# Macrocyclization Strategies in Natural Product Total Synthesis

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DENMARK GROUP MEETING

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# Overview

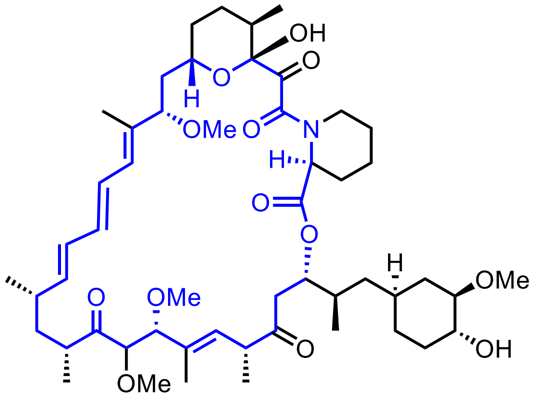
Classics:
Substrate rigidification to pay entropic penalty. Covalent modifications of the cyclization precursor.

$$\Delta G = \Delta H - T\Delta S$$

Macrocycle requirement: $\Delta S \ll 0$

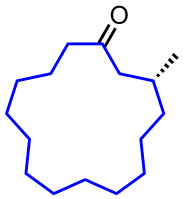
Goal: $\downarrow \Delta H$

Modern:
Substrate preorganization via templates and transition metal catalysts. Chelating events help offset the entropic penalty.

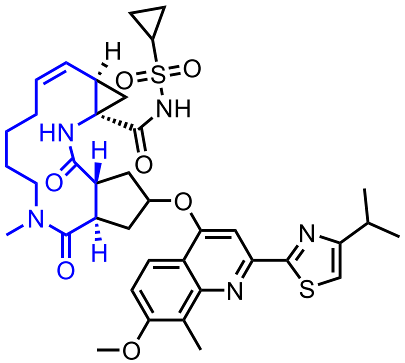



**rapamycin**
mTOR inhibitor

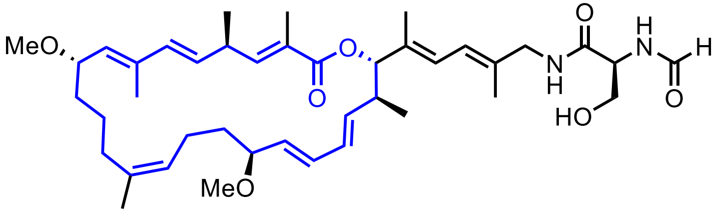
Bioactive macrocycles:




**muscone**
smelly



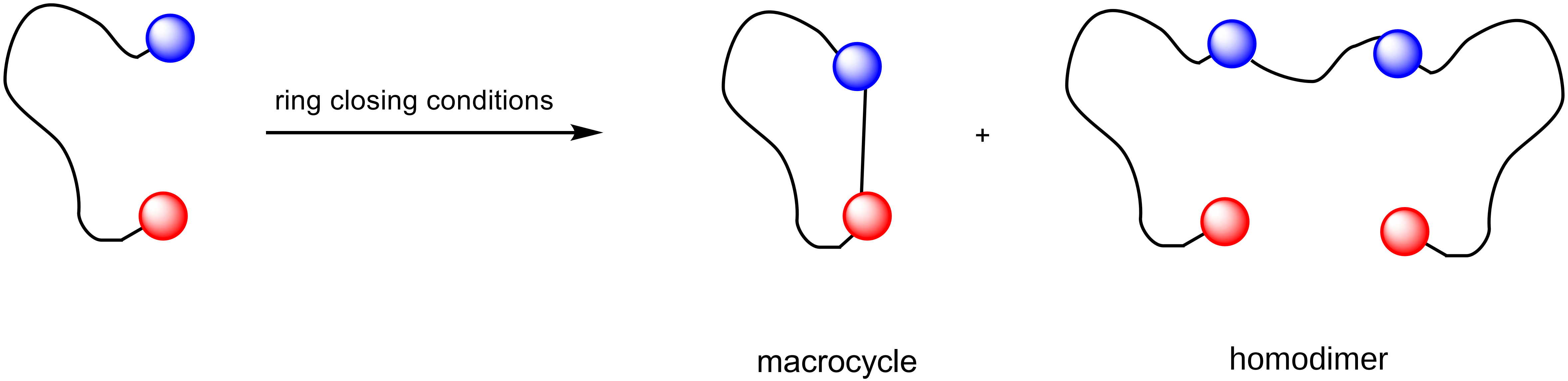

**simeprevir**
HCV protease inhibitor




**iejimalide B**
V-ATPase inhibitor

# Macrocyclization requires an entropic penalty

Macrocylization requires a unimolecular process to outcompete bimolecular processes:




Macrocyclizations require an entropic penalty to be paid in organizing the cyclization precursor.

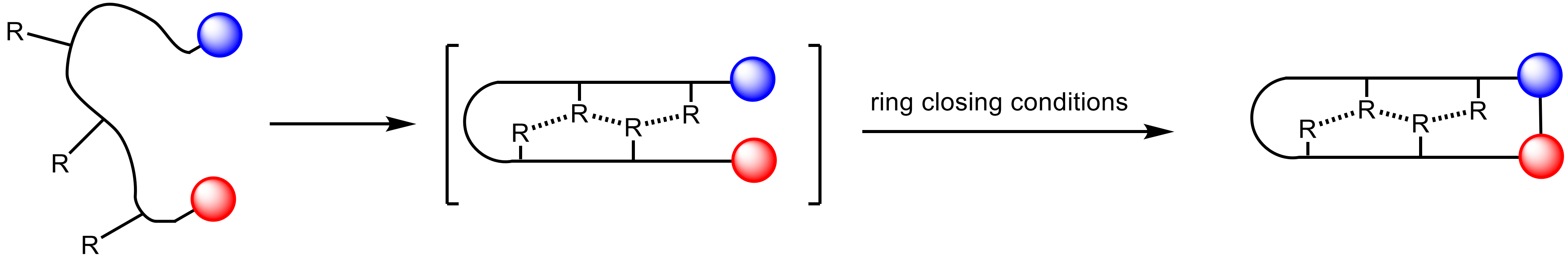
High dilution (< 1 mM) is typically required to get appreciable yields of the macrocyclized product.

*Eur. J. Org. Chem.* **2005**, 1949–1964. *Chem. Rev.* **2015**, 115, 8736-8834.

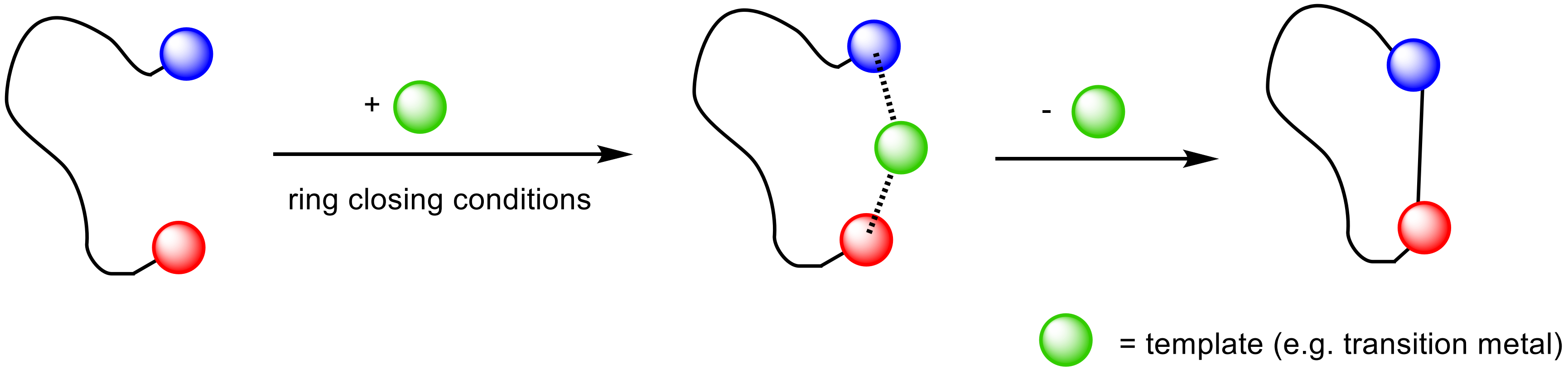
# Macrocyclization requires an entropic penalty

The efficiency of macrocyclizations is dependent on preorganization of the substrate prior to cyclization.

Substrate-induced preorganization favoring macrocyclization:

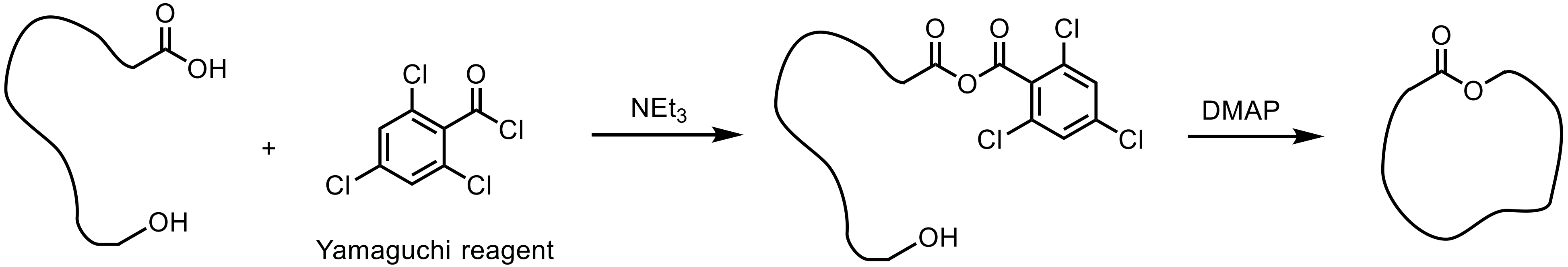



Template-assisted macrocylization:

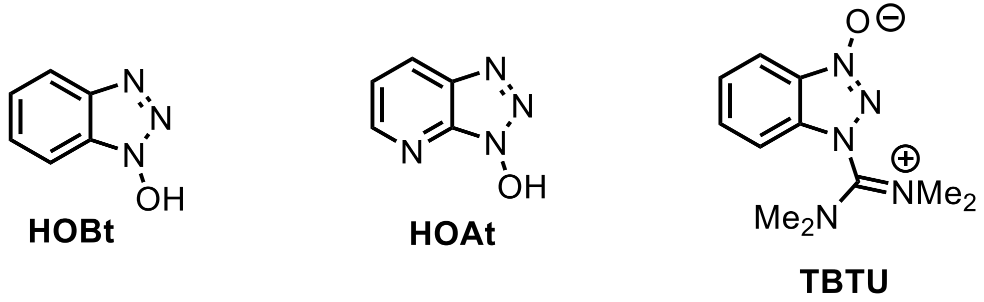


# Classical macrocyclization methods

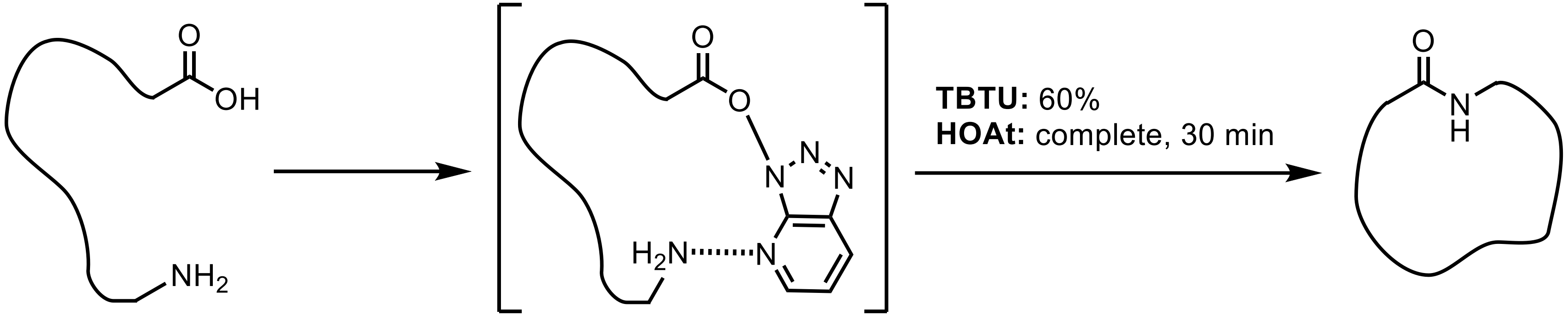
Many methods based around activation via a mixed anhydride:




Peptide coupling reagents are also highly effective.



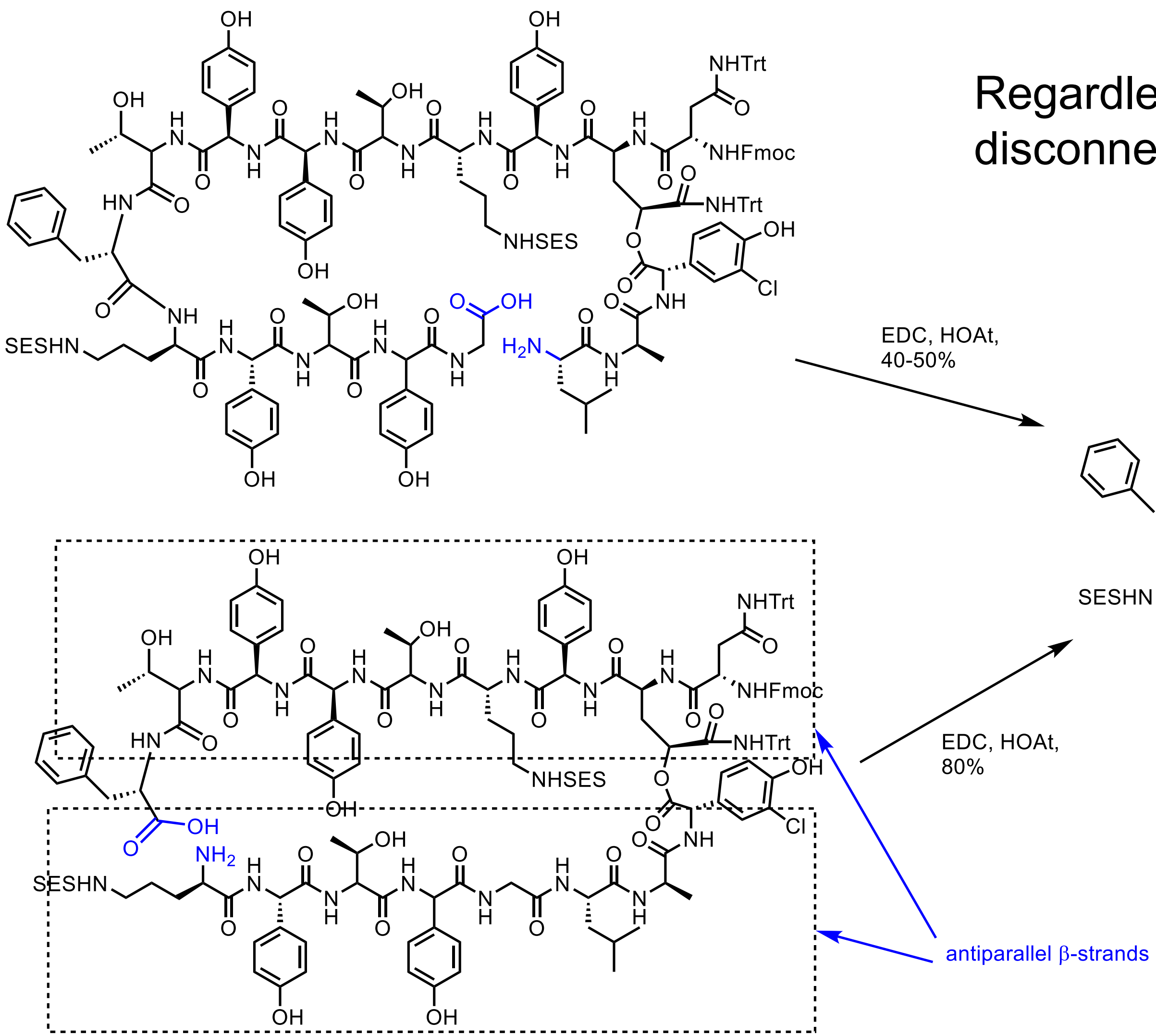

Aza-benzotriazole coupling reagents help preorganization by intramolecular H-bonding interactions.

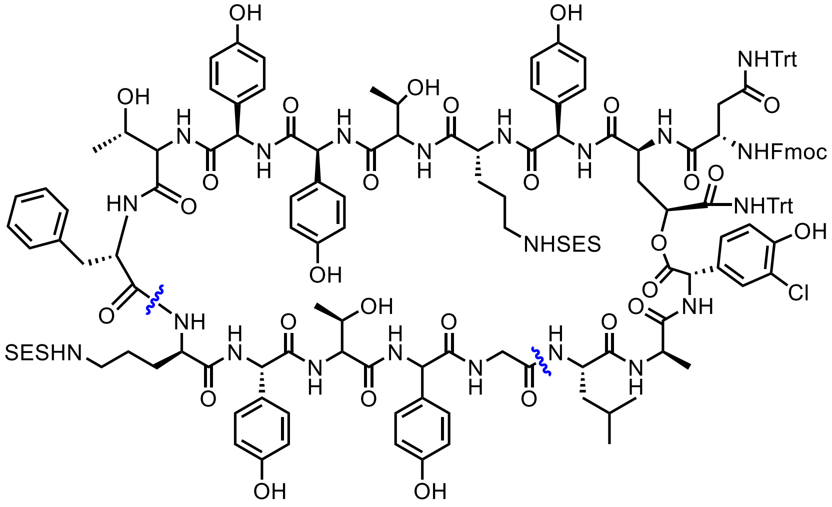



Ehrlich *et al .J. Org. Chem.* **1996**, 61, 8831-8838. Yamaguchi *et al. Bull. Chem. Soc. Jpn.* **1979,** 52, 1989.

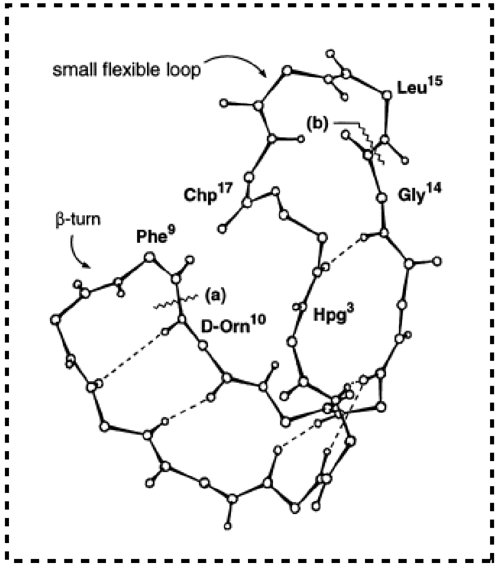
# Classical macrocyclization methods: the disconnection matters

Regardless of conditions, the choice of macrocylization disconnection has a huge impact on overall yield.



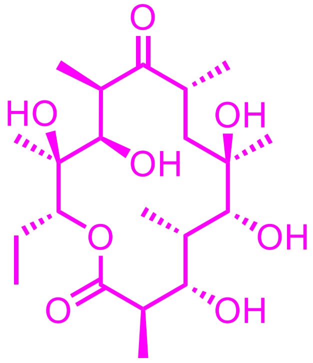




**Ramoplanin A**

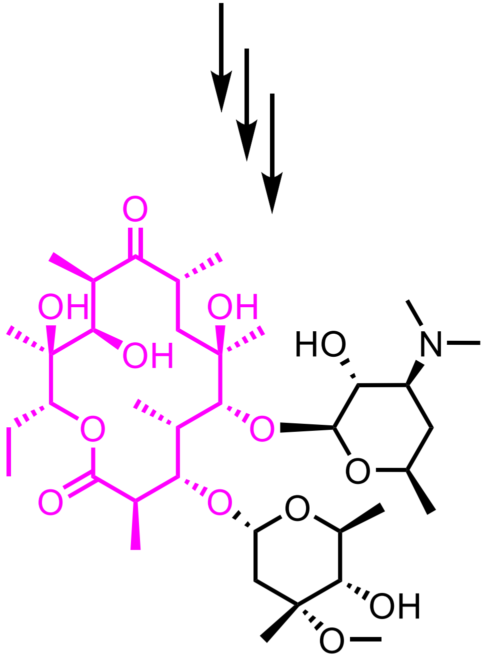



Boger's synthesis of Ramoplanin A shows strategic disconnection at the end of a β-turn, exploiting natural H-bond driven preorganization in peptide.

# Substrate preorganization: rigidification with cyclic protecting groups




erythronolide A

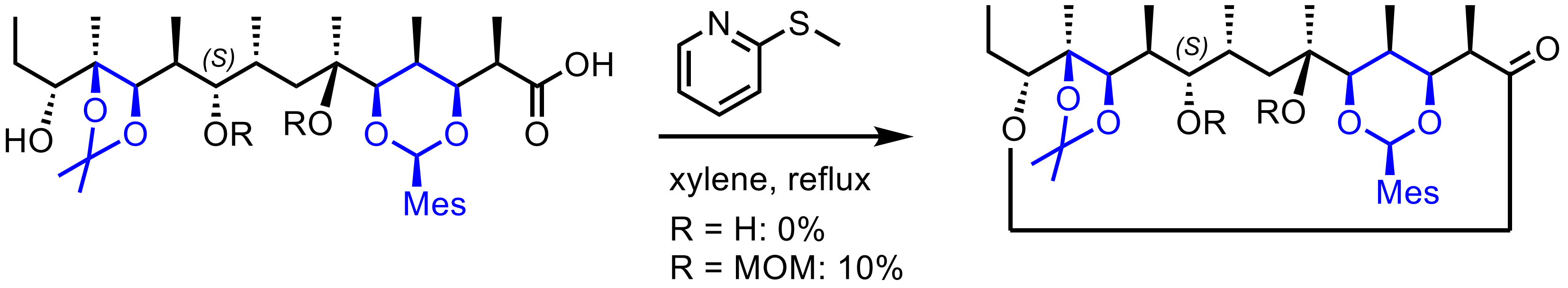


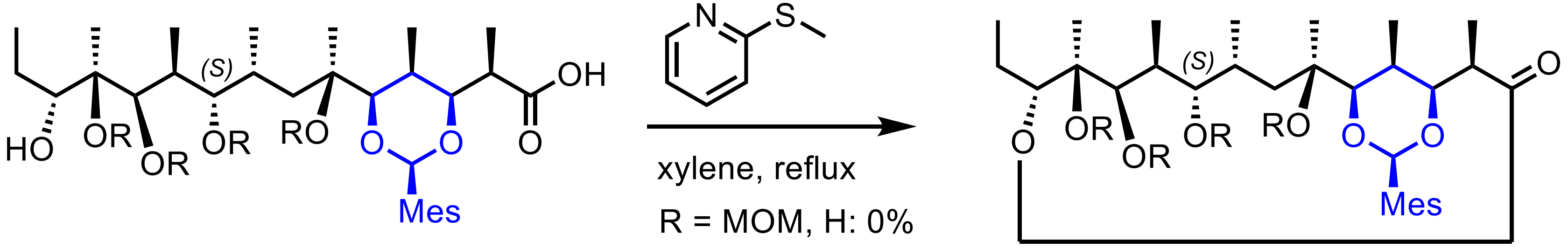

erythromycin

Erythronolide A comprises the macrolide portion of the antibiotic erythromycin.

First total synthesis by Woodward *et al* (1981) ran in to problems with macrolactonization via acid activation.

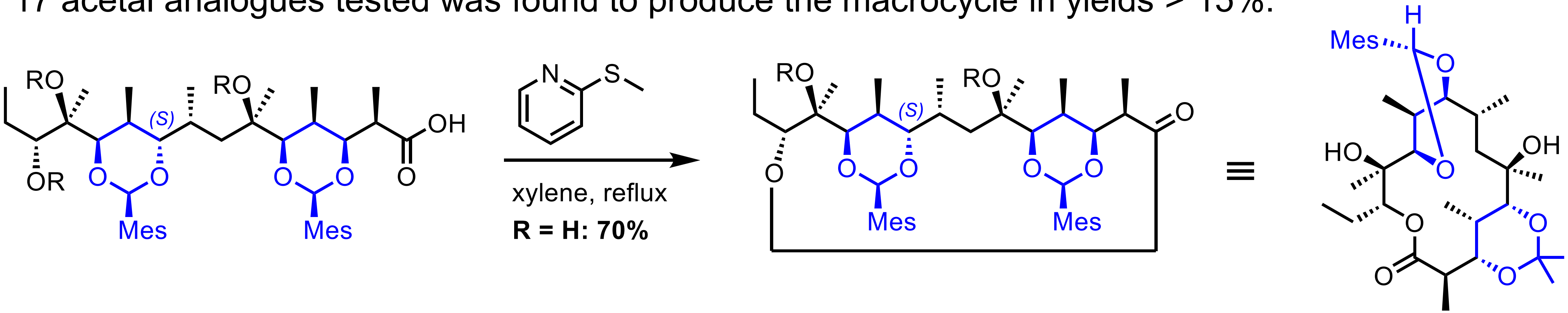
Introduction of cyclic protecting groups was intended to rigidify the *seco*-acid precursor in a conformation that favored macrolactonization:



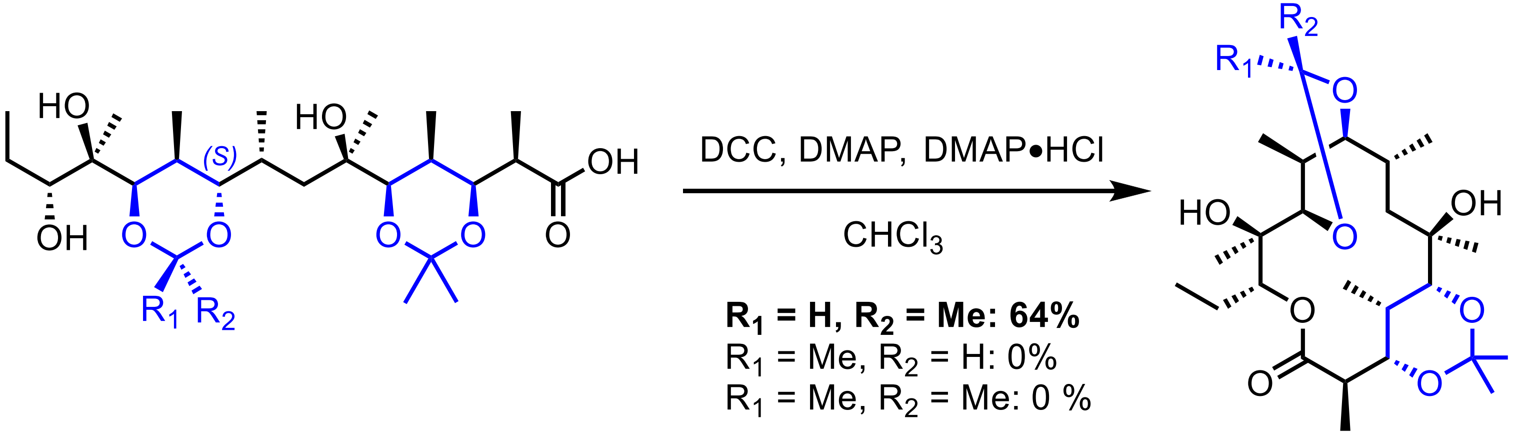



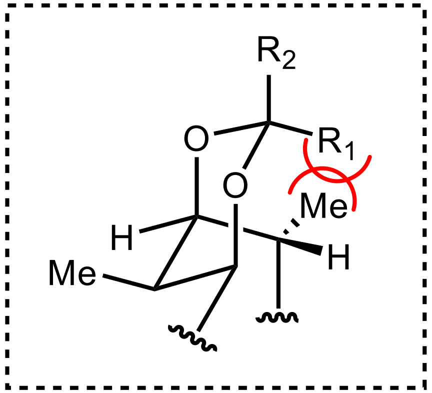
# Substrate preorganization: rigidification with cyclic protecting groups

Only 1 of 17 acetal analogues tested was found to produce the macrocycle in yields > 15%:



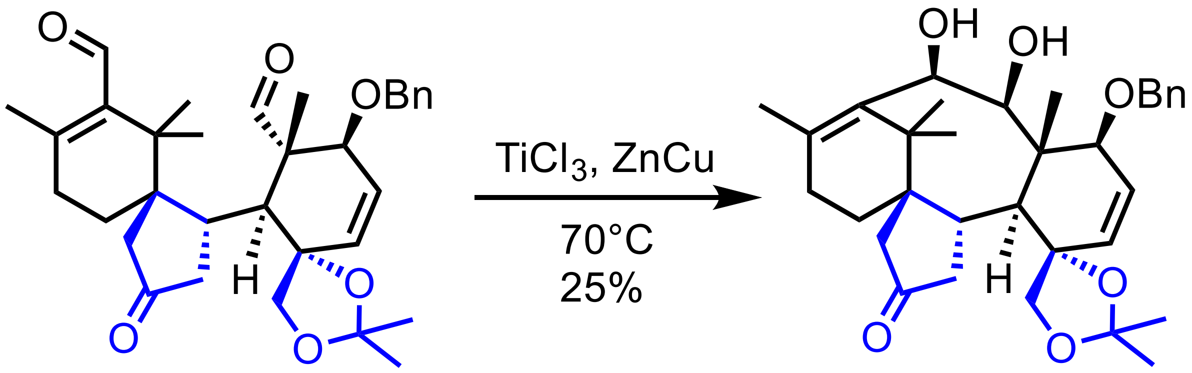

Structure-reactivity studies suggest favorable substrate preorganization results when steric interaction with neighboring Me is avoided:

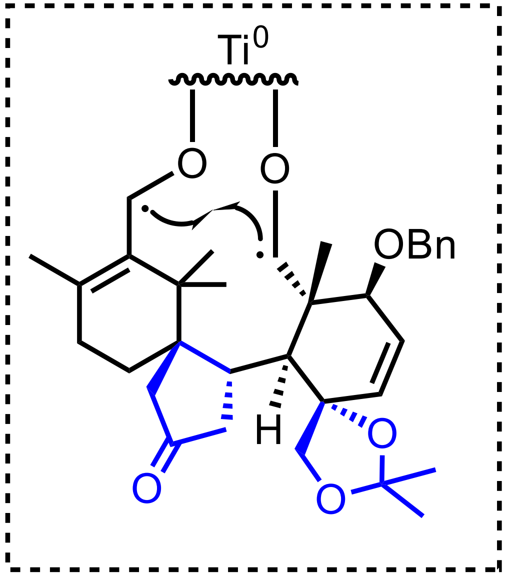


# Substrate preorganization: rigidification with cyclic protecting groups

A similar rigidification strategy was employed by Nicolaou *et al* in the total synthesis of taxol (1994):

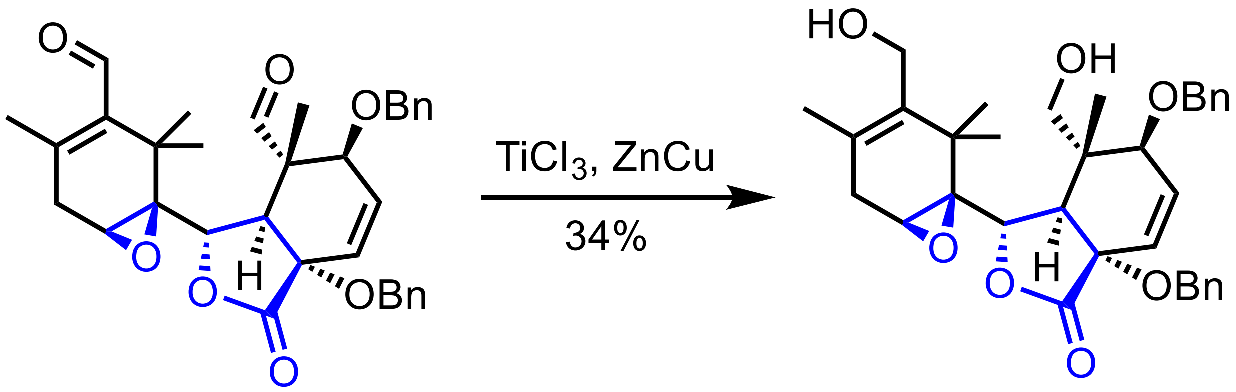


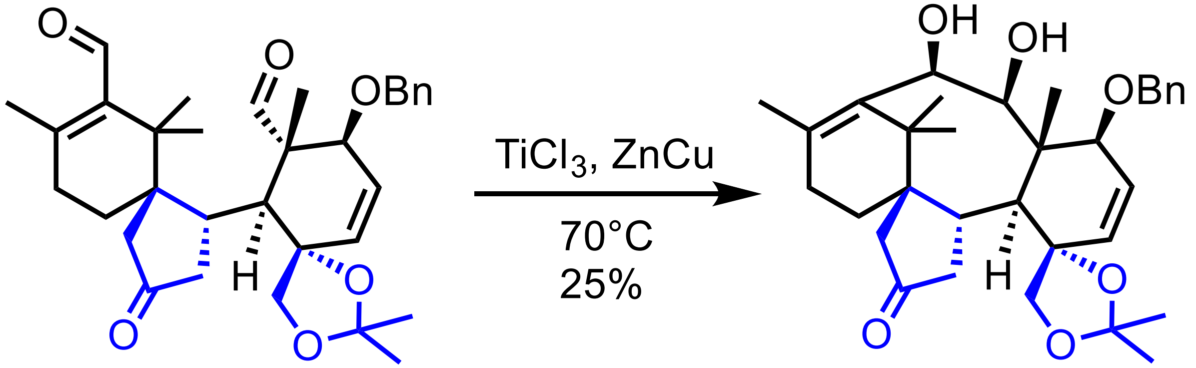




Metal reaction centers provide a templating effect, bringing the reactive sites in close proximity.

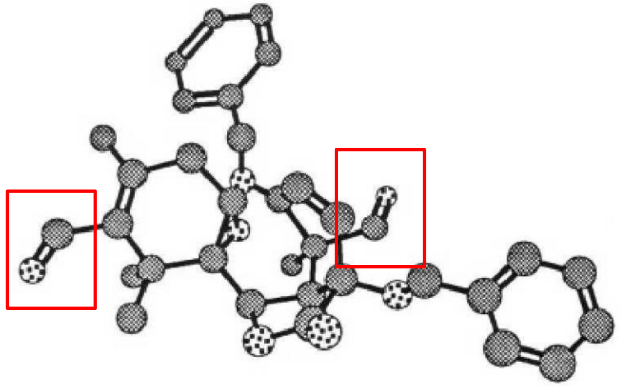
# Substrate preorganization: rigidification with cyclic protecting groups

The first attempt failed and could have been avoided by modelling substrates before macrocyclization:

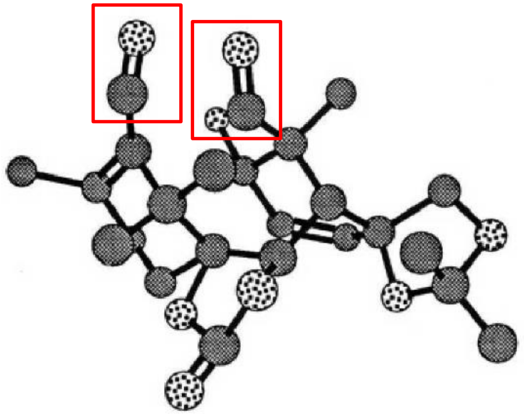



Distal aldehydes:



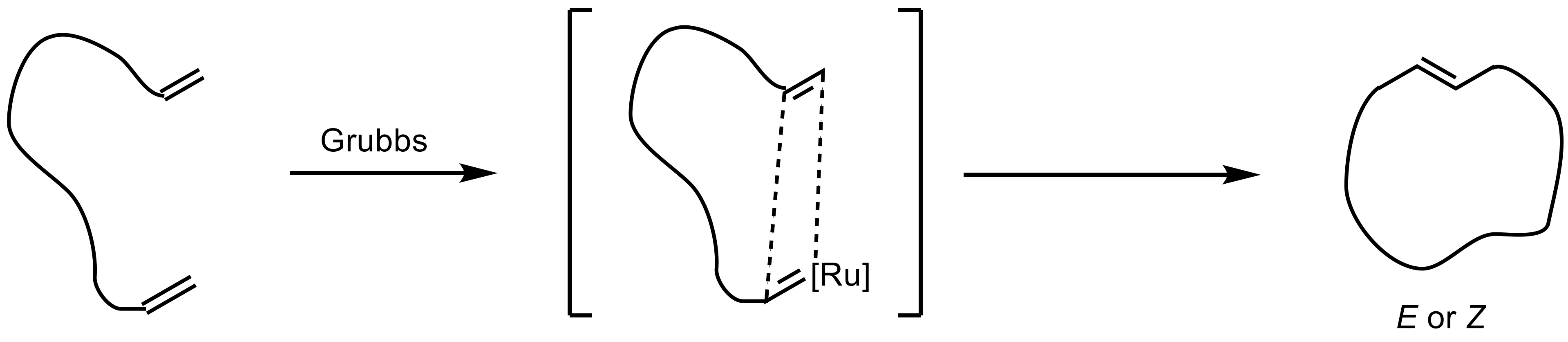
Proximal aldehydes:



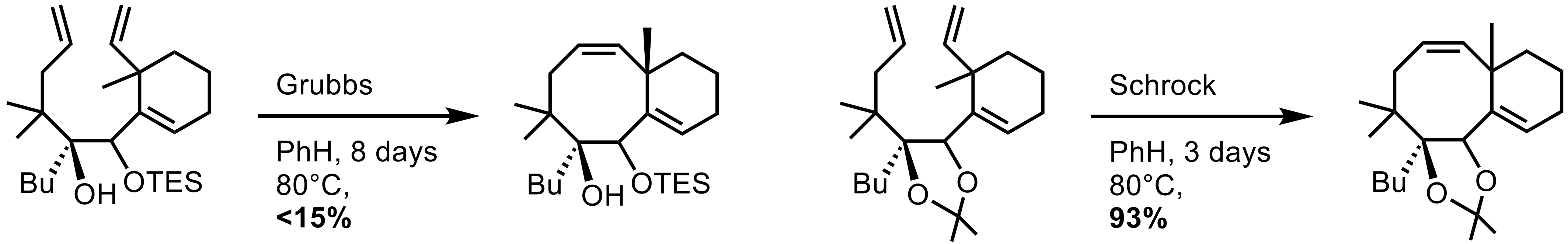
Low-theory Chem3d optimization correctly predicts approximation of reactive sites

# Moving past substrate-preorganization to templates via transition metal catalysts

Grubbs olefin metathesis provides a metal alkylidene template for cyclization:

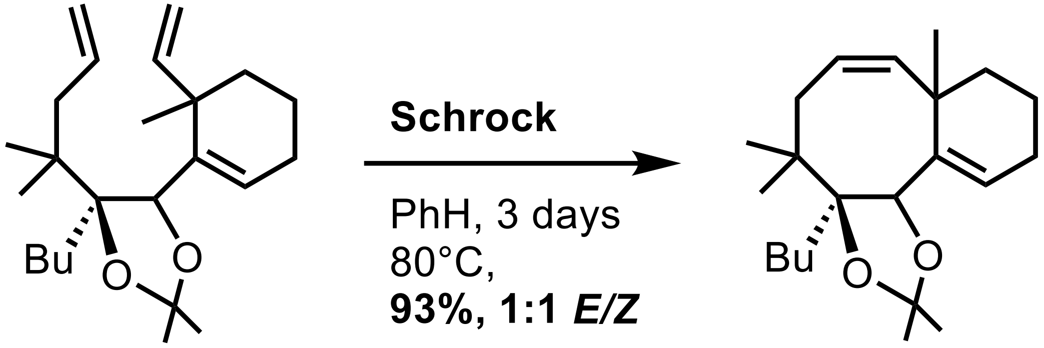


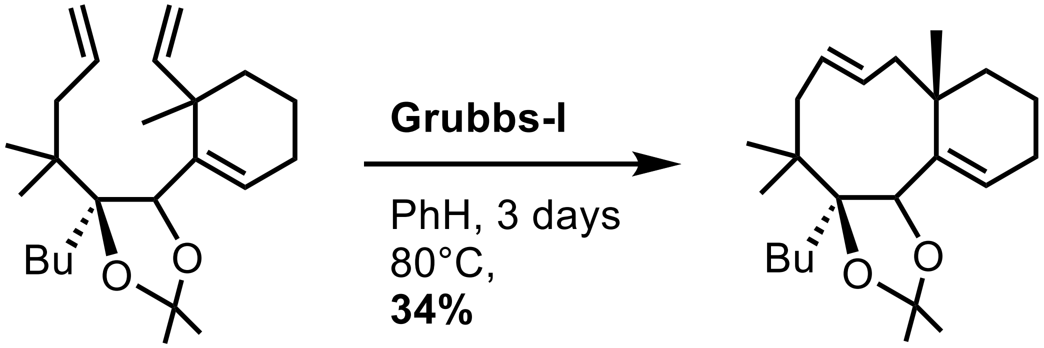

Ring-closing metathesis methods still require some substrate preorganization and benefit from rigidification:

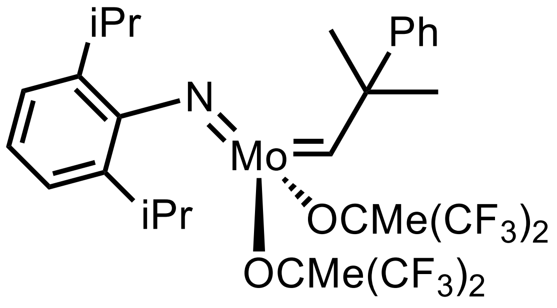


# Moving past substrate-preorganization to templates via transition metal catalysts

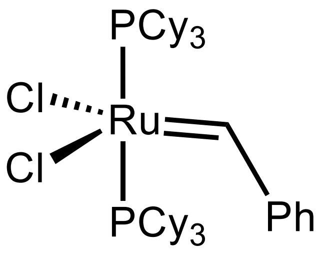
Stereoselectivity in the olefin can be challenging to control (more on this later):



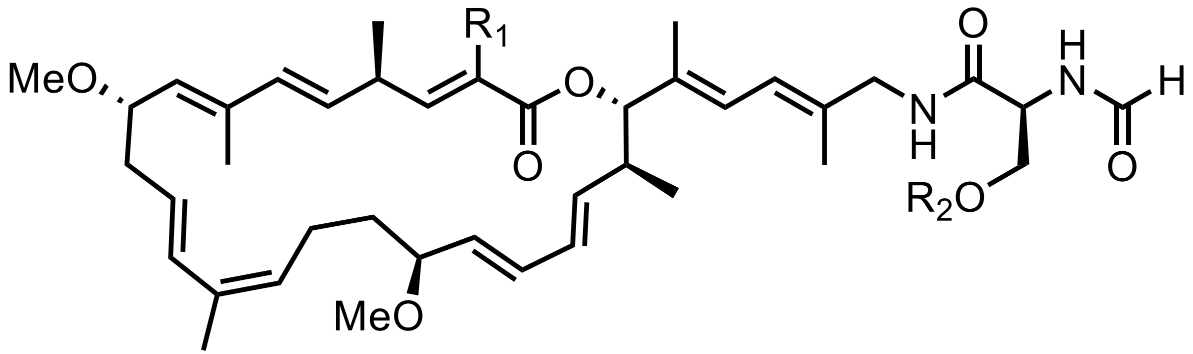

**Schrock**




**Grubbs-I**

Maier. *Angew. Chem. Int. Ed.* **2000**, 39, 2073.

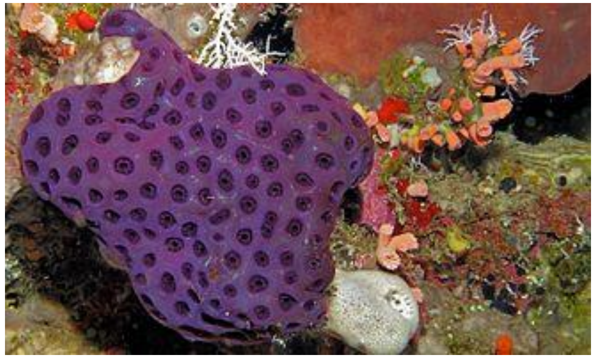
# Strategies for the synthesis of iejimalide B




Iejimalide A: $R_1 = R_2 = H$
Iejimalide B: $R_1 = Me$, $R_2 = H$
Iejimalide C: $R_1 = H$, $R_2 = SO_3Na$
Iejimalide D: $R_1 = Me$, $R_2 = SO_3Na$

Paul Helquist,
Notre Dame

Alois Furstner,
Max Planck Institute

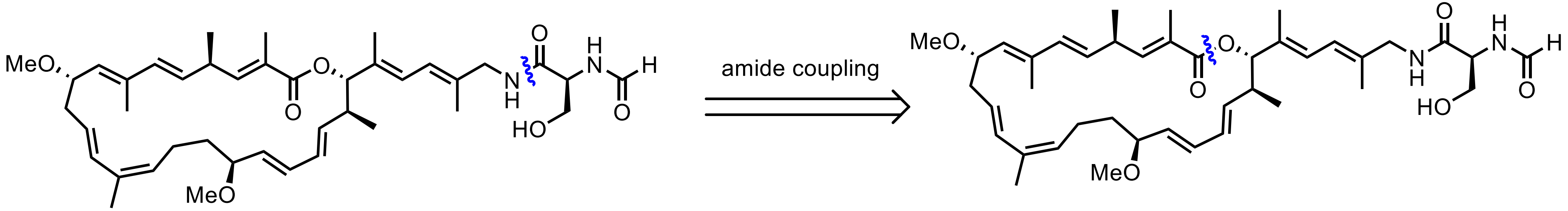


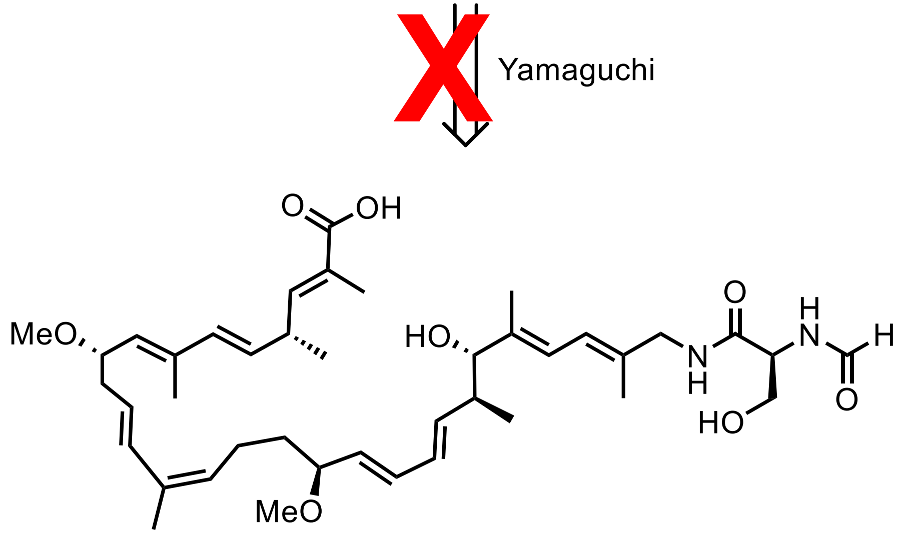
- First isolated from sea squirt *Eudistoma rigida* in 1988
- Stereochemistry was fully elucidated in 2003 via 2D NMR analysis and chiral HPLC analysis of hydrolysate
- Minute quantities of 0.0003-0.0006% by weight from natural source
- Vacuolar-type ATPase inhibitor showing growth inhibition potencies of < 5 nM against 40/60 cell lines in NCI cancer screen

Furstner *et al. Angew. Chem. Int. Ed.* **2006**, 45, 5837–5842. Helquist *et al. J. Org. Chem.* **2011**, 76, 5157–5169. Helquist *et al. Org. Lett.* **2007**, 9, 22, 4619.

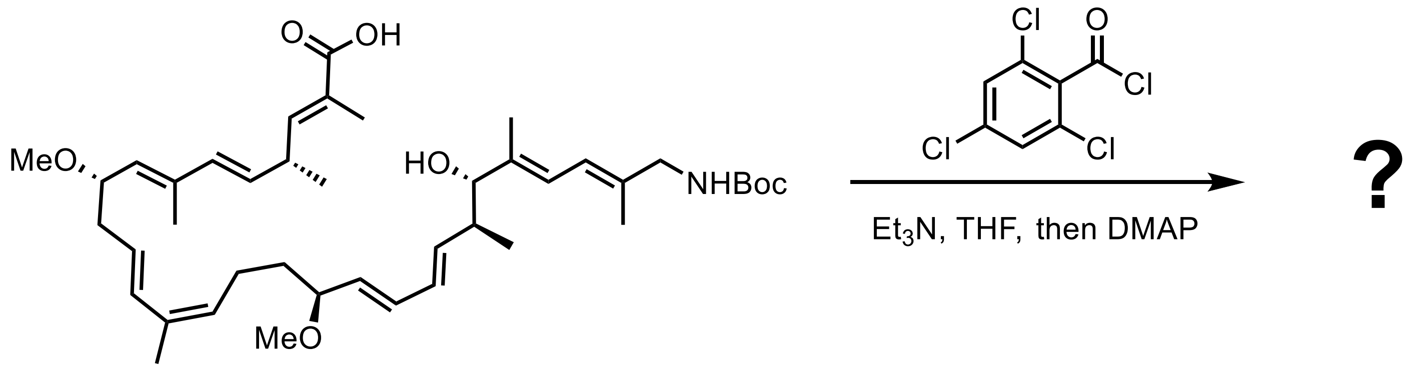
# Failure of classical macrolactonization methods in the synthesis of iejimalide B

Initial retrosynthetic analysis based on Yamaguchi macrolactonization to close the ring:

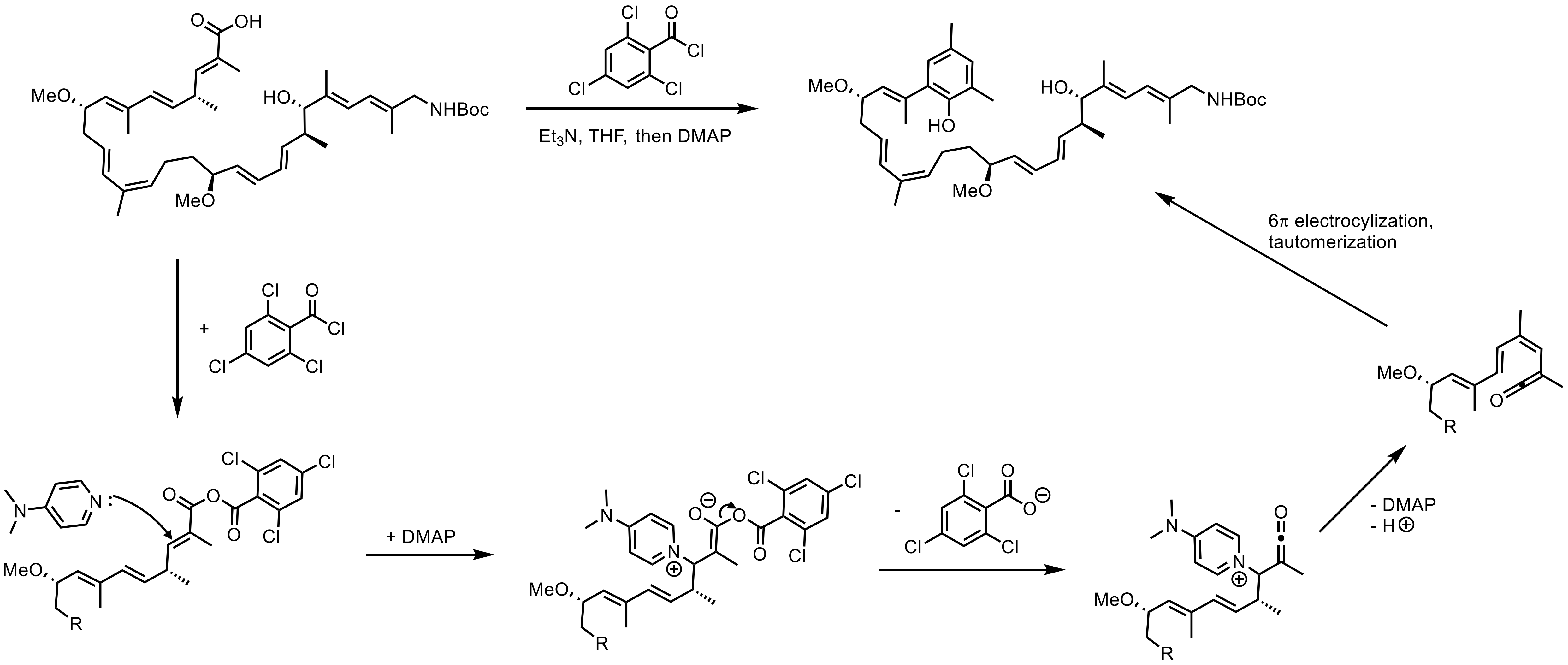



Yamaguchi conditions did not furnish the desired product:

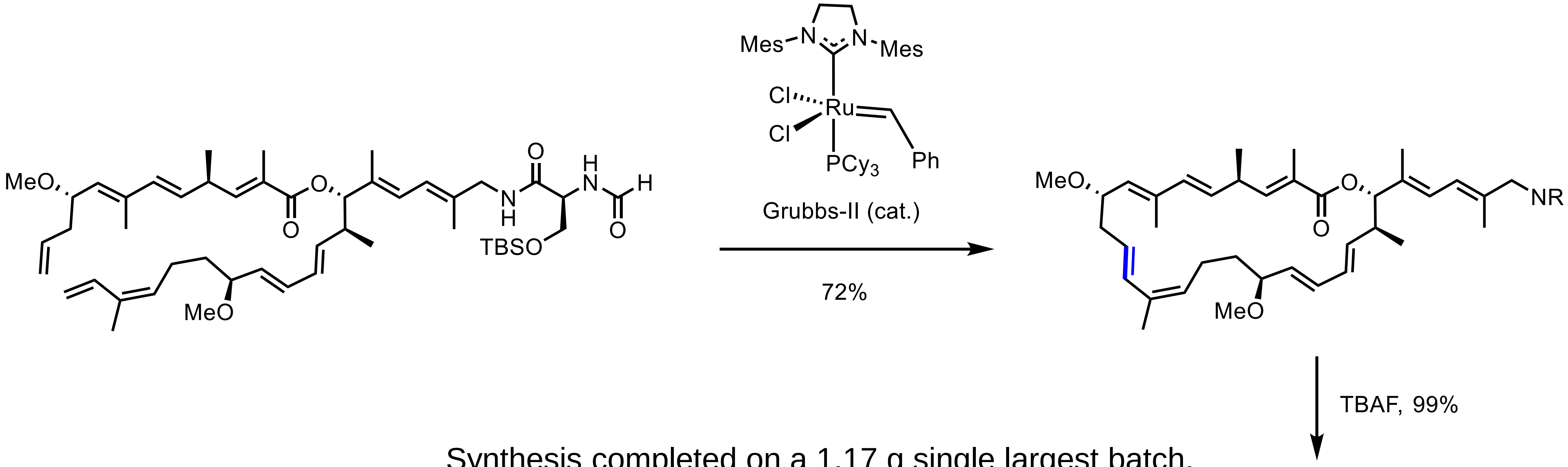


# Failure of classical macrolactonization methods in the synthesis of iejimalide B



# Second generation routes to iejimalide B based on transition metal catalysis

Grubbs ring-closing metathesis allows macrocylization in good yields:

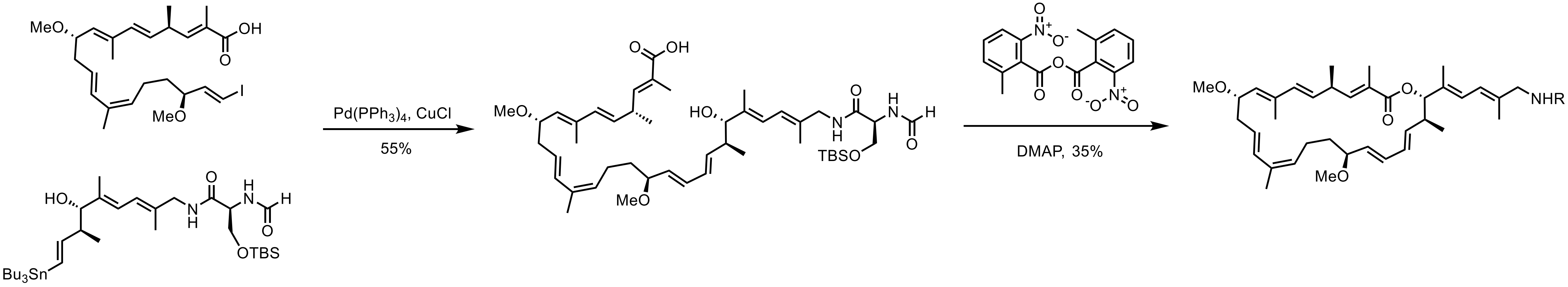



**iejimalide B**

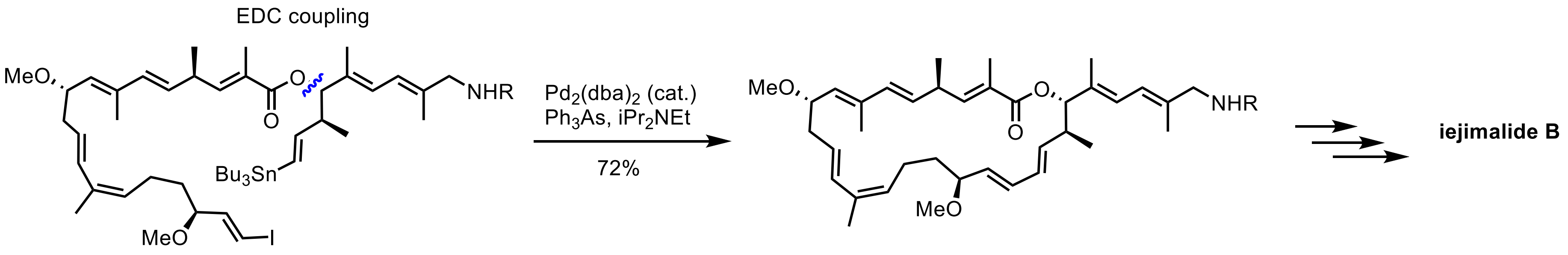
Synthesis completed on a 1.17 g single largest batch.
7% overall yield, 16 step LLS, 41 steps total

# Iejimalide B routes based on Stille couplings

Macrolactonization with the Shiina reagent permitted low yields where Yamaguchi had failed:



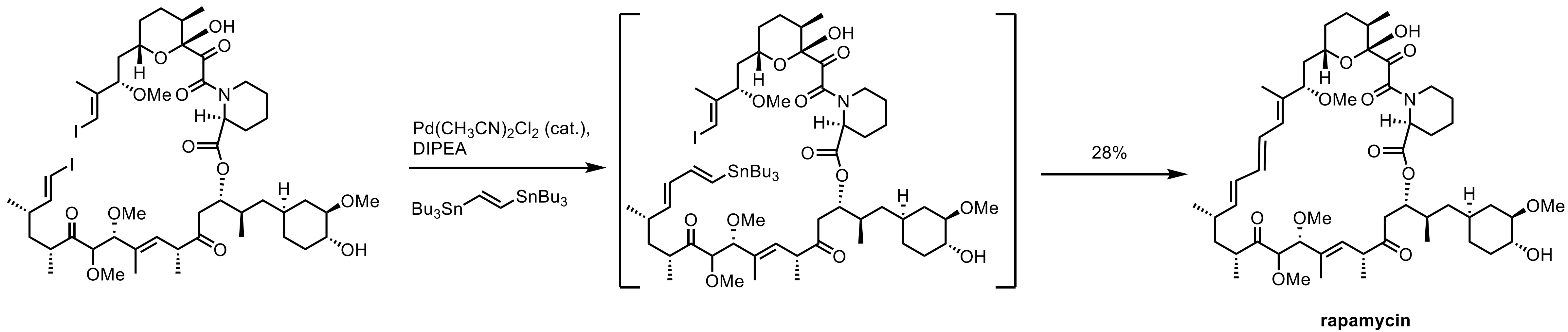

Best route to date uses a late stage Stille coupling to close the ring (Helquist 2011):



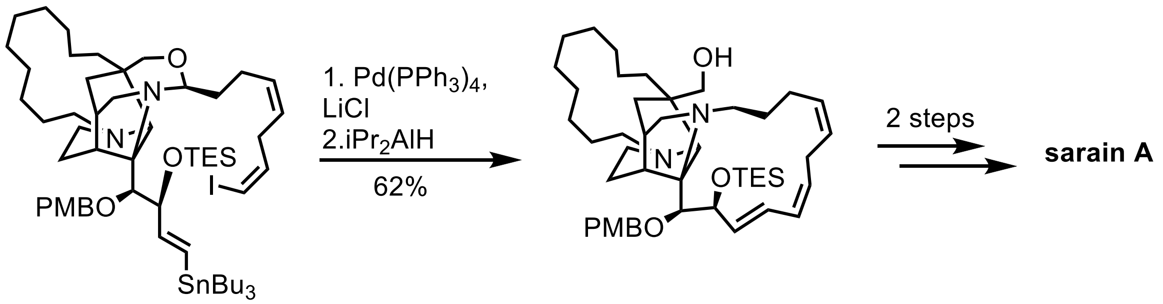

19.5% yield,
15 step LLS

# Stille couplings have seen great success in macrocylizations of late-stage intermediates

Nicalaou employs a ‘zipper’ double Stille coupling to forge the last bond in his synthesis of rapamycin:

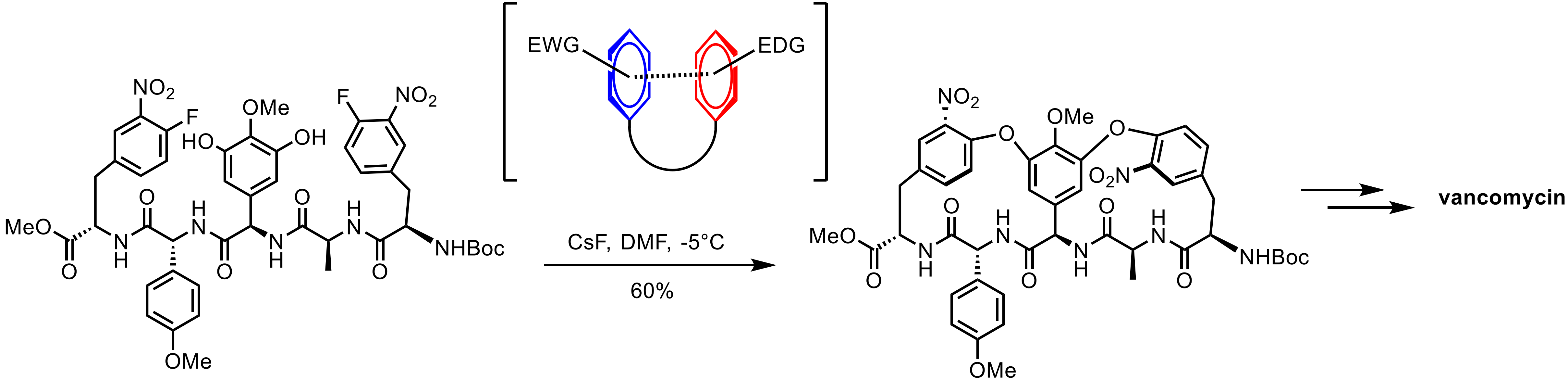



Late-stage Stille coupling in Overman’s synthesis of sarain A:

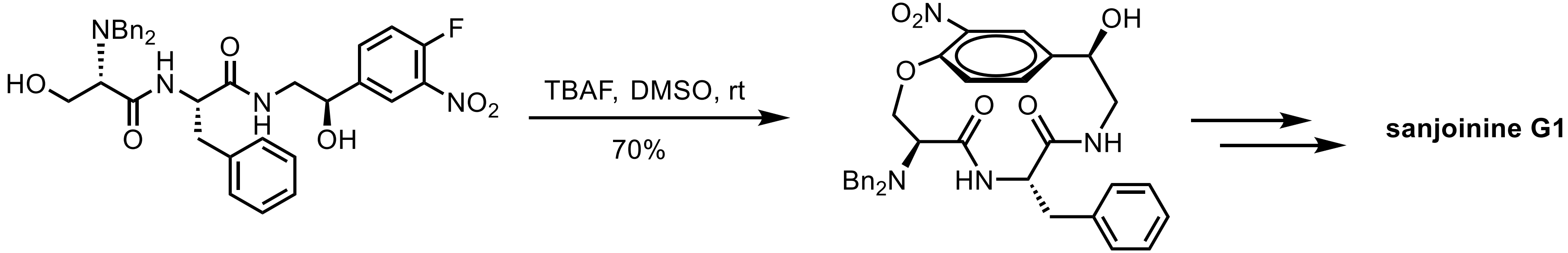


# π stacking effects to preorganize macrocylization substrates

It is common to exploit SnAr reactivity for macrocyclizations. Electron-rich and electron-poor arenes preorganize due to π stacking effects, increasing efficiency of macrocyclization:



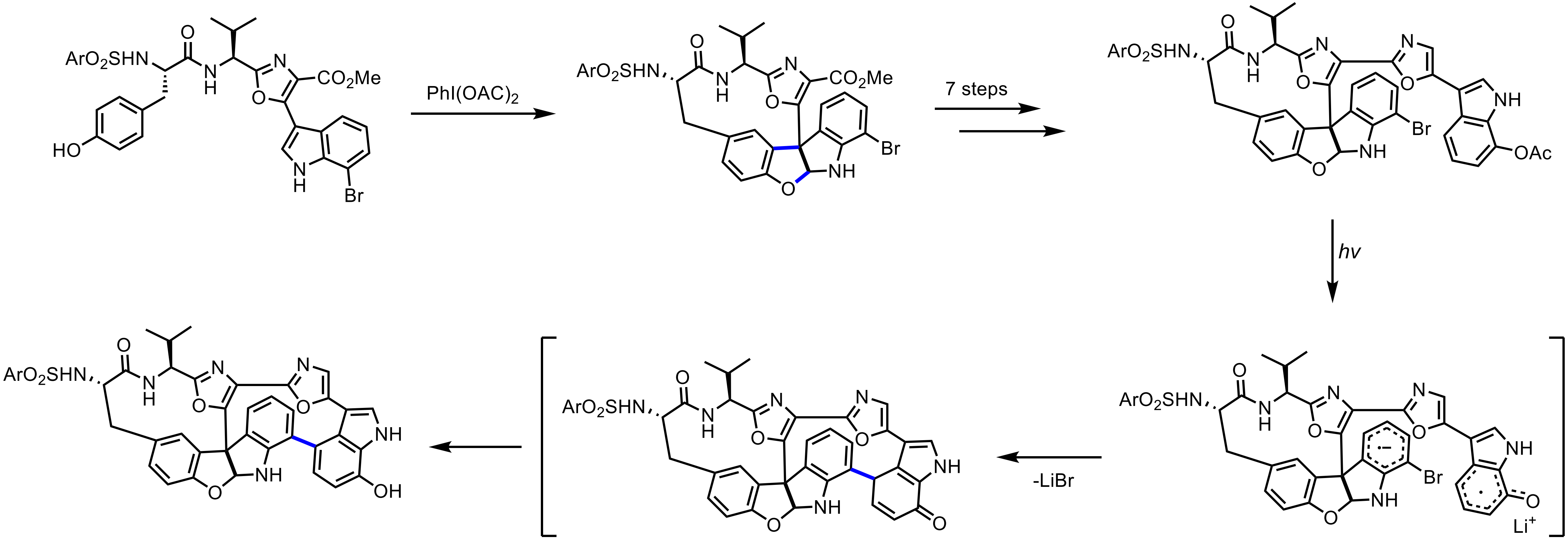

This effect is often overstated in the literature, and stacking is invoked unnecessarily.




No second arene and reactive sites are still predicted to be within 4.7Å of each other (OPLS)!

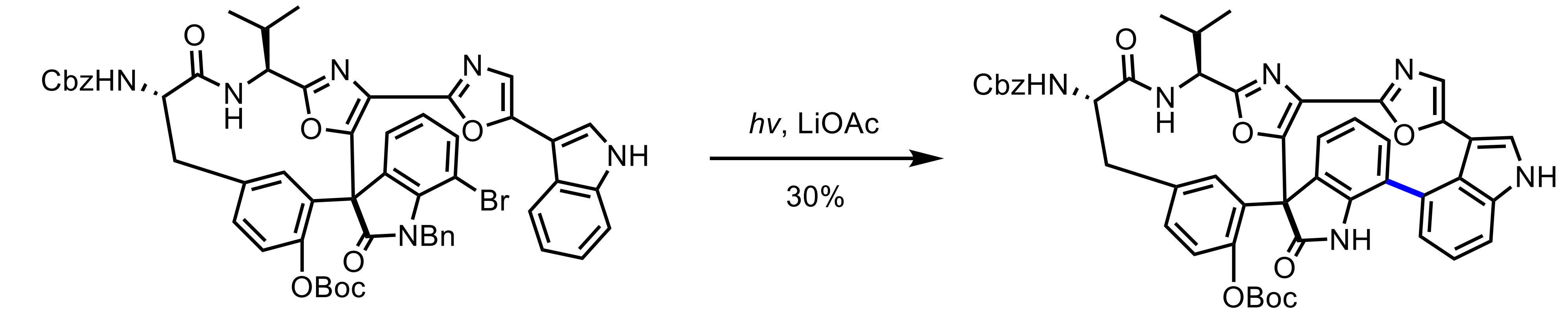
# Electron rich vs. neutral arenes in the synthesis of diazonamide A

Harran's route employs oxidative cyclization and Witkop cyclization to form macrocycles:

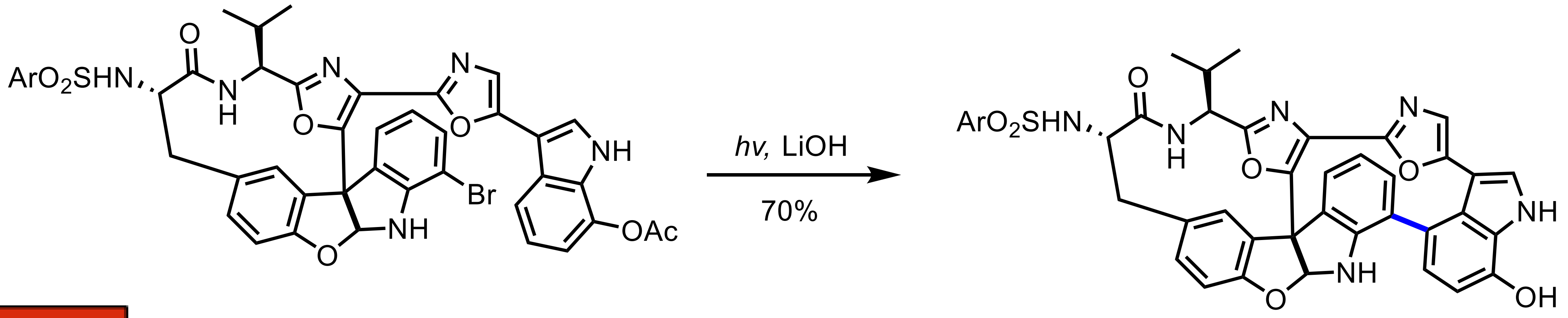


# Electron rich vs. neutral arenes in the synthesis of diazonamide A

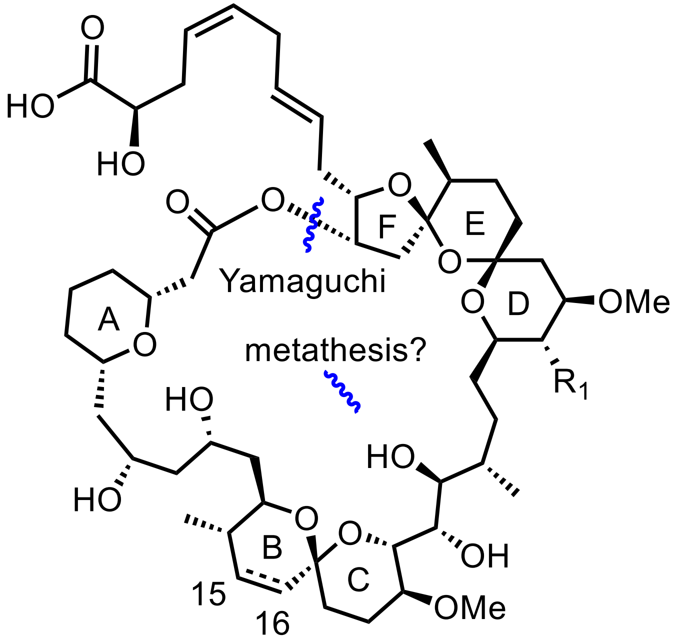
Nicolaou’s original route to diazonamide did not include any electronic biasing elements for cyclization:




Electron rich phenol approximates rings prior to cyclization due π pi stacking, giving higher yields:



# Spirastrellolide macrocyclizations: comparing metathesis routes

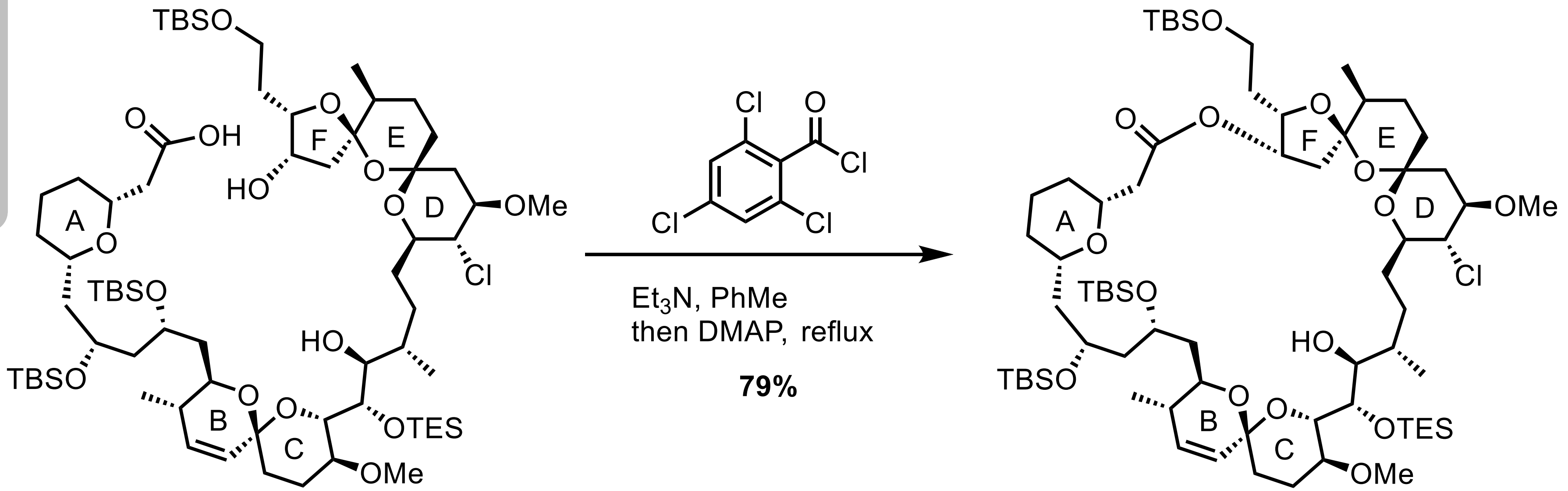



Spirastrellolide A: $R_1$ = Cl, $\Delta^{15,16}$
Spirastrellolide B: $R_1$ = H
Spirastrellolide F: $R_1$ = Cl

Isolated from marine sponge *Spirastrella coccinea.*

Unusual pharmacodynamics accelerates cell entry into mitosis, then arrests mitotic activity, killing the cell.

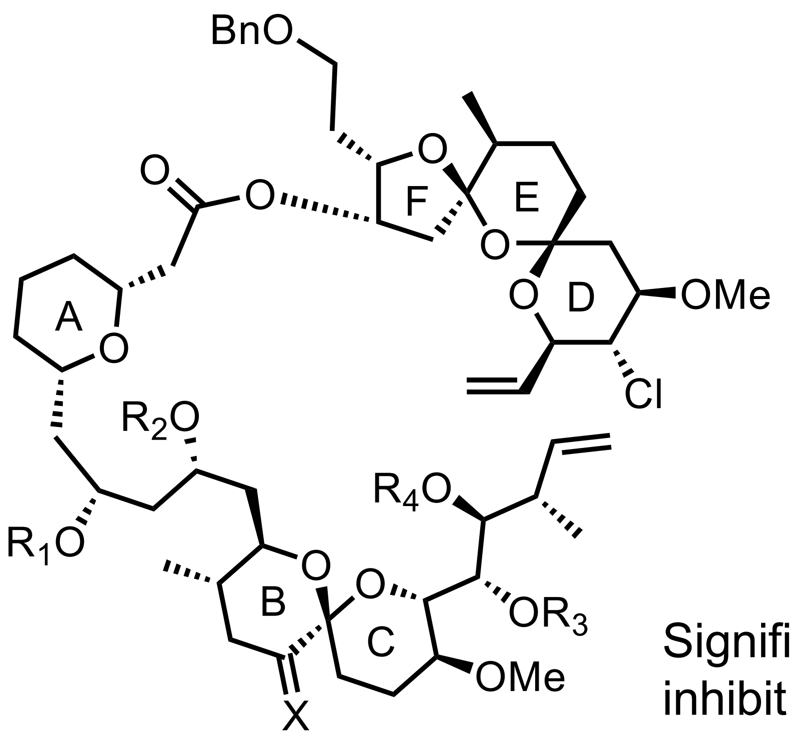
First total synthesis by Patterson employs a Yamaguchi macrolactonization:

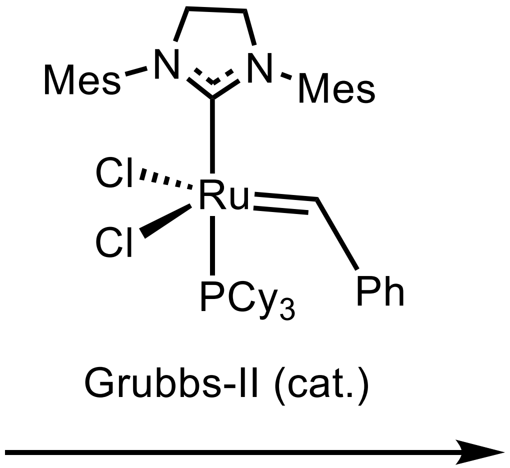



Can we think of an imaginative disconnect for RCM?

# Spirastrellolide macrocyclizations: comparing metathesis routes

First attempt at late-stage RCM on spirastrellolide was met with failure:



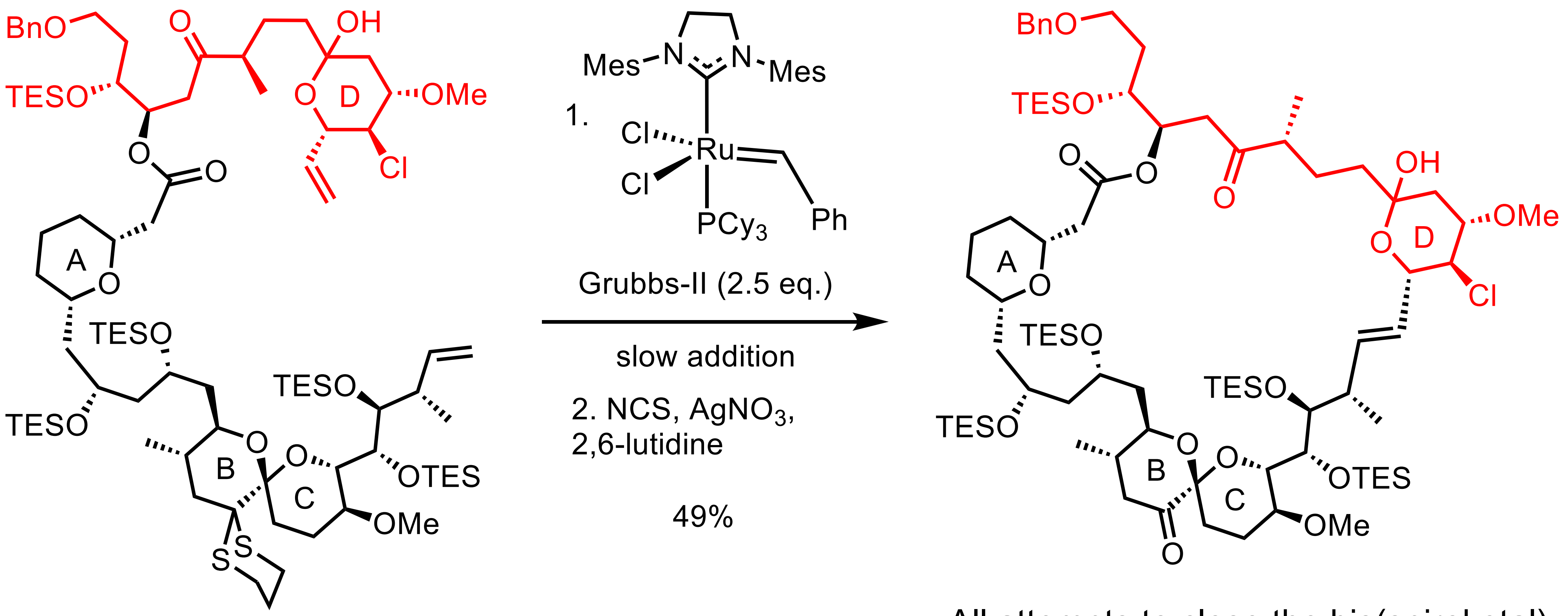




no RCM in any conditions

Significant steric hindrance around the bis(spiroketal) is thought to inhibit binding of the catalyst to the metathesis reactive sites.

# Spirastrellolide macrocyclizations: the olefin metathesis route

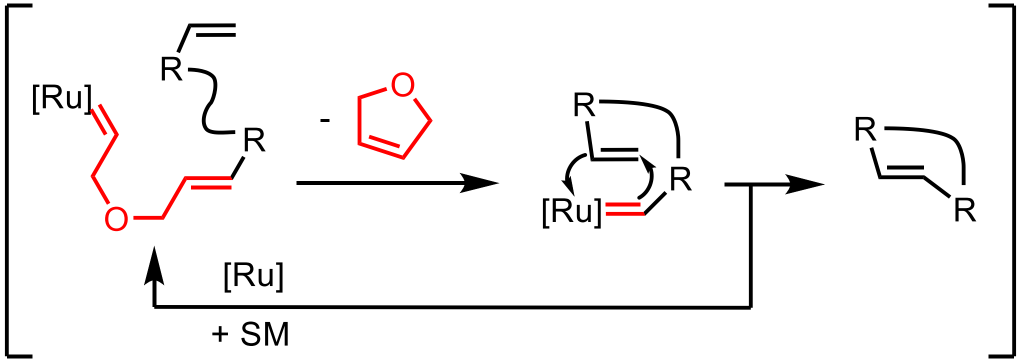
Successful ring-closing metathesis when strain in bis(spiroketal) is relieved:



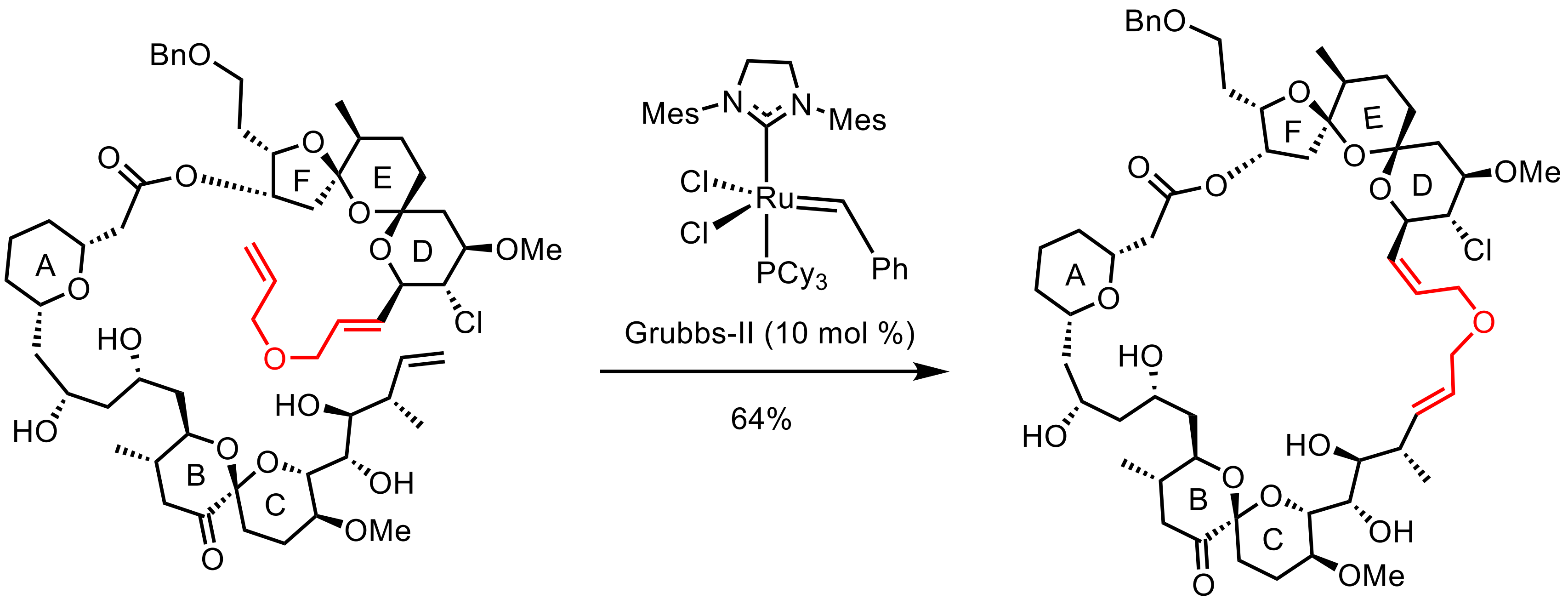

All attempts to close the bis(spiroketal) from this intermediate were unsuccessful.

# Spirastrellolide macrocyclizations: the olefin metathesis route

Relay ring-closing metathesis strategy. Approximate Ru-alkylidene to reactive site with a sterically accessible sacrificial alkene:

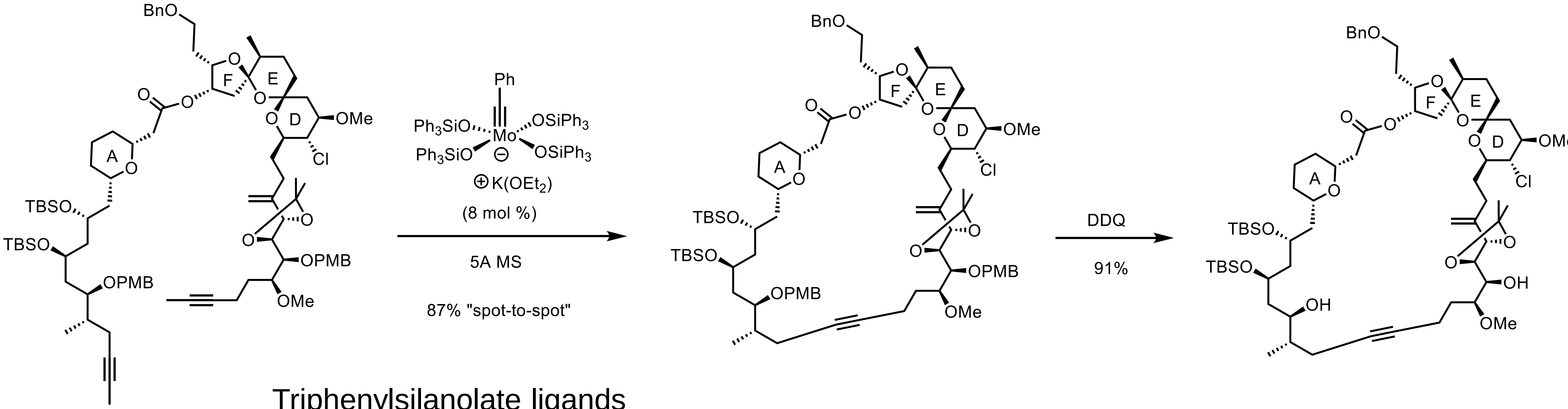



Only undesired ring-expanded products were obtained:



# Spirastrellolide macrocyclizations: transannular spiroketalization enabled by alkyne metathesis

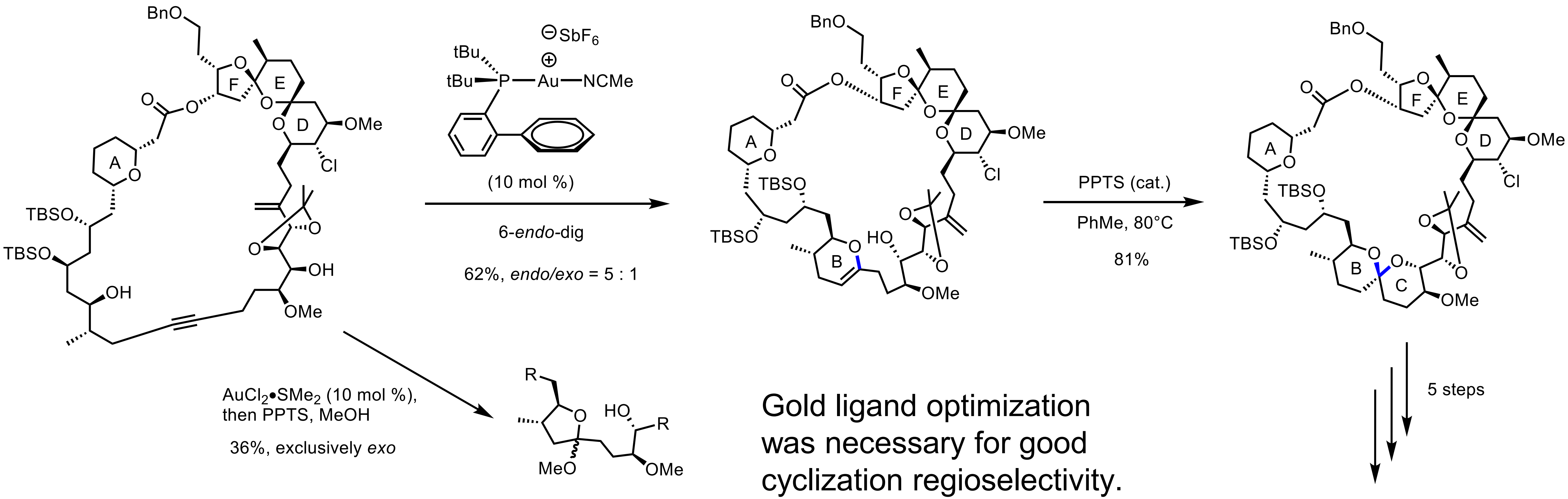
Mo(VI) catalyst provides chemoselective ring-closing alkyne metathesis. Orthogonal alcohol deprotection affords alkyne δ,γ-diol primed for spiroketalization:




Triphenylsilanolate ligands are essential to attenuate Lewis acidity of Mo(VI) center.

# Spirastrellolide macrocyclizations: transannular spiroketalization enabled by alkyne metathesis

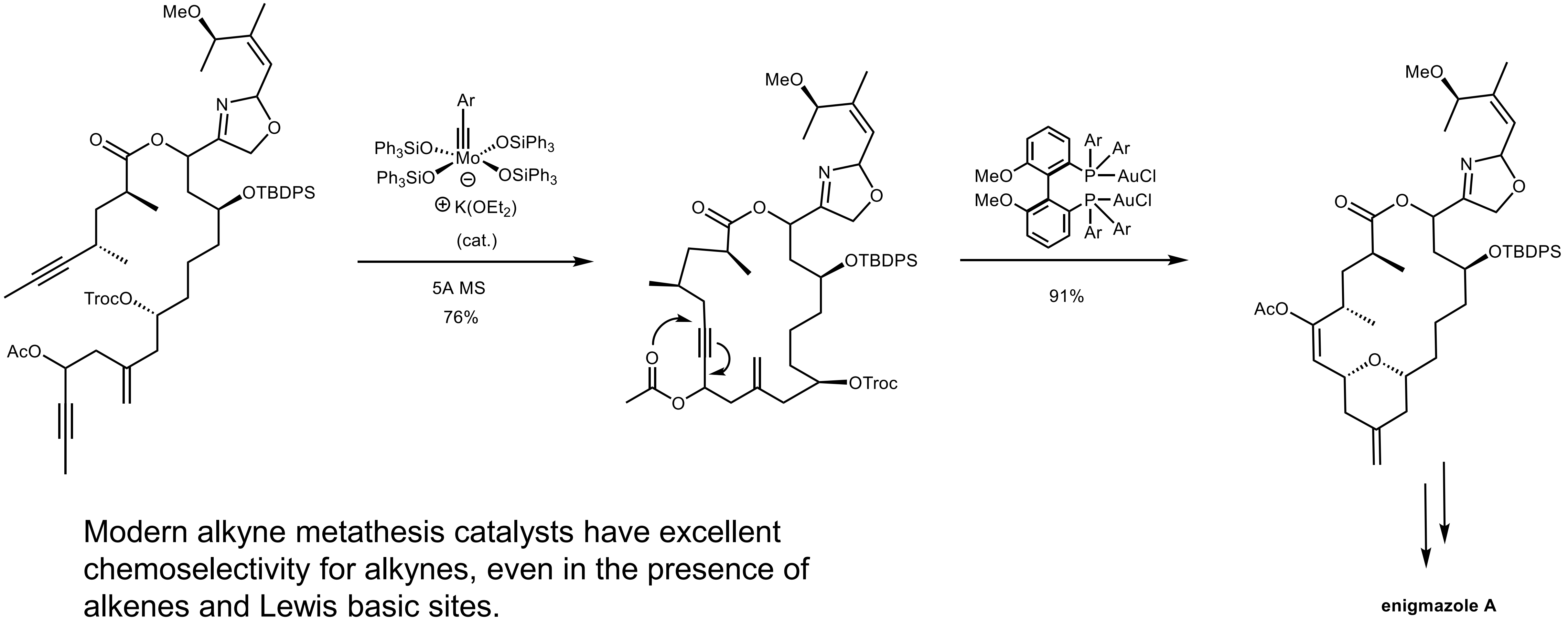
Gold-catalyzed transannular ring-closing and acid-catalyzed spiroketalization installs B and C rings in 2 steps:




spirastrellolide F methyl ester

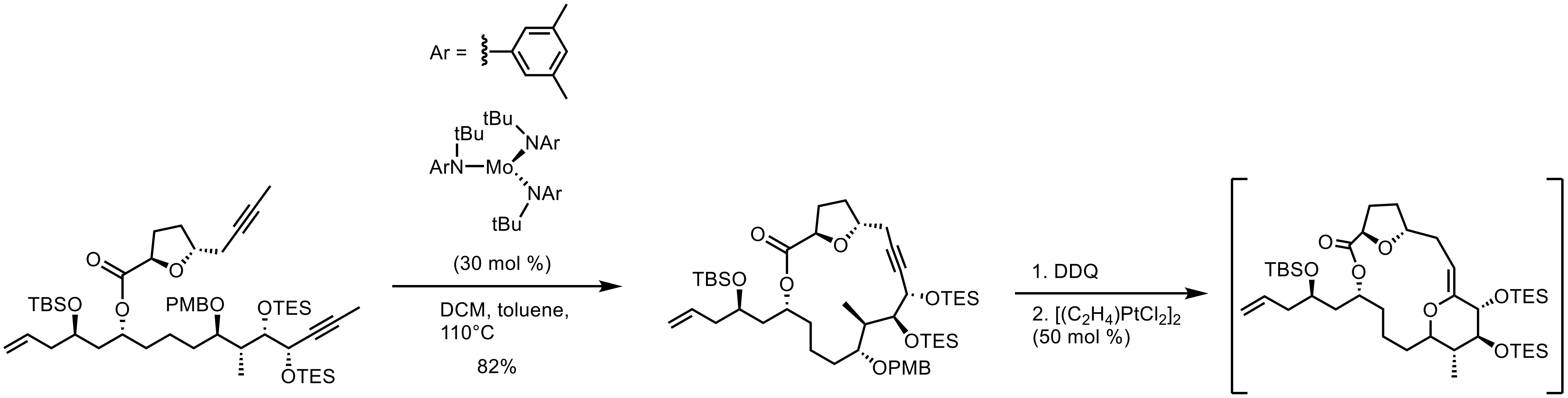
Gold ligand optimization was necessary for good cyclization regioselectivity.

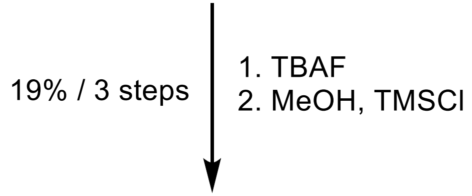
# Alkyne metathesis strategy en route to enigmazole A



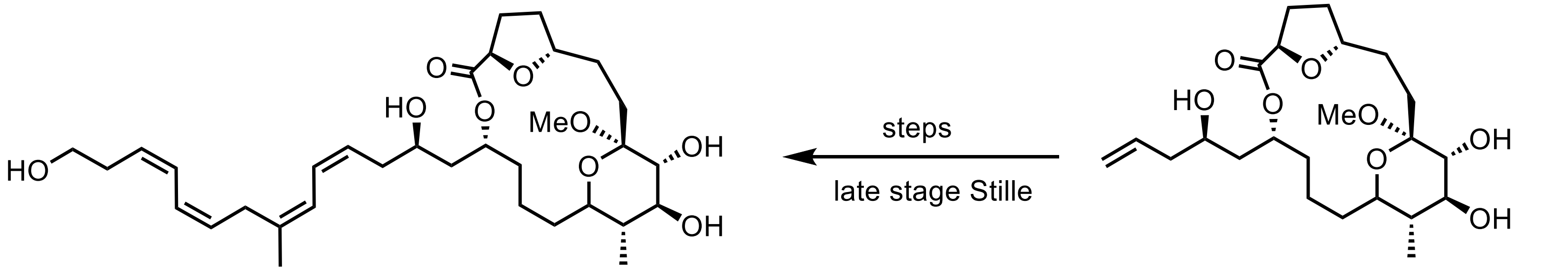

Modern alkyne metathesis catalysts have excellent chemoselectivity for alkynes, even in the presence of alkenes and Lewis basic sites.

# Alkyne metathesis and transannular hydroalkoxylation



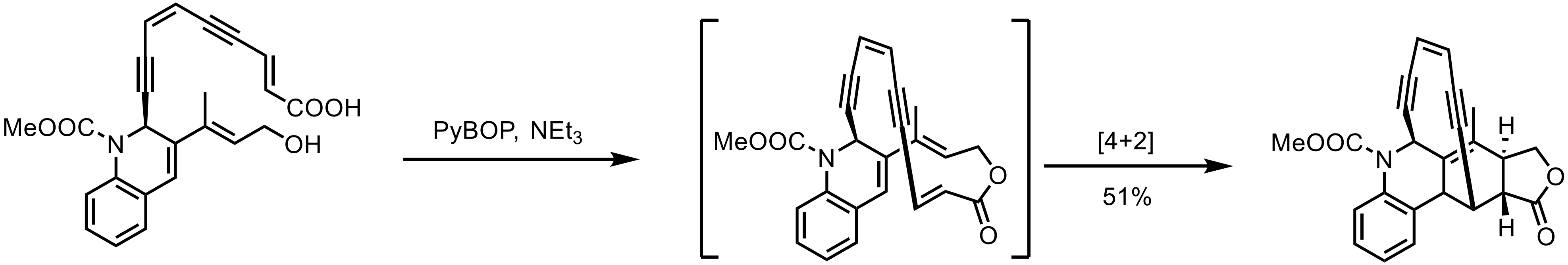

*In situ* generation of Mo(VI) catalyst by exposing Mo(III) pre-catalyst to DCM.



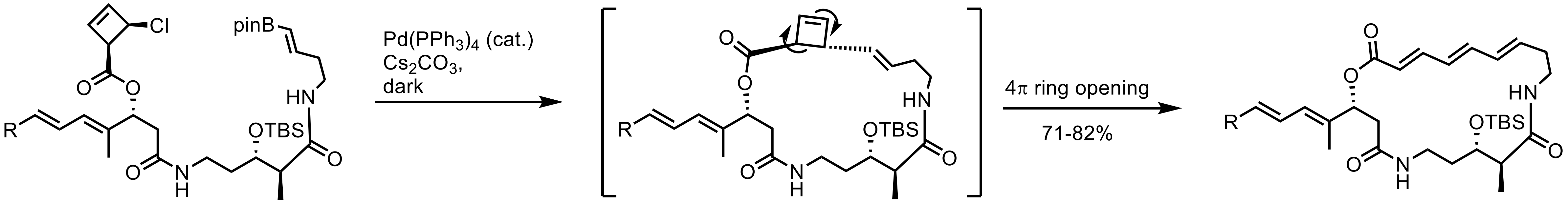

**formosalide B**

# Pericyclic reactions can also be useful in exploiting post-macrocyclization transannular reactivity

Cycloaddition reaction on esterification in the synthesis of a dynemicin A core derivative:



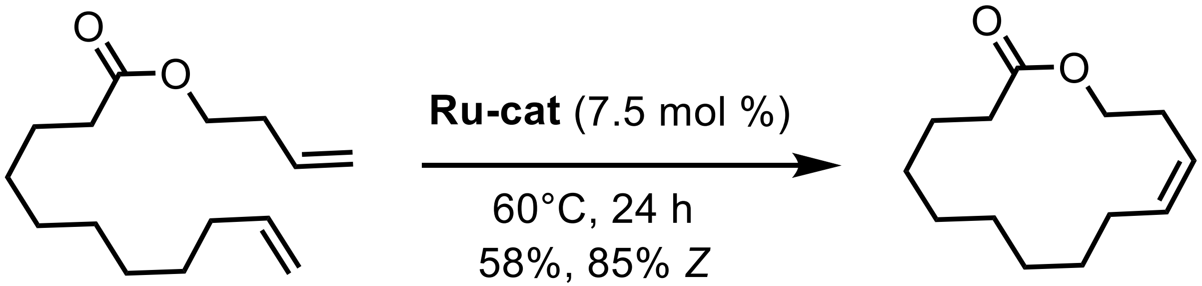

Domino Suzuki coupling, electrocyclic ring opening installs light sensitive triene:

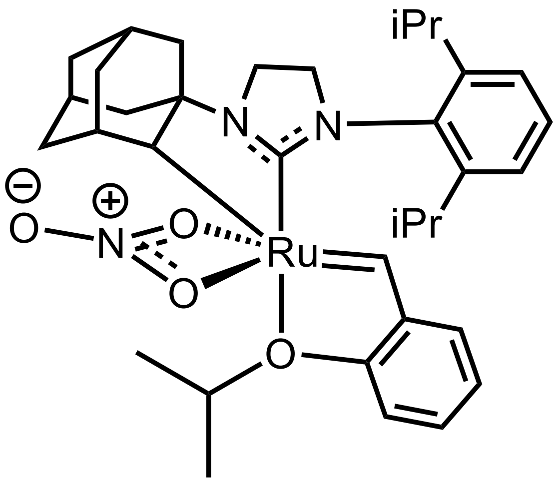



Previous Shiina based cyclization routes led to isomerization to (*Z,E,E*) triene.

# Ruthenium alkylidene catalysts for *Z*-selective ring-closing metathesis

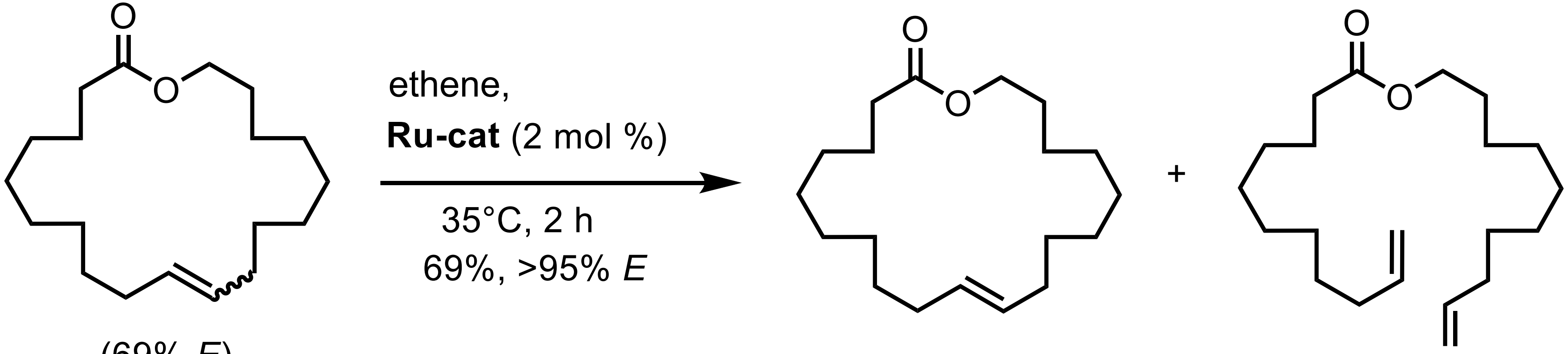
Grubbs Ru catalyst can provide good selectivity for forming *Z* macrocycles:




**Ru-cat**

Enriched *E* alkenes can be obtained by *Z*-selective ethenolysis of inseparable mixtures:

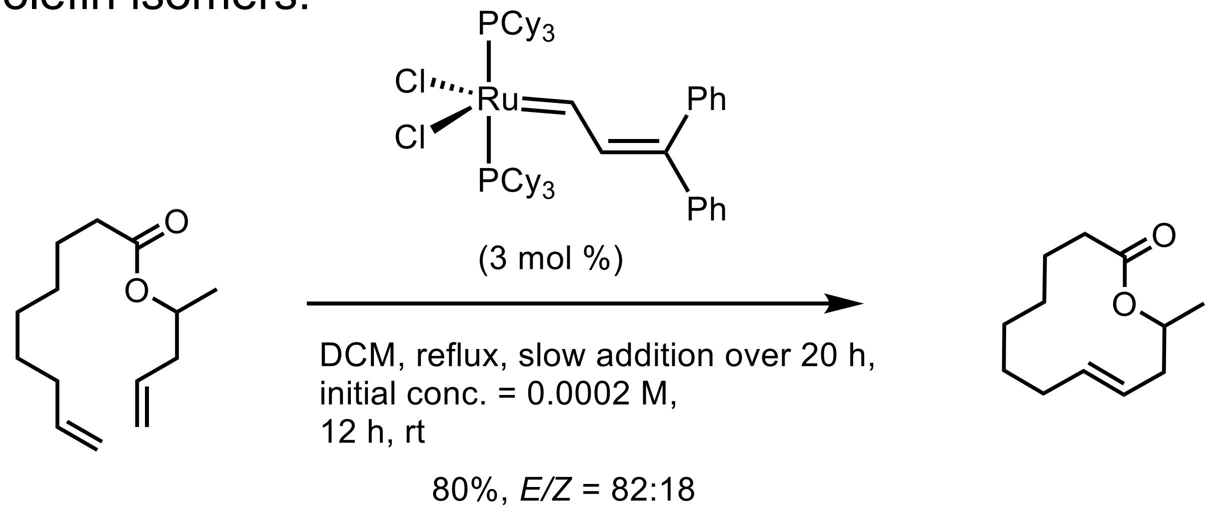



(69% *E*)

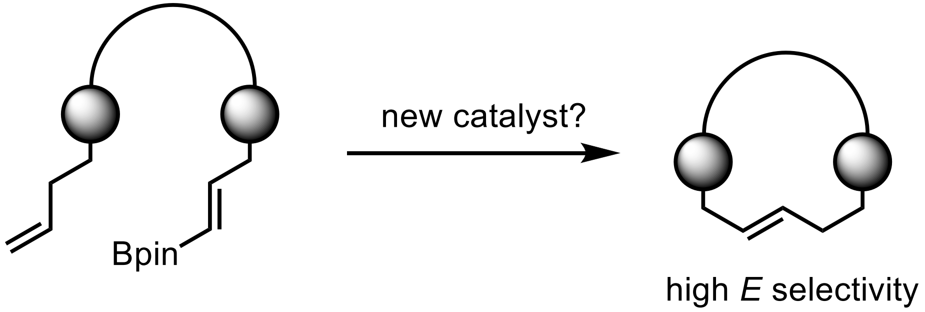
81% based on *Z* isomer left over

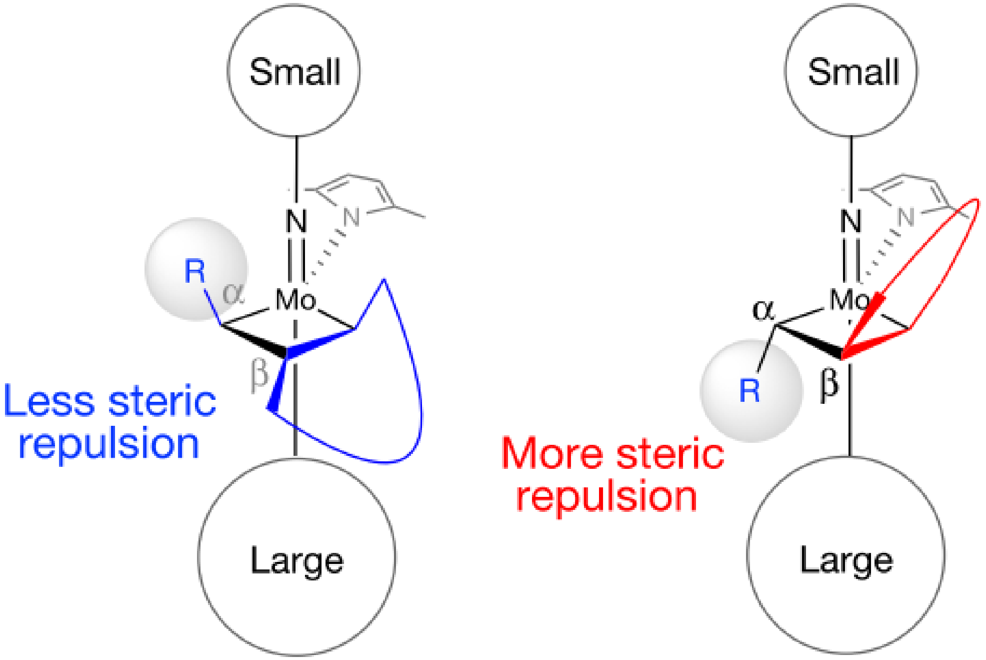
# Molybdenum alkylidene catalysts for *E*-selective ring-closing metathesis

Minor erosion of *E/Z* selectivity leads to inseparable olefin isomers:




Can we bias selectivity by including another group?



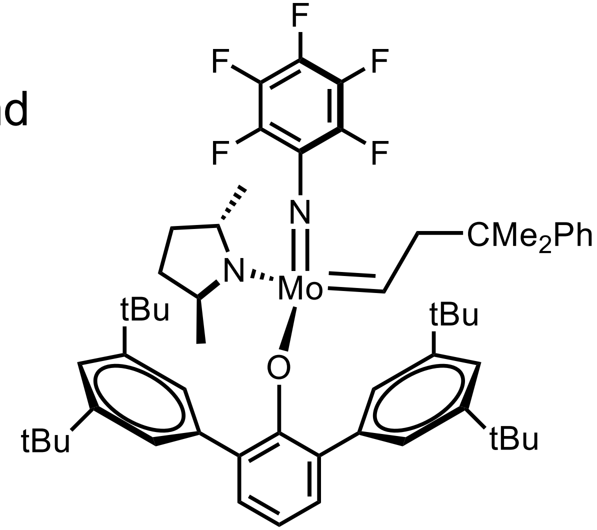



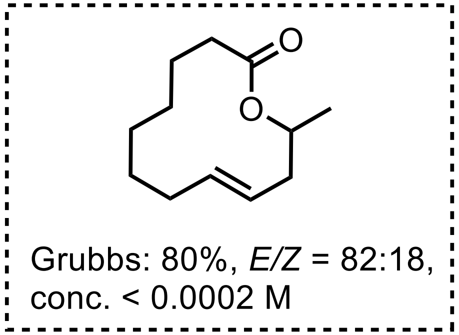

Steric effects of the Bpin substituent bias the metallocycle intermediate to adopt a *trans* configuration around the forming olefin.

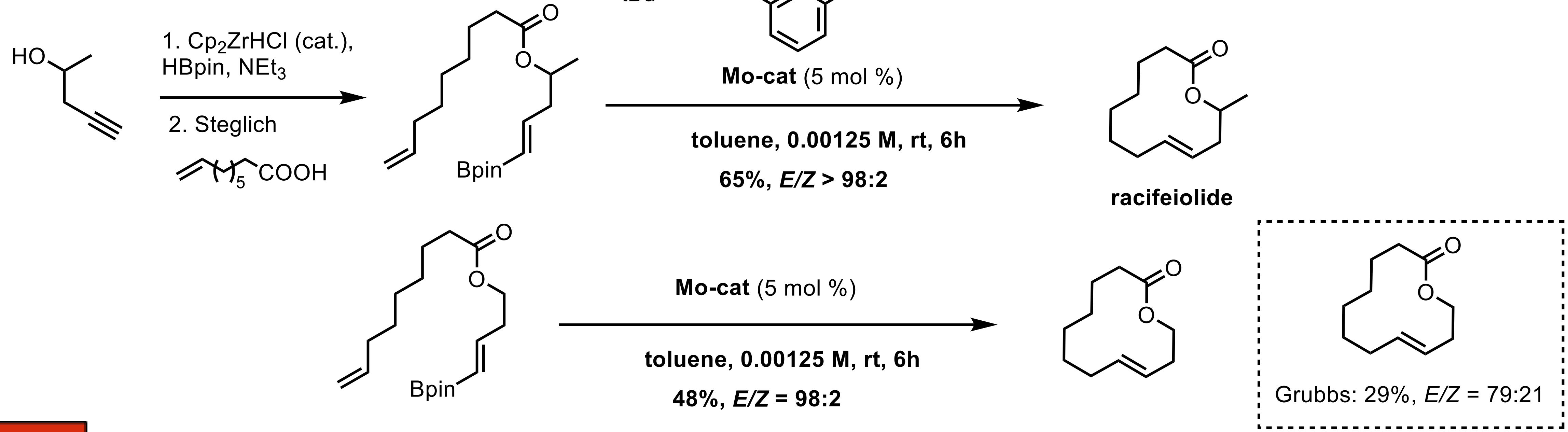
# Molybdenum alkylidene catalysts for *E*-selective ring-closing metathesis

Mo alkylidenes permit higher concentration cyclizations, with excellent *E/Z* selectivity and comparable yields to Ru alkylidenes.

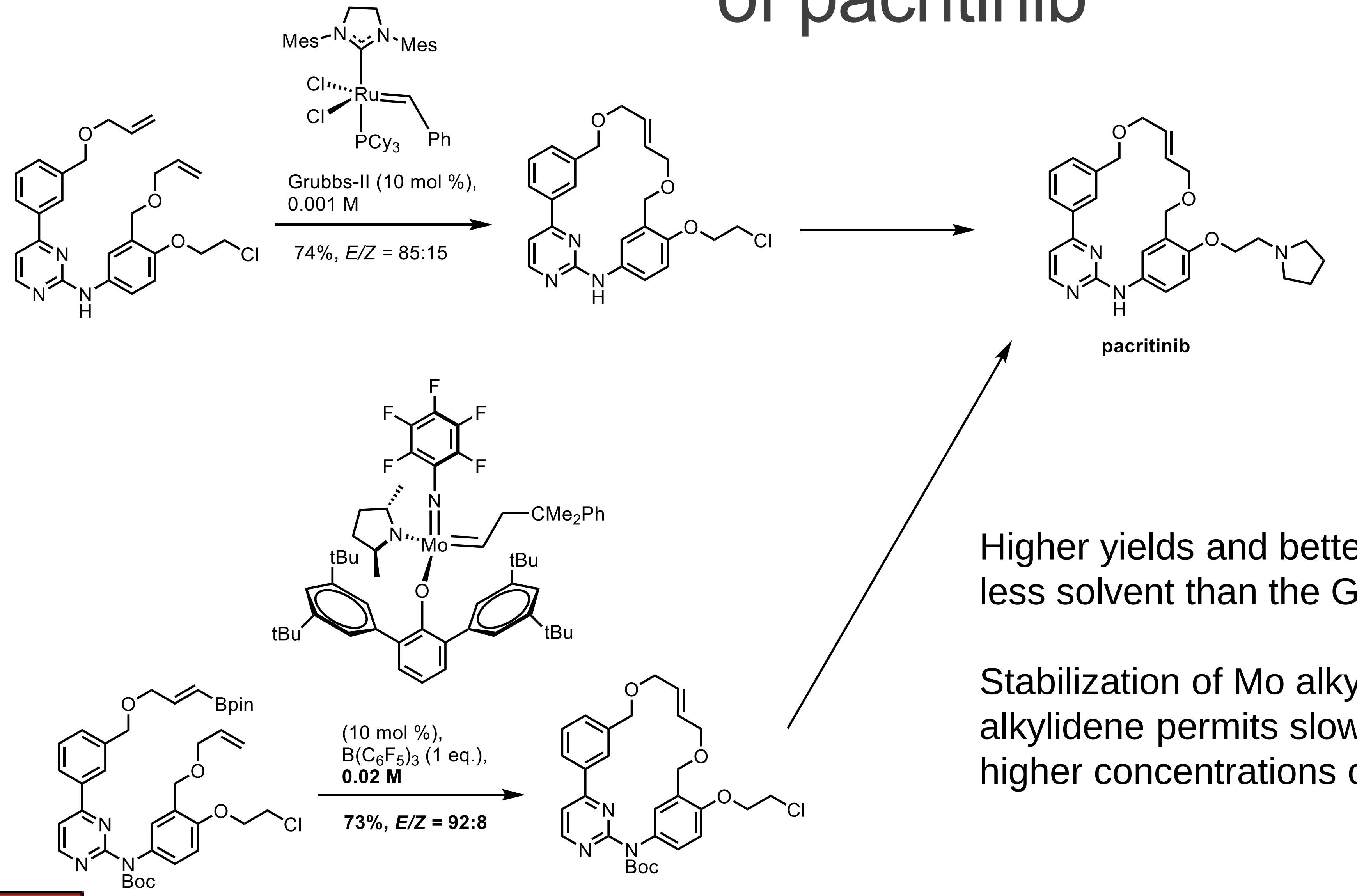
Thorpe-Ingold biasing shows cycle benefits from substrate preorganization.



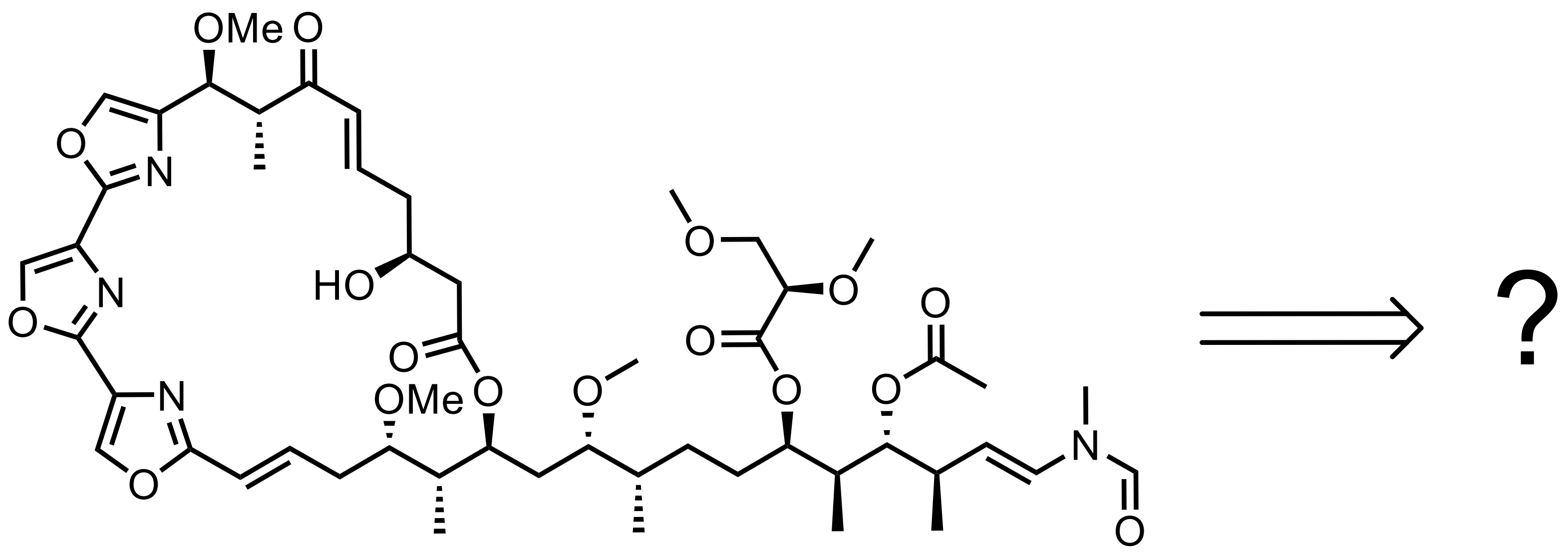
# Comparing metathesis catalysts in the synthesis of pacritinib




Higher yields and better *E/Z* selectivity with 20x less solvent than the Grubbs methods.

Stabilization of Mo alkylidene relative to Ru alkylidene permits slower homocoupling rates and higher concentrations of diene.

# Combining strategies in the synthesis of mycalolide macrolactone

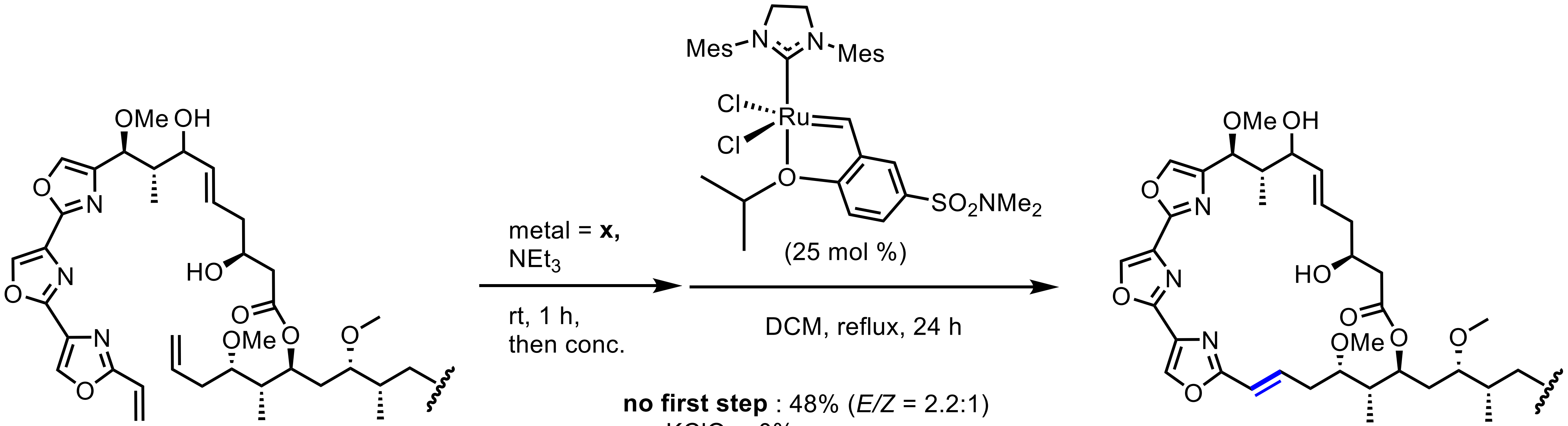



**mycalolide B**

The mycalolide macrolactone has clear structural features suggesting a *strategic* macrocylization...

# Combining strategies in the synthesis of mycalolide macrolactone

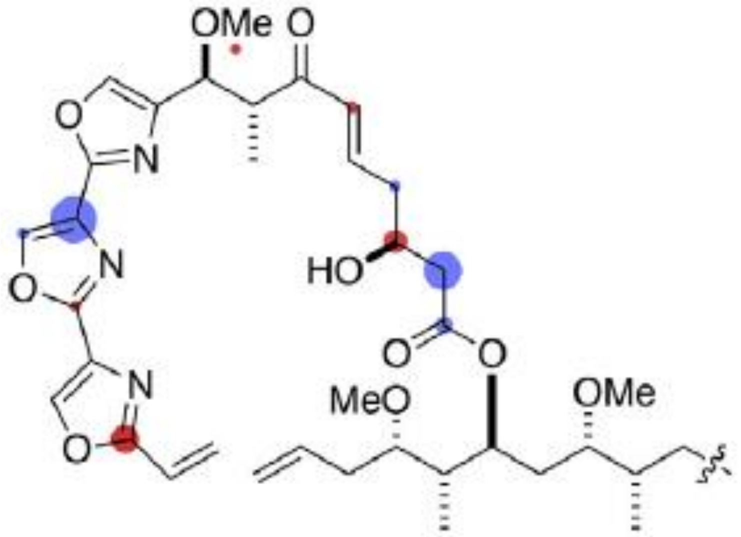
Biasing *E/Z* selectivity with chelating additives:

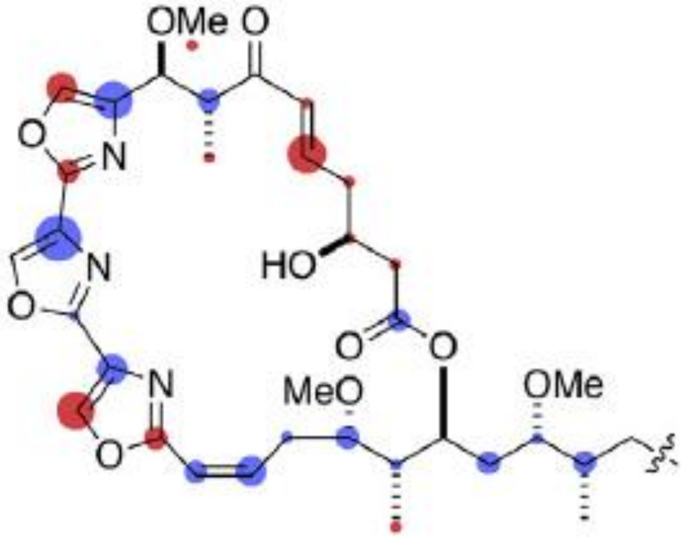


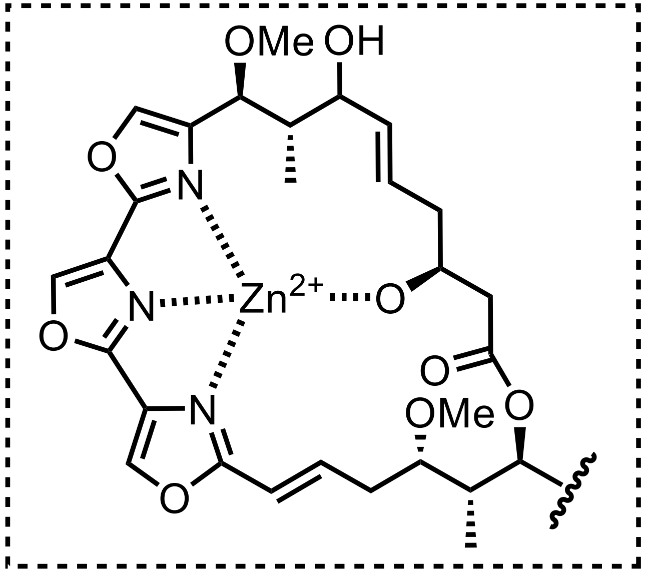

**no first step** : 48% (*E/Z* = 2.2:1)
**x** = $KClO_4$ : 0%
**x** = $Mg(OTf)_2$ : 70% (*E/Z* = 3.5:1)
**x** = $Ni(OTf)_2$ : 75% (*E/Z* = 2.6:1)
**x** = $Zn(OTf)_2$ : 32% (*E* only)

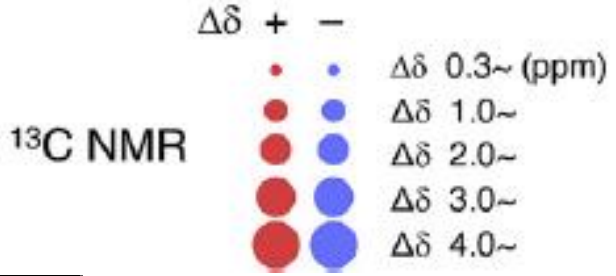
# Combining strategies in the synthesis of mycalolide macrolactone

starting material —$+Zn(OTf)_2$→ take NMR    product —$+Zn(OTf)_2$→ take NMR



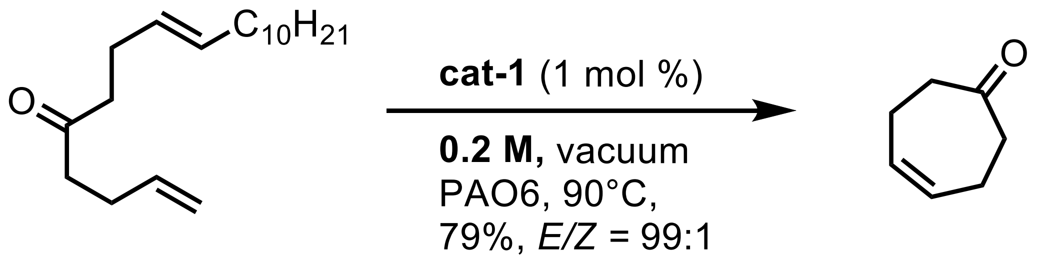



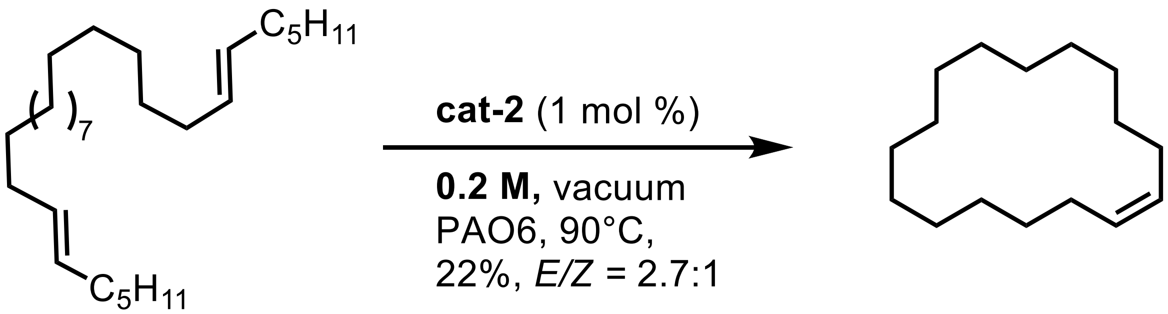

Changes in chemical shift suggest Zn(II) is acting as a template to facilitate macrocyclization.

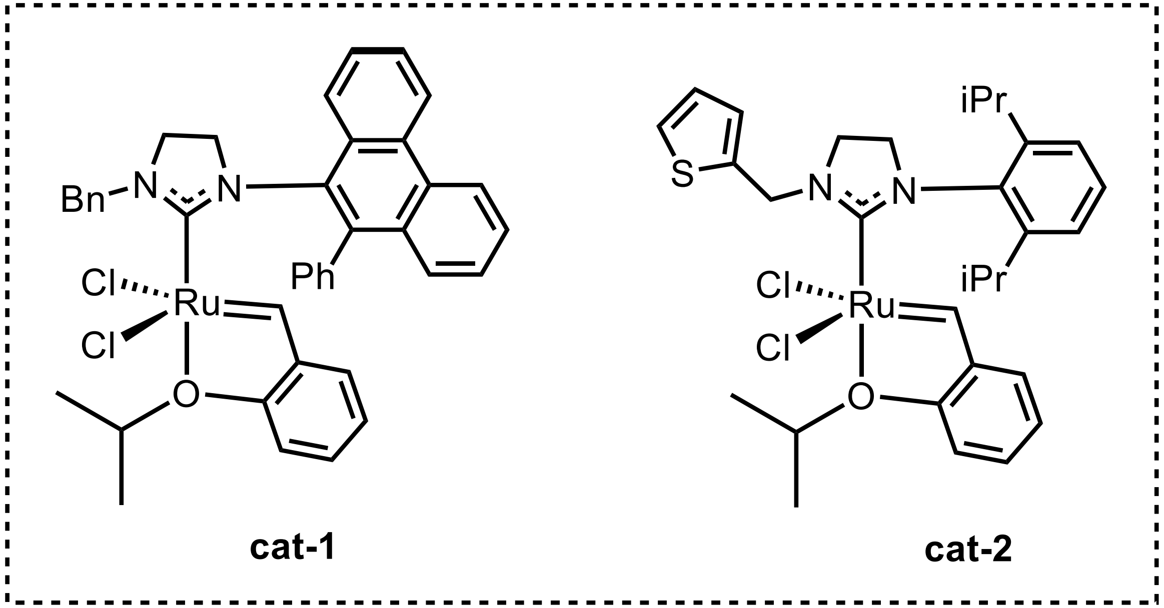
Olefin regioselectivity is not just a function of catalyst.

# Distilling off the product to increase concentration in macrocylization

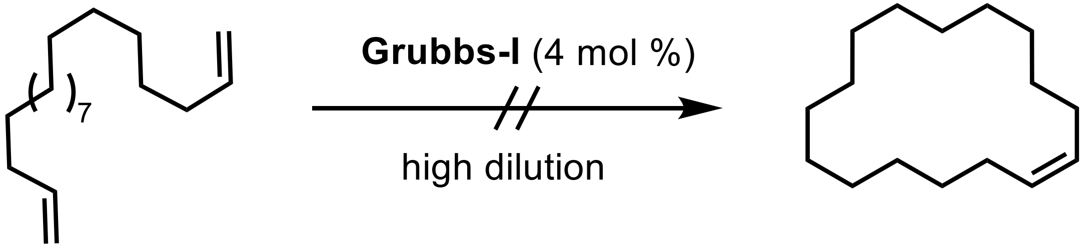
Applying vacuum allows sequestering of product from non-volatile reaction solvent, avoids oligomerization side products, and permits normal concentrations:



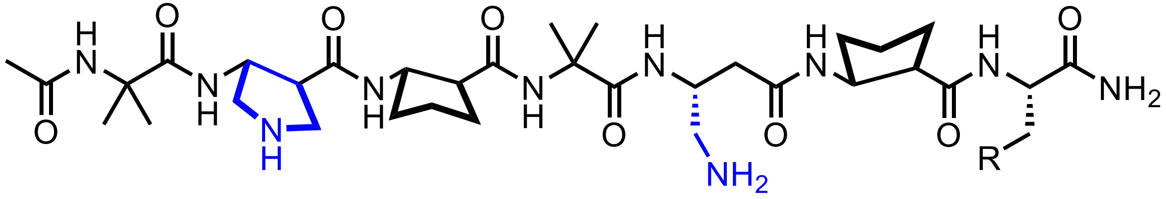




Furstner attempted this in 2002:

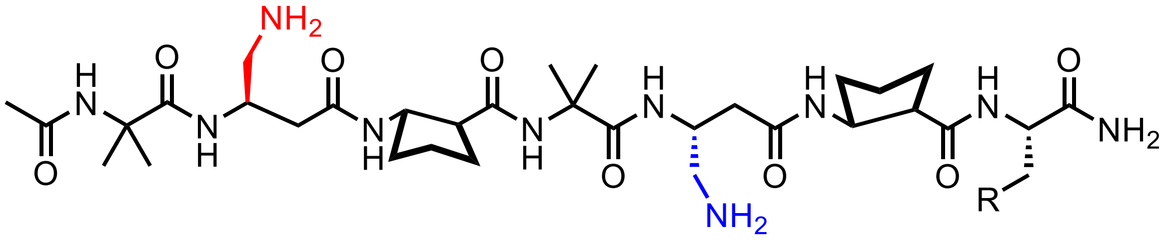



(only oligomers detected)

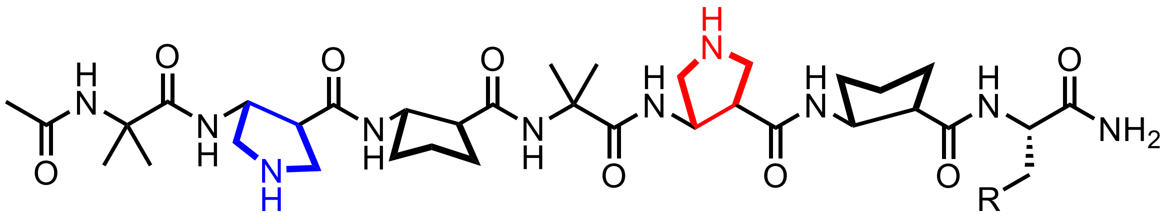
# Foldamer catalysts provide both catalytic activation and preorganization in aldol macrocylizations




**Foldamer 1**



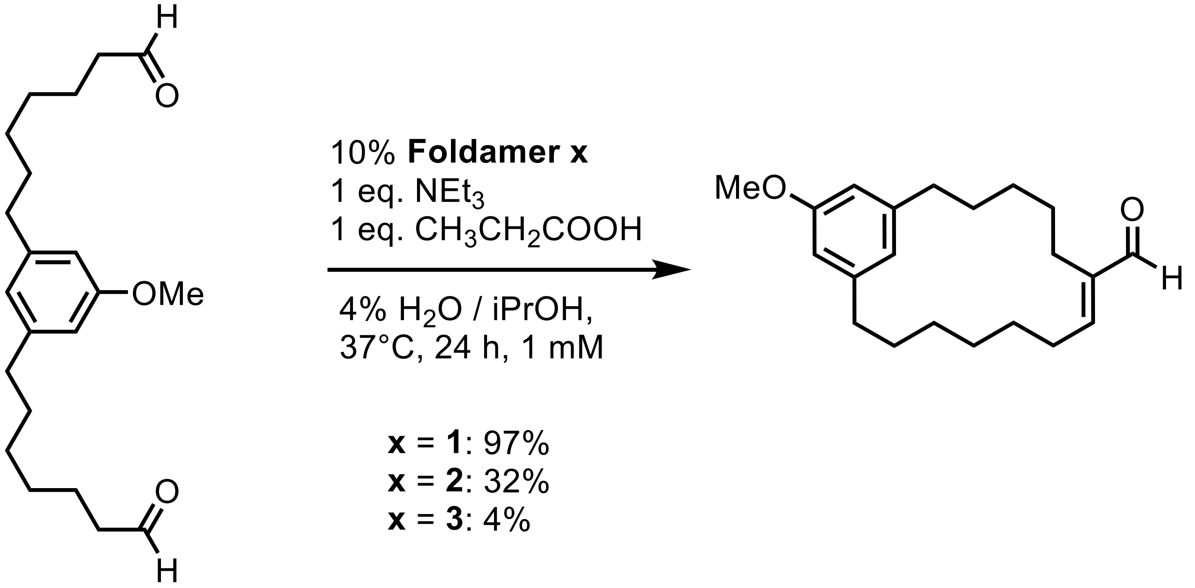

**Foldamer 2**



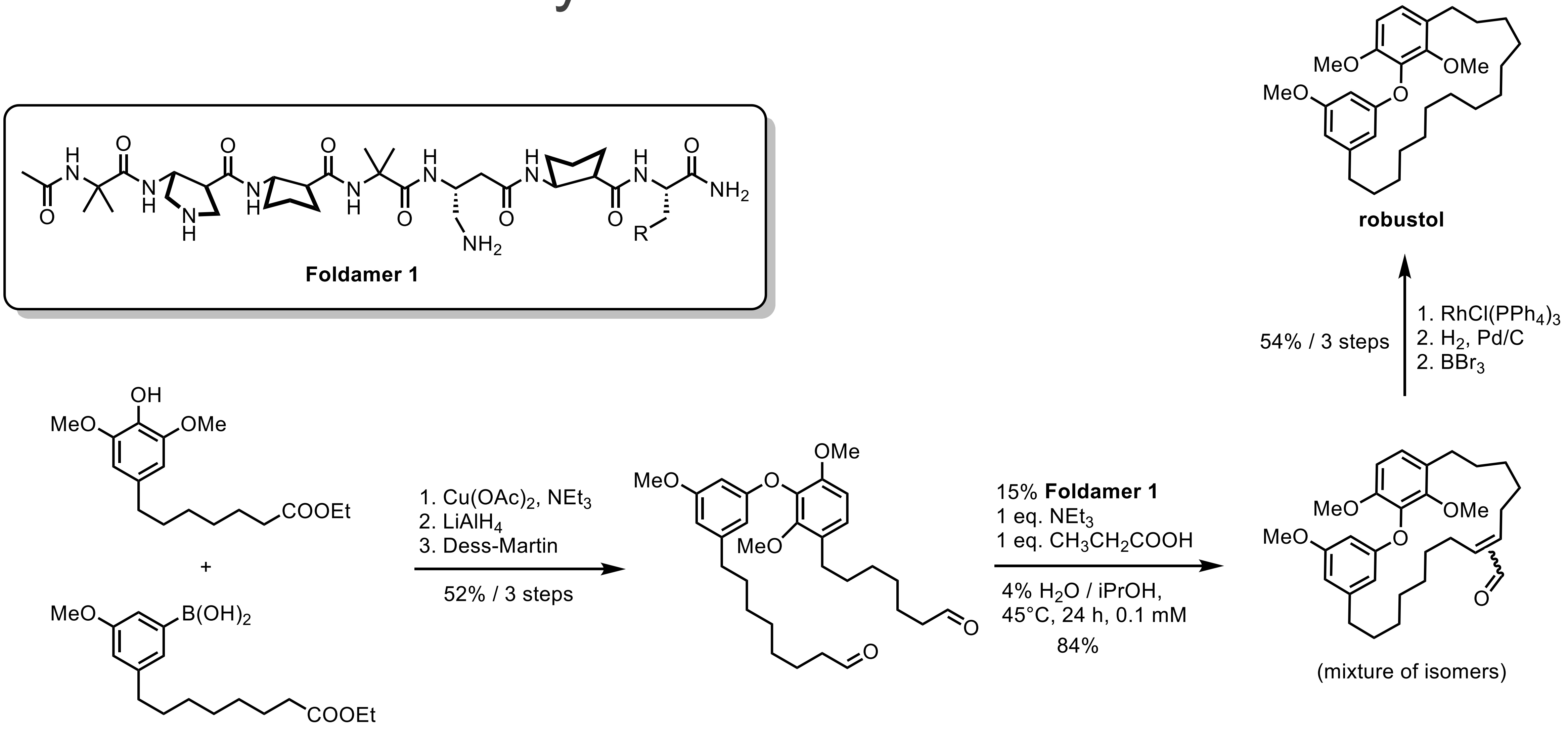

**Foldamer 3**

Optimal oligopeptides have both secondary and primary amine. Activation to enamine-iminium is organized by catalyst template.

*i*,*i+3* spacing of residues is also essential for proper preorganization.



# Foldamer-catalyzed macrocyclization in the total synthesis of robustol



# Outlooks and conclusions

Substrate preorganization is a key factor for making a macrocyclization work.

Rigidification of the macrocycle precursor can be highly effective, but often requires covalent modification

Ring closing metathesis can fail when steric hindrance is high. Stereoselectivity in the reaction can also be a problem.

Strategic approaches
- Sequential alkyne metathesis/gold alkyne functionalization
- Templating with Lewis acids
- Biasing electronics to enforce pre-organization
- Model BEFORE you try to cyclize an advanced intermediate
- Plan late-stage transannular modifications to exploit functionality used in macrocyclization

If all else fails, just do a late stage Stille coupling- it will probably work!

# Useful Reviews and Accounts

CHEMICAL REVIEWS
Review
pubs.acs.org/CR

**Macrocyclization Reactions: The Importance of Conformational, Configurational, and Template-Induced Preorganization**

Vicente Martí-Centelles, Mrituanjay D. Pandey,[†] M. Isabel Burguete, and Santiago V. Luis*

*Chem. Rev.* **2015**, 115, 8736-8834.

ACCOUNTS of chemical research
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Article

**Lessons from Natural Product Total Synthesis: Macrocyclization and Postcyclization Strategies**

*Published as part of the Accounts of Chemical Research special issue "Total Synthesis of Natural Products".*

Alois Fürstner*

*Acc. Chem. Res.* **2021**, 54, 861-874.

MICROREVIEW

**Conformation-Directed Macrocyclization Reactions**

Jörg Blankenstein[a,b] and Jieping Zhu*[a]

*Eur. J. Org. Chem.* **2005**, 1949–1964.



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http://pubs.acs.org/journal/acscii
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**Unconventional Macrocyclizations in Natural Product Synthesis**

Iakovos Saridakis,[§] Daniel Kaiser,[§] and Nuno Maulide*

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*ACS Cent. Sci.* **2020**, 6, 1869-1889.