Construction of Axial and Planar Chirality in Vancomycin

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2024.04.12

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PART ONE

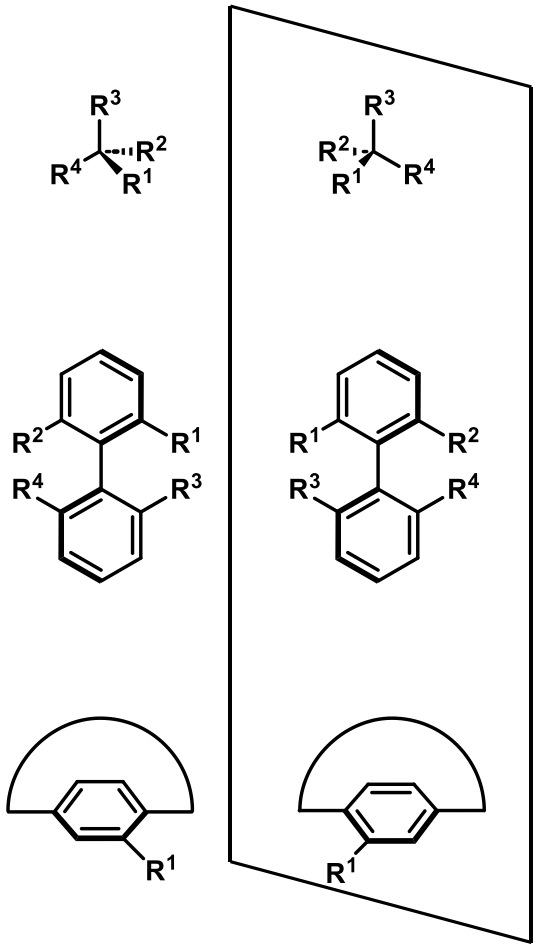
01

Background

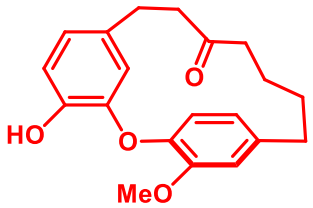
復旦大學
Fudan University

Axial and Planar Chirality

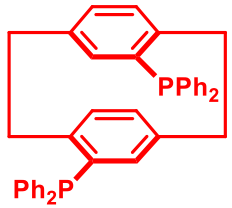
Three Types of Chirality



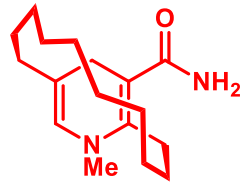
Molecules with Only Planar Chirality



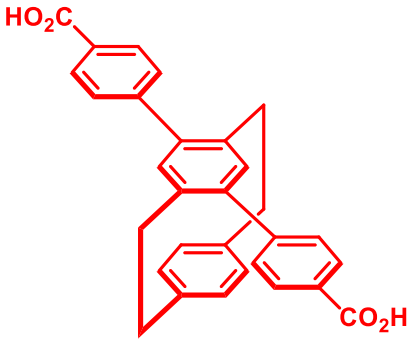
Galeon
[7,1]-metaparacyclophane



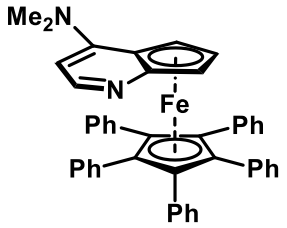
(R)-phanephos
[2,2]-paracyclophane



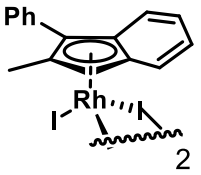
NADH analogue
[10]-paracyclophane



MOF building block
[2,2]-paracyclophane



Fu's catalyst
metallocene



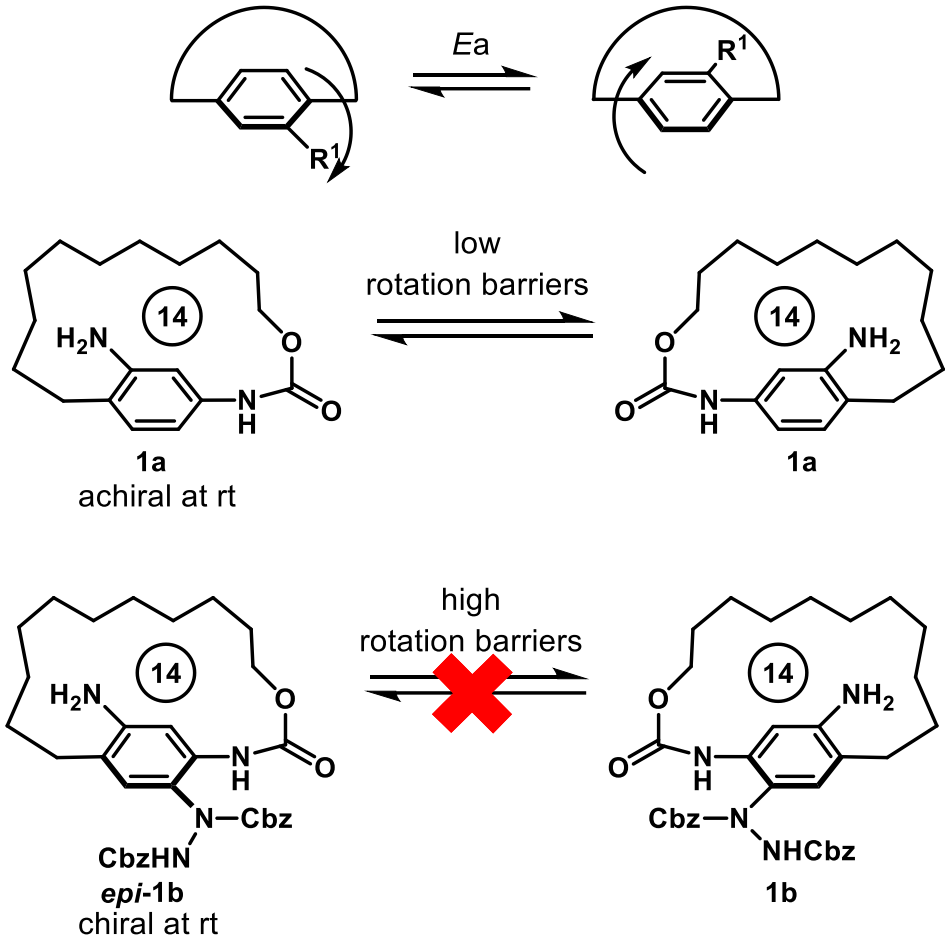
chiral catalyst
metallocene

Planar chirality were generated by hindered rotation

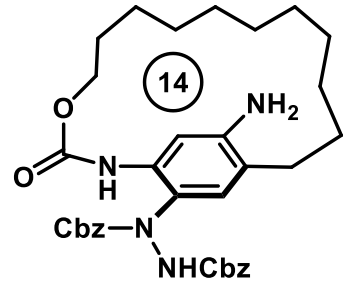
Rosa Llpez and Claudio Palomo, *Angew. Chem. Int. Ed*. **2022**, *61*, e202113504.
Jun Wang et al, *Angew. Chem. Int. Ed*. **2022**, *61*, e202201522.

Planar Chirality

Cyclophane-Rotation Barrier

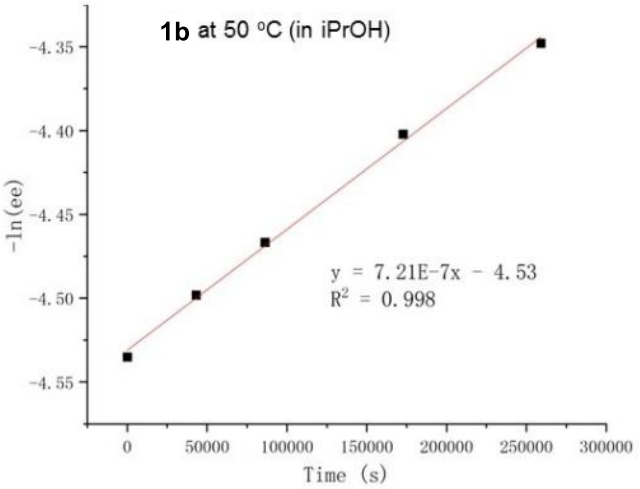


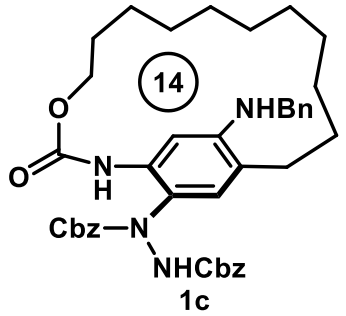
Racemization of Cyclophane



1b

$t_{1/2}$ = 267 h (50 °C)





1c

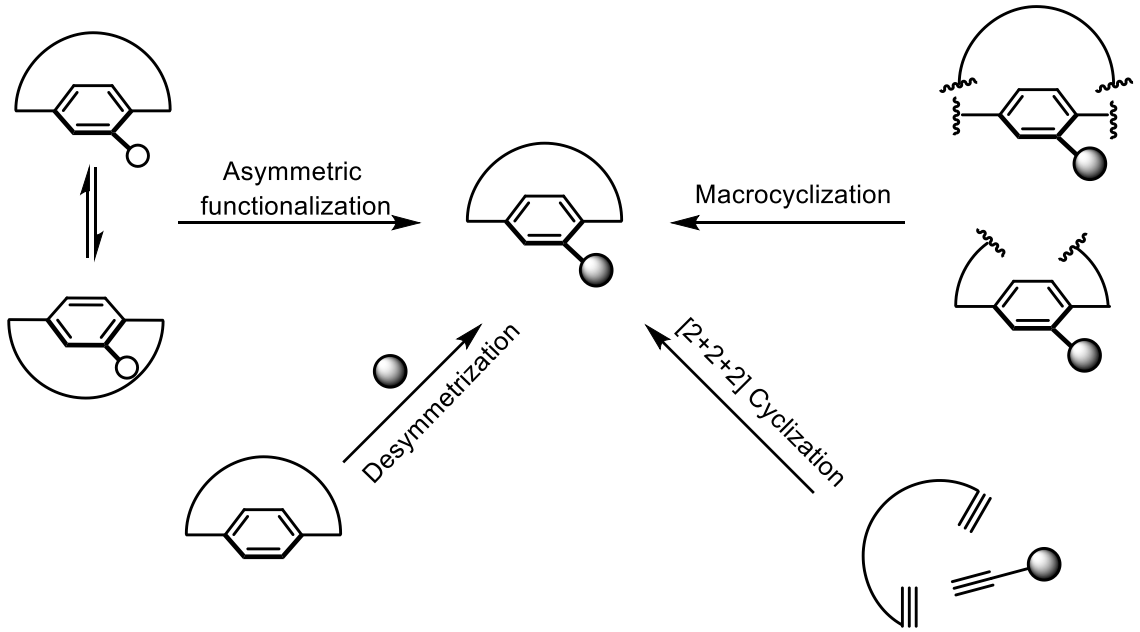
ee retained after heating
at 100 °C in toluene for 12 days

1. Planar chirality of cyclophane was generated by hindered rotation of the benzene ring
2. Cyclophane can racemize at specific temperatures, depending on its rotation barrier.

Rosa Llpez and Claudio Palomo, *Angew. Chem. Int. Ed*. **2022**, *61*, e202113504.
Xiaoyu Yang et al, *Angew. Chem. Int. Ed*. **2022**, *61*, e202201064

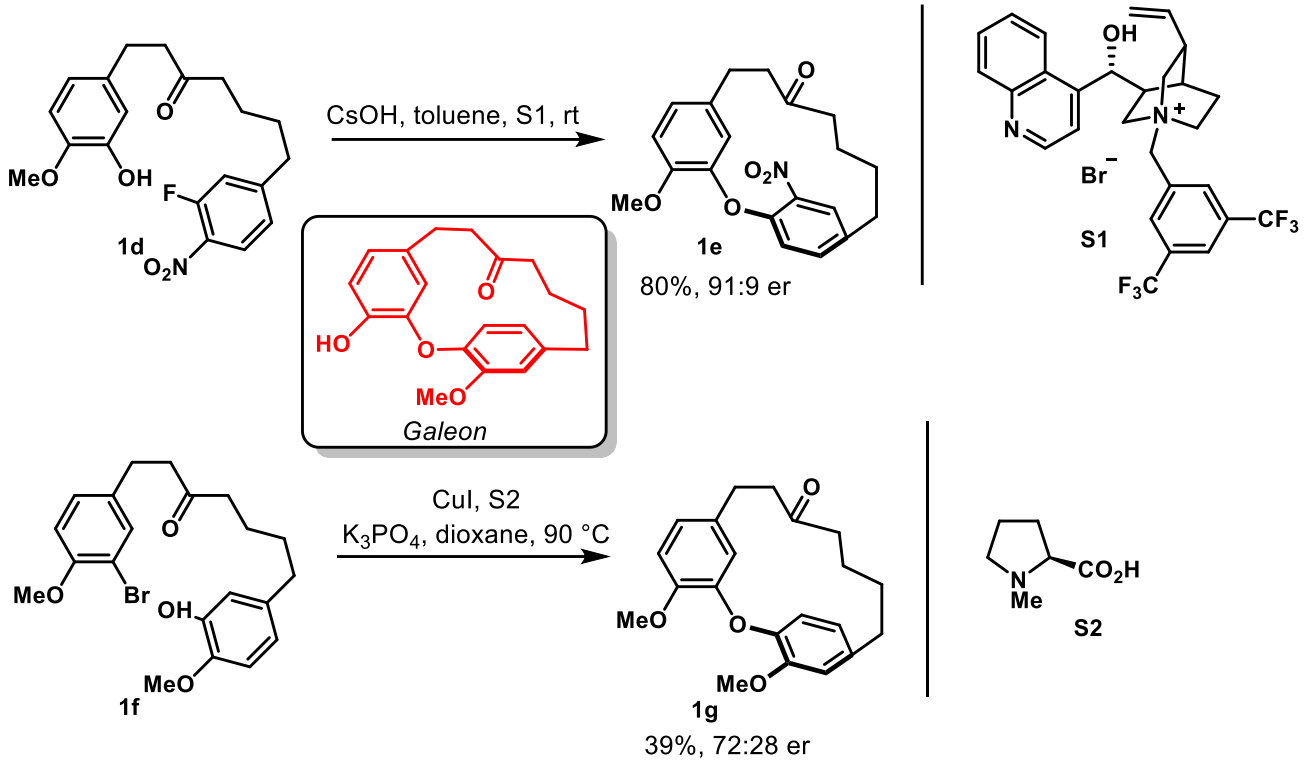
Construction of Planar chirality

1. Asymmetric Catalysis



Four ways to construct planar chirality, which was similar to the construction of axial chirality

Macrocyclization for synthesis of Nature Products



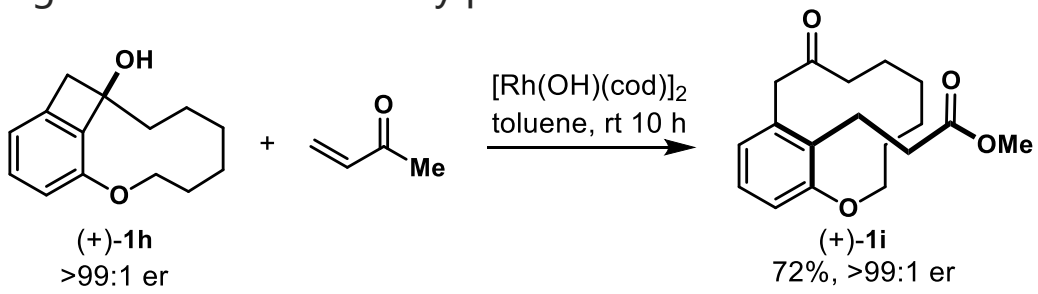
For natural products containing planar chirality, macrocyclization is the most commonly used method

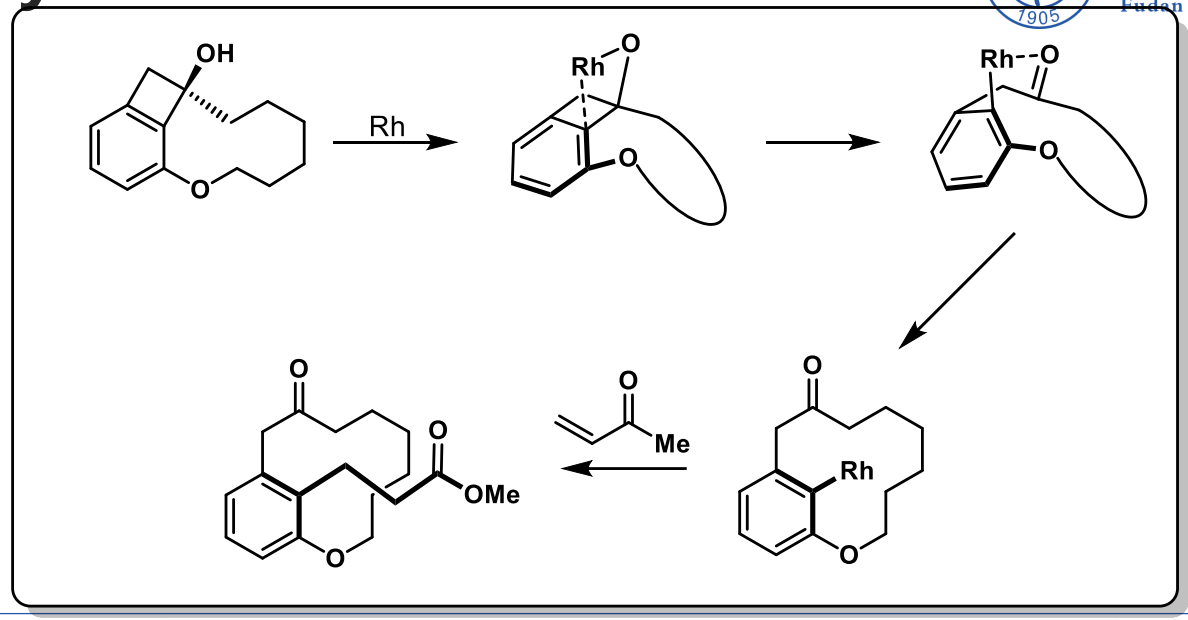
Rosa Llpez and Claudio Palomo, *Angew. Chem. Int. Ed*. **2022**, *61*, e202113504.
Qian Cai et al, *Org. Lett*. **2017**, *19*, 1804−1807. Christopher M. Beaudry et al, *Org. Lett*. **2013**, *17*, 4540-4543.

Construction of Planar chirality

2. Point to Planar Chirality Transfer

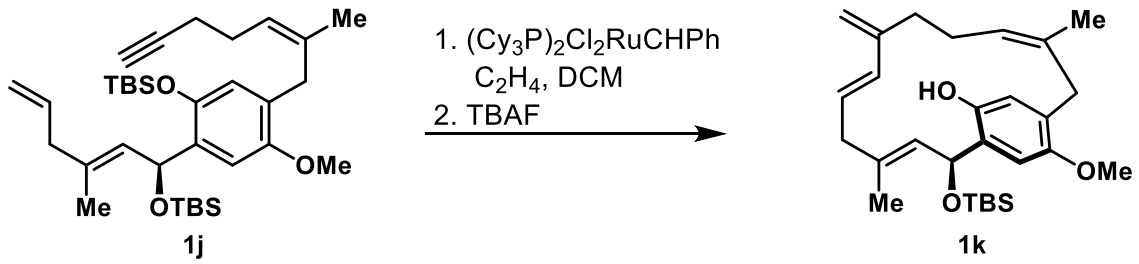
Chiral centers disappear and new chiral plane generated with chirality preserved

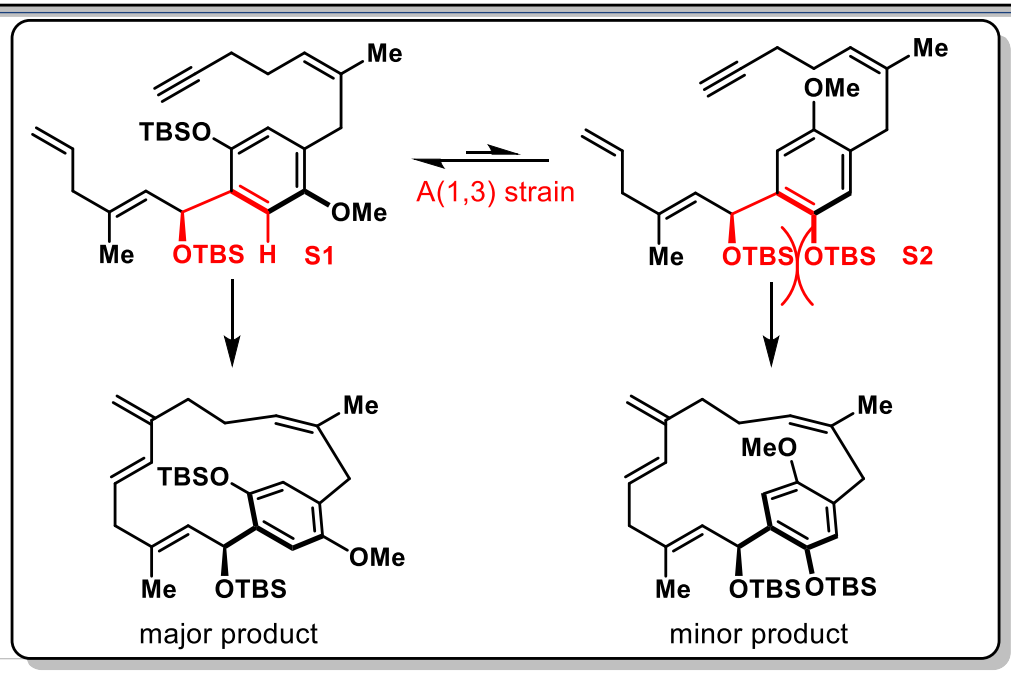




3. Chiral induction

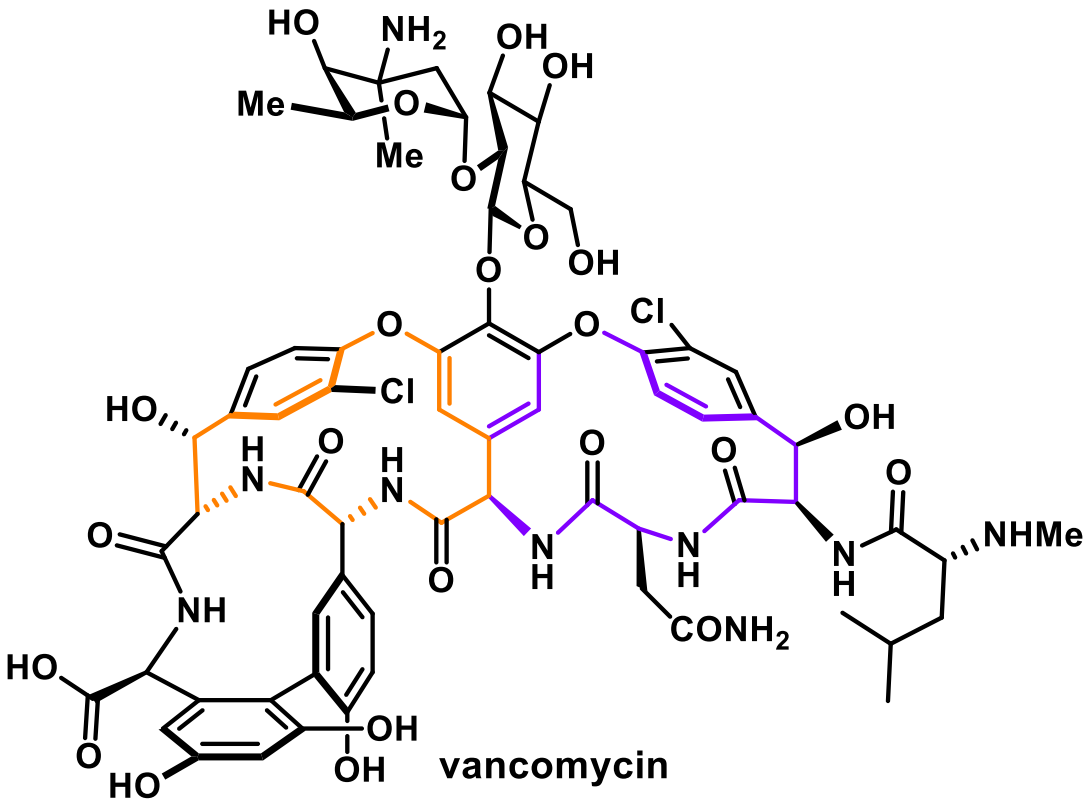
Chiral centers are retained, and new chiral plane generated with high diastereoselectivity





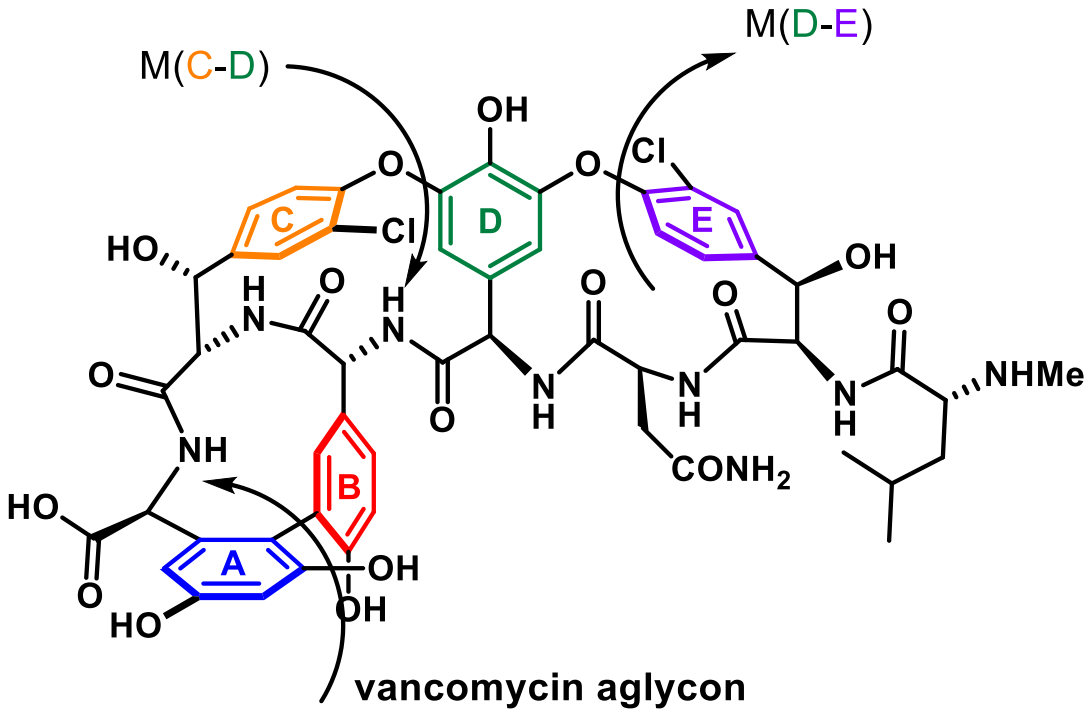
Murakami, M. et al, *Nat. Commun.* **2014**, *5*, 3111−3120.
Shair, M. D. et al, *J. Am. Chem. Soc.* **2002**, *124*, 773−775.

Vancomycin and Vancomycin aglycon



vancomycin

1. Isolated in 1956 from *Streptomyces orientalis*
2. Last resort against infections
3. Two 16-membered diaryl ethers (orange and purple)
4. [12]paracyclophane
5. Arylglycine-rich heptapeptide



vancomycin aglycon

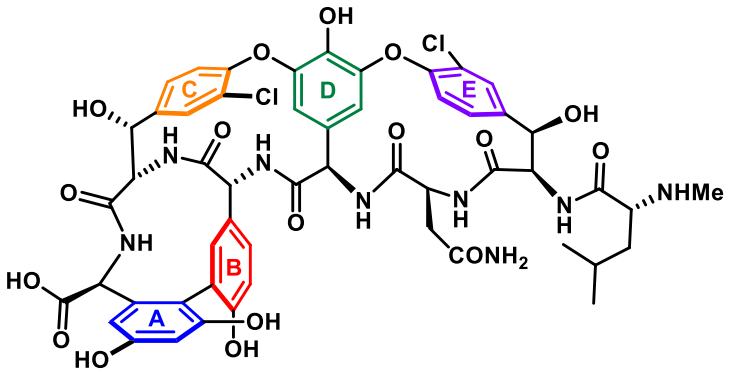
M(A-B)

1. M(A-B) axial chirality
2. M(C-D) planar chirality
3. M(D-E) planar chirality

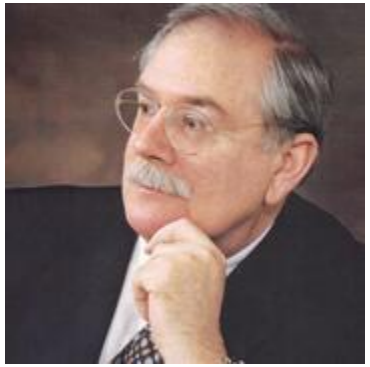
K. C. Nicolaou et al, *Angew. Chem. Int. Ed.* **1999**, *38*, 2096-2152.

Total synthesis of Vancomycin and Vancomycin aglycon

Vancomycin aglycon



vancomycin aglycon

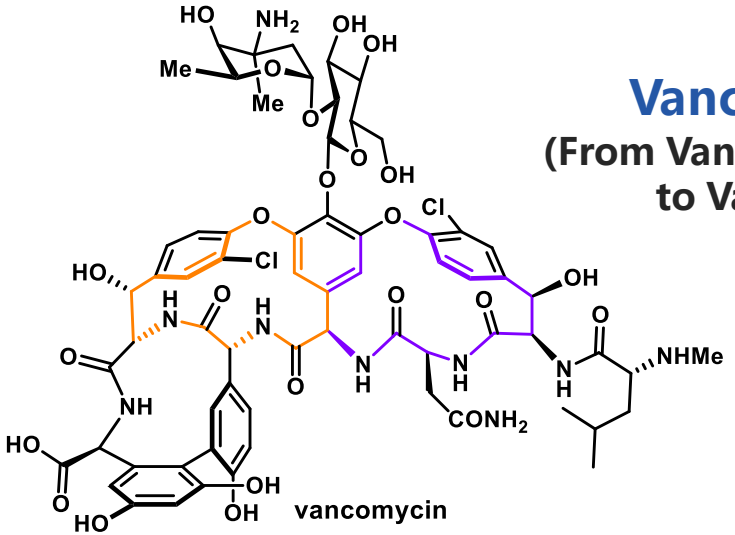


David A. Evans
1998
32 LLS
0.4% overall yield

K. C. Nicolaou
1998
24 LLS
0.05% overall yield

Dale L. Boger
1999
25 LLS
0.2% overall yield

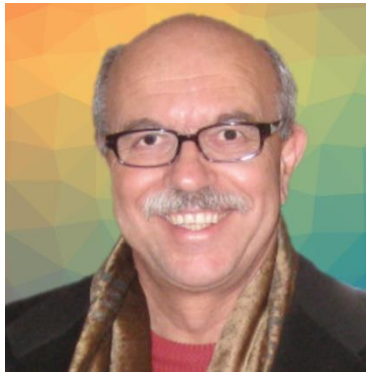
2020
17 LLS
5% overall yield



vancomycin

Vancomycin

(From Vancomycin aglycon to Vancomycin)



K. C. Nicolaou
1998
11 LLS
14% overall yield
chemical method

Dale L. Boger
2014
2 LLS
80% overall yield
enzymatic method

David A. Evans et al, *Angew. Chem. Int. Ed*. **1998**, *37*, 2700-2704.

K. C. Nicolaou et al, *Angew. Chem. Int. Ed*. **1998**, *19*, 2708-2714.

Dale L. Boger et al, *J. Am. Chem. Soc*. **1999**, *121*, 10004-10011.

Dale L. Boger et al, *J. Am. Chem. Soc*. **2020**, *142*, 16039−16050.

Dale L. Boger eet al, *Org. Lett*. **2014**, *16*, 3572−3575

02

PART TWO

Construction of Axial and Planar Charity in Vancomycin

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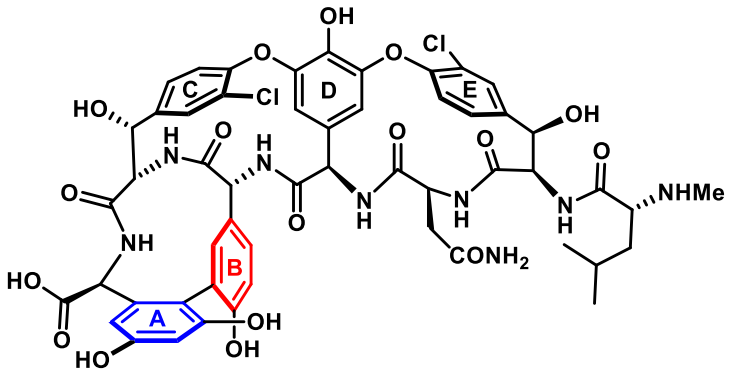
Fudan University

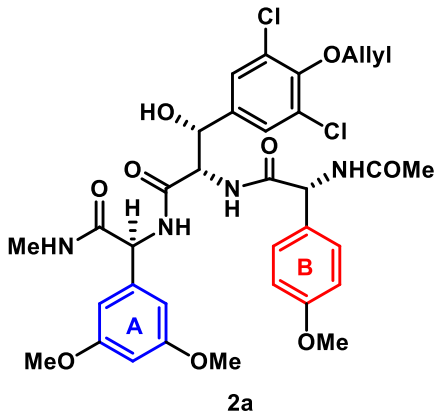
A-B Axial Chirality

Vanadium mediated oxidative coupling

David A. Evans

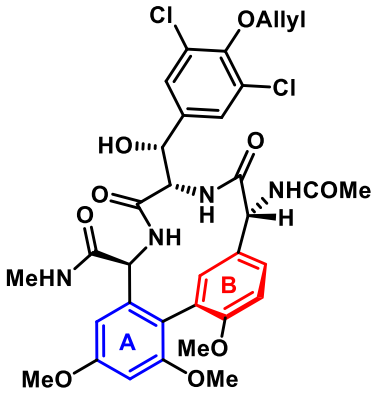


vancomycin aglycon



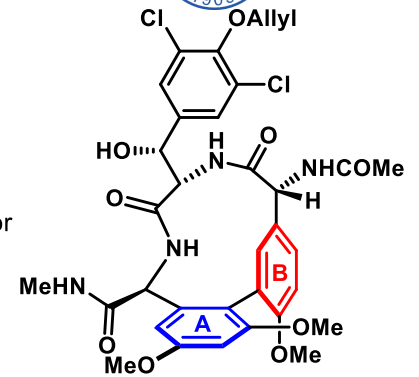
2a

various conditions



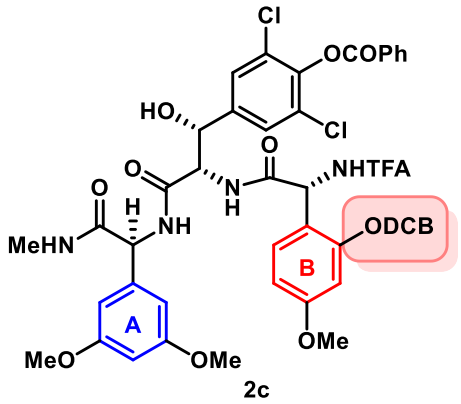
2b
unnatural configuration
ND

or



epi-2b
natural configuration
ND

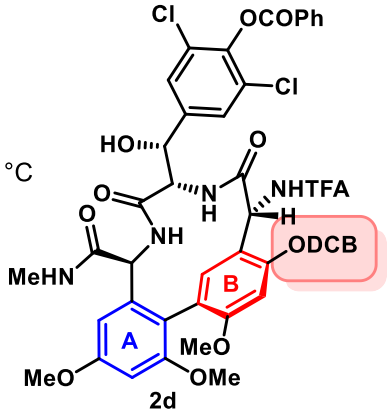
dimeric biaryl coupling resulting from the union of A
only product



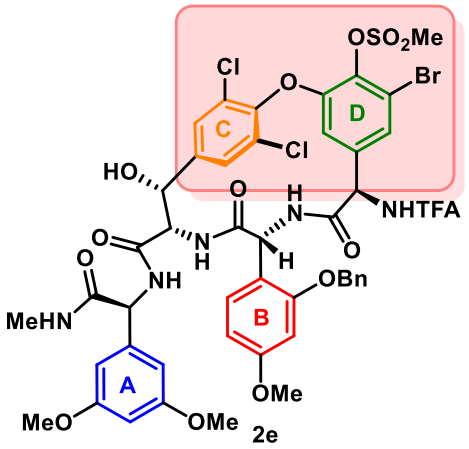
2c

VOF_3, BF_3•OEt_2
TFAA, TFA, DCM, 0 °C
then Zn

58%, >19:1 dr



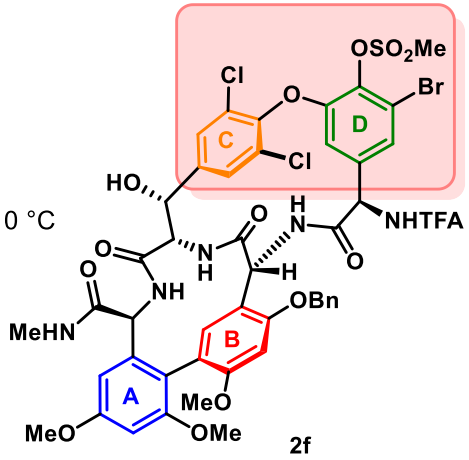
2d
unnatural configuration



2e

VOF_3, BF_3•OEt_2
TFAA, TFA, DCM, 0 °C
then Zn

72%, >19:1 dr



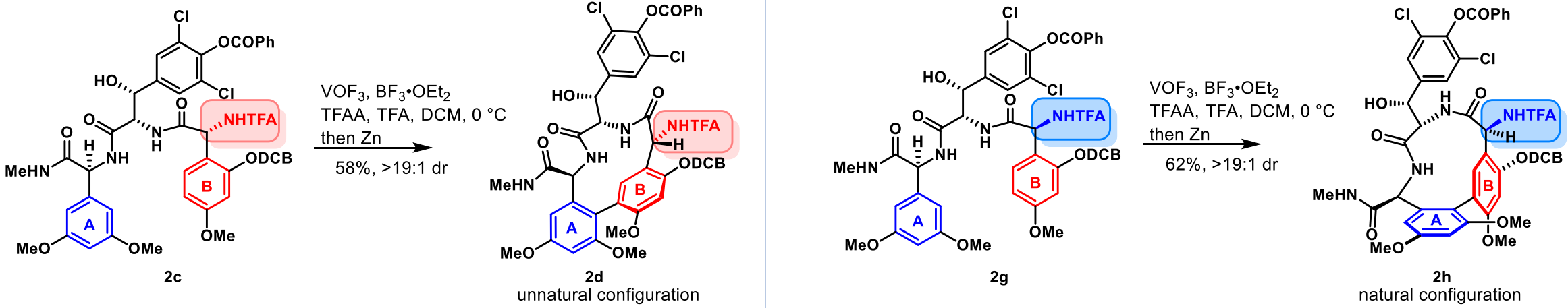
2f
unnatural configuration

David A. Evans et al, *J. Am. Chem. Soc.* **1993**, *115*, 6426-6427. David A. Evans et al, *J. Am. Chem. Soc.* **1997**, *119*, 3417-3418.

A-B Axial Chirality

A(1,3) strain → A-B Axial chirality

David A. Evans

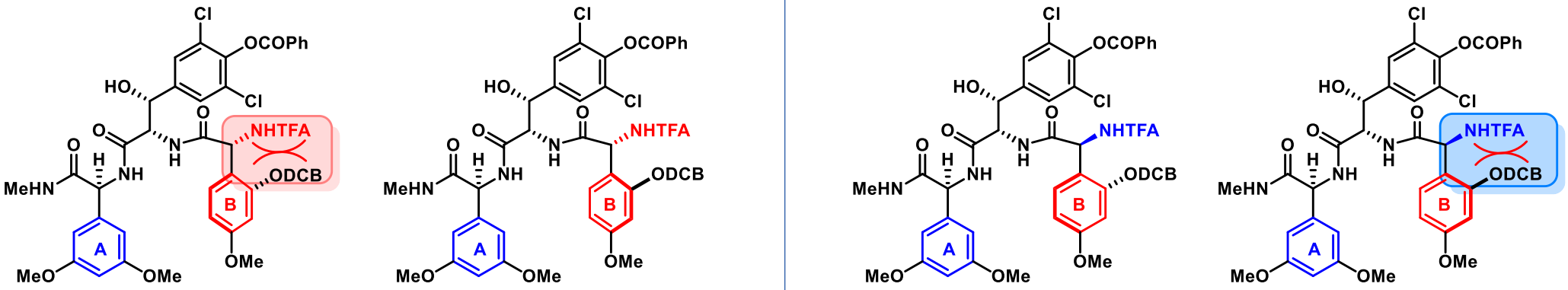


2c

2d
unnatural configuration

2g

2h
natural configuration



2c-1
unfavorable

2c-2
favorable

2g-1
favorable

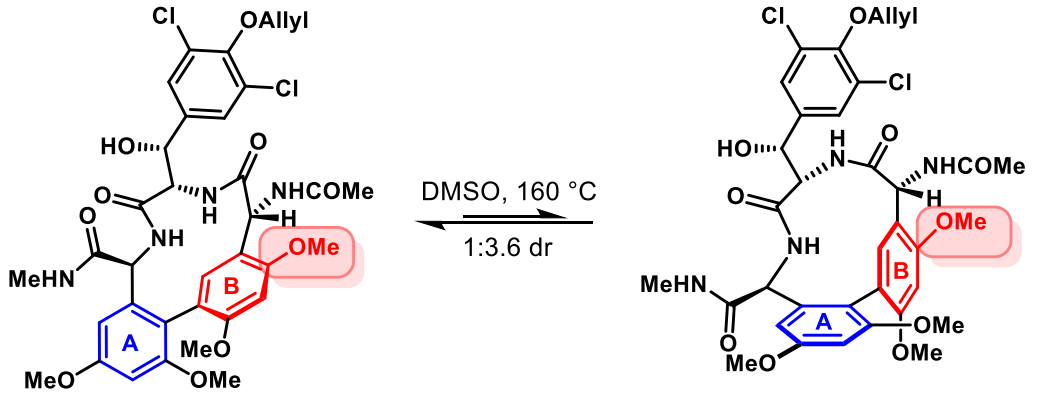
2g-2
unfavorable

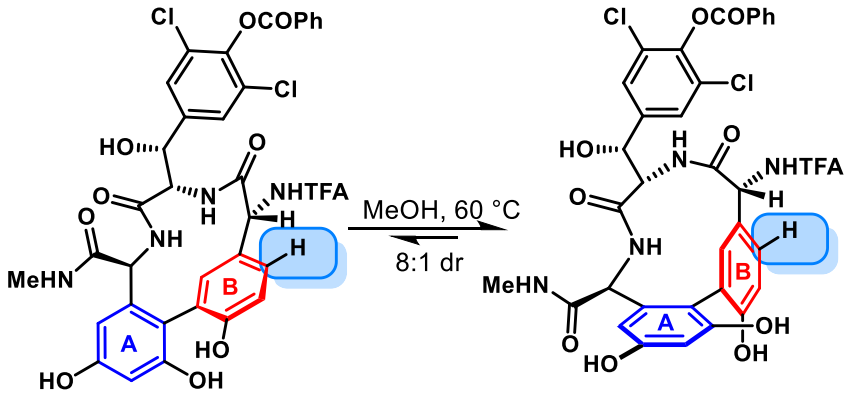
David A. Evans et al, *Angew. Chem. Int. Ed.* **1998**, *37*, 2700-2704.

A-B Axial Chirality

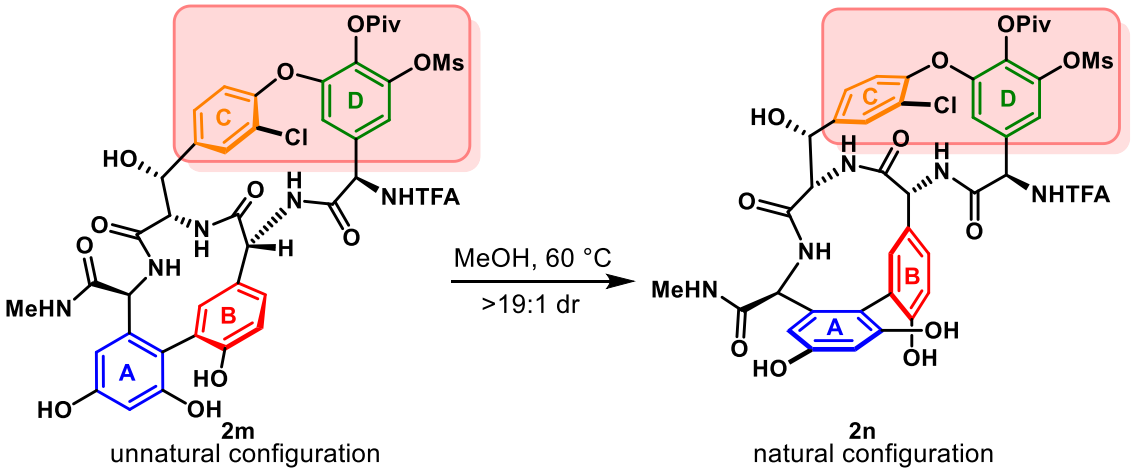
Thermal equilibrium ➡ A-B Axial chirality

David A. Evans

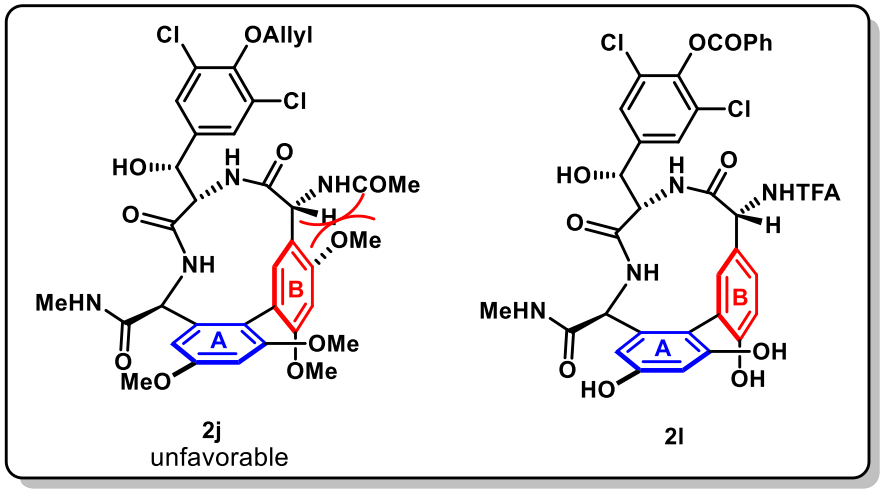




Removal of intalled methoxy group



Preorganization of C-D macrocycle



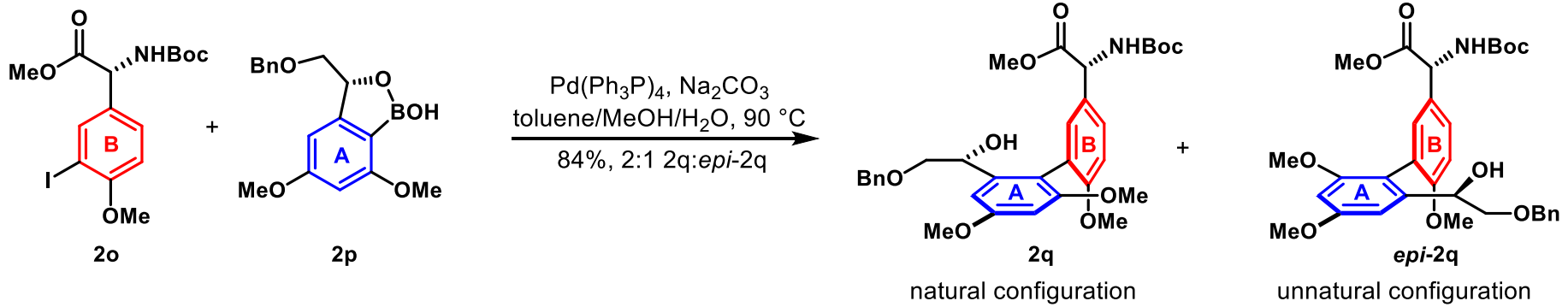
A(1,3) strain

David A. Evans et al, *Angew. Chem. Int. Ed.* **1998**, *37*, 2700-2704.

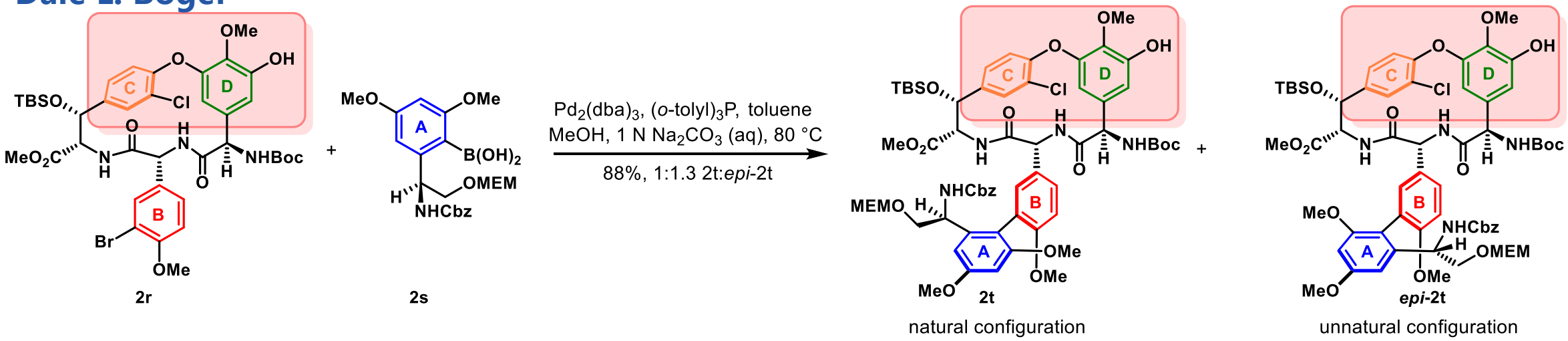
A-B Axial Chirality

Suzuki-Mayaura coupling

K. C. Nicolaou



Dale L. Boger

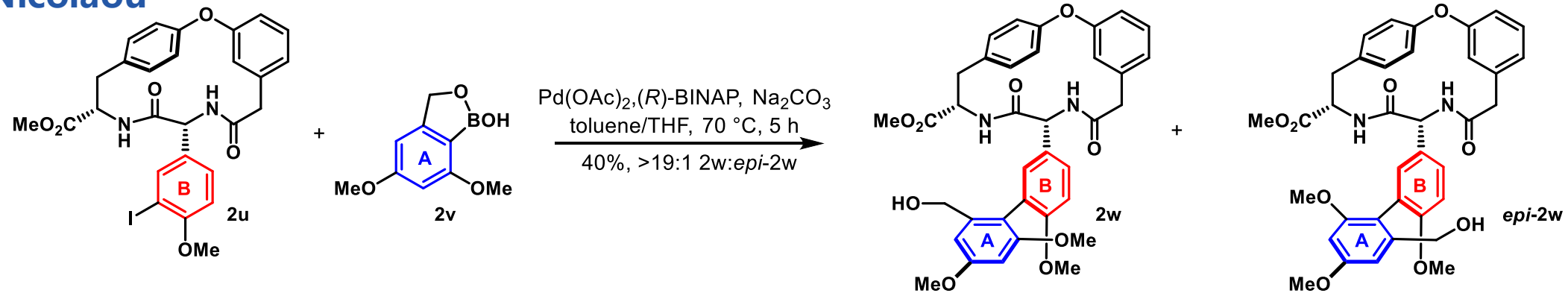


K. C. Nicolaou et al, *Angew. Chem. Int. Ed*. **1998**, *19*, 2708-2714. Dale L. Boger et al, *J. Am. Chem. Soc*. **1999**, *121*, 10004-10011.

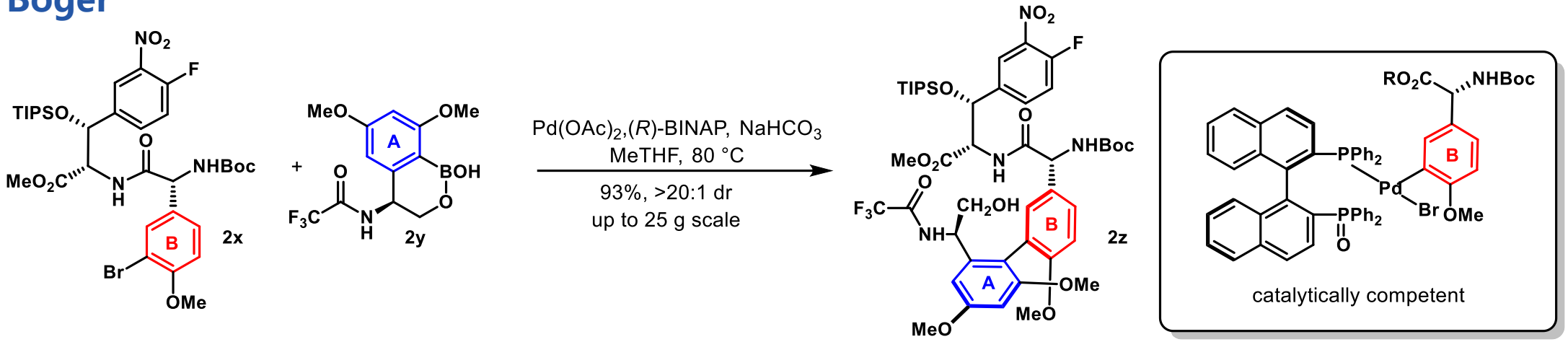
A-B Axial Chirality

Chiral ligand ➡ A-B Axial chirality

K. C. Nicolaou



Dale L. Boger

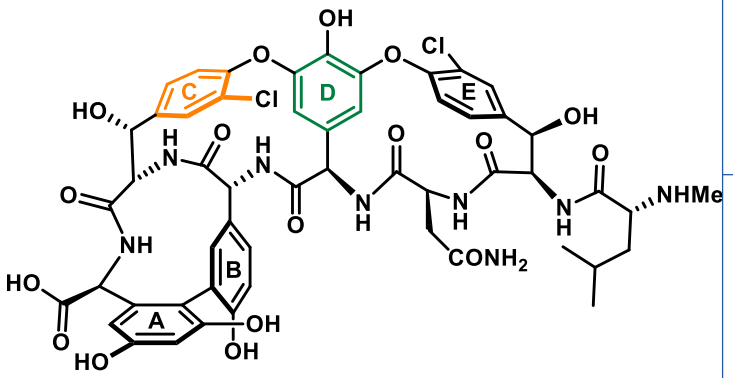


K. C. Nicolaou et al, *Chem. Eur. J.* **1999**, *9*, 2584-2601.

Dale L. Boger et al, *J. Am. Chem. Soc.* **2020**, *142*, 16039−16050.

C-D planar chirality

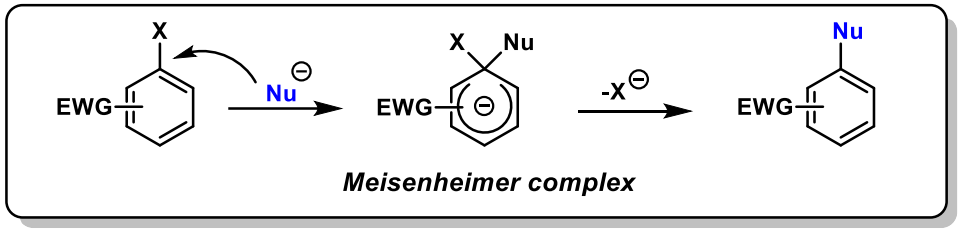
David A. Evans

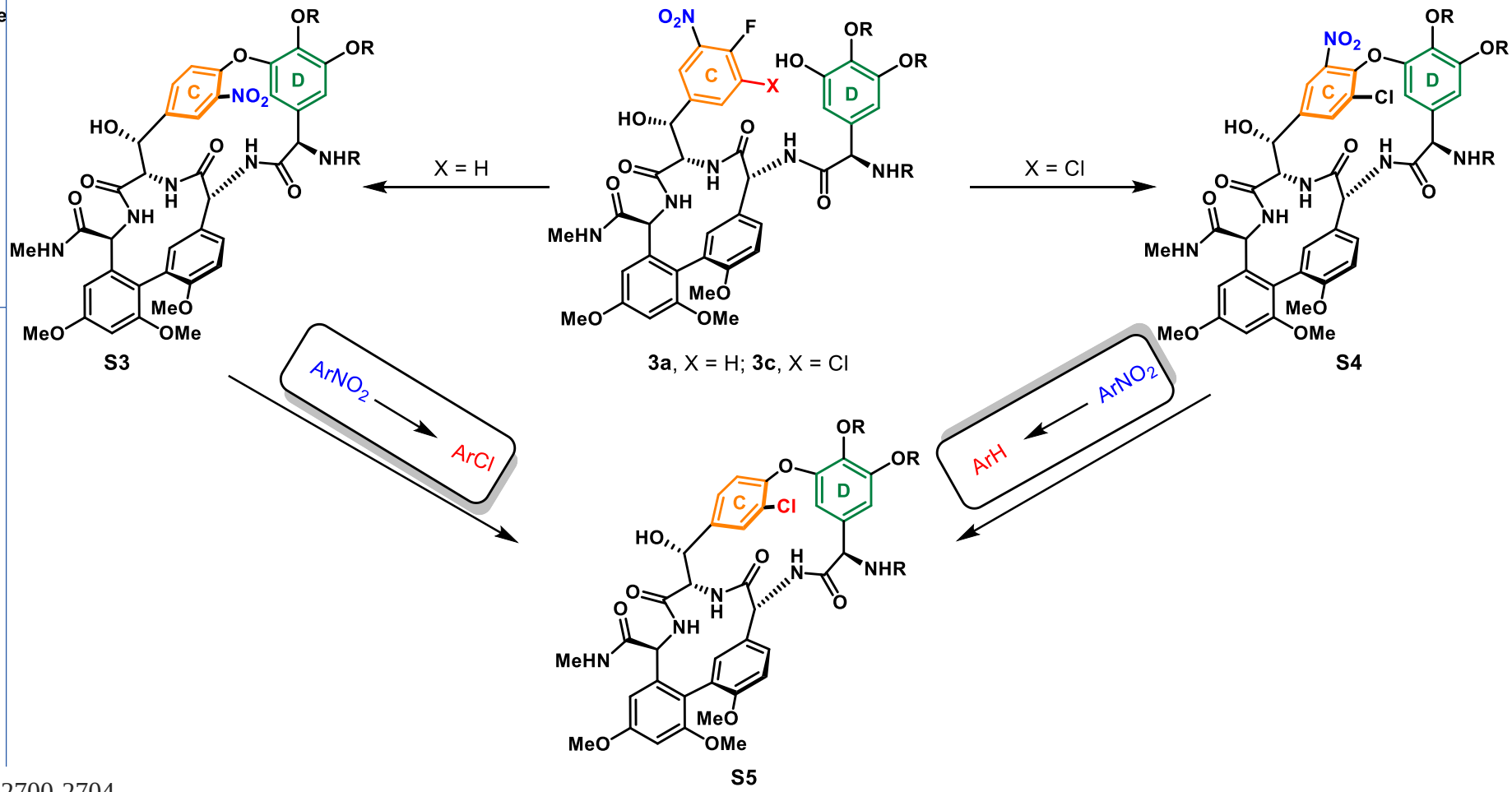


vancomycin aglycon

1. Hindered rotation of benzene C
2. C-Cl facing outward from the paper
3. SN_{Ar} Reaction followed by Sandmeyer Reaction (NO_2 to Cl or H)

S_NAr Reaction



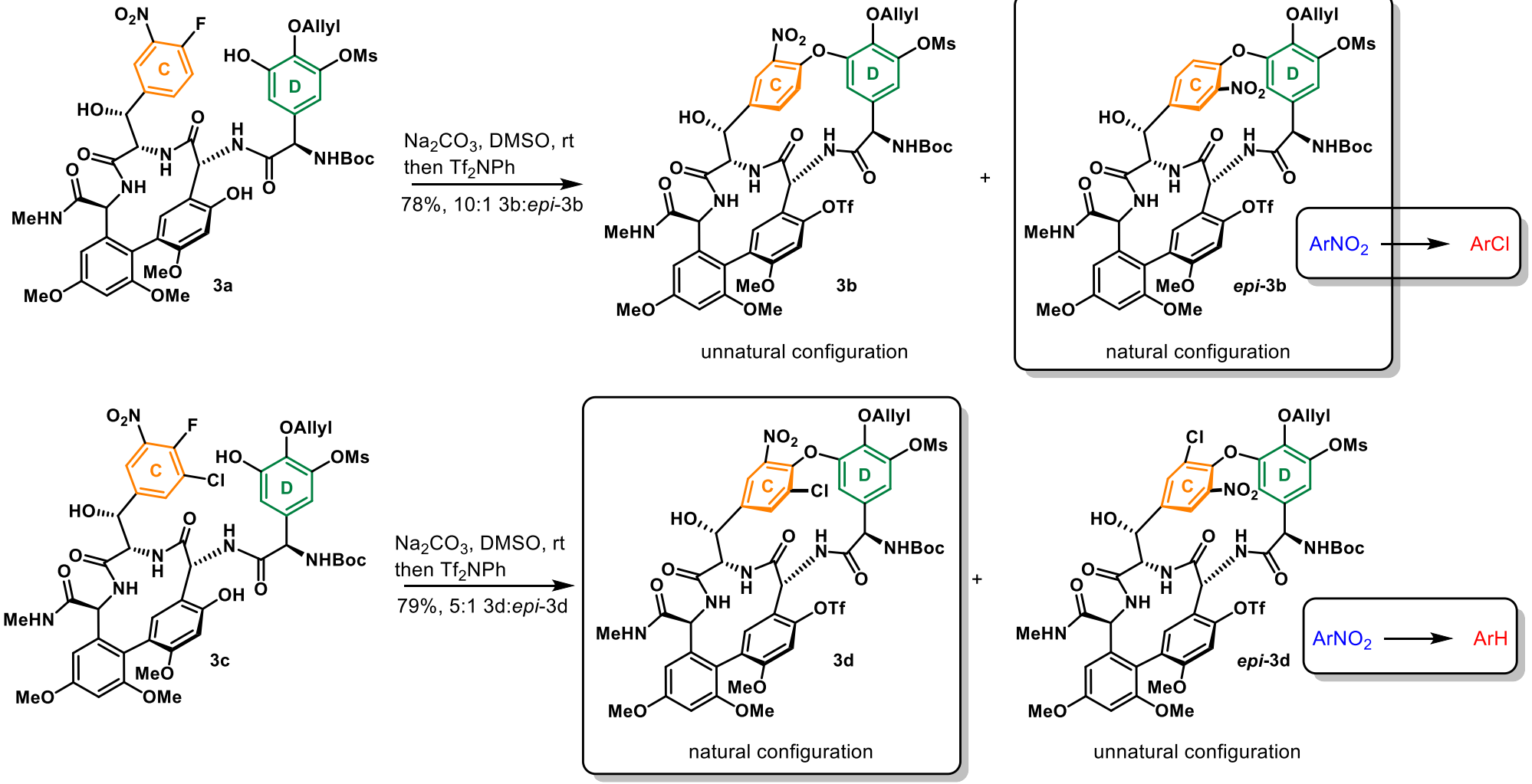


David A. Evans et al, *Angew. Chem. Int. Ed.* **1998**, *37*, 2700-2704.

C-D planar chirality

David A. Evans

S_NAr Reaction

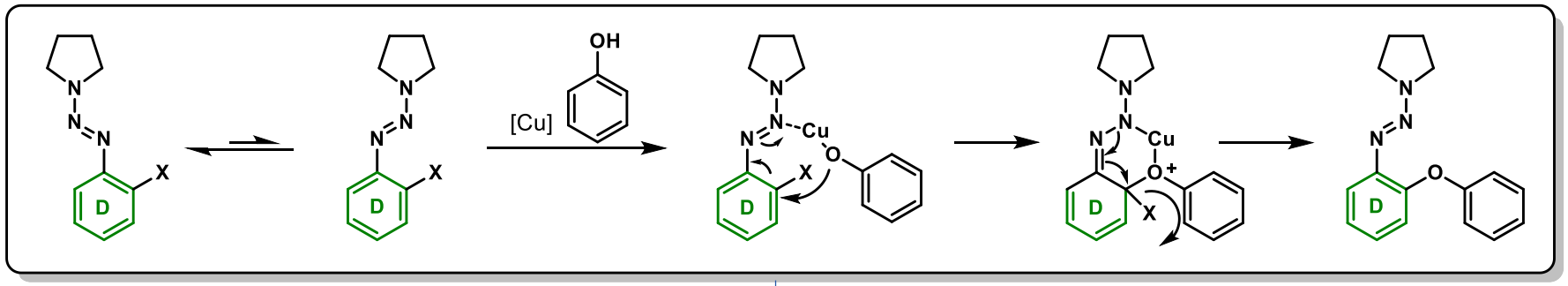


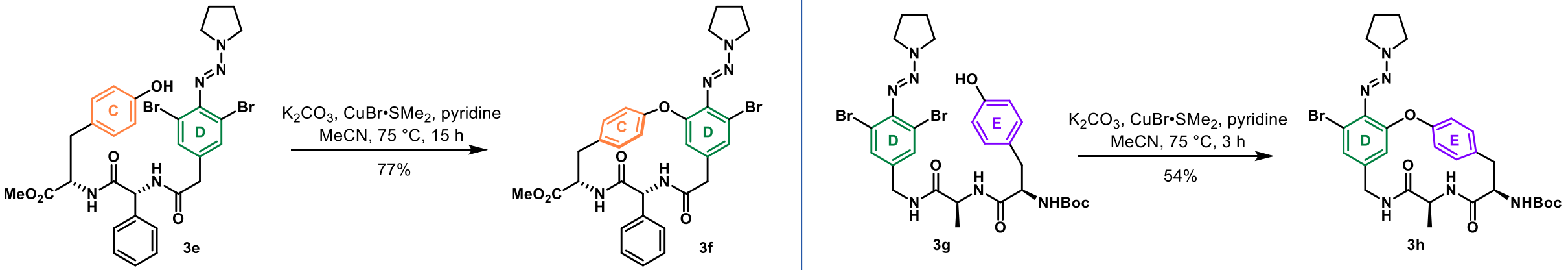
David A. Evans et al, *Angew. Chem. Int. Ed.* **1998**, *37*, 2700-2704.

C-D planar chirality

Ullmann coupling

K. C. Nicolaou





Triazene unit

1. **Electron sink**
2. **Attract the Nu^- through coordination with Cu(I)**

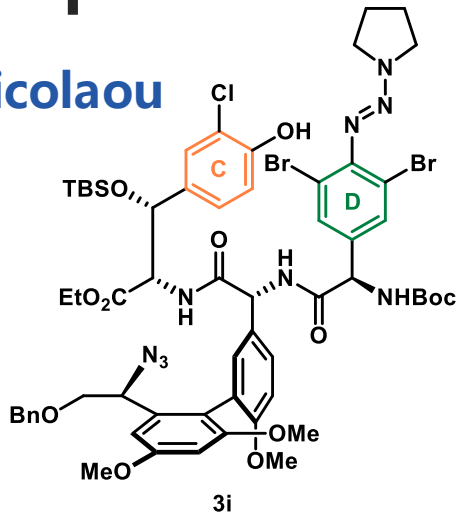
The Triazene based Ullmann reaction successfully achieved macrocyclization
How about the planar chirality control of these two cyclophanes?

K. C. Nicolaou et al, *J. Am. Chem. Soc.* **1997**, *119*, 3421-3422.

C-D planar chirality

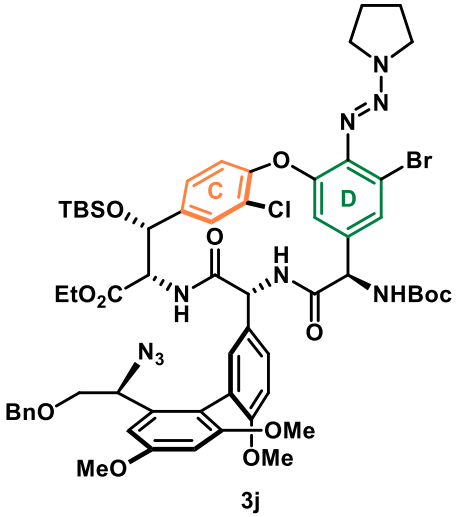
A(1,3) strain → C-D planar chirality

K. C. Nicolaou



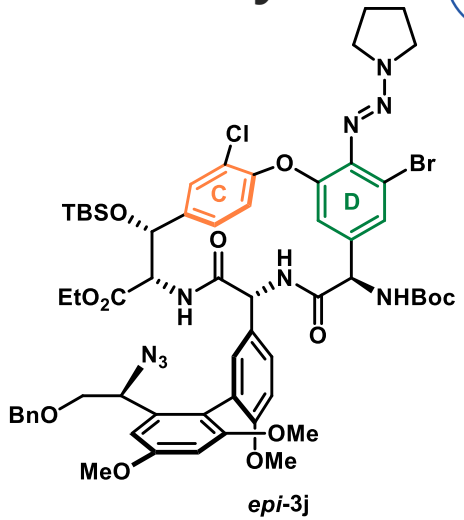
3i

60%, 1:1 3j:*epi*-3j



3j

+

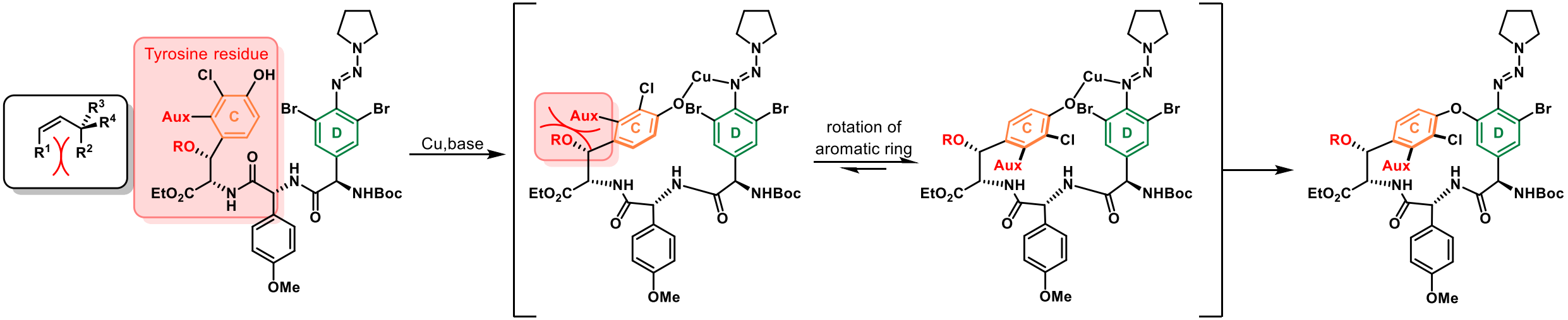


epi-3j

No planar selectivity

How to make dr higher to a single atropisomer?

Design: A(1,3) strain



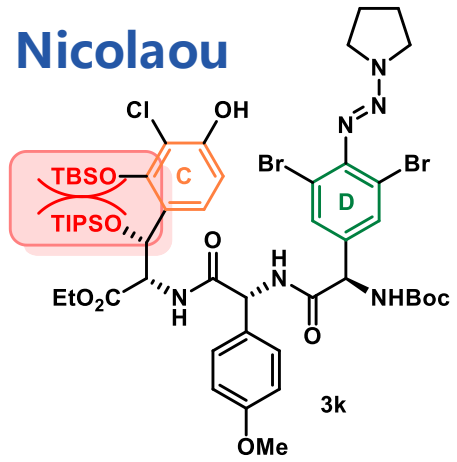
K. C. Nicolaou et al, *Angew. Chem. Int. Ed.* **1998**, *19*, 2708-2714.

K. C. Nicolaou et al, *J. Am. Chem. Soc.* **2002**, *124*, 10451-10455.

C-D planar chirality

A(1,3) strain ➡ C-D planar chirality

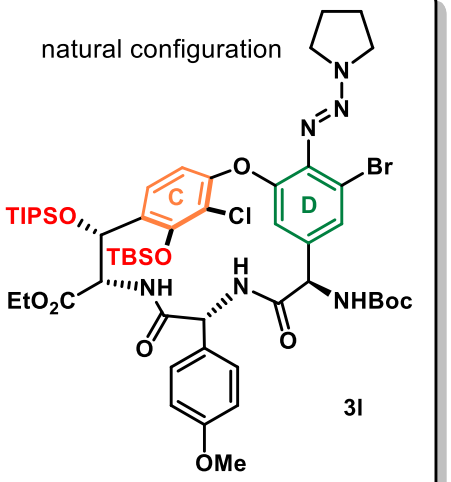
K. C. Nicolaou



3k

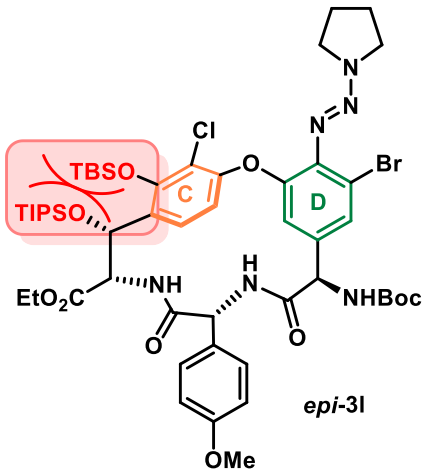
$CuBr{\cdot}SMe_2$
K_2CO_3, pyridine
94%, single atopisomer 3l

natural configuration



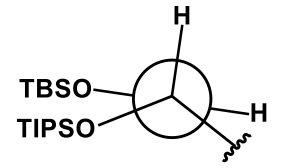
3l

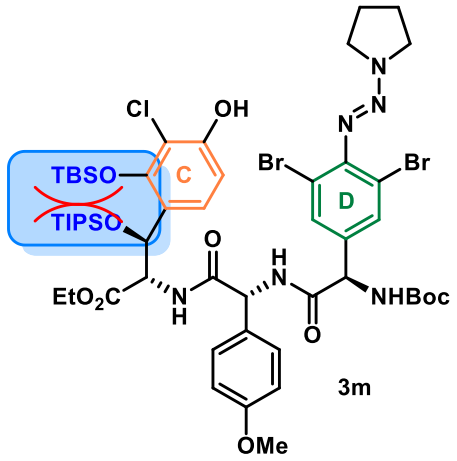
+



epi-3l

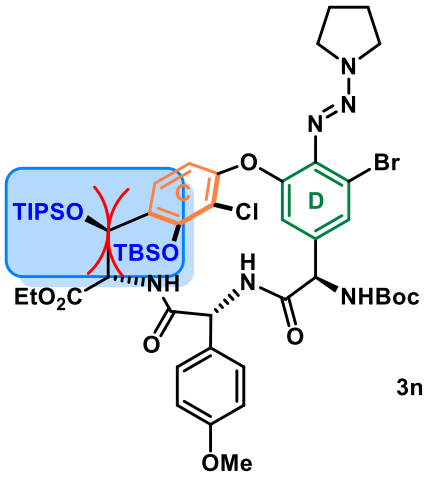
highly unfavorable
eclipsed conformation





3m

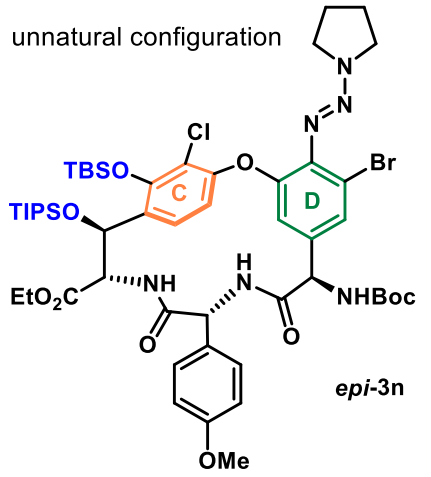
$CuBr{\cdot}SMe_2$
K_2CO_3, pyridine
55%, 1:2 3n:*epi*-3n



3n

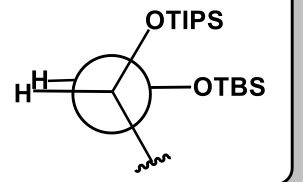
+

unnatural configuration



epi-3n

moderately unfavorable
staggered conformation

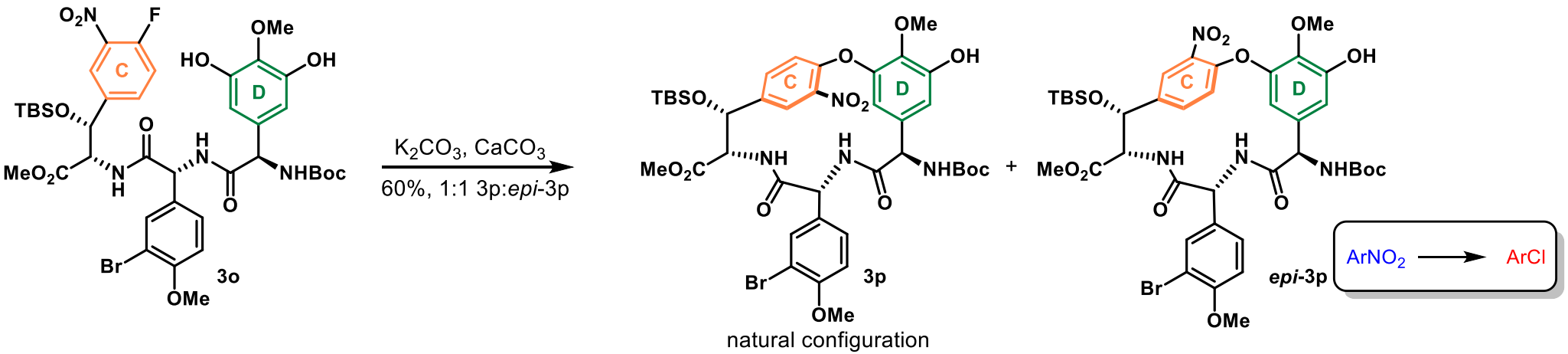


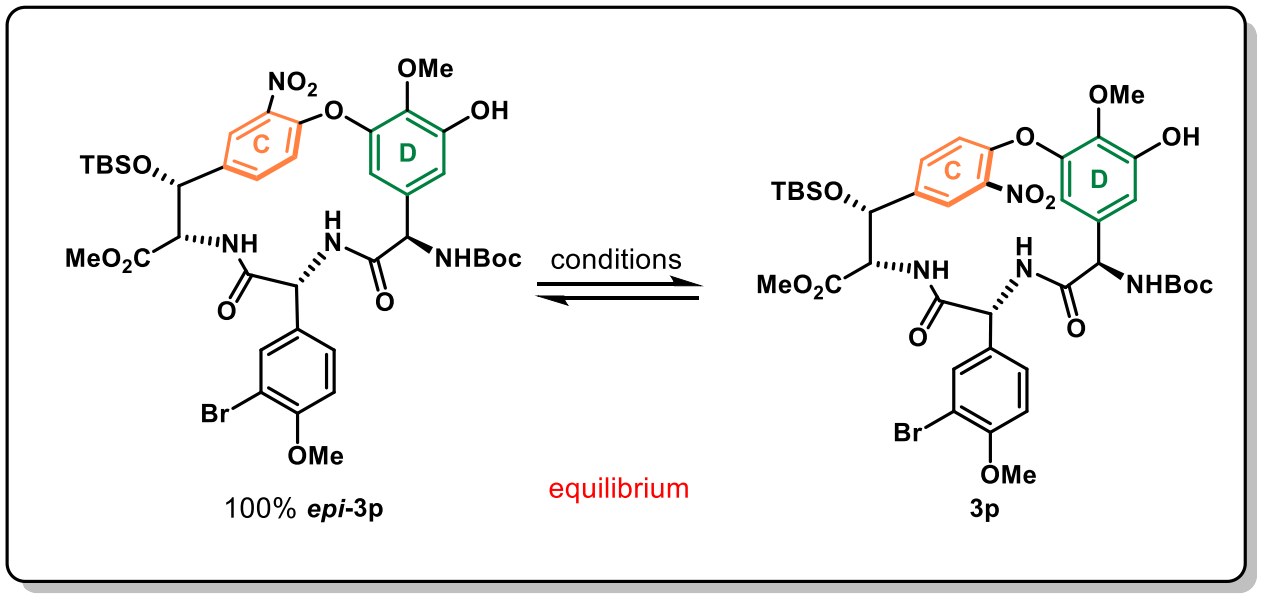
K. C. Nicolaou et al, *J. Am. Chem. Soc.* **2002**, *124*, 10451-10455.

C-D planar chirality

Thermal equilibrium ➡ C-D planar chirality

Dale L. Boger





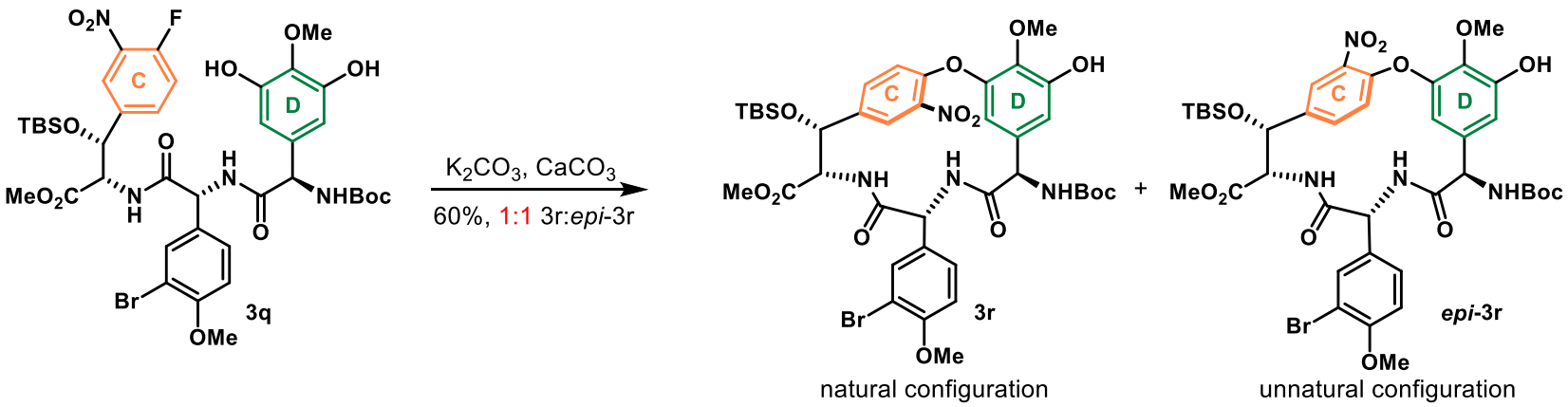
conditions	*epi*-3p:3p	conditions	*epi*-3p:3p
DMSO, 120 °C, 1 h	100:0	DMF, 120 °C, 1 h	100:0
DMSO, 155 °C, 1.3 h	2:1	DMF, 155 °C, 0.5 h	1.7:1
DMSO, 155 °C, 4 h	1.7:1 (72%)	DMF, 155 °C, 1.1 h	1.2:1 (57%)
DMSO, 140 °C, 5 min	>20:1	*o*-$C_6H_4Cl_2$, 140 °C, 20 min	>20:1
DMSO, 140 °C, 0.5 h	10:1	*o*-$C_6H_4Cl_2$, 140 °C, 2 h	11:1
DMSO, 140 °C, 1 h	5:1	*o*-$C_6H_4Cl_2$, 140 °C, 3 h	8:1
DMSO, 140 °C, 1.5 h	3.5:1	*o*-$C_6H_4Cl_2$, 140 °C, 16 h	1.6:1
DMSO, 140 °C, 3.5 h	2:1	*o*-$C_6H_4Cl_2$, 140 °C, 56 h	1.1:1
DMSO, 140 °C, 7 h	1.2:1		

Dale L. Boger et al, *J. Am. Chem. Soc.* **1999**, *121*, 10004-10011.

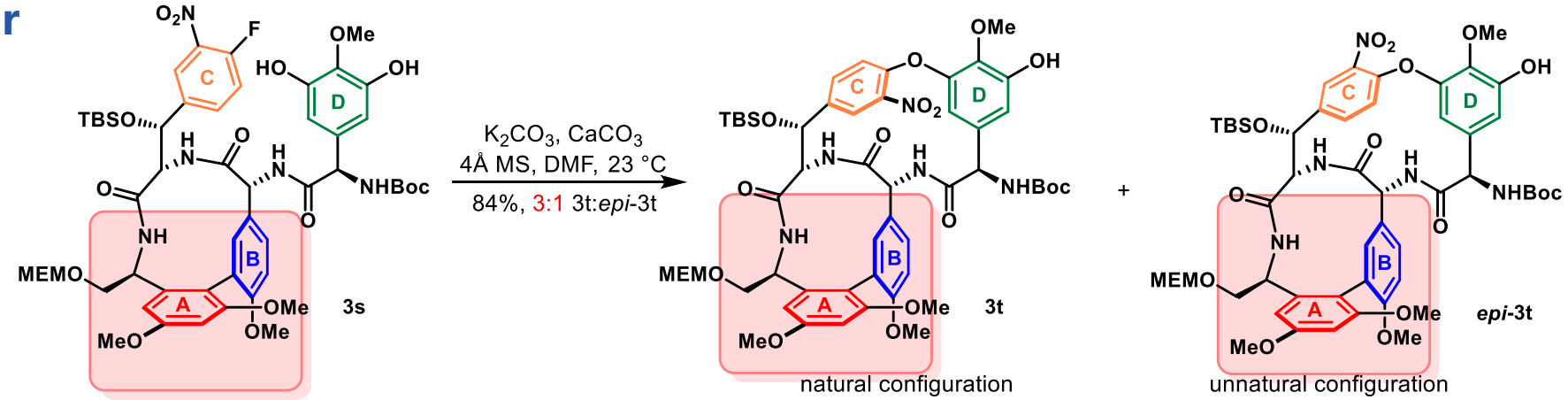
C-D planar chirality

Intact A-B macrocycle ➡ C-D planar chirality

Dale L. Boger



Dale L. Boger



natural A-B ring system improves C-D atropselectivity

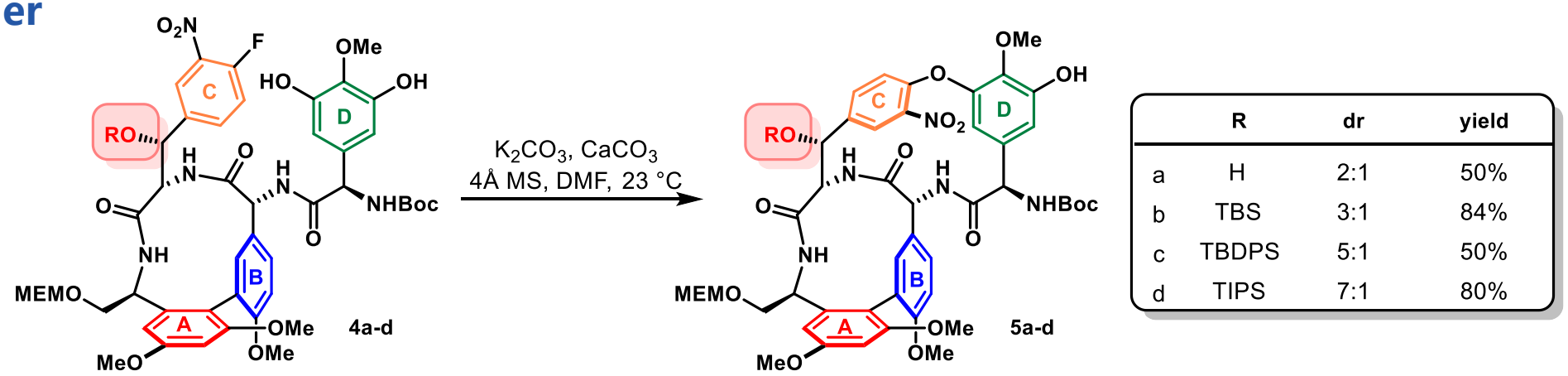
Dale L. Boger et al, *J. Am. Chem. Soc*. **2020**, *142*, 16039−16050.

C-D planar chirality

Steric hindrance ➡ C-D planar chirality

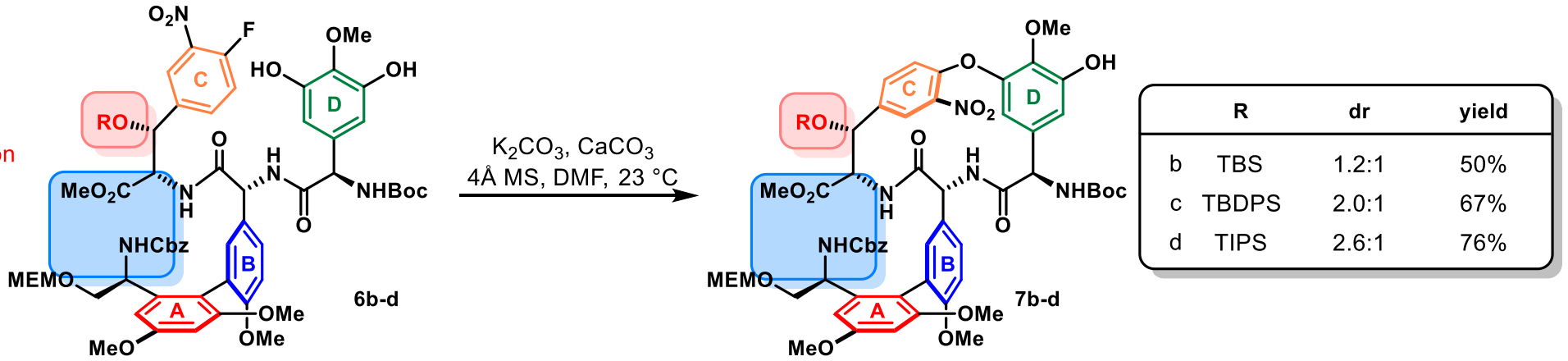
Dale L. Boger

With preorganization



	R	dr	yield
a	H	2:1	50%
b	TBS	3:1	84%
c	TBDPS	5:1	50%
d	TIPS	7:1	80%

Without preorganization



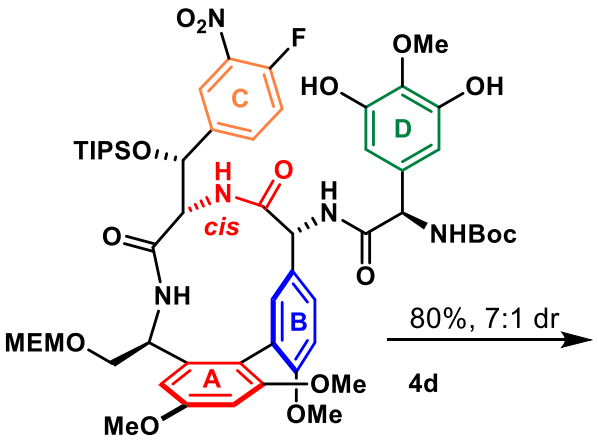
	R	dr	yield
b	TBS	1.2:1	50%
c	TBDPS	2.0:1	67%
d	TIPS	2.6:1	76%

1. **Increase in silyl ether protecting group improved diastereoselctivity**
2. **Substrate with intact A-B ring system affords higher dr**

Dale L. Boger et al, *J. Am. Chem. Soc.* **2020**, *142*, 16039−16050.

C-D planar chirality

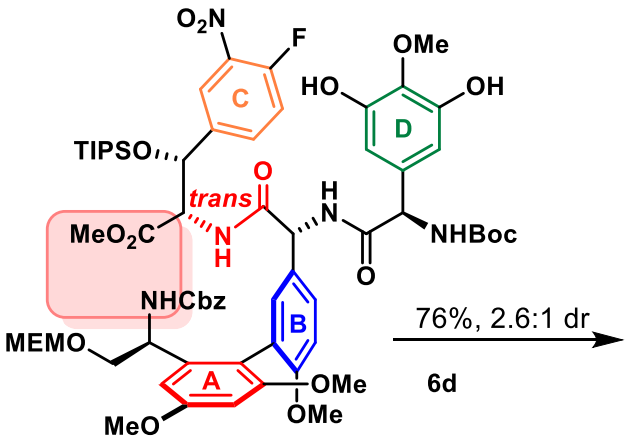
Steric hindrance ➡ C-D planar chirality



80%, 7:1 dr

4d

With preorganization
cis amide conformation

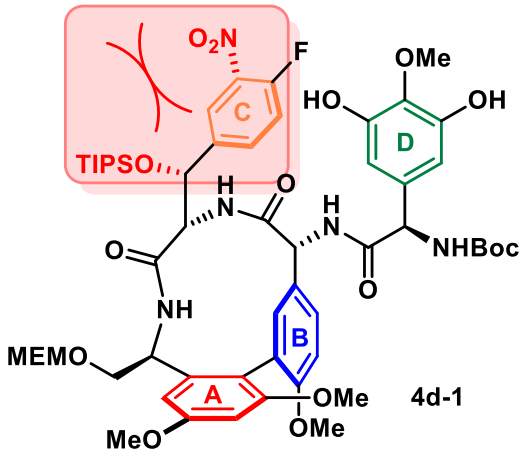


76%, 2.6:1 dr

6d

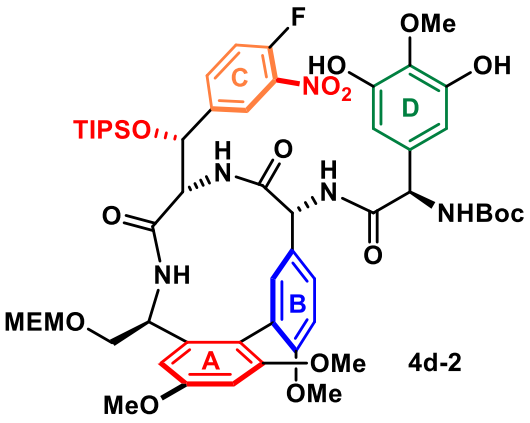
Without preorganization
trans amide conformation

4d with preorganization of AB ring system adopts a cis amide conformation



4d-1

less favorable rotamer



4d-2

more favorable rotamer

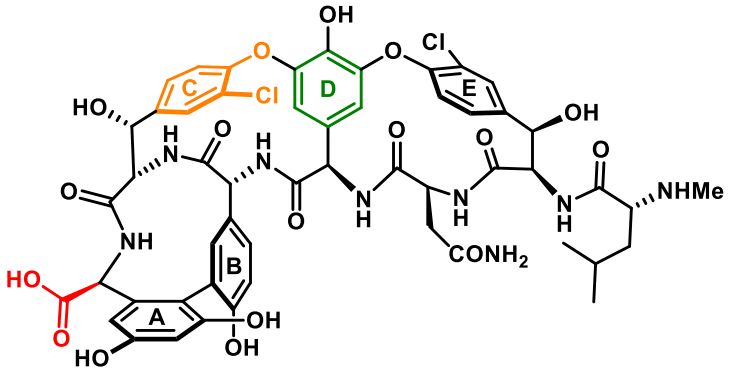
substituent effect that sterically further directs the nitro group distal to the large silyl ether

Dale L. Boger et al, *J. Am. Chem. Soc*. **2020**, *142*, 16039−16050.

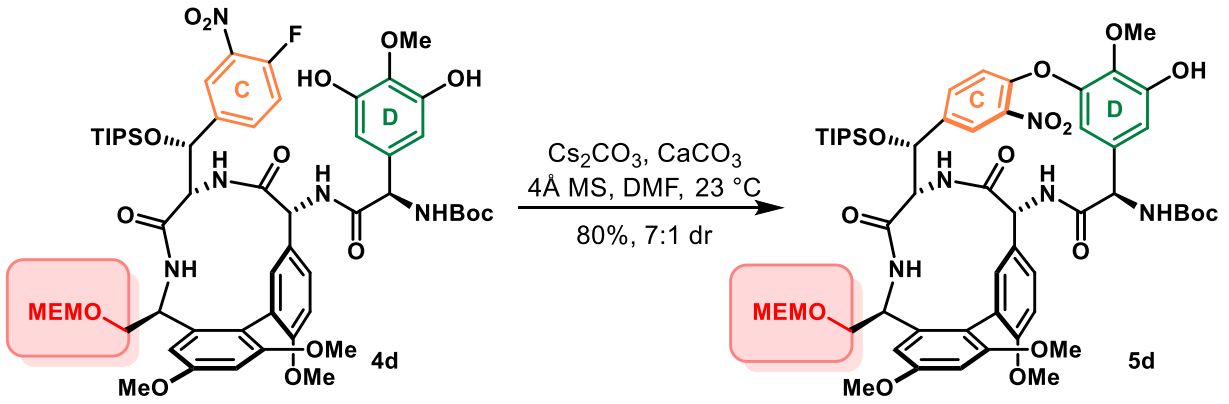
C-D planar chirality

Remote ester group ➡ C-D planar chirality

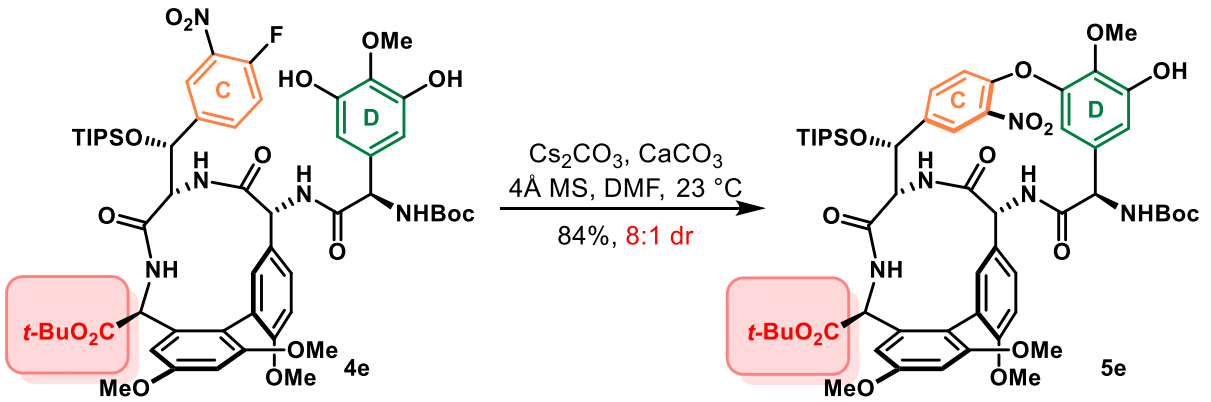
Dale L. Boger



vancomycin aglycon



1. **MEM ether** was used to preclude C-terminus **epimerization**
2. Introduce of MEM ether along with an efficient deprotection-oxidation sequcene (**53%, 4 steps**)
3. *tert*-butyl ester with judicious choice of reaction condition **avoid epimerization**
4. *tert*-butyl ester afford a higher dr



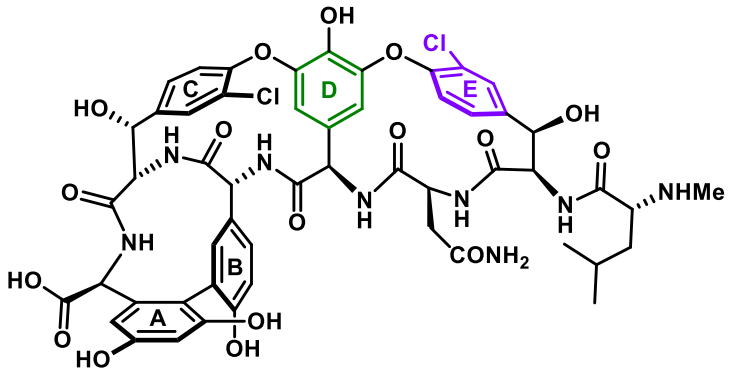
Next-generation total synthesis

Dale L. Boger et al, *J. Am. Chem. Soc.* **2020**, *142*, 16039−16050.

D-E planar chirality

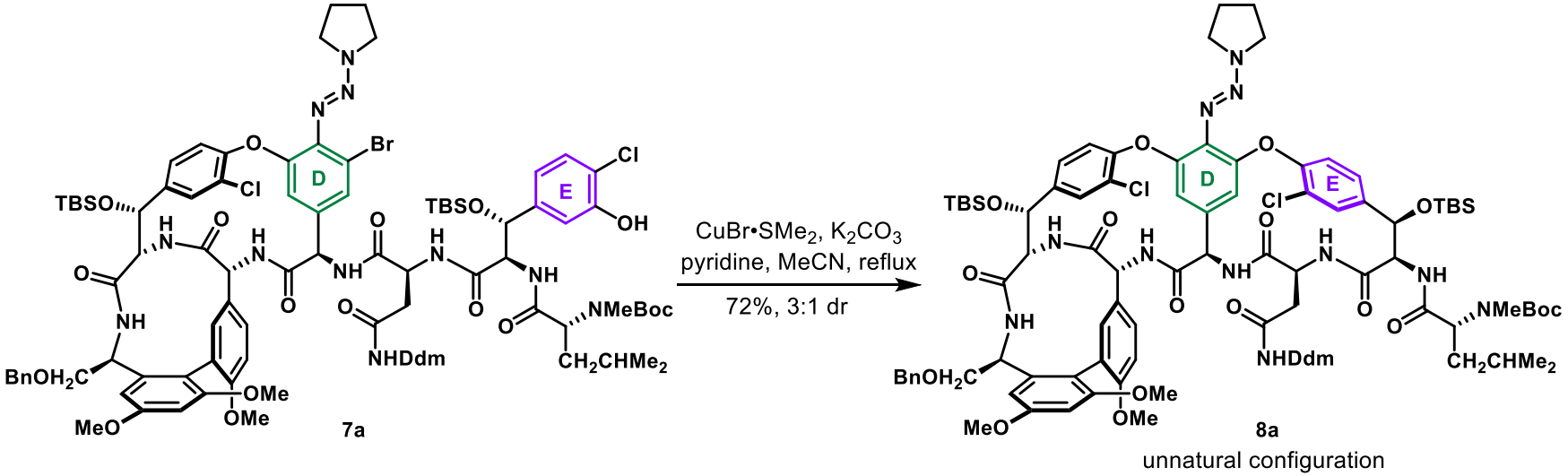
Thermal equilibrium ➡ D-E planar chirality

K. C. Nicolaou



vancomycin aglycon

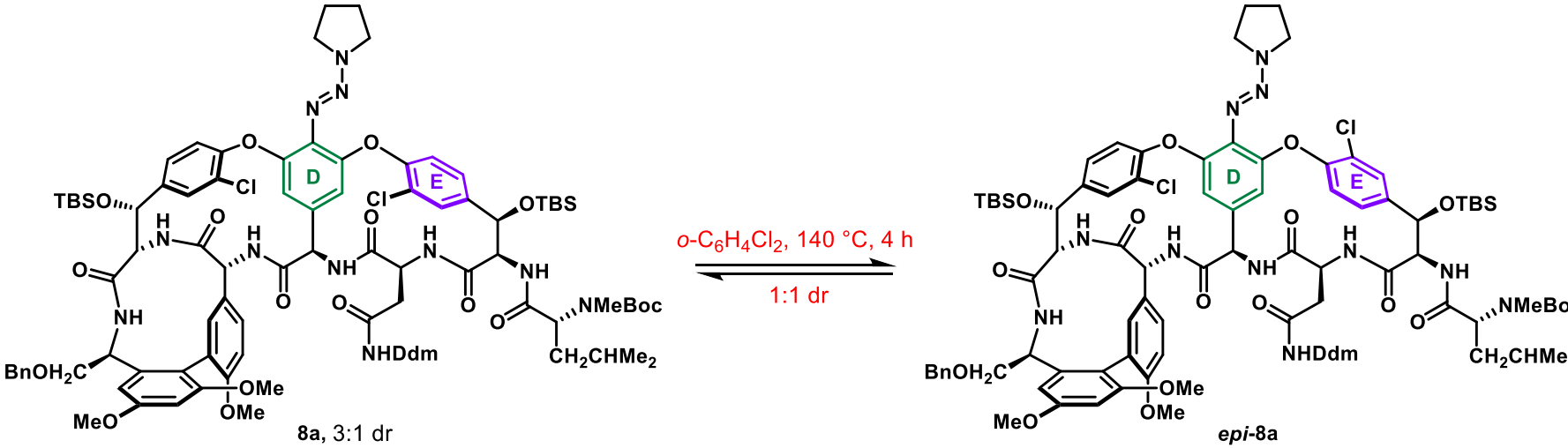
1. C-Cl Facing inside the paper surface
2. Ullmann coupling favors unnatural D-E macrocycle
3. Thermal equilibrium gives a 1:1 dr



7a

8a

unnatural configuration



8a, 3:1 dr

unnatural configuration

epi-8a

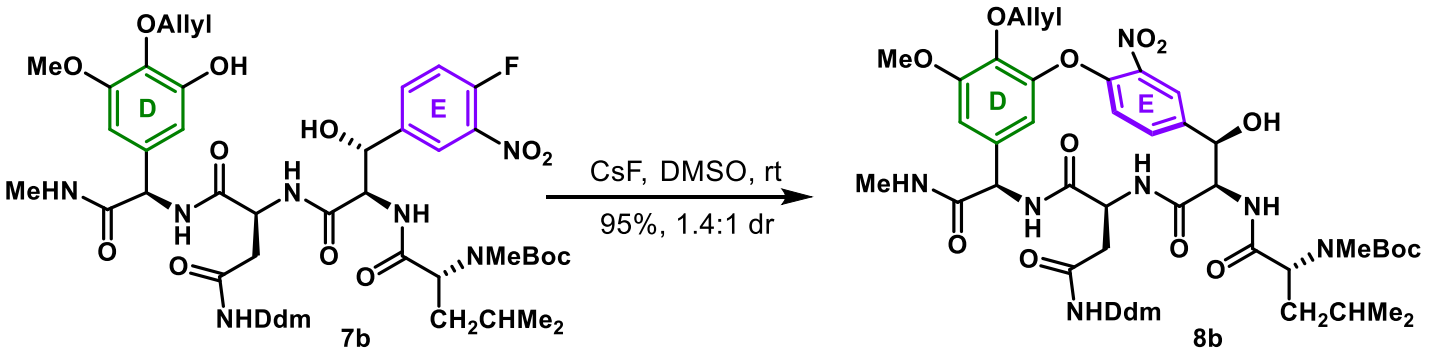
natural configuration

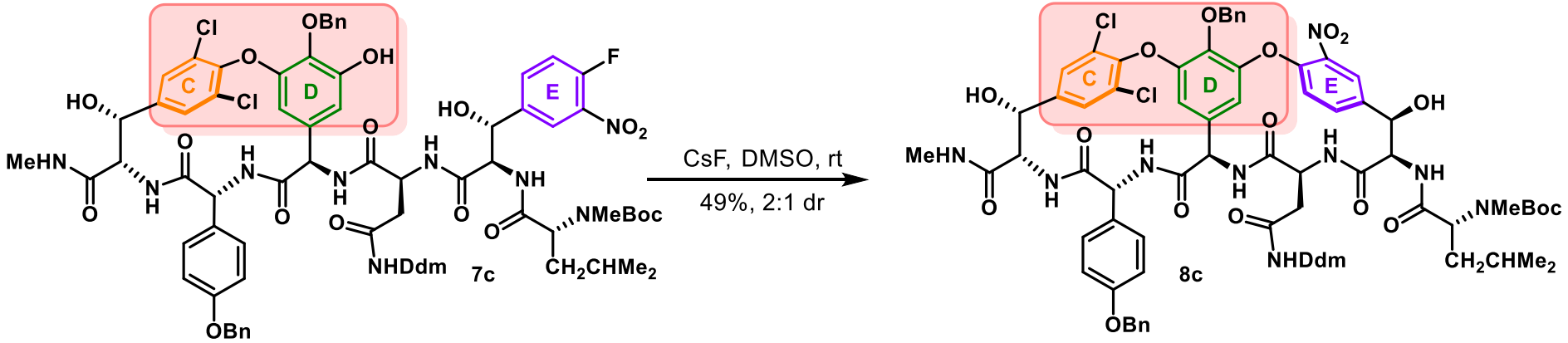
K. C. Nicolaou et al, *Angew. Chem. Int. Ed.* **1998**, *19*, 2708-2714.

D-E planar chirality

Intact C-D configuration ≠ D-E planar chirality

David A. Evans



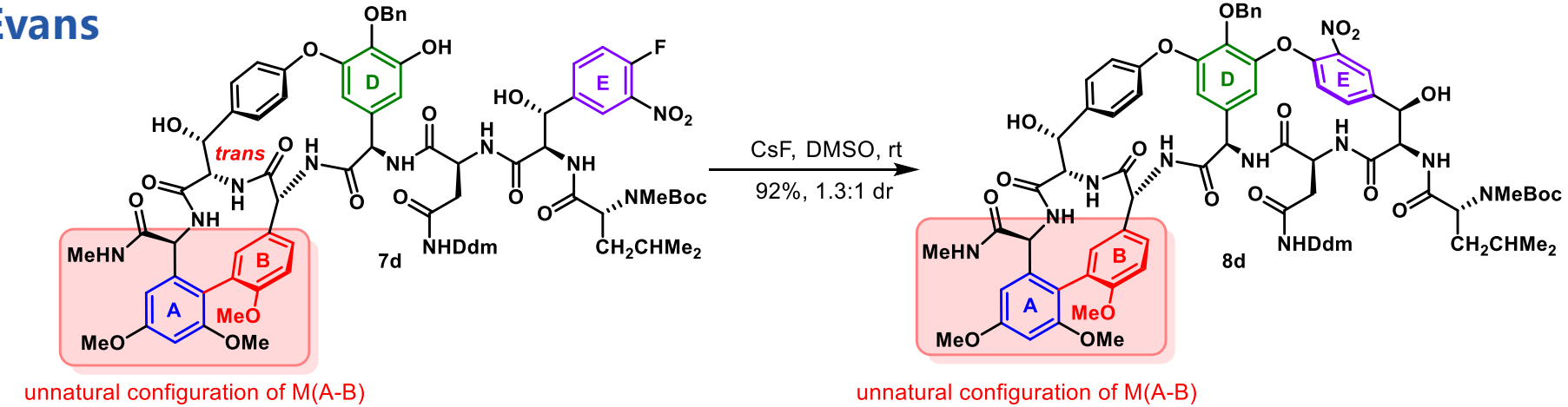


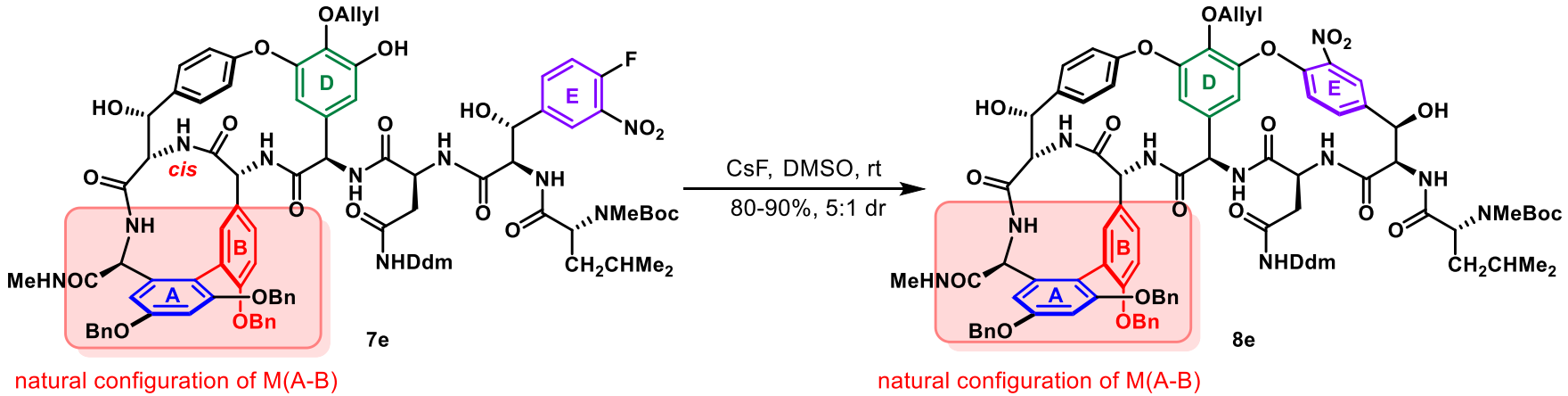
David A. Evans et al, *Angew. Chem. Int. Ed.* **1998**, *37*, 2700-2704.

D-E planar chirality

Natural A-B configuration ➡ D-E planar chirality

David A. Evans





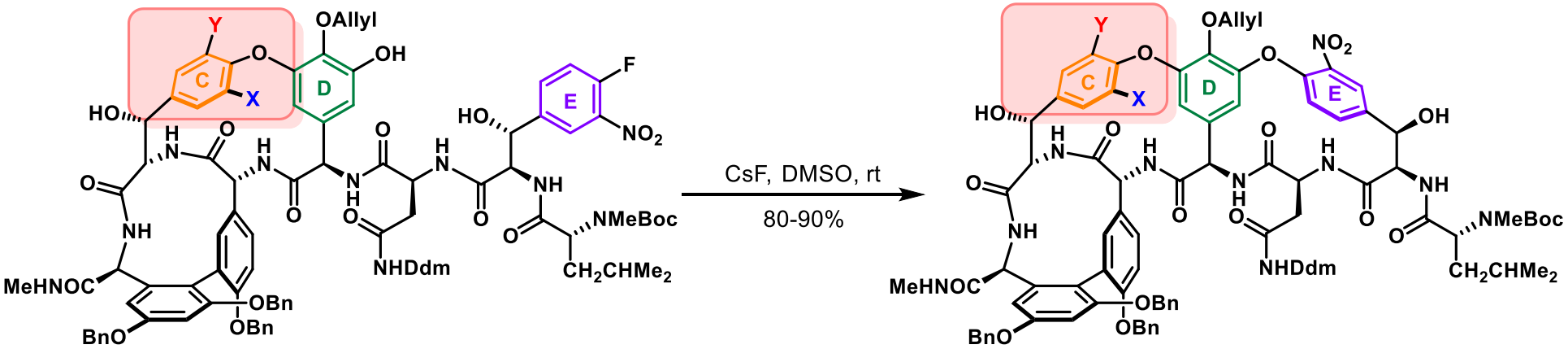
The cis amide conformation may cause high atropselectivity

David A. Evans et al, *Angew. Chem. Int. Ed.* **1998**, *37*, 2700-2704.

D-E planar chirality

Natural C-D configuration ≠ D-E planar chirality

David A. Evans



Three Correct Natural Atropisomerism

7e X = H, Y = H	8e X = H, Y = H	dr = 5:1
7f X = Cl, Y = Cl	8f X = Cl, Y = Cl	dr = 7:1
7g X = Cl, Y = H	8g X = Cl, Y = H	dr = 5:1

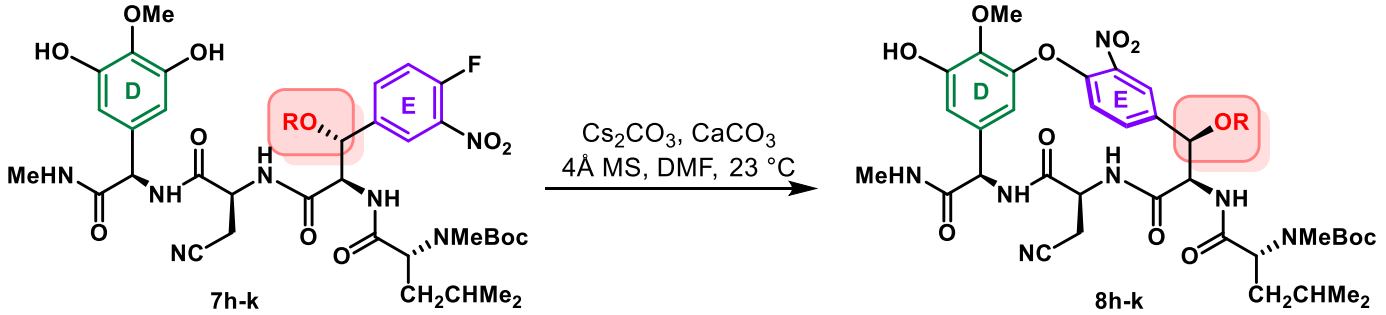
Chloro substituent in ring C is not a dominant stereochemical determinant

David A. Evans et al, *Angew. Chem. Int. Ed.* **1998**, *37*, 2700-2704.

D-E planar chirality

Steric hindrance → D-E planar chirality

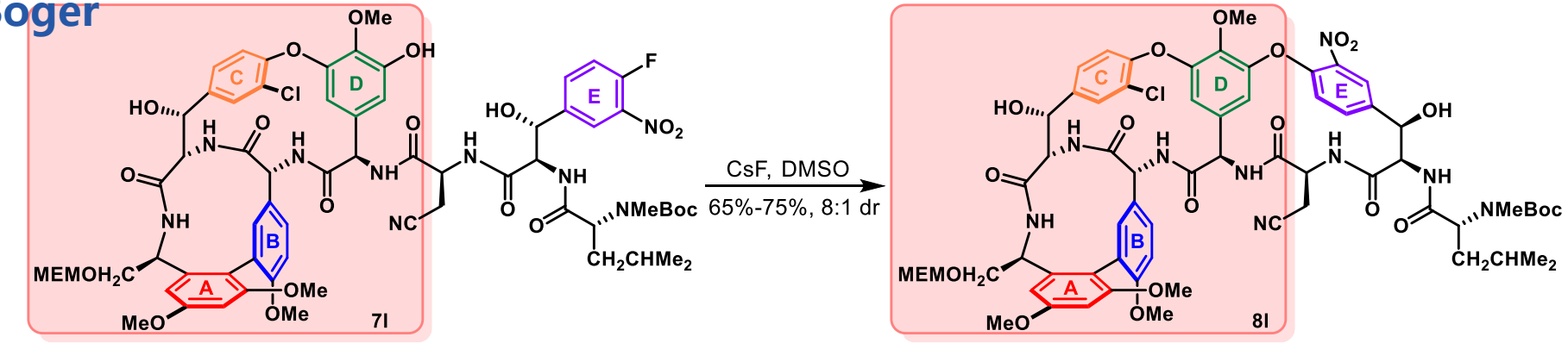
Dale L. Boger



	R	dr	yield
h	H	0.59:1	69%
i	TBS	0.67:1	67%
j	TBDPS	0.77:1	76%
k	TIPS	1.1:1	53%

Increase in silyl ether protecting group slightly improved diastereoselctivity

Dale L. Boger



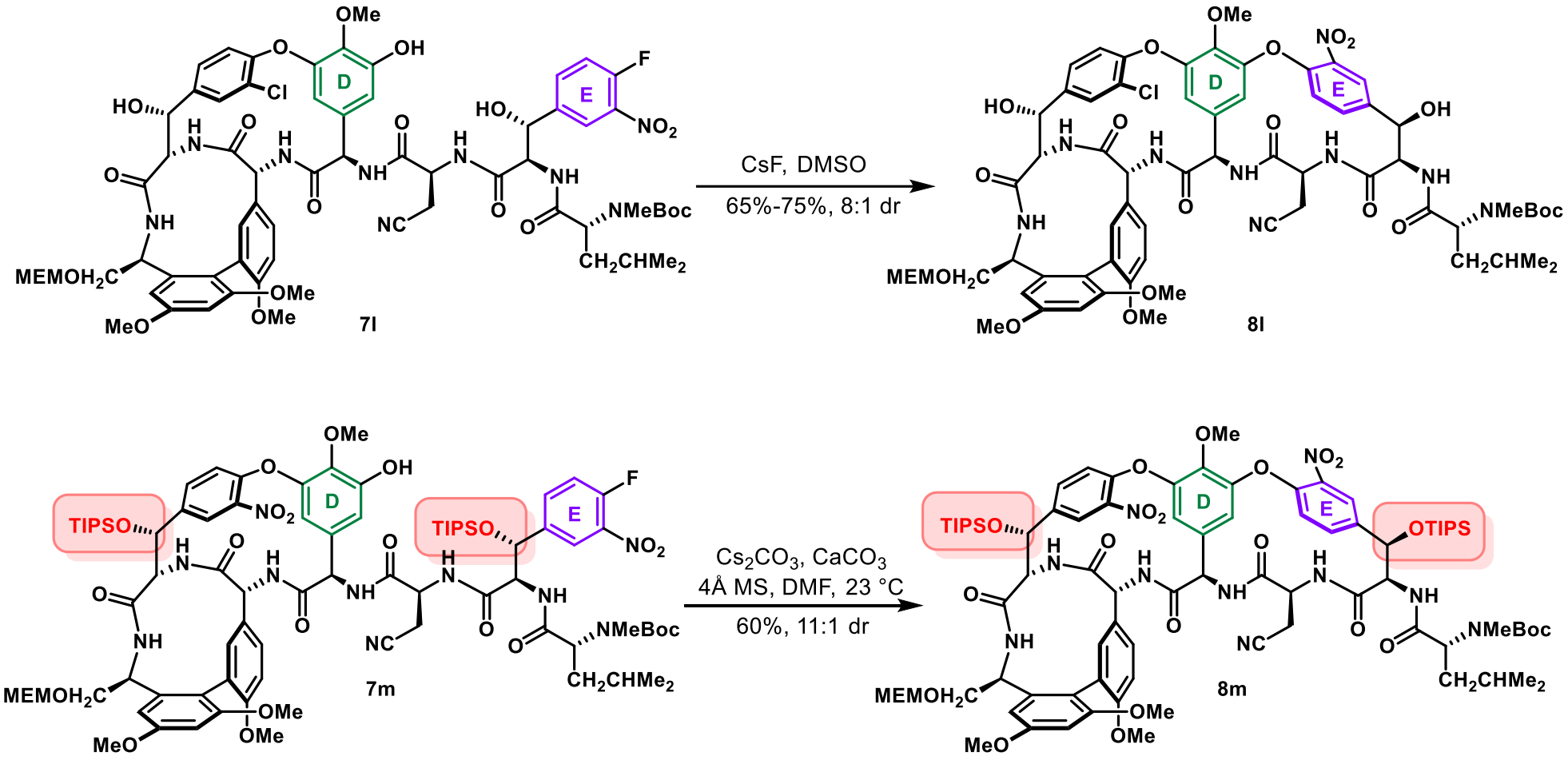
Preorganization of A-B and C-D macrocycle significantly improves dr

Dale L. Boger et al, *J. Am. Chem. Soc*. **1999**, *121*, 10004-10011. Dale L. Boger et al, *J. Am. Chem. Soc*. **2020**, *142*, 16039−16050.

D-E planar chirality

Steric hindrance ➡ D-E planar chirality

Dale L. Boger

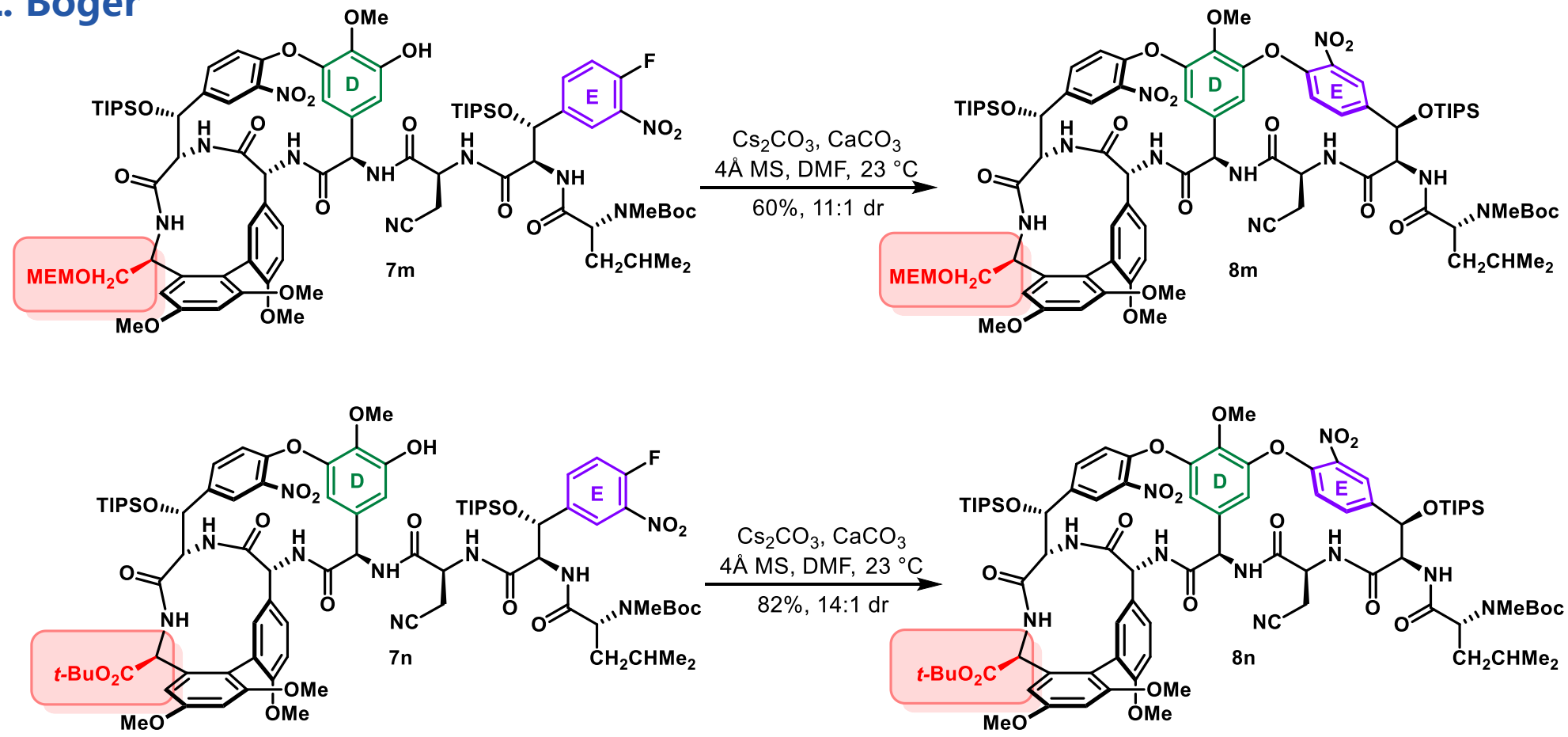


Dale L. Boger et al, *J. Am. Chem. Soc*. **1999**, *121*, 10004-10011. Dale L. Boger et al, *J. Am. Chem. Soc*. **2020**, *142*, 16039−16050.

D-E planar chirality

Remote ester group ➡ D-E planar chirality

Dale L. Boger



Dale L. Boger et al, *J. Am. Chem. Soc.* **2020**, *142*, 16039−16050.

PART Three

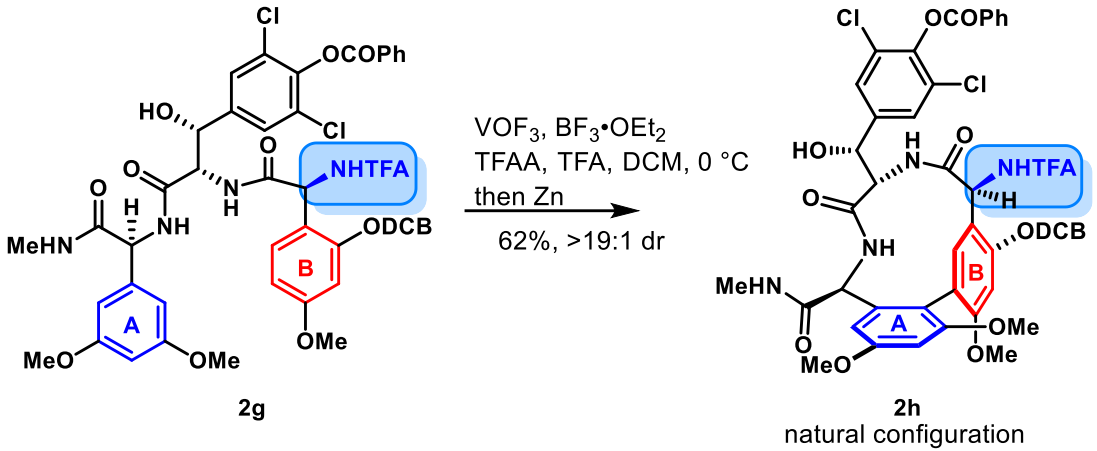
Summary and Outlook

復旦大學
Fudan University

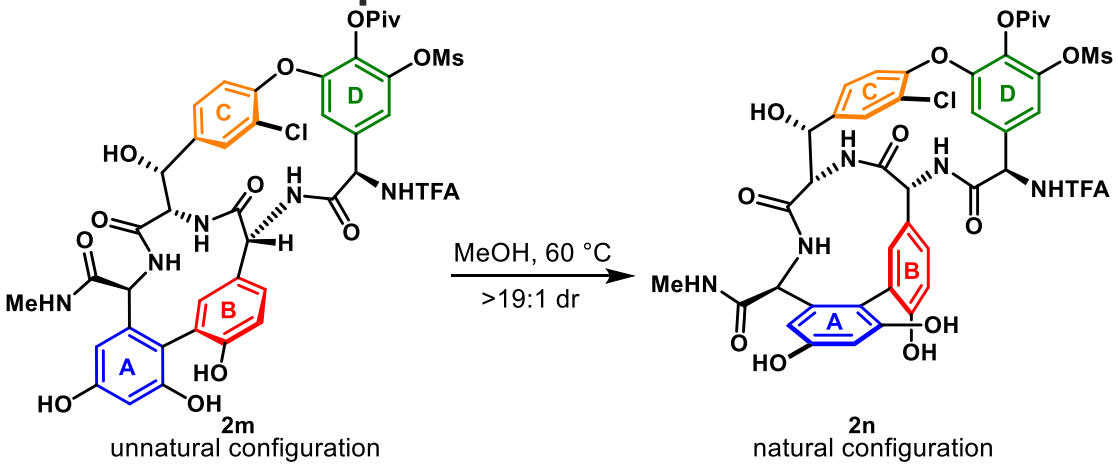
Summary

A-B Axial Chirality

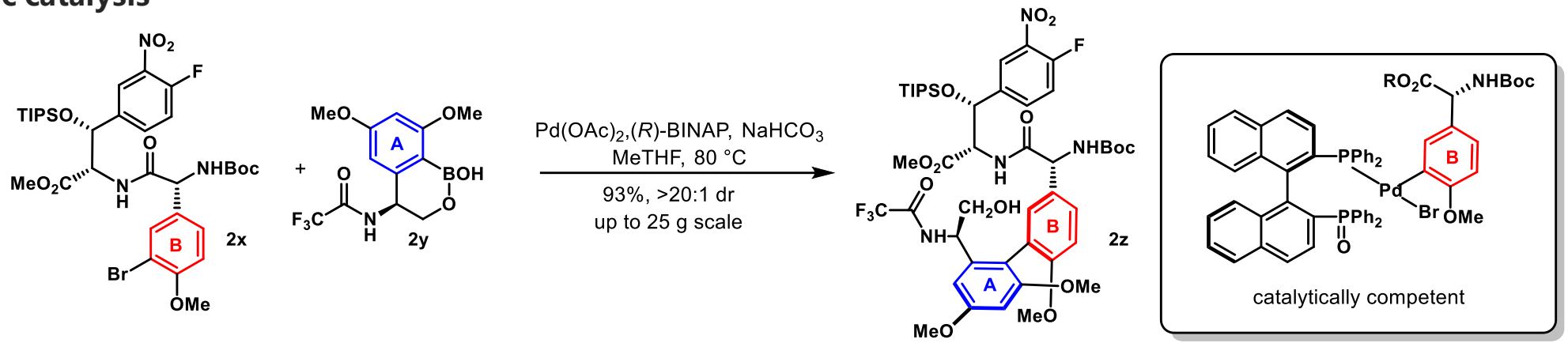
1. A(1,3) strain



2. Thermal equilibrium



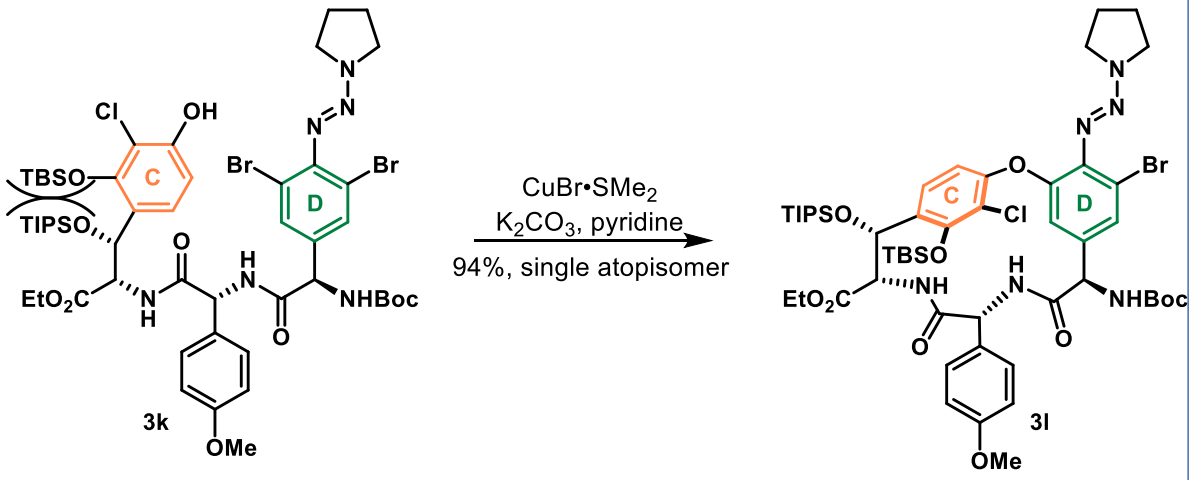
3. Asymmetric catalysis



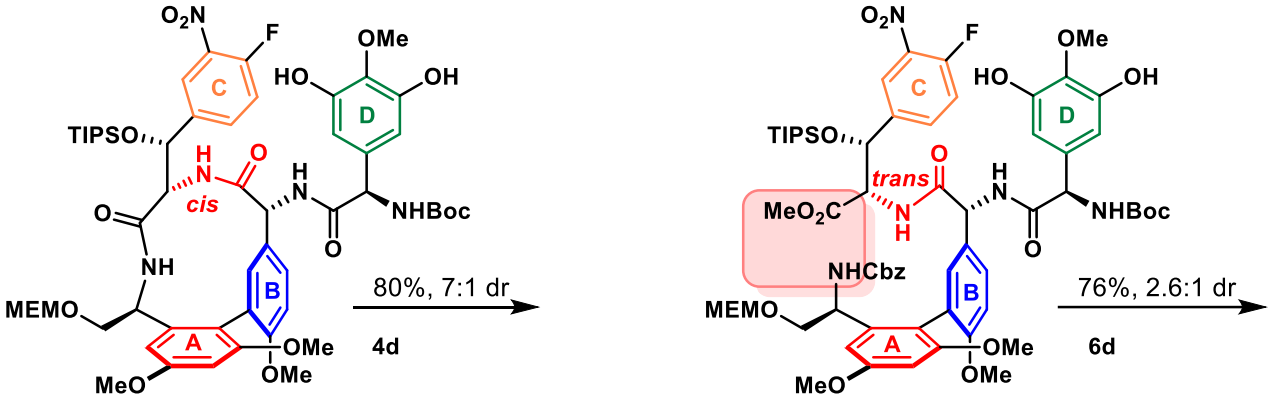
Summary

C-D planar chirality

1. A(1,3) strain



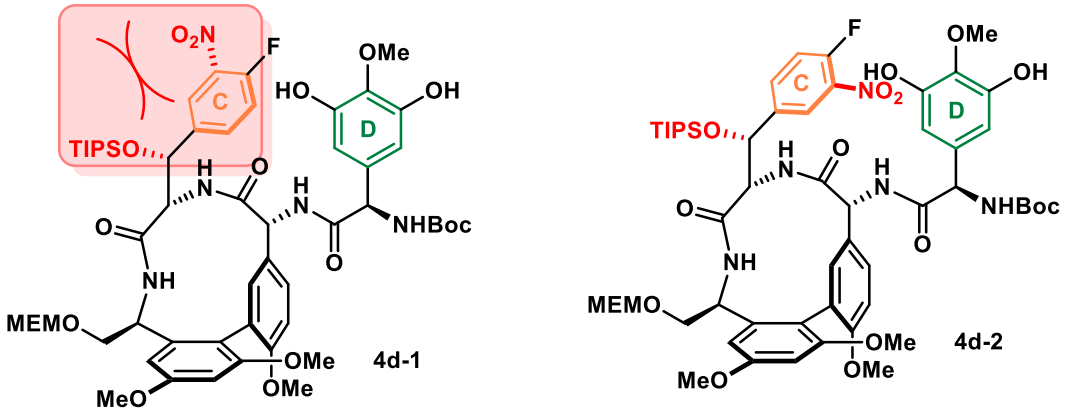
2. Sequence



With preorganization
cis amide conformation

Without preorganization
trans amide conformation

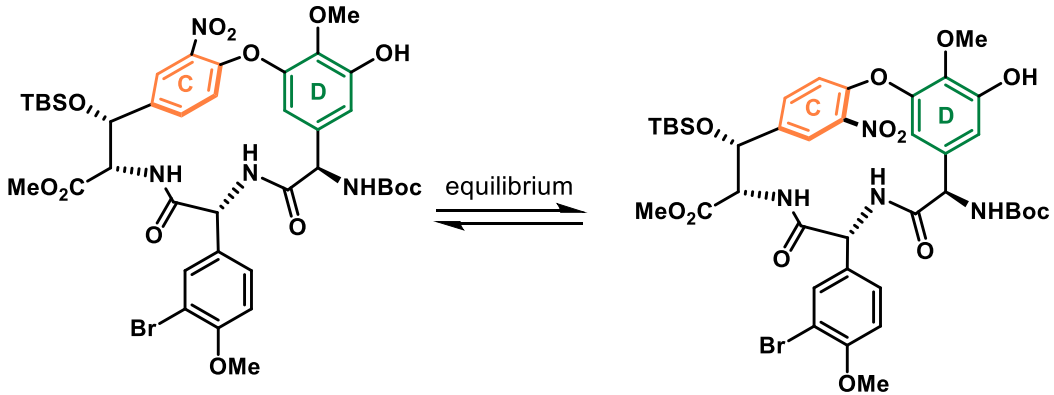
3. Steric hindrance



less favorable rotamer

more favorable rotamer

4. Thermal equilibrium



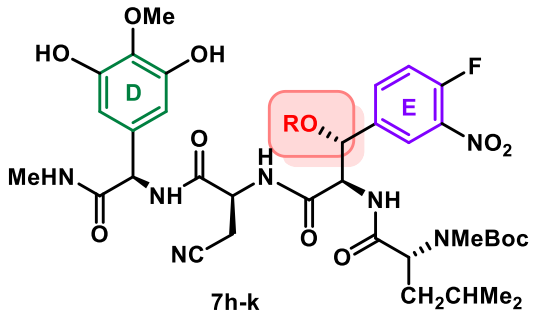
100% *epi*-3p

3p

Summary

D-E planar chirality

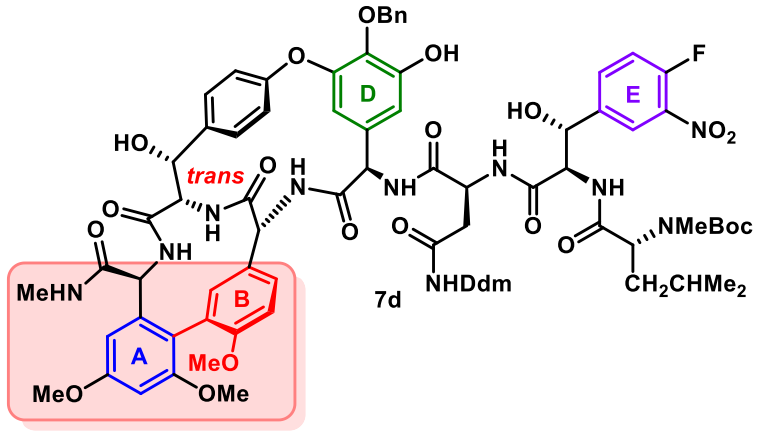
1. Steric hindrance



7h-k

	R	dr	yield
h	H	0.59:1	69%
i	TBS	0.67:1	67%
j	TBDPS	0.77:1	76%
k	TIPS	1.1:1	53%

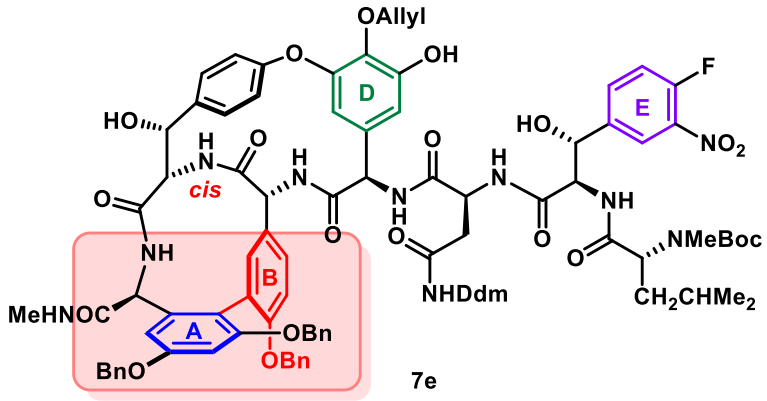
2. Sequence



7d

92%, 1.3:1 dr

unnatural configuration of M(A-B)

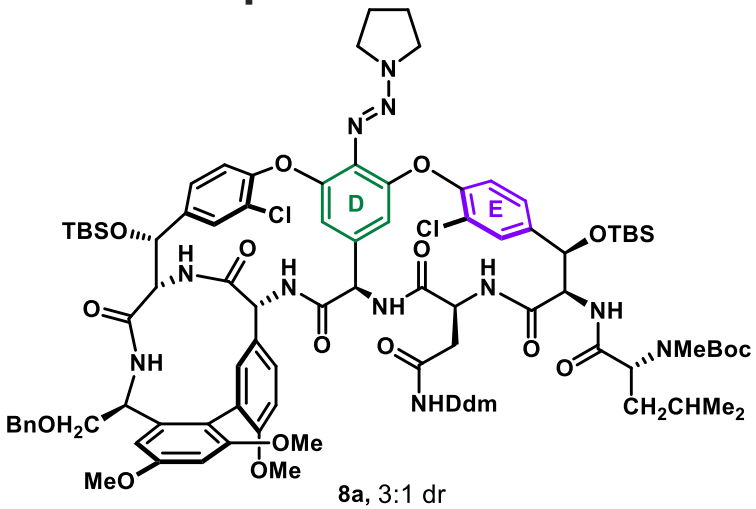


7e

80-90%, 5:1 dr

natural configuration of M(A-B)

3. Thermal equilibrium



8a, 3:1 dr
unnatural configuration

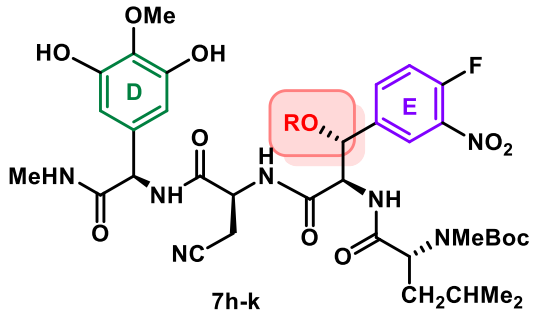
o-$C_6H_4Cl_2$, 140 °C, 4 h

1:1 dr

Outlook

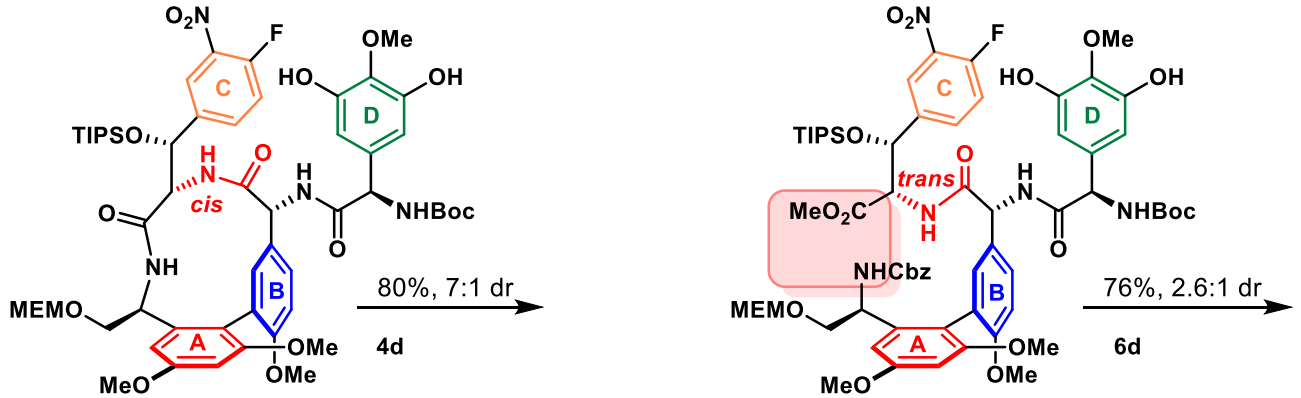
Total synthesis of nature products with chiral cyclophane

Steric hindrance

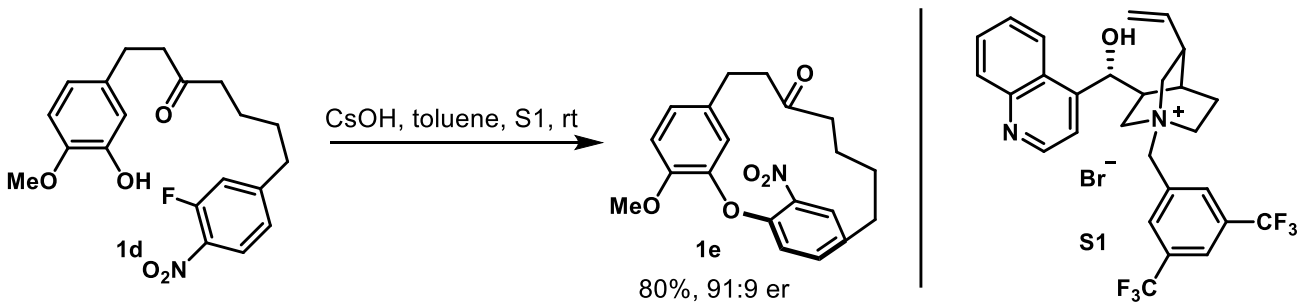


	R	dr	yield
h	H	0.59:1	69%
i	TBS	0.67:1	67%
j	TBDPS	0.77:1	76%
k	TIPS	1.1:1	53%

Assemble Sequence

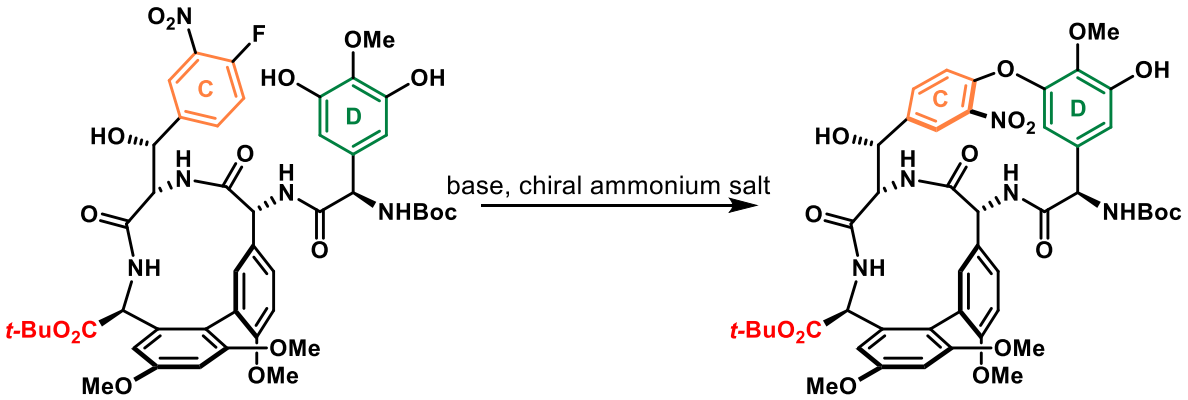


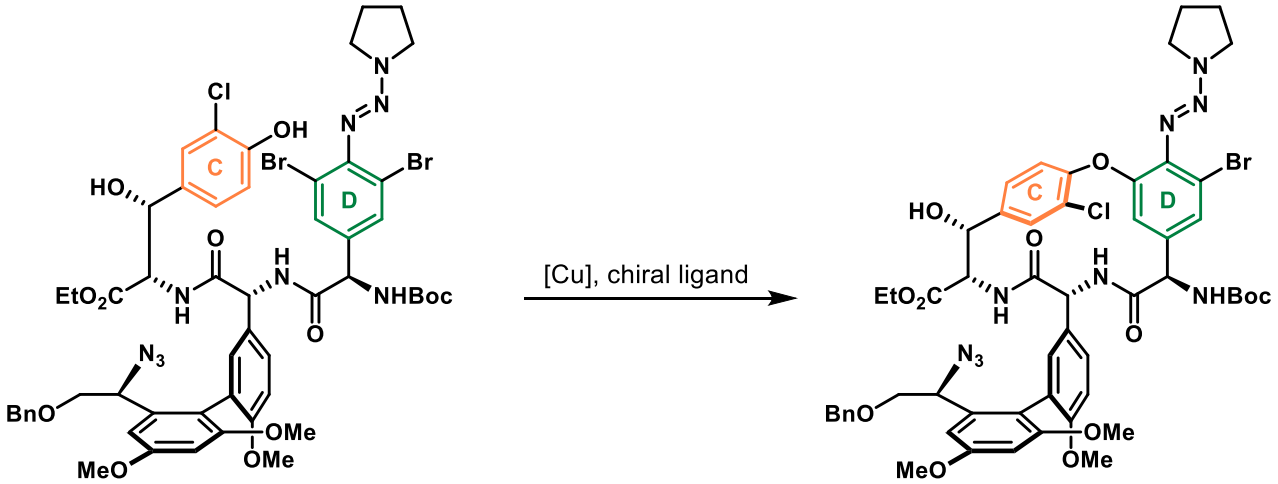
Asymmetric catalysis



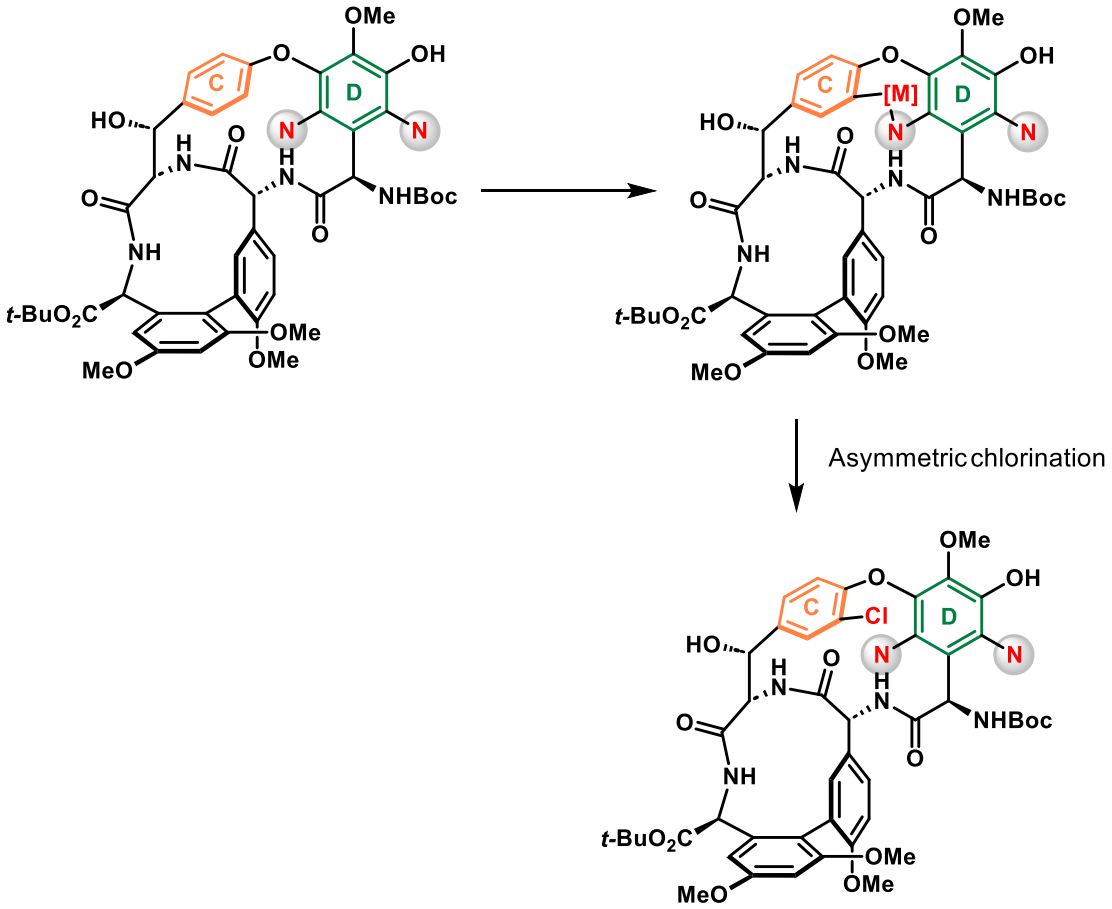
Outlook

Asymmetric catalysis





Desymmetry strategy



PART Three

Thanks for Listening

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图所示，首先选定导向原子 P：P 原子与手性平面内的氧原子直接相连，但是自身却在平面之外，并且为连接至溴原子路径最短的面外原子；从与 P 直接相连的手性平面上的 a 原子开始，按照原子优先顺序建立趋势线 a→b→c；从导向原子 P 向手性平面观察，趋势线 a→b→c 为逆时针，标记为 S_p。用同样方法得到图 2 右图的趋势线为顺时针，标记为 R_p。另外需要注意的是："手柄"-碳桥的长度要合适，如果过长，碳桥则能够绕着平面自由翻转，那么手柄化合物就会失去平面手性[5-7]。以化合物 A 为例，如果 n 大于 6，那么碳桥就能够自由翻转，则没有稳定的对映异构体[6]。

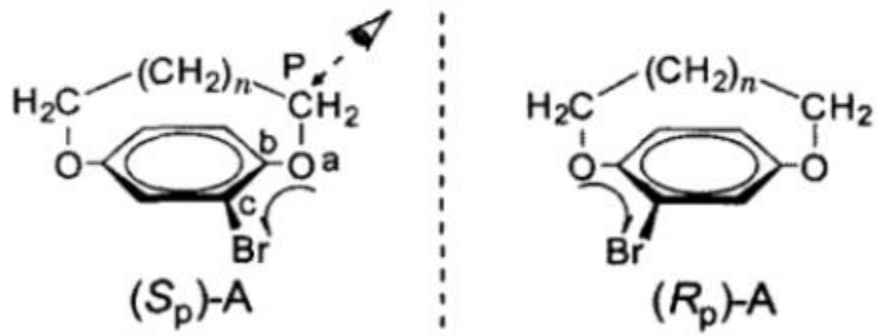

Fig. 2 The absolute configuration of ansa compound A

存在不对称取代时，就会出现对映异构现象。以图 3 化合物 B 为例，选定导向原子 P 后，从属于手性平面上的与 P 直接相连的 a 原子开始，按原子优先顺序建立趋势线 a→b→c，并从导向原子 P 向手性平面观察发现：趋势线为逆时针，标记为 S_p（左图）。图 3 右图与左图互为对映异构体，趋势线为顺时针，标记为 R_p。和手柄化合物类似，具有平面手性的环蕃化合物需要连接 2 个芳环的链足够短，使芳环不能自由翻转，从而形成稳定的对映异构体[5]。

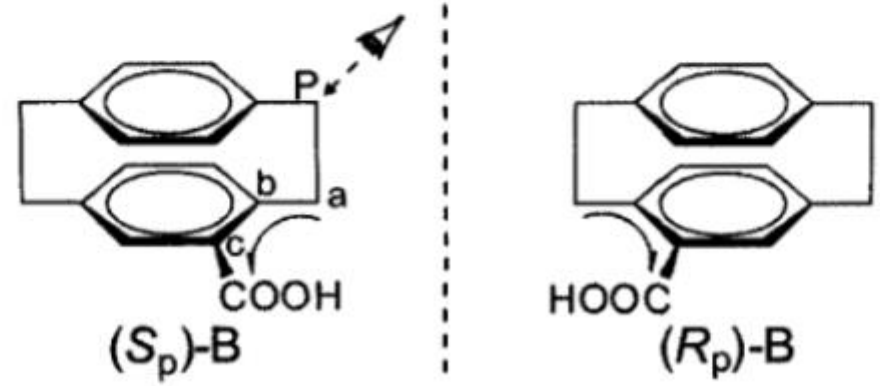

Fig. 3 The absolute configuration of cyclophane compound B