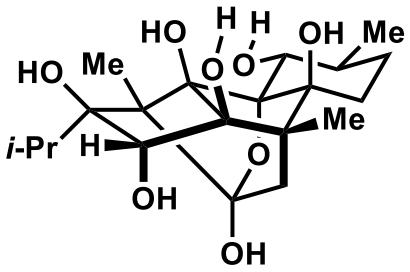
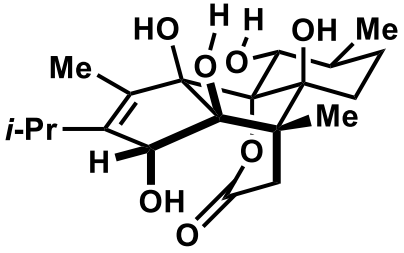
Synthesis of Anhydroryanodol and formal total synthesis of ryanodol



Ryanodol



Anhydroryanodol

Reporter: Jing Chen

Supervisors: *Prof.* Tao Ye

***Dr.* Yian Guo**

July 13st, 2020

Contents

Introduction

Glenn C. Micalizio

Education & Current job:

-B.S.: 1996, Univ. of Oxford
-Ph.D.: 2001, Univ. of Michigan
-Postdoctoral Fellow: 2001-2003, Univ. of Harvard
-Assistant Professor: 2003-2008, Univ. of Yale
- Associate Professor: 2008-2013, Scripps Research Institute
- Professor: 2013-now, Dartmouth College

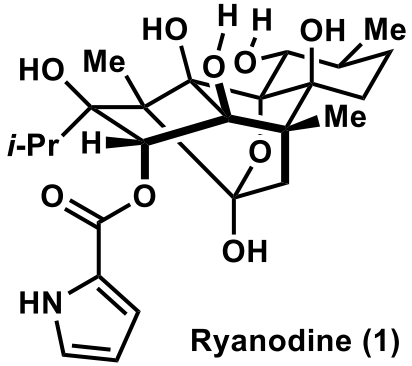
Research Interests & Areas:

Reaction Methodology/Synthesis Strategy

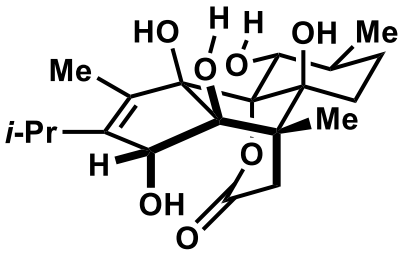
Natural Product Synthesis

Natural Product-Inspired Function- or "Discovery"-Oriented Synthesis

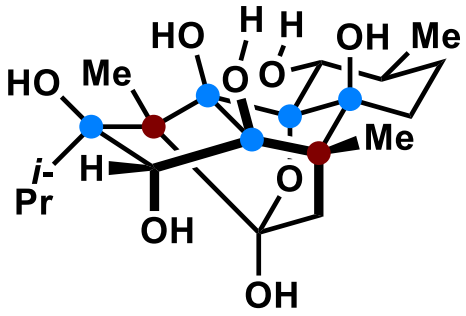
Introduction



Ryanodine (1)



Anhydroryanodol (2)



Ryanodol (3)

Isolation

- Ryanodine, isolated from the South American plant ***Ryana speciosa Vahl*** in 1948.

Biological activities:

- Ryanodol, was known to regulate a family of calcium ion channels.

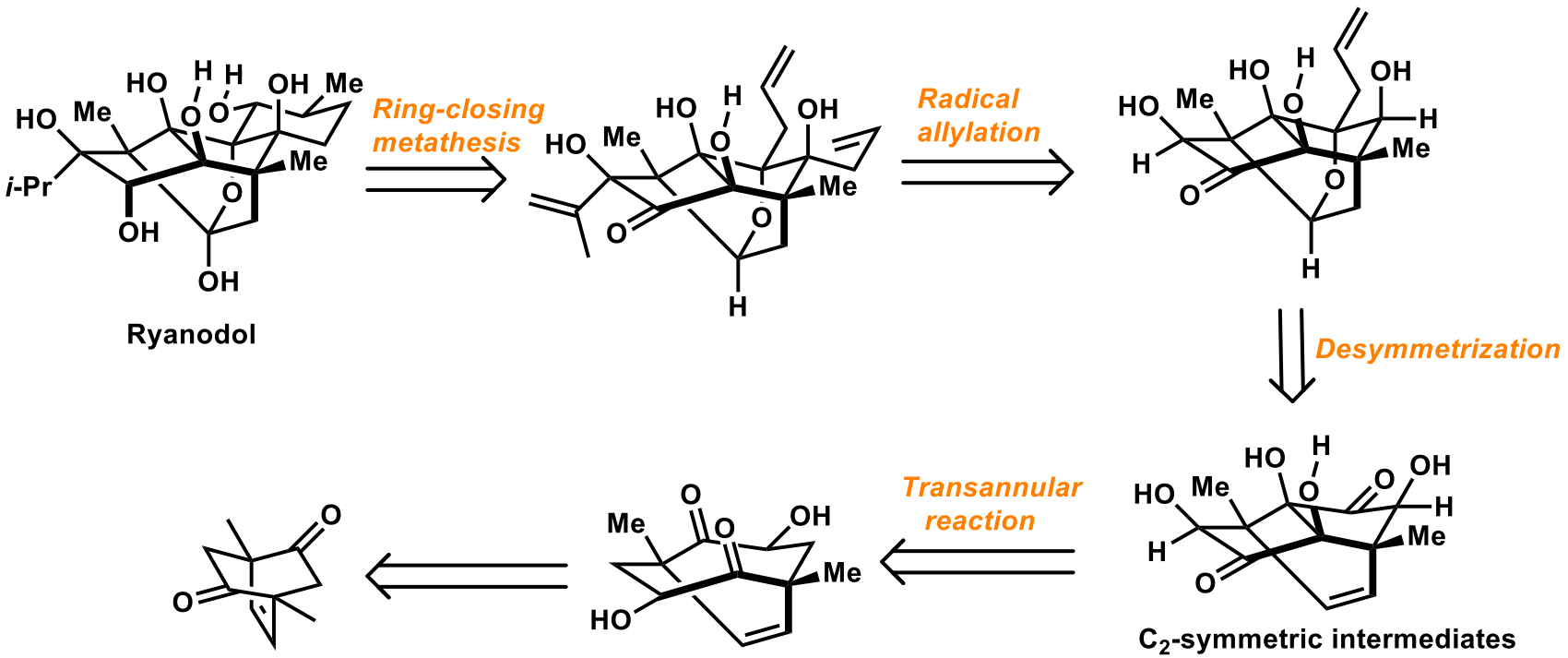
Structural features

- Highly oxygenated cyclic carboskeletons
- 11 stereogenic centers
- 7 contiguous tetrasubstituted stereocenters

Folkers, K. et al, *J. Am. Chem. Soc.* **1948**, *70,* 3086−3088.

Introduction

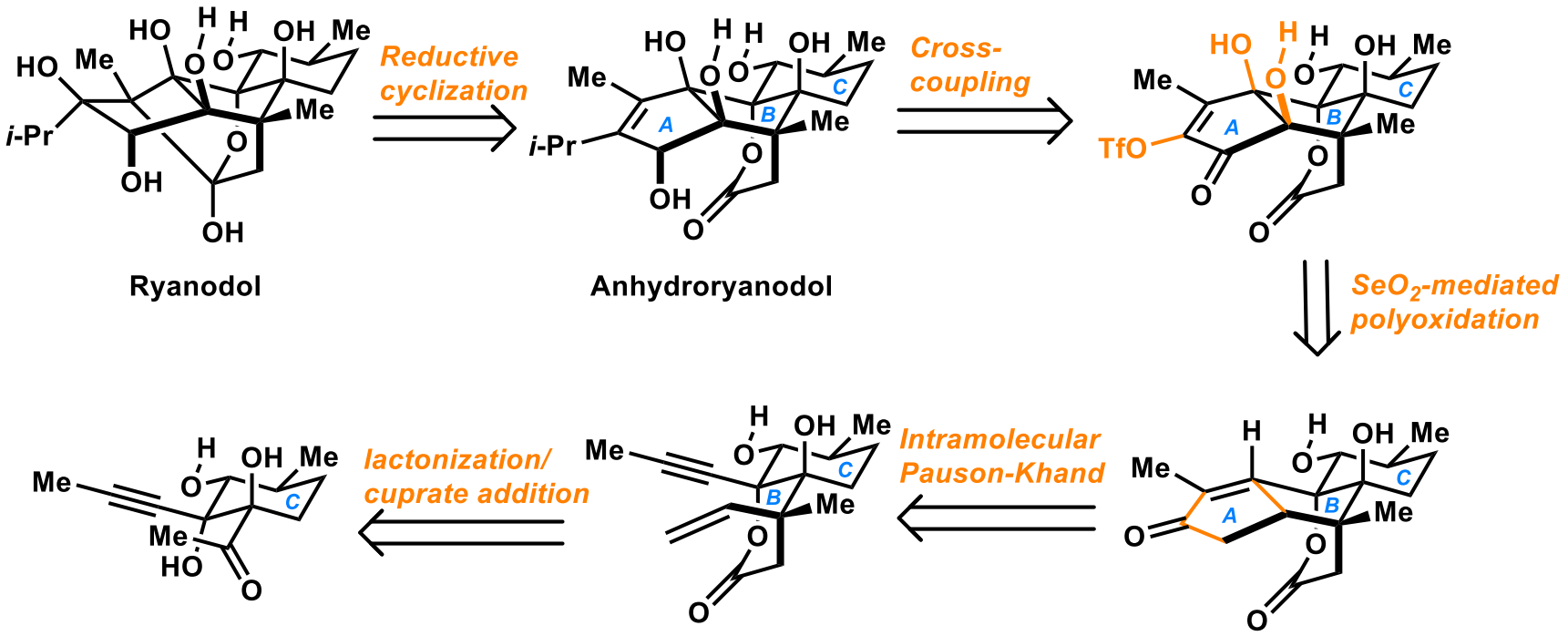
Ryanodol, Inoue, 2013 (24 steps)



Masayuki Inoue et al, *Chem. Sci.*, **2013**, *4*, 1615–1619

Introduction

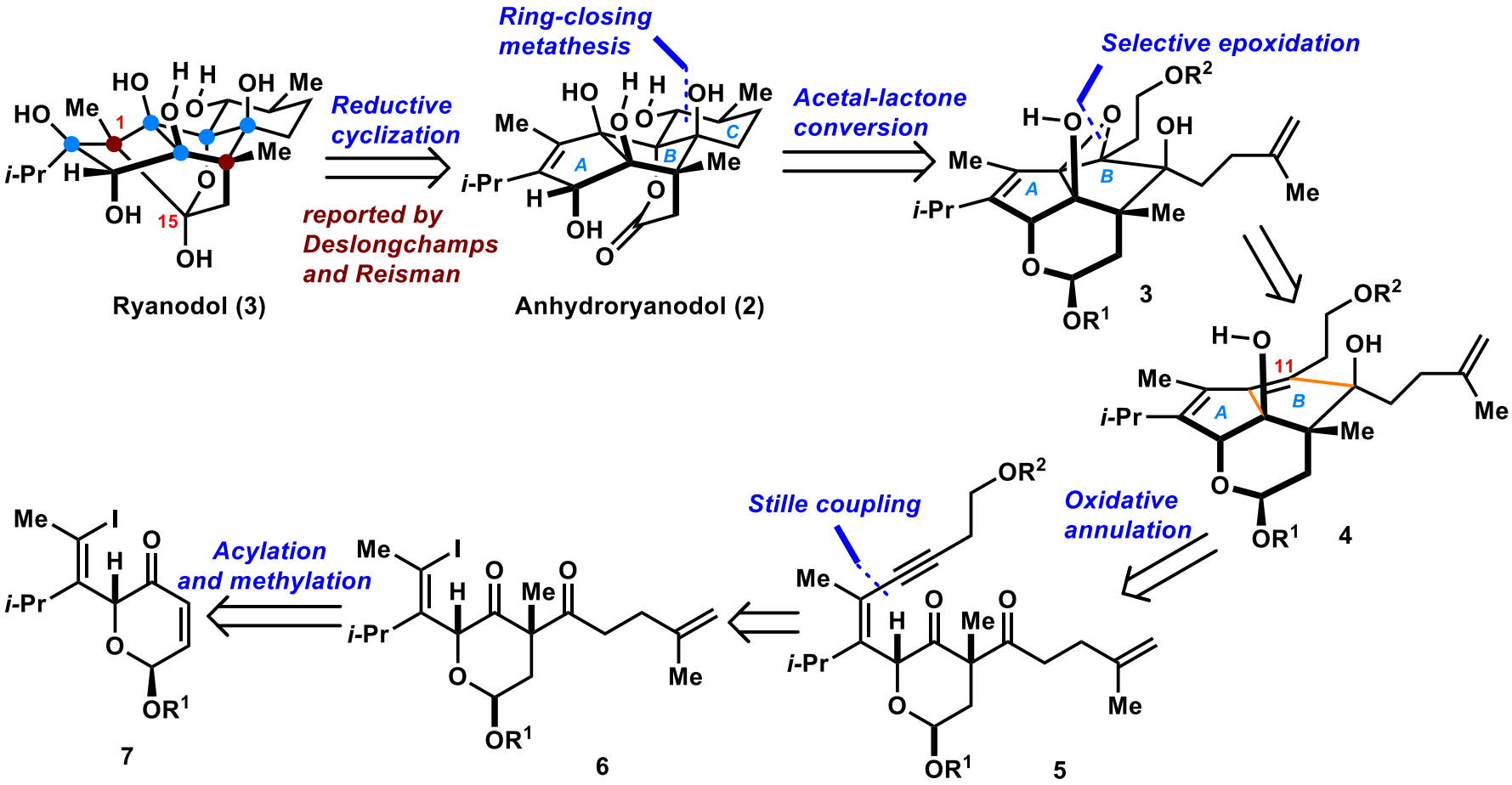
Ryanodol, Reisman, 2016 (15 steps)



Reisman, S. E. et al, *Science* **2016**, *353*, 912-915

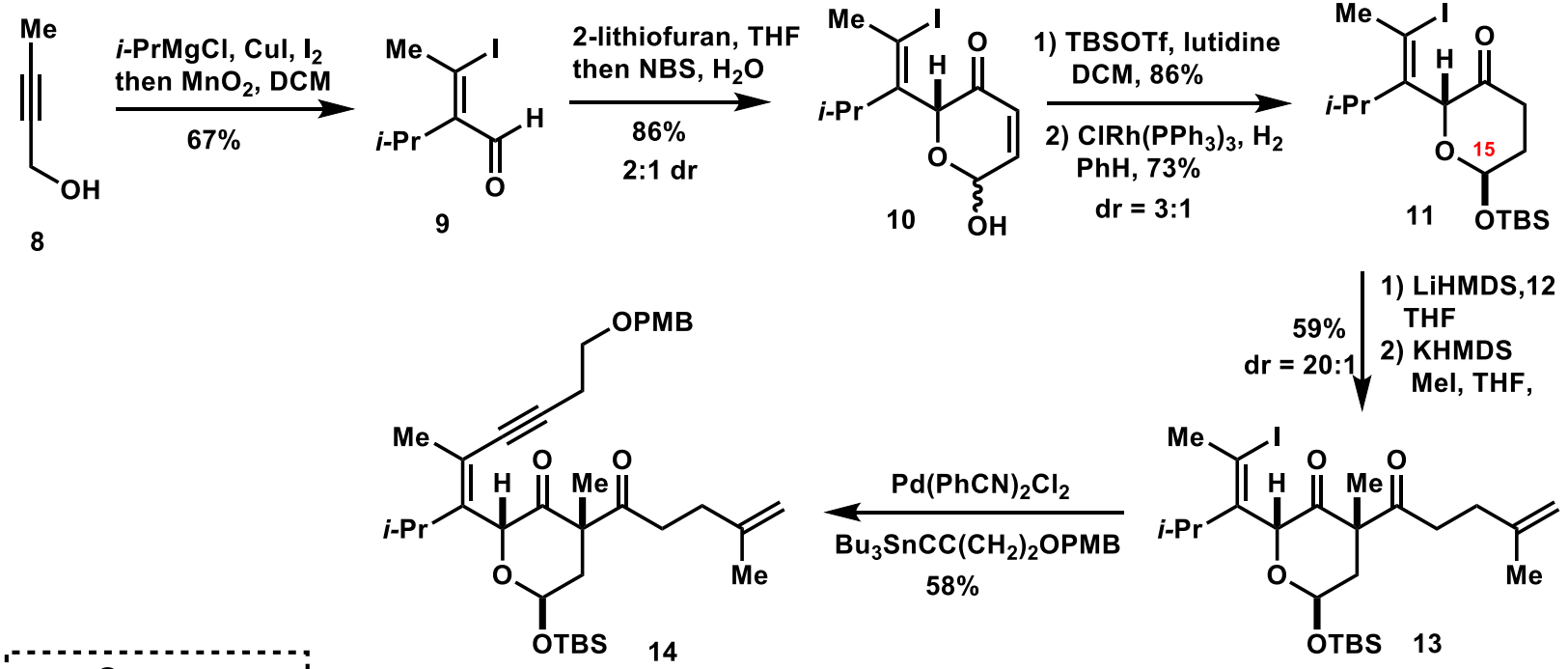
Contents

Retrosynthetic Analysis



Synthetic Route

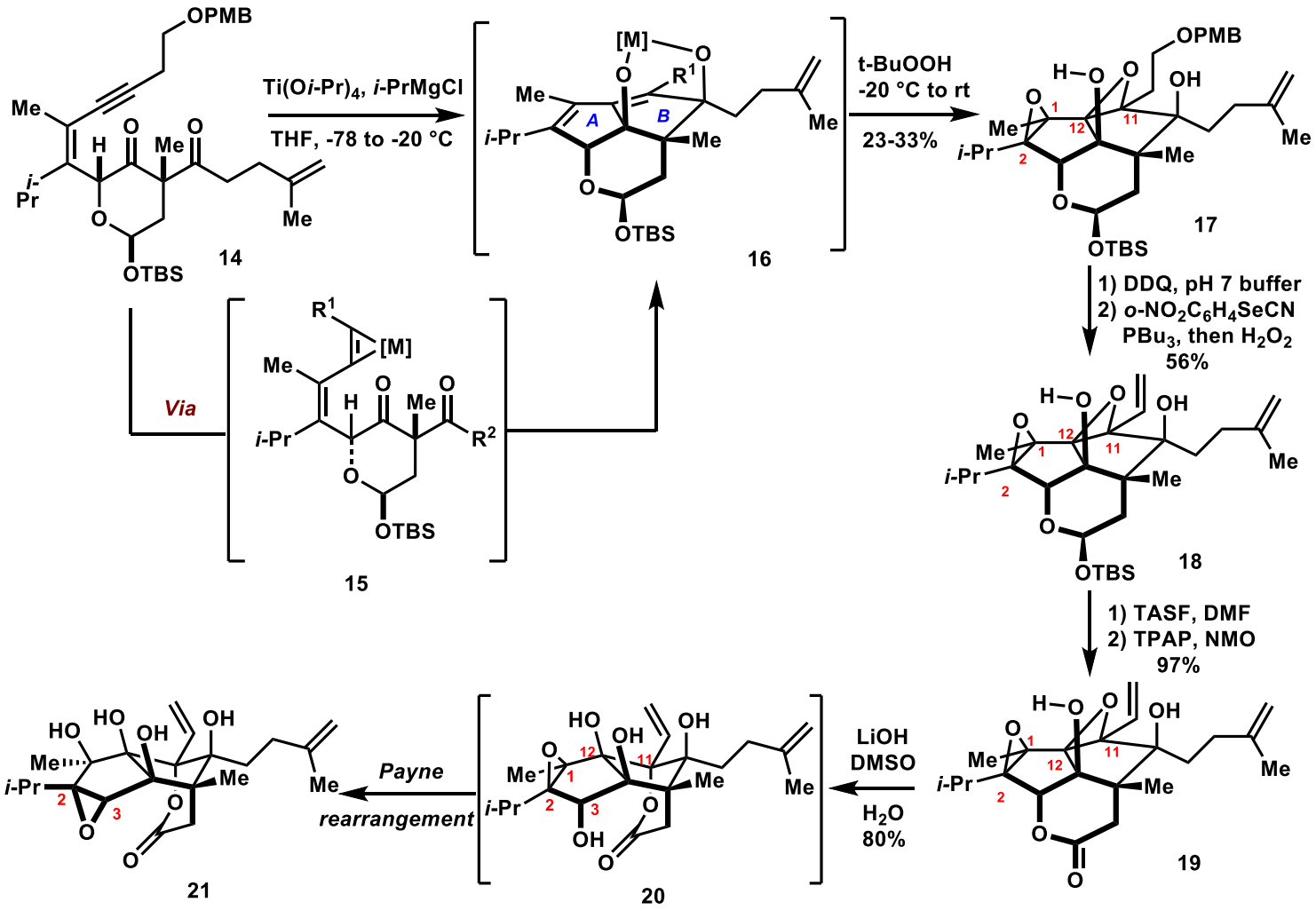
Synthesis of annulation substrate 14



Ma, S. et al, *Org. Biomol. Chem.* **2009**, *7*, 3258−3263.
Wilkinson, G. et al, *J. Chem. Soc.* **1966**, 1711−1732.

Synthetic Route

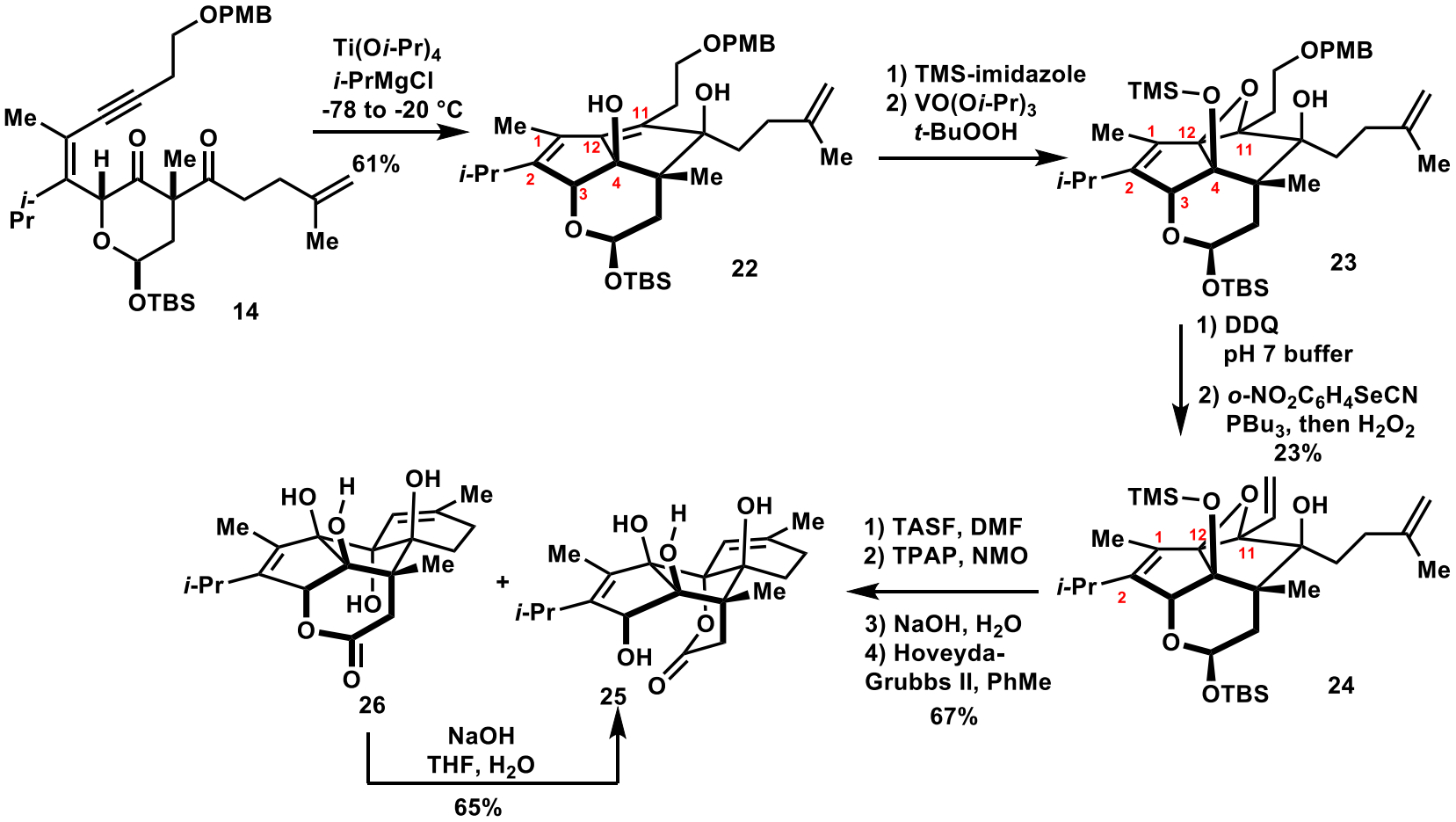
Investigation of the oxidative annulation:



Glenn C. Micalizio et al, *Org. Lett.* **2018**, *20*, 6457−6461.

Synthetic Route

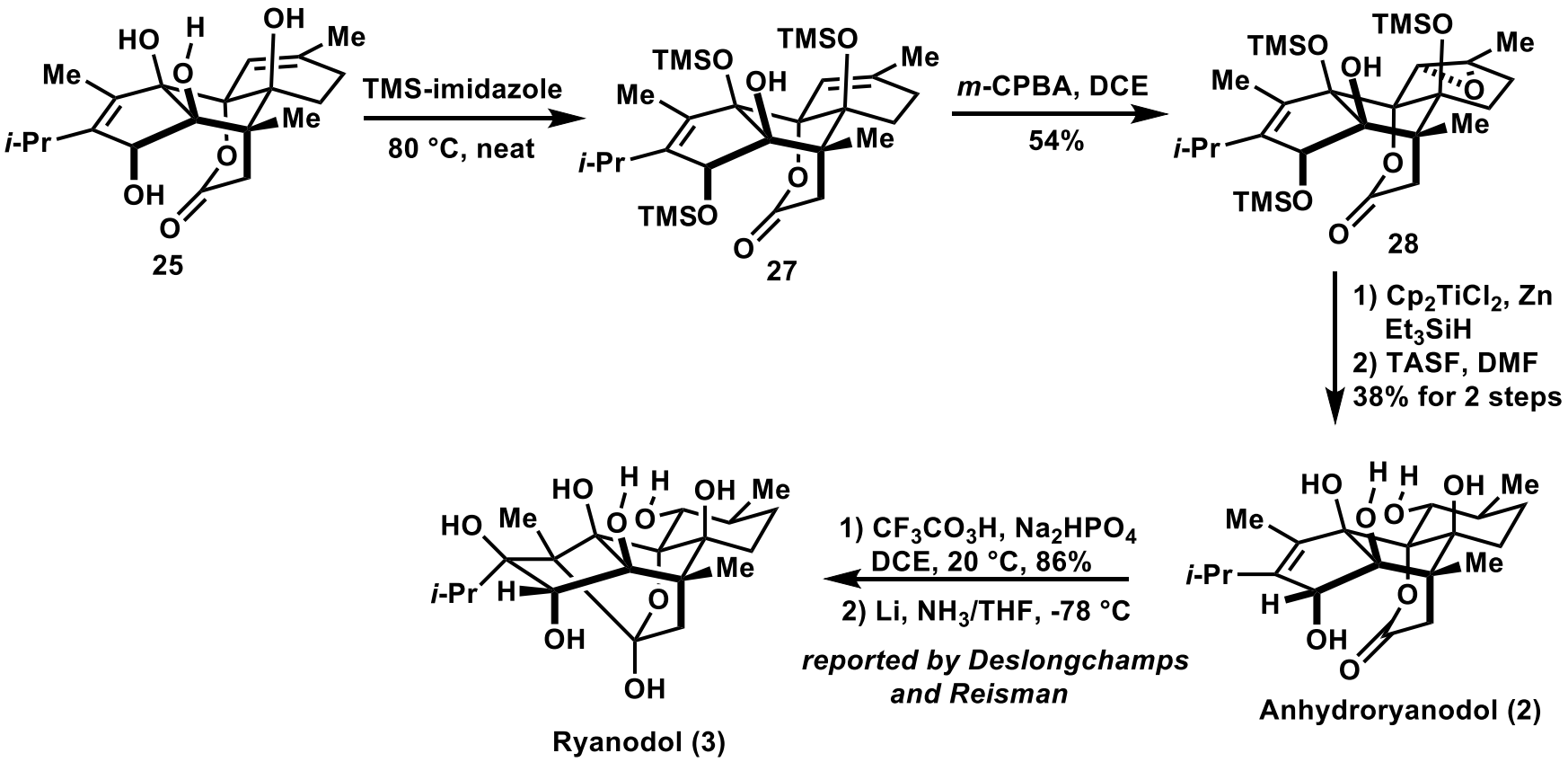
Completed synthesis of Anhydroryanodol and formal total synthesis of Ryanodol



Fox, J. M et al, *Org. Lett.* **2005**, *7*, 3593.
Suriano, J. A. et al, *J. Am. Chem. Soc*. **1993**, *115*, 1154.

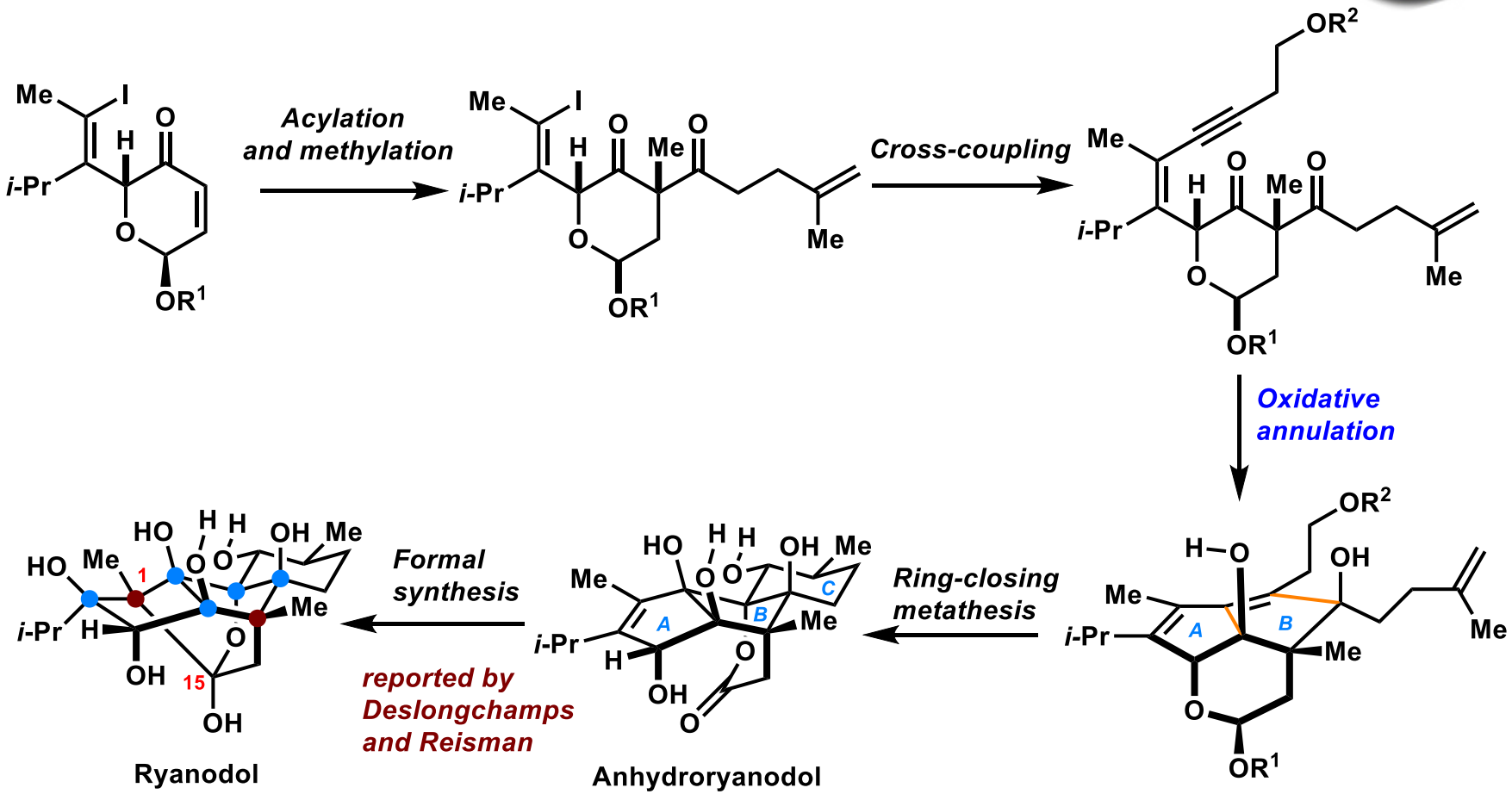
Synthetic Route

Completed synthesis of Anhydroryanodol and formal total synthesis of Ryanodol



Hoveyda, A. H. et al, *J. Am. Chem. Soc.* **2000**, *122,* 8168−8179.

Summary


Me
I
H
O
i-Pr
O
OR1
Acylation
and methylation
Me
I
H
O
Me
O
i-Pr
O
Me
OR1
Cross-coupling
OR2
Me
H
O
Me
O
i-Pr
O
Me
OR1
Oxidative
annulation
OR2
H–O
OH
Me
i-Pr
A
B
Me
Me
O
OR1
Ring-closing
metathesis
HO
H
H
OH
Me
Me
A
B
C
i-Pr
H
O
Me
OH
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Formal
synthesis
reported by
Deslongchamps
and Reisman
HO
H
H
OH
Me
HO
Me
1
O
O
i-Pr
H
Me
O
OH
15
OH
Ryanodol
Anhydroryanodol

Acknowledgement

Prof. Tao Ye and Dr. Yi-an Guo;

All professors and faculties in SCBB;

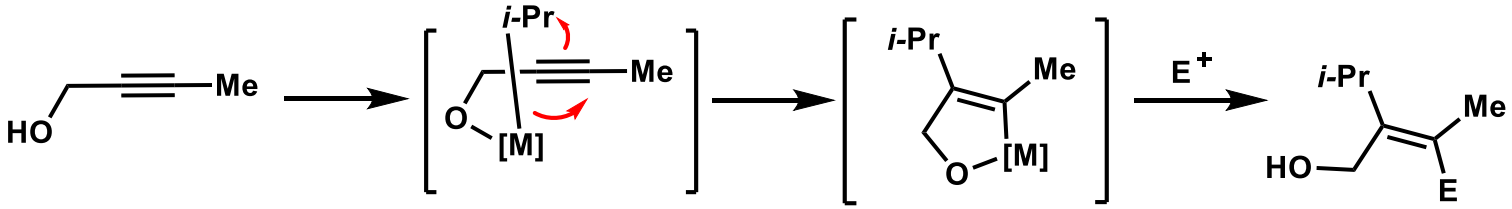
All my labmates in F211!

The End

Thanks for your attention!

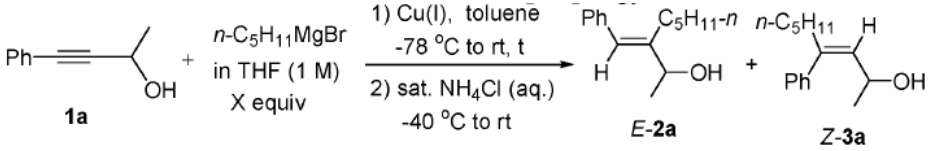
Supporting Materials

copper-mediated addition

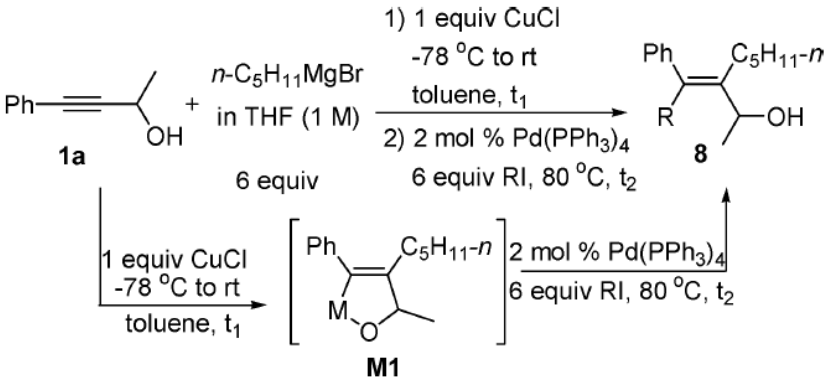


Supporting Materials

copper-mediated addition

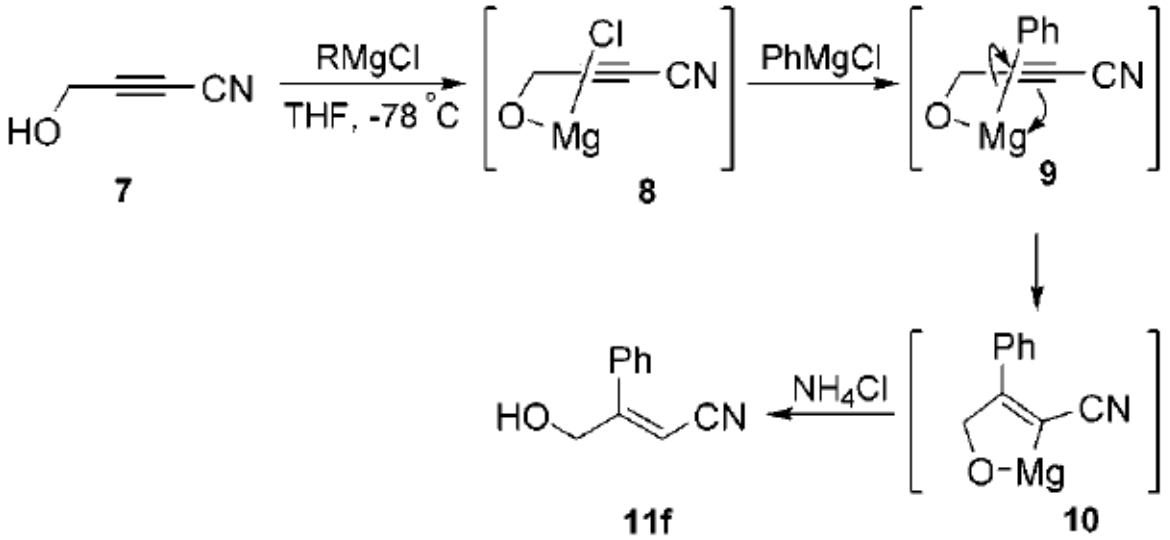


Entry	X	Cu(I) (equiv)	t (h)	NMR yield (%) *E*-**2a**	*Z*-**3a**	Recovery of **1a**
1	3.5	CuI (0.5)	12.1	46	9	33
2	3.5	CuCl (1.0)	11.6	44	9	40
3	4.5	CuCl (1.0)	11.6	87	3	8
4	6.0	CuCl (1.0)	11.6	95	2	2
5	6.0	CuI (1.0)	12.0	70	8	8
6	6.0	CuBr (1.0)	12.0	70	10	8
7	6.0	CuCl (1.5)	13.2	95	3	5
8	6.0	CuCl (0.5)	13.2	88	4	6
9	6.0	CuCl (2.0)	13.0	85	4	13



Supporting Materials

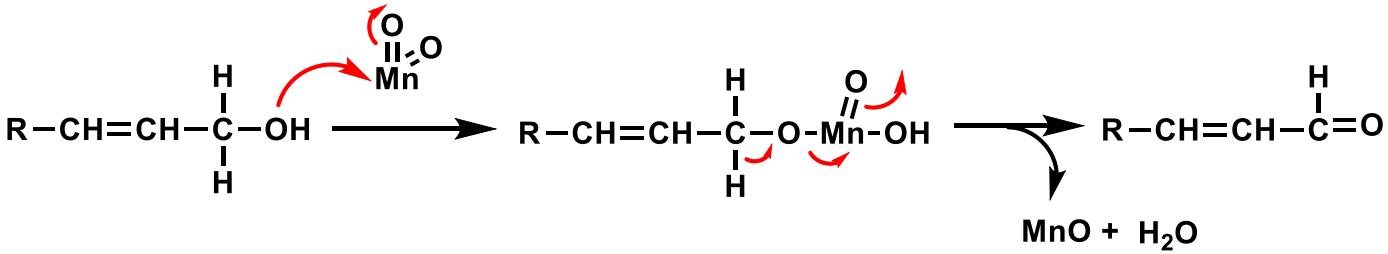
copper-mediated addition



Supporting Materials

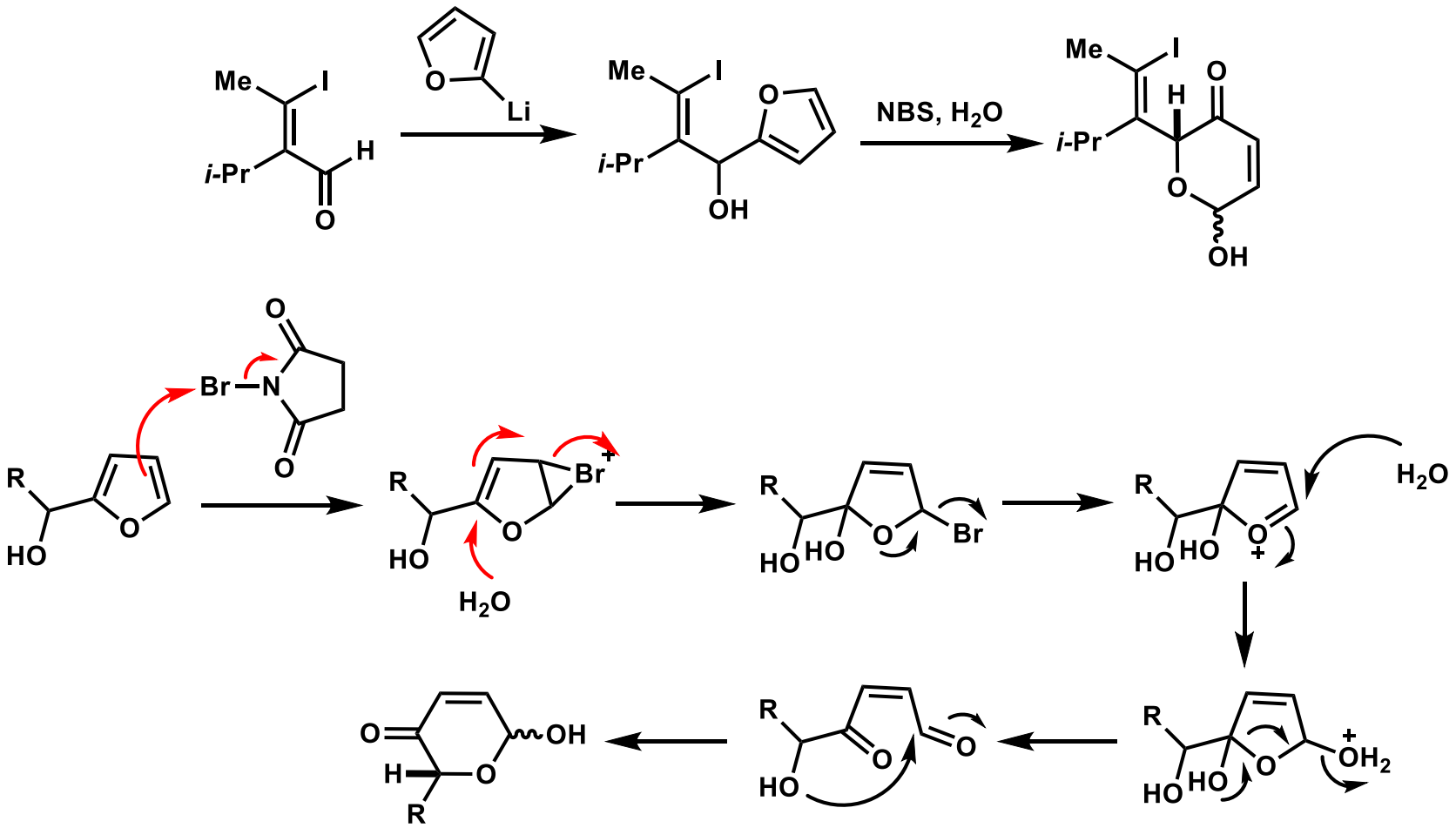
MnO2-Oxidation

$$cis-RCH=CHCH_2OH + MnO_2 \longrightarrow cis-RCH=CHCHO + H_2O + MnO$$



Supporting Materials

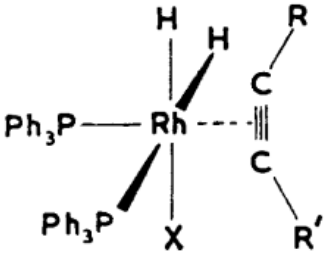
Achmatowicz rearrangement



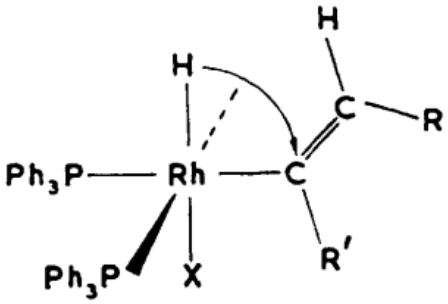
Supporting Materials

Selective hydrogenation Wilkinson's catalyst

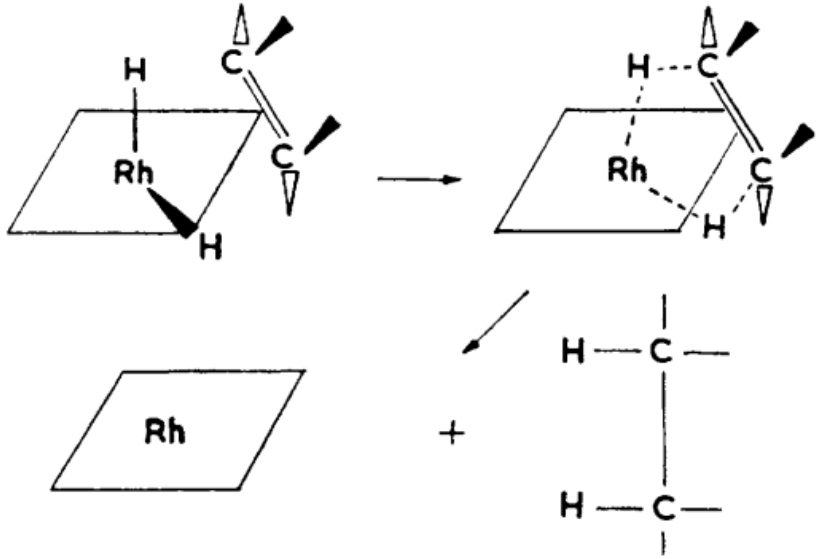
$$RhCl(PPh_3)_2 + H_2 \underset{}{\overset{K_1}{\rightleftharpoons}} RhCl(PPh_3)_2H_2$$



(IVa)



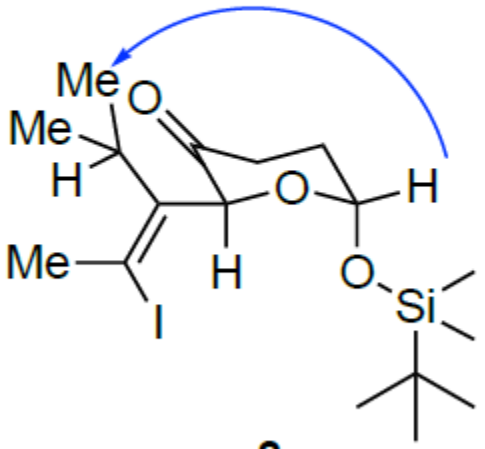
(IVb)



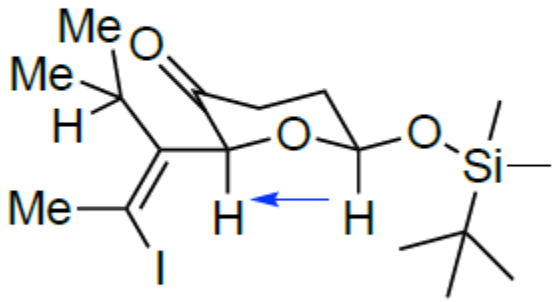
Supporting Materials

Selective hydrogenation Wilkinson's catalyst

Selected nOe interaction of compound 8 and 9



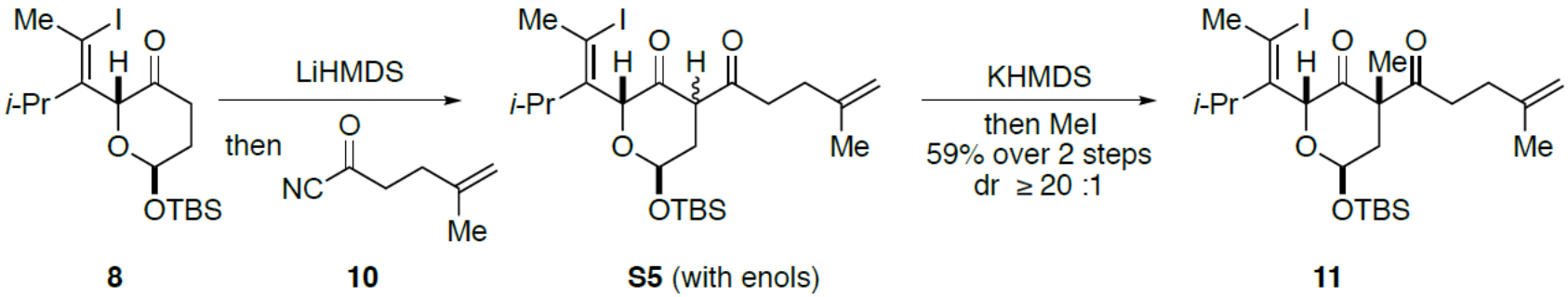
8



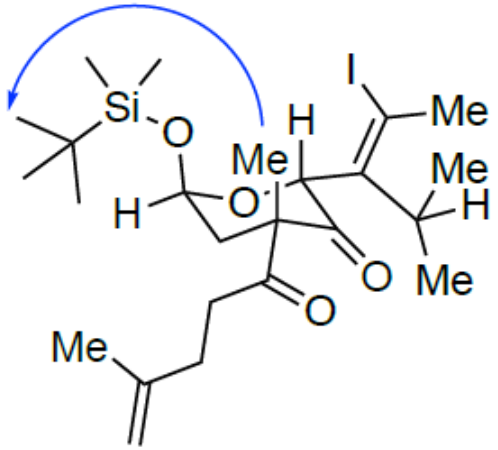
9

Supporting Materials

Acylation and methylated

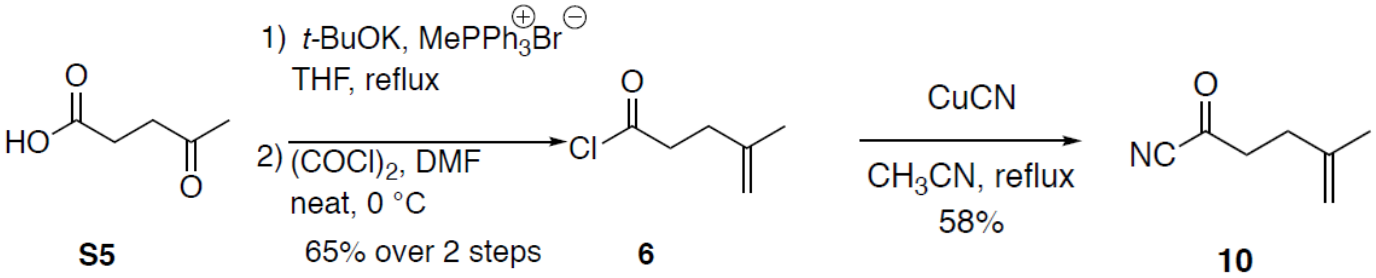


8 **10** **S5** (with enols) **11**



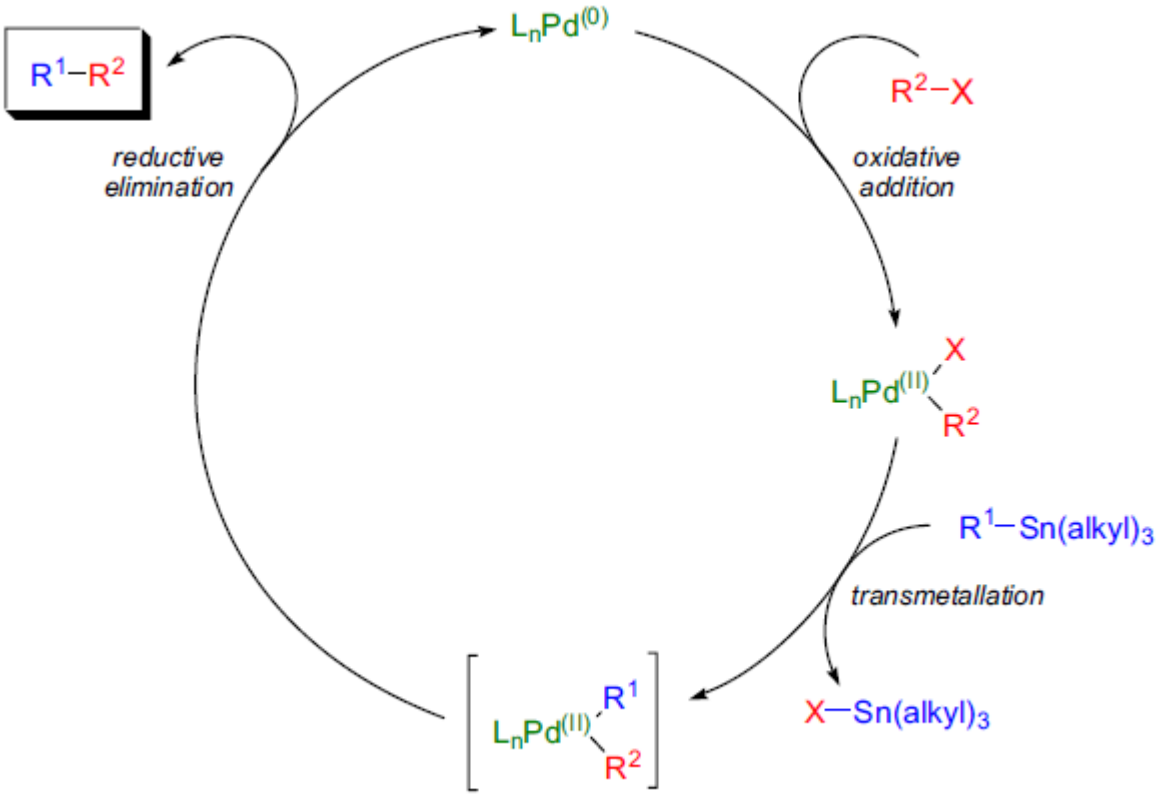
Supporting Materials

Synthesis of 10



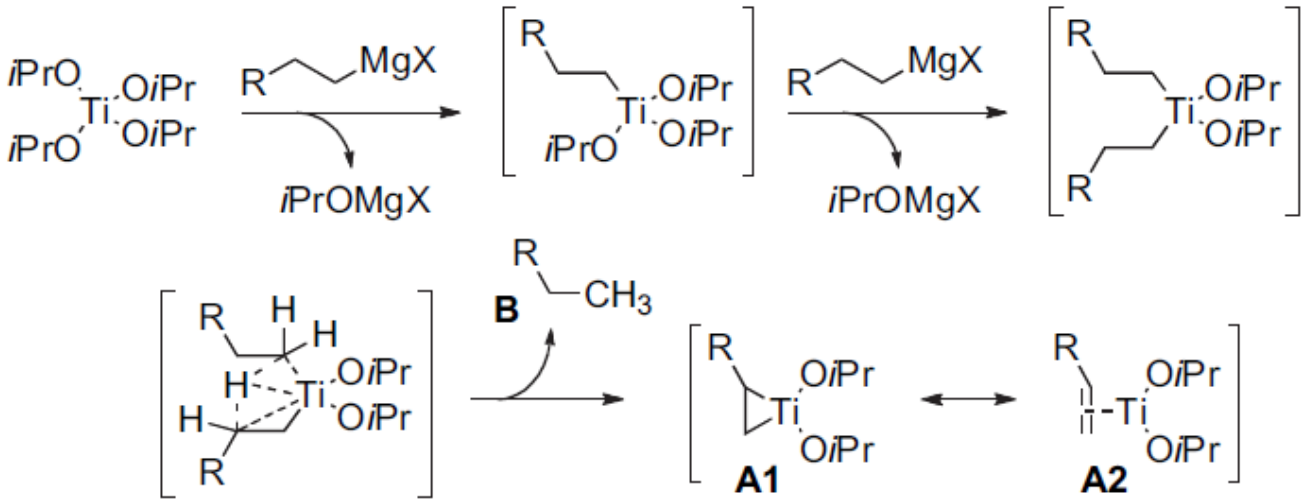
Supporting Materials

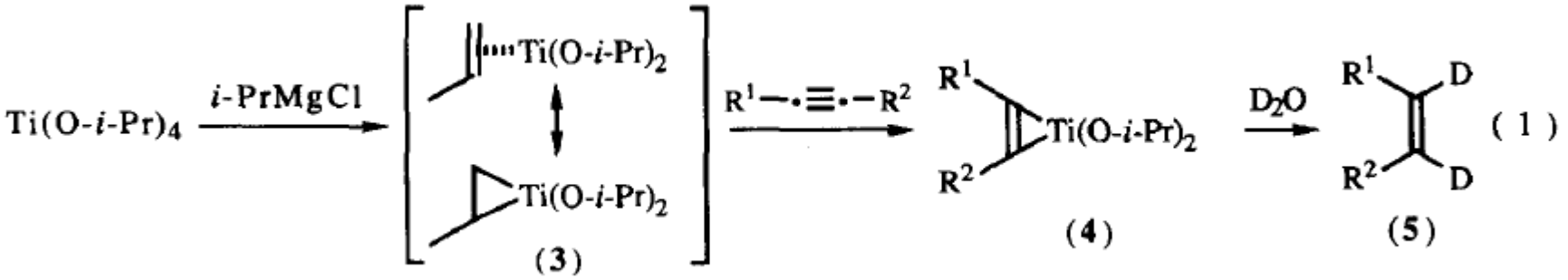
Stille coupling



Supporting Materials

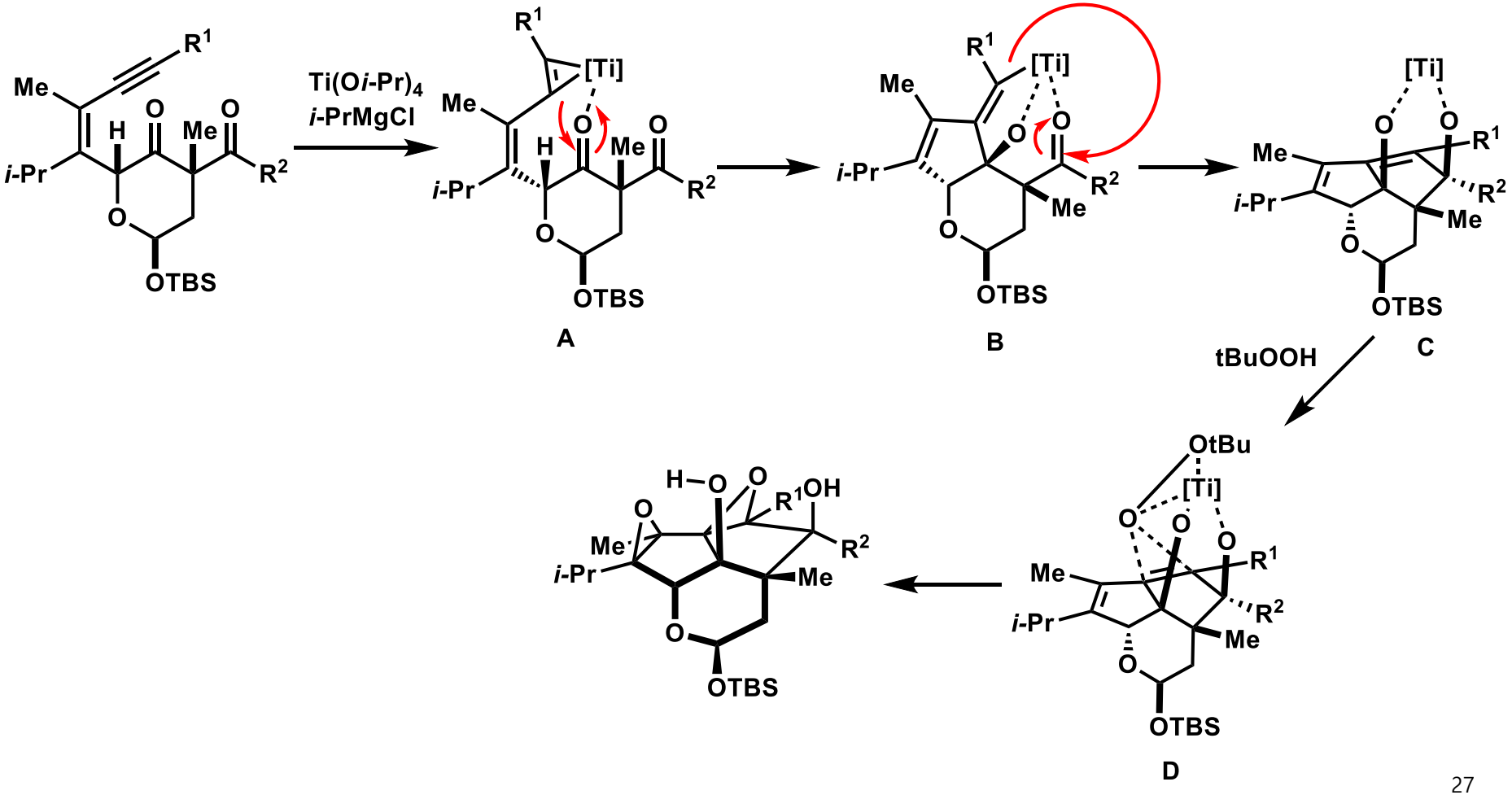
Ti-acyclemediated intramolecular coupling of an alkyne and a 1,3-diketone





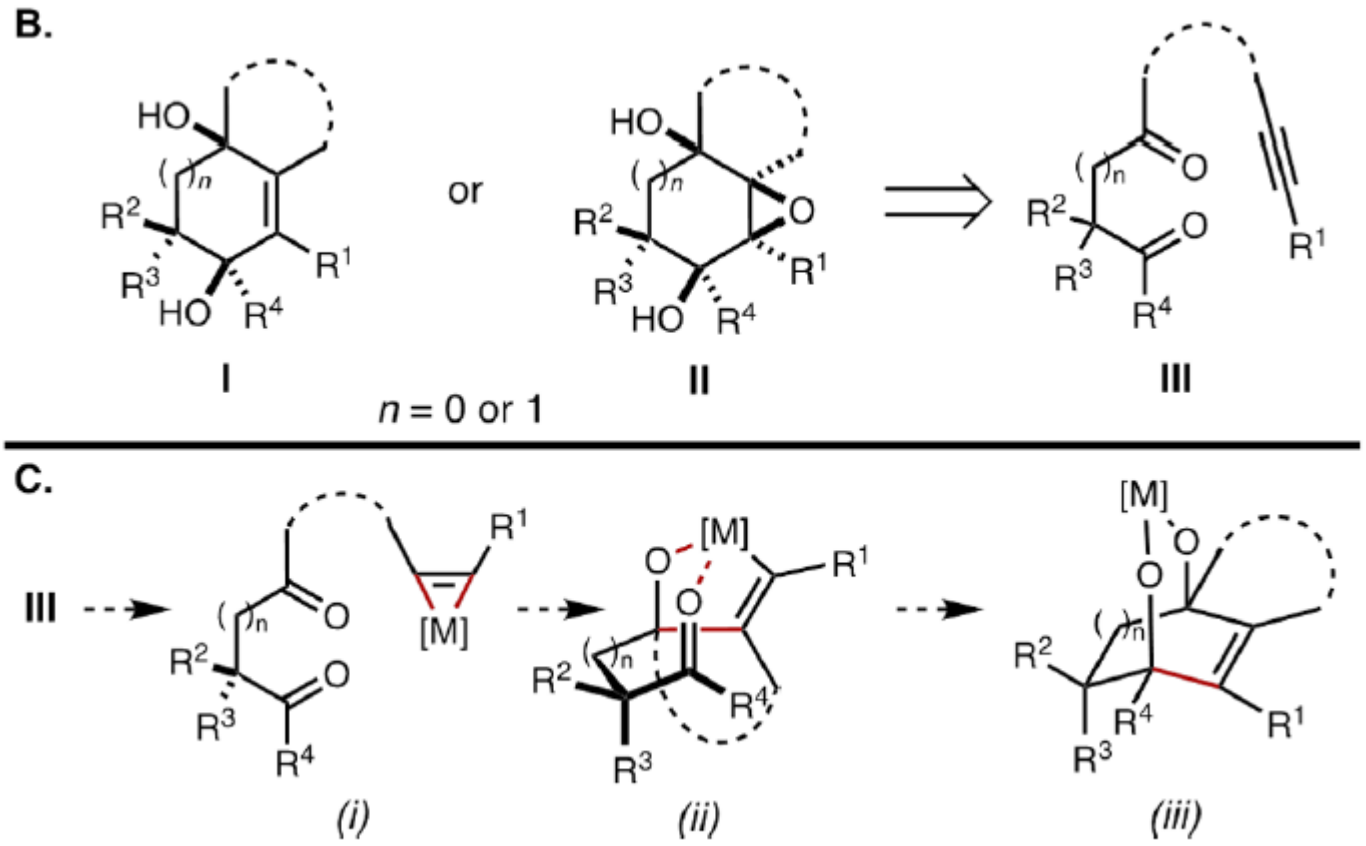
Supporting Materials

Ti-acyclemediated intramolecular coupling of an alkyne and a 1,3-diketone



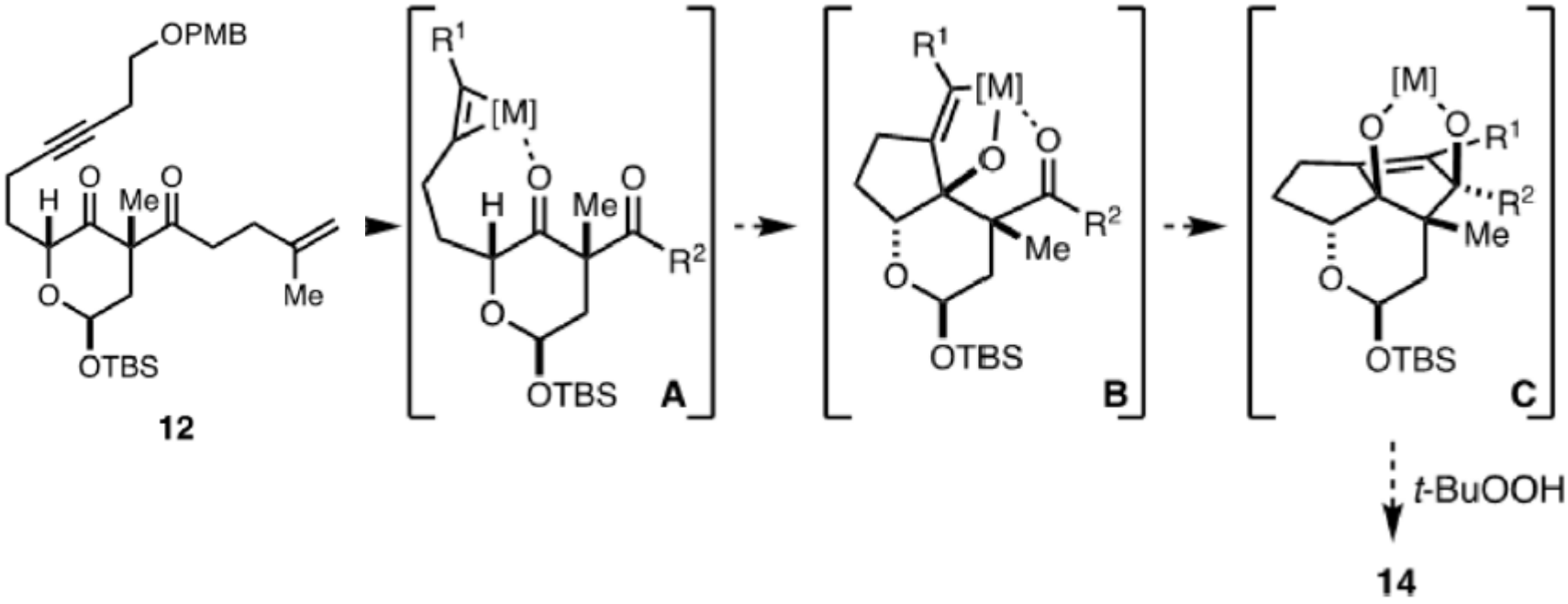
Supporting Materials

Ti-acyclemediated intramolecular coupling of an alkyne and a 1,3-diketone



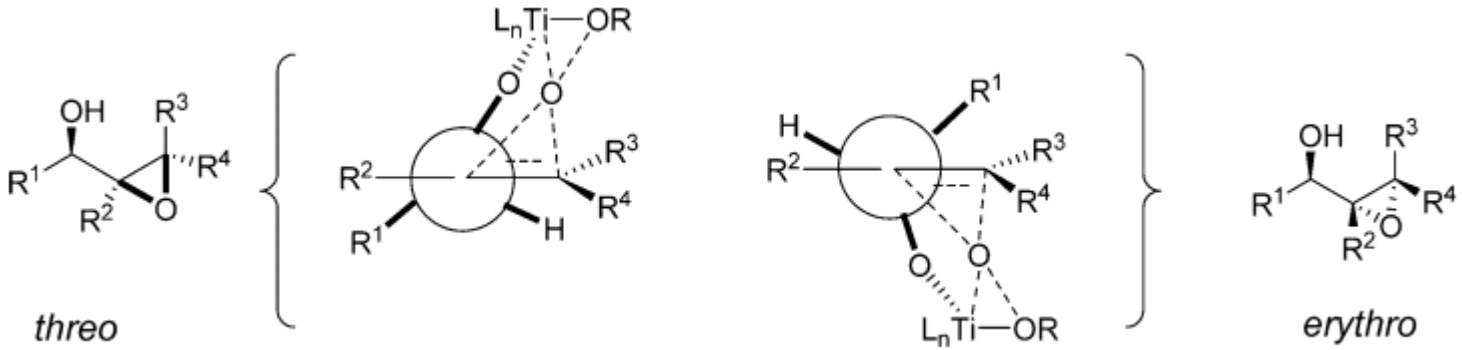
Supporting Materials

Ti-acyclemediated intramolecular coupling of an alkyne and a 1,3-diketone



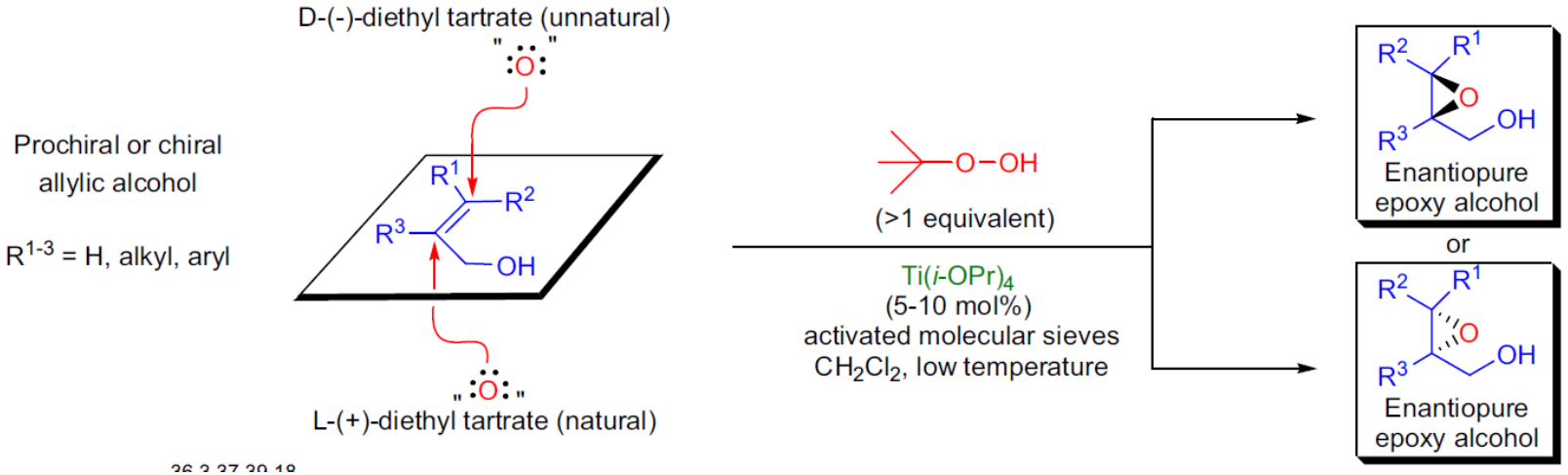
Supporting Materials

Ti-mediated epoxidation

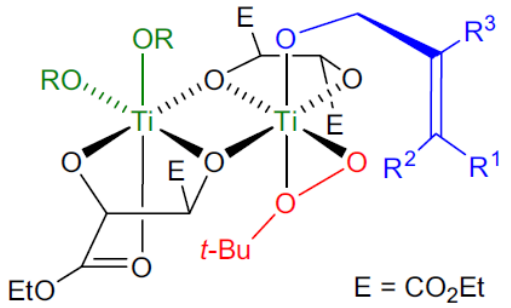


Supporting Materials

SHARPLESS ASYMMETRIC EPOXIDATION



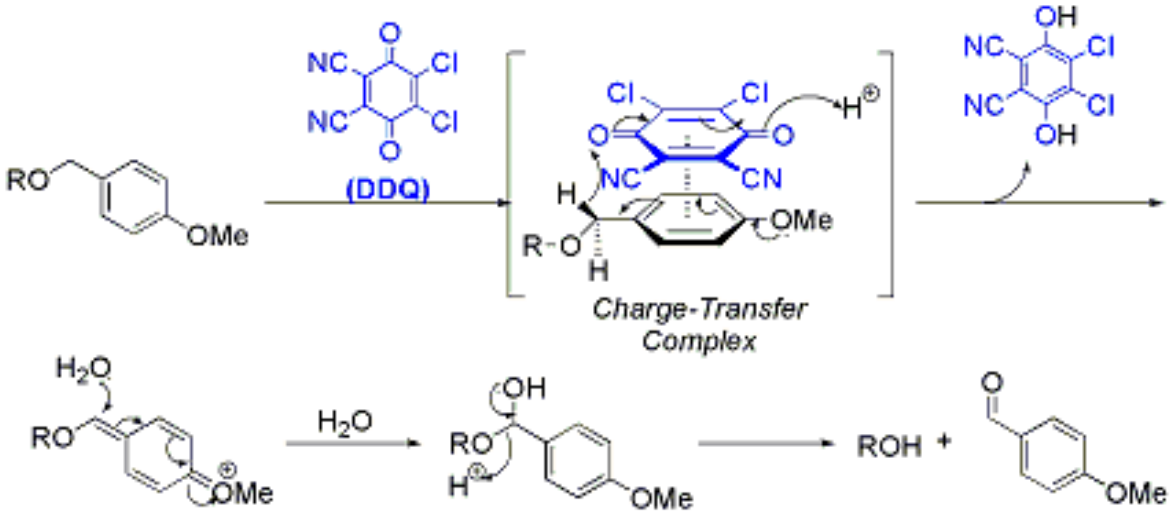
Transition state of epoxidation:



$$\text{Rate} = \frac{[\text{Ti}(\text{O}i\text{-Pr})_2(\text{DET})]\,[\text{TBHP}]\,[\text{ROH}]}{[i\text{-PrOH}]^2}$$

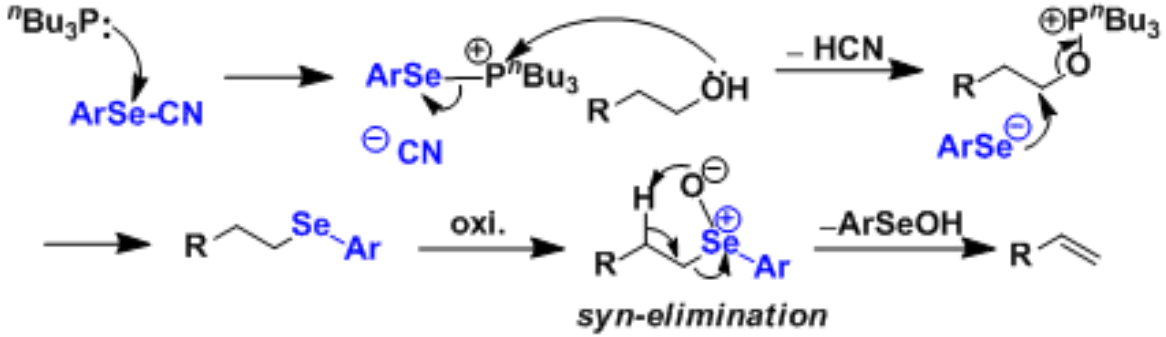
Supporting Materials

Removal of the PMB ether



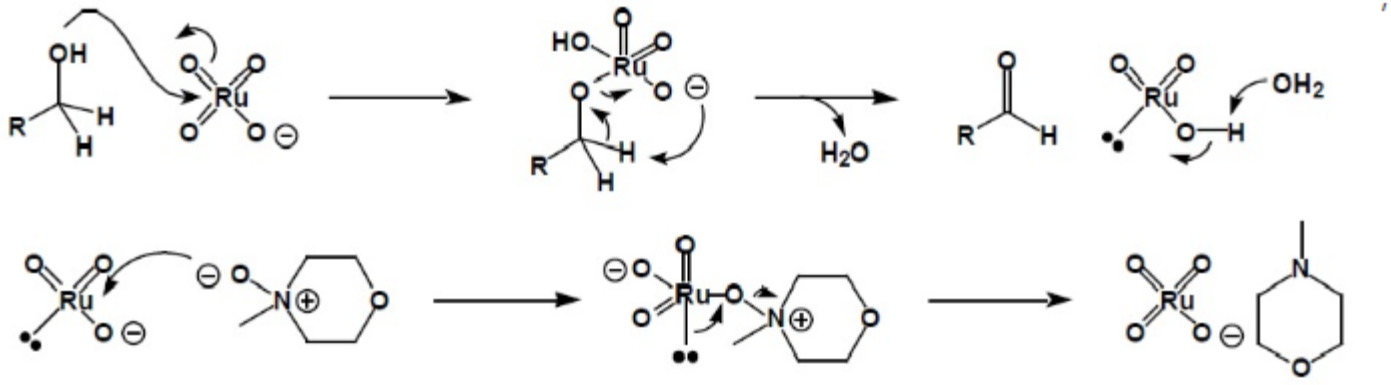
Supporting Materials

Grieco elimination



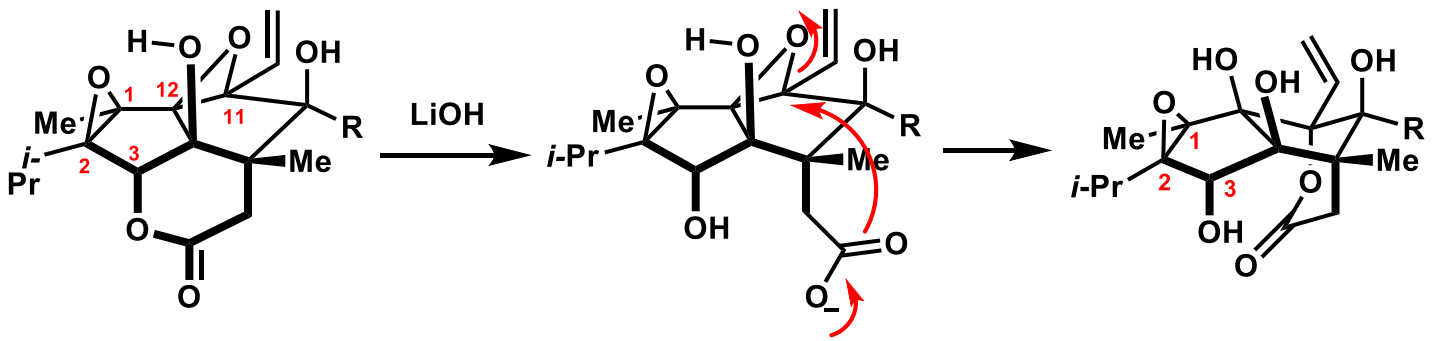
Supporting Materials

Ley oxidation



Supporting Materials

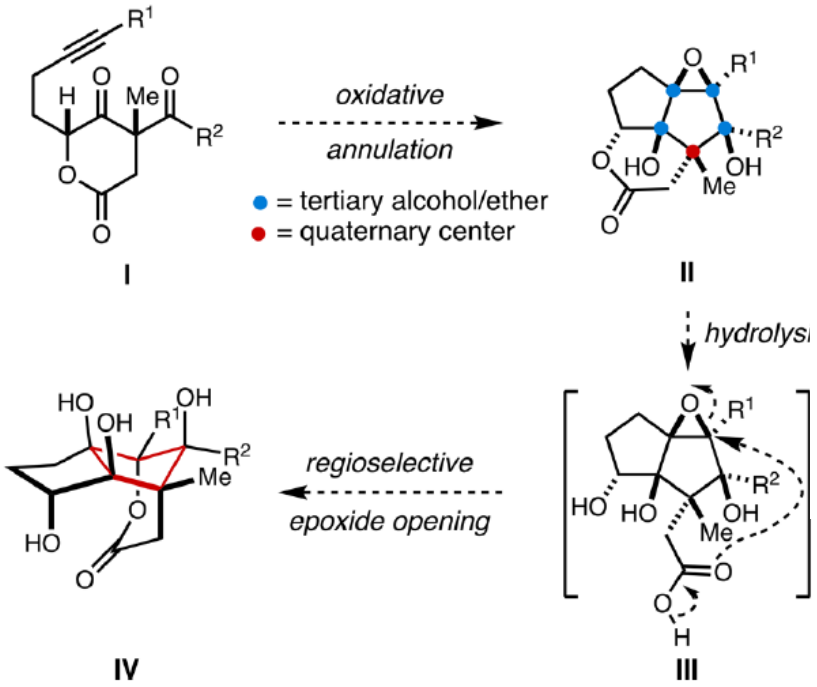
Selective epoxide opening at C11



This molecular transformation presumably begins by lactone hydrolysis fo llowed by regioselective epoxide opening in a stereoelectronically favored **6-exo manner.** Two factors may play a significant role in controlling the regioselectivity for this reaction: **(1) nucleophilic addition at C12 would result in a highly strained trans-fused bicyclo[3.3.0]octane motif,19 an d (2) the C11 position is activated by the neighboring alkene**

Supporting Materials

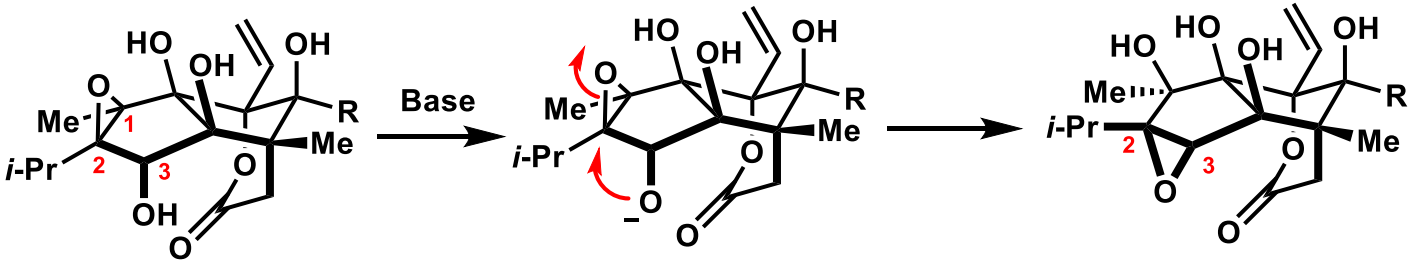
Selective epoxide opening at C11



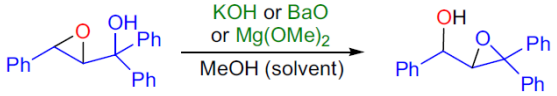
71% overall yield.[6] This molecular transformation presumably begins by lactone hydrolysis followed by regioselective epoxide opening in a stereoelectronically favored 6-exo manner. While both electrophilic sites of the epoxide may participate in a 6-exo ring opening process,[18] two factors may play a significant role in controlling the regioselectivity for this reaction: (1) nucleophilic addition at C12 would result in a highly strained *trans*-fused bicyclo[3.3.0]octane motif,[19] and (2) the C11 position is activated by the neighboring alkene.[20] While those

Supporting Materials

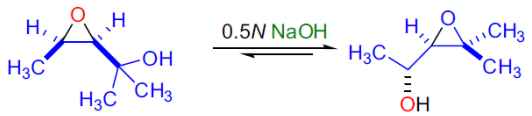
PAYNE REARRANGEMENT



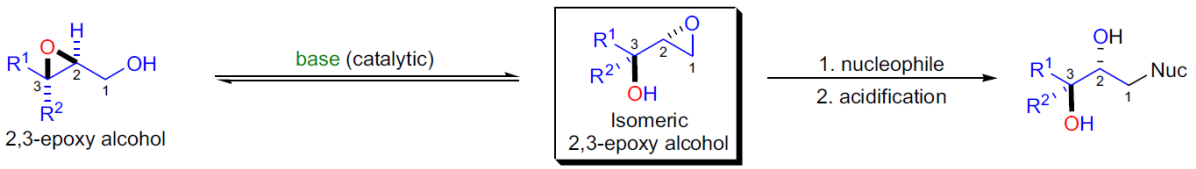
Kohler & Bickel (1935):



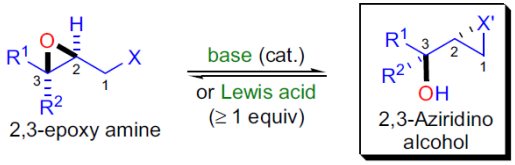
Payne (1962):



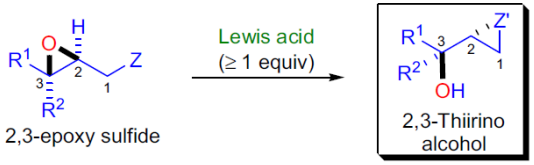
Payne rearrangement followed by nucleophilic epoxide ring-opening:



Aza-Payne rearrangement (can be true equilibrium):



Thia-Payne rearrangement (only forward direction):

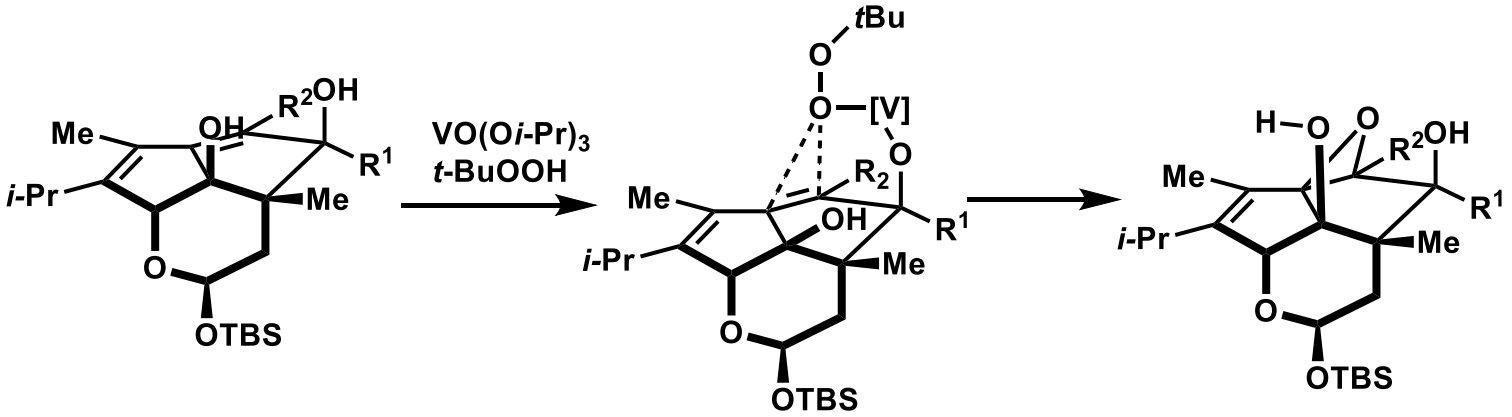


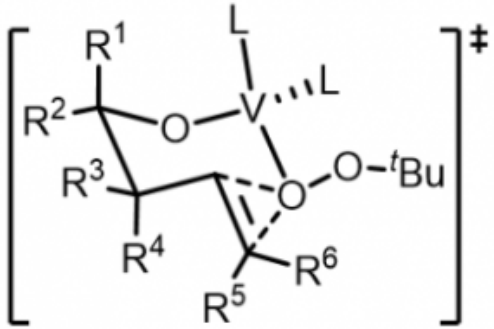
R^{1-2} = H, alkyl, aryl; when X = NR_2, X' = NR_2^+; when X = NHMs, X' = NMs; when Z = SAc, Z' = S; when Z = SR, Z' = SR^+

base: NaOH, KOH, NaOR, NaH, KH; Lewis acid: $AlMe_3$, TMSOTf, $PhB(OH)_2$, $BF_3{\cdot}OEt_2$, $Ti(O\textit{i}\text{-}Pr)_4$

Supporting Materials

Single epoxidation of the C11-C12 alkene

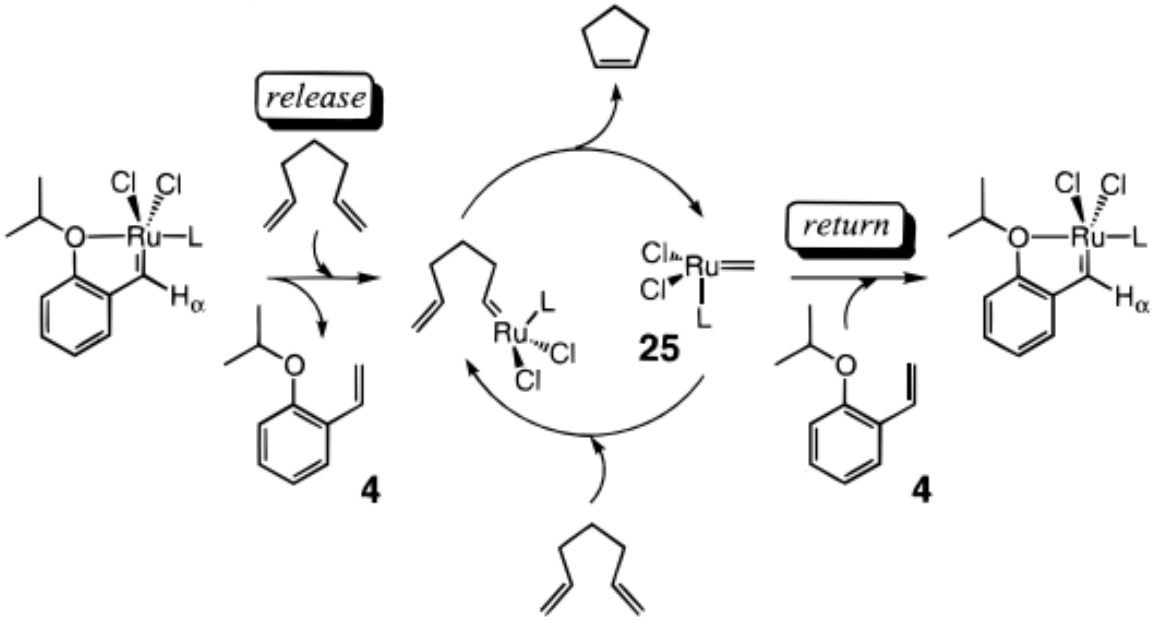




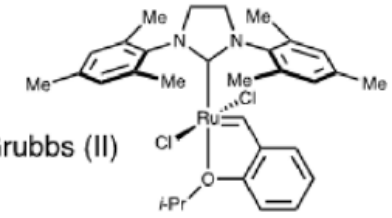
chair-like TS

Supporting Materials

Ring-closing metathesis



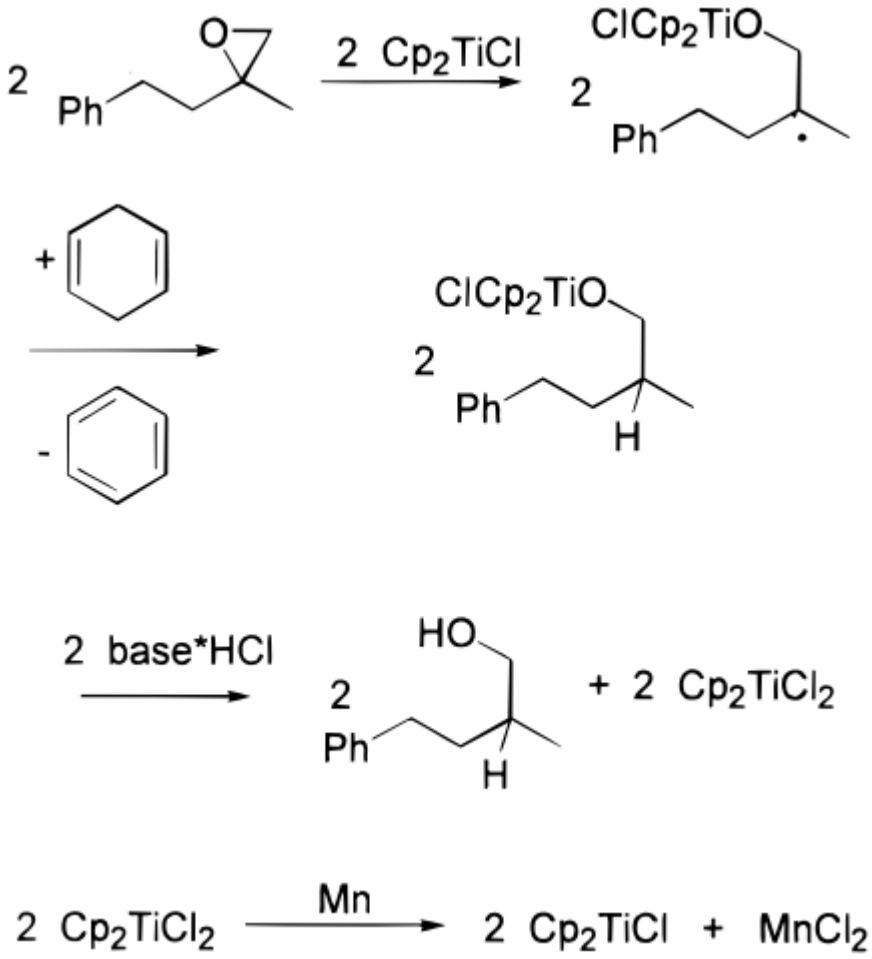
6



Hoveyda–Grubbs (II)

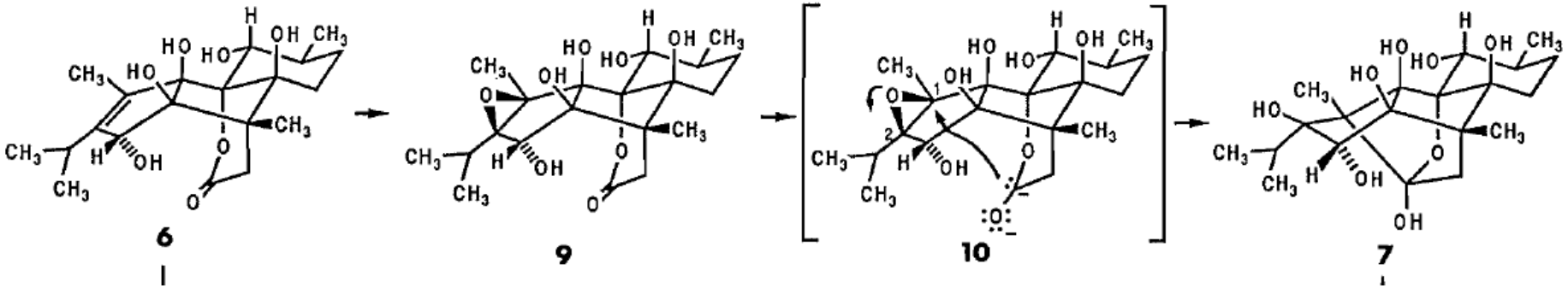
Supporting Materials

Reductive cleavage of epoxide



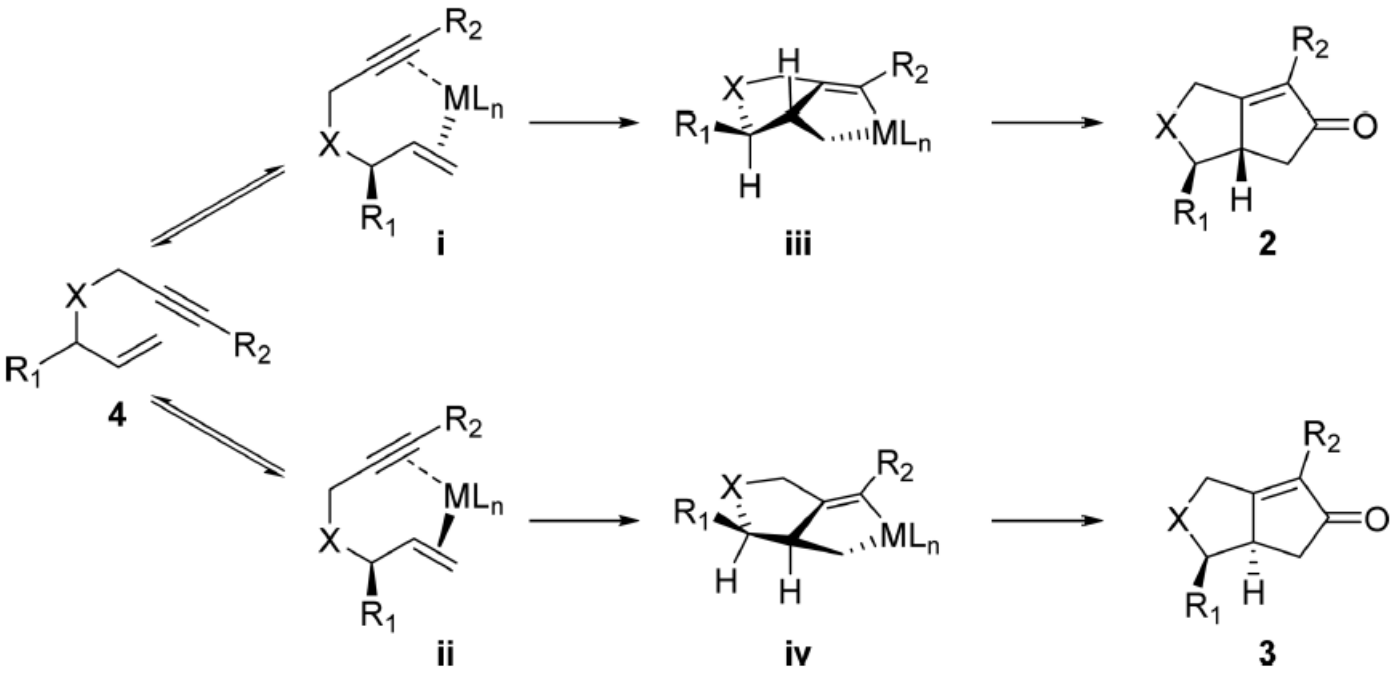
Supporting Materials

Reductive cyclization



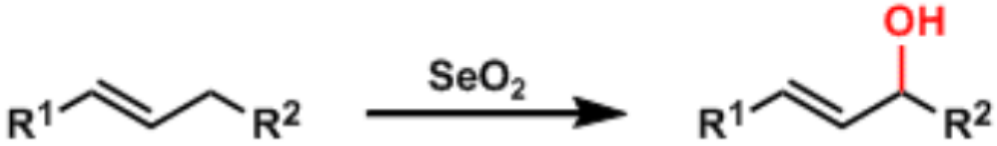
Supporting Materials

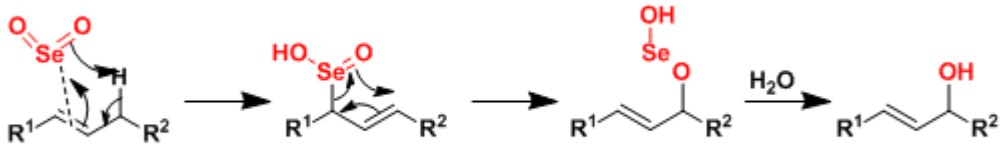
Rh-Catalyst Pauson-Khand Reaction

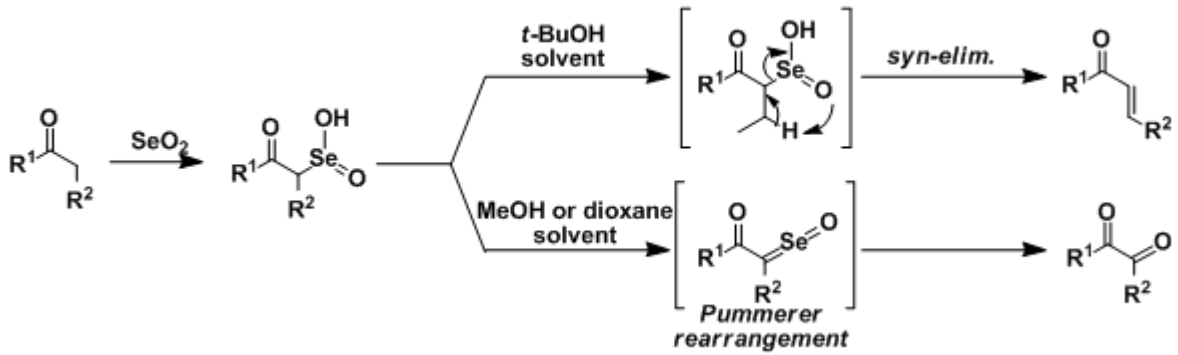


Supporting Materials

Reily oxidation

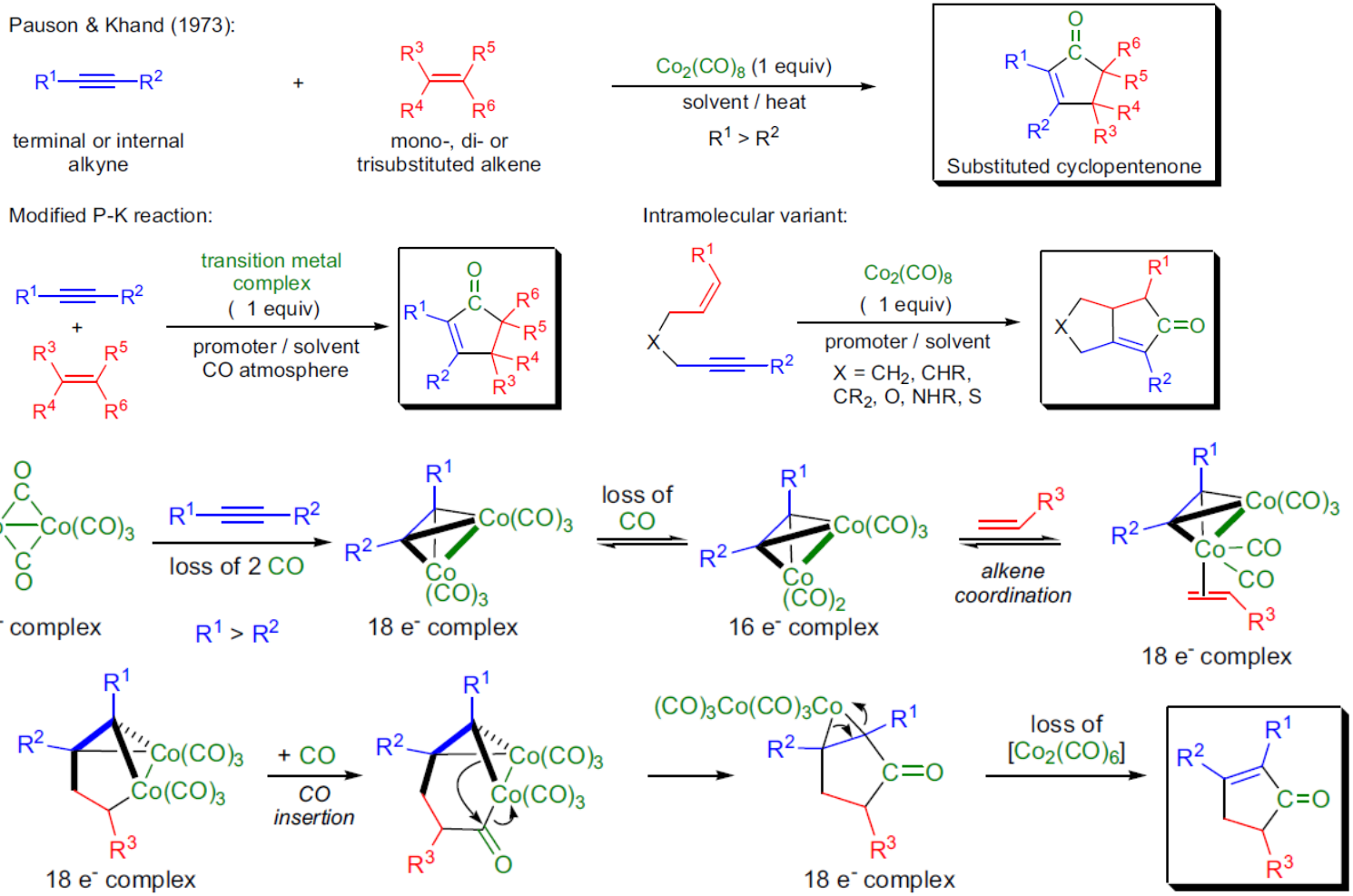






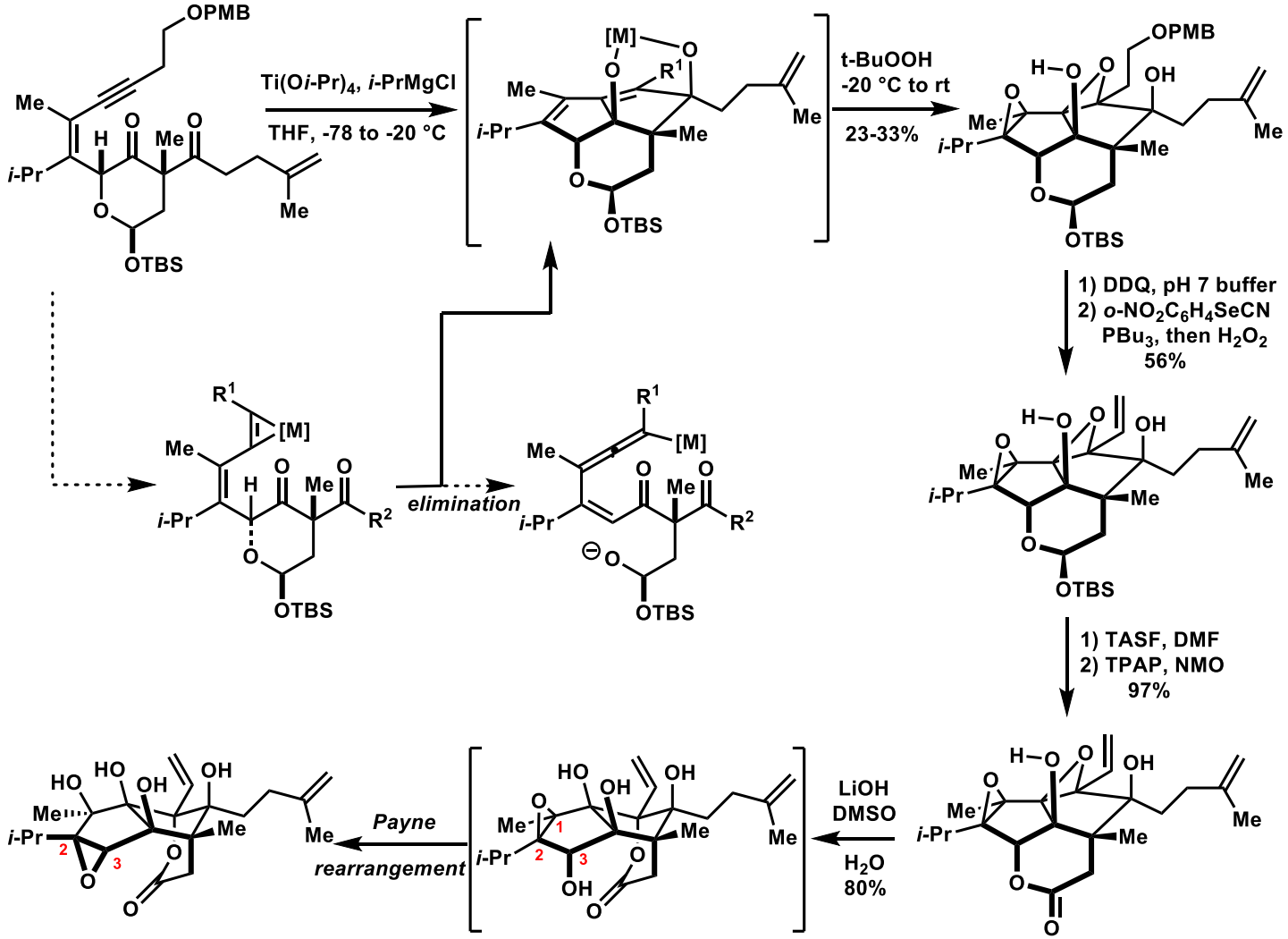
Supporting Materials

Pauson-Khand Reaction



Supporting Materials

Oxidized by singlet oxygen



Supporting Materials

Oxidized by singlet oxygen