Zu Group Meeting

Science

Total Synthesis of Bryostatin 3

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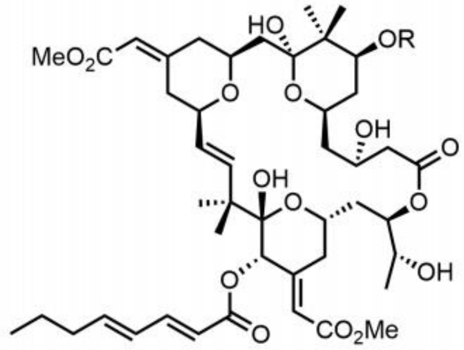
Introduction

marine bryozoan *bugula neritina*

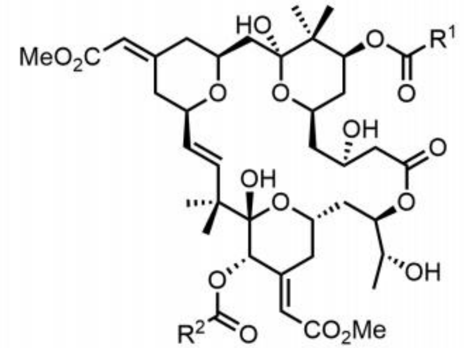
potent biological activities

1. potent antineoplastic
2. immunopotentiating
3. synaptogenesis inducing
4. latent HIV–modulating activity
5. beneficial effects as a post-stroke treatment
6. blood-brain barrier
7. agonists of protein kinase C



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)

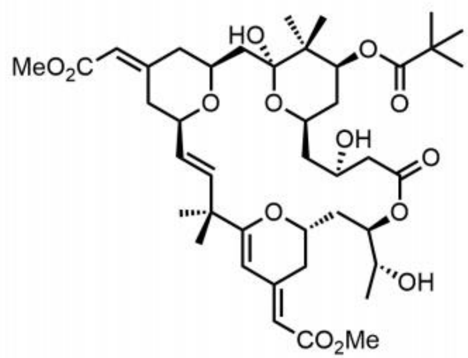
Bryostatin 2: R = H, PKC K_i = 5.86 nM
Evans 1999, 42 steps (LLS), 72 steps (TS)



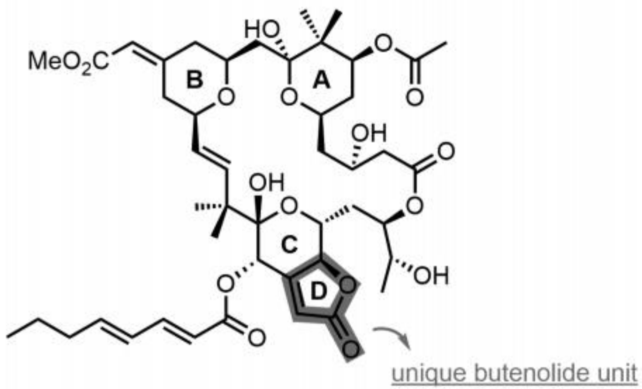
Bryostatin 7: R^1 = Me, R^2 = Me, PKC K_i = 0.84 nM
Masamune 1990, 41 steps (LLS), 79 steps (TS)
Krische 2011, 20 steps (LLS), 36 steps (TS)

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)

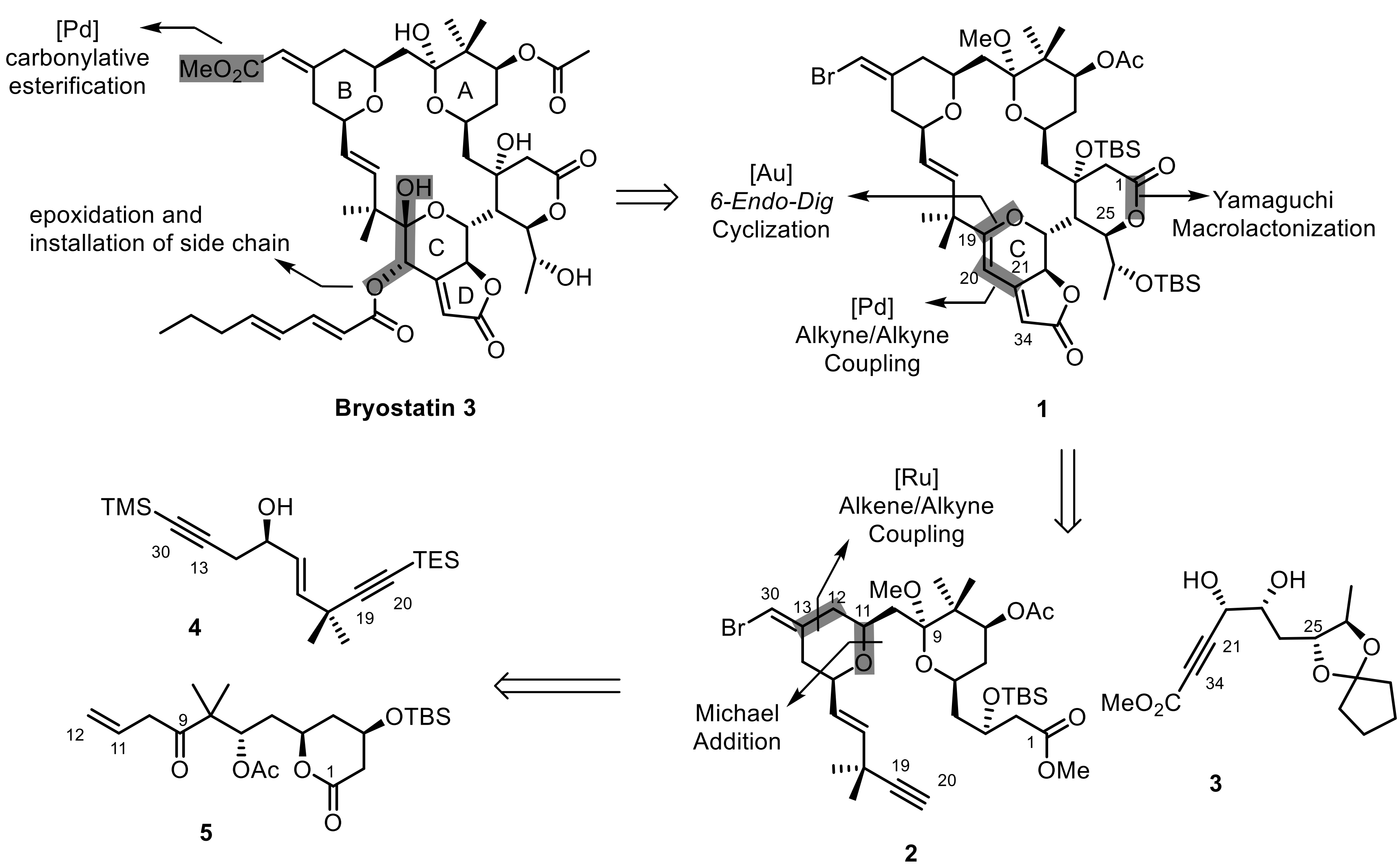


Bryostatin 16: PKC K_i = 118 nM
Trost 2008, 28 steps (LLS), 42 steps (TS)



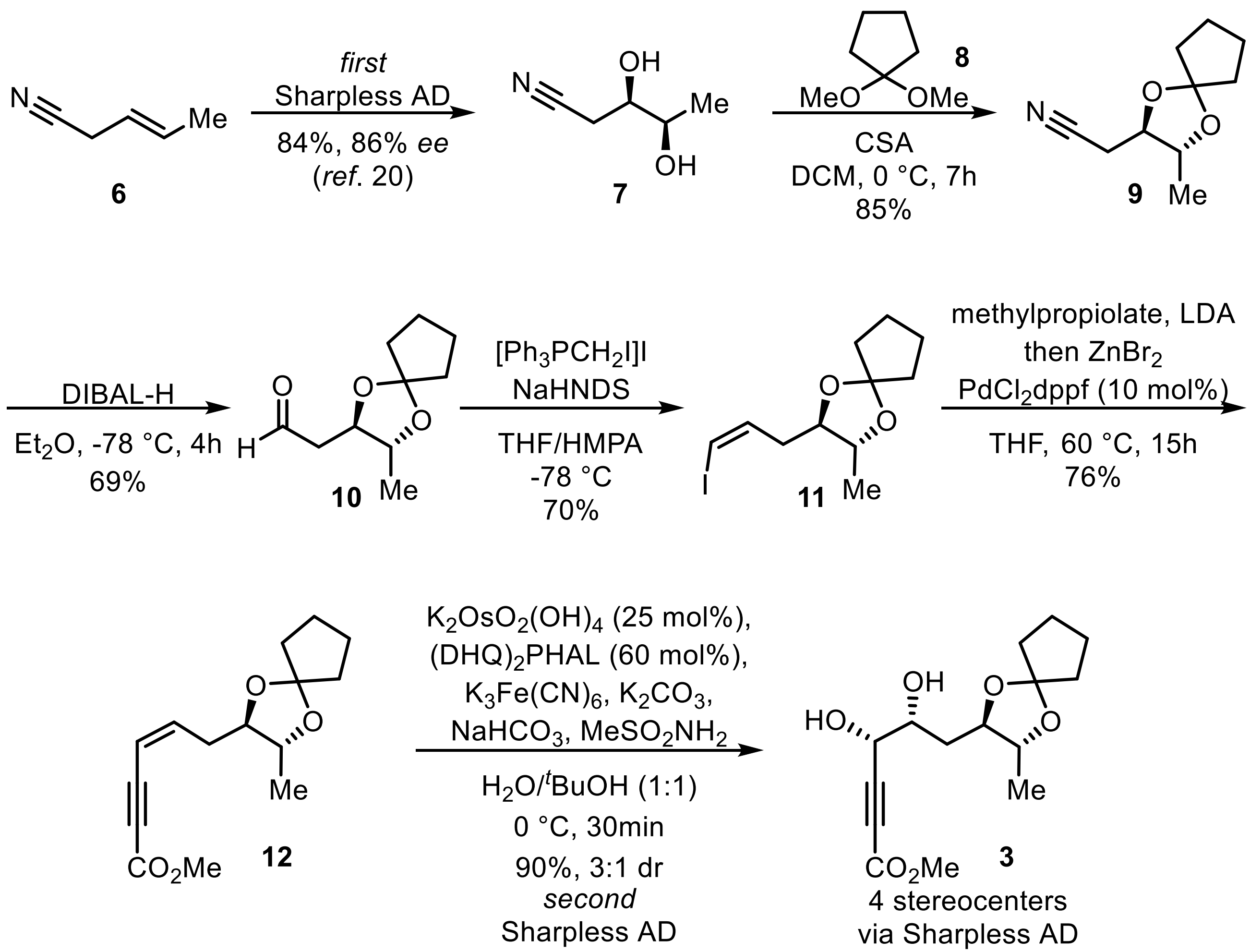
Bryostatin 3: PKC K_i = 2.75 nM
Yamamura 2000, 43 steps (LLS), 88 steps (TS)
This work, 22 steps (LLS), 31 steps (TS)

Retrosynthetic Analysis

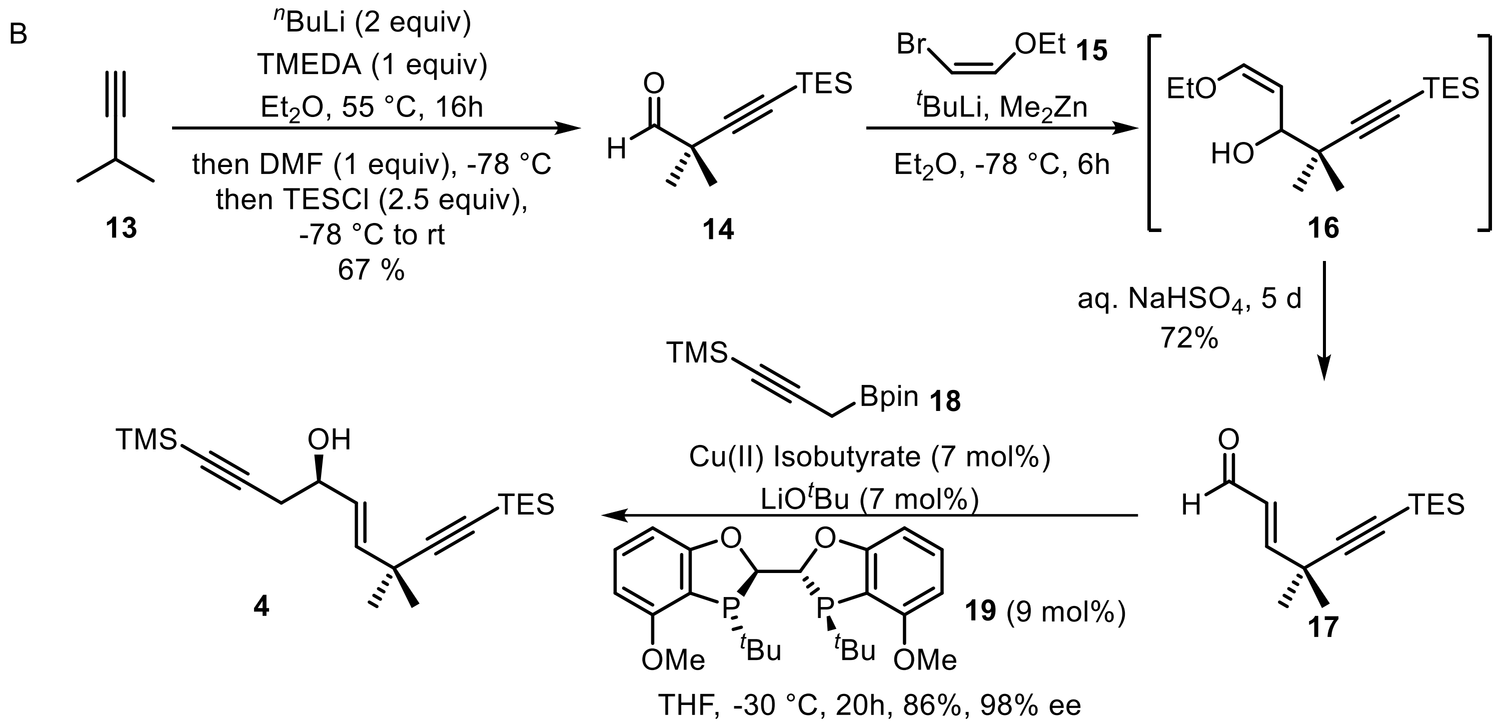


Synthetic Route: Synthesis of Fragment 3

A

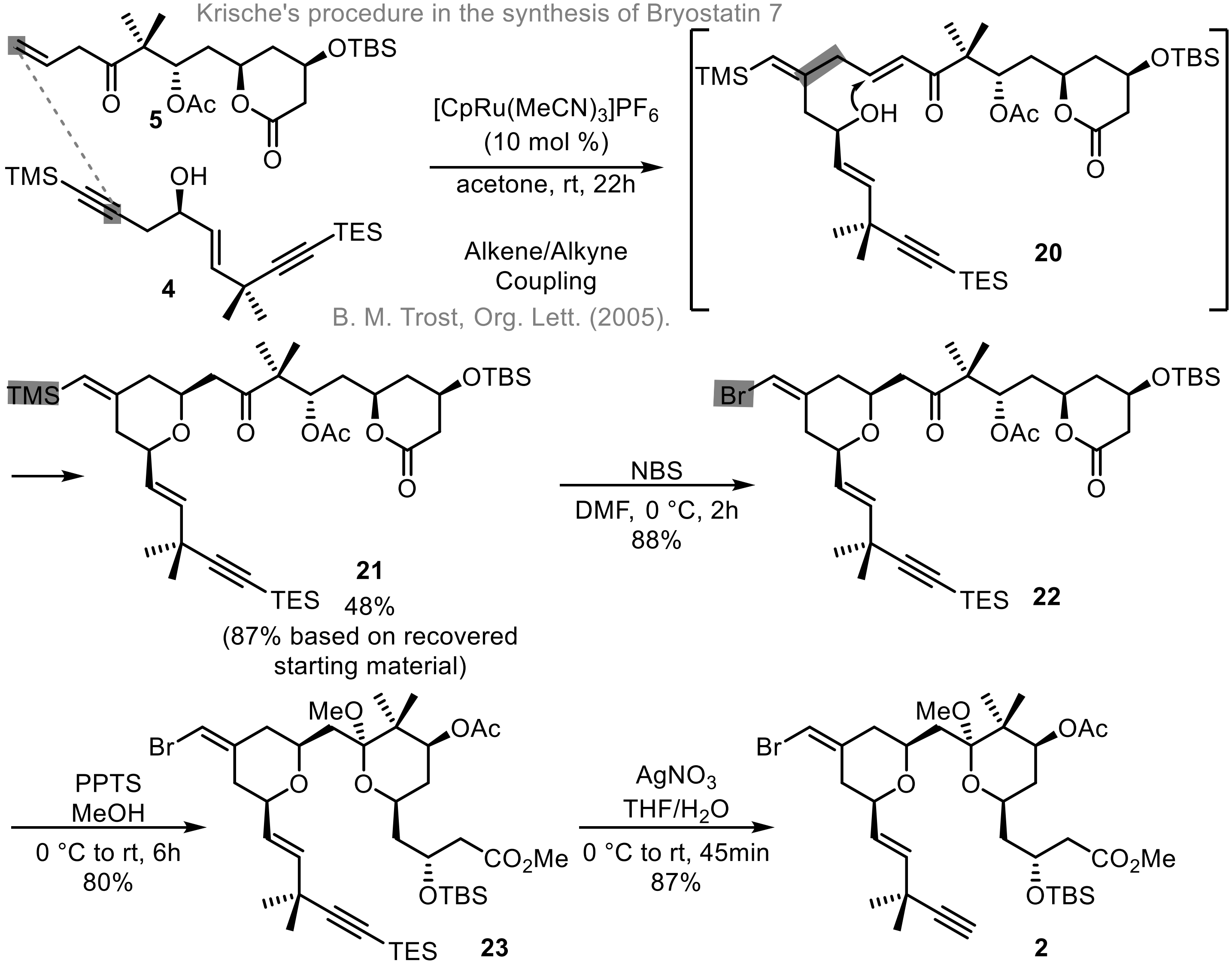


Synthetic Route: Synthesis of Fragment 4

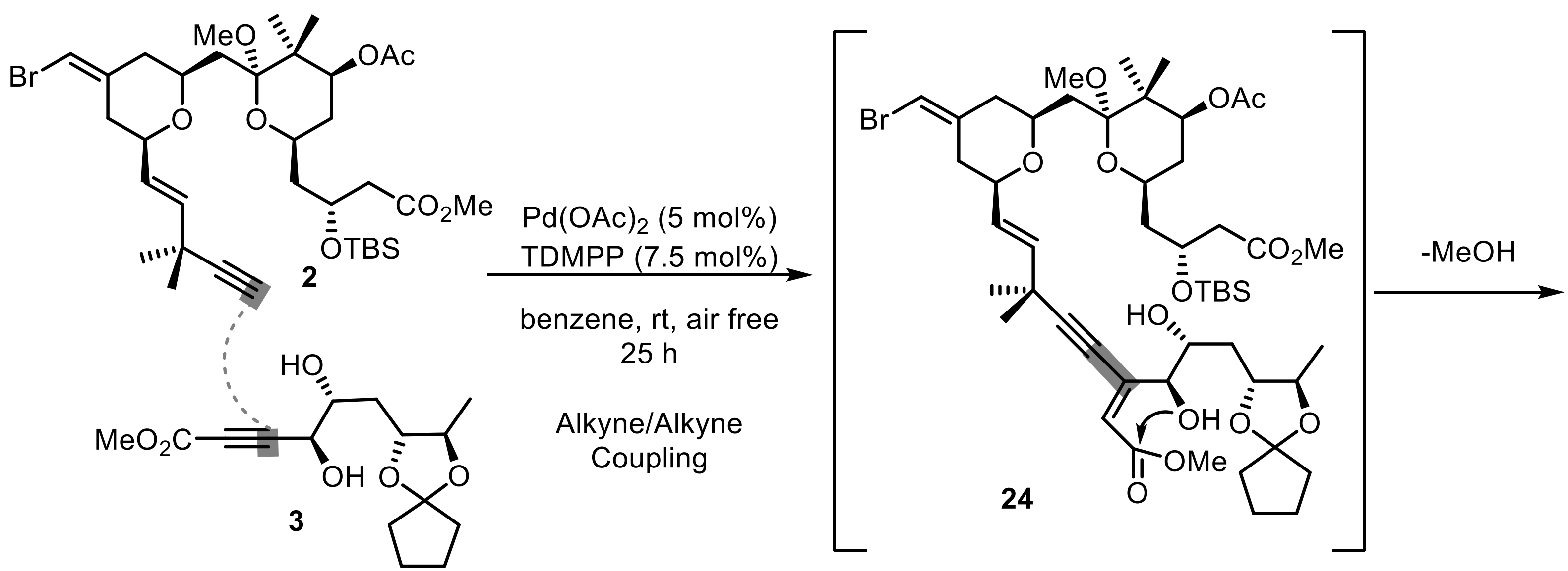


Synthetic Route: Synthesis of Intermediate 2

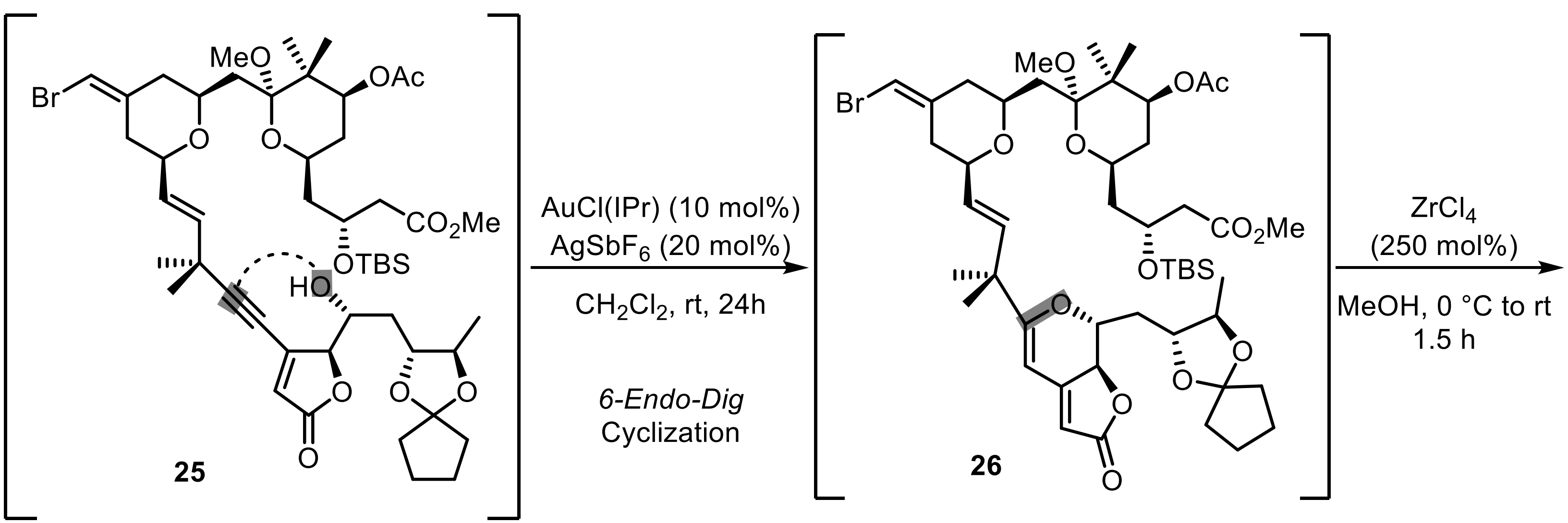
C



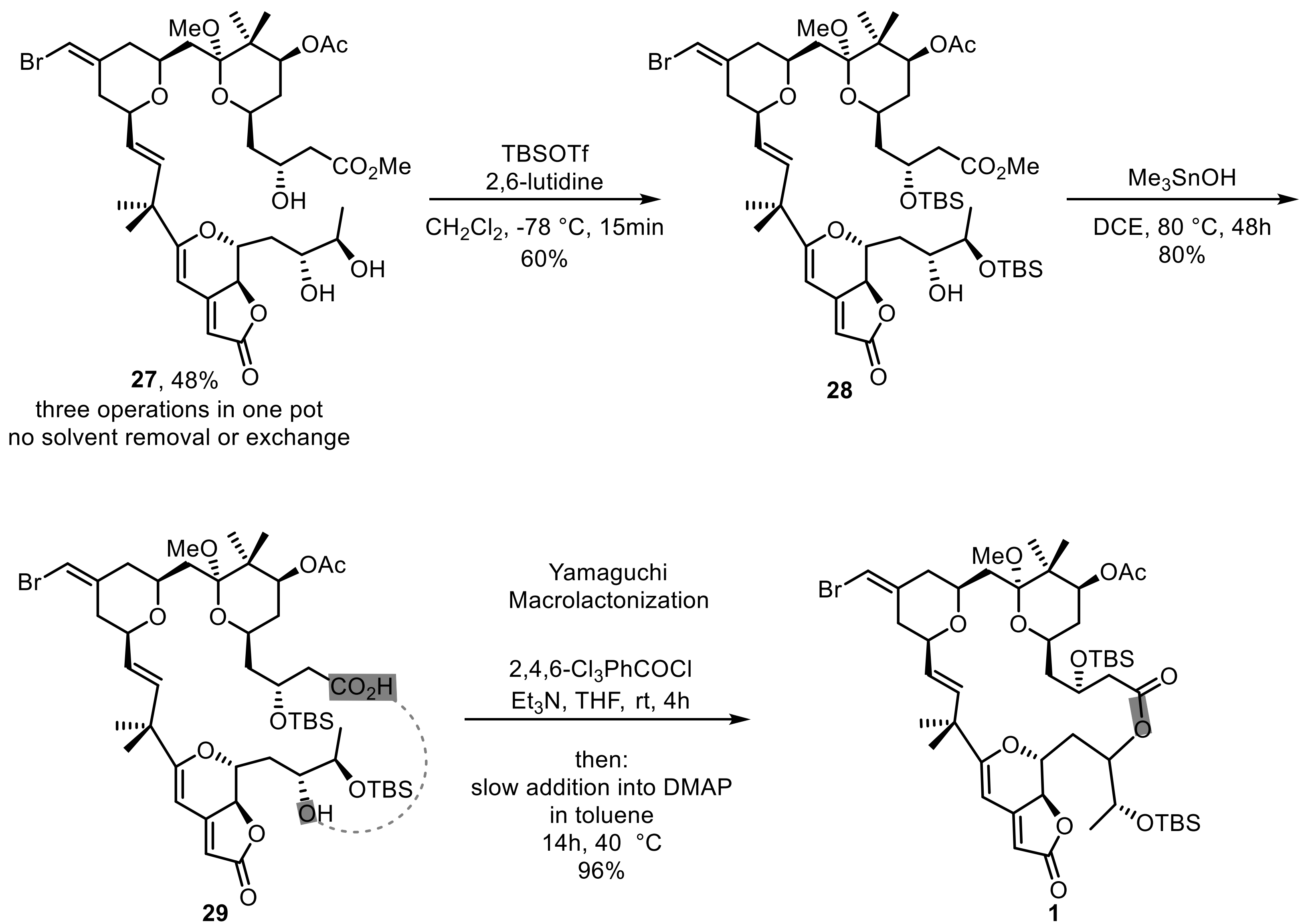
Synthetic Route: Synthesis of Intermediate 1



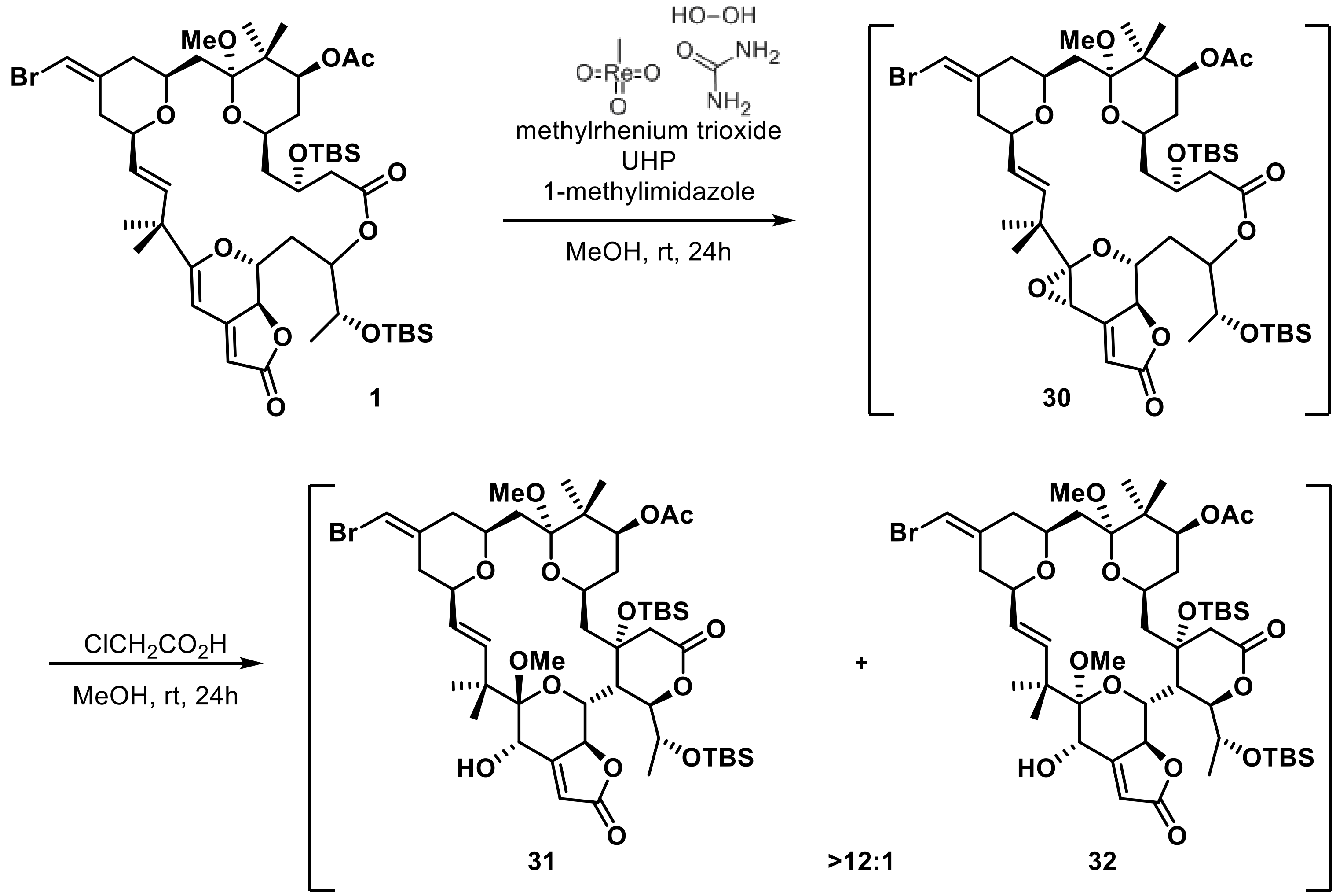
B. M. Trost, J. Am. Chem. Soc. (1997).



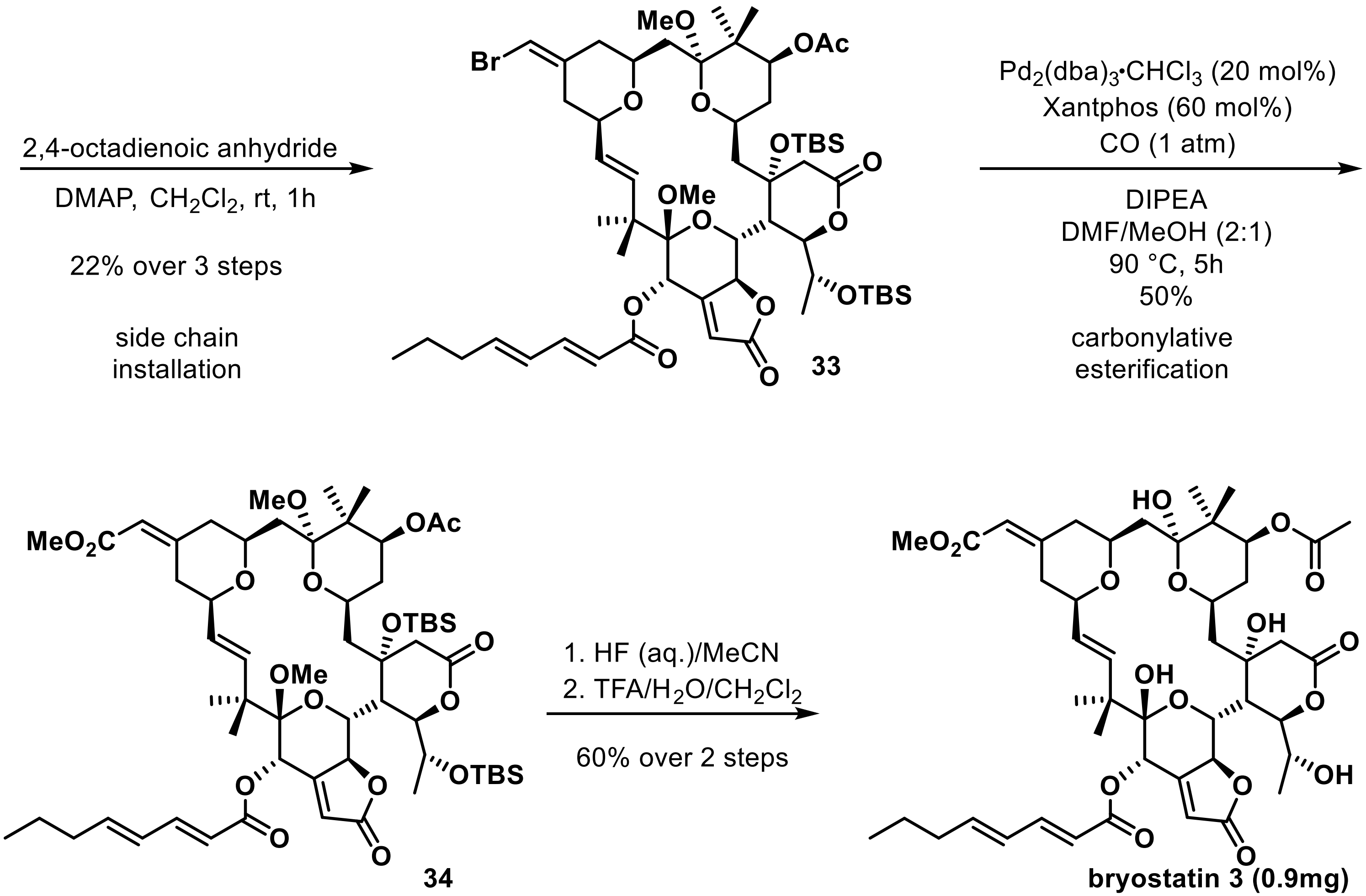
Synthetic Route: Synthesis of Intermediate 1



Synthetic Route: Synthesis of Bryostatin 3



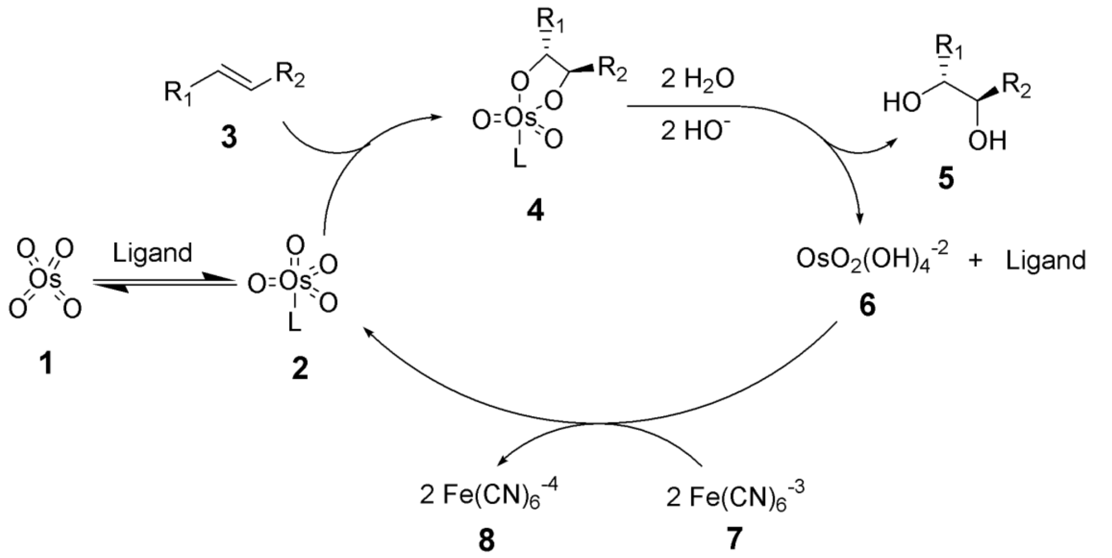
Synthetic Route: Synthesis of Bryostatin 3

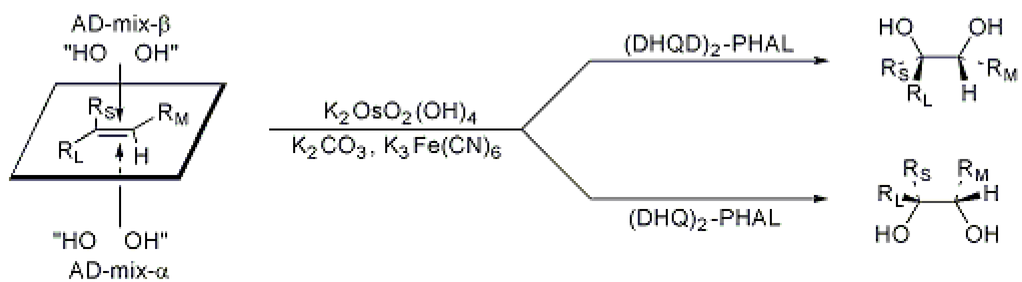


Summary

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



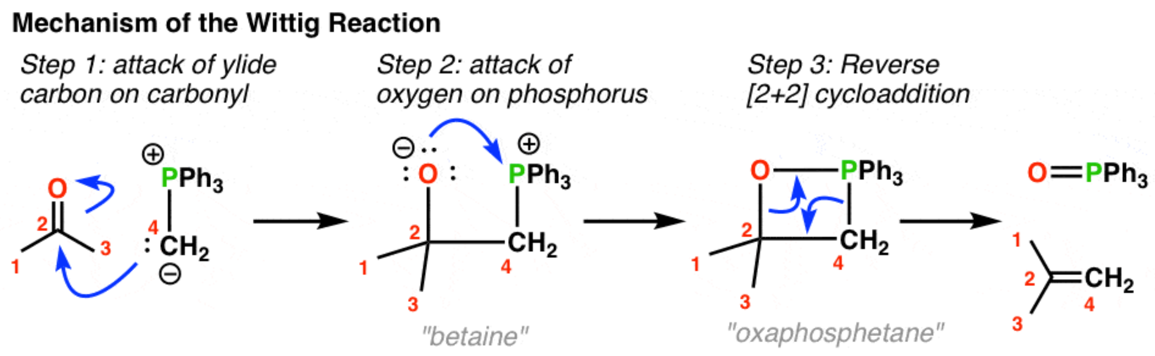


A premix of the four reagent components is commercially available. The composition containing $(DHQD)_2$-PHAL is termed AD-mix-β; the composition containing $(DHQ)_2$-PHAL is termed AD-mix-α.

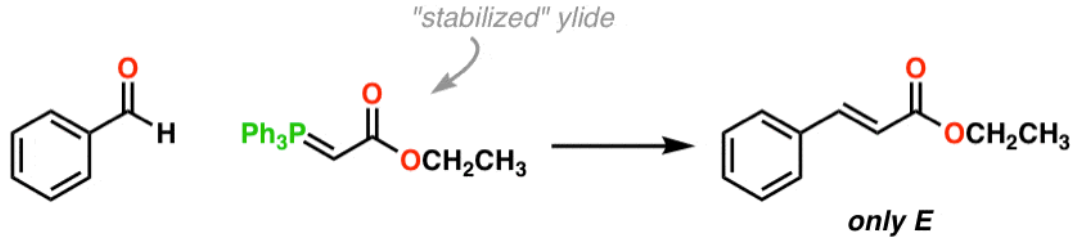
$(DHQD)_2$-PHAL = 1,4-bis(9-O-dihydroquinidine)phthalazine; $(DHQ)_2$-PHAL =1,4-bis(9-O-dihydroquinine)phthalazine.

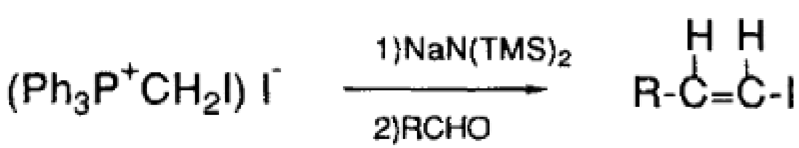
R_L = largest substituent; R_M = medium-sized substituent; R_S = smallest substituent.

Wittig and Stork Wittig

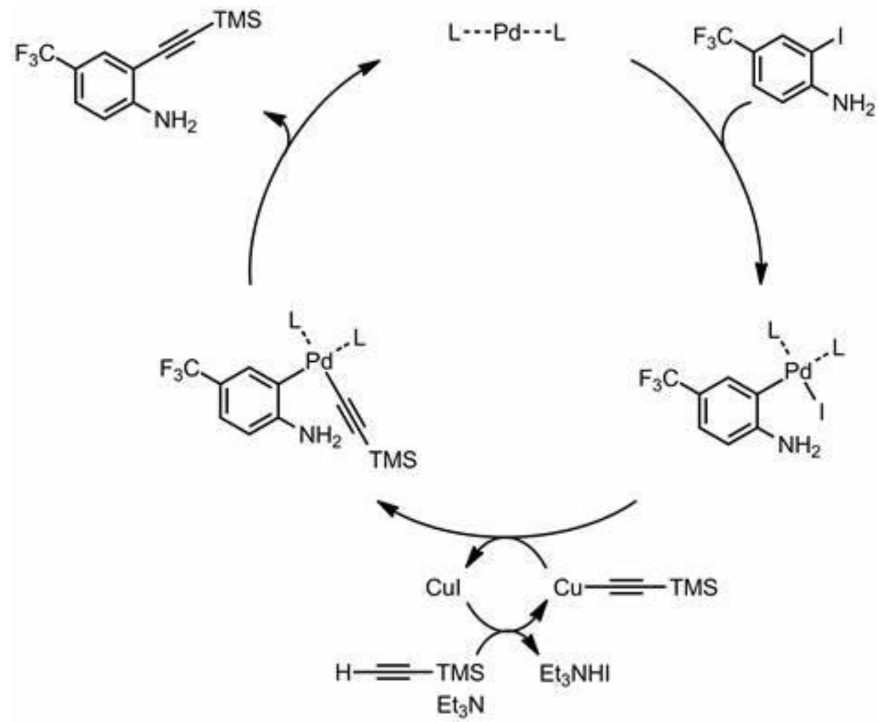


• *Ylides bearing electron-withdrawing groups tend to give E alkenes:*





Sonogashira coupling



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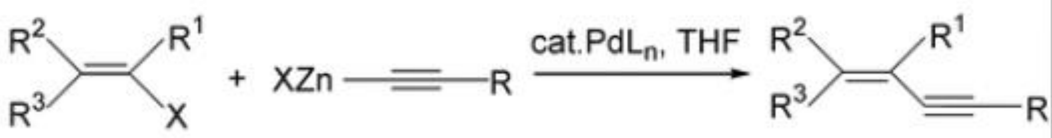


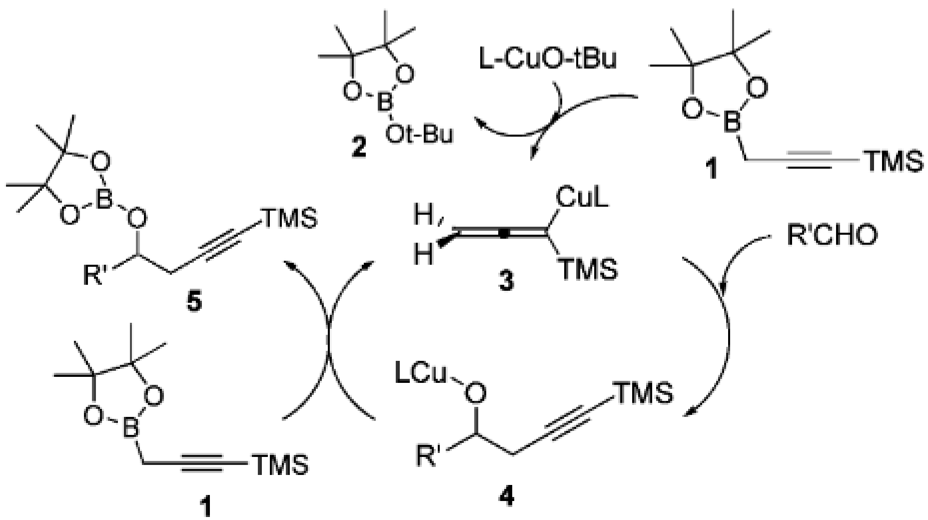
R = COOMe, COOEt, COPh, COC_6H_{11}-*c*, CH=CMeCOOEt, CH=CHCH=CMeCOOEt, Ph, *n*-Hex.

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,

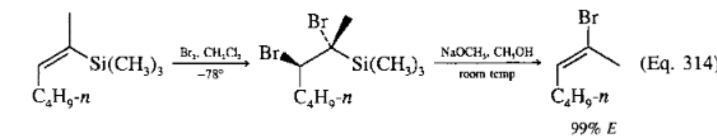
Scheme 1. Proposed Mechanism for a Cu Catalyzed Propargylation of Aldehydes with a Propargyl Borolane

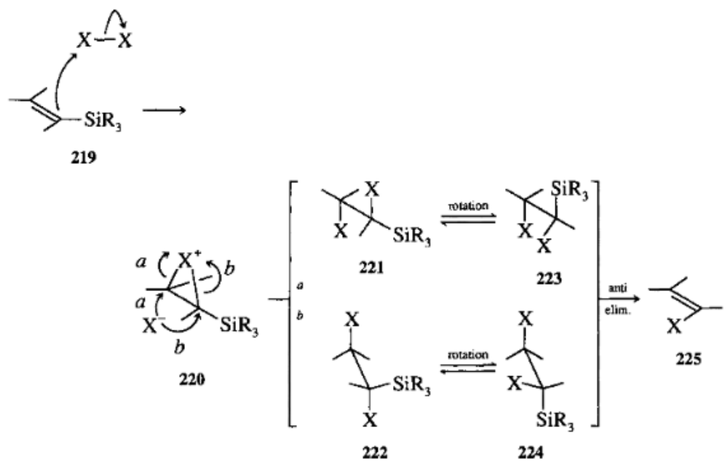


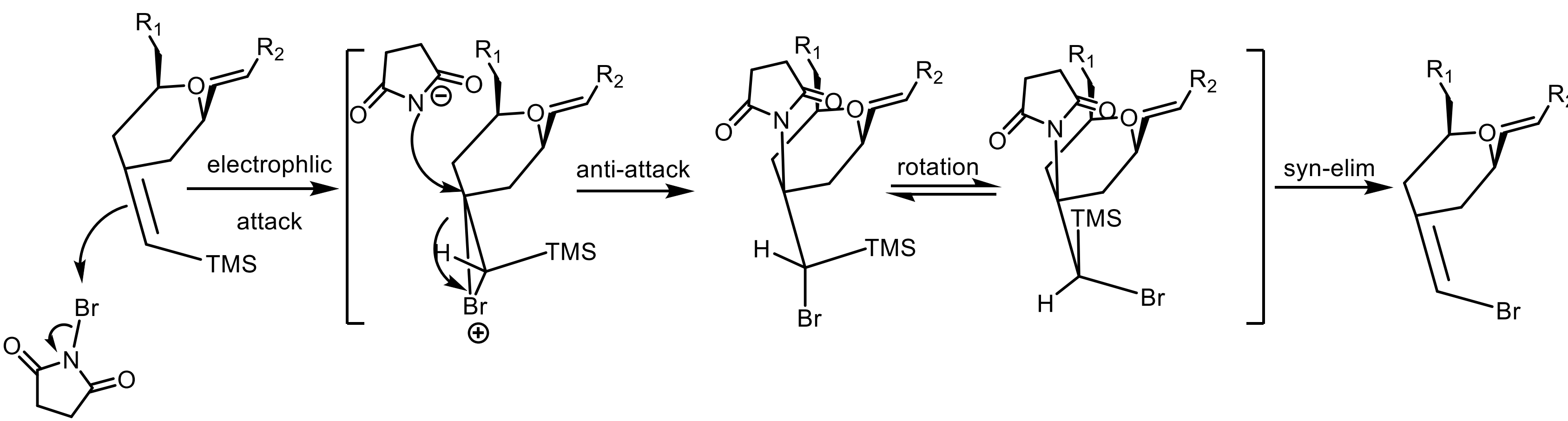
a Cu-alkoxide species would be regenerated, and a catalytic cycle would be established. The two key operations in this catalytic cycle

ipso-brominaton

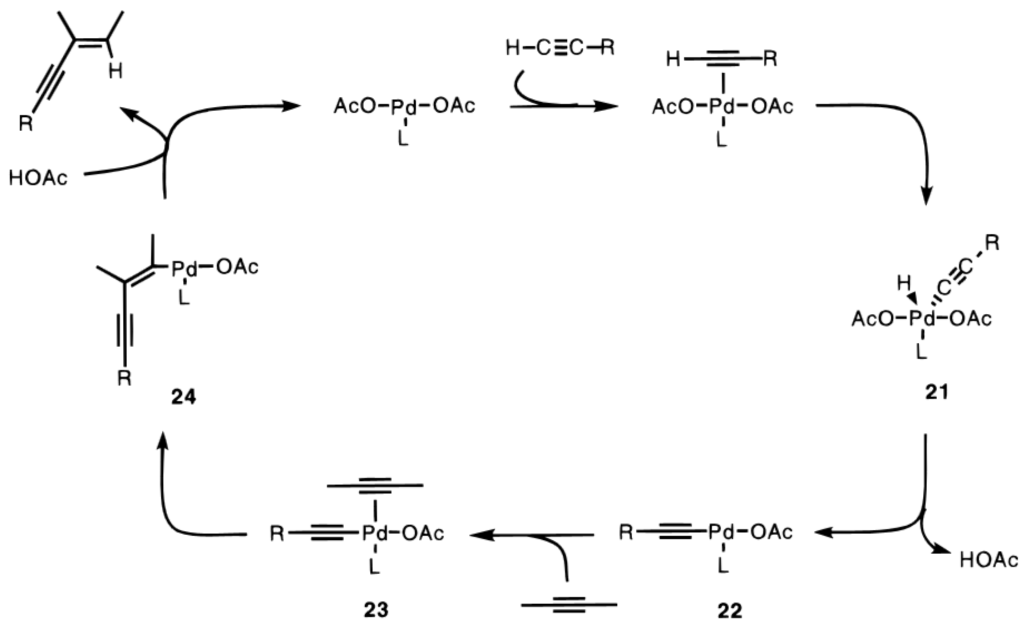
mations **223** or **224**. Both of these pathways lead to the vinyl bromide or chloride **225** that is the product of inversion of configuration.[14,481]







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.