Total Synthesis of Vancomycin Aglycon
Boger's Group

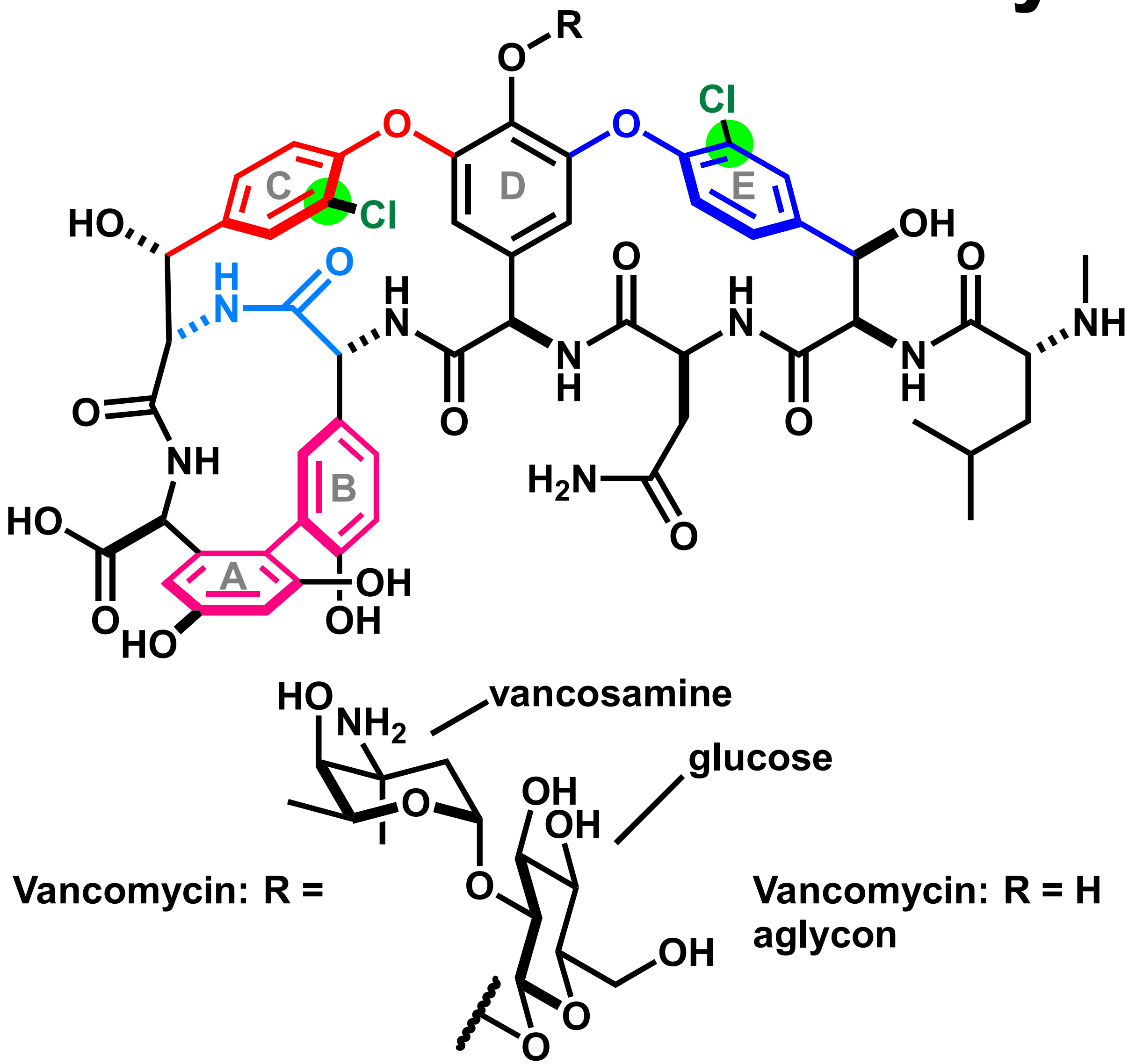
2021.11.20. Literature Seminar

M2 Yuto Hikone

Contents

* Reagent structures are listed in page 35.

Vancomycin



Isolation[1)]
- Domain: Bacteria
  Genus: *Amycolatopsis orientalis*
  (1950s at Eli Lilly and Company)

Biological activity
- gram-positive organisms
  ex). penicillin-resistant staphylococci

Clinical use
- from 1958

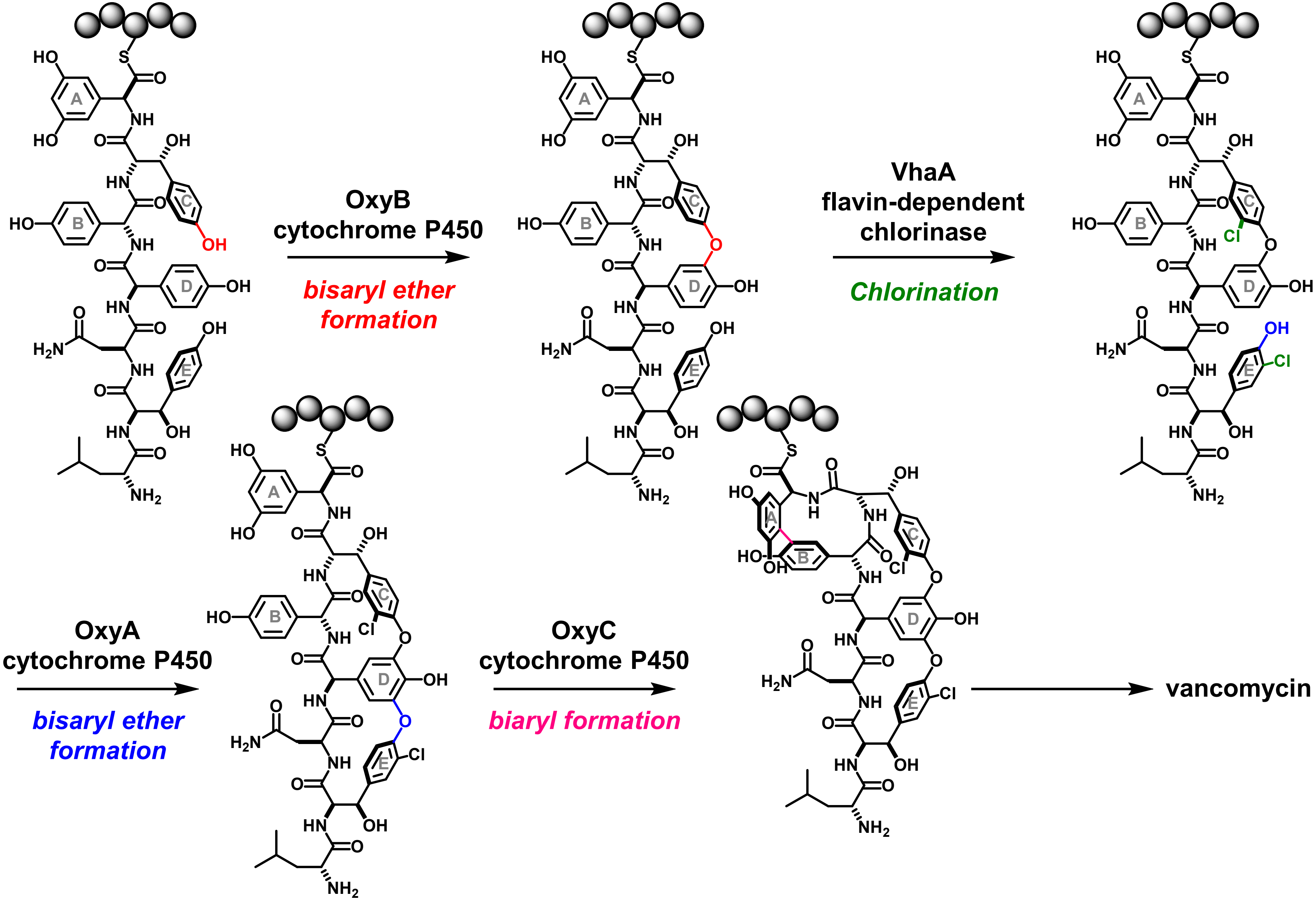
Full Structure assignment[2)]
- Harris, C. M and Harris, T. M. (1982)

Structural features
- heptapeptide composed of unnatural amino acid units
- biaryl linkage (AB) -> axial chirality
- bisaryl ether linkage (C-*O*-D and D-*O*-E) -> planar chirality

Total synthesis
Evans (1998)[3)]
Nicolaou (1998)[4)]
Boger (1999, 2020)[5,6)]

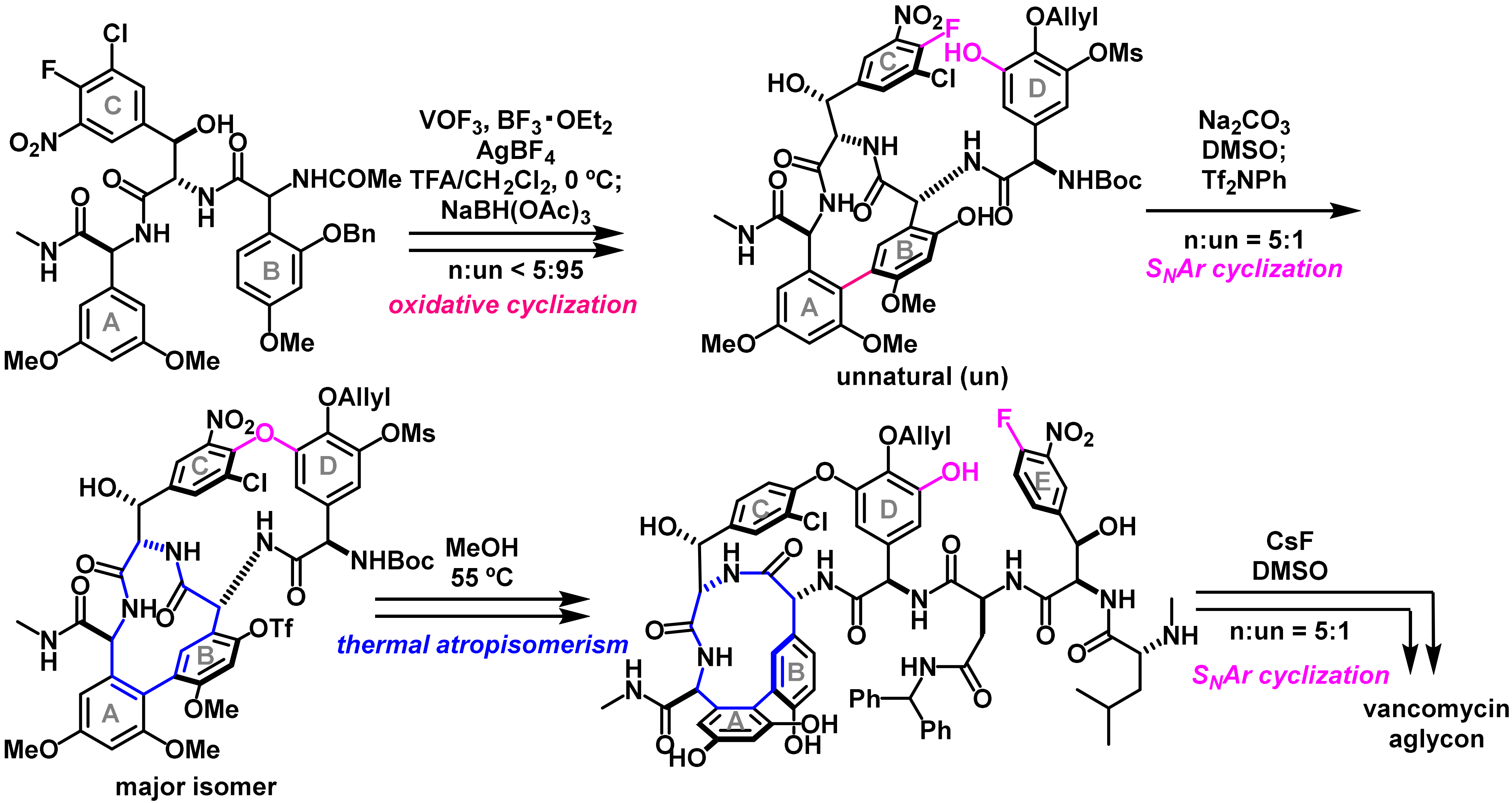
1) Levine, D. Vancomycin: a history. Clin. Infect. Dis. 2006, 42, S5−S122).
2) Harris, C. M.; Harris, T. M. *J. Am. Chem. Soc.* **1982**, *104*, 4293−4295.
3) Evans, D. A. et al. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700−2704.
4) Nicolaou, K. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 240−244.
5) Boger, D. L. et al. *J. Am. Chem. Soc.* **1999**, *121*, 10004−10011.
6) Boger, D. L. *J. Am. Chem. Soc.* **2020**, *142*, 16039−16050

Proposed Biosynthesis



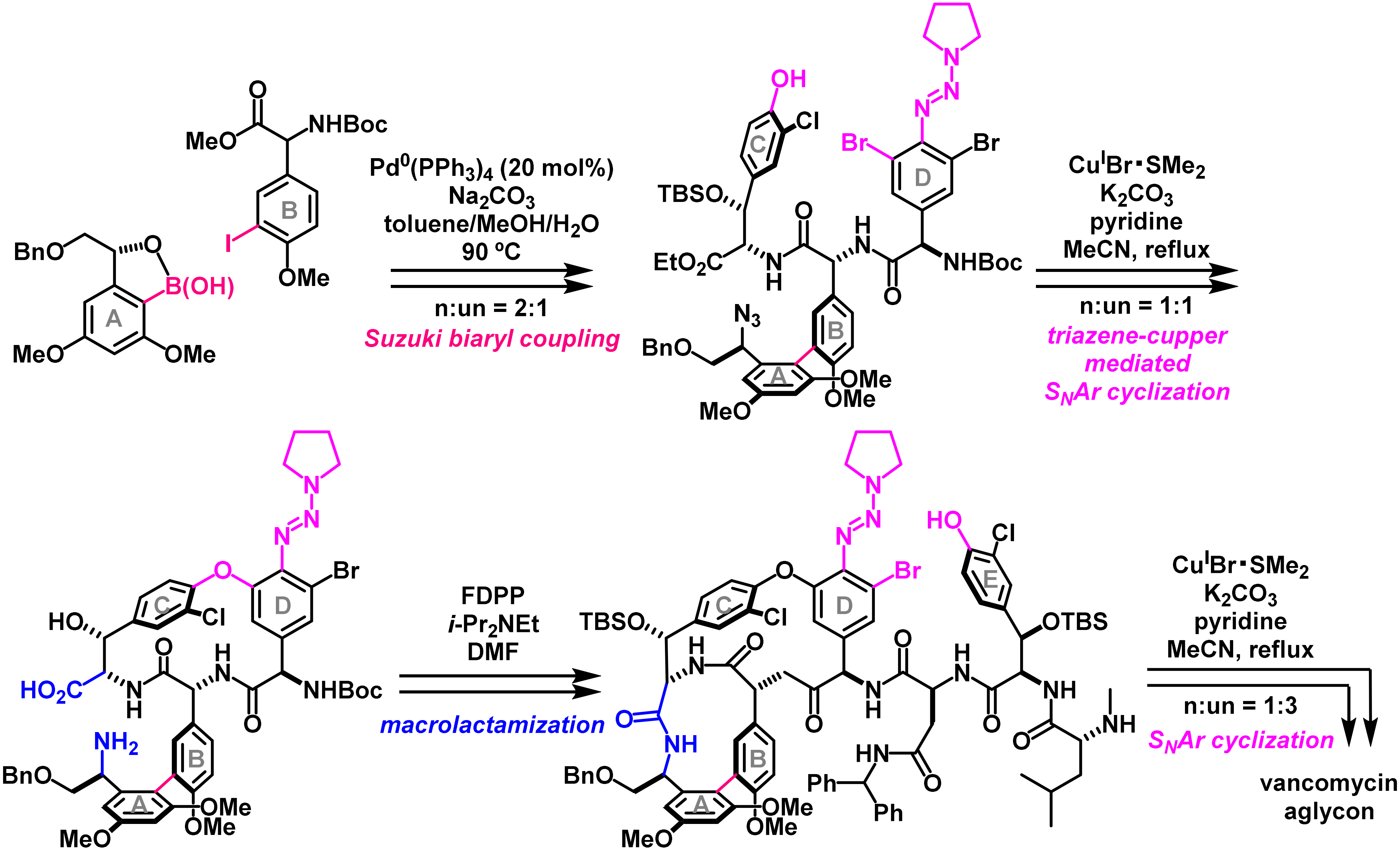
Forneris, C. C.; Ozturk, S.; Gibson, M. I.; Sorensen, E. J.; Seyedsayamdost, M. R. *ACS Chem. Biol*. **2017**, *12*, 2248−2253.

Evans' Total Synthesis (1998)



Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700−2704.

Nicolaou's Total Synthesis (1998)



1) Nicolaou, K. C. et al. *Angew. Chem., Int. Ed*. **1998**, *37*, 2717−2719.
2) Nicolaou, K. C. et al. *Angew. Chem., Int. Ed*. **1999**, *38*, 240−244.
3) Nicolaou, K. C. Et al. *Chem. - Eur. J.* **1999**, *5*, 2584−2601.

Contents

Prof. Dale L. Boger

Career:

-1975 : B.S. @ University of Kansas
-1980 : Ph.D. @ Harvard University (Prof. E. J. Corey)
1979-1985 : Assistant/Associate professor of Medicinal Chemistry @ University of Kansas
1985-1991 : Associate Professor/Professor of Chemistry @ Purdue University
1991-1993 : Associate Professor. @University of Illinois at Urbana-Champaign
1991- : Professor. @ The Scripps Research Institute

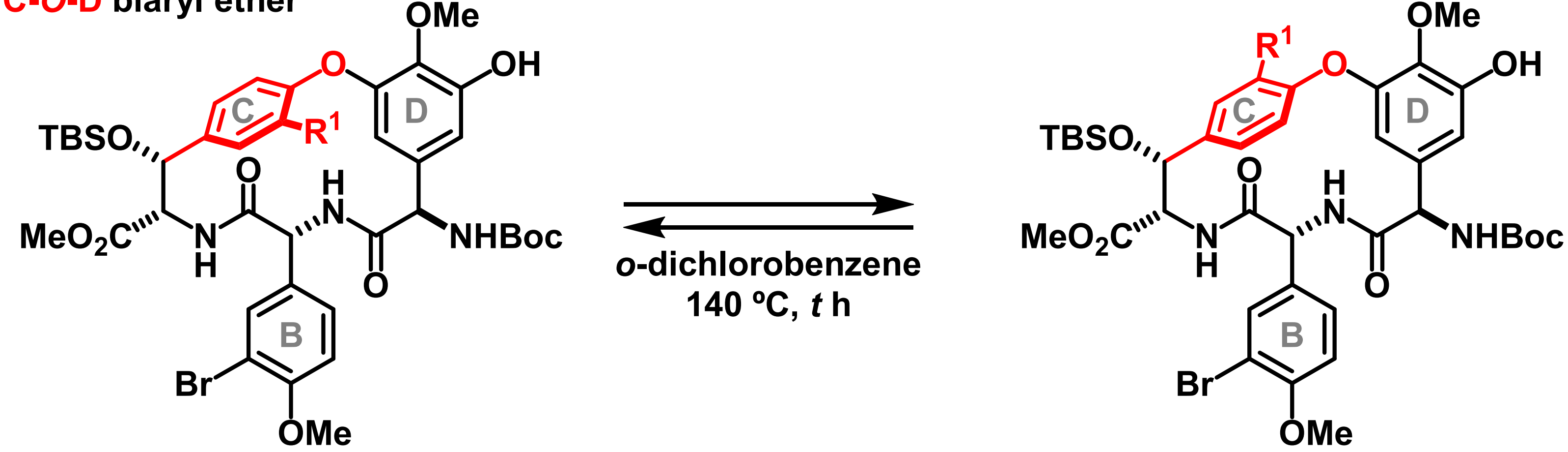
Research interests:

1. synthetic methodology development
2. natural product total synthesis
3. study of DNA-agent interactions

https://www.scripps.edu/boger/Dale%20L.%20Boger.html

Model Study for Thermal Atropisomerism (1)

C-*O*-D biaryl ether



R^1	equibilium	E_a [kcal/mol]	$t_{1/2}$ (h)	*t* (h)
NO_2	1 : 1.1	26.6	9.77	56
Cl	1 : 1.2	30.4	44.0	

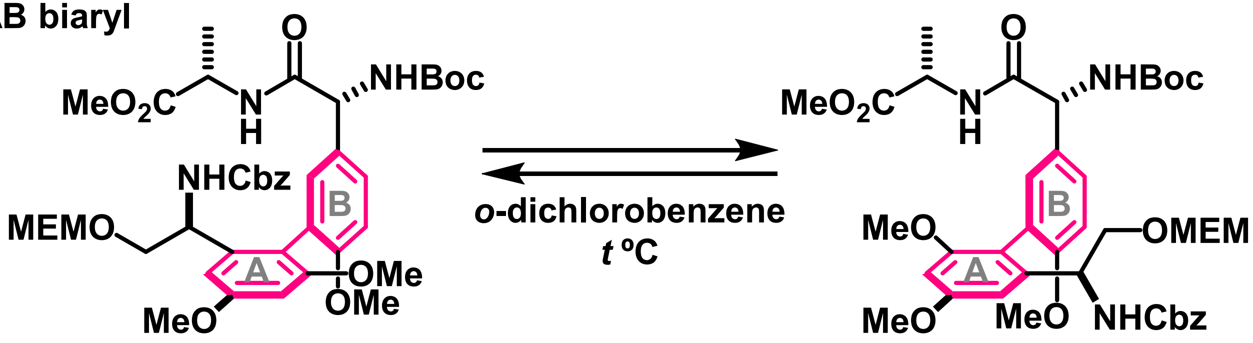
D-*O*-E biaryl ether

R^2	equibilium	E_a [kcal/mol]	$t_{1/2}$ (h)	*t* (min)
NO_2	1 : 1	15.3	0.17	60
Cl	1 : 1	nd	0.39	

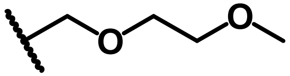
1) Boger, D. L.; Borzilleri, R. M.; Nukui, S.; Beresis, R. T. *J. Org. Chem*. **1997**, *62*, 4721−4736.
2) Boger, D. L.; Castle, S. L.; Miyazaki, S.; Wu, J. H.; Beresis, R. T.; Loiseleur, O. *J. Org. Chem*. **1999**, *64*, 70−80.

Model Study for Thermal Atropisomerism (2)

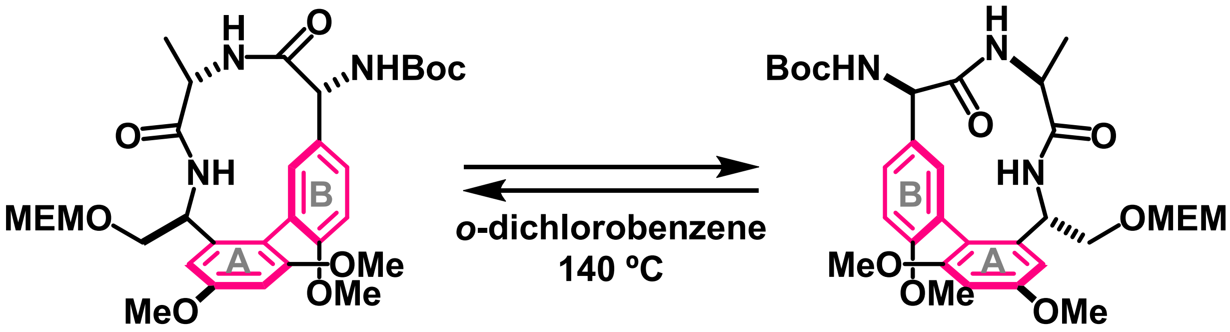
AB biaryl



t (°C)	equibilium	E_a [kcal/mol]	$t_{1/2}$ (h)
120	3 : 1	25.2	6.12
140	nd		1.28

MEM = 

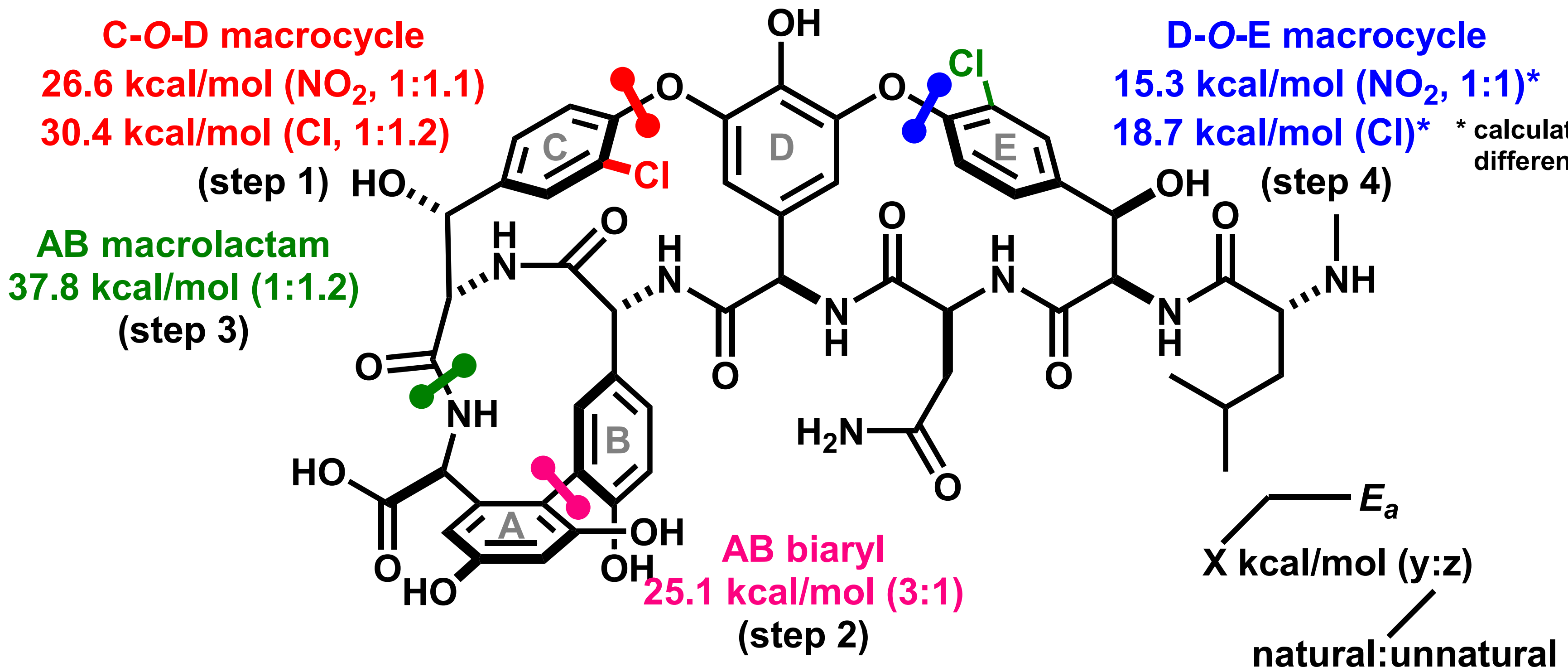
AB macrolactam



equibilium	E_a [kcal/mol]	$t_{1/2}$ (h)
1 : 1.2	37.8	10.9

Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004−10011.

Synthetic Plan (First-Generation, 1999)



Thermodynamic parameters of atropisomerism (model study)

C-*O*-D macrocycle (30.4 kcal/mol) > AB biaryl (25.1 kcal/mol) > D-*O*-E macrocycle (18.7 kcal/mol)

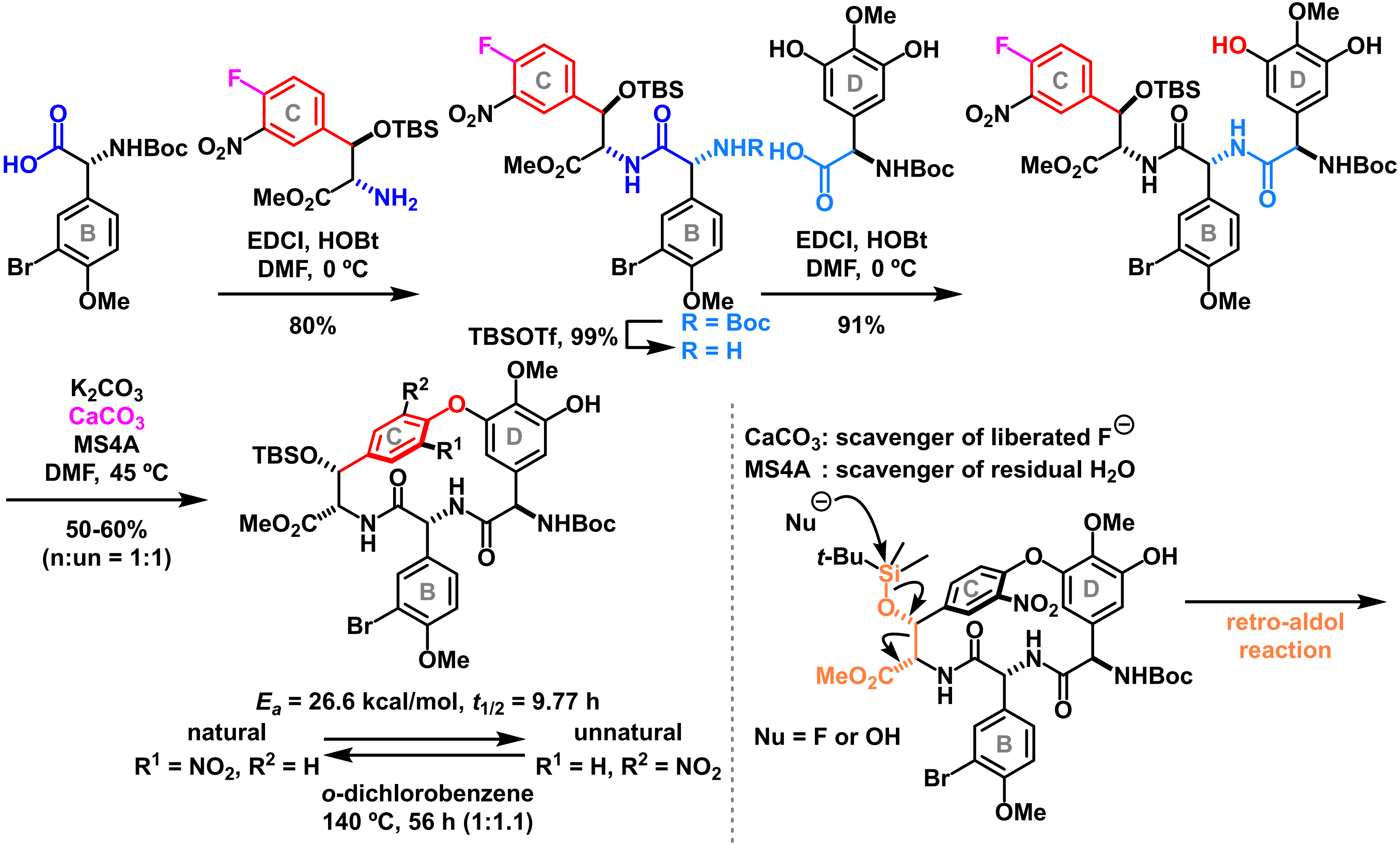
↓ based on these studies

Rational order of Ring system construction

C-*O*-D macrocycle —> AB biaryl —> AB macrolactam —> D-*O*-E macrocycle —> vancomycin (aglycon)

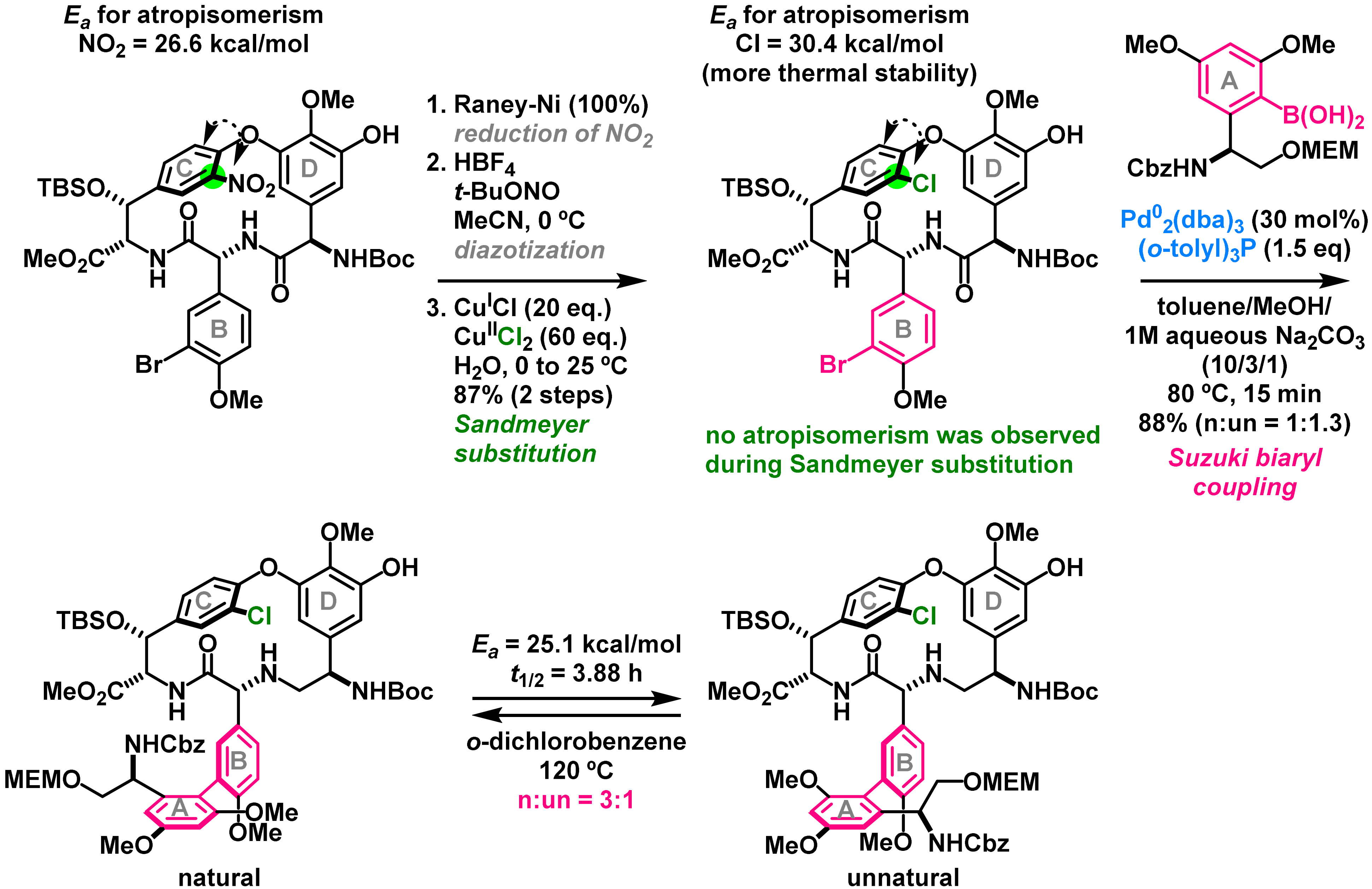
Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004−10011.

C-*O*-D Macrocycle Synthesis



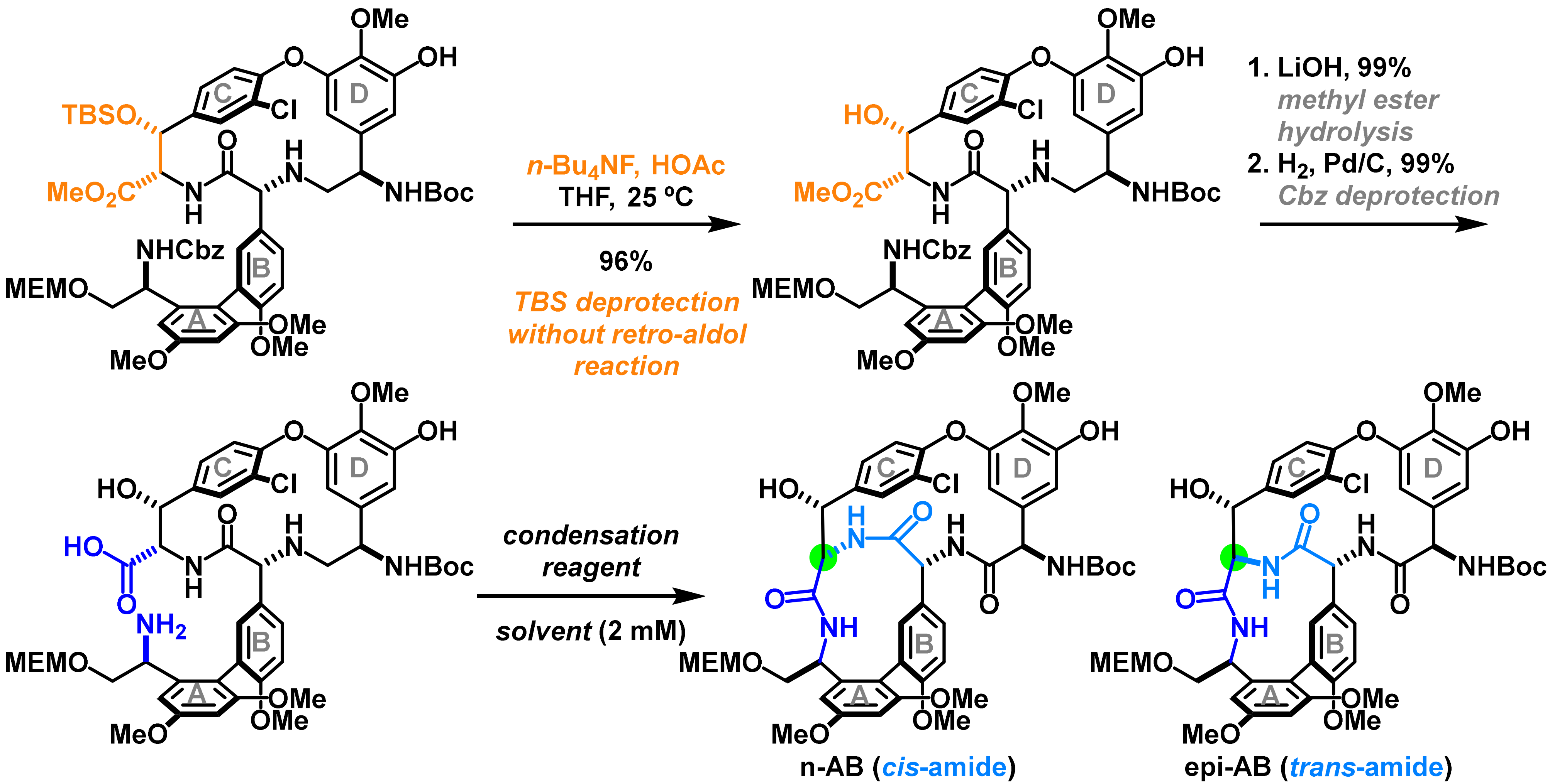
Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004−10011.

AB Biaryl Synthesis



Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004−10011.

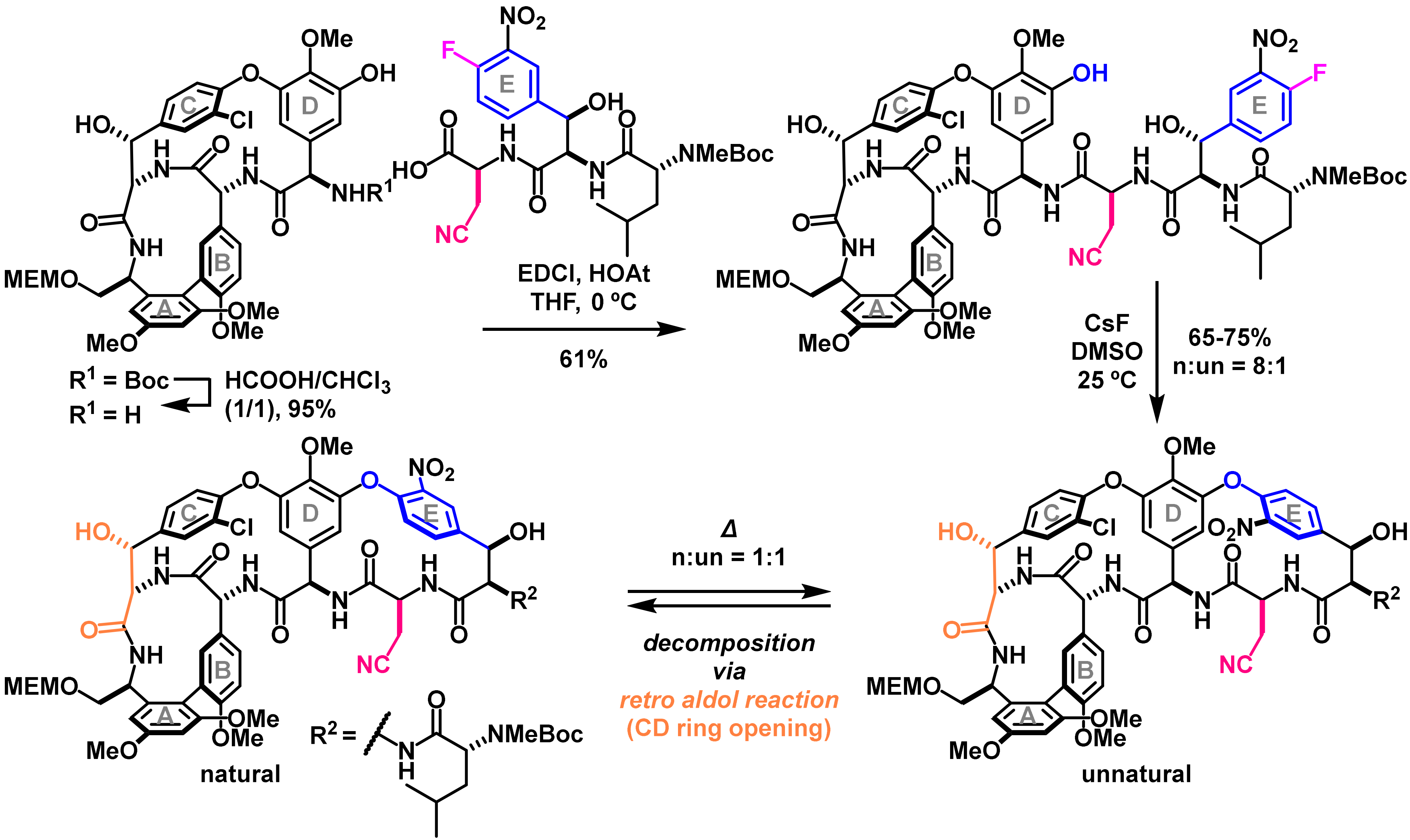
AB Macrolactamization



condensation reagent	*solvent*	n-AB (%), epi-AB (%)
PyBOP (4 eq), DMAP (4 eq)	DMF	trace, 60%
EDCI (5 eq), HOBt (5 eq)	DMF	16%, 54%
EDCI (5.5 eq), HOBt (5 eq)	CH_2Cl_2/DMF (5/1)	62%, 10-17%

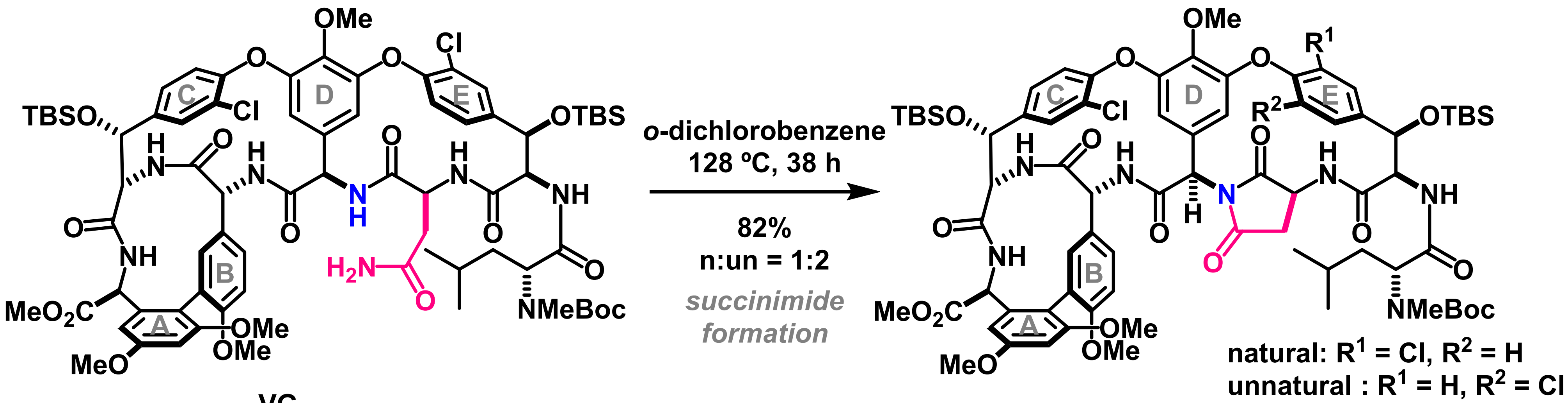
Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004−10011.

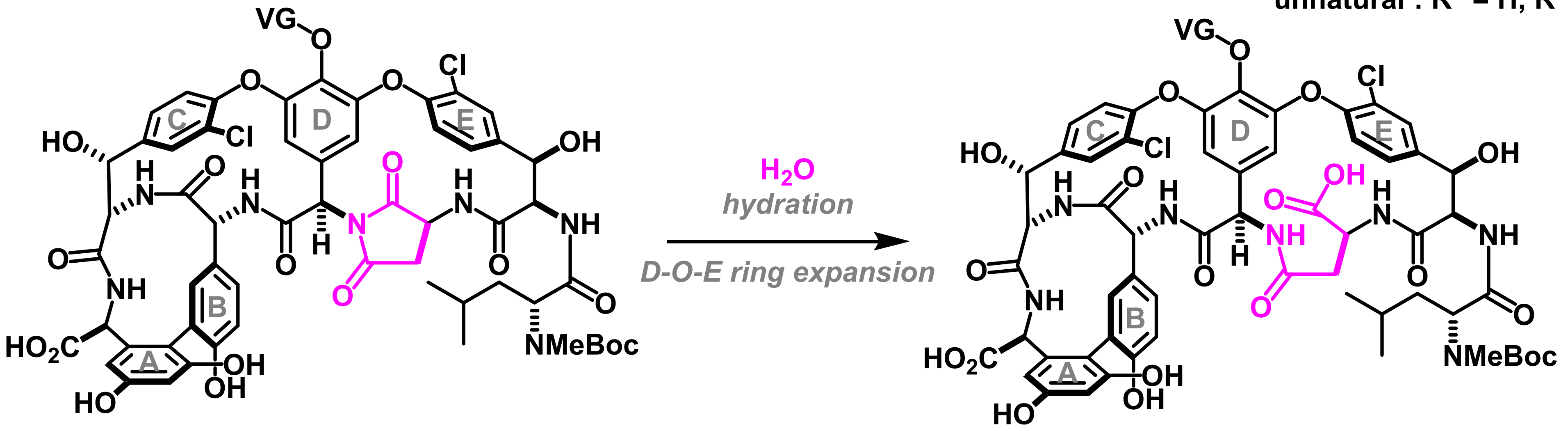
D-*O*-E Macrocycle Synthesis



Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004−10011.

Role of Nitrile in the Thermal Atropisomerism

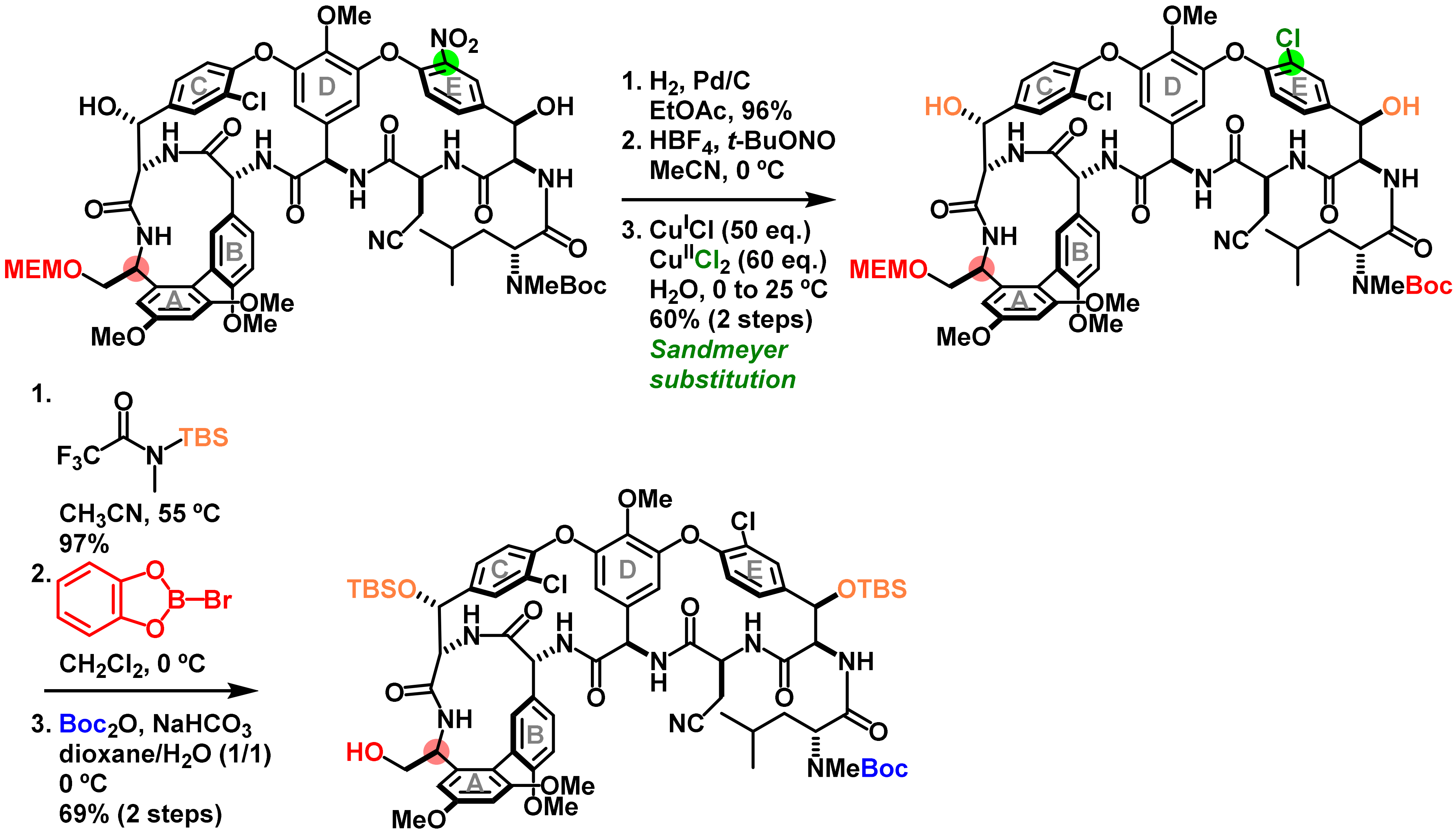




Installation of nitrile, which is dehydrated form of carboxyamide, has an important role in the thermal atropisomerism.

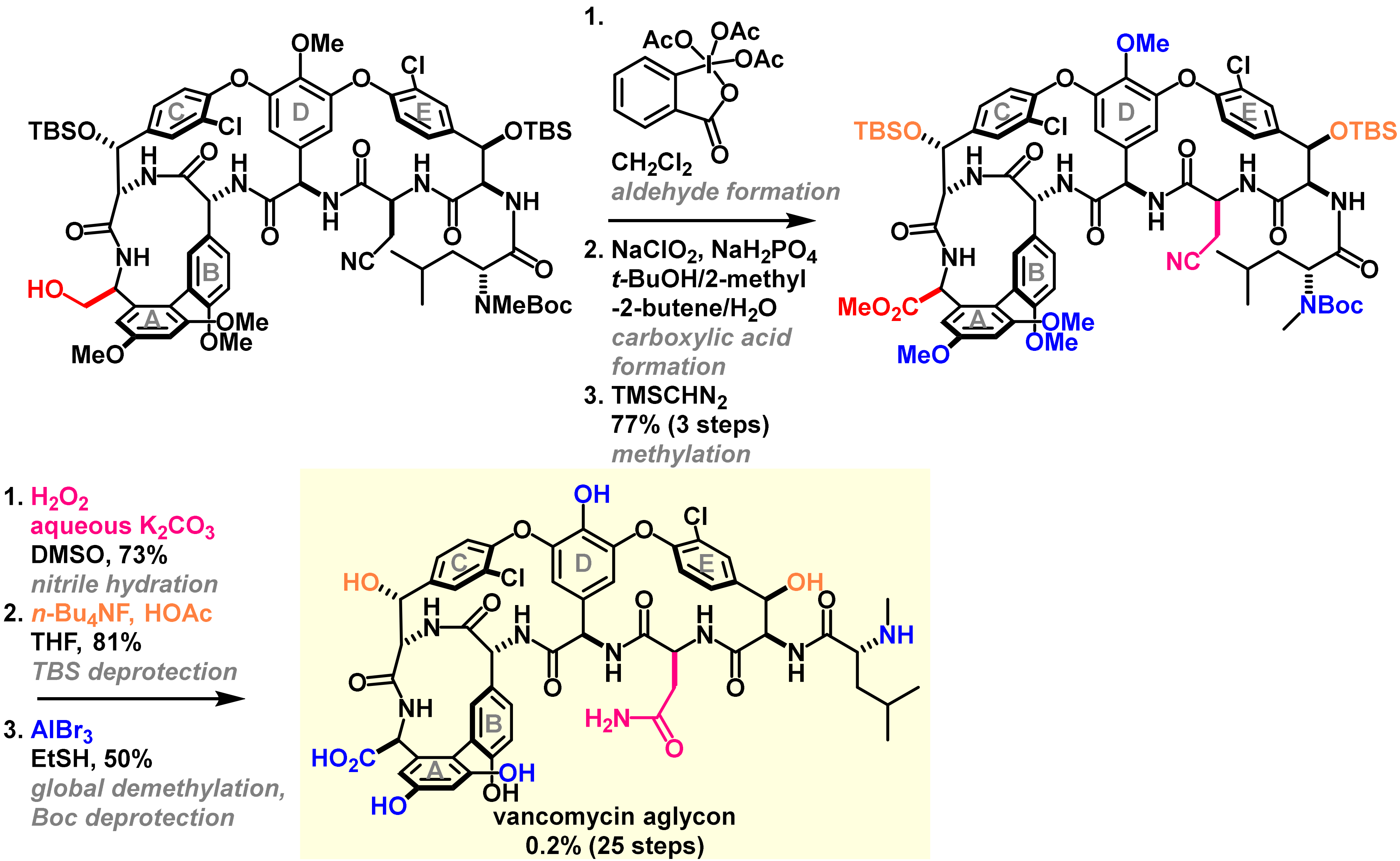
1) Sheldrick, G. M.; Jones, P. G.; Kennard, O.; Williams, D. H.; Smith, G. A. *Nature* **1978**, *271*, 223−225.
2) Boger, D. L.; Miyazaki, S.; Loiseleur, O.; Beresis, R. T.; Castle, S. L.; Wu, J. H.; Jin, Q. *J. Am. Chem. Soc.* **1998**, *120*, 8920−8926.

Deprotection of C-Terminus MEM Ether



Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004−10011.

First-Generation Synthesis



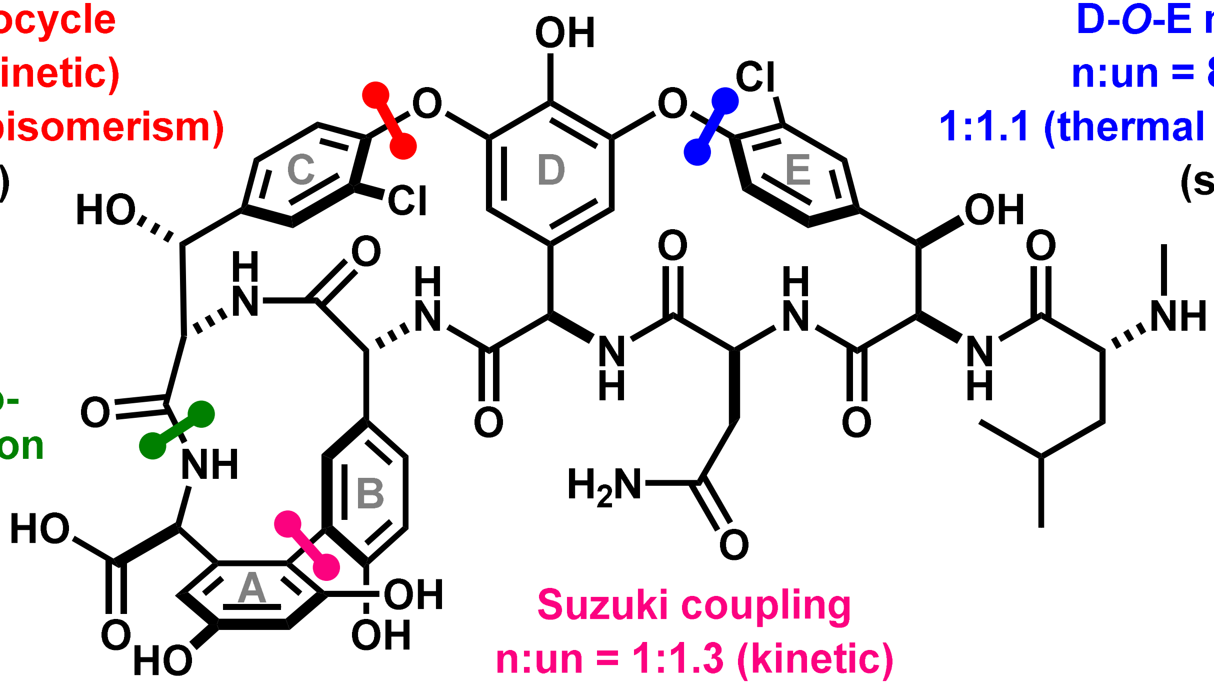
Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 10004−10011.

Short Summary

C-*O*-D macrocycle
n:un = 1:1 (kinetic)
1:1.1 (thermal atropisomerism)
(step 1)

D-*O*-E macrocycle
n:un = 8:1 (kinetic)
1:1.1 (thermal atropisomerism)
(step 4)

AB macro-
lactamization
(step 3)



Suzuki coupling
n:un = 1:1.3 (kinetic)
3:1 (thermal atropisomerism)
(step 2)

Earlier introduction of more rigid modular
(C-*O*-D macrocycle —> AB biaryl (—> AB macrolactam) —> D-*O*-E macrocycle)
based on the model studies of thermal atropisomerism

↓

Successful control of thermal atropisomerism
without affecting other modules already installed

1) Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Castle, S. L.; Loiseleur, O.; Jin, Q. *J. Am. Chem. Soc*. **1999**, *121*, 10004−10011.
2) Boger, D. L.; Miyazaki, S.; Kim, S. H.; Wu, J. H.; Loiseleur, O.; Castle, S. L. *J. Am. Chem. Soc*. **1999**, *121*, 3226−3227.

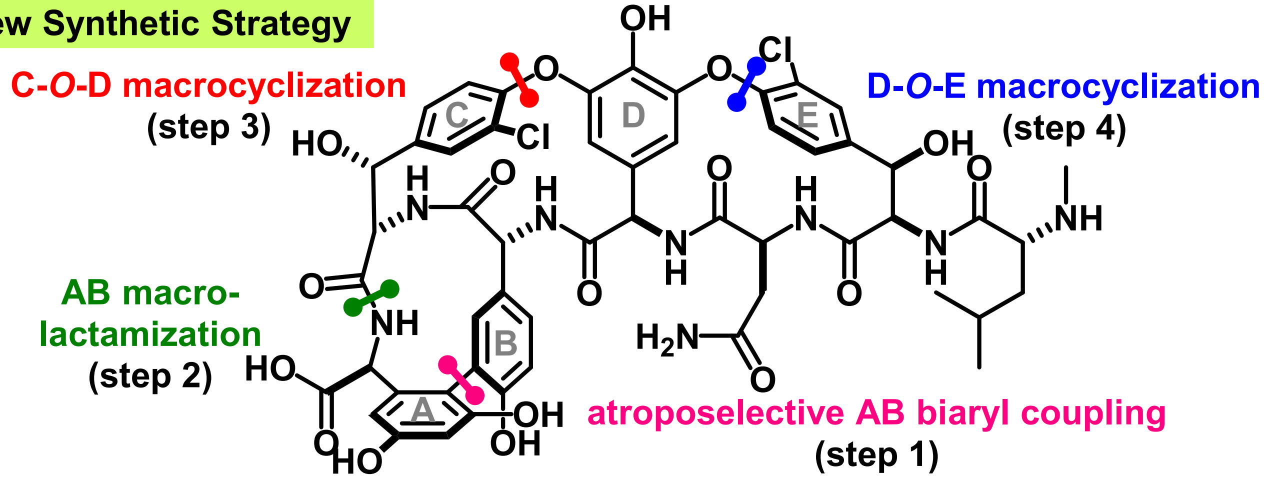
Contents

New Strategy

Remained problems

- **Unsatisfactory kinetic atroposelectivities**
  C-*O*-D macrocycle (n:un = 1:1), AB biaryl (n:un = 1:1.3)
  vs D-*O*-E macrocycle (n:un = 8:1)
- **Inefficiency in recycling of the unnatural atropisomer with thermal isomerism**
  C-*O*-D macrocycle (n:un = 1:1.1), AB biaryl (n:un = 3:1)

New Synthetic Strategy



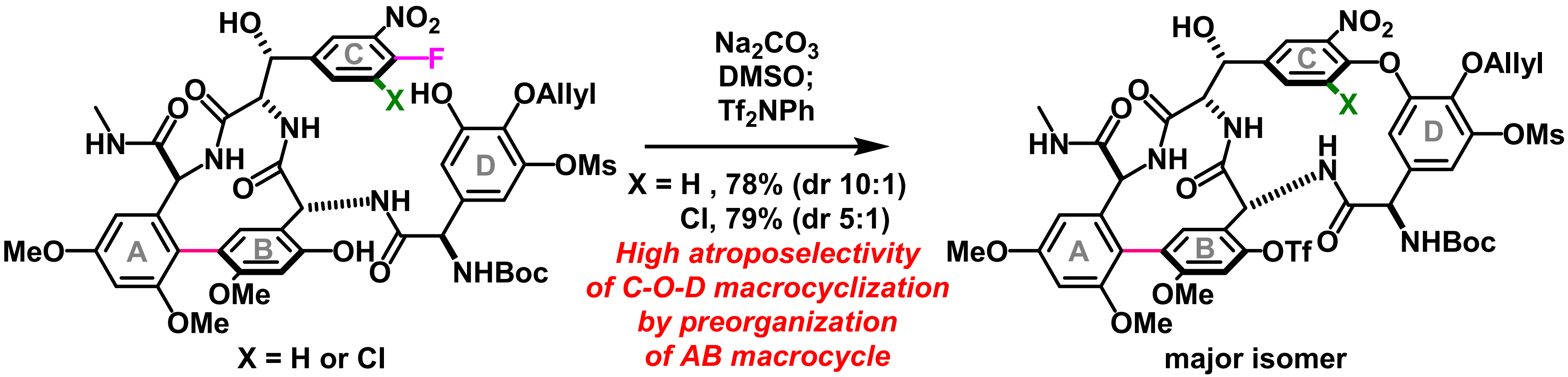
order of module assembly

AB macrolactam (step 1,2)

C-*O*-D macrocycl (step 3)

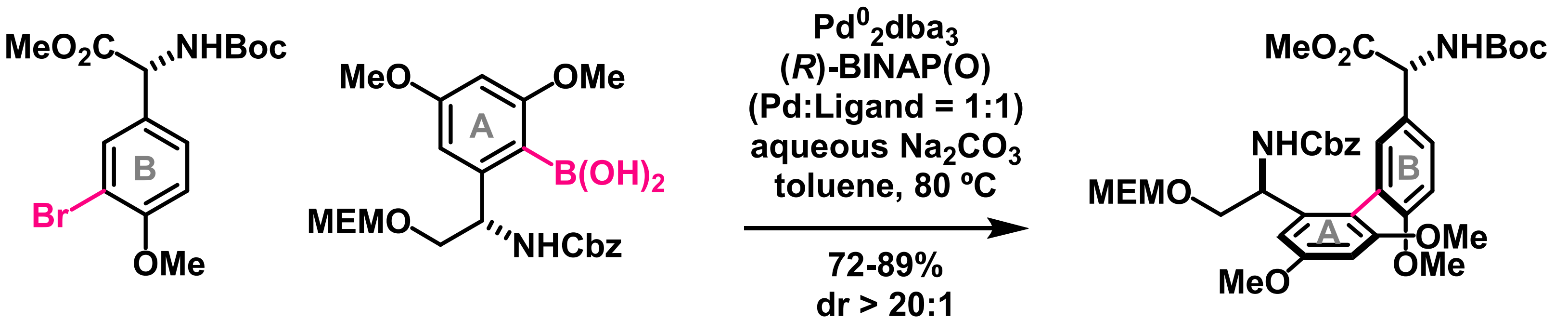
D-*O*-E macrocycl (step 4)

cf. Evans' C-*O*-D macrocyclization

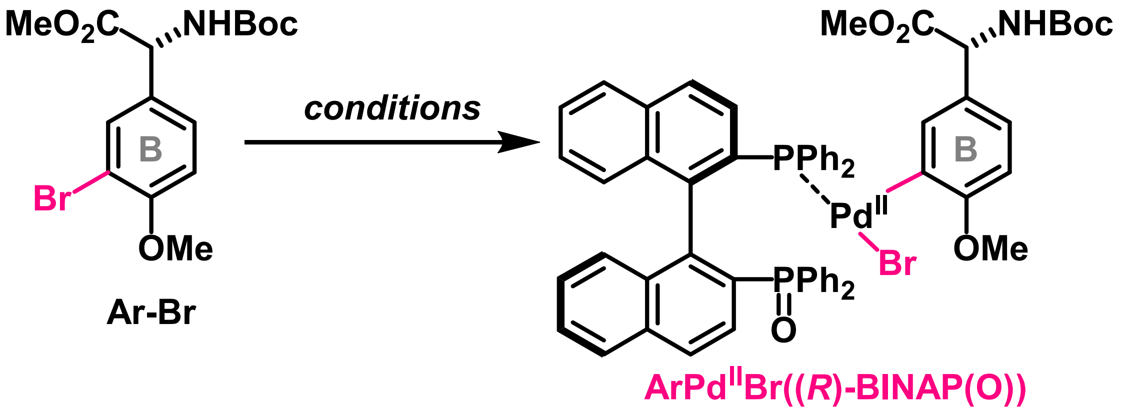


Evans, D. A.; Wood, M. R.; Trotter, B. W.; Richardson, T. I.; Barrow, J. C.; Katz, J. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 2700−2704.

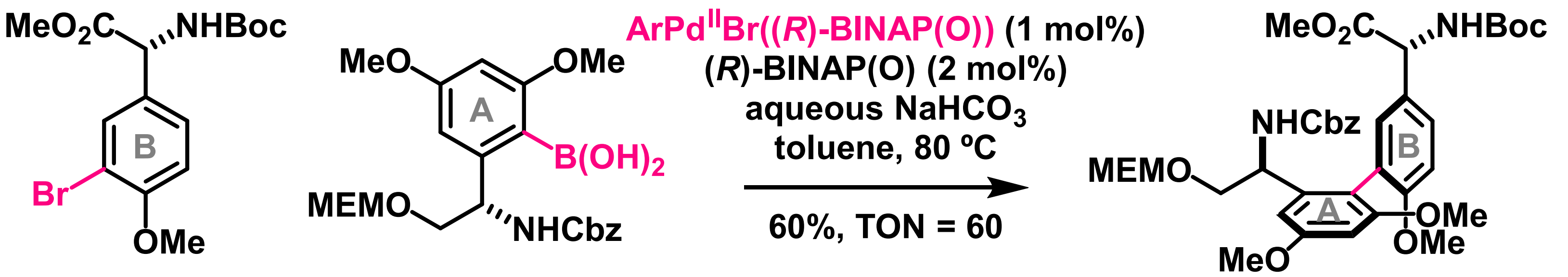
Atroposelective AB Biaryl Coupling (1)



$Pd^0{}_2dba_3$/(*R*)-BINAP was ineffective in this biaryl coupling → Pd^0- ligated (*R*)-BINAP(O) was the active species

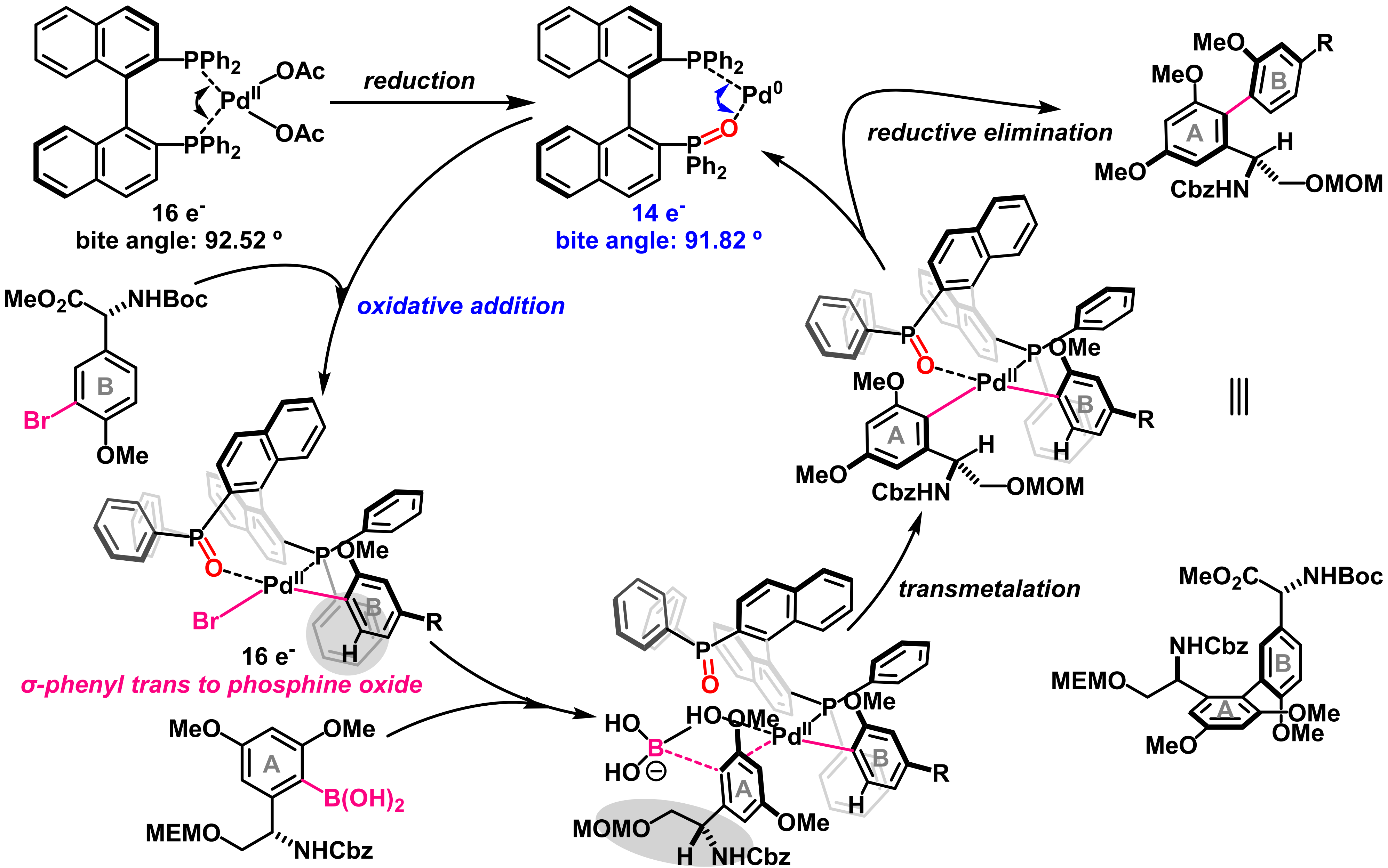


conditions	yield
$Pd^0{}_2dba_3$, (*R*)-BINAP(O)	24%
$Pd^{II}(OAc)_2$, (*R*)-BINAP aqueous $NaHCO_3$ MeTHF, 80 ºC	91%



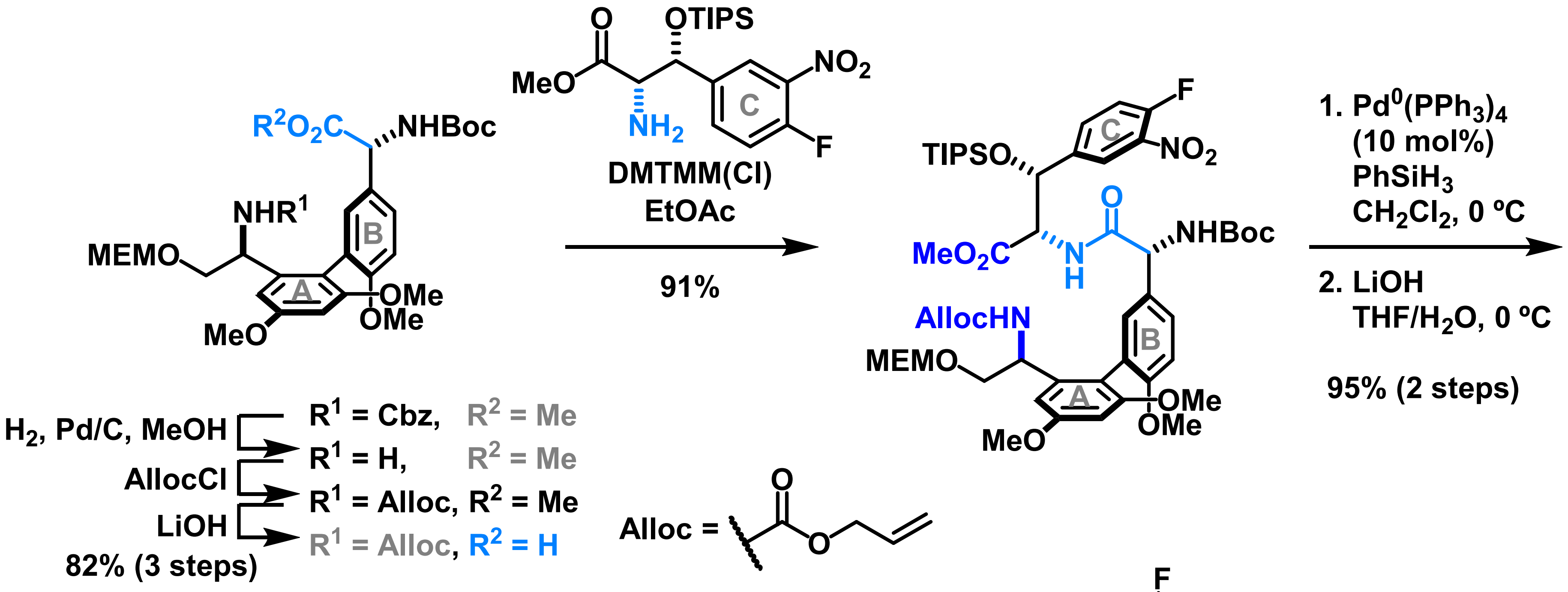
Moore, M. J.; Qu, S.; Tan, C.; Cai, Y.; Mogi, Y.; Jamin Keith, D.; Boger, D. L. *J. Am. Chem. Soc.* **2020**, *142*, 16039−16050.

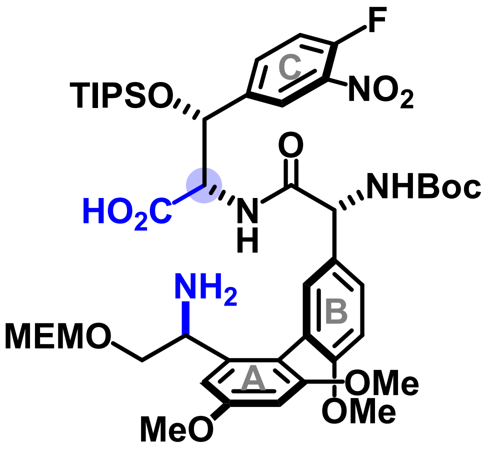
Atroposelective AB Biaryl Coupling (2)



1) Moore, M. J.; Qu, S.; Tan, C.; Cai, Y.; Mogi, Y.; Jamin Keith, D.; Boger, D. L. *J. Am. Chem. Soc.* **2020**, *142*, 16039−16050.
2) Marshall, W. J.; Grushin, V. V. *Organometallics* **2003**, *22*, 555−562.

AB Macrolactamization

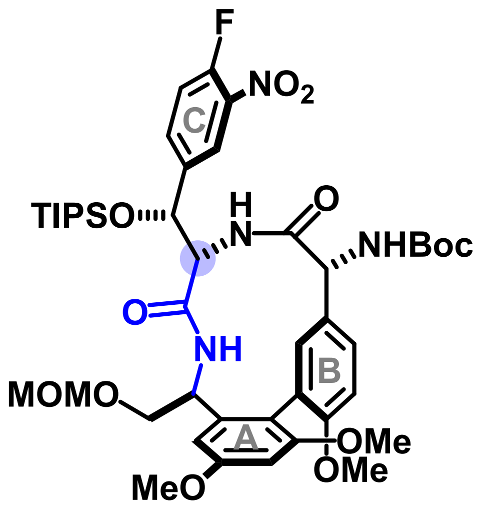


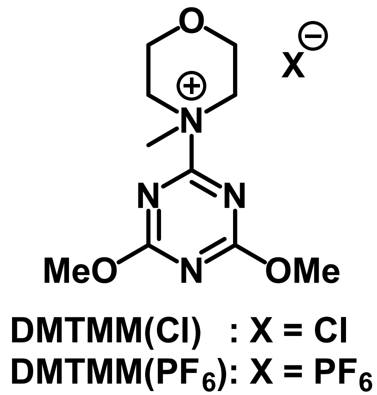


conditions

AB macrolactamization

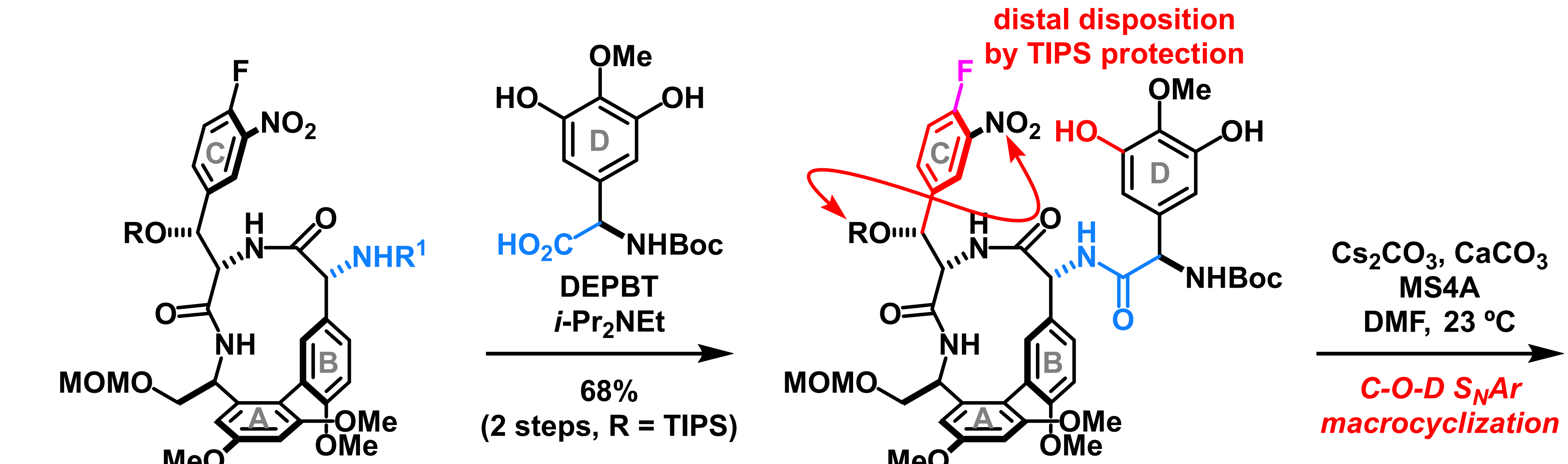
conditions	yield	dr
DMTMM(Cl) DMF (0.001 M)	29%	>95:5
DMTMM(PF_6) DMP (0.1 M)	61%	98:2

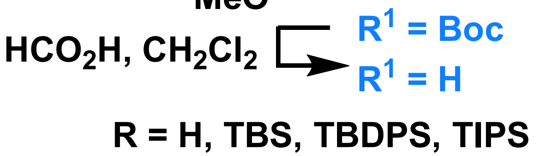




Moore, M. J.; Qu, S.; Tan, C.; Cai, Y.; Mogi, Y.; Jamin Keith, D.; Boger, D. L. *J. Am. Chem. Soc.* **2020**, *142*, 16039−16050.

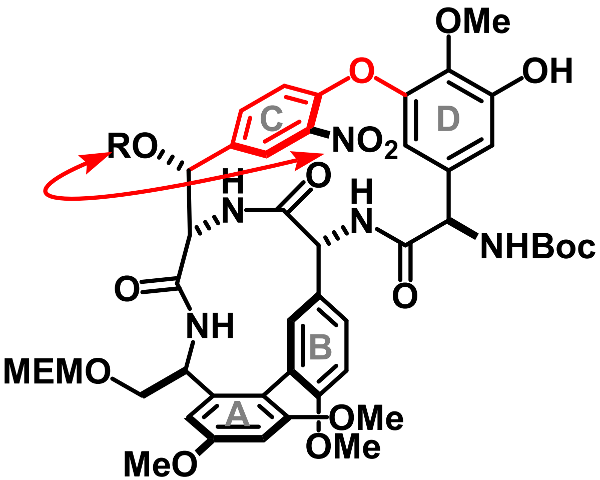
C-*O*-D Macrocylization





R	dr (n:un)	yield
H	2:1	50%
TBS	3:1	84%
TBDPS	5:1	50%
TIPS	7:1	80%

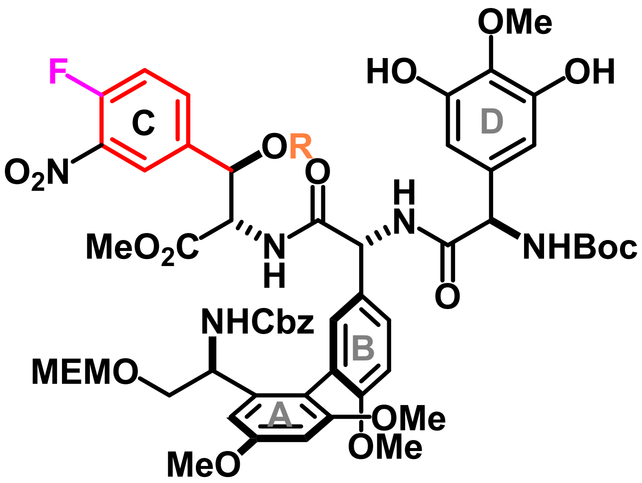
* tolerance of silyl ether against;
NaOH in MeOH: TBS<TBDPS<TIPS
n-Bu_4NF : TBS<TIPS<TBDPS



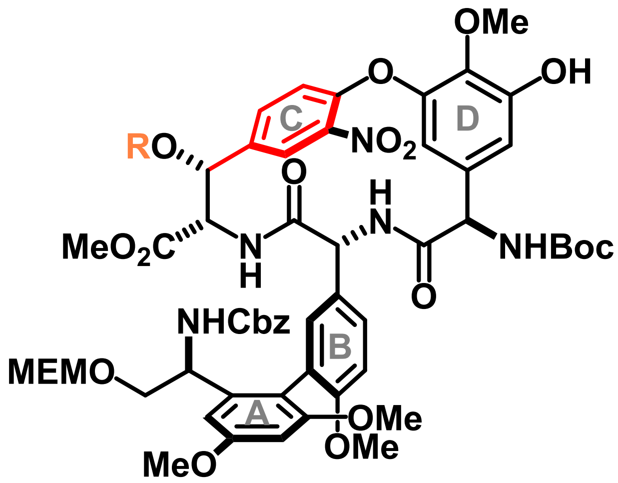
Moore, M. J.; Qu, S.; Tan, C.; Cai, Y.; Mogi, Y.; Jamin Keith, D.; Boger, D. L. *J. Am. Chem. Soc.* **2020**, *142*, 16039−16050.

Effect of Preorganized AB Macrolactam

C-*O*-D Macrocyclization before AB macrolactamization

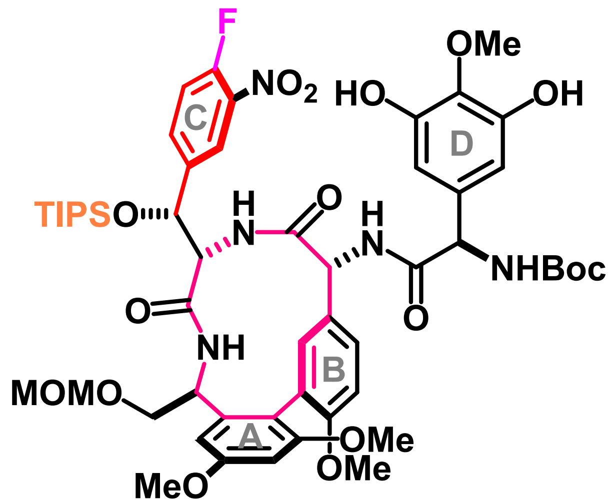


Cs_2CO_3, $CaCO_3$
MS4A
DMF, 23 ºC
10 h



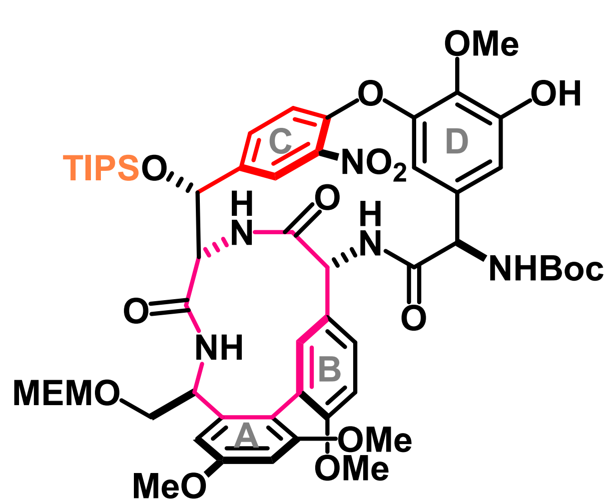
R	dr	yield
TBS	1.2:1	50%
TBDPS	2.0:1	67%
TIPS	2.6:1	76%

C-*O*-D Macrocyclization after AB macrolactamization



Cs_2CO_3, $CaCO_3$
MS4A
DMF, 23 ºC
3-5 h
n: un = 7:1

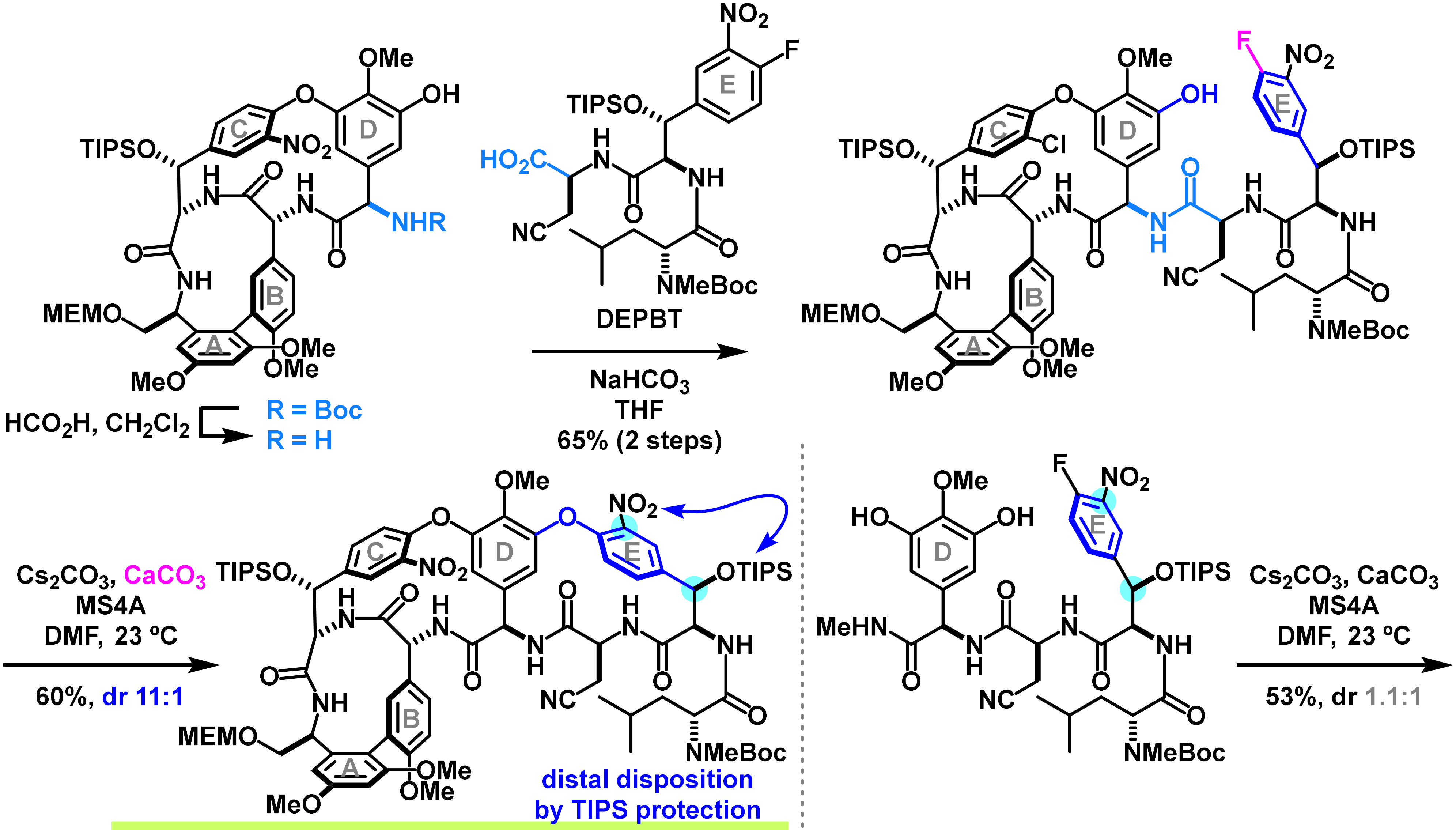
faster cyclization and High atroposelectivity



Preorganization of AB macrolactam → fast and highly atroposelective C-*O*-D maclocyclization

Moore, M. J.; Qu, S.; Tan, C.; Cai, Y.; Mogi, Y.; Jamin Keith, D.; Boger, D. L. *J. Am. Chem. Soc.* **2020**, *142*, 16039−16050.

D-*O*-E Macrocyclization

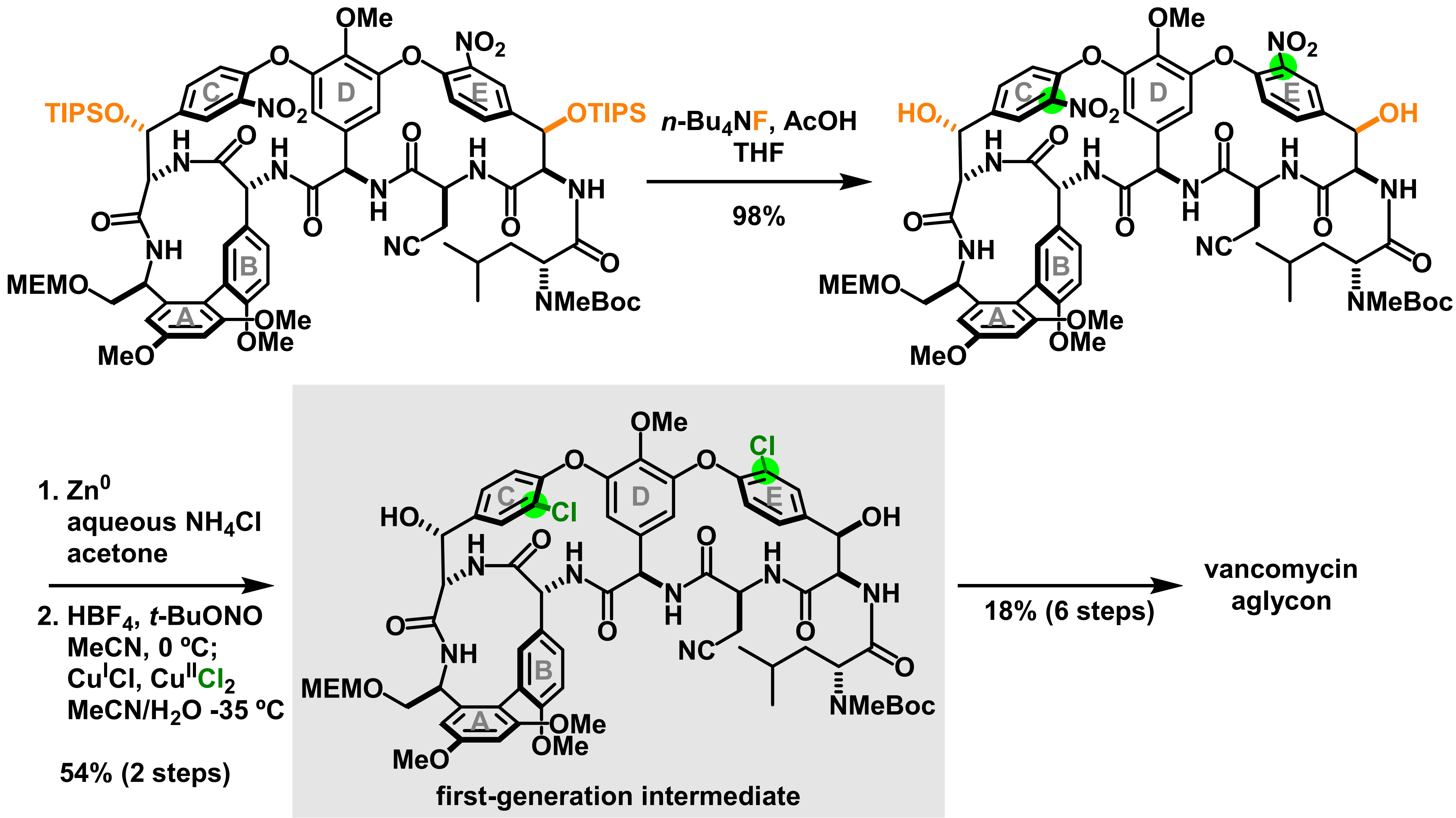


Preorganization of
{AB macrolactam
{C-*O*-D macrocycle
→ high atroposelective D-*O*-E macrocyclization

no AB macrolactam
no C-*O*-D macrocycle
→ poor diastereoselective D-*O*-E macrocyclization

Moore, M. J.; Qu, S.; Tan, C.; Cai, Y.; Mogi, Y.; Jamin Keith, D.; Boger, D. L. *J. Am. Chem. Soc.* **2020**, *142*, 16039−16050.

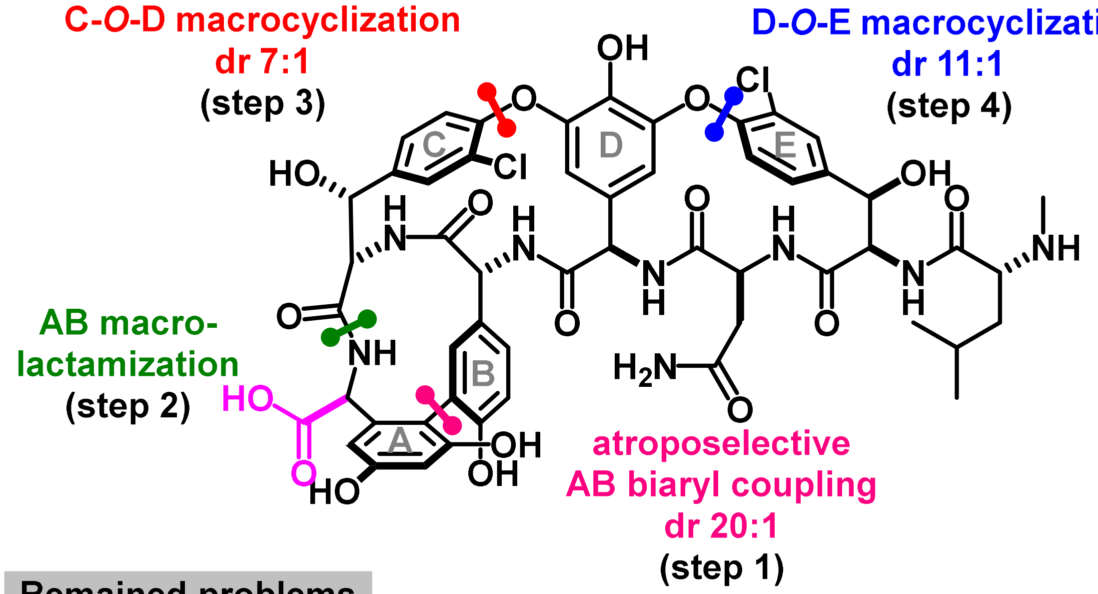
Formal Synthesis of Vancomycin Aglycon



Moore, M. J.; Qu, S.; Tan, C.; Cai, Y.; Mogi, Y.; Jamin Keith, D.; Boger, D. L. *J. Am. Chem. Soc.* **2020**, *142*, 16039−16050.

Further Improvement

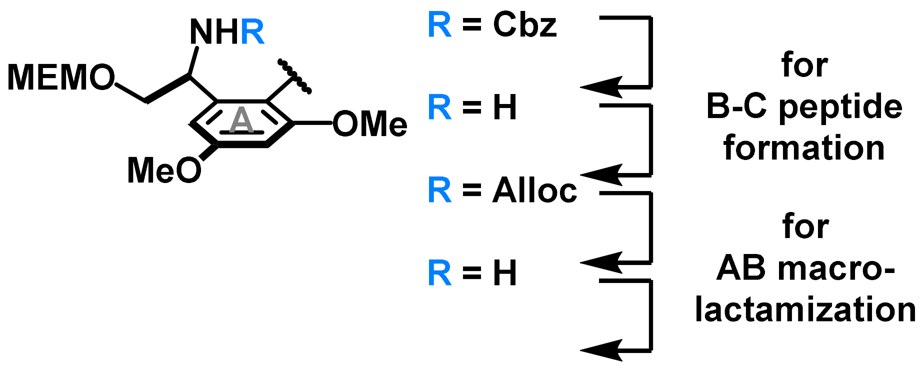
Improved points



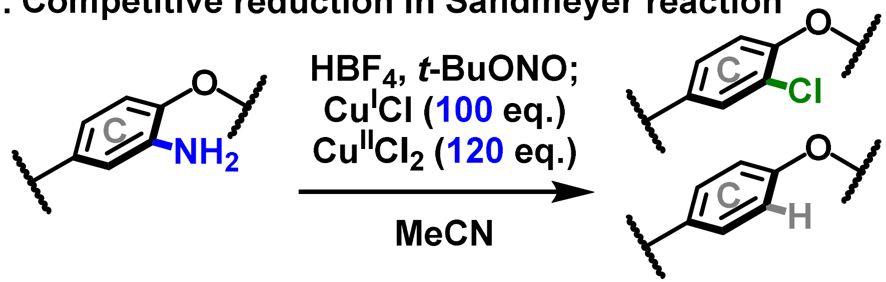
vancomycin aglycon	overall yield	kinetic atropselectivity AB	C-*O*-D	D-*O*-E
1999 (first)	0.2% (25 steps)	1:1	1:1	8:1
2020 (formal)	0.7% (26 steps)	20:1	7:1	11:1

Remained problems

1. Protecting group manipulations of A-ring amine



2. Competitive reduction in Sandmeyer reaction

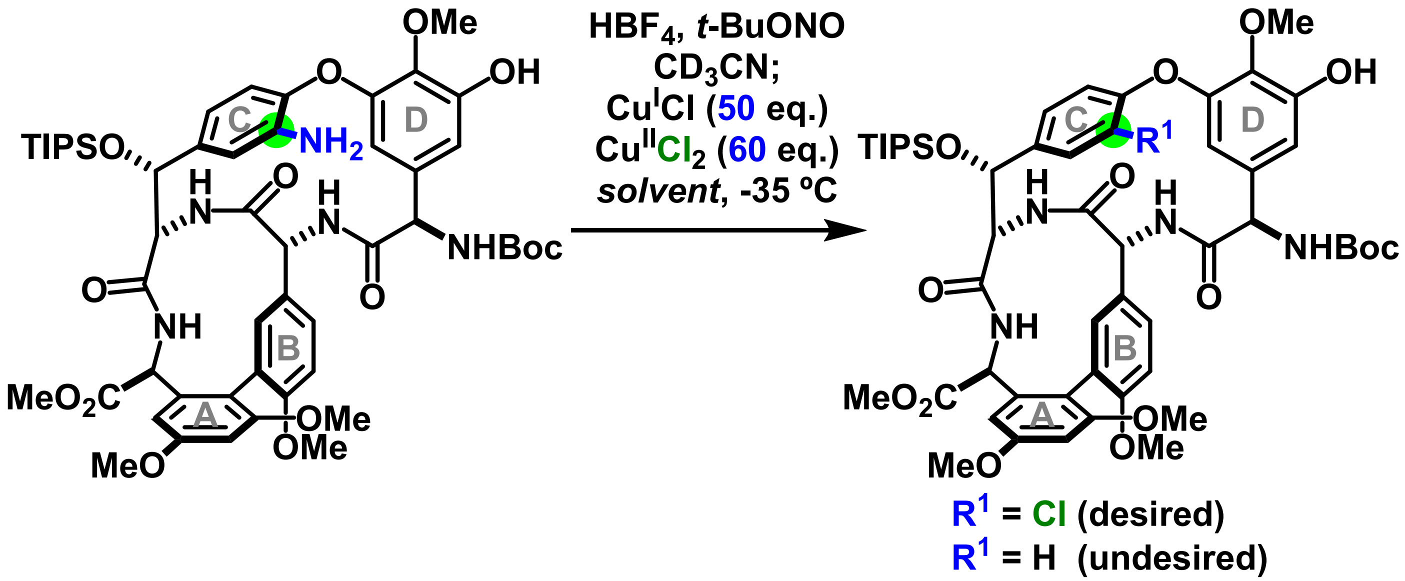


3. Early introduction of C-terminus ester

Moore, M. J.; Qu, S.; Tan, C.; Cai, Y.; Mogi, Y.; Jamin Keith, D.; Boger, D. L. *J. Am. Chem. Soc.* **2020**, *142*, 16039−16050.

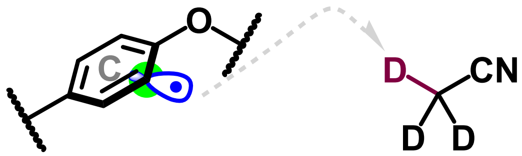
Improvement

- Optimization of Sandmyer reaction

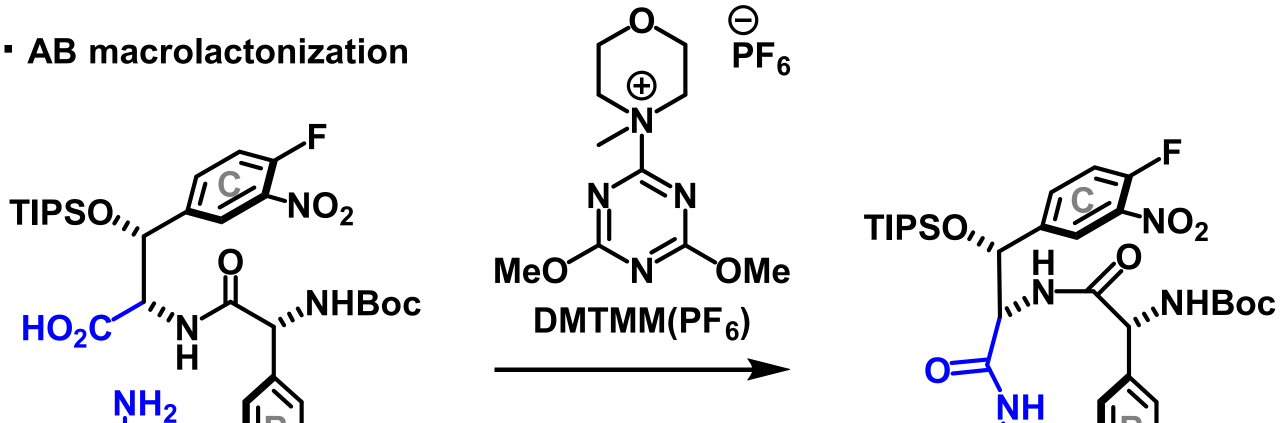


solvent	R^1 = Cl : H
CH_3CN/H_2O = 1/1	9:1*
CD_3CN/H_2O = 1/1	32:1 (77%)

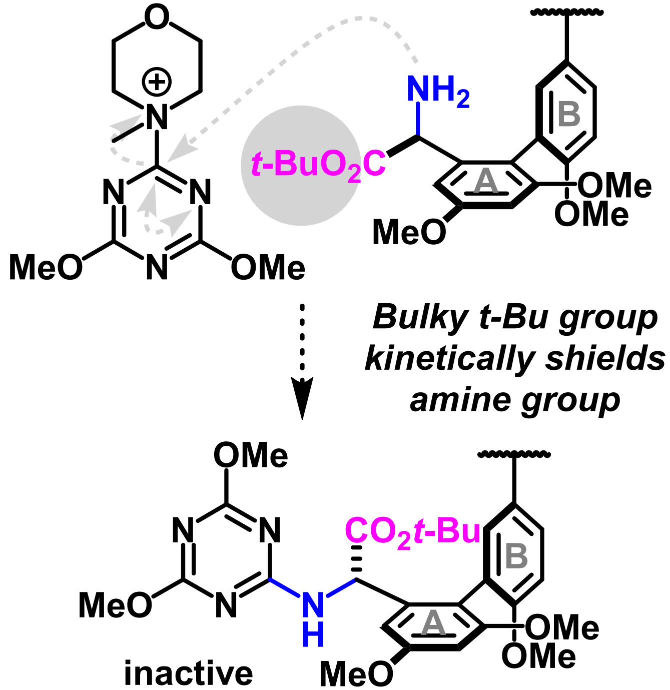
* diazonium formation was conducted in CH_3CN



- AB macrolactonization

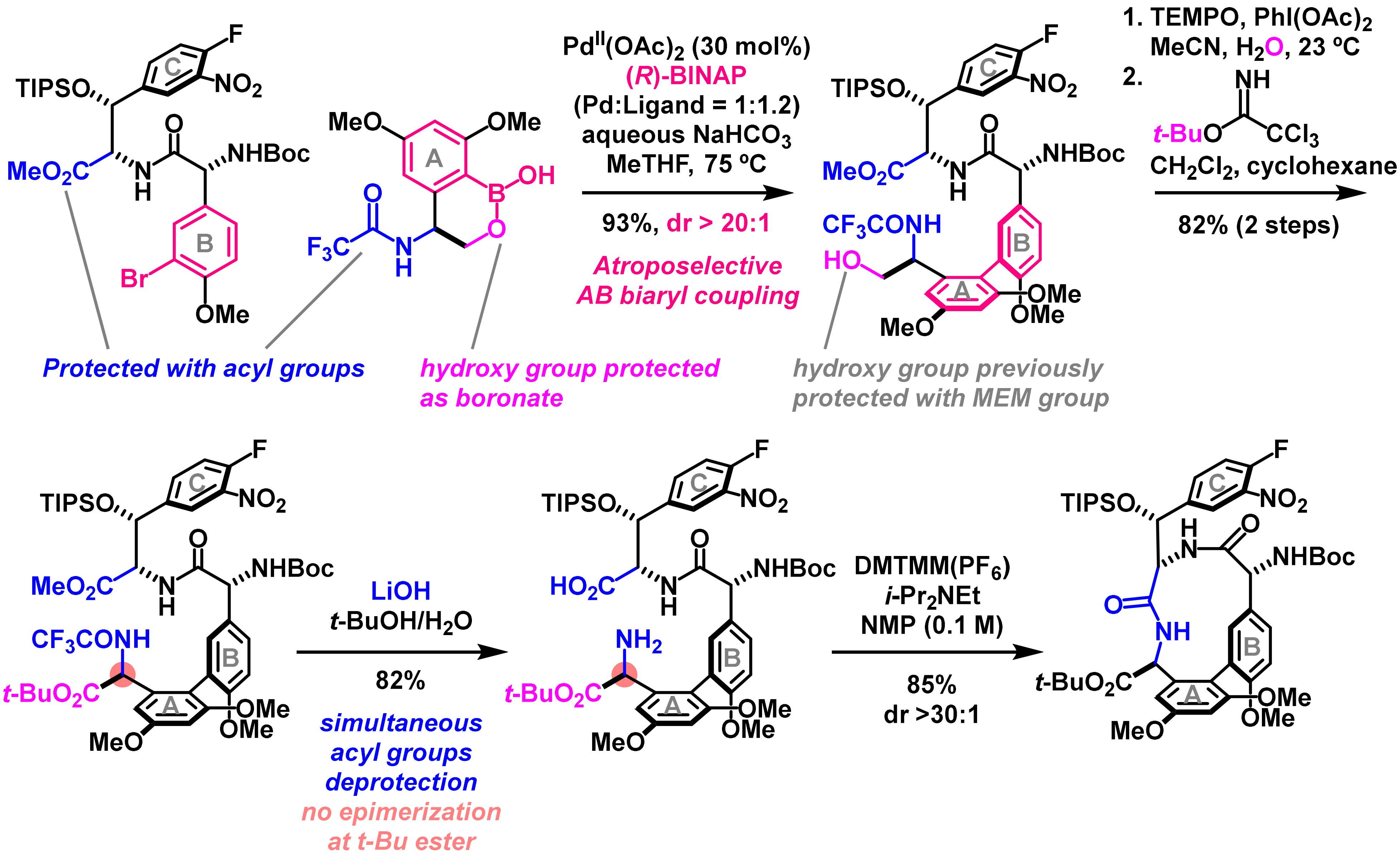


R^2	yield
CH_2OMEM	61%
CO_2t-Bu	85%13:1



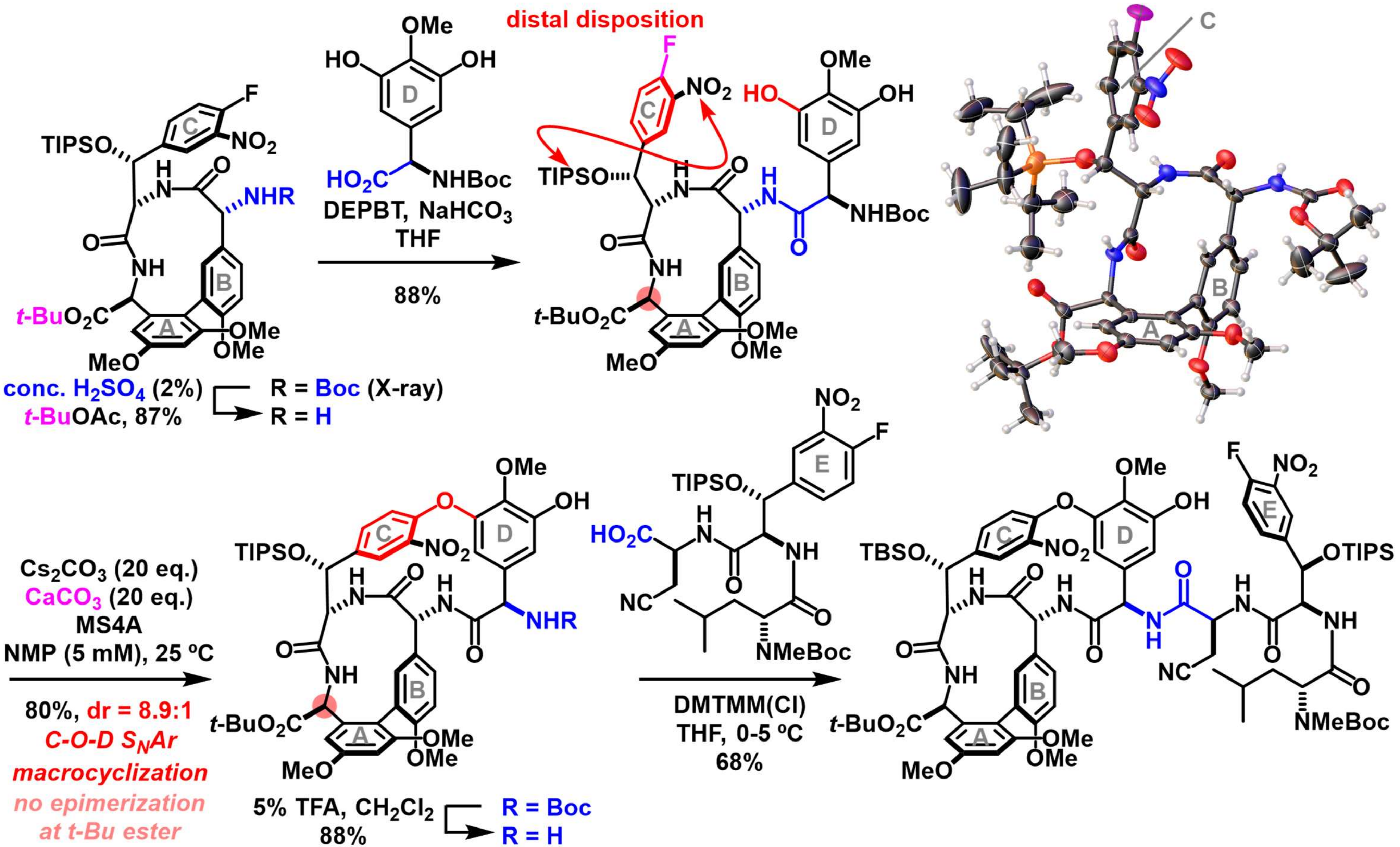
Moore, M. J.; Qu, S.; Tan, C.; Cai, Y.; Mogi, Y.; Jamin Keith, D.; Boger, D. L. *J. Am. Chem. Soc.* **2020**, *142*, 16039−16050.

AB Biaryl coupling/Macrolactamization



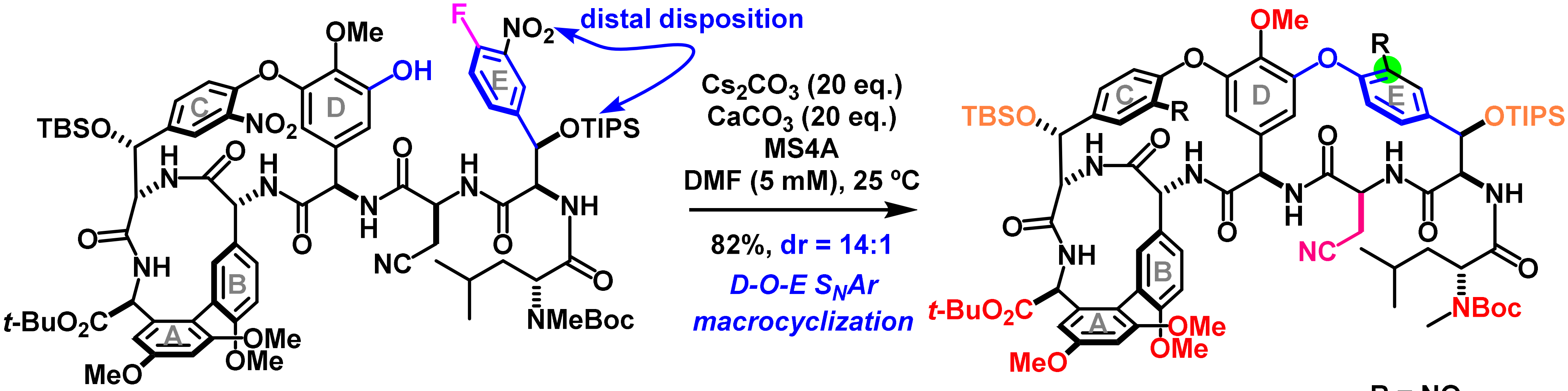
Moore, M. J.; Qu, S.; Tan, C.; Cai, Y.; Mogi, Y.; Jamin Keith, D.; Boger, D. L. *J. Am. Chem. Soc.* **2020**, *142*, 16039−16050.

C-*O*-D Macrocyclization



Moore, M. J.; Qu, S.; Tan, C.; Cai, Y.; Mogi, Y.; Jamin Keith, D.; Boger, D. L. *J. Am. Chem. Soc.* **2020**, *142*, 16039−16050.

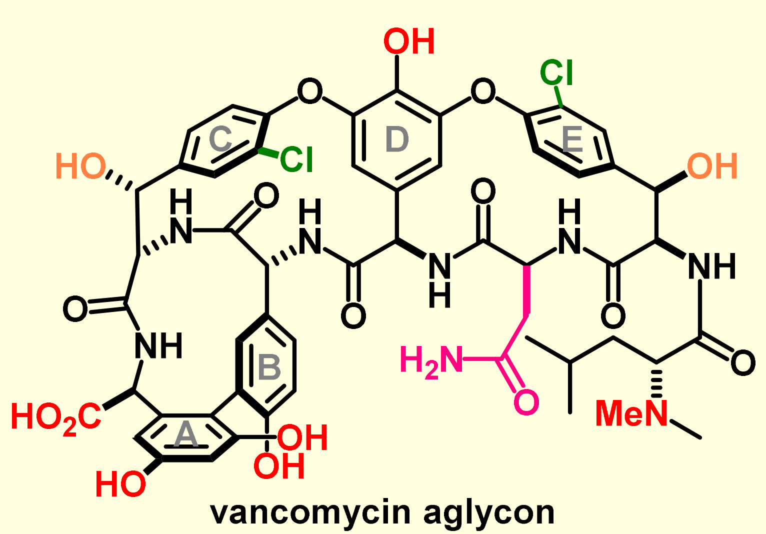
Next-Generation Synthesis



1. Zn^0, aqueous NH_4Cl, acetone
2. HBF_4, *t*-BuONO, CD_3CN, 0 ºC; Cu^ICl (100 eq.), $Cu^{II}Cl_2$ (120 eq.) CD_3CN/H_2O, -35 ºC
63% (2 steps)

R = NO_2 → R = Cl

1. *n*-Bu_4NF, AcOH THF
2. TFA (neat)
3. $AlBr_3$, EtSH; MeOH, 0 ºC
53%
(3 steps in one-pot)
deprotection

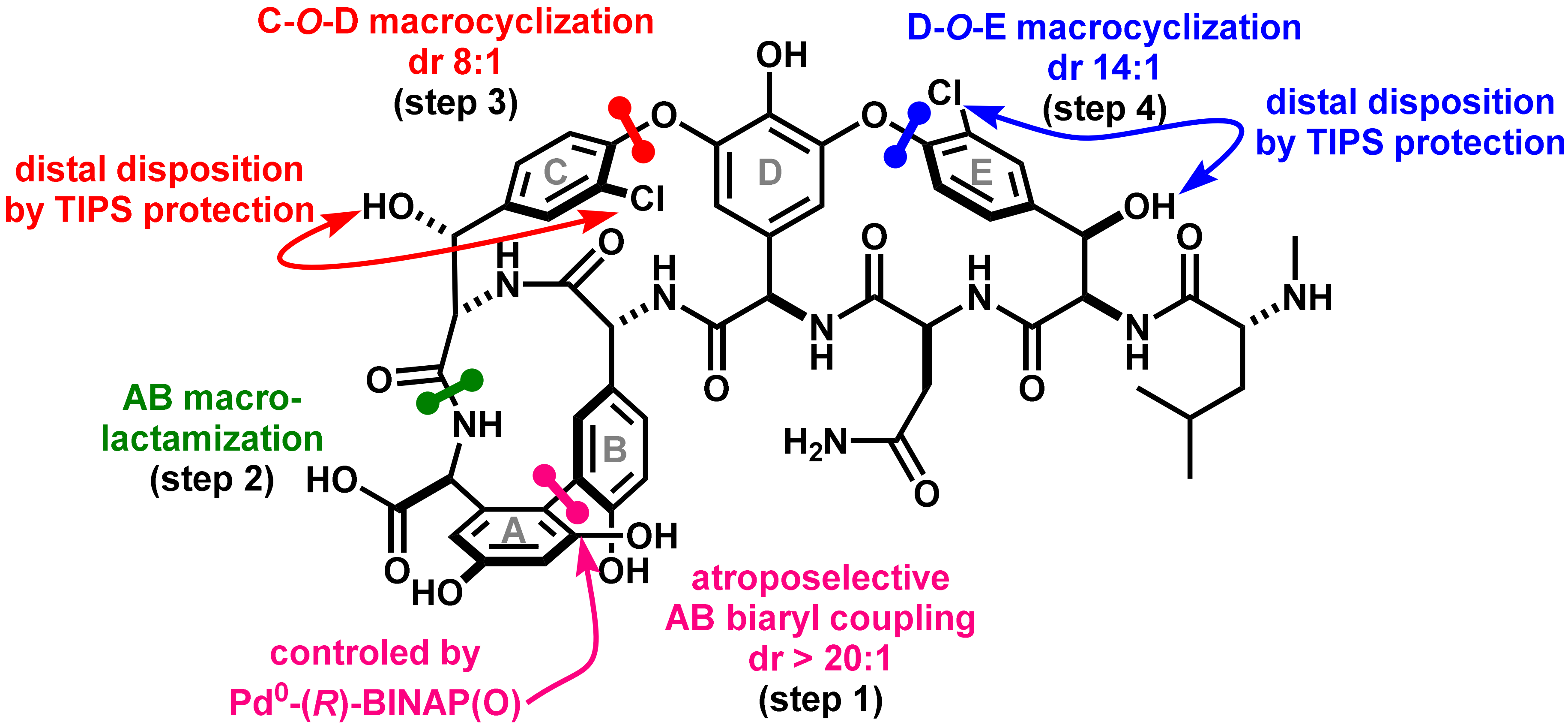


vancomycin aglycon

vancomycin aglycon	overall yield	kinetic atropselectivity AB	C-*O*-D	D-*O*-E
1999	0.2% (25 steps)	1:1	1:1	8:1
2020	5% (17 steps)	>20:1	8:1	14:1

Moore, M. J.; Qu, S.; Tan, C.; Cai, Y.; Mogi, Y.; Jamin Keith, D.; Boger, D. L. *J. Am. Chem. Soc.* **2020**, *142*, 16039−16050.

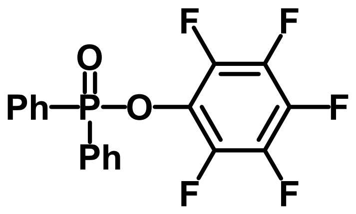
Summary



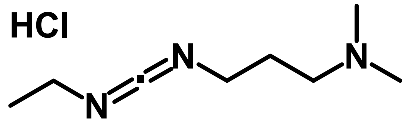
Rational order of Ring system construction enabled by catalyst and substrate control	→	Kinetical introduction of all atropisomerism with high diastereoselectivities (AB > 20:1, C-*O*-D = 8:1, D-*O*-E = 14:1)
Sophisticated substrate design (functional groups and protecting groups)	→	Improvement in both synthetic steps and overall yield (17 steps in 5% vs 25 steps in 0.2%)

Moore, M. J.; Qu, S.; Tan, C.; Cai, Y.; Mogi, Y.; Jamin Keith, D.; Boger, D. L. *J. Am. Chem. Soc.* **2020**, *142*, 16039−16050.

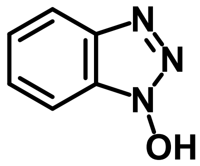
Reagent List



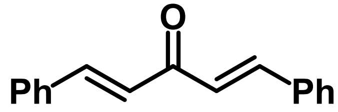
FDPP



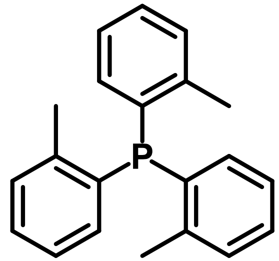
EDCI



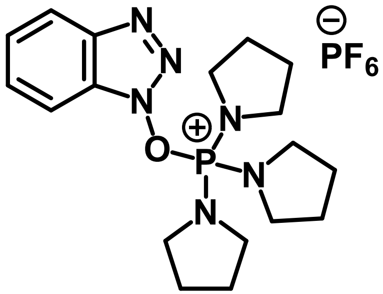
HOBt



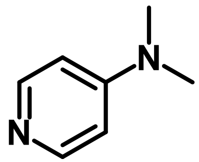
dba



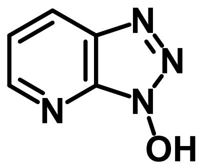
(*o*-tolyl)$_3$P



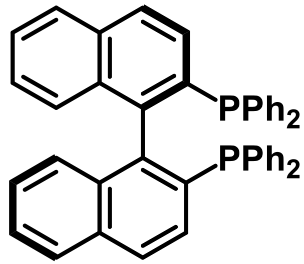
PyBOP



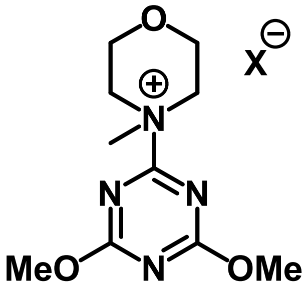
DMAP



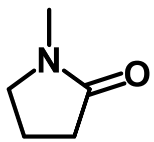
HOAt



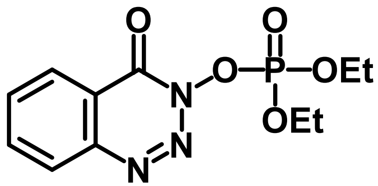
(*R*)-BINAP



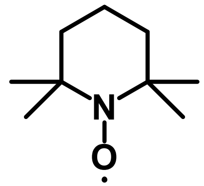
DMTMM(Cl) : X = Cl
DMTMM(PF_6): X = PF_6



DMP



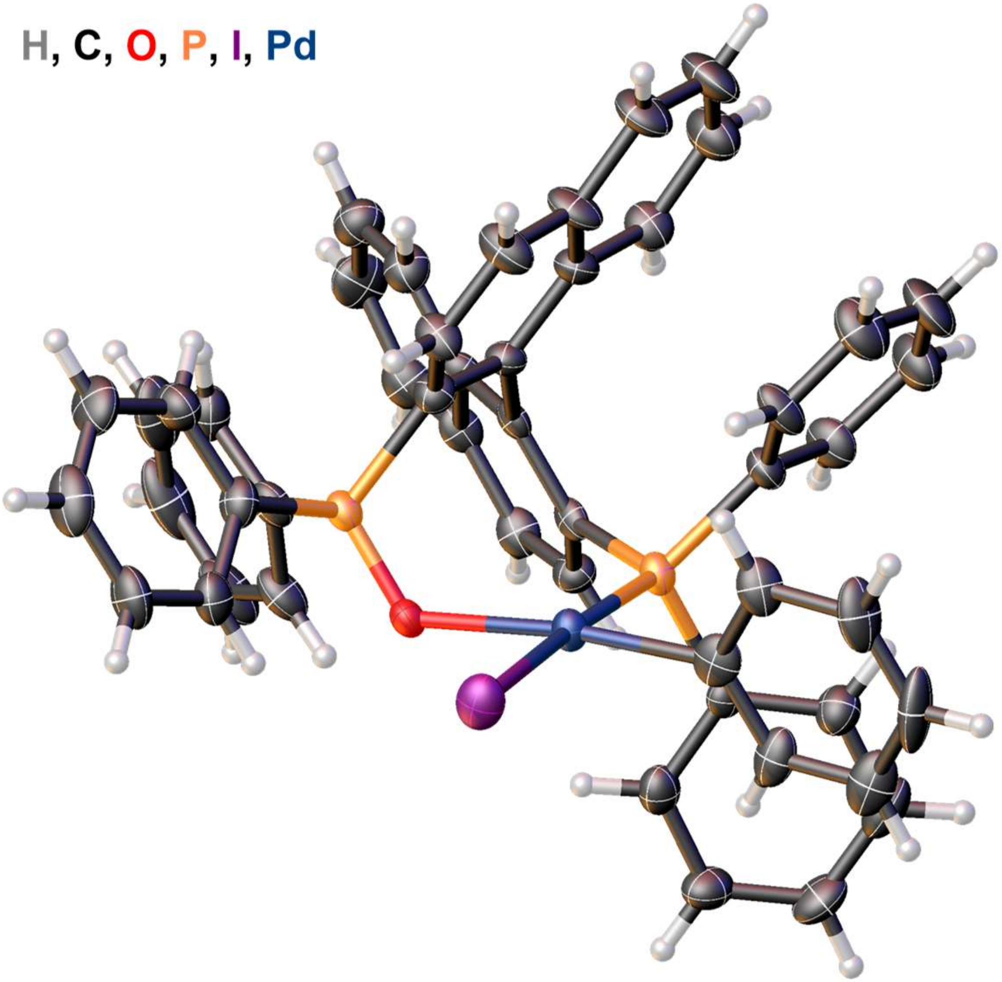
DEPBT



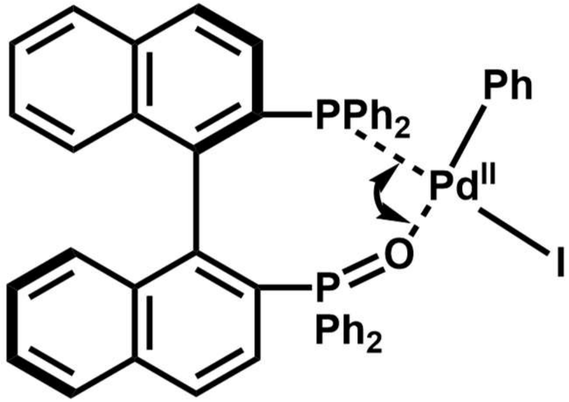
TEMPO

Appendix

X-ray Structure of [((R)-BINAP(O)-κ2P,O)Pd-(Ph)I]



[((*R*)-BINAP(O)-*κ*^{2}*P*,*O*)Pd-(Ph)I]



bite angle: 91.82 º

Marshall, W. J.; Grushin, V. V. *Organometallics* **2003**, *22*, 555−562.