Zu Group Meeting

Total Synthesis of Bryostatin 3

Ken Ohmori, Yasuyuki Ogawa,Tetsuo Obitsu,Yuichi Ishikawa, Shigeru Nishiyama, Shosuke Yamamura

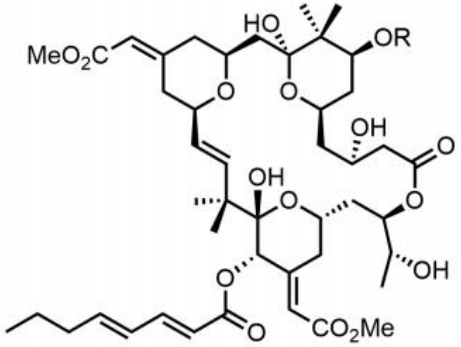
reporter: chenlu
20200612

Introduction

marine bryozoan *bugula neritina*

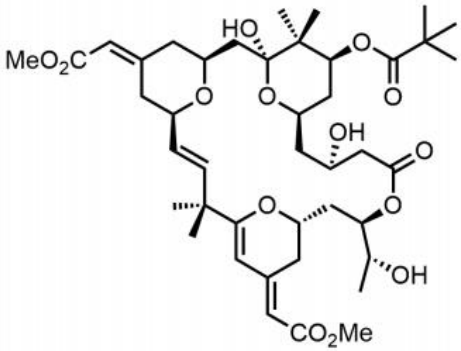
生物活性

1. 有效的抗肿瘤活性
2. 免疫增强活性
3. 诱导突触发育
4. 潜在的HIV调制活性
5. 有益于中风后遗症的治疗
6. 修复血脑屏障
7. 蛋白激酶C激动剂

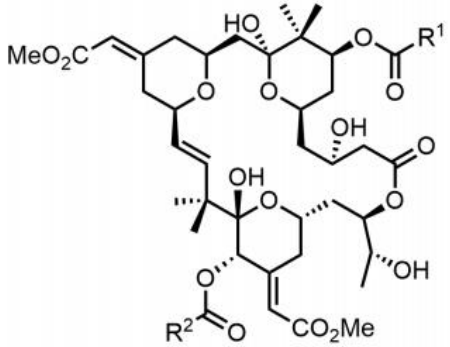


Bryostatin 1: R = Ac, PKC K_i = 1.35 nM
Keck 2011, 31 steps (LLS), 58 steps (TS)
Wender 2017, 19 steps (LLS), 29 steps (TS)

Bryostatin 2: R = H, PKC K_i = 5.86 nM
Evans 1999, 42 steps (LLS), 72 steps (TS)



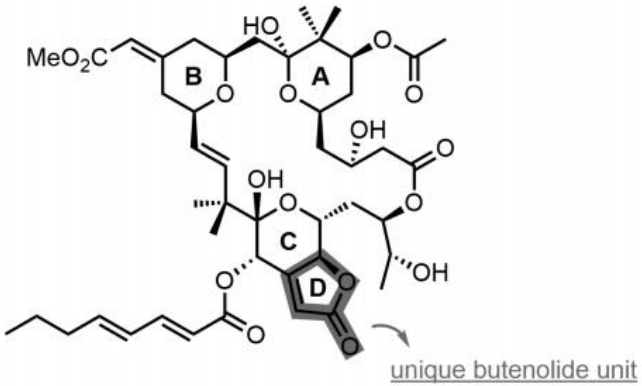
Bryostatin 16: PKC K_i = 118 nM
Trost 2008, 28 steps (LLS), 42 steps (TS)



Bryostatin 7: R^1 = Me, R^2 = Me, PKC K_i = 0.84 nM
Masamune 1990, 41 steps (LLS), 79 steps (TS)
Krische 2011, 20 steps (LLS), 36 steps (TS)

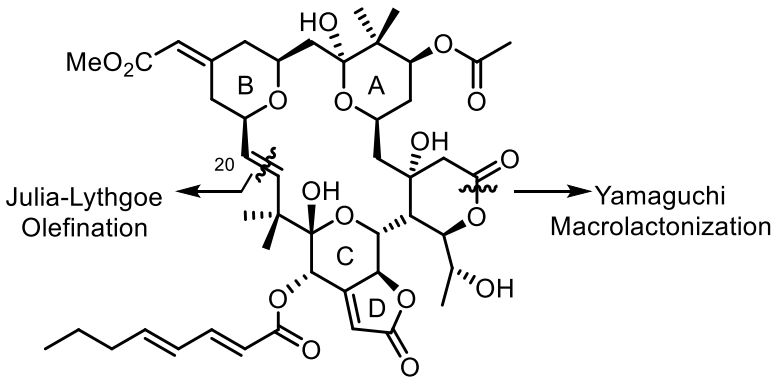
Bryostatin 8: R^1 = ^{n}Pr, R^2 = ^{n}Pr, PKC K_i = 1.72 nM
Song 2018, 29 steps (LLS), 51 steps (TS)

Bryostatin 9: R^1 = Me, R^2 = ^{n}Pr, PKC K_i = 1.31 nM
Wender 2011, 25 steps (LLS), 43 steps (TS)



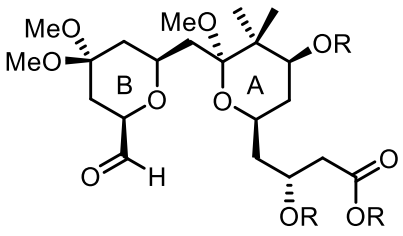
Bryostatin 3: PKC K_i = 2.75 nM
Yamamura 2000, 43 steps (LLS), 88 steps (TS)
This work, 22 steps (LLS), 31 steps (TS)

Retrosynthetic Analysis



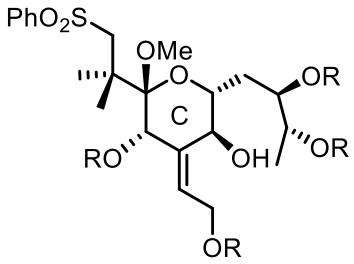
Bryostatin 3

22 steps



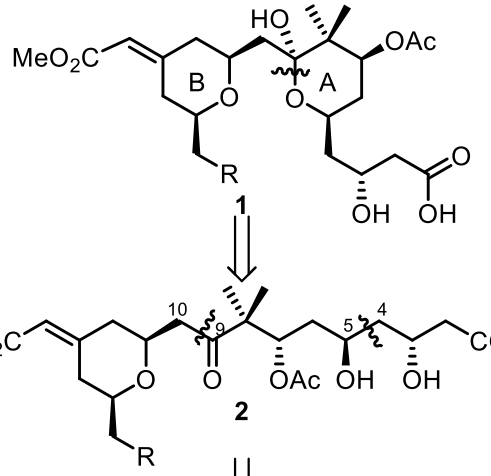
I (29 steps)

Tetrahedron Lett. **1993**, *34*, 4981-4984.



II (37steps)

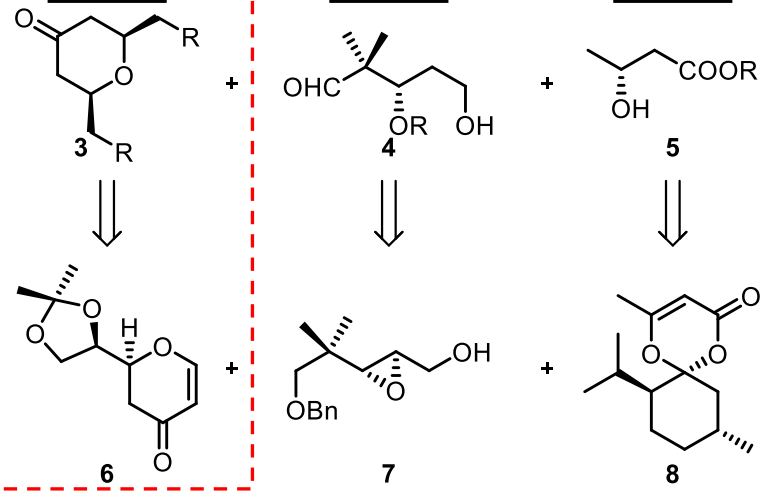
Tetrahedron Lett. **1998**, *39*, 7349-7352.



1

2

C10-C16 | C5-C9 | C1-C4



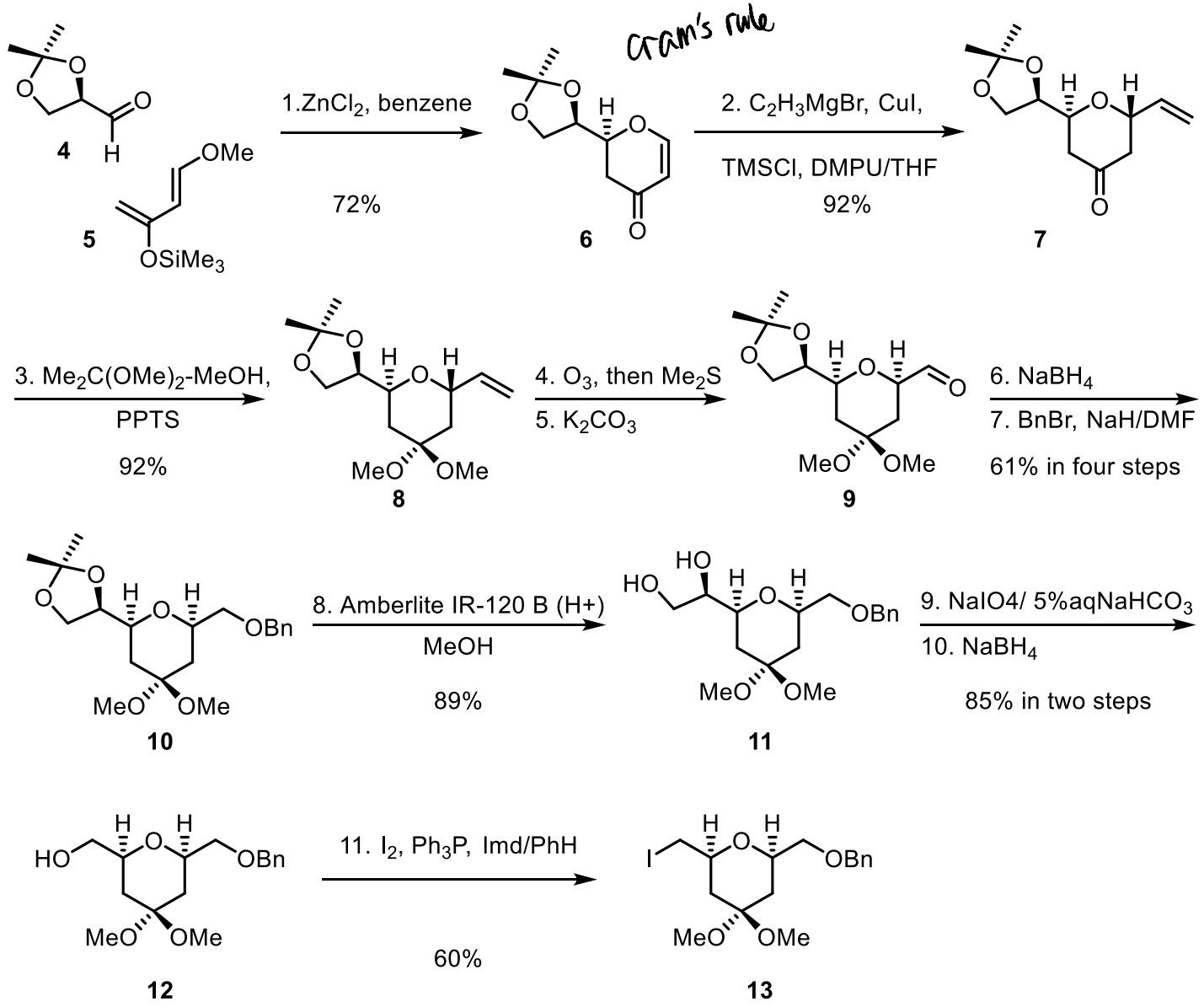
3 **4** **5** **6** **7** **8**

Context

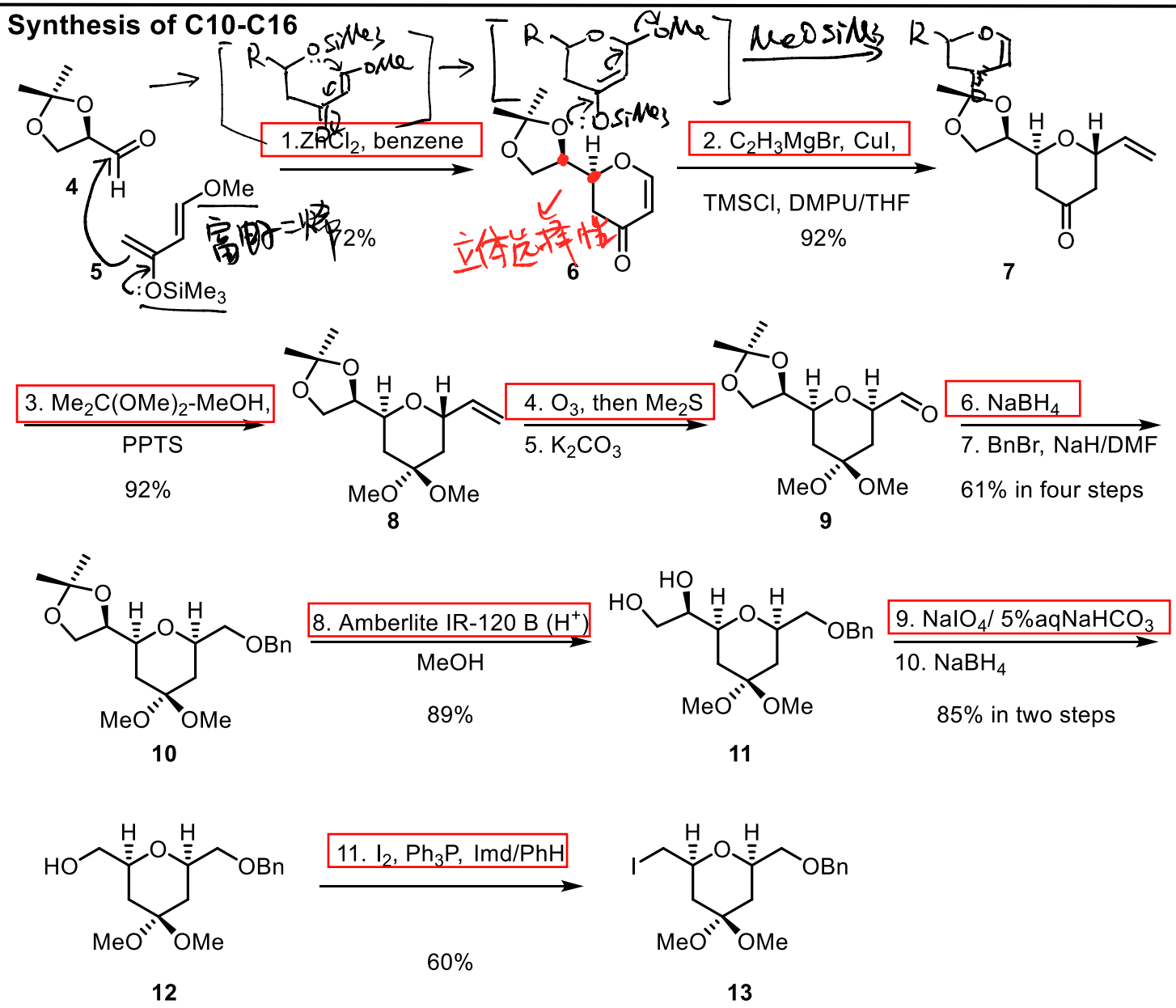
1. Synthesis of the C10-C16 Fragment
2. More Details of Name Reactions
3. Mechanisms of Main Conversions.

Synthesis of the C10-C16 Fragment

Synthesis of C10-C16



Synthesis of the C10-C16 Fragment



Felkin-Anh's Rule and Cram's Chelating Rule

Donald J. Cram
Facts

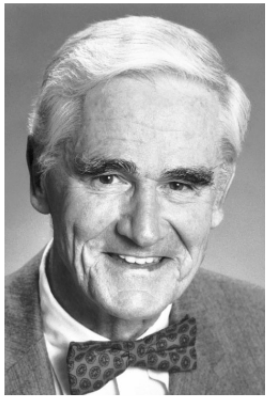


Photo from the Nobel Foundation archive.

Donald J. Cram
The Nobel Prize in Chemistry 1987

Born: 22 April 1919, Chester, VT, USA

Died: 17 June 2001, Palm Desert, CA, USA

Affiliation at the time of the award: University of California, Los Angeles, CA, USA

Prize motivation: "for their development and use of molecules with structure-specific interactions of high selectivity."
具有高选择性的结构特异性相互作用的分子的开发和使用
Prize share: 1/3

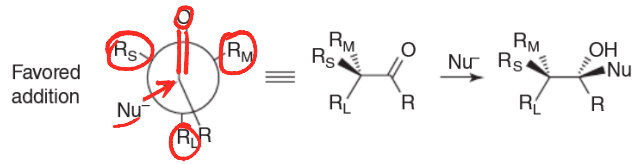


Figure 1 *Cram's model for nucleophilic addition.*

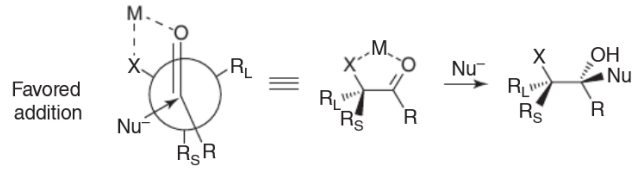


Figure 2 *Cram's chelating model for nucleophilic addition.*

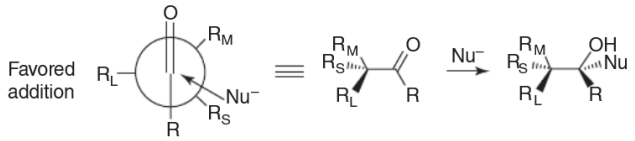
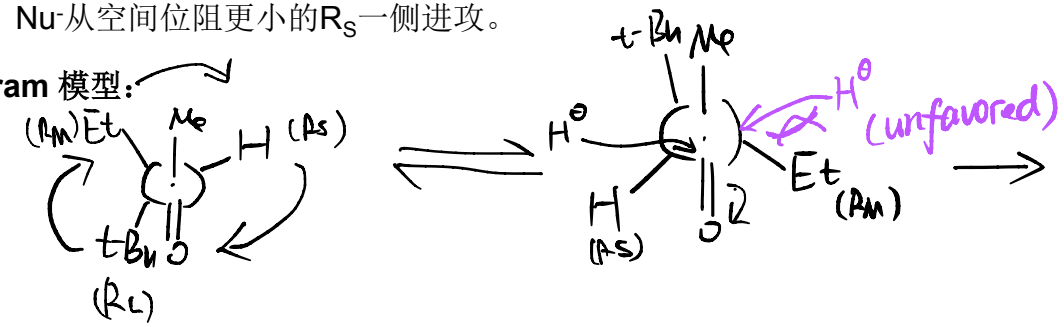


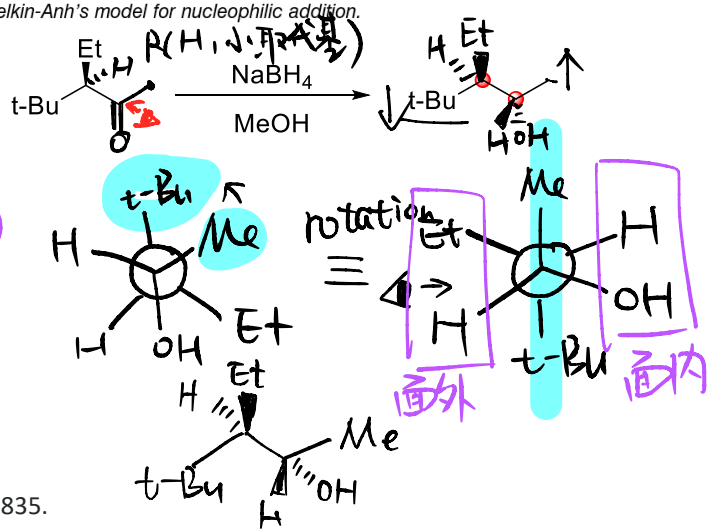
Figure 3 *Felkin-Anh's model for nucleophilic addition.*

Cram 规则：
为了解释和预测亲核试剂对α-手性醛加成的立体选择性
模型特点：

1. α-手性碳上带有"R_L，R_M，R_S"三个基团， 在纽曼投影式中R_L与羰基处于**对位**交叉式。
2. Nu^-从空间位阻更小的R_S一侧进攻。

Cram 模型：





J. Am. Chem. Soc. **1952,** *74* (23), 5828–5835.

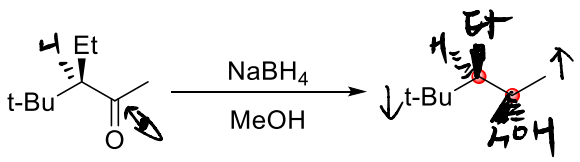
Felkin-Anh's Rule and Cram's Chelating Rule

Felkin-Anh 模型规则：

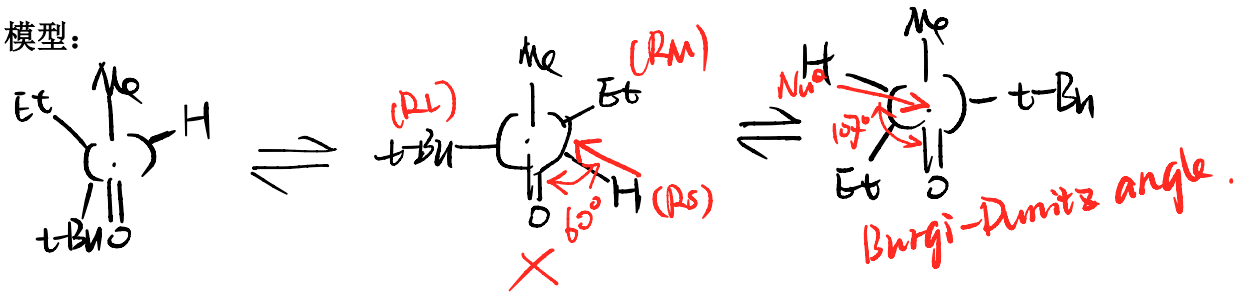
为了解释和预测亲核试剂对α-手性醛酮加成的立体选择性

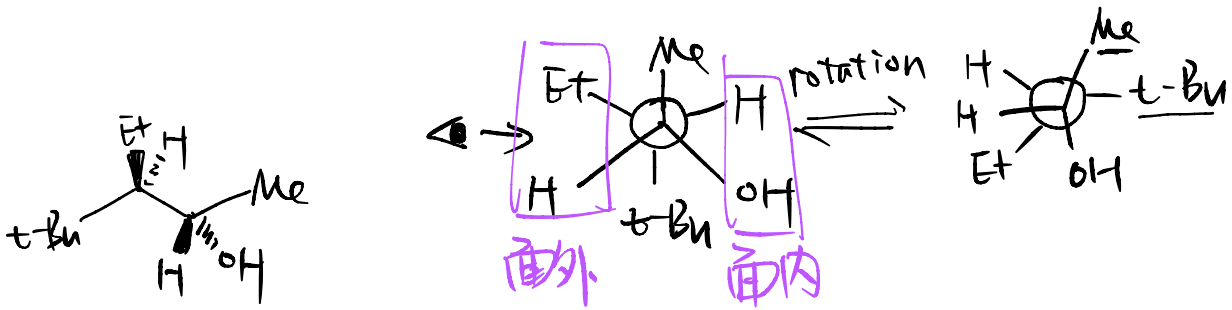
模型特点：

1. 首先画出纽曼投影式的反应构型
2. R_L与羰基处于**垂直**交叉式。
3. Nu^-从空间位阻更小的R_S一侧进攻。
4. Nu^-从Burgi−Dunitz 轨道（107°）进攻。



Felkin-Anh 模型：





Tetrahedron Lett. **1968,** *9* (18), 2199–2204

Felkin-Anh's Rule and Cram's Chelating Rule

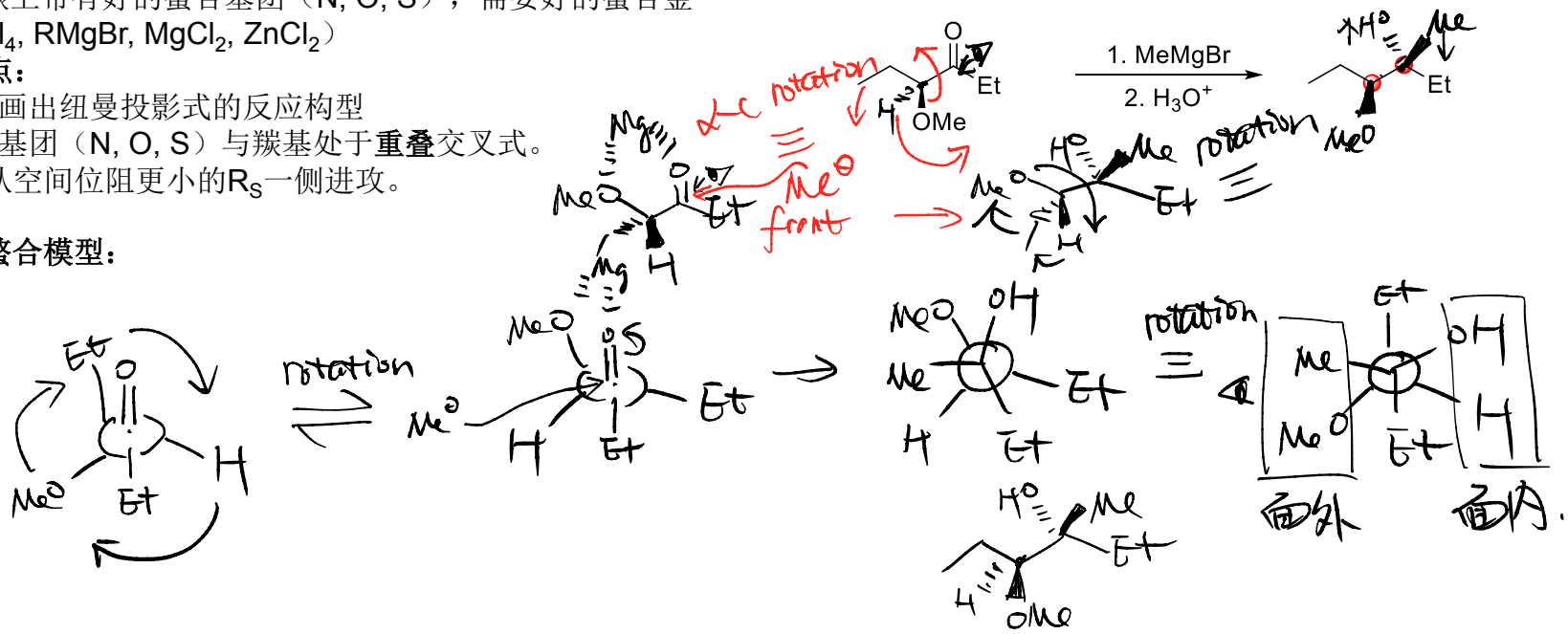
Cram 螯合规则：

α-手性碳上带有好的螯合基团（N, O, S），需要好的螯合金属（$TiCl_4$, RMgBr, $MgCl_2$, $ZnCl_2$）

模型特点：

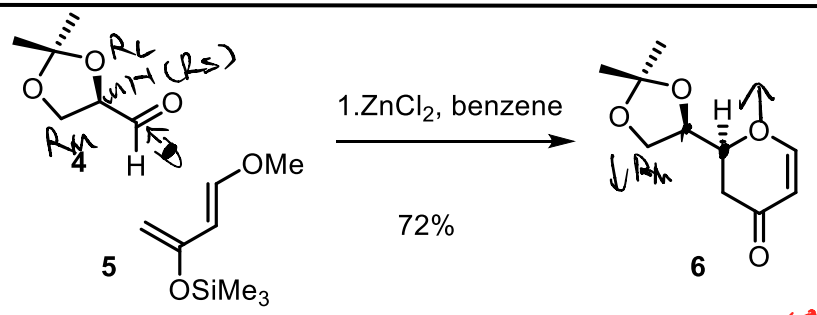
1. 首先画出纽曼投影式的反应构型
2. 螯合基团（N, O, S）与羰基处于**重叠**交叉式。
3. Nu^-从空间位阻更小的R_S一侧进攻。

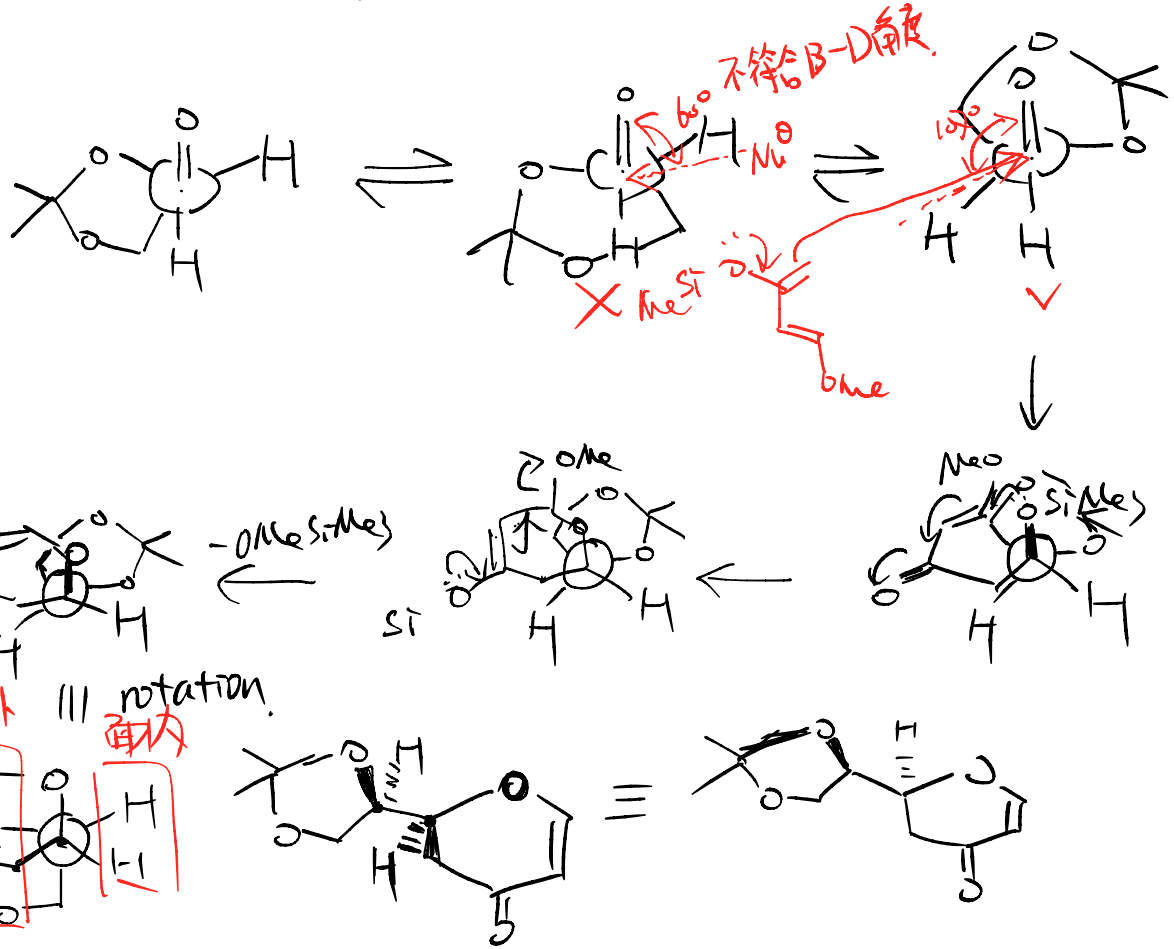
Cram 螯合模型：



J. Am. Chem. Soc. **1952,** *74* (23), 5828–5835.

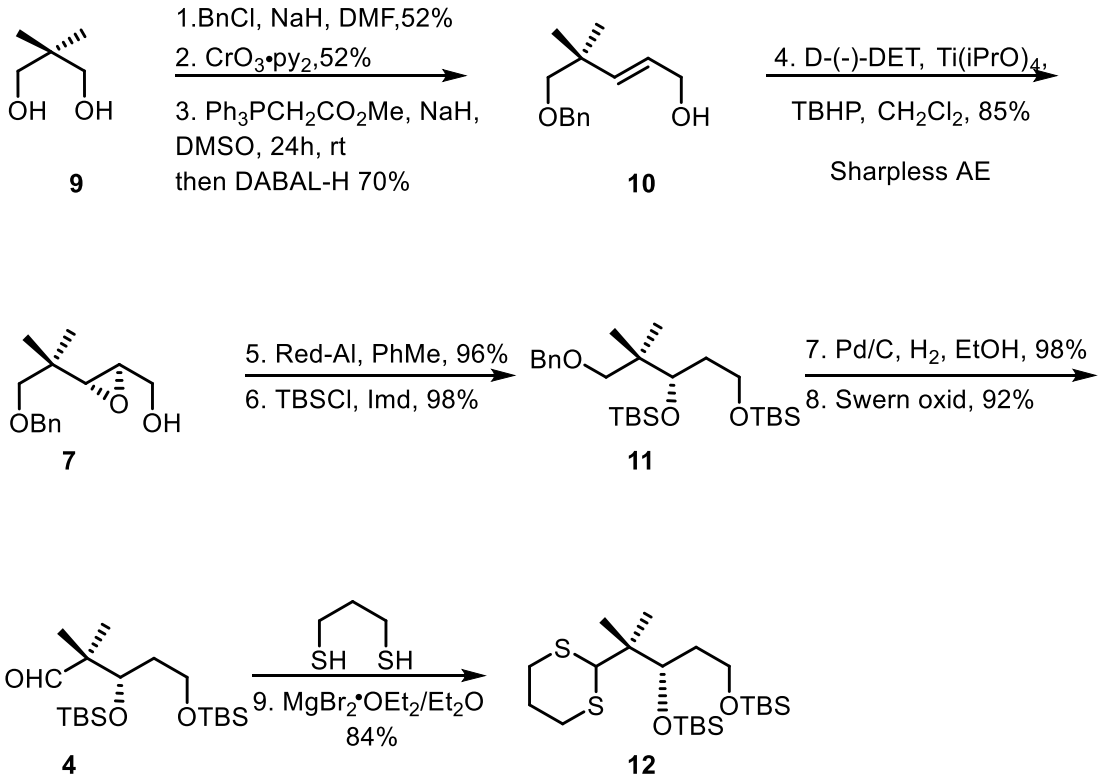
Felkin Anh's Rule and Cram's Chelating Rule





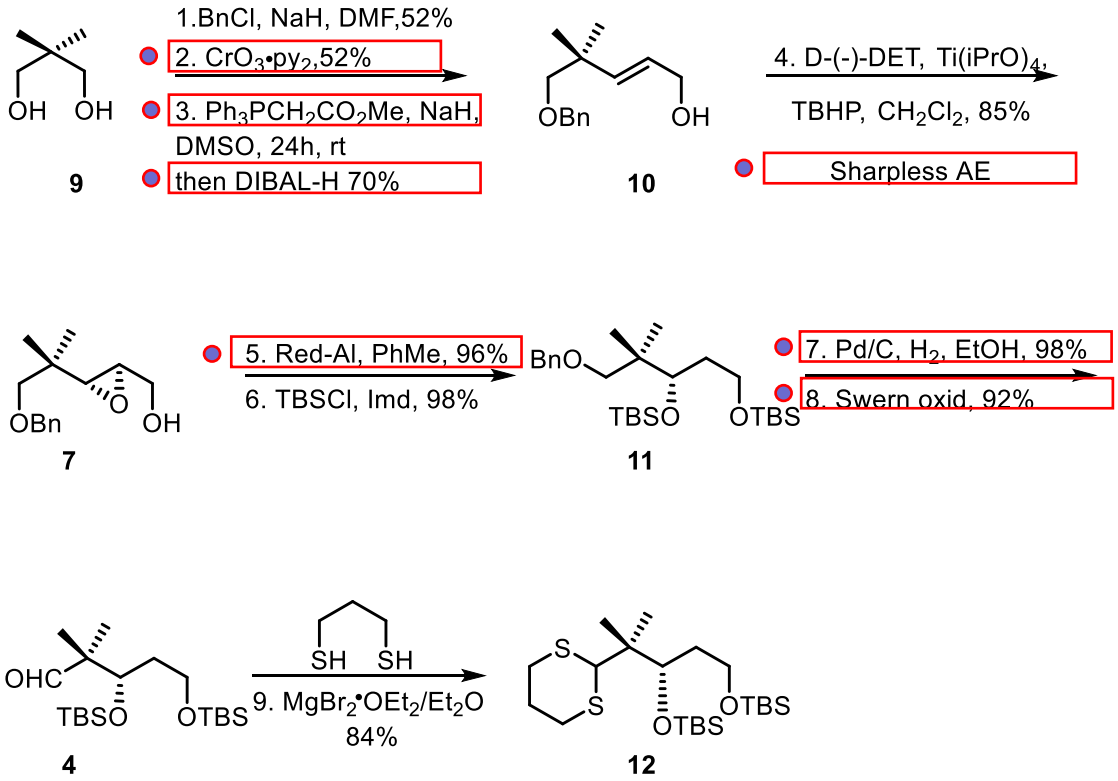
Synthesis of the C5-C9 Fragment

Synthesis of C5-C9

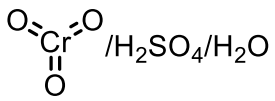


Synthesis of the C5-C9 Fragment

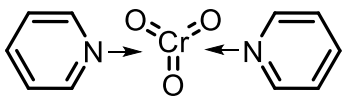
Synthesis of C5-C9



Collins Oxidation



Jones reagent (1946)

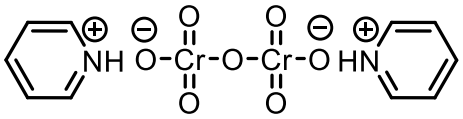


三氧化铬二吡啶

Sarett reagent (1953)

Collins reagent (1968)

(Sarett reagent in CH_2Cl_2)

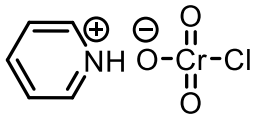


重铬酸吡啶嗡盐

PDC

Coates and Corrigan (1969)

Corey and Schmidt (1979)

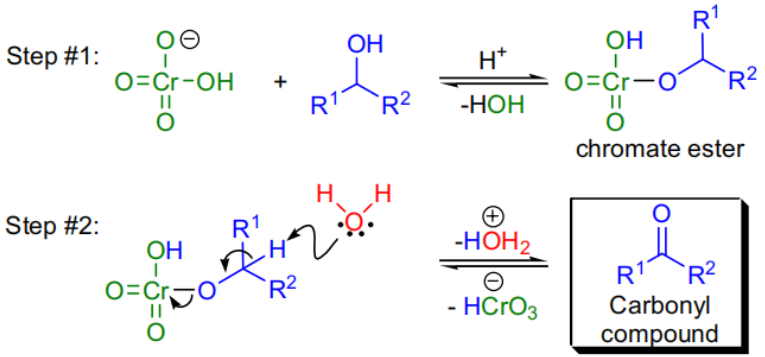


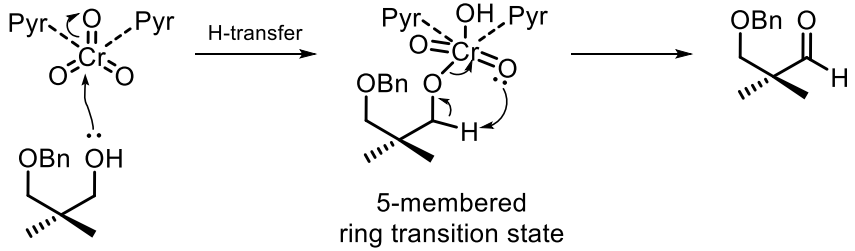
氯铬酸吡啶盐

PCC was first prepared in 1899

Corey and Suggs (1975)

Mechanism





- 铬化合物、特别是六价的铬毒性特别强、所以反应中以及反应后的处理特别需要注意

Oxidation of Alcohols to Aldehydes and Ketones. Tojo., Fernández. *Springer Berlin*, **2006**, 1-97.

Wittig Olefination Reaction

Georg Wittig
Facts

Photo from the Nobel Foundation archive.

Georg Wittig
The Nobel Prize in Chemistry 1979

Born: 16 June 1897, Berlin, Germany

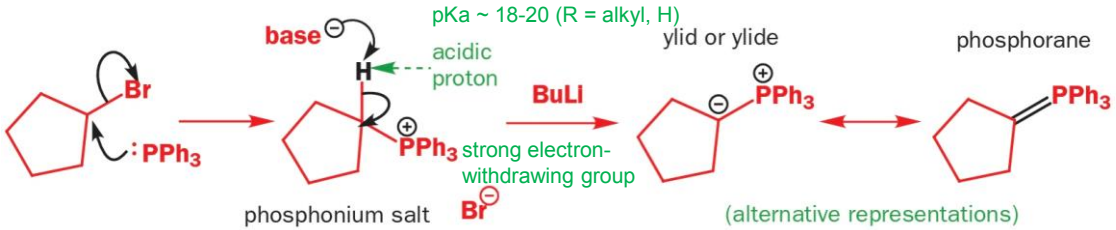
Died: 26 August 1987, Heidelberg, West Germany (now Germany)

Affiliation at the time of the award: University of Heidelberg, Heidelberg, Federal Republic of Germany

Prize motivation: "for their development of the use of boron- and phosphorus-containing compounds, respectively, into important reagents in organic synthesis."

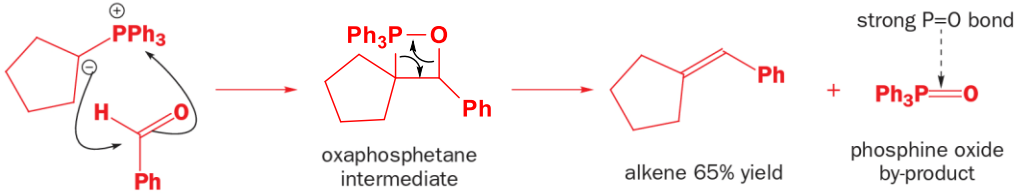
Prize share: 1/2

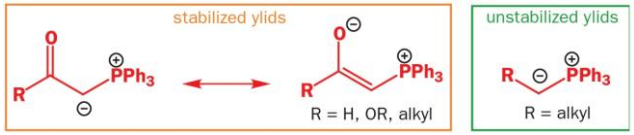
Formation of ylid



base = LDA, PhLi, BuLi, NaH, NHMDS

Mechanism

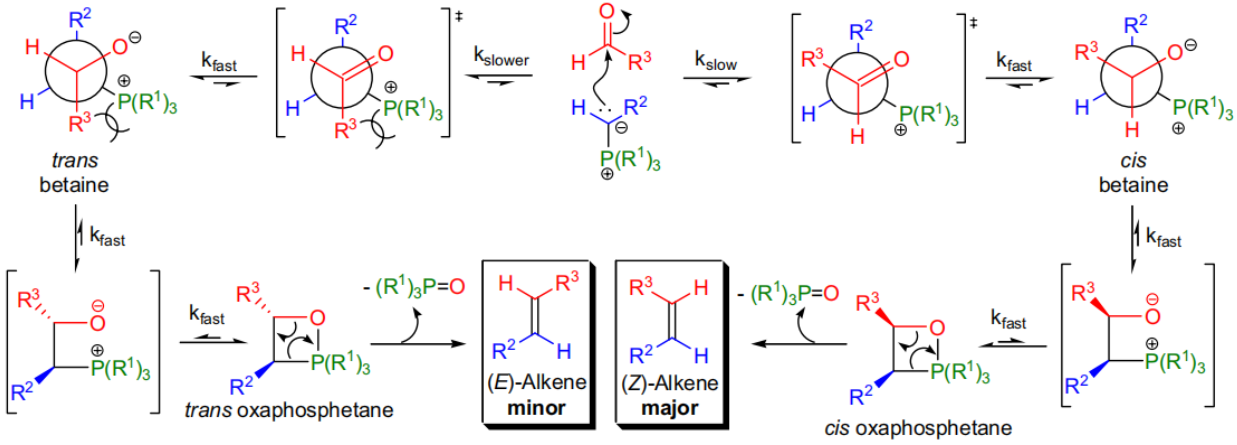




The stereochemistry of the Wittig reaction

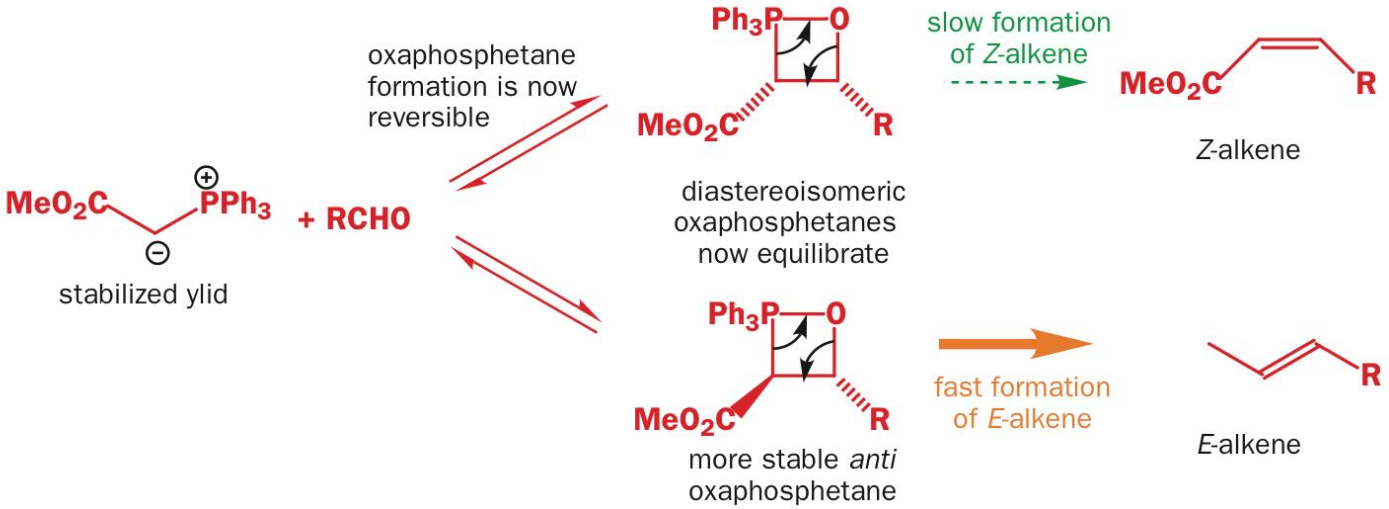
The general rule is:

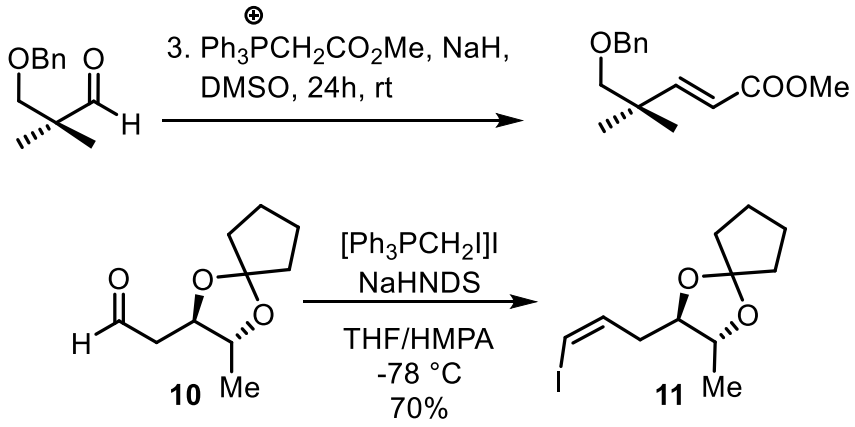
- with *stabilized* ylids the Wittig reaction is *E* selective
- with *unstabilized* ylids the Wittig reaction is *Z* selective



G. Wittig., U. Schöllkopf. *Chem. Ber.***1954**, *87*, 1318.

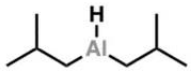
Wittig Olefination Reaction



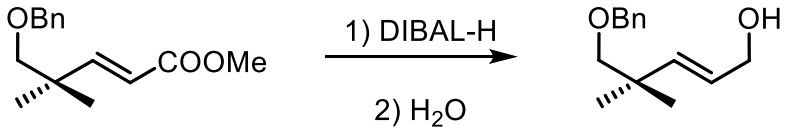


DIBAL-H

DIBAL (Di-isobutyl aluminum hydride)

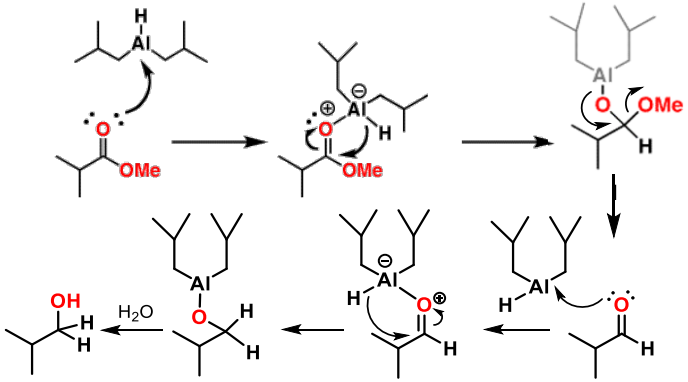


Also known as: DIBAL-H, DIBAH



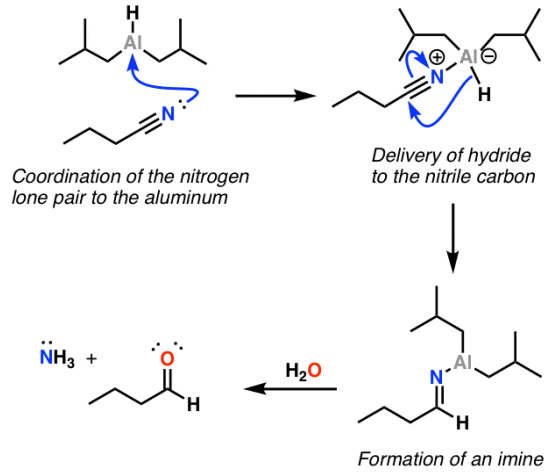
- Reduction Of Esters To Aldehydes
- Reduction Of Ketones And Aldehydes To Alcohols
- Reduction Of Nitriles To Imines
  (And Subsequent Hydrolysis To Aldehydes)

Reduction of ester



This product is stable at low temperatures until water (or acid) is added to quench

Reduction of nitriles



Coordination of the nitrogen lone pair to the aluminum

Delivery of hydride to the nitrile carbon

Formation of an imine

Sharpless Asymmetric Epoxidation

Barry Sharpless Facts

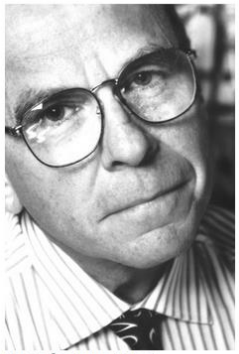


Photo from the Nobel Foundation archive.

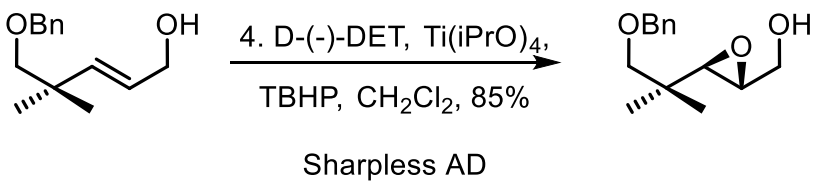
K. Barry Sharpless
The Nobel Prize in Chemistry 2001

Born: 28 April 1941, Philadelphia, PA, USA

Affiliation at the time of the award: The Scripps Research Institute, La Jolla, CA, USA

Prize motivation: "for his work on chirally catalysed oxidation reactions."

Prize share: 1/2



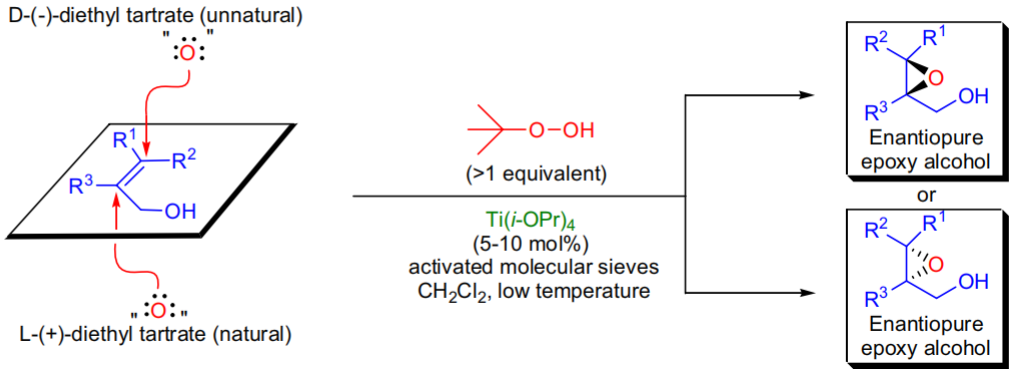
Sharpless AD

反应特点：

1. 只适用于烯丙醇，因为羟基的存在是必须的。
2. 在其它烯烃存在时，烯丙醇能够高化学选择性地发生不对称环氧化。
3. 不对称环氧化过程完全由试剂控制：对于同一烯丙醇底物，左旋和右旋酒石酸酯所得到的环氧产物构型完全相反，具有非常好的面选择性。将烯丙醇的羟基朝右放置于平面上，D-酒石酸酯形成的环氧在平面上方，L-酒石酸酯催化得到的环氧在平面的下方。（无一例外）

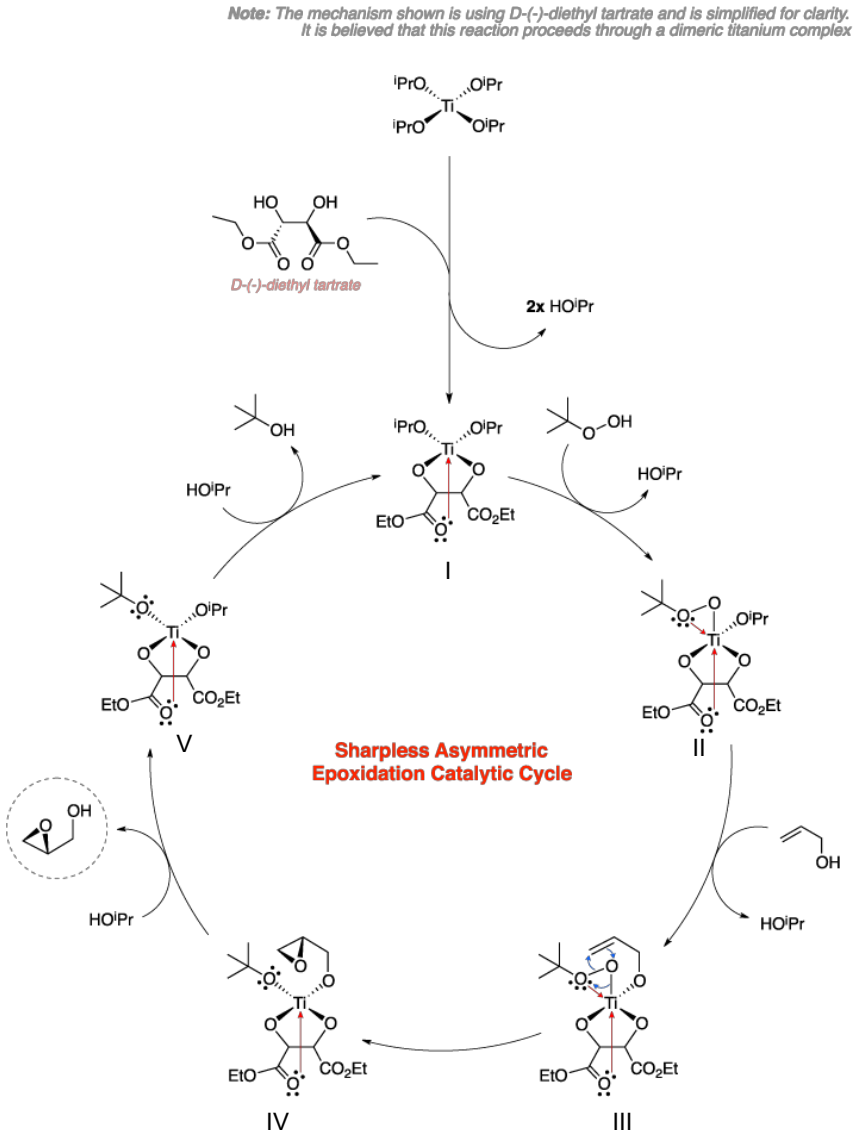
Prochiral or chiral allylic alcohol

R^{1-3} = H, alkyl, aryl

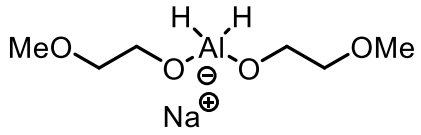


Katsuki, T., Sharpless, K. B. The first practical method for asymmetric epoxidation. *J. Am. Chem. Soc.* **1980**, 102, 5974-5976

Sharpless Asymmetric Epoxidation

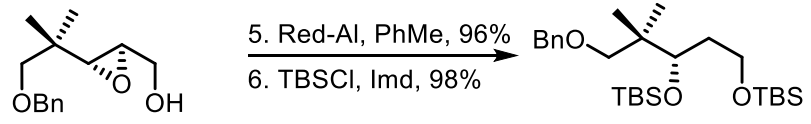


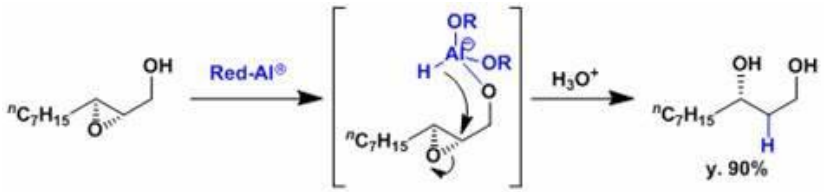
Red-Al

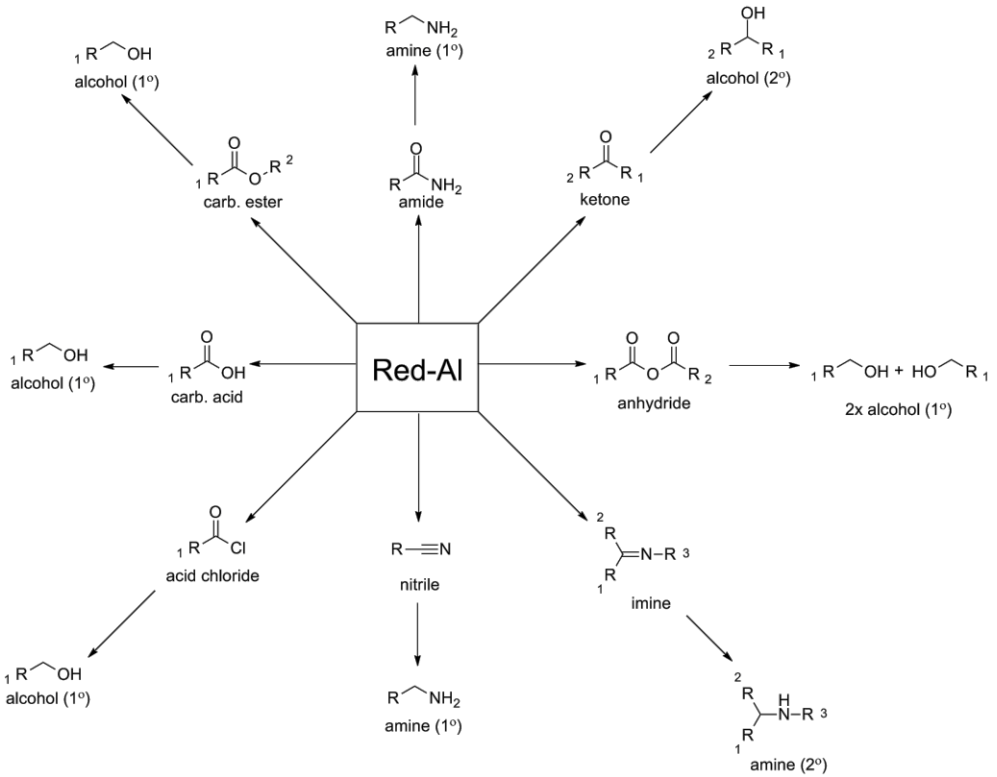


Red-Al, Sodium bis(2-methoxyethoxy)aluminumhydride

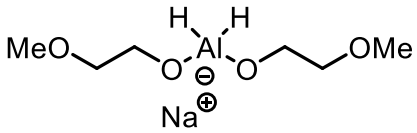
二氢（双-2-甲氧基乙氧基）铝酸钠





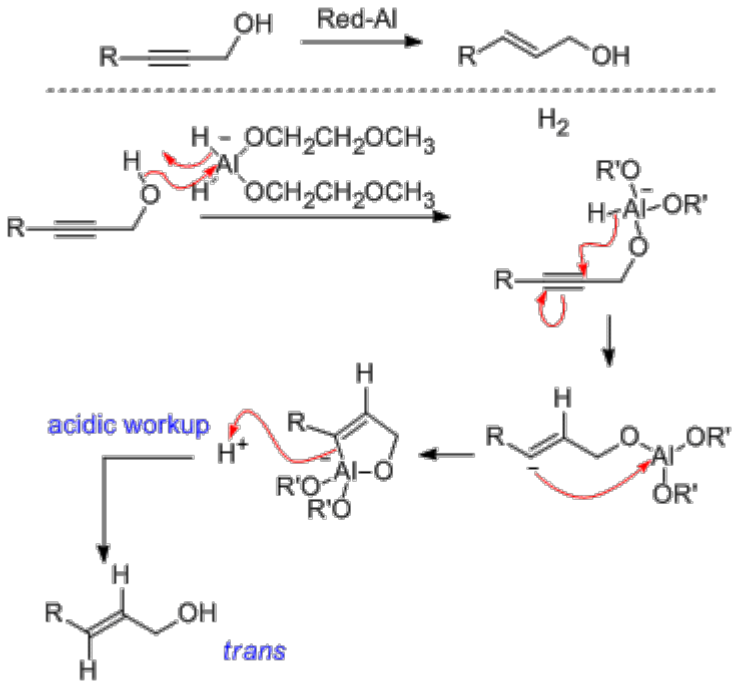


Red-Al

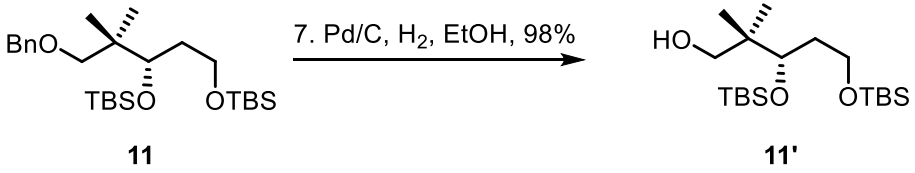


Red-Al, Sodium bis(2-methoxyethoxy)aluminumhydride

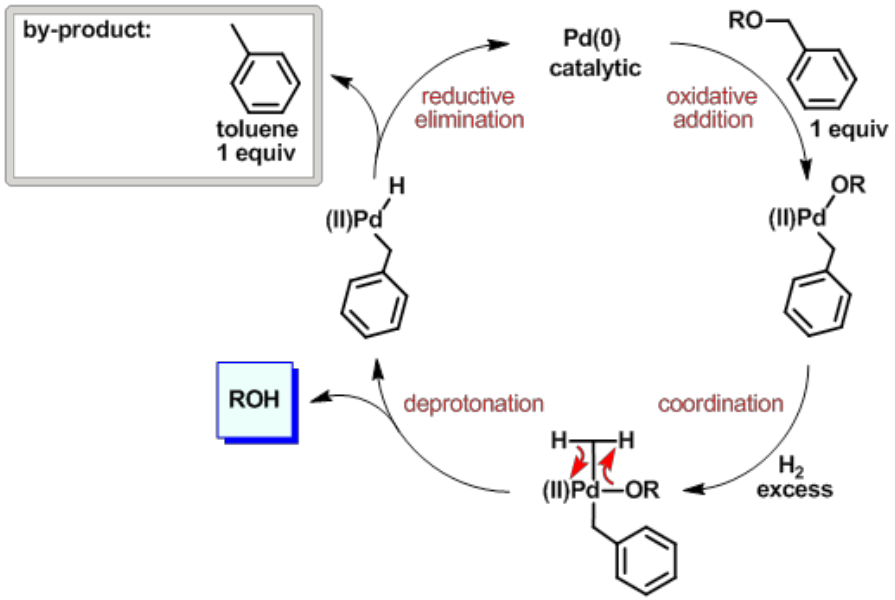
二氢（双-2-甲氧基乙氧基）铝酸钠



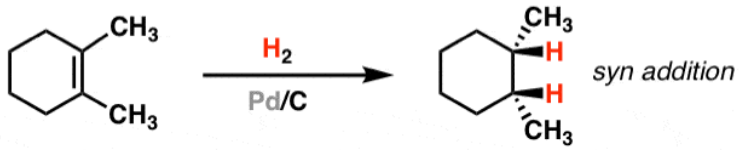
H_2 Pd/C Debenzylation



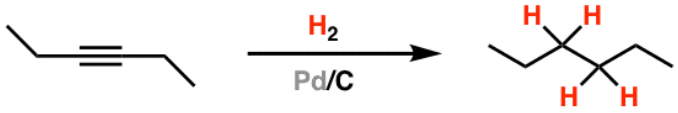
11 **11'**



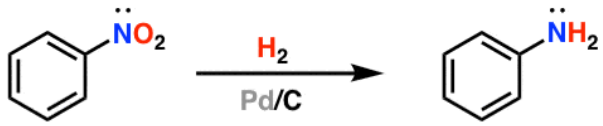
Example 1: Reduction of alkenes



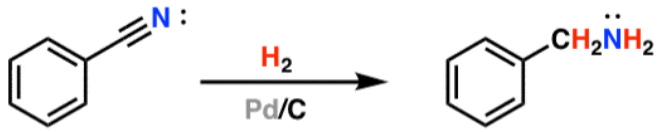
Example 2: Reduction of alkynes



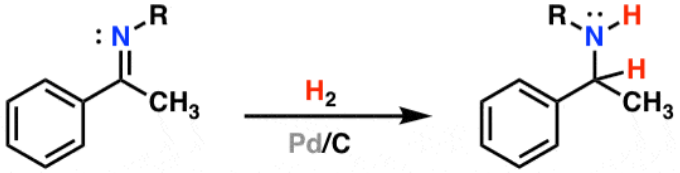
Example 3: Reduction of nitro groups:



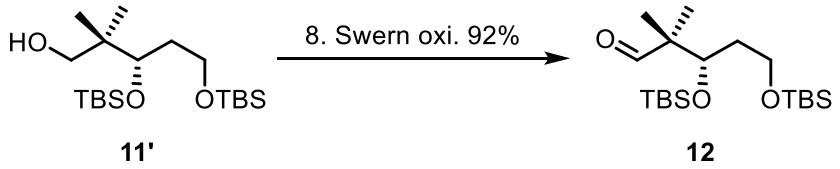
Example 4: Reduction of nitriles



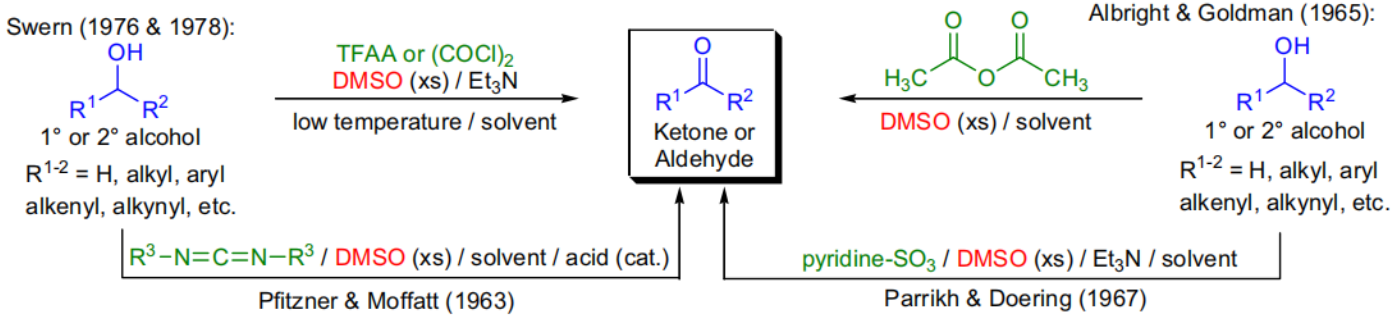
Example 5: Reduction of imines



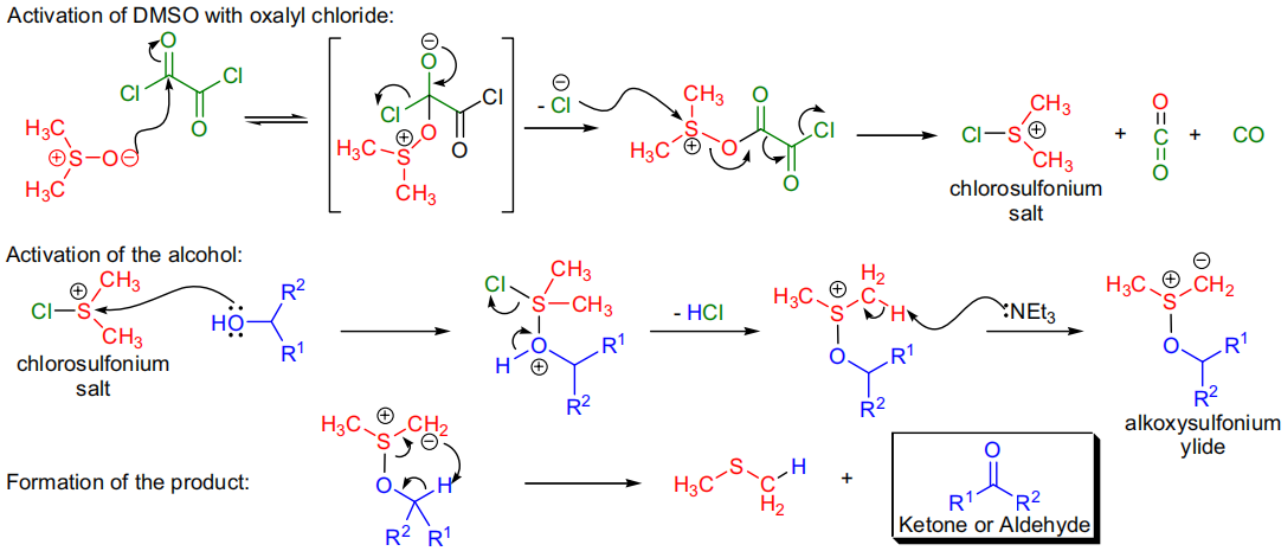
Swern Oxidation



11' **12**



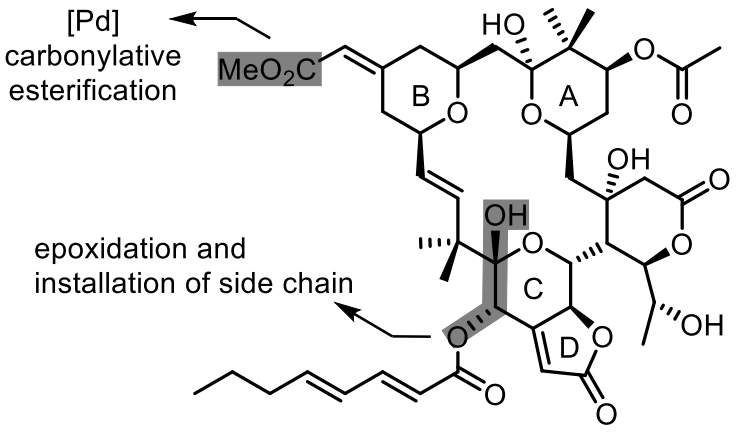
Mechanism



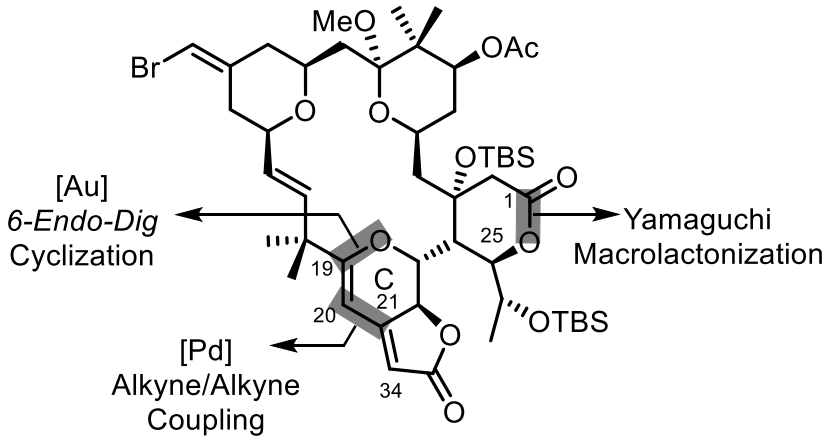
Summary

1. Synthesis of the C5-C9 Fragment
2. Collins Oxidation
3. Wittig Olefination
4. DIBAL-H/Red-Al
5. Sharpless Asymmetric Epoxidation
6. H_2 Pd/C Debenzylation
7. Swern Oxidation

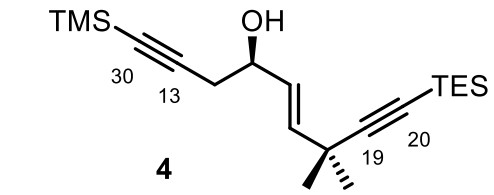
Retrosynthetic Analysis



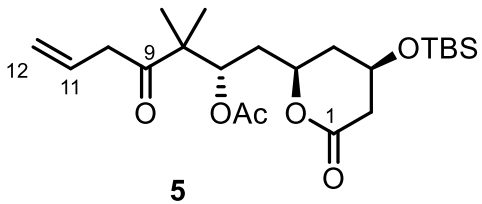
Bryostatin 3



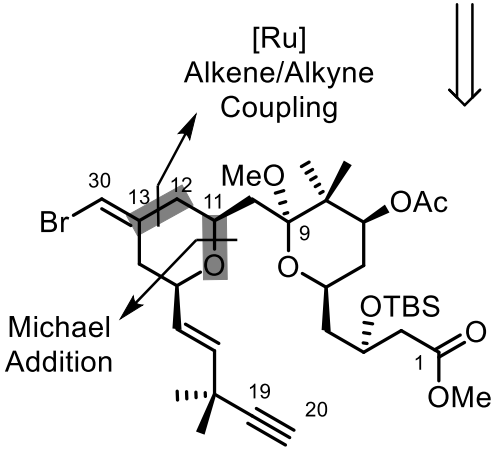
1



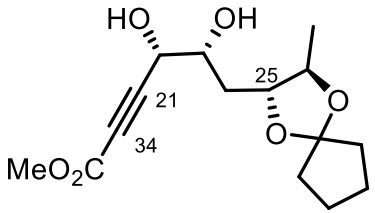
4



5

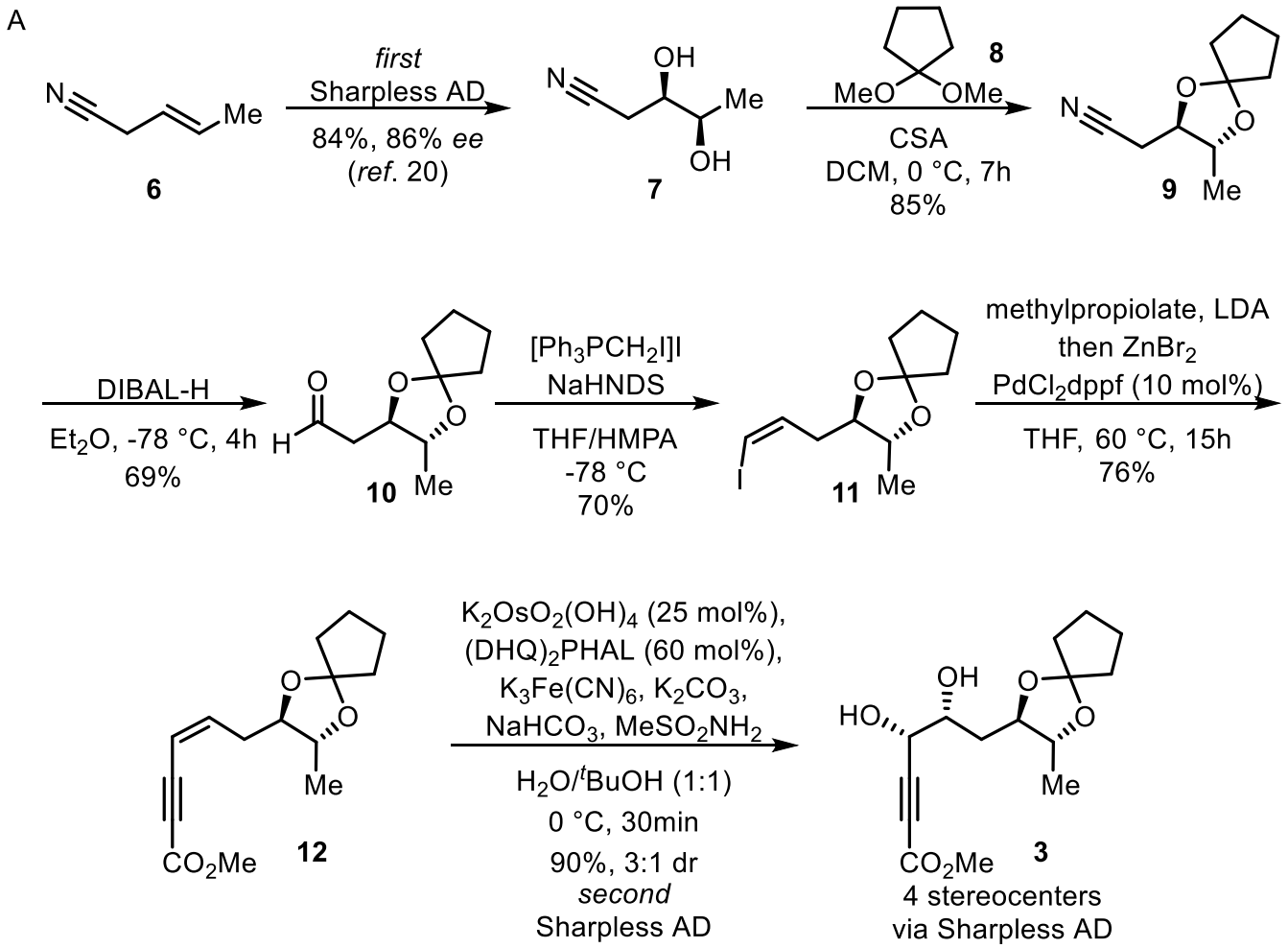


2

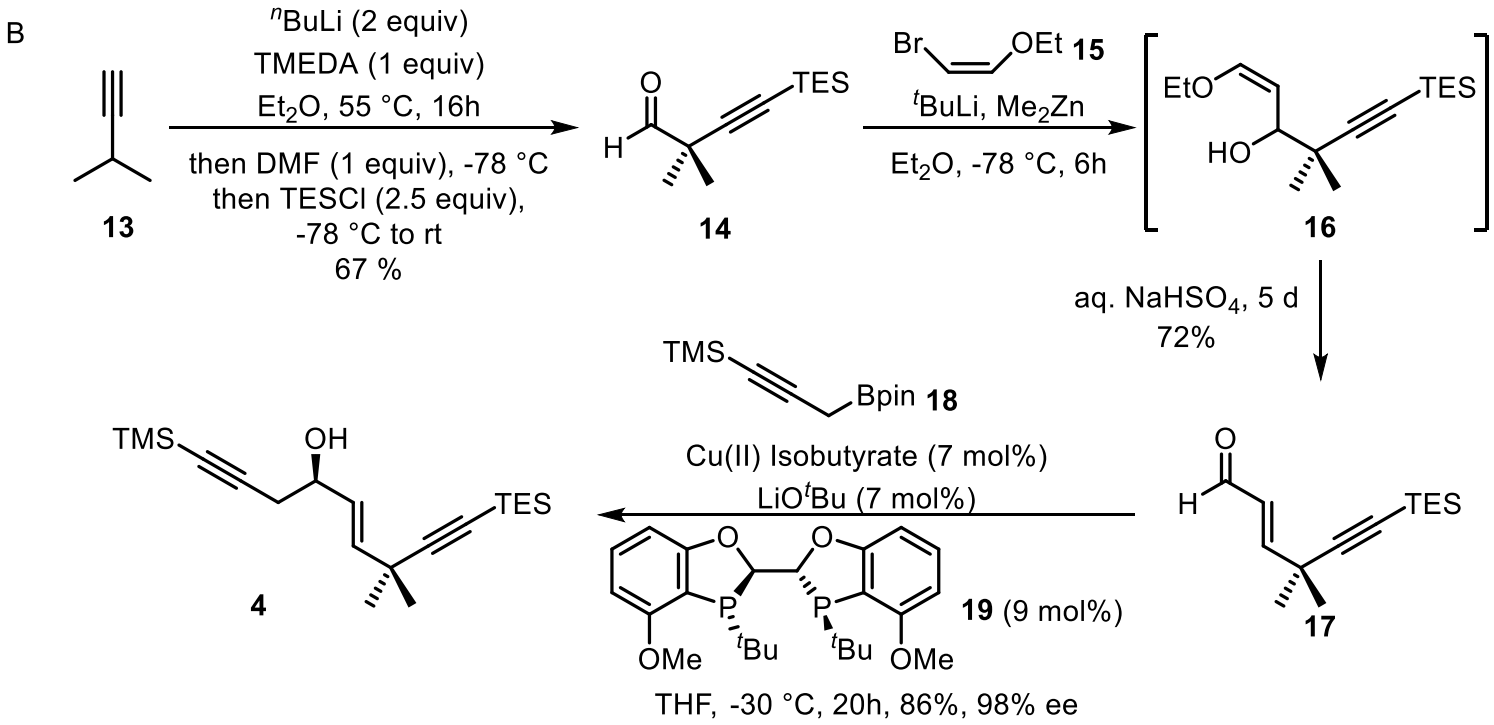


3

Synthetic Route: Synthesis of Fragment 3

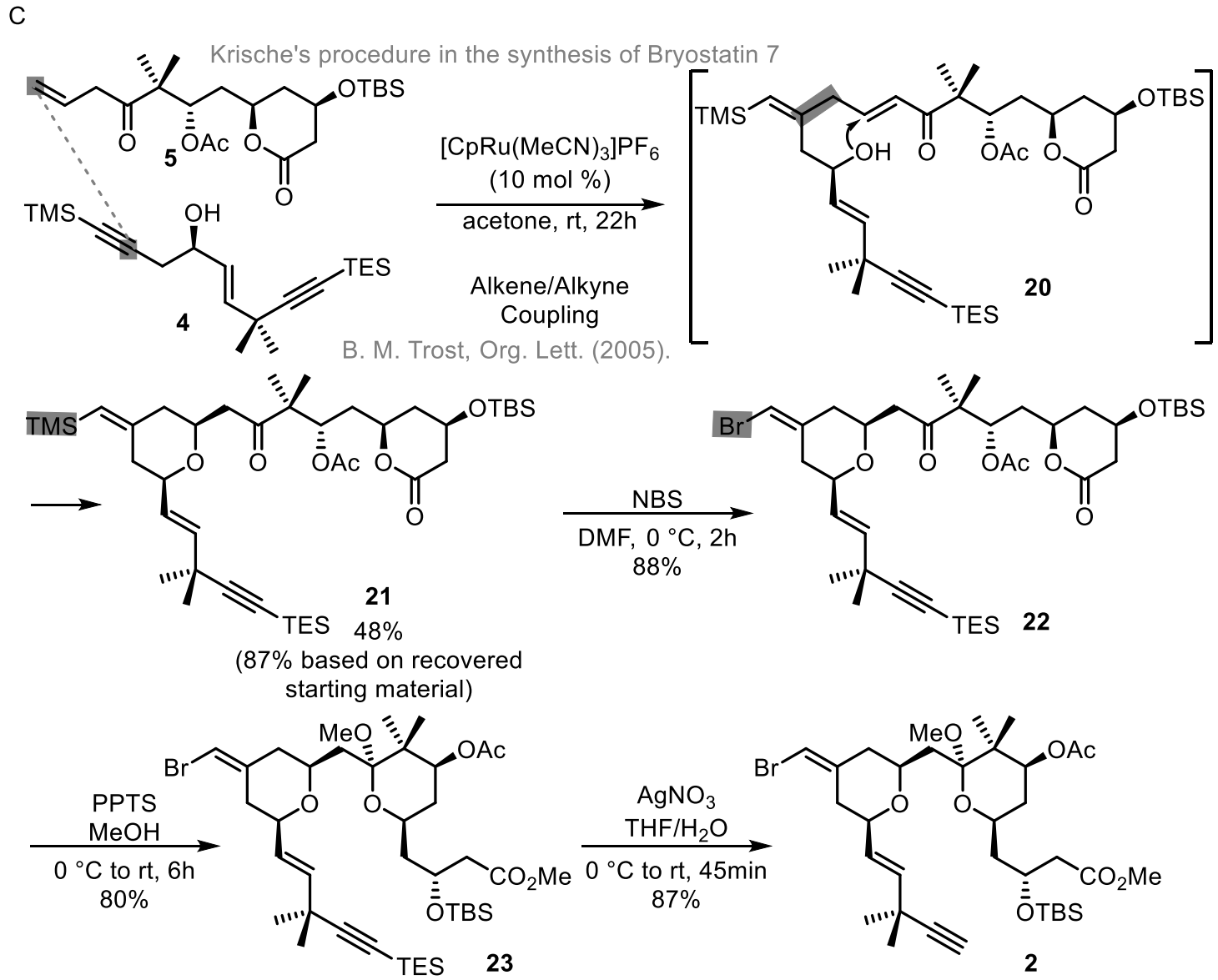


Synthetic Route: Synthesis of Fragment 4

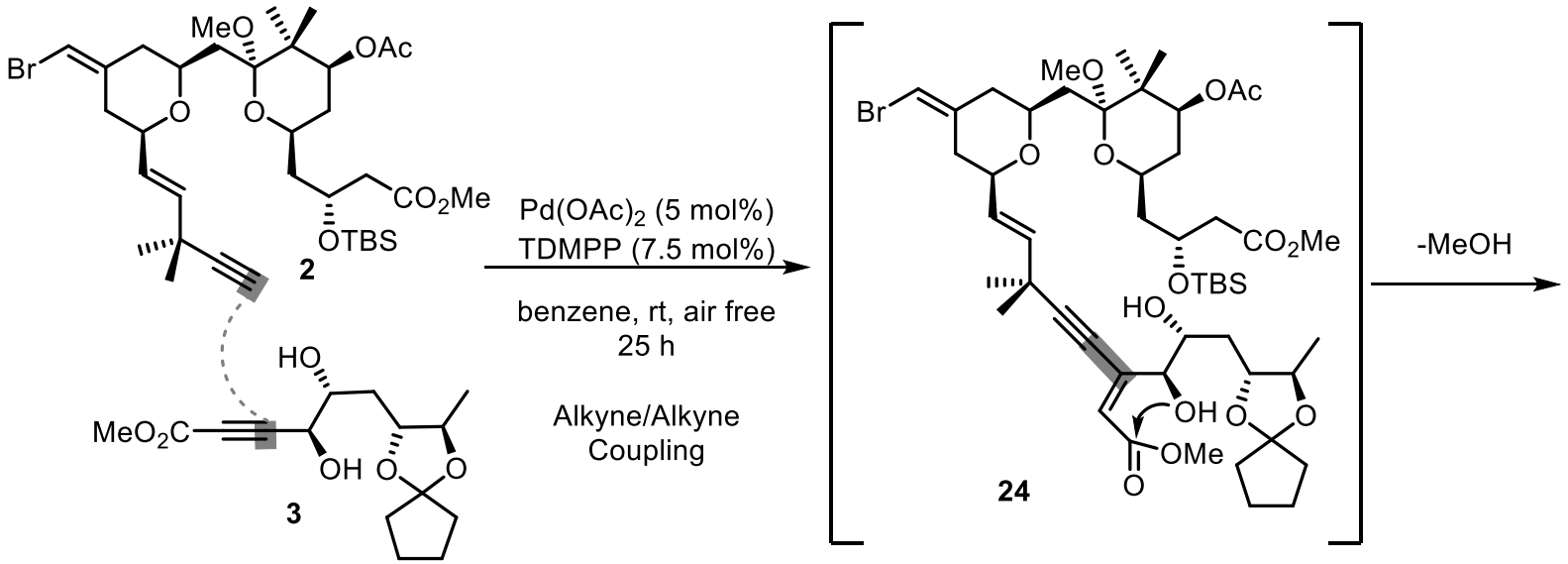


Synthetic Route: Synthesis of Intermediate 2

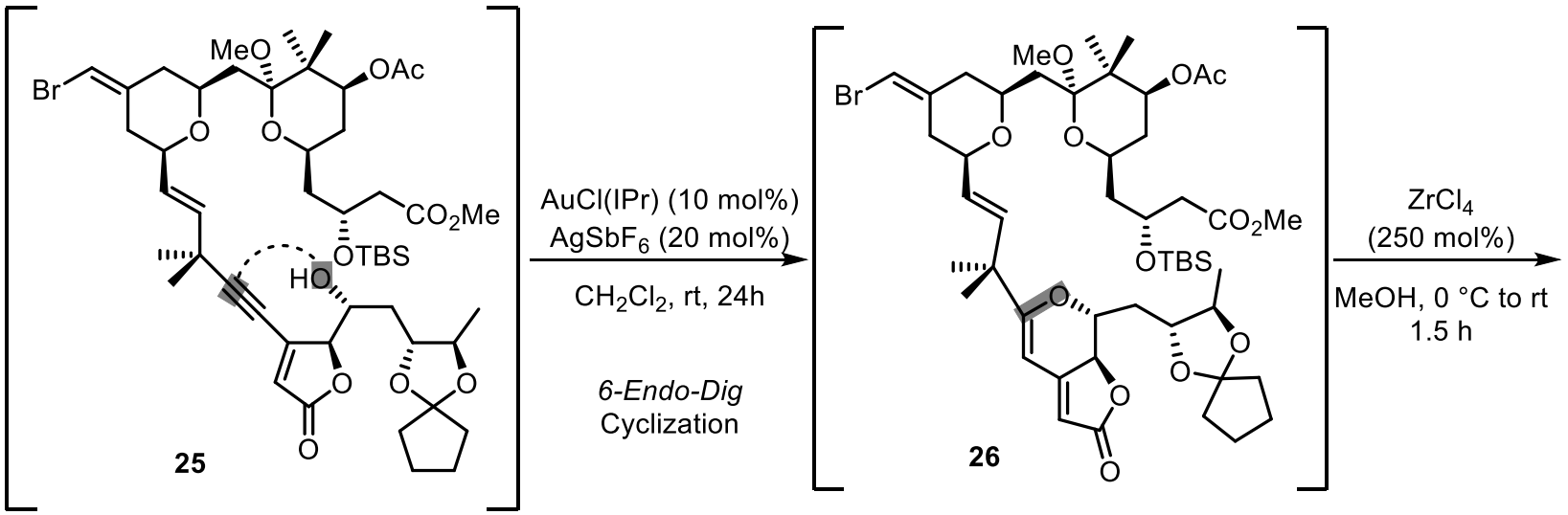
C



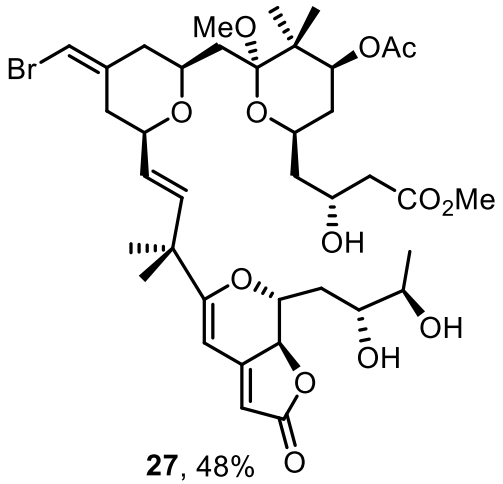
Synthetic Route: Synthesis of Intermediate 1



B. M. Trost, J. Am. Chem. Soc. (1997).

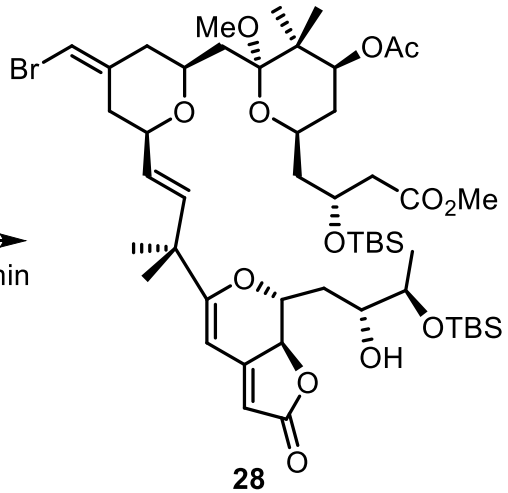


Synthetic Route: Synthesis of Intermediate 1



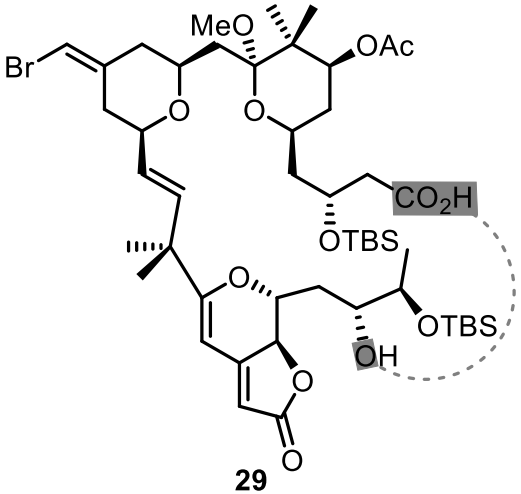
27, 48%
three operations in one pot
no solvent removal or exchange

TBSOTf
2,6-lutidine
CH_2Cl_2, -78 °C, 15min
60%



28

Me_3SnOH
DCE, 80 °C, 48h
80%

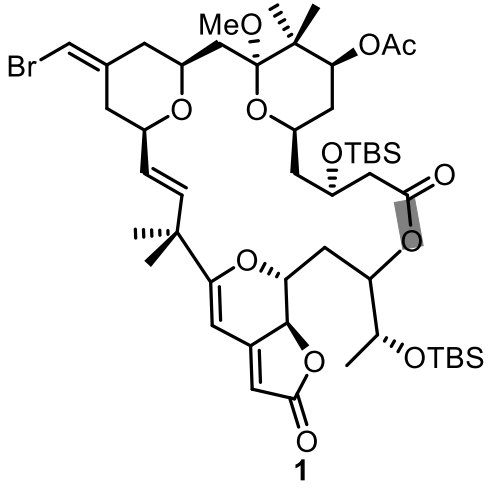


29

Yamaguchi
Macrolactonization

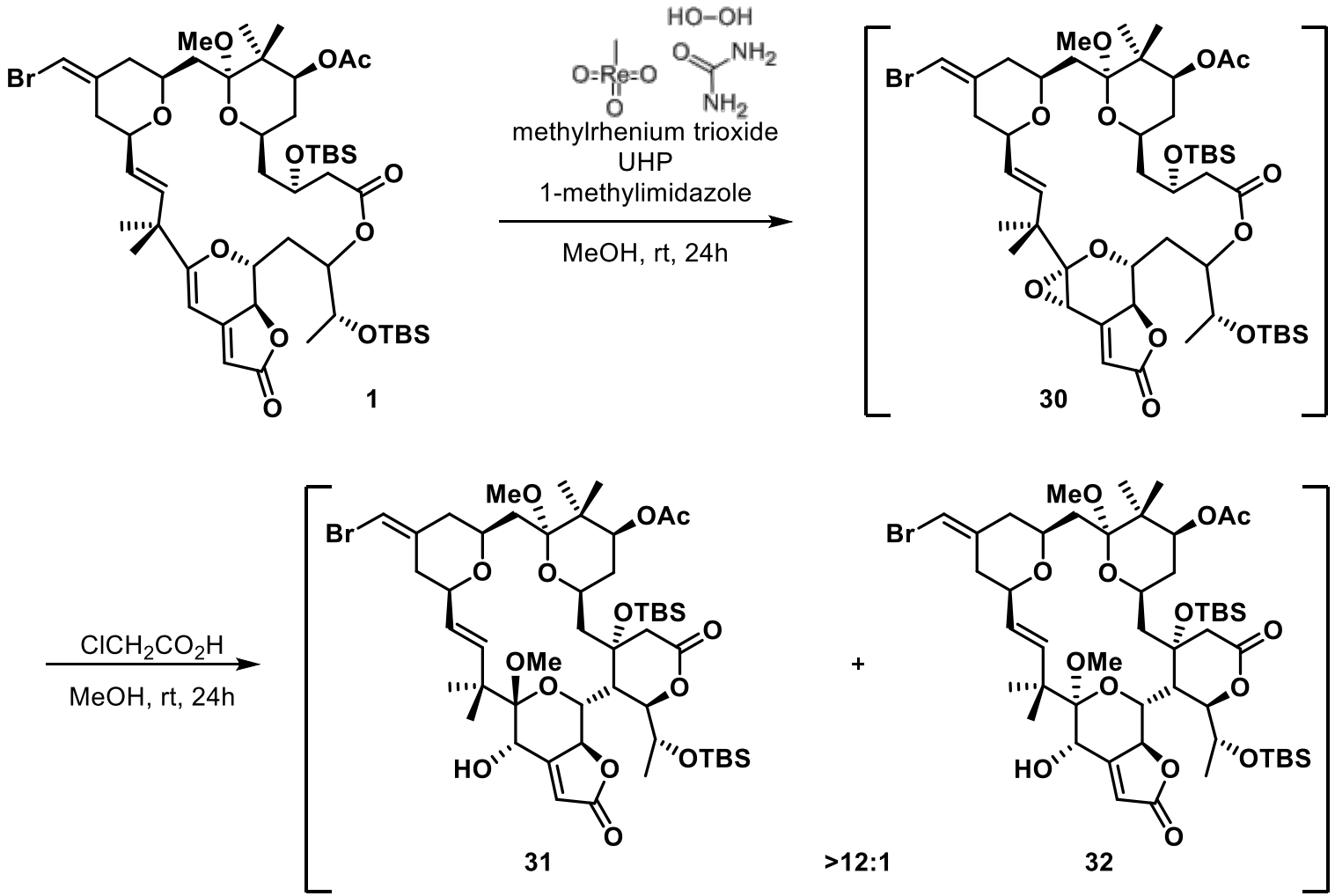
2,4,6-$Cl_3PhCOCl$
Et_3N, THF, rt, 4h

then:
slow addition into DMAP
in toluene
14h, 40 °C
96%

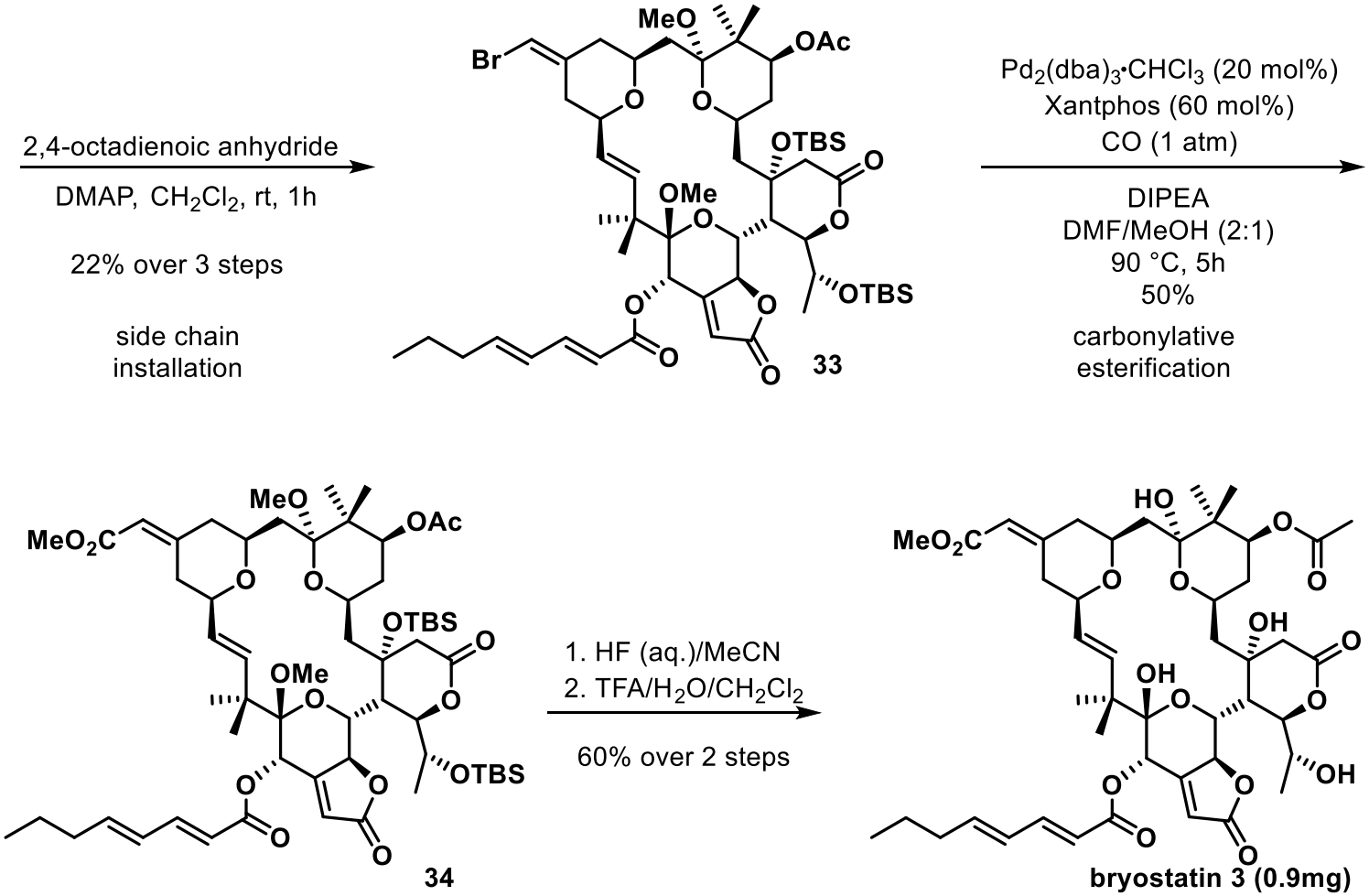


1

Synthetic Route: Synthesis of Bryostatin 3



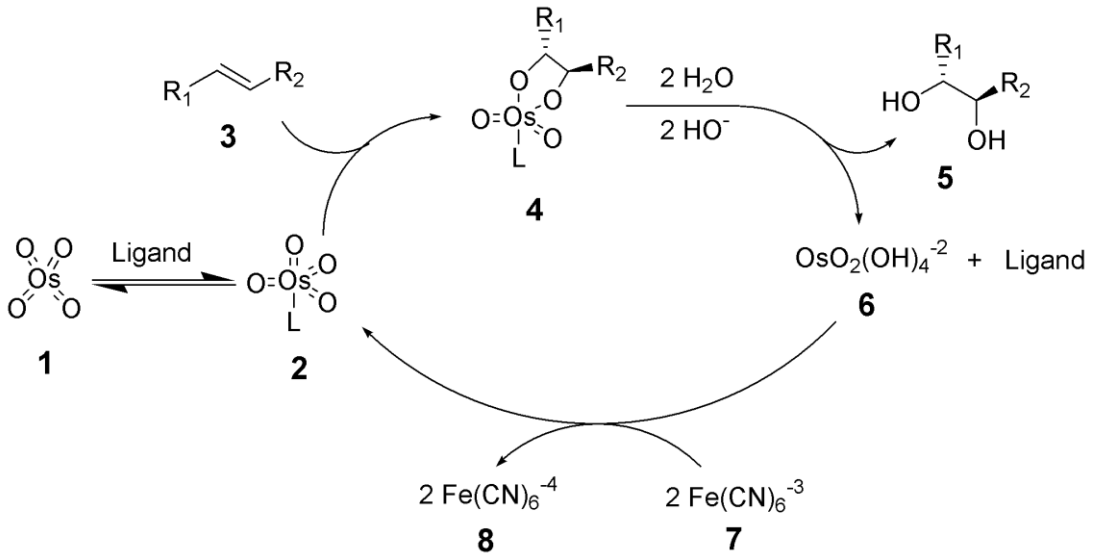
Synthetic Route: Synthesis of Bryostatin 3

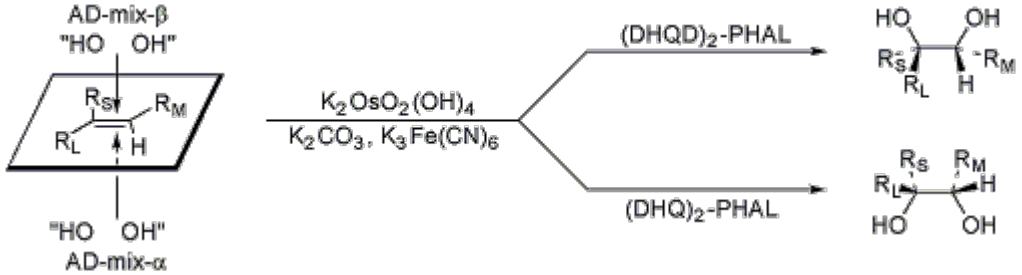


Summary

1. A concise total synthesis of bryostatin 3
2. It used 22 steps in the longest linear sequence and 31 total steps
3. A highly convergent synthetic plan
4. A highly atom-economical and chemoselective transformations
5. Allowing for structure-activity-relationship (SAR) studies.

Sharpless AD





A premix of the four reagent components is commercially available. The composition containing $(DHQD)_2$-PHAL is termed AD-mix-β; the composition containing $(DHQ)_2$-PHAL is termed AD-mix-α.

$(DHQD)_2$-PHAL = 1,4-bis(9-O-dihydroquinidine)phthalazine; $(DHQ)_2$-PHAL =1,4-bis(9-O-dihydroquinine)phthalazine.

R_L = largest substituent; R_M = medium-sized substituent; R_S = smallest substituent.

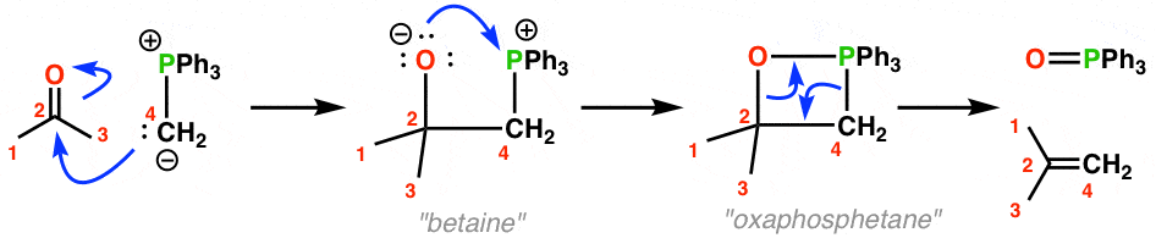
Wittig and Stork Wittig

Mechanism of the Wittig Reaction

Step 1: attack of ylide carbon on carbonyl

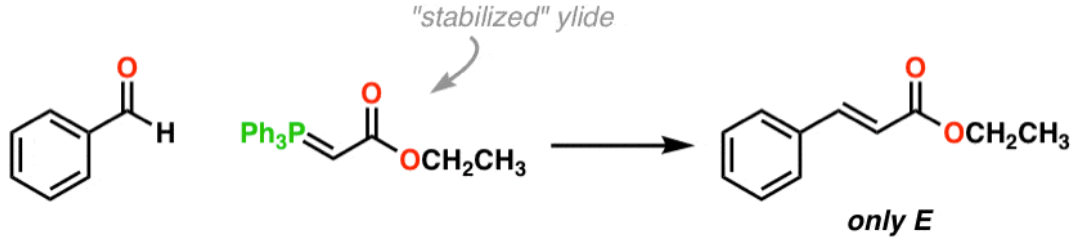
Step 2: attack of oxygen on phosphorus

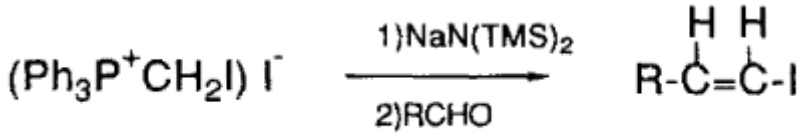
Step 3: Reverse [2+2] cycloaddition



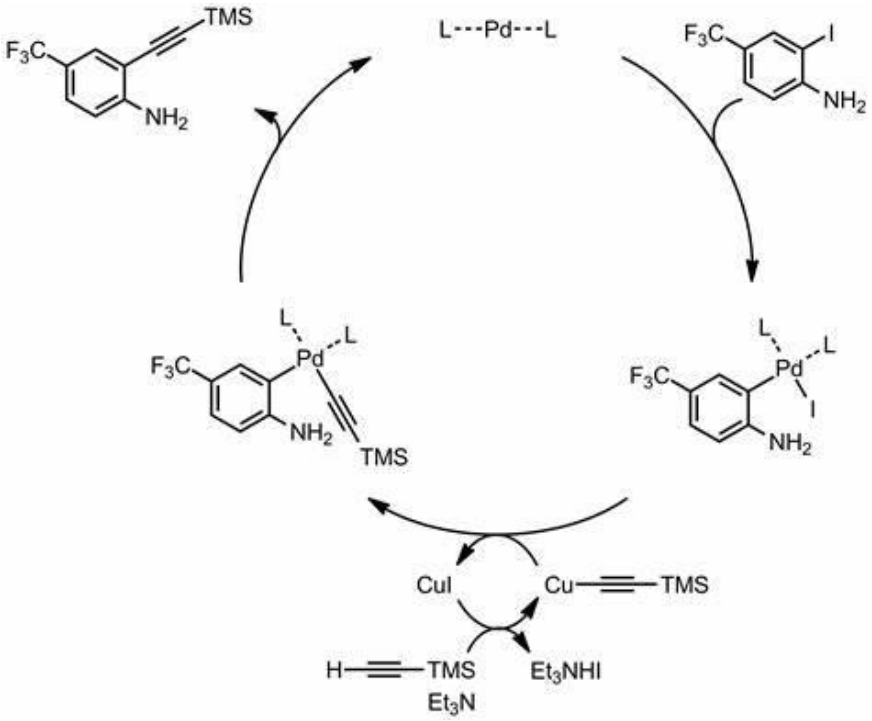
[Note: in many cases, step 1 and step 2 happen essentially simultaneously]

- *Ylides bearing electron-withdrawing groups tend to give E alkenes:*

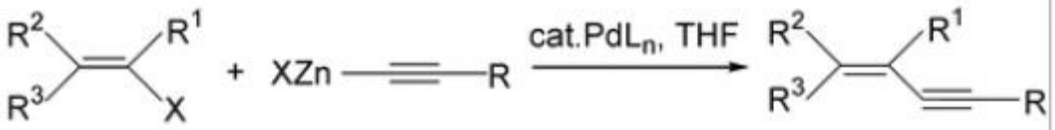




Sonogashira coupling



the artical case



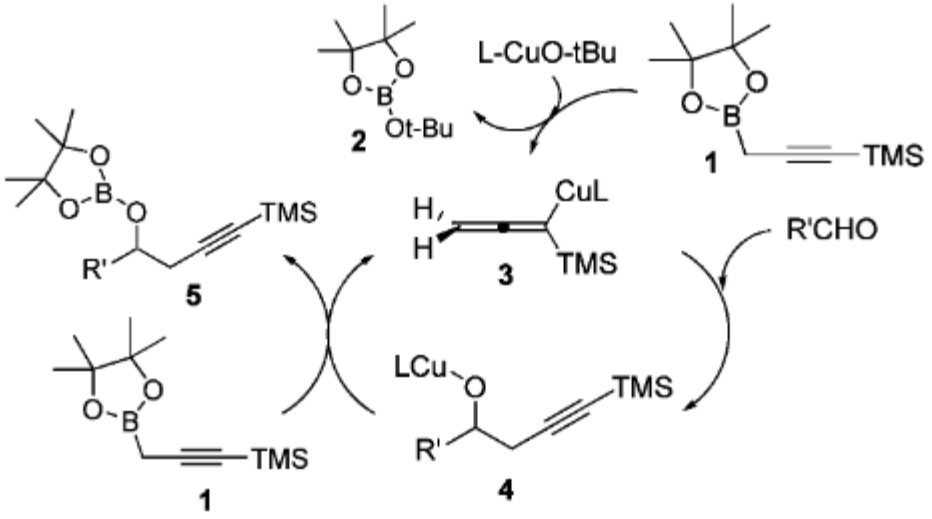
R = COOMe, COOEt, COPh, COC_6H_{11}-*c*, CH=CMeCOOEt,
CH=CHCH=CMeCOOEt, Ph, *n*-Hex.

R^1, R^2, R^3 = C, H, or Br. X = halogens or OTf.

Propargylation of Aldehydes

The proposed catalytic cycle is based on a Cu-alkoxide mediated B/Cu exchange with the propargyl borolane **1** to generate an allenyl Cu intermediate **3** (Scheme 1). After propargylation of an aldehyde,

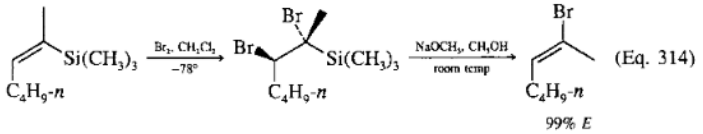
Scheme 1. Proposed Mechanism for a Cu Catalyzed Propargylation of Aldehydes with a Propargyl Borolane



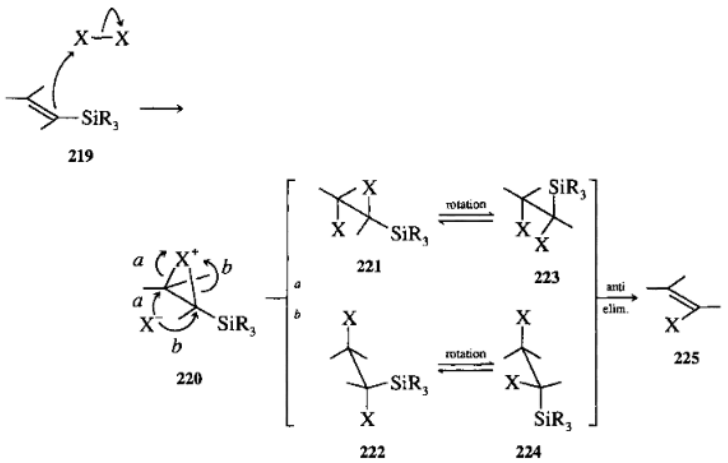
a Cu-alkoxide species would be regenerated, and a catalytic cycle would be established. The two key operations in this catalytic cycle

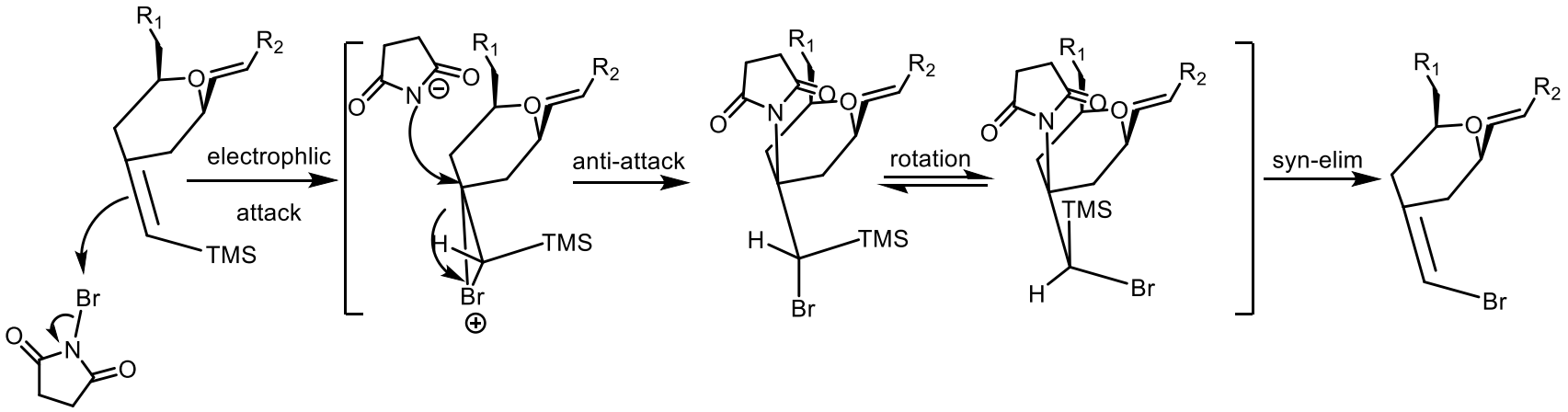
ipso-brominaton

mations **223** or **224**. Both of these pathways lead to the vinyl bromide or chloride **225** that is the product of inversion of configuration.[14,481]

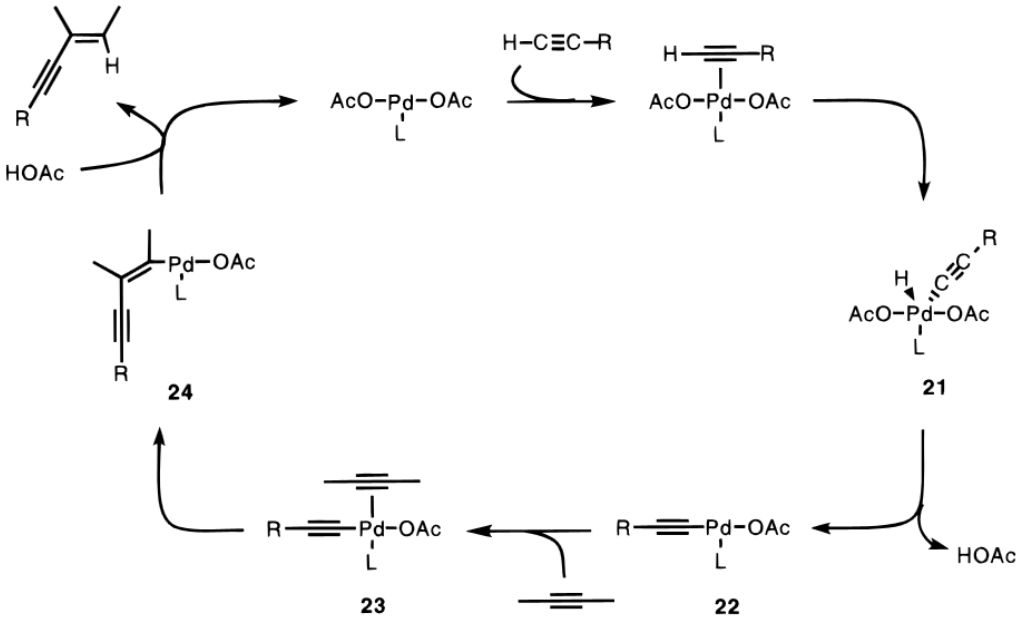


(Eq. 314)





Alkyne/Alkyne Coupling



be excluded. This mechanism accounts for the overall event of a *cis* addition in a Markovnikov fashion for the homo-coupling and in a Michael fashion for the cross-coupling.

How it works *Oxidation of primary alcohols to aldehydes*

The alcohol coordinates to the chromium(VI) atom, displacing chlorine, which then acts as a base, resulting in oxidation of the alcohol and reduction of Cr(VI) to Cr(IV)