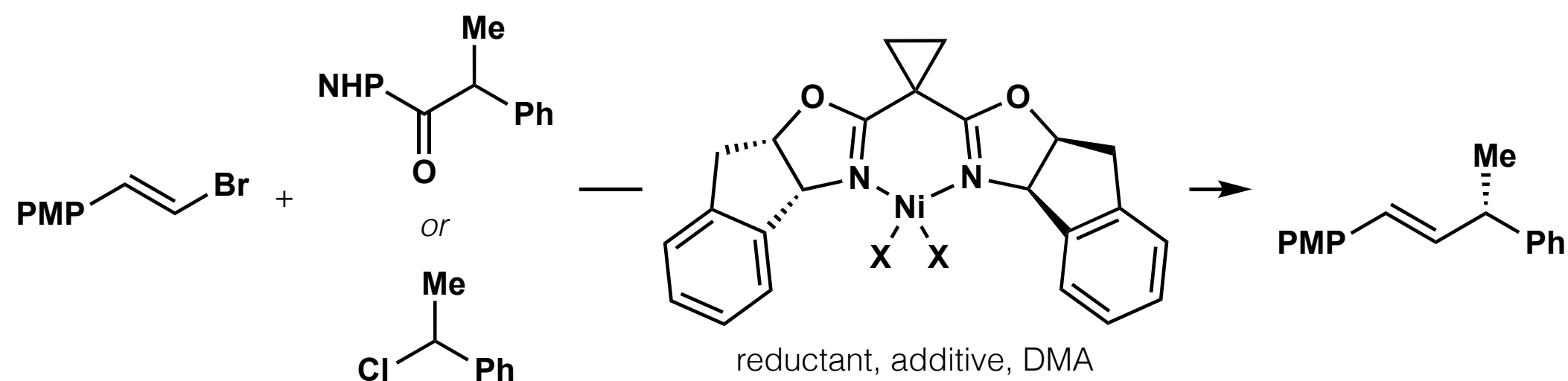
- Reaction tolerates aryl triflates and boronates
- Steric bulk at the benzylic carbon not tolerated



- NHPI esters as a method to overcome alkyl halides synthesis
- tetrakis(N,N-dimethylamino)-ethylene (TDAE) better performing than heterogeneous reductants

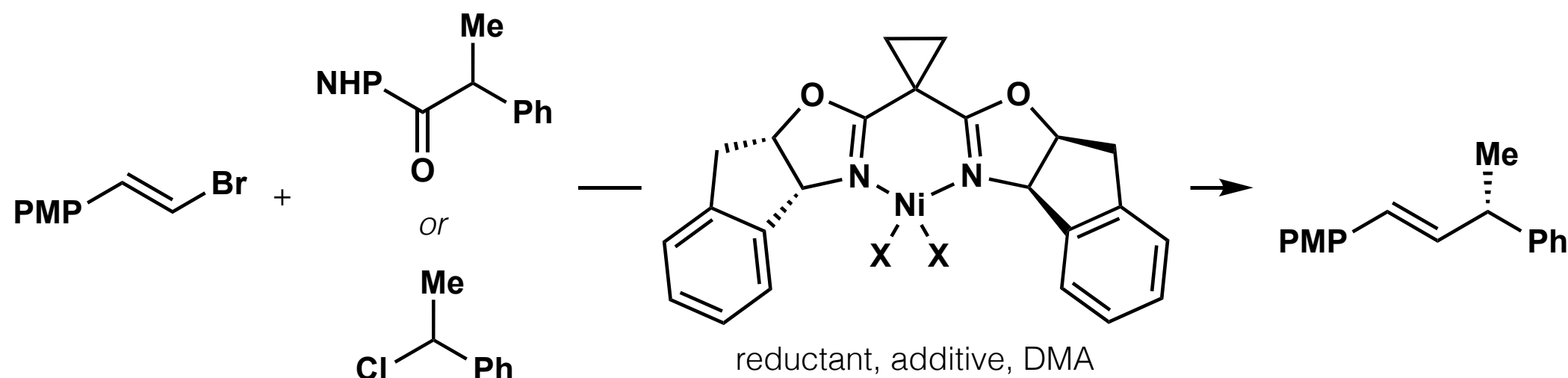
Ni-Catalyzed ARA: Mechanistic Insights

87



Ni-Catalyzed ARA: Mechanistic Insights

88



I. $\text{BOX} \cdot \text{Ni}^{\text{II}}$ and $\text{BiOX} \cdot \text{Ni}^{\text{II}}$ complexes reduce at very negative potentials ($\text{Ni}^{\text{II}} \rightarrow \text{Ni}^{\text{I}}$, then $\text{Ni}^{\text{I}} \rightarrow \text{Ni}^0$ require $E < -2.0$ V)

- Ni^0 is **not** accessible under Mn^0 , Zn^0 , or TDAE conditions.
- The cycle must start with $\text{Ni}^{\text{I}} \rightarrow \text{Ni}^{\text{II}} \rightarrow \text{Ni}^{\text{III}}$.

II. When $\text{L}_n\text{Ni}^{\text{II}}\text{X}_2$ is reduced in presence of alkenyl bromide, CV shows increased current with increased SM concentration. Same trend with benzylic chloride.

- Ni^{I} can activate both vinyl bromide and benzylic chloride.

III. When NHP ester is treated with TDAE and TMSBr with no Ni, the homodimer product is observed.

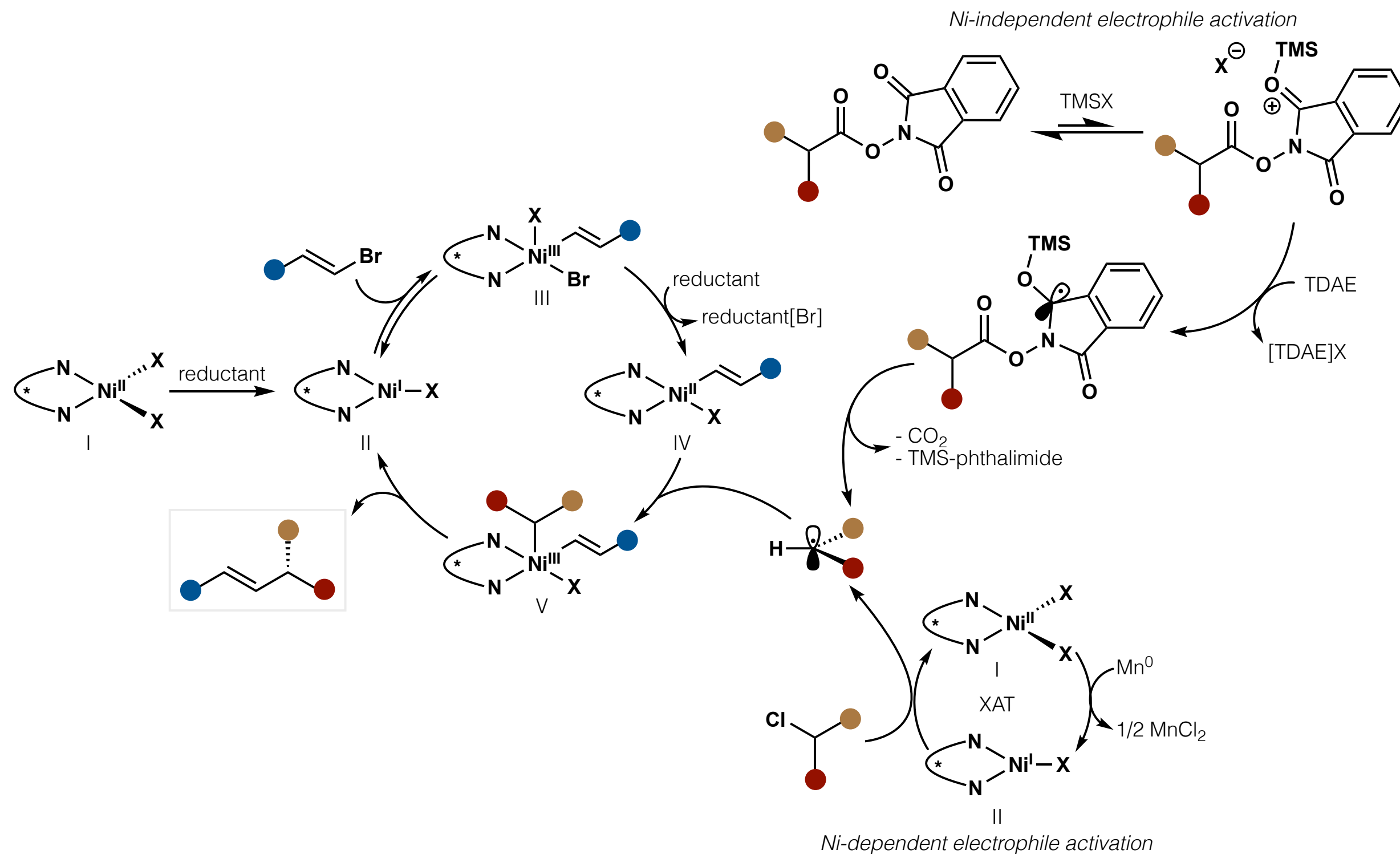
- The radical formation for NHP ester does **not** involve nickel.

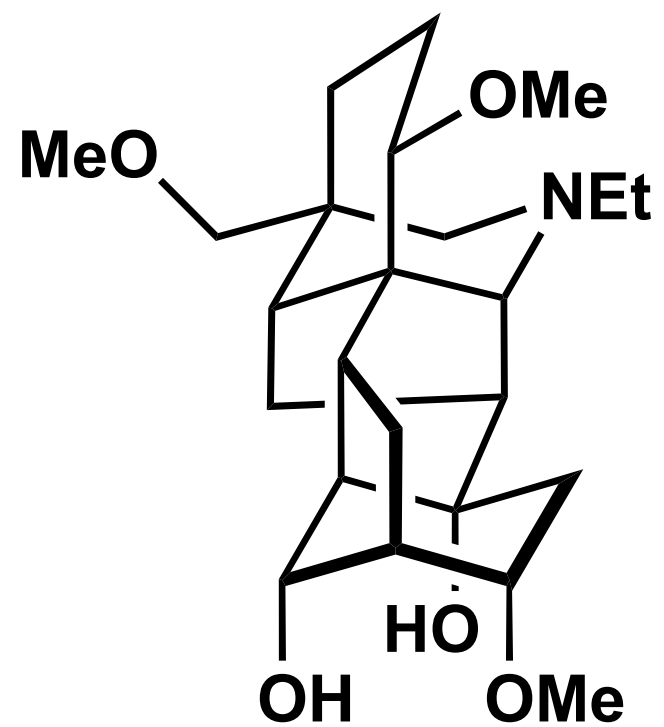
IV. $\text{Ni}^{\text{II}}(\text{alkenyl})\text{X}$ is observed though NMR.

- Most likely this is the resting state.

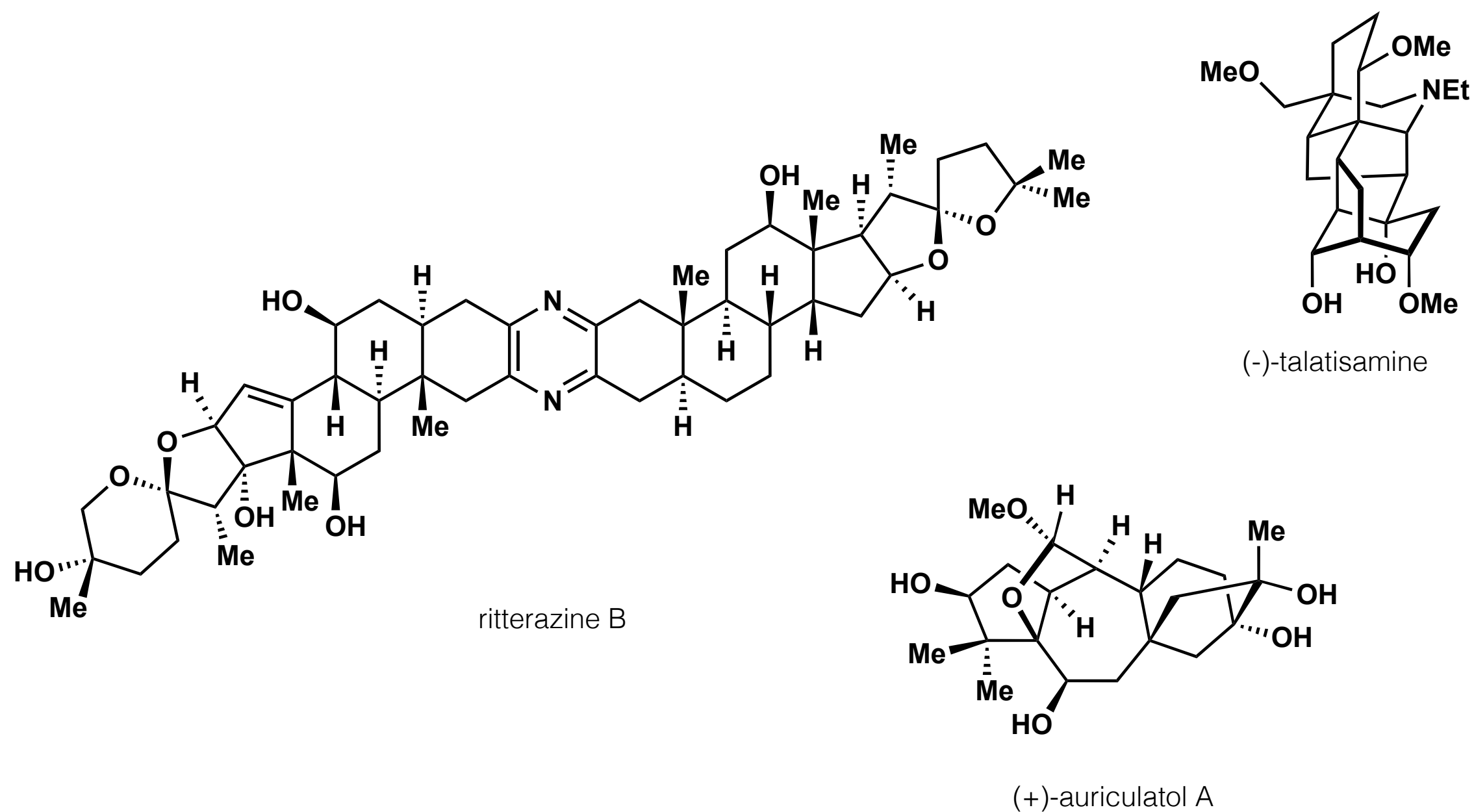
Ni-Catalyzed ARA: Mechanistic Insights

89



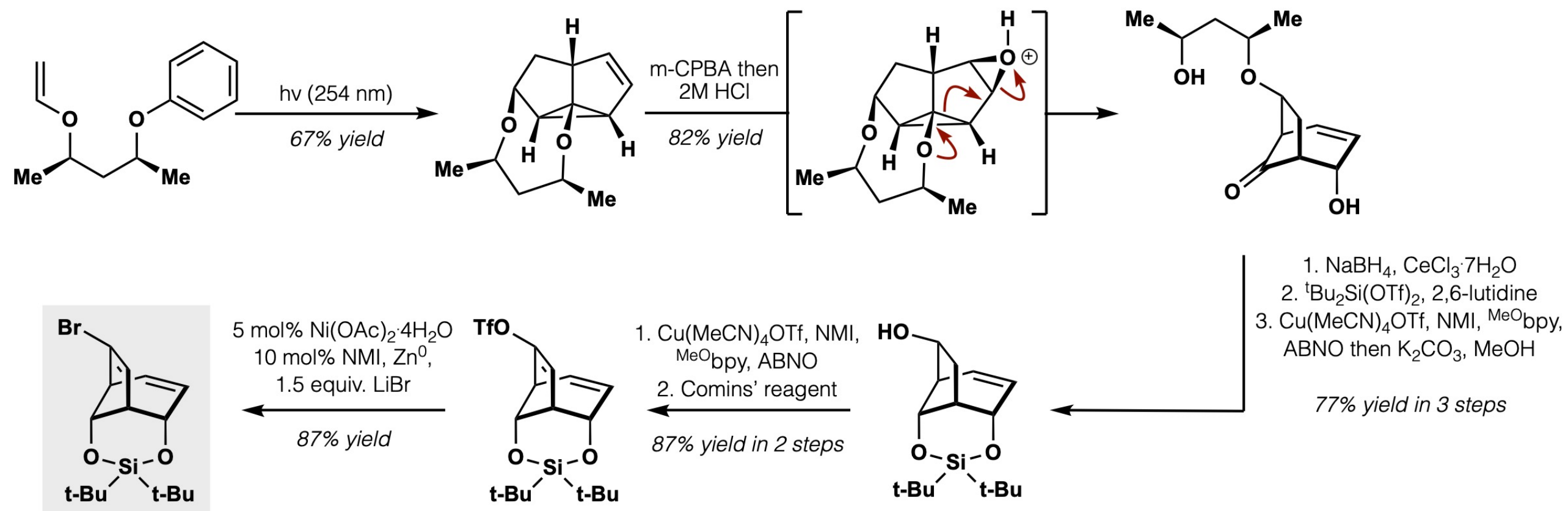
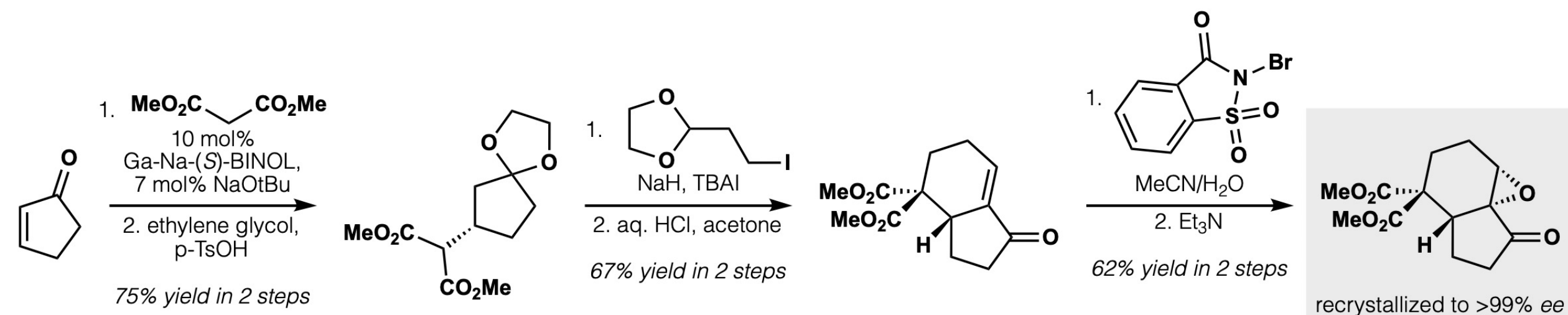


The Modern Era



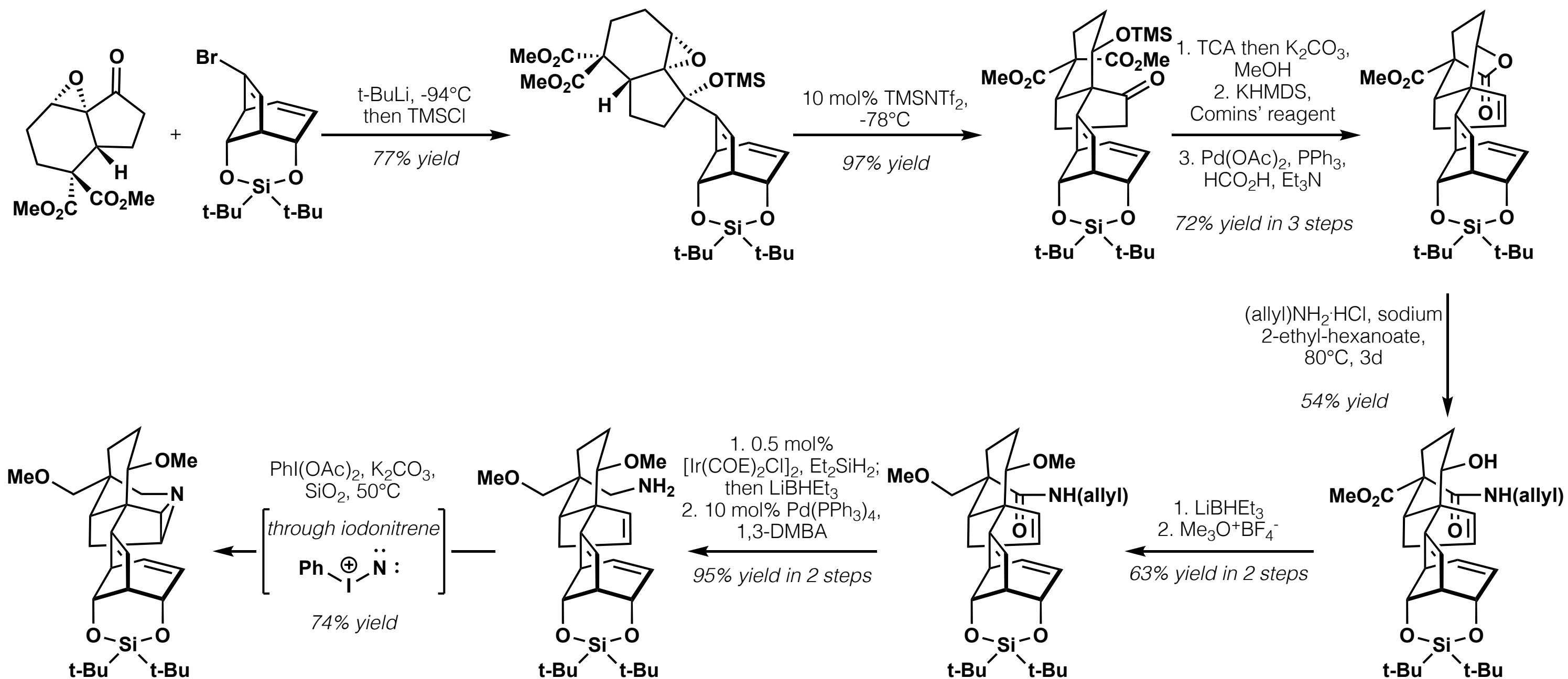
Total Synthesis of (-)-talatisamine

93



Total Synthesis of (-)-talatisamine

94

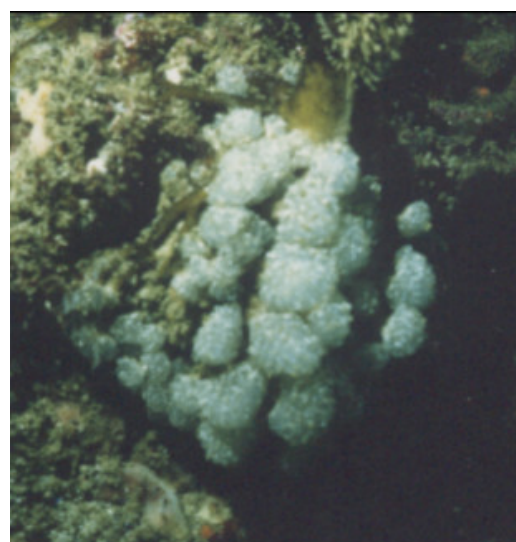


95

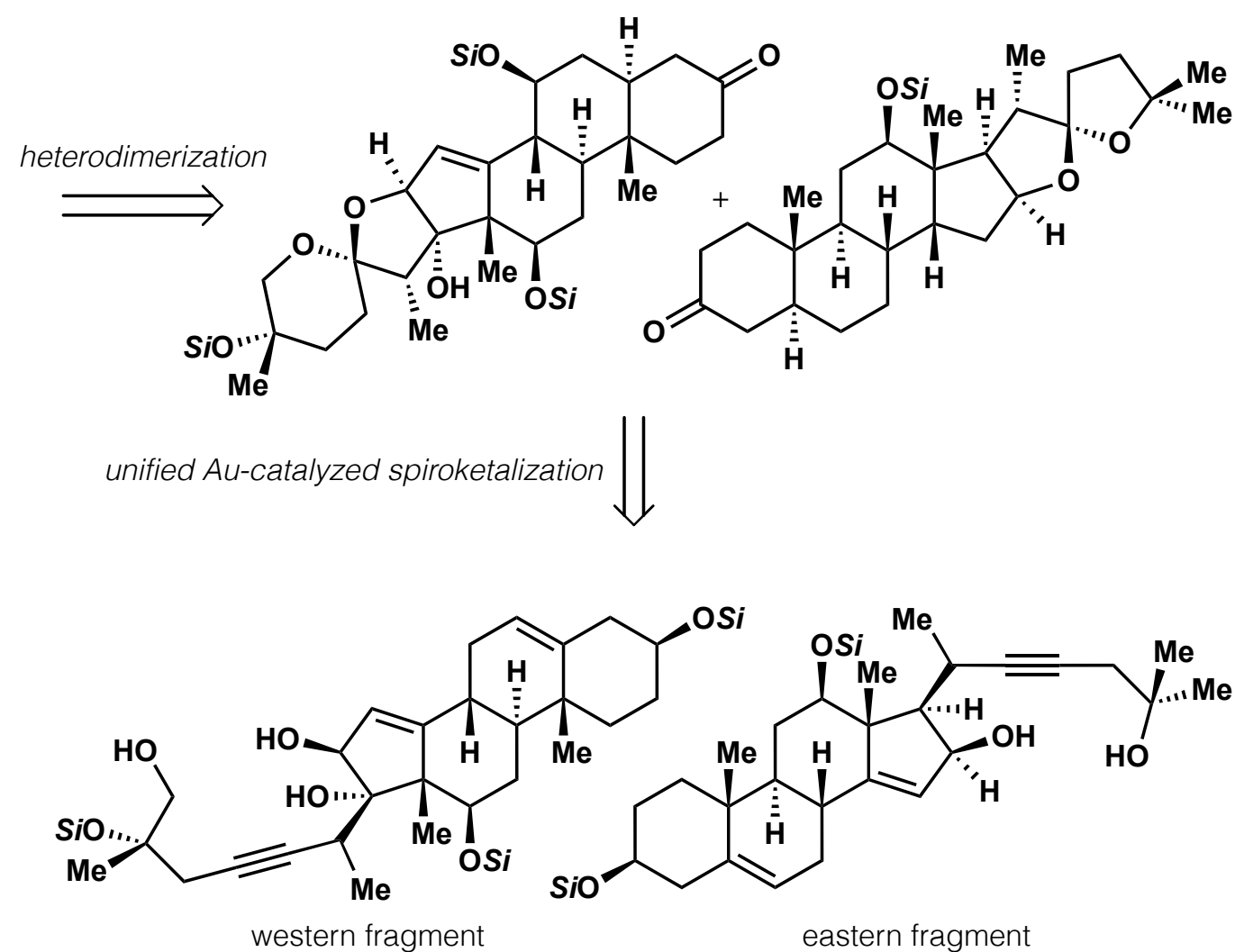
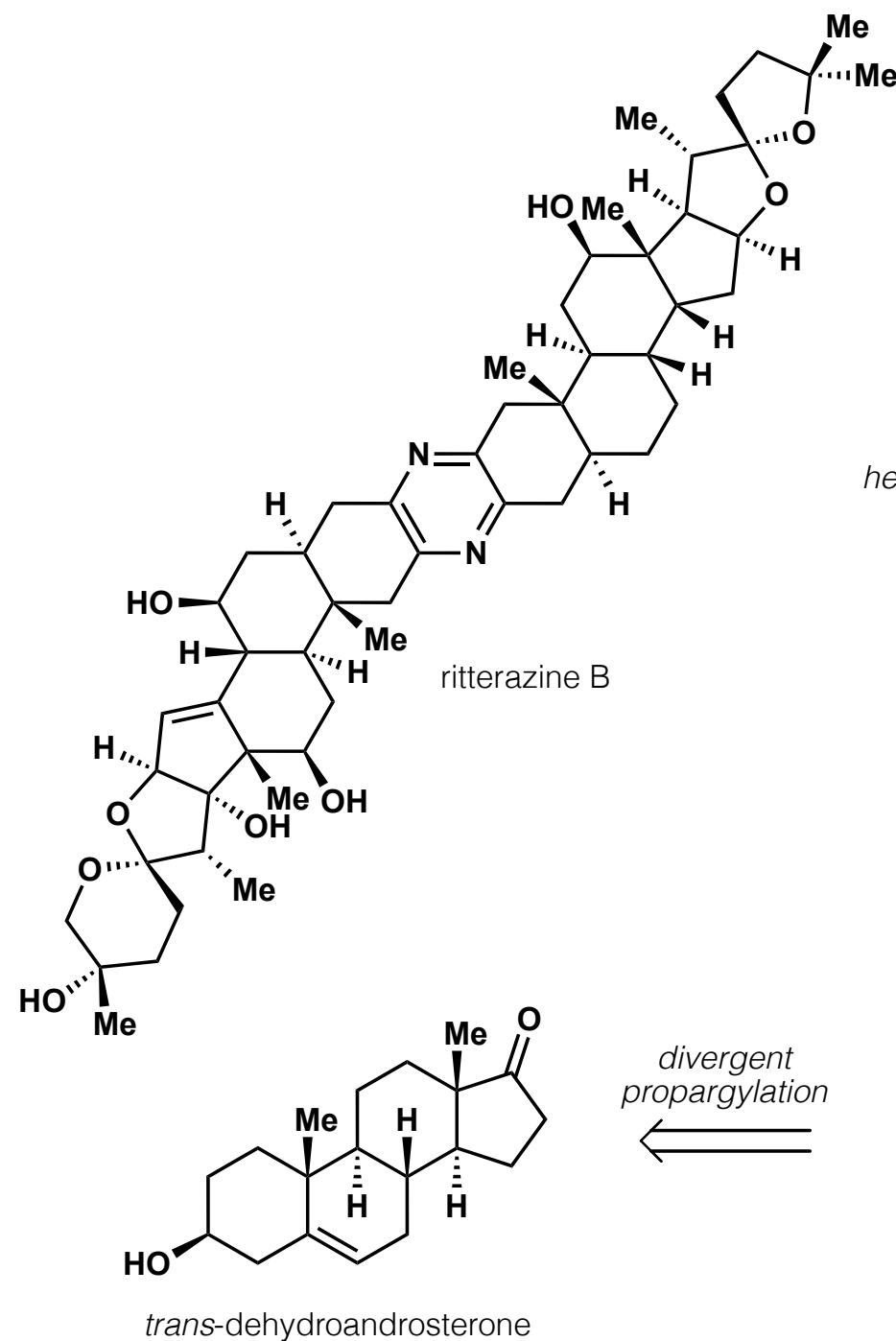


Total Synthesis of ritterazine B

96

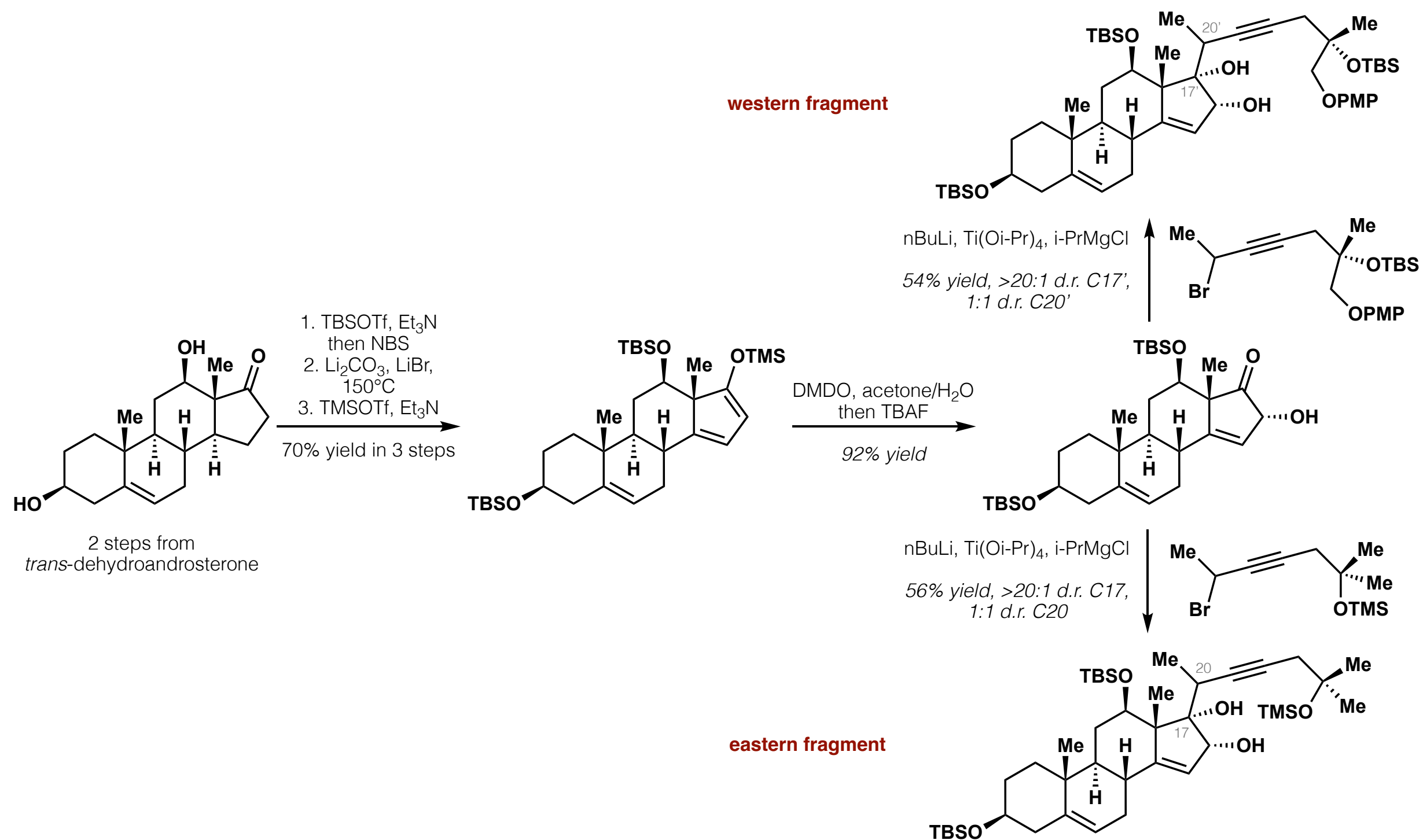


- Bis-steroidal pyrazine (BSP) isolated in 1995 from *Ritterella tokioka* in Japan
- NCI recognizes it as **one of the most potent growth inhibitors ever tested** (0.17 nM IC₅₀ for P388 leukemia cells and an average GI₅₀ of 3.2 nM in the NCI-60 cell line screen)



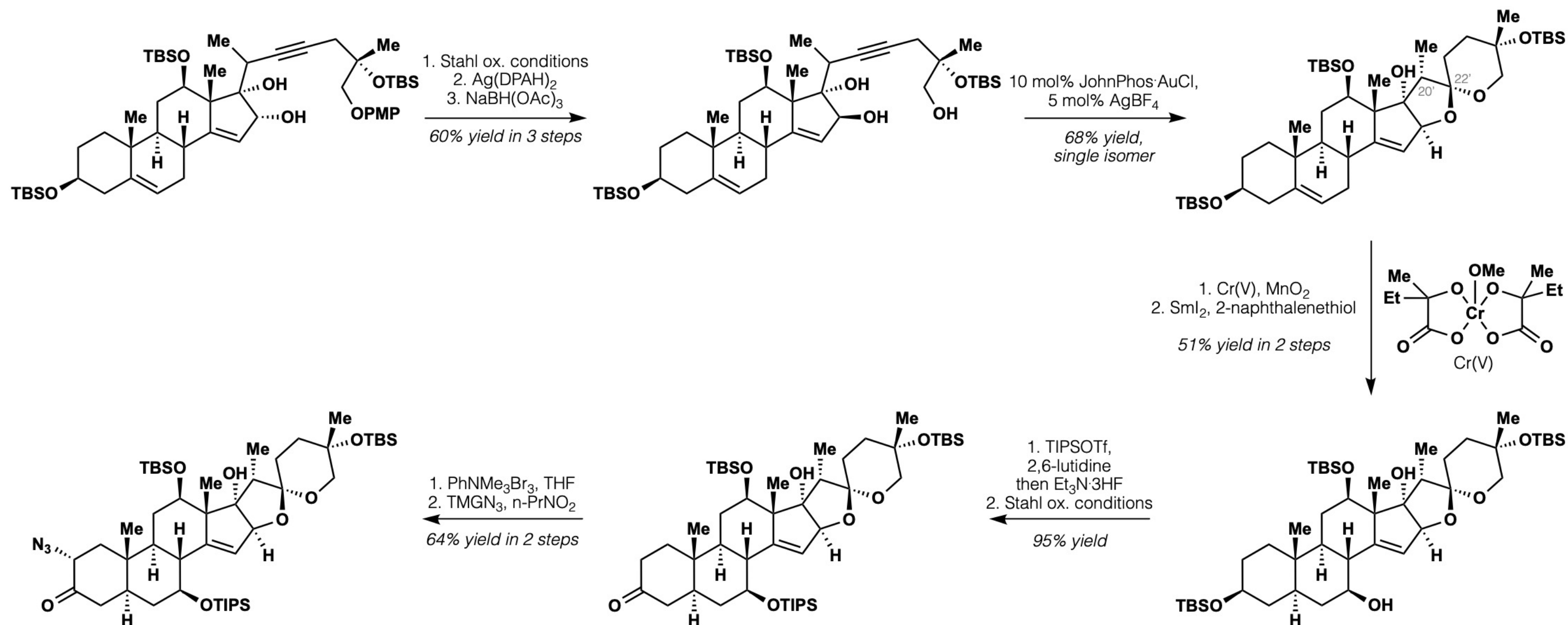
Total Synthesis of ritterazine B

97



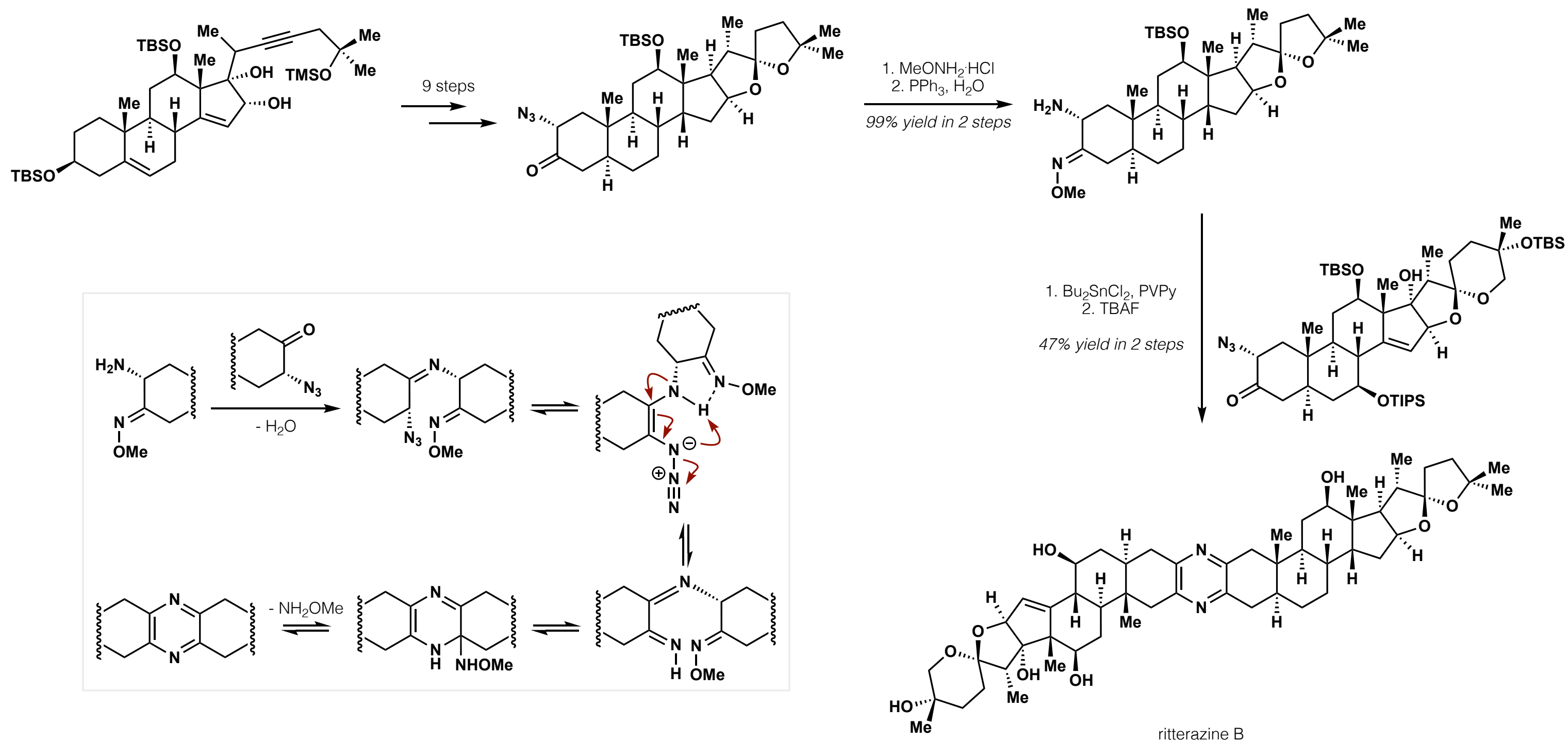
Total Synthesis of ritterazine B

98



Total Synthesis of ritterazine B

99

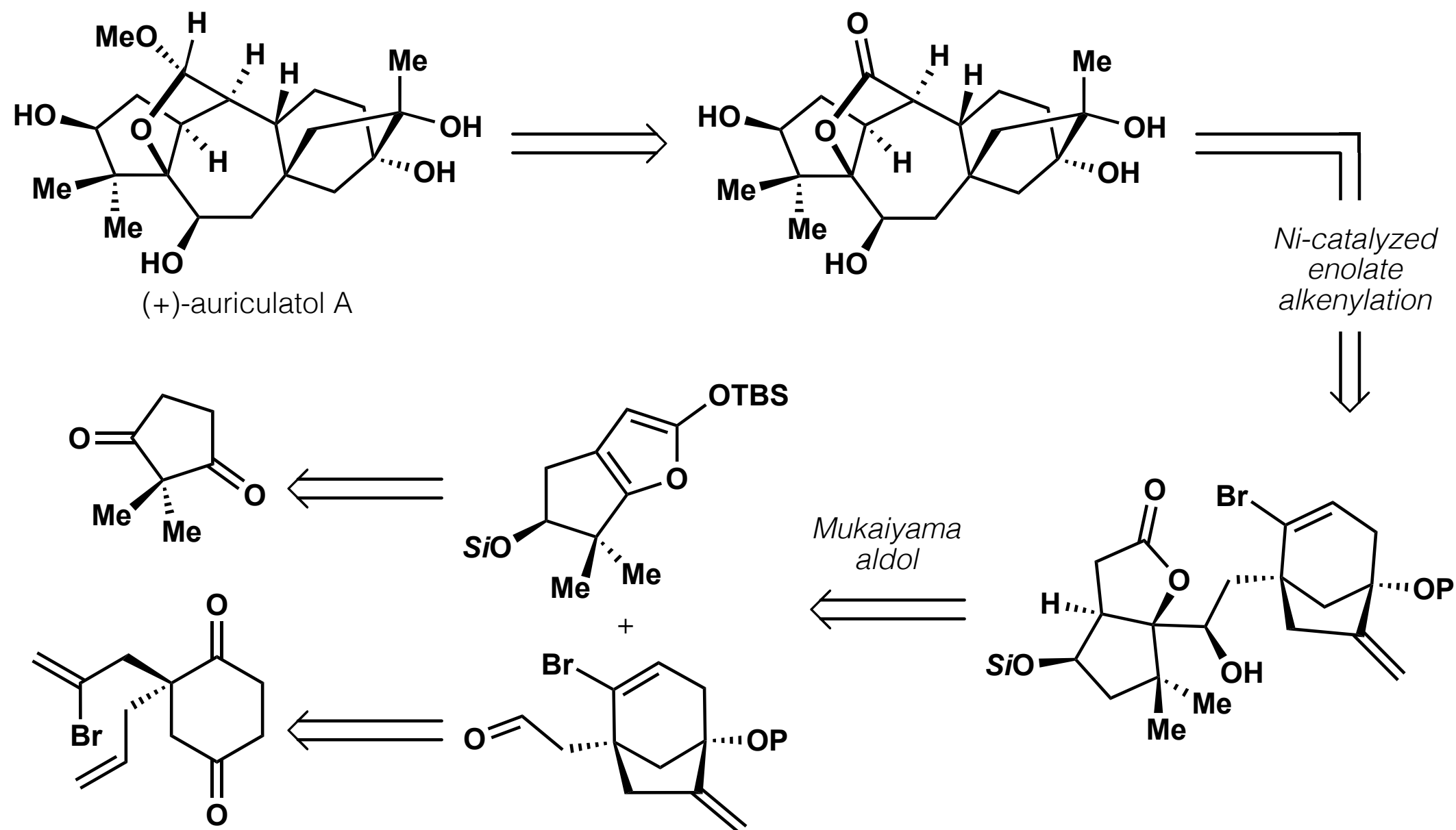


Total Synthesis of (+)-auriculatol A

100

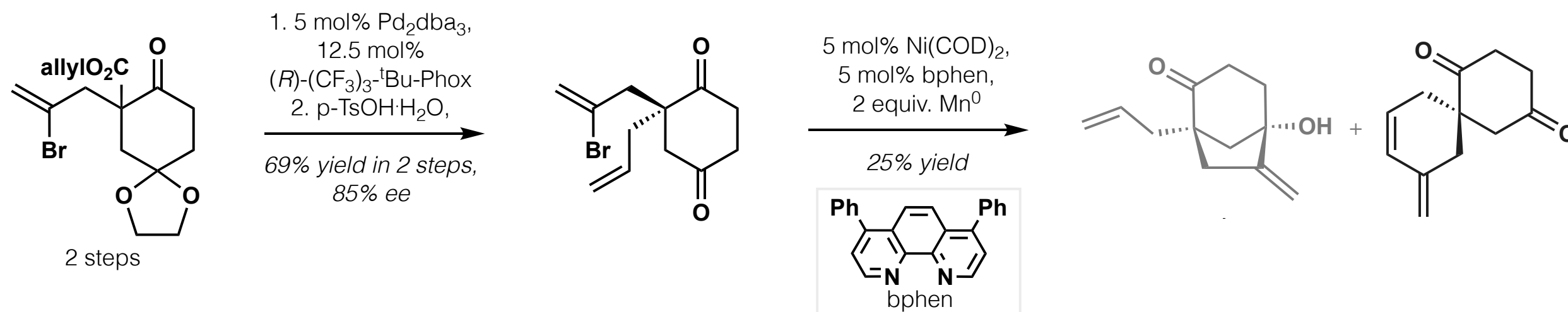
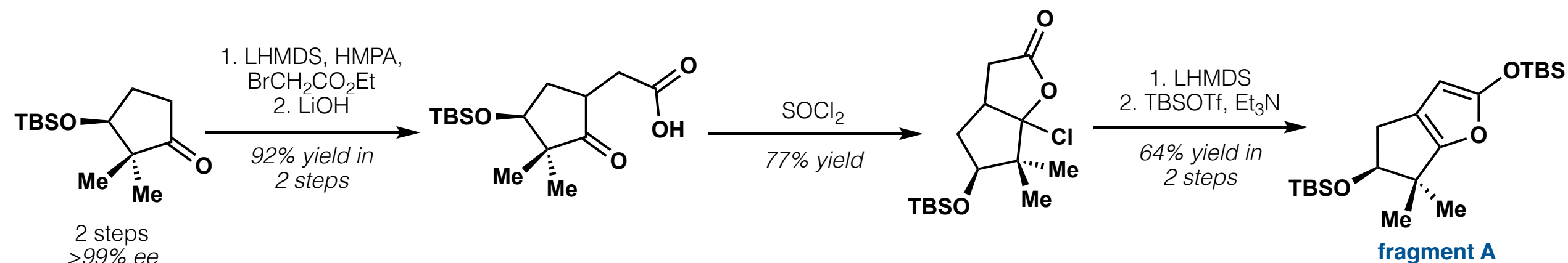


- First isolated in 2019 from the leaves of *Rhododendron auriculatum*
- Shown to possess antinociceptive properties
- No prior synthesis



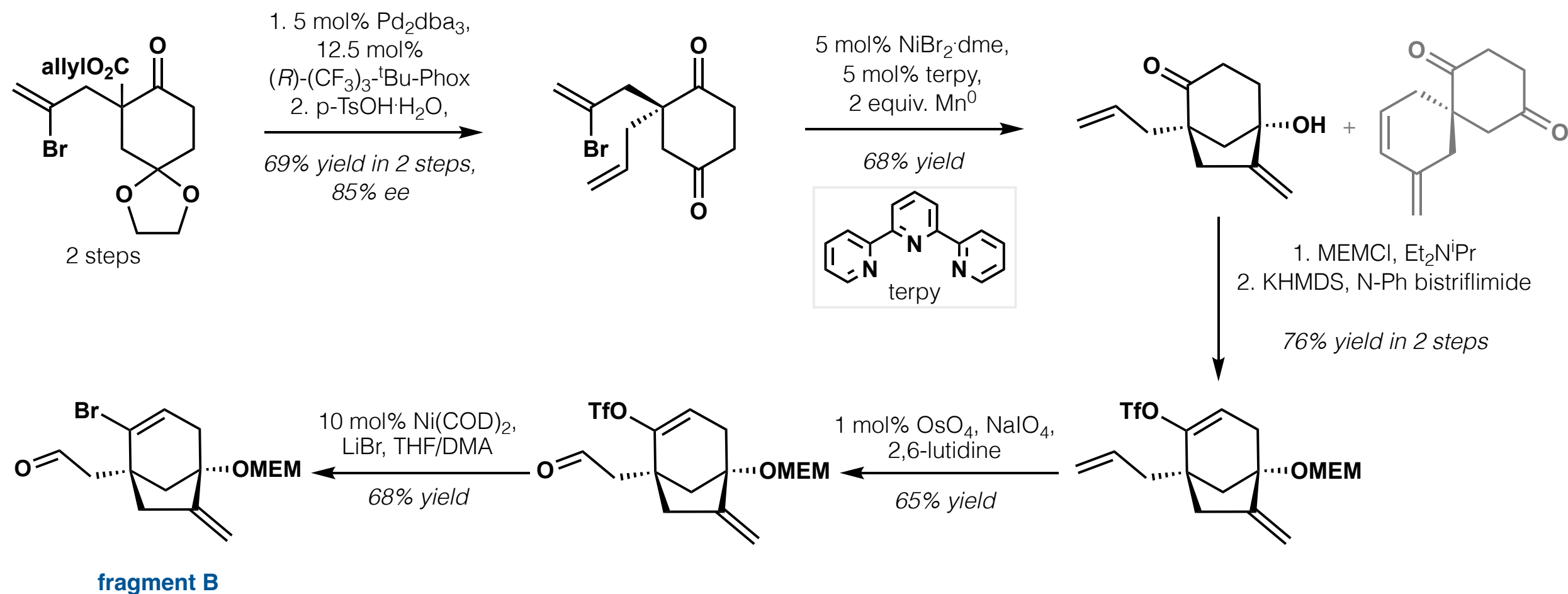
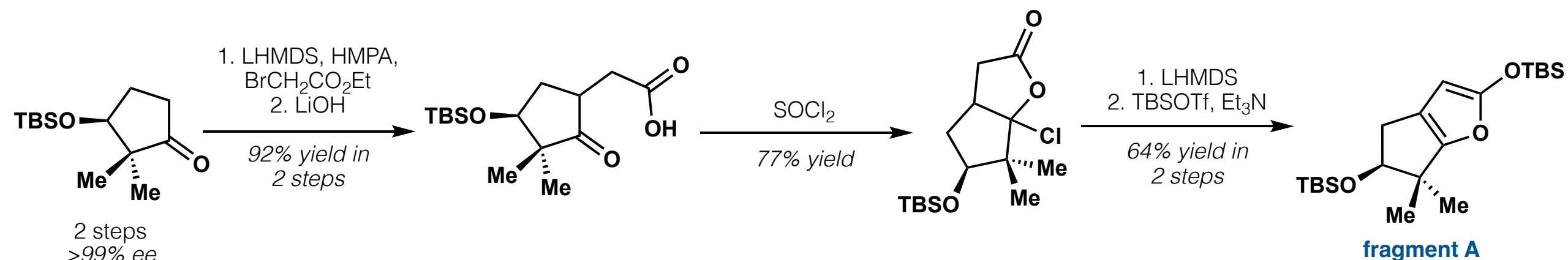
Total Synthesis of (+)-auriculatol A

101



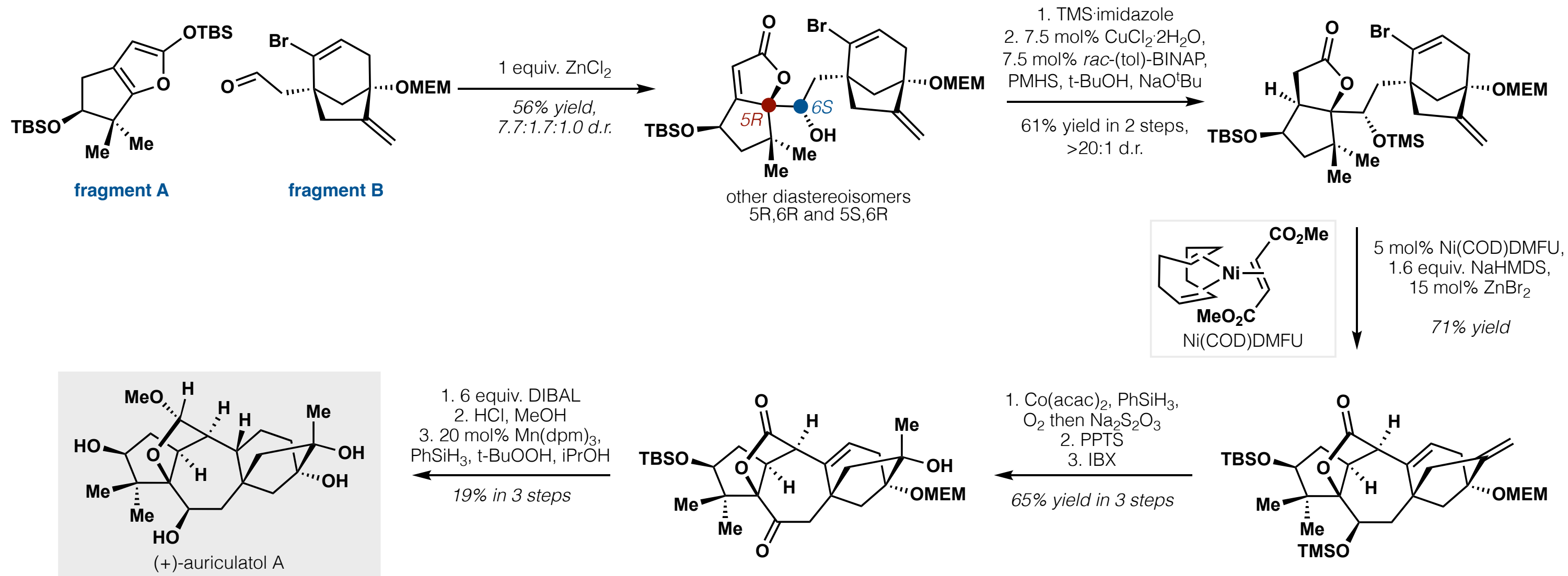
Total Synthesis of (+)-auriculatol A

102



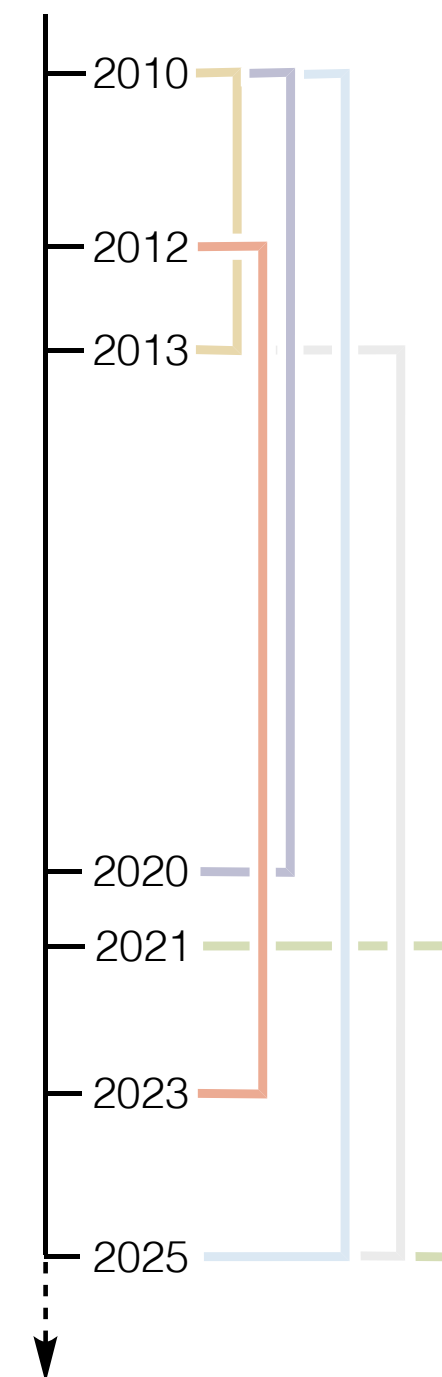
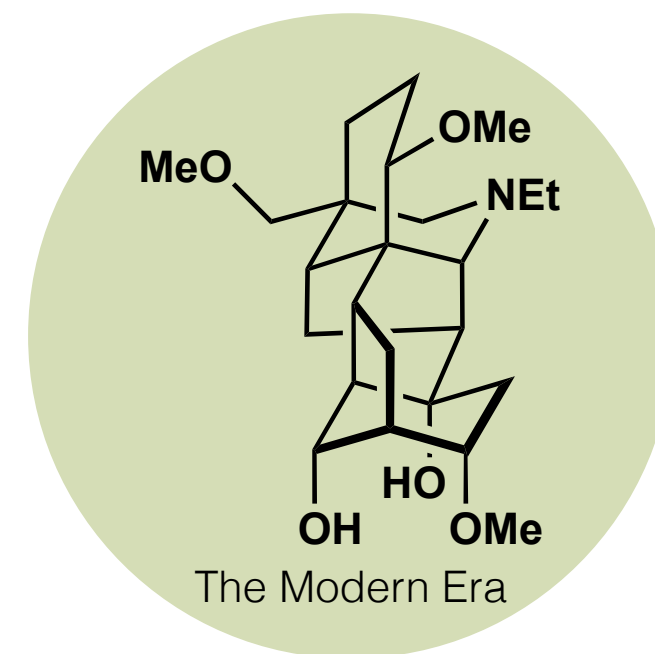
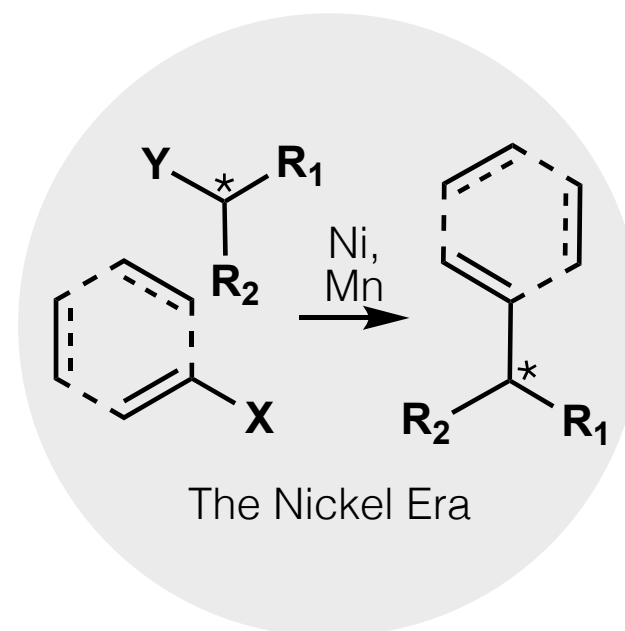
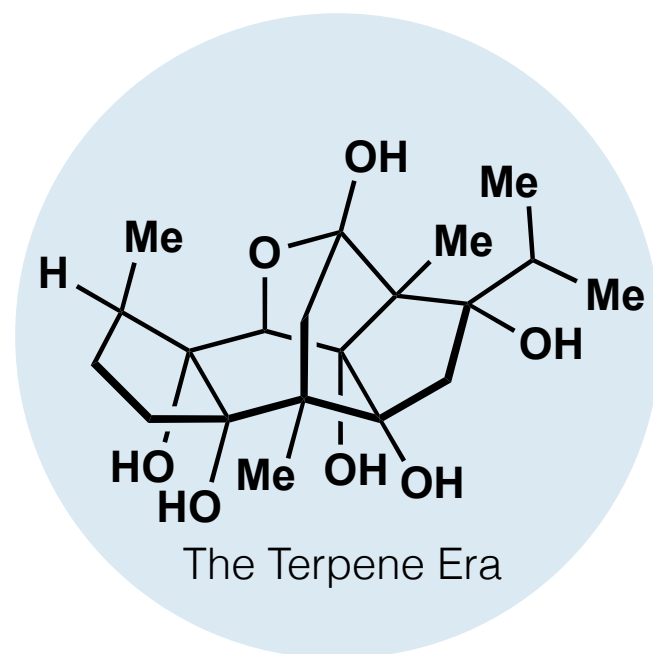
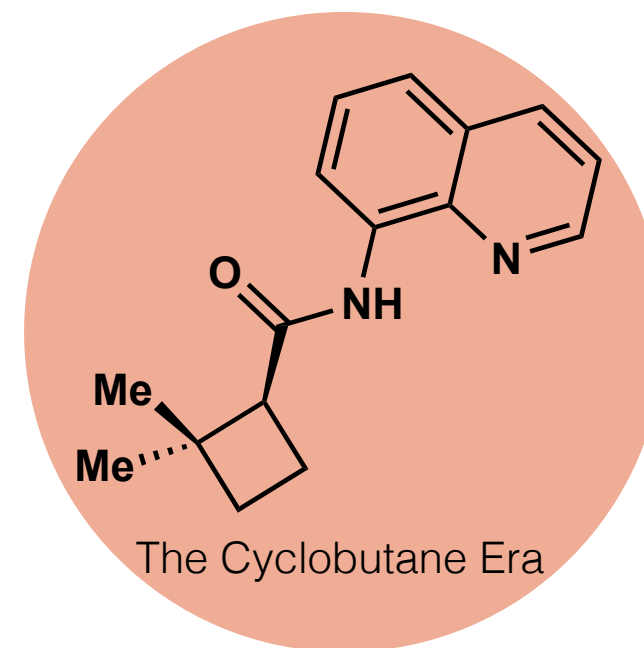
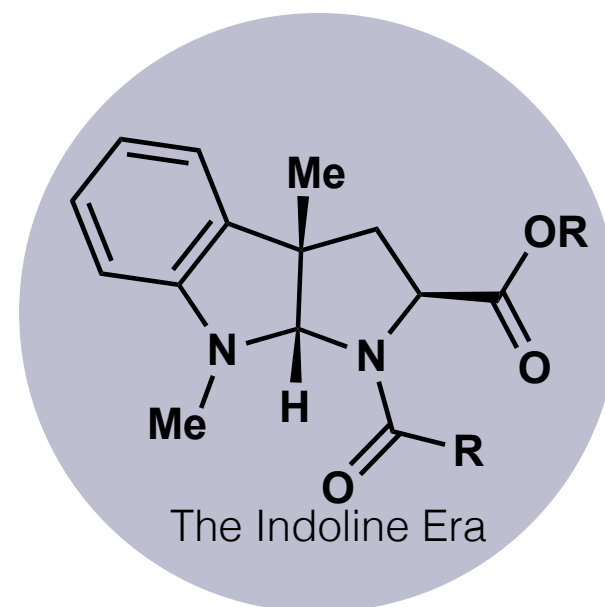
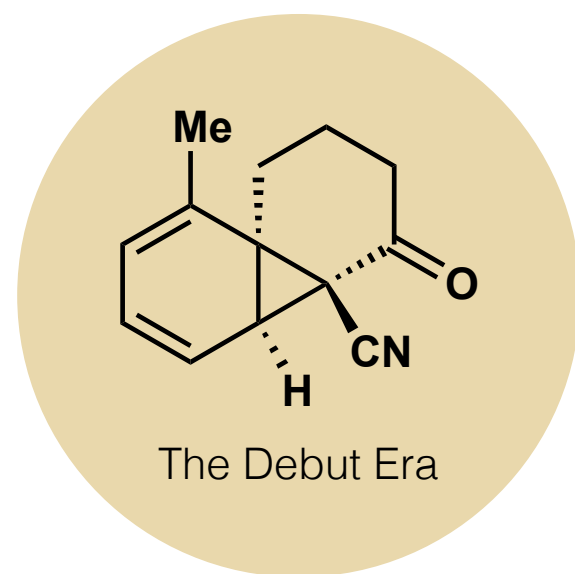
Total Synthesis of (+)-auriculatol A

103



The Eras Tour: Sarah's Version

104



Average Show Runtime


3 hours
23 minutes
Eras

Average seminar in the Shenvi lab?

The End.