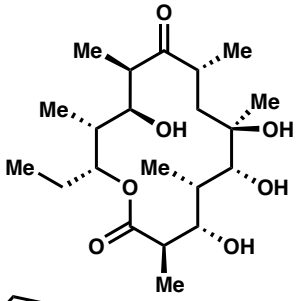
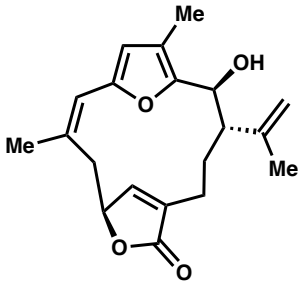
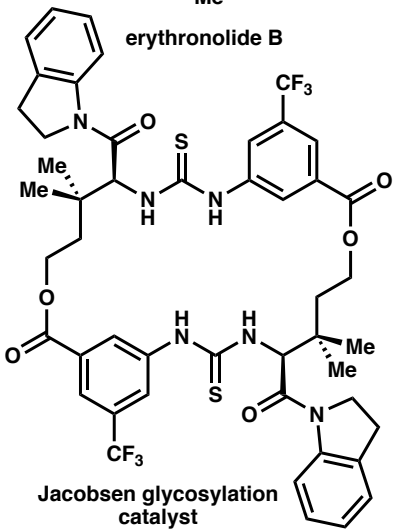


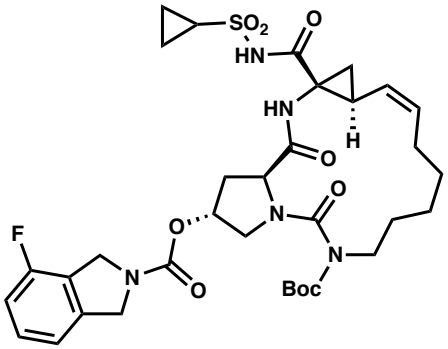
erythronolide B



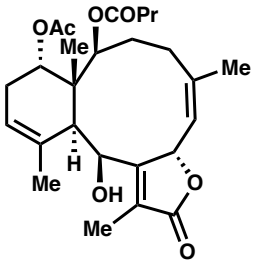
bipinnatin J



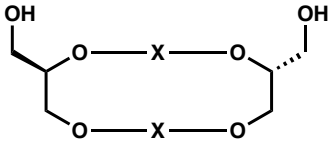
Jacobsen glycosylation catalyst



Danoprevir (phase II)



briareolide J



GDGT-0

Challenges associated with macrocyclization:

- **ring strain present in large rings**
- **entropic penalty going from linear to cyclic systems**
- **competing cyclization and head to tail oligomerization pathways**

Commonly employed solutions:

- **high dilution**
- **substrate perorganization**
- **metal or organic templating**

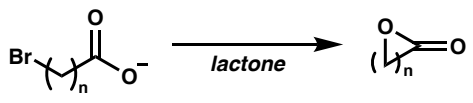
Ring strain by ring size:

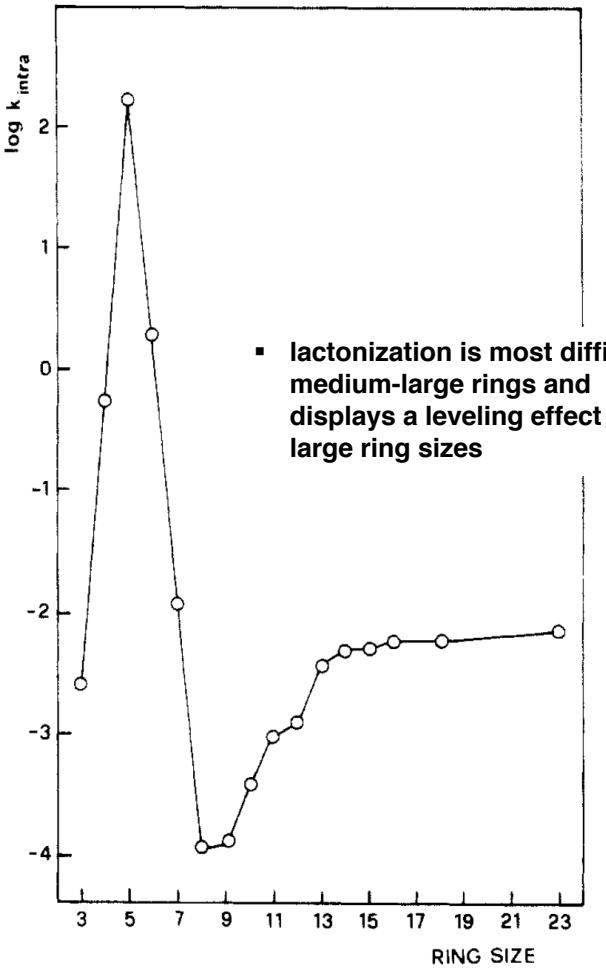
Ring size *n*	Cycloalkanes[a]	Lactones[b]
3	27.5	40.4[c]
4	26.1	23.3[d]
5	6.2	7.7[d]
6	0.1	9.5[d]
7	6.0	10.7
8	9.4	12.4
9	12.2	11.6
10	12.2	8.2
11	11.1	7.3
12	4.0[e]	7.1
13	5.0[e]]	6.7
14	3.2[e]]	4.5
15	1.7	
16	1.8	

- **Ring strain is most pronounced in the small end of macrocycles due to transannular and eclipsing interactions not seen in larger cycles, which have greater conformational flexibility**

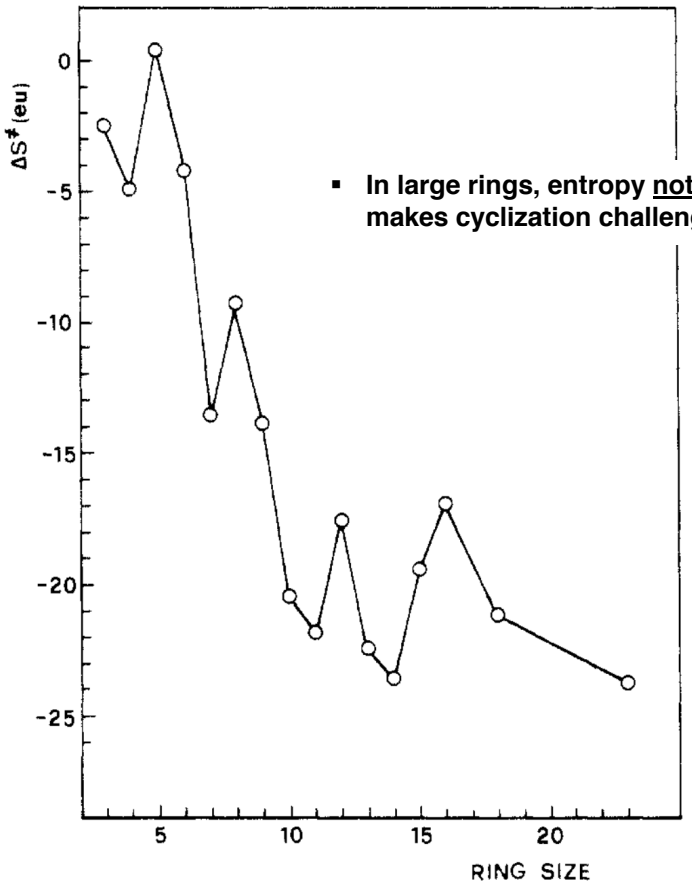
Eur. J. Org. Chem. **2000**, 3117–3125.

Lactone kinetics





- **lactonization is most difficult for medium-large rings and displays a leveling effect for large ring sizes**



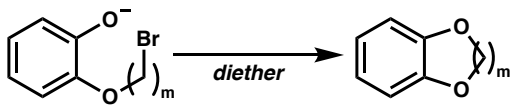
- **In large rings, entropy <u>not</u> strain makes cyclization challenging**

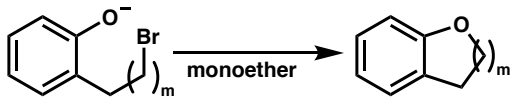
- **In addition to the entropic barrier, conformational effects hinder large ring formation**

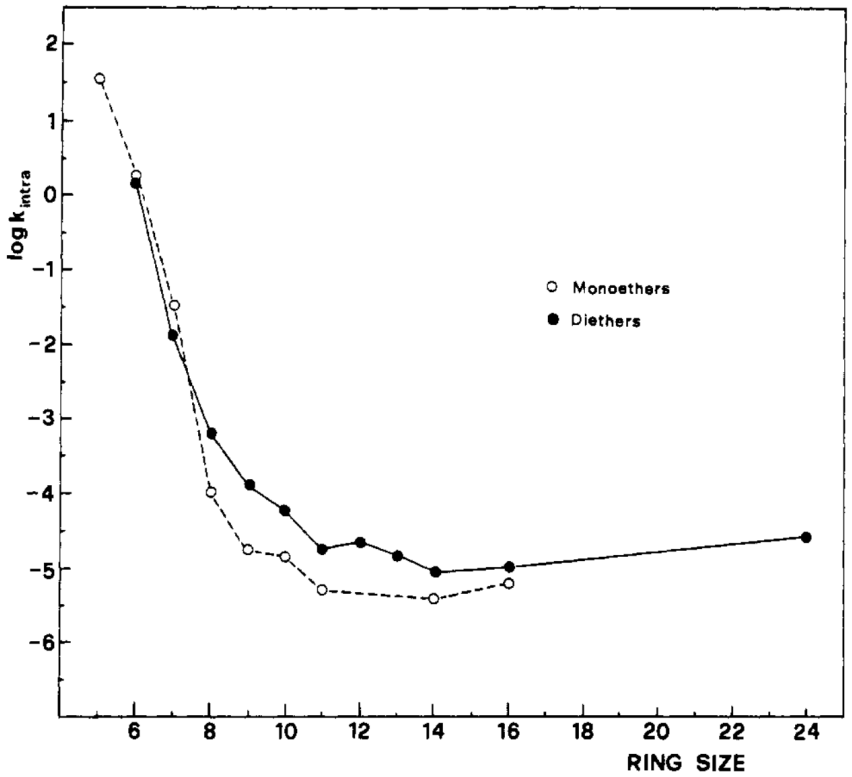
Acc. Chem. Res. **1981**, *14* (4), 95–102.

gem-substituted substrate	ring size	$k_{intra}^{gem}/k_{intra}$
$Br(CH_2)_2C(CH_3)_2CH_2CO_2^-$	6	38.5
$Br(CH_2)_5C(CH_3)_2CH_2CO_2^-$	9	6.62
$Br(CH_2)_6C(CH_3)_2CH_2CO_2^-$	10	1.13
$Br(CH_2)_7C(CH_3)_2CH_2CO_2^-$	11	0.61
$Br(CH_2)_6C(CH_3)_2(CH_2)_7CO_2^-$	16	1.22

- **The Thorpe-Ingold effect is significantly diminished as ring size increases due to a negligible contribution to preorganization**
- **Significant conformational biasing is required to effectively promote macrocyclization**





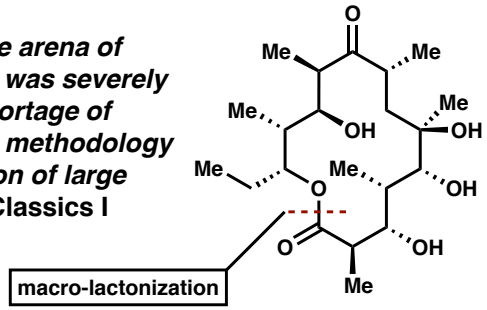


ring size	6	7	8	9	10	11	14	16	inter
$k_{intra}^{diether}/k_{intra}^{monoether}$	0.81	0.42	6.42	7.55	4.16	4.67	2.65	1.91	1.36

Acc. Chem. Res. **1981**, *14* (4), 95–102.

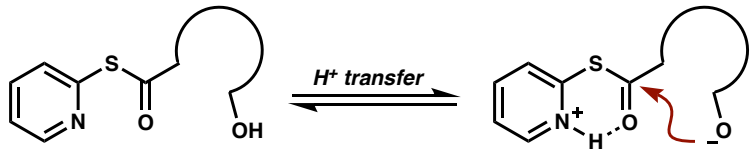
A case study: the Corey erythronolide B synthesis

- ***"… progress in the arena of organic synthesis was severely hampered by a shortage of efficient synthetic methodology for the construction of large ring lactones."*** **– Classics I**



erythronolide B

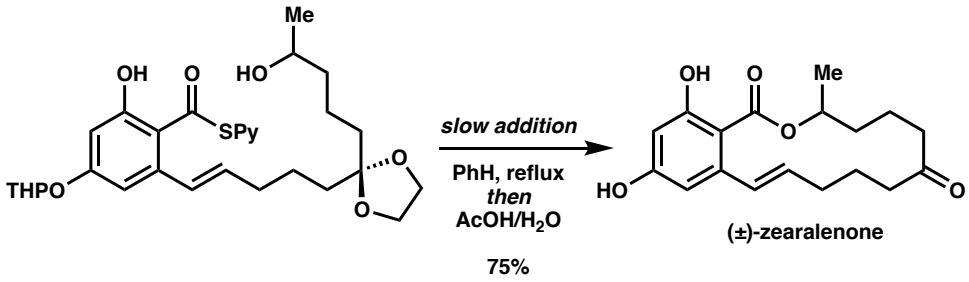
- **Corey–Nicolaou macrolactonization:**



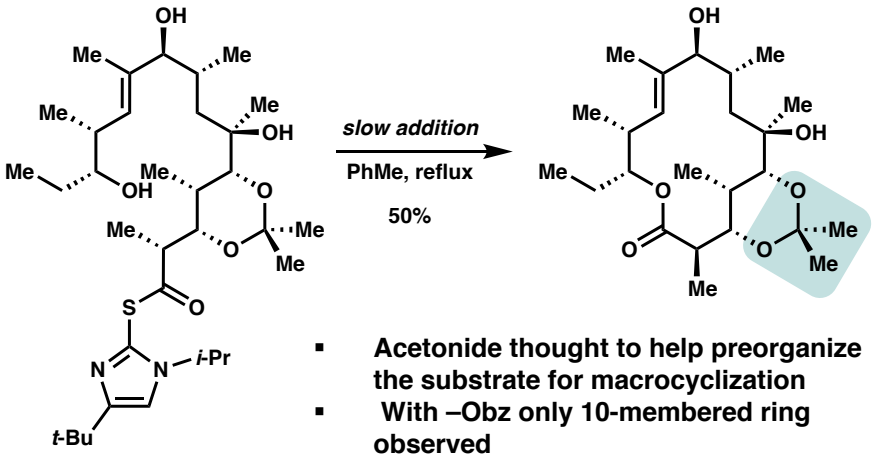
		Lactone			Diolide	
n	Solvent	Ring size	Glc yield (%)	Isolated yield (%)	Ring size	Isolated yield (%)
5[a]	Benzene	7	87	71	14	7
7[b]	Xylenes	9	25	8	18	41
10[c]		12	64	47	24	30
11[a]		13	76	66	26	7
12[a]		14	79	68	28	6
14[a]		16	88	80	32	5

Slow addition of thioate to refluxing solvent was followed by [a] 10 hr at reflux, [b] 30 hr at reflux, [c] 20 hr at reflux.

J. Am. Chem. Soc. **1974**, *96* (17), 5614–5616.



- **Previously 8% using basic transesterification**

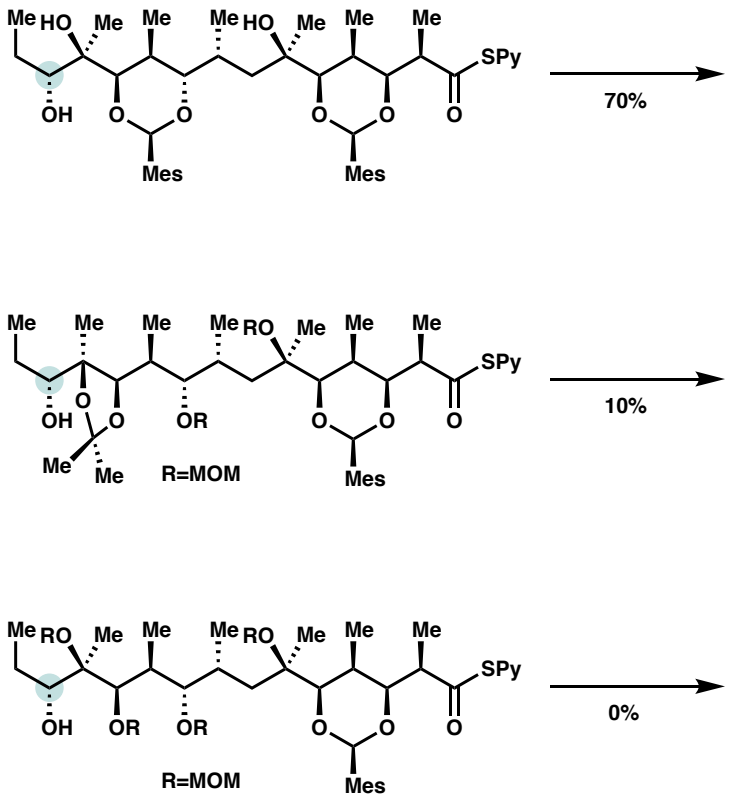


- **Acetonide thought to help preorganize the substrate for macrocyclization**
- **With –Obz only 10-membered ring observed**

- **The influence of conformational biasing was further investigated by Woodward**

J. Am. Chem. Soc. **1978**, *100* (14), 4620–4622.
J. Org. Chem. **1968**, *33* (11), 4176–4179.

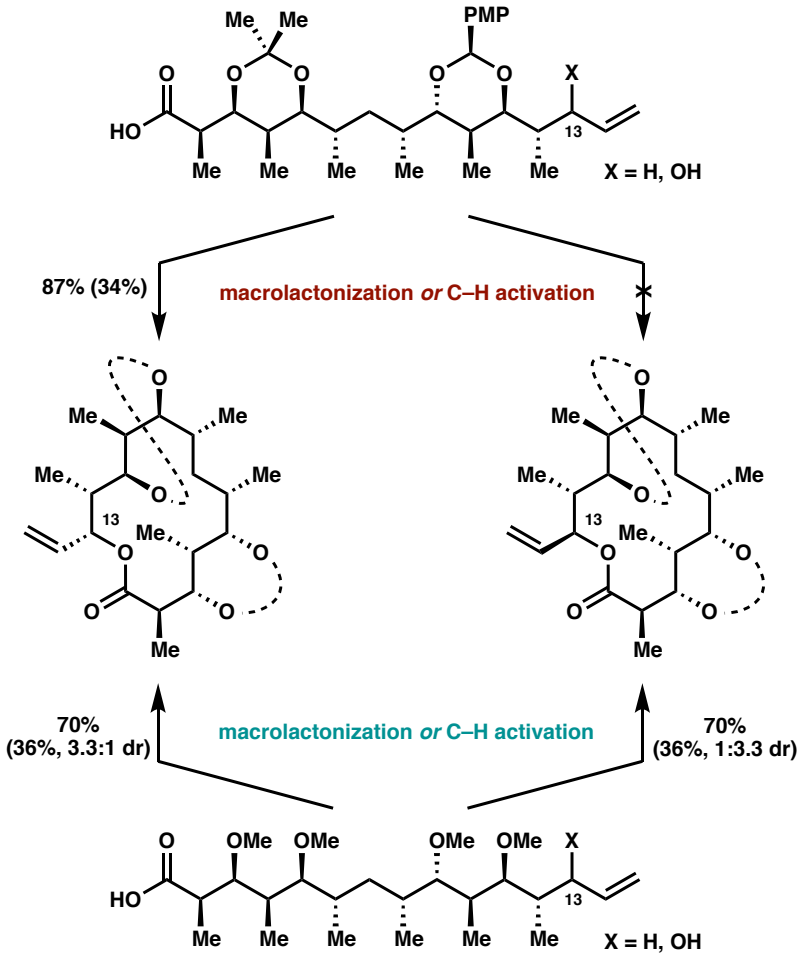
From Woodward's erythromycin synthesis:



- **Of 17 substrates tested, only one afforded appreciable yield**
- **"…cyclic protecting groups at C-3/C-5 and C-9/C-11 are required for efficient lactonization."**

J. Am. Chem. Soc. **1981**, *103* (11), 3213–3215.

- **However, Woodward never tested any substrates lacking cyclic protecting groups**

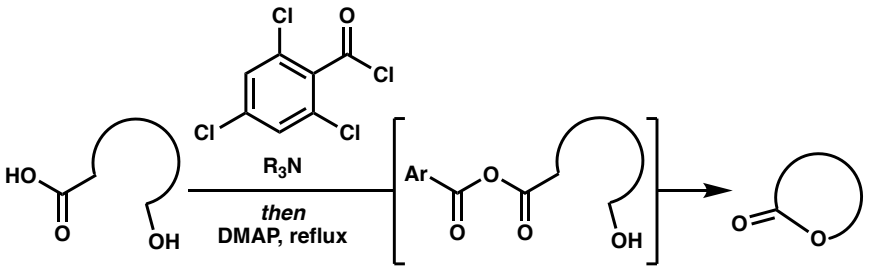


- **Substrate preorganization is difficult to reliably predict and is not necessarily required for efficient cyclization**

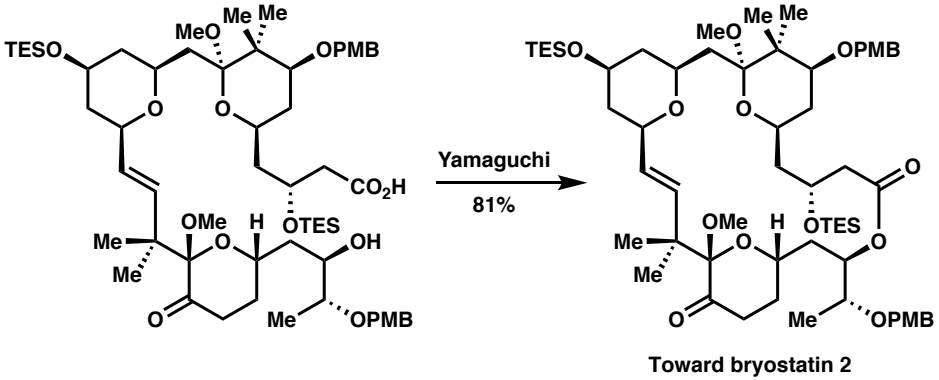
Angew. Chemie - Int. Ed. **2011**, *50* (9), 2094–2097.

Lactones cont.

- **Yamaguchi macrolactonization:**



- **Trichloro-aryl group proposed to sterically block nucleophilic attack leading to acyl-transfer rather than lactonization**



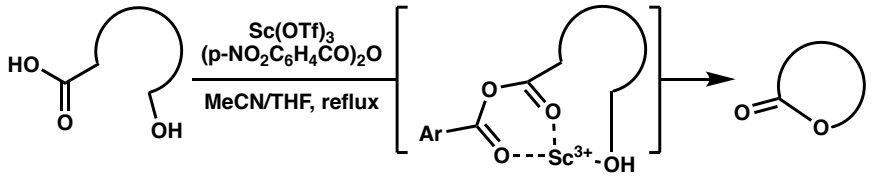
Toward bryostatin 2

- **Extensive use in total synthesis for medium and large rings**

J. Am. Chem. Soc. **1999**, *121* (33), 7540–7552.

Bull. Chem. Soc. Jpn. **1979**, pp 1989–1993.

- **Yamamoto macrolactonization**



- **Metal chelate between alcohol and mixed anhydride proposed to accelerate lactonization**

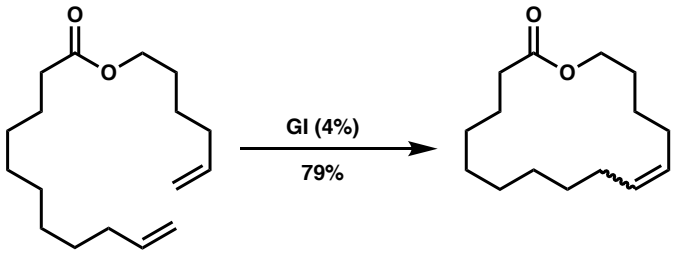
n	$Sc(OTf)_3$ (mol %)	slow addition[a] (h)	reaction time[b] (h)	yield[c] (%) of lactone	yield[c] (%) of diolide
5	20	15	5	>99	<1
6	20	15	5	71	<1
7	20	15	5	52	3
8	20	15	5	87	<5
9	20	15	5	77	2
10	10	15	0	78	2
11	10	6	0	91	3
12	10	15	5	94	<1
13	10	15	5	99	<1
14	10	9	0	99	<1
15	10	9	0	92	<1

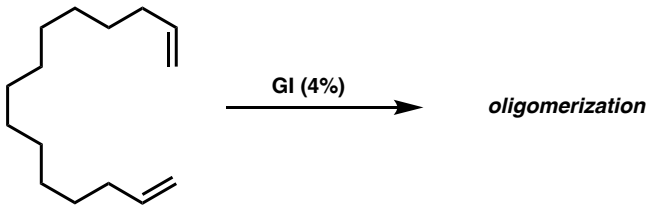
- **Generally outperforms Yamaguchi conditions for rings <15 but has seen little use in synthesis**

J. Org. Chem. **1996**, *61* (14), 4560–4567.

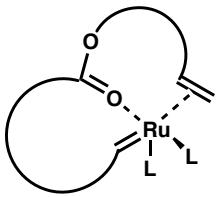
C=C bond forming reactions

- **Olefin metathesis (RCM)**
- **The "go to" reaction for many trying to form a large carbocycle**
- **Stereochemistry, oligomerization, and catalyst decomposition pathways are complicating factors**
- **Modern advances have helped solve many of these issues**

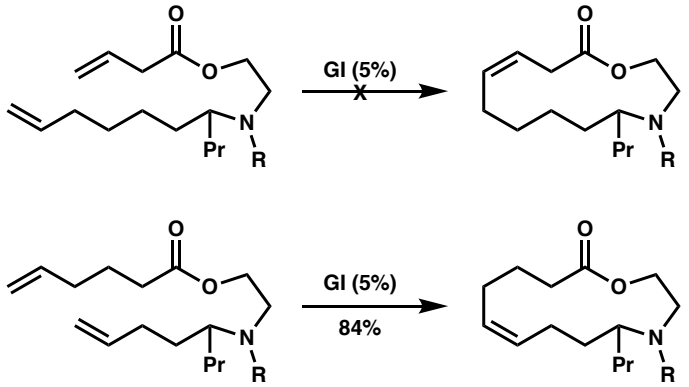




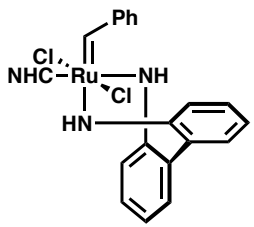
- **Polar functional groups thought to assist metathesis through coordination of Ru**

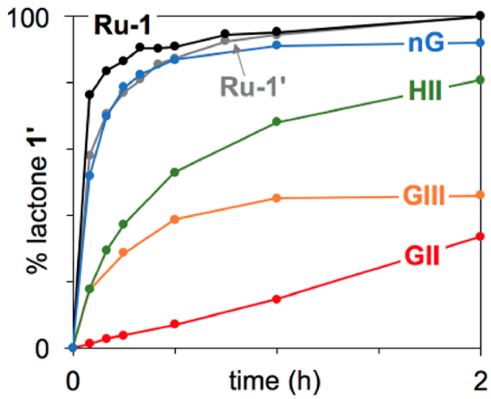


Top. Catal. **1997**, *4* (3–4), 285–299.



- **Catalyst proposed to form an unproductive stable chelate which shuts down catalyst activity in top case**
- **Efficiency of successful macrocyclic RCM limited by Ru-alkylidene and metallocyclobutane decomposition under high dilution and elevated temperatures**

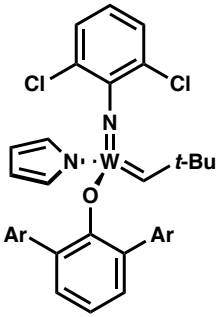




- **Hemilabile ligand slows down ligand dissociation in catalyst decomposition pathway and allows for coordination by polar functionality**

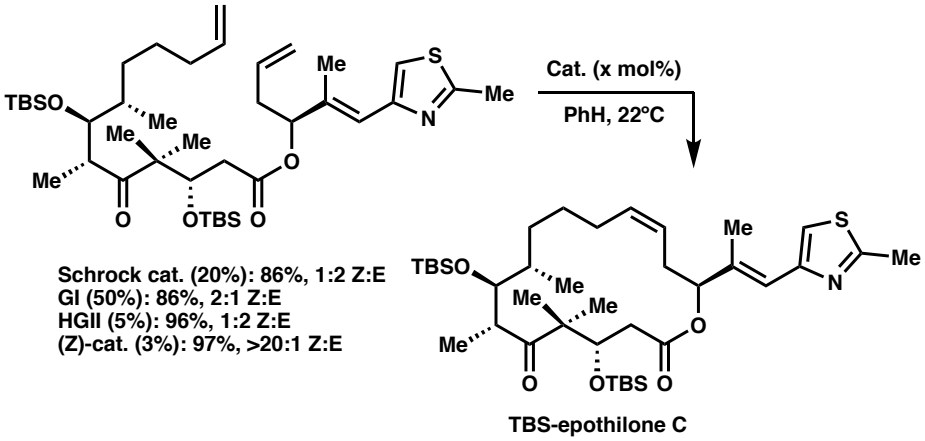
J. Am. Chem. Soc. **2018**, *140* (5), 1604–1607.

- **Issues of stereoselectivity in a macrocyclic context have been addressed by (Z)-selective catalysts**



Ar = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$

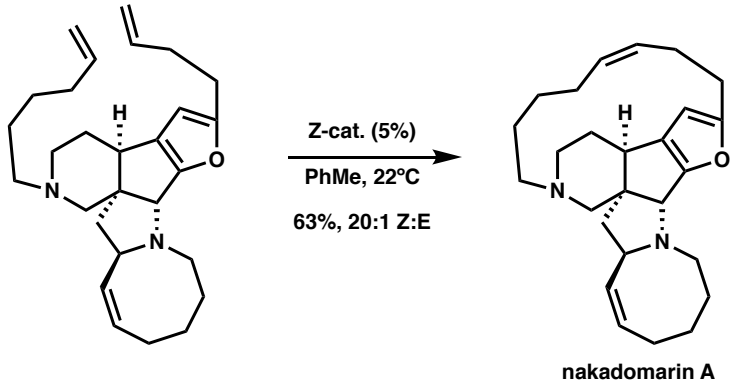
- **High catalyst efficiencies and >9:1 Z:E in most cases**
- **Bulky phenoxide proposed to enforce Z-selectivity**



Schrock cat. (20%): 86%, 1:2 Z:E
GI (50%): 86%, 2:1 Z:E
HGII (5%): 96%, 1:2 Z:E
(Z)-cat. (3%): 97%, >20:1 Z:E

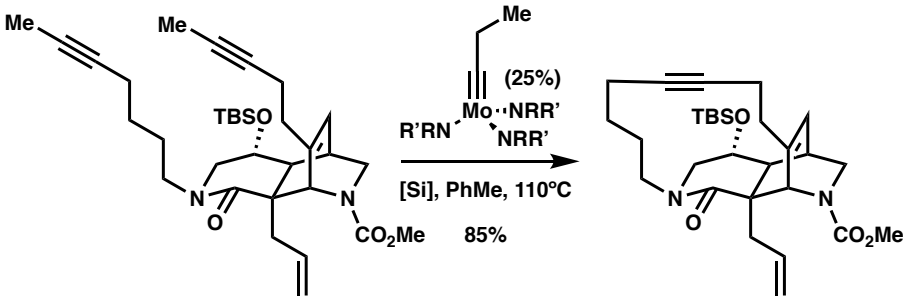
TBS-epothilone C

Nature **2011**, *479* (7371), 88–92.



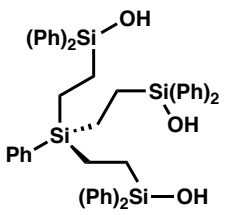
nakadomarin A

- **Ring closing alkyne metathesis (RCAM) has also seen significant use in synthesis**



Toward (–)-xestocyclamine A

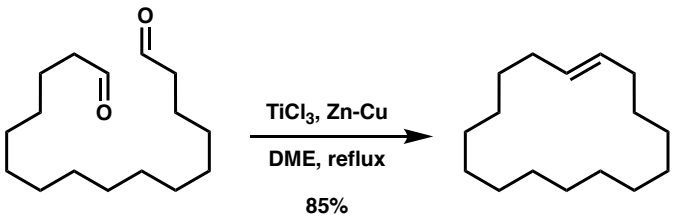
[Si] =



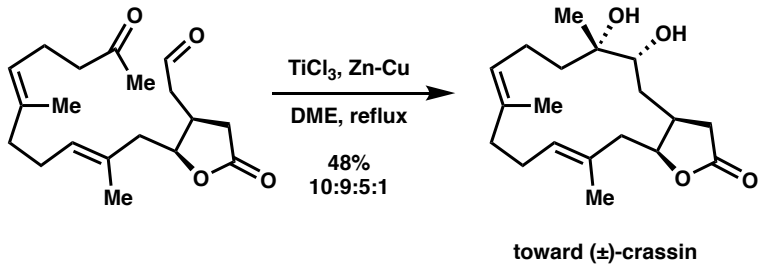
- **Silanol slows down ligand dissociation mediated decomposition pathways**

Total Synthesis of Putative Xestocyclamine A. **2020**,No. 1.
Chem. A Eur. J. **2016**, *22* (25), 8494–8507.

- **The McMurry coupling is also capable of forming large rings and does not have a requirement of polar functionality to prevent oligomerization**



- **The reducing conditions are less tolerant of sensitive functionality than modern metathesis catalysts**



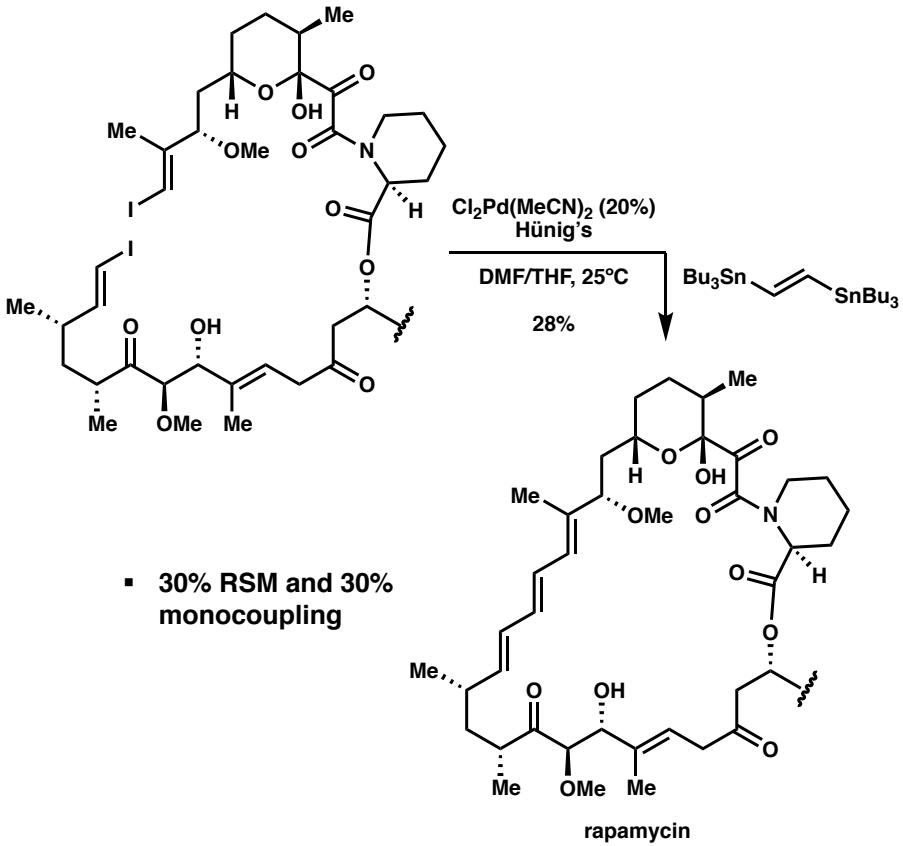
toward (±)-crassin

- **The equivalent Pinacol coupling can also be used, but diastereoselectivity can be difficult to control in a macrocyclic context**

J. Org. Chem. **1977**, *42* (15), 2655–2656.
J. Am. Chem. Soc. **1989**, *111* (24), 8928–8929.

- **sp^2–sp^x cross couplings have also been used extensively to form macrocycles**

- **Stille**

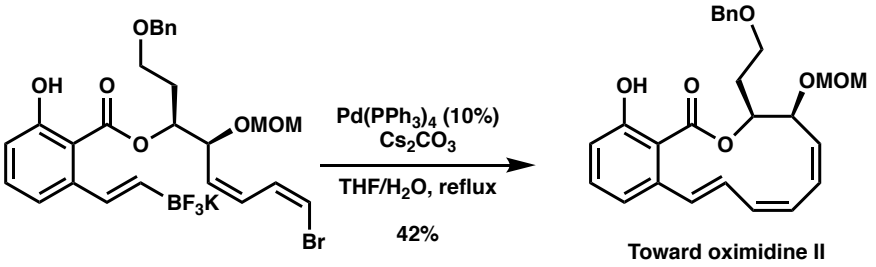


rapamycin

- **30% RSM and 30% monocoupling**

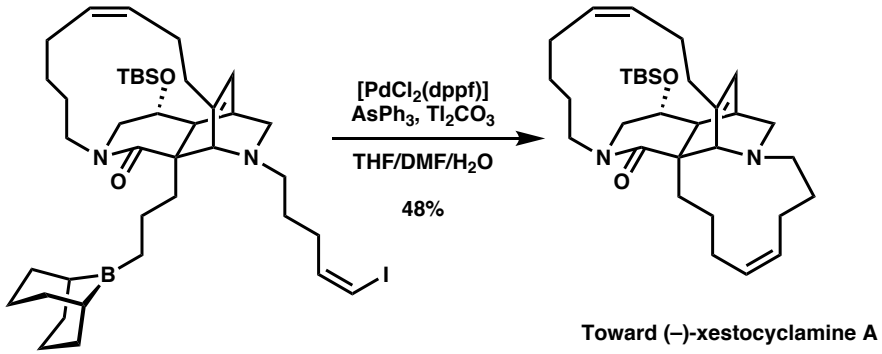
J. Am. Chem. Soc. **1993**, *115* (10), 4419–4420.

- **Suzuki reactions also possible**



Toward oximidine II

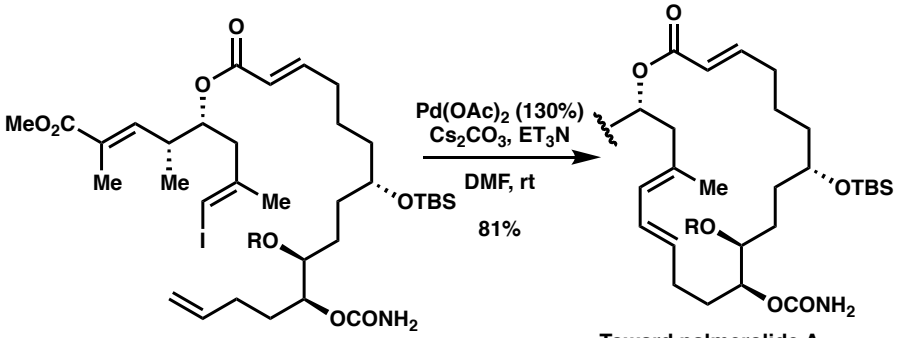
- **Larger rings tend to require higher catalyst loadings added portion-wise**



Toward (–)-xestocyclamine A

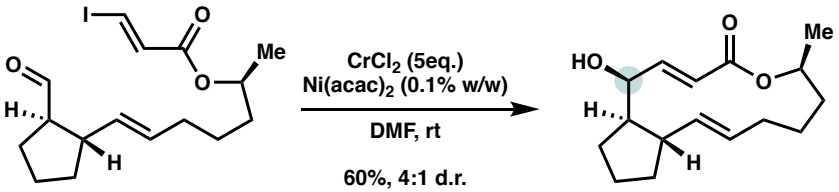
- **B-alkyl Suzuki also possible for many ring sizes, however specialized conditions are typically required**

- **Macrocyclic Heck reactions are less common but can be accomplished with high [Pd] loading**



Toward palmerolide A

- **Addition into aldehydes (e.g. NHK) is one of the most robust and widely utilized C–C macrocyclization strategies among a wide range of ring sizes**



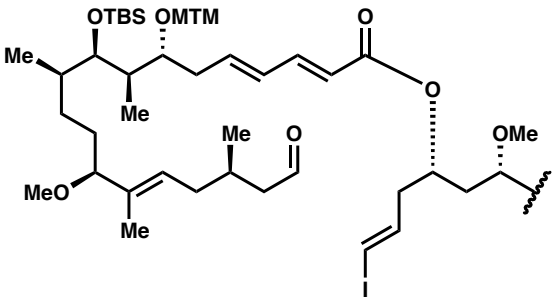
4-*epi*-brefeldin C

- **Stereochemistry of the resulting alcohol is determined by ring conformational preferences and is not necessarily easy to predict**

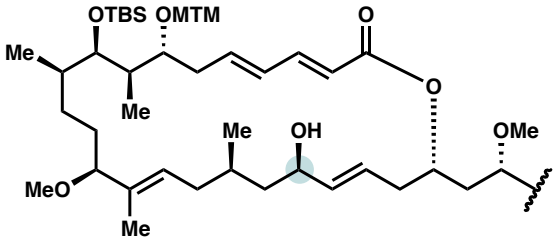
J. Am. Chem. Soc. **2004**, *126* (33), 10313–10318.
Total Synthesis of Putative Xestocyclamine A. **2020**,No. 1.

Tetrahedron **2015**, *71* (34), 5678–5692.
Nat. Prod. Rep. **2019**, *36* (11), 1546–1575.

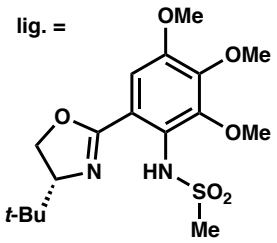
- **Overturning substrate bias is sometimes possible using asymmetric NHK methodology but is generally inefficient**



cond.	d.r.
$NiCl_2$ (10%) $CrCl_2$ (20eq.)	1:1.1
$NiCl_2$dppp (4%) $CrCl_2$ (10 eq.) P.S., lig. (10 eq.)	1.8:1

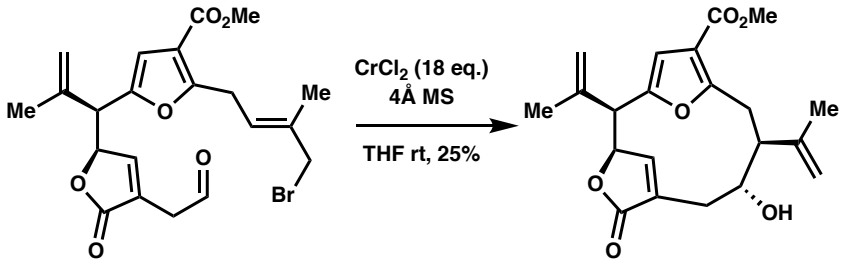


lig. =



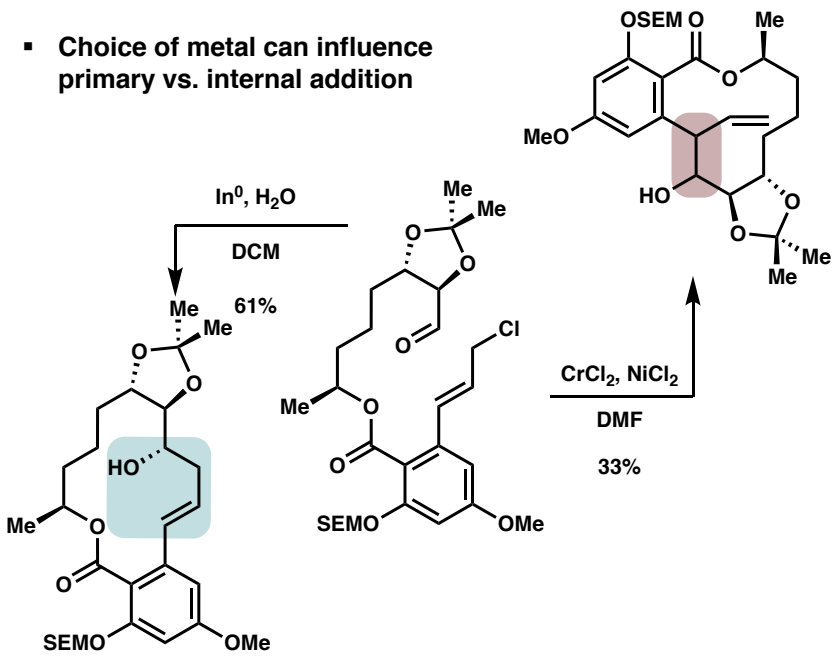
- **High ligand loadings required for macrocyclizations due to low activity in catalytic systems**

Org. Lett. **2012**, *14* (5), 1290–1293.



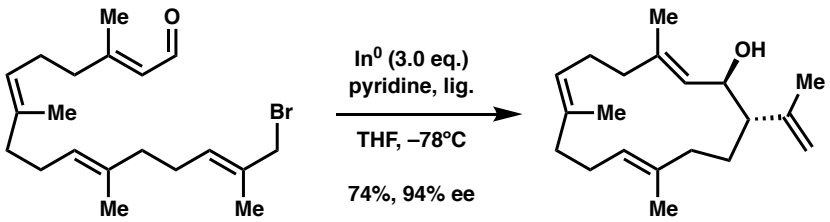
dihydropseudopterollide

- **Diastereoselectivity in allylic cases can be easier to predict as the reaction proceeds in a rigid, 6-membered transition state**
- **Choice of metal can influence primary vs. internal addition**



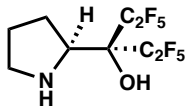
Toward paecilomycin F

Nat. Prod. Rep. **2019**, *36* (11), 1546–1575.



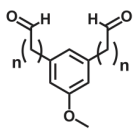
Toward mukulone

lig. =

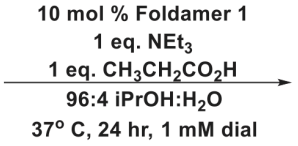


- **Enantioselective cyclization also applicable to related 10, 18-membered systems with high ee**

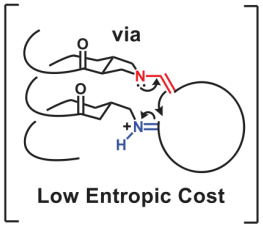
- **Templating offers a strategy to reduce the entropic cost of macrocyclization and potentially reduce the need for extreme dilution**



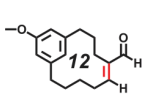
(D1 - D4)
n = 4, 5, 6, 7



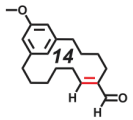
Macrocycle
(E1 - E4)



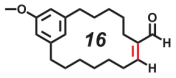
Low Entropic Cost



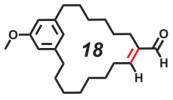
55 %
19 % cyclodimer



Foldamer : 86 %
Small Molecule : 3 %



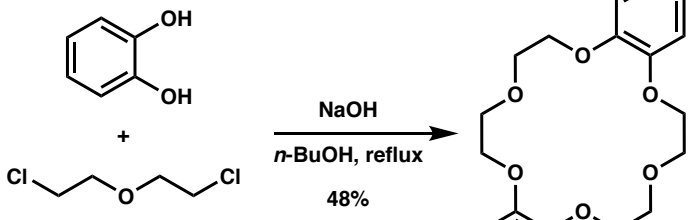
Foldamer : 88 %
Small Molecule : 7 %

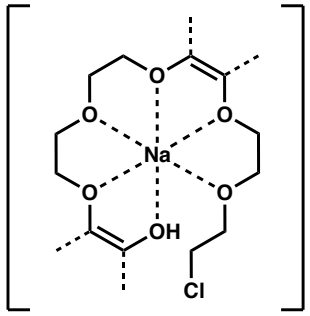


Foldamer : 97 %
Small Molecule : 8 %

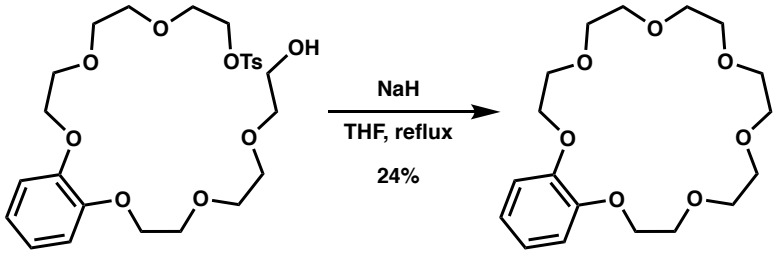
- **As seen in Ciara's lit. meeting last week**

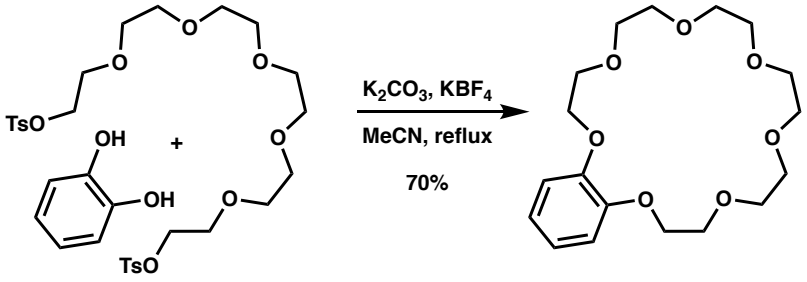
J. Am. Chem. Soc. **2018**, *140* (49), 16909–16913.
Science **2019**, *366* (6472), 1528–1531.



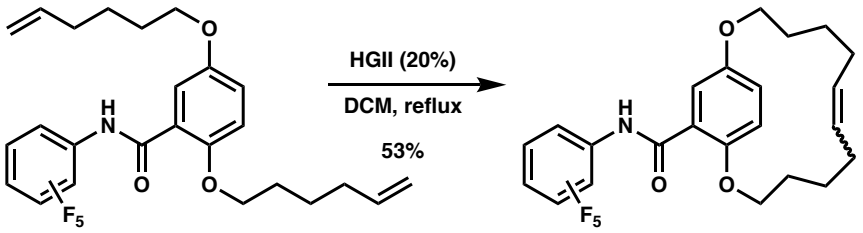


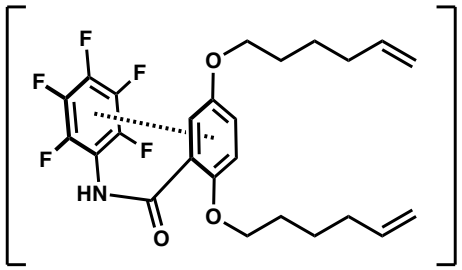
- **Favorable templating around a metal cation promotes selective formation of a specific crown ether**



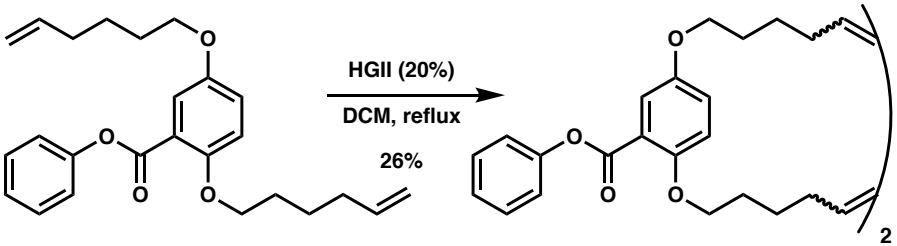


Chem. Rev. **2015**, *115* (16), 8736–8834.

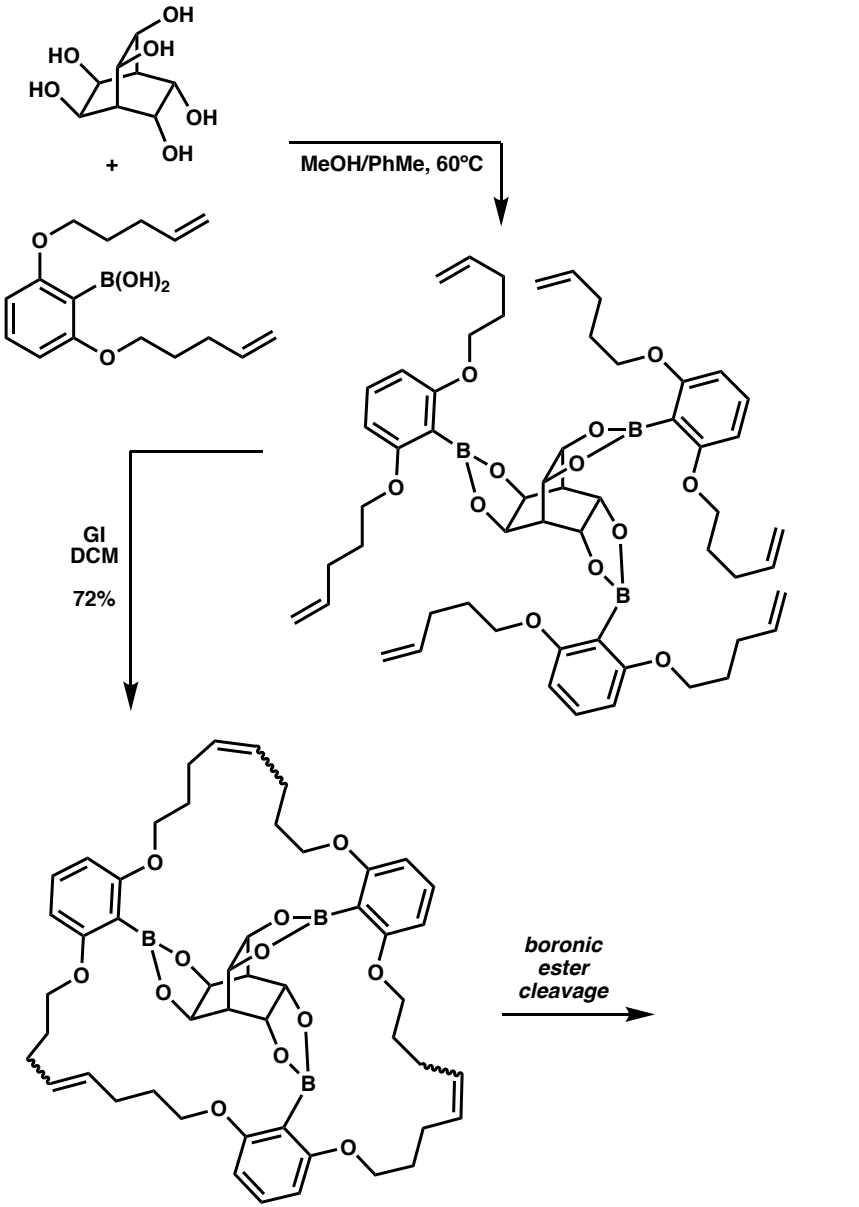




- Pi stacking pushes the two olefins into a reactive conformation necessary for macrocyclization



- In the absence of a suitable arene, only homodimerization is observed



Chem. Rev. **2015**, *115* (16), 8736–8834.

- **Macrocyclizations fight both strain and entropy in their formation**
- **High dilution to artificially increase the relative concentration of chain ends is (usually) a minimum requirement**
- **The stereochemical outcome of point chirality producing macrocyclizations is difficult to reliably predict**
- **Few enantioselective macrocyclic transformations exist**
- **Templating can be an effective tool, but is difficult to map on to a synthetically relevant context**