ASAP Report

Reporter: Jing Chen

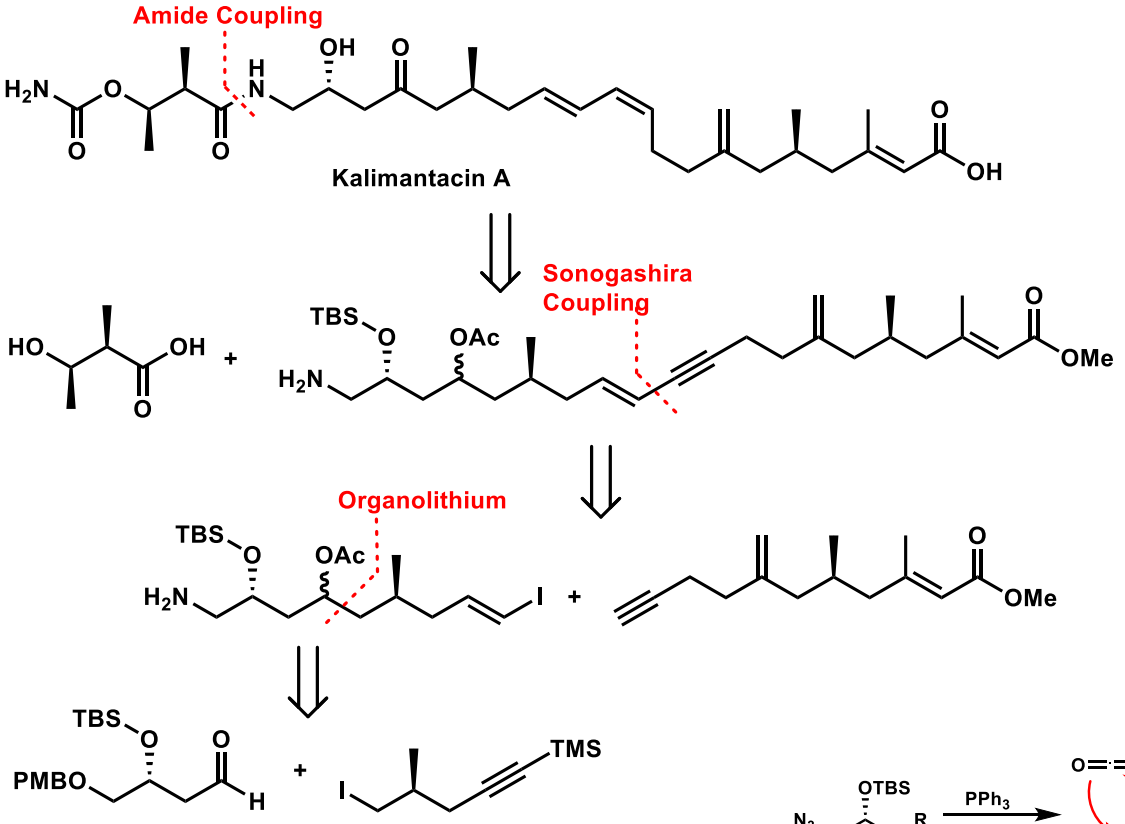
Supervisors: *Prof.* Tao Ye

***Dr.* Yian Guo**

Sep. 14st, 2020

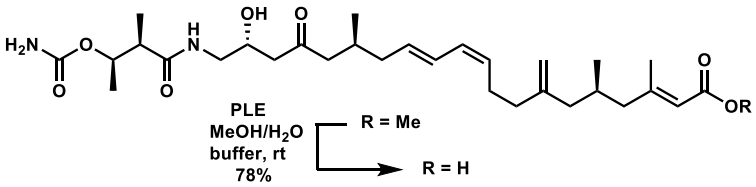
Introduction

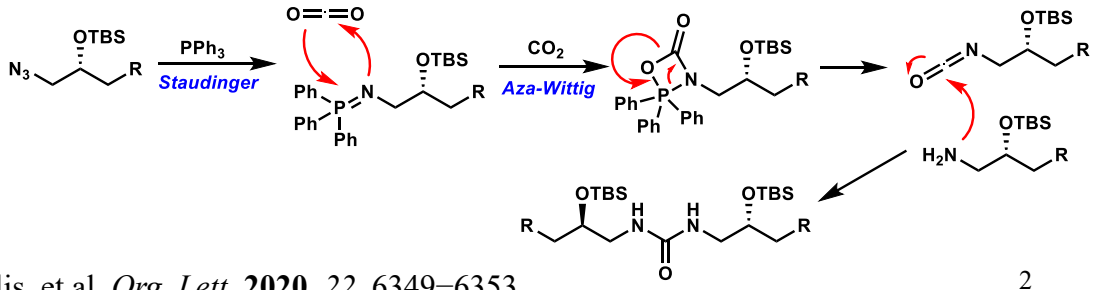
Part I :Total synthesis of **Kalimantacin A**



Biological activities:

- display potent and antibiotic activity against multidrug resistant strains of *Staphylococcu aureus*.

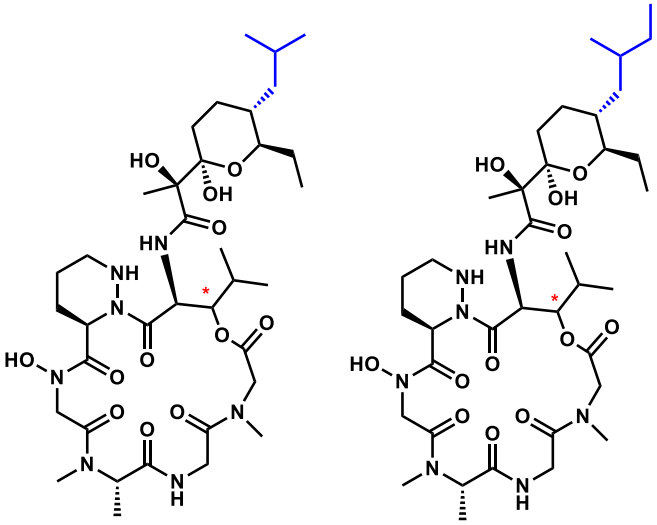




Christine L. Willis. et al, *Org. Lett.* **2020**, *22*, 6349−6353.

Introduction

Part II: **Meliponamycins**, antimicrobials from ***Stingless Bee-Associated Streptomyces sp.***



Meliponamycin A

Meliponamycin B

(new compounds, first isolated)

Isolation

- Two novel cyclic hexadepsipeptides were isolated from ***Streptomyces sp. ICBG1318*** isolated from *M. scutellaris nurse bees*.

Biological activities:

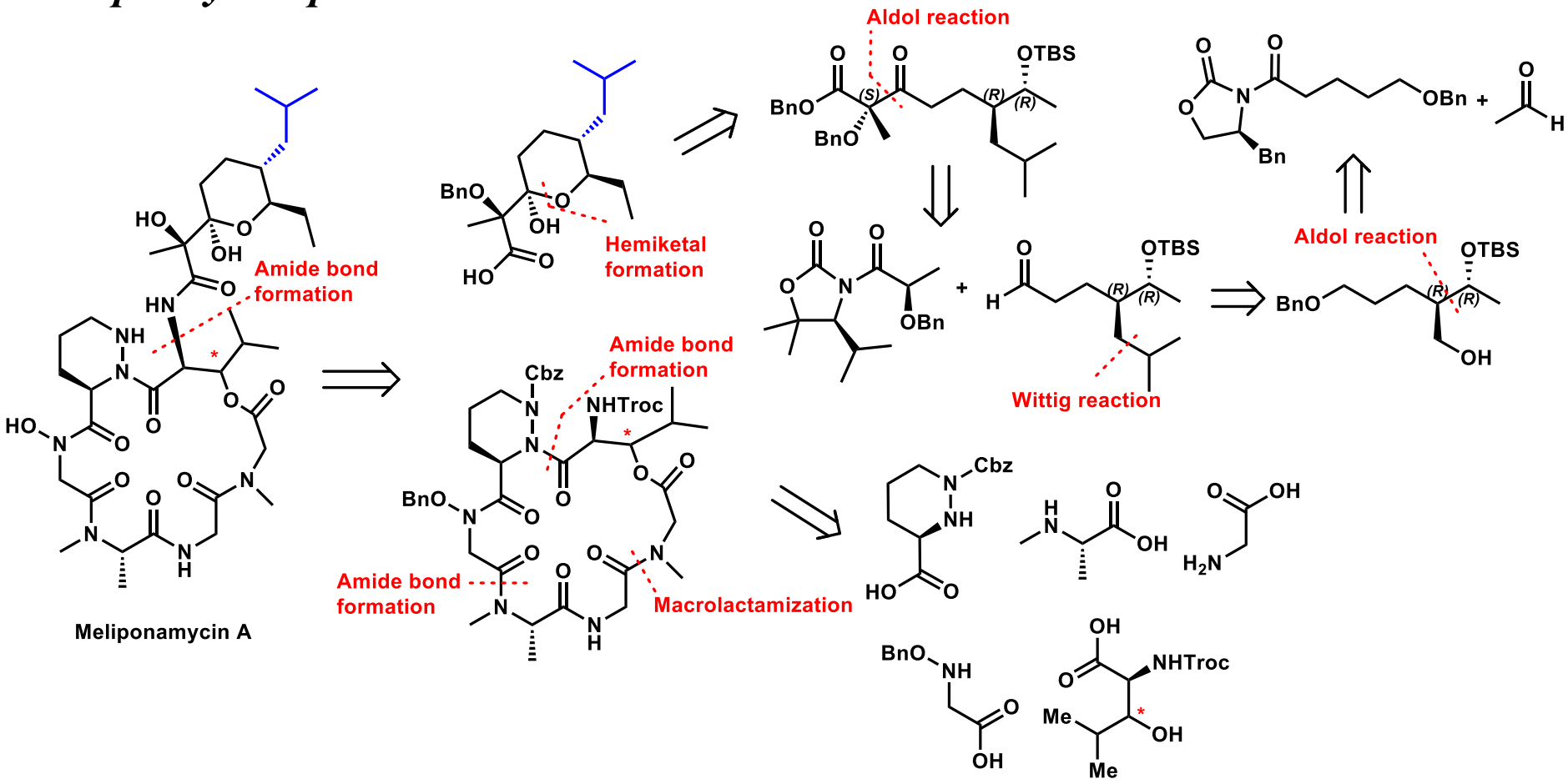
- Showed strong activity against the entomopat hogen *Paenibacillus larvae* and human *pathogens Staphylococcus aureus* and *Leishmania infantum.*

	L. infantum[a]			*P. larvae*	*S. aureus*
compound	IC_{50} (μM) intracellular amastigotes	CC_{50} (μM) THP-1[b]	selectivity index[c]	MIC (μg/mL)	MIC (μg/mL)
1	2.19 ± 0.25	1.05 ± 0.05	0.47	0.43	1.72
2	1.03 ± 0.08	0.70 ± 0.03	0.67	0.43	0.86
miltefosine	2.40 ± 0.22				
doxorubicin		1.80 ± 0.16			
tetracycline				3.45	0.05

Mônica Tallarico Pupo. et al, *J. Nat. Prod.* **2020**, *83*, 610−616.

Introduction

Part II: **Meliponamycins**, antimicrobials from ***Stingless Bee-Associated Streptomyces sp.***

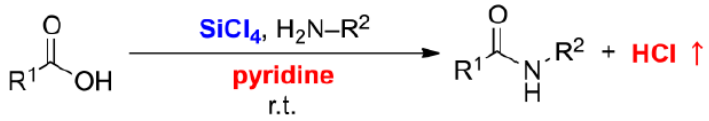


Mônica Tallarico Pupo. et al, *J. Nat. Prod.* **2020**, *83*, 610−616.

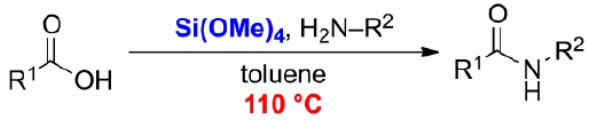
Introduction

Part III: Peptide bond-formation via **Amino Acid Silyl Esters**

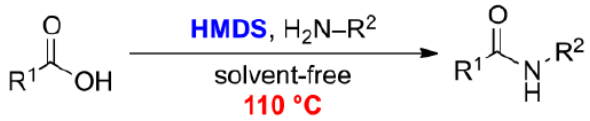
a) Chan's method



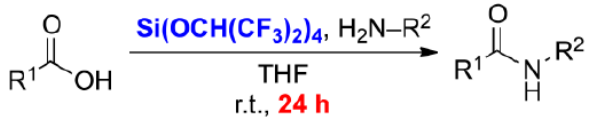
b) Braddock's method



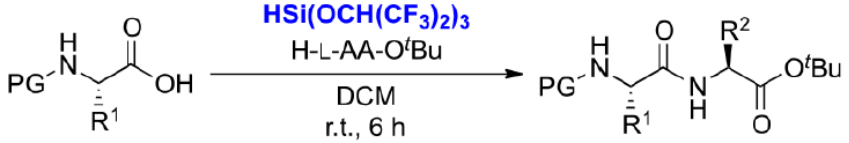
c) Chou's method



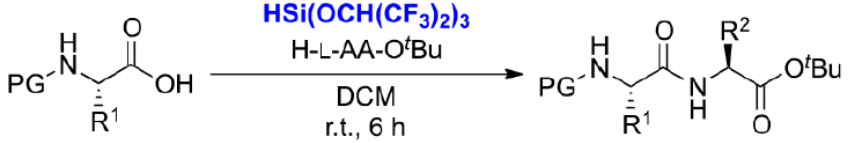
d) Mukaiyama's method



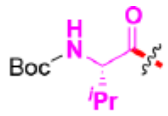
h) This report



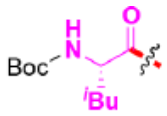
i) This report cat. PMBNHSi(OCH(CF$_3$)$_2$)$_3$



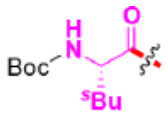
Minimum Substrate Use
(Electrophile/Nucleophile/Silylating reagent = 1:1:1)



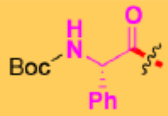
Boc-Val–Ala-O^{t}Bu (2g)
80% yield, >99:1 dr[a]



Boc-Leu–Ala-O^{t}Bu (2h)
96% yield, >99:1 dr[a,c]

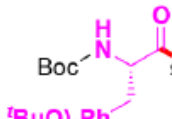


Boc-Ile–Ala-O^{t}Bu (2i)
77% yield, >99:1 dr[a]



Boc-Phg–Ala-O^{t}Bu (2j)
79% yield, **>99:1 dr[a]**

Boc-Phe–Ala-O^{t}Bu (2k)
96% yield, >99:1 dr[a]

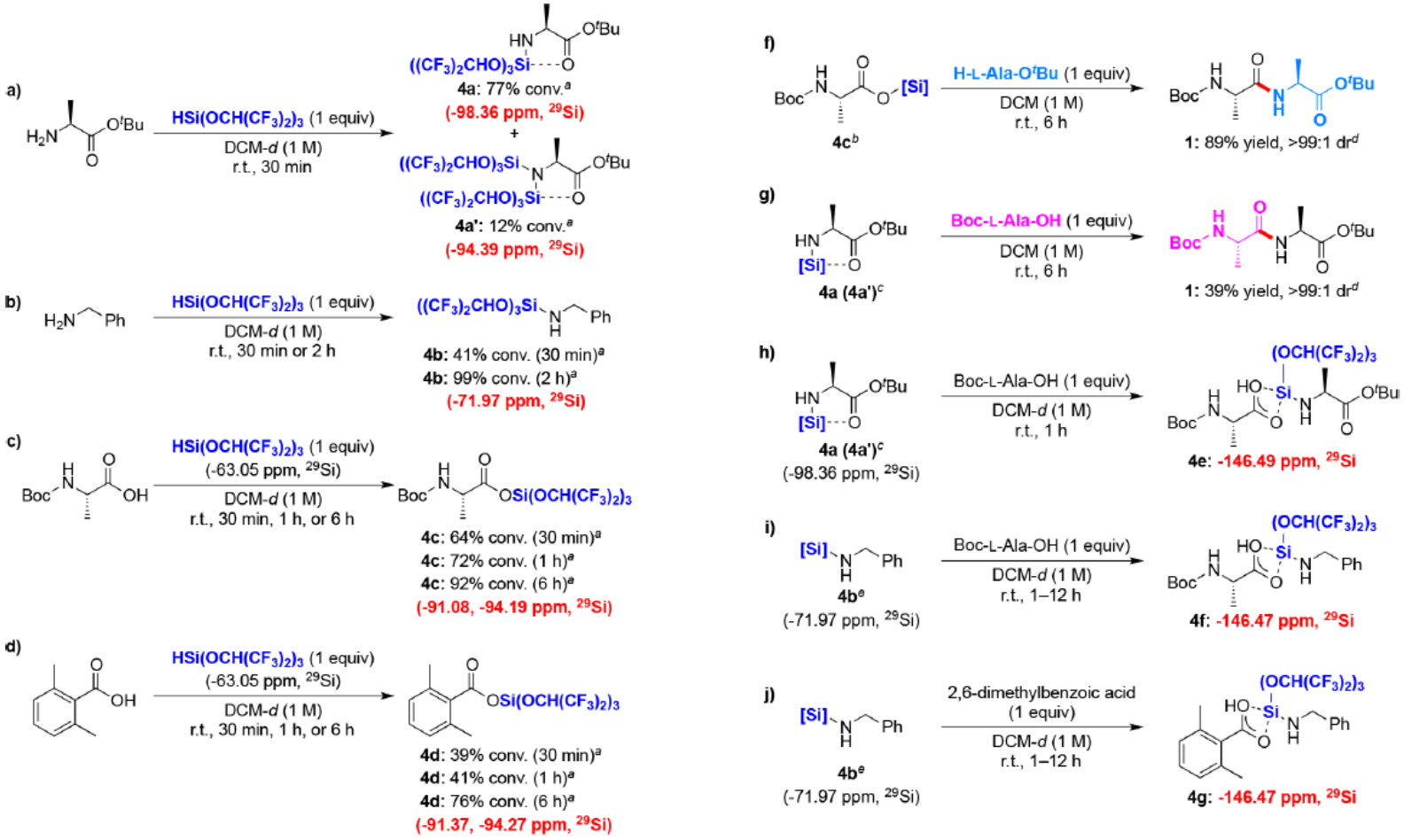


Boc-Tyr–Ala-O^{t}Bu (2l)
93% yield, >99:1 dr[a]

Hisashi Yamamoto. et al, *ACS Catal.* **2020**, *10*, 9594−9603.

Introduction

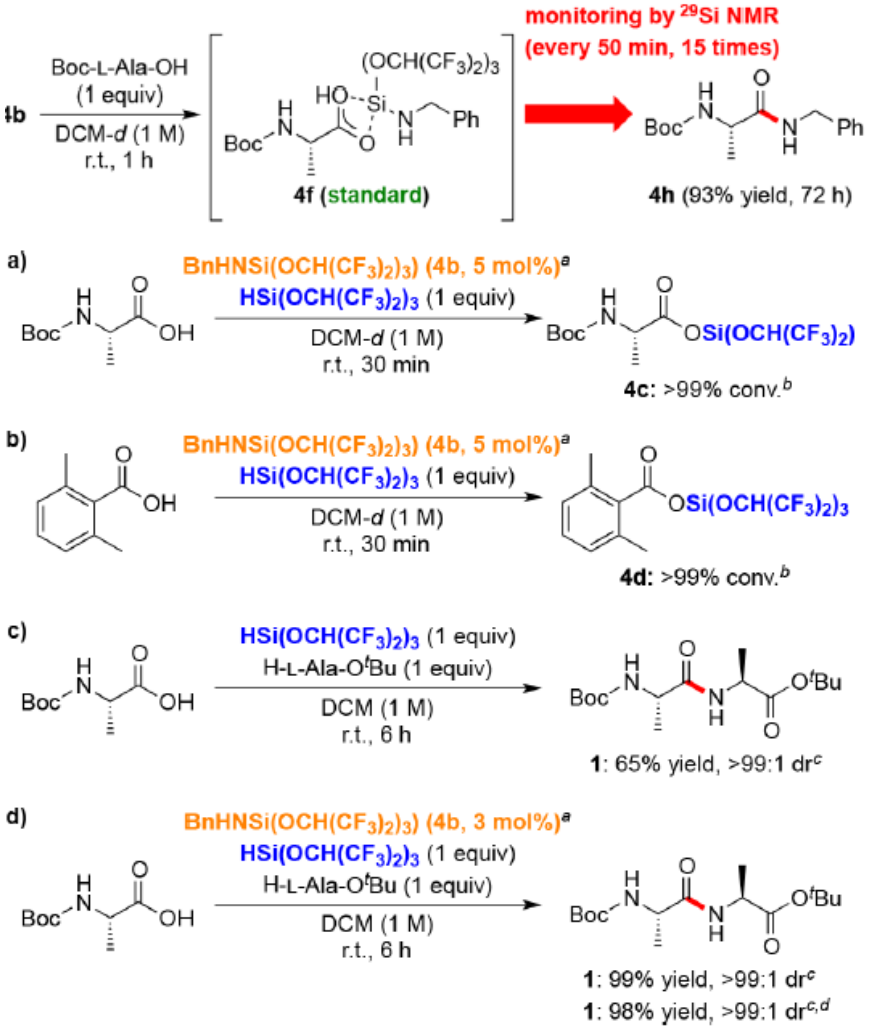
Part III: Peptide bond-formation via **Amino Acid Silyl Esters**

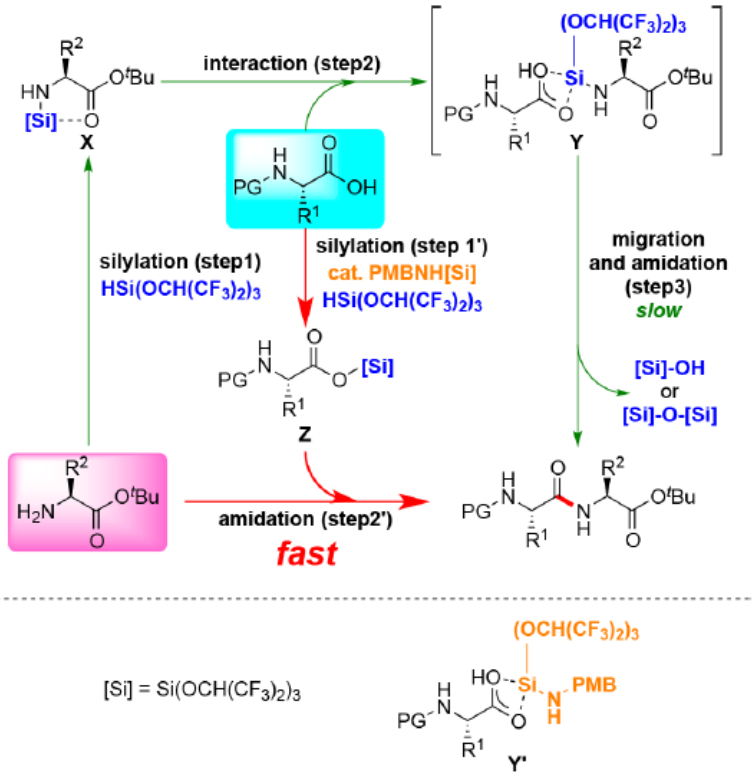


Hisashi Yamamoto. et al, *ACS Catal.* **2020**, *10*, 9594−9603.

Introduction

Part III: Peptide bond-formation via **Amino Acid Silyl Esters**

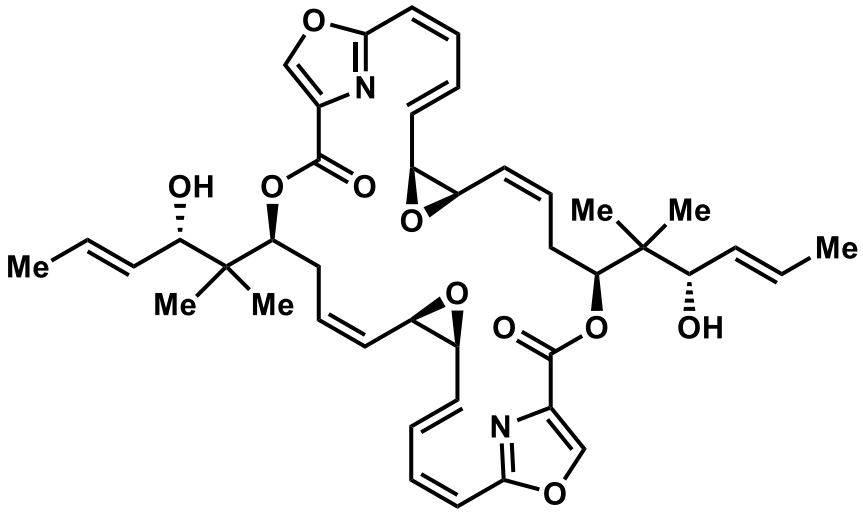




Plausible mechanistic pathway

Hisashi Yamamoto, et al, *ACS Catal.* **2020**, *10*, 9594−9603.

Streamlined Symmetrical Total Synthesis of Disorazole B_1 and It's Analogues



disorazole B_1

K. C. Nicolaou et al, *J. Am. Chem. Soc.* 10.1021/jacs.0c07094

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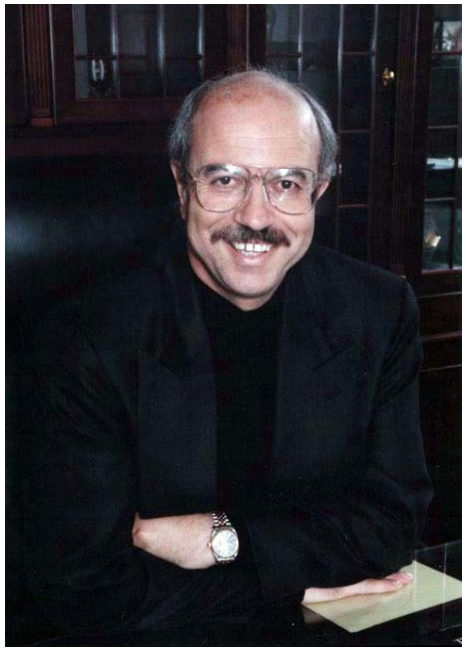
Introduction



Nicolaou, K.C.

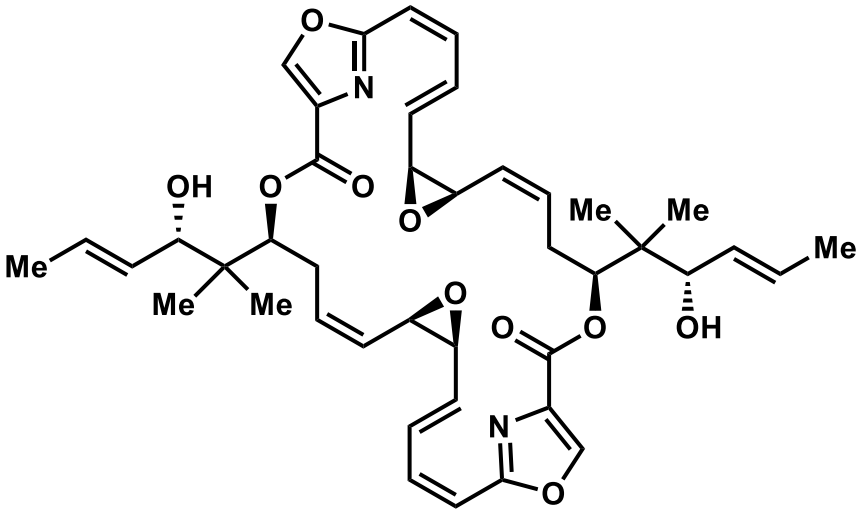
Education & Current job:

-B.S.: 1969, University of London
-Ph.D.: 1972, University of London
-Postdoctoral Fellow: 1972-1973, Columbia University
1973-1976, University of Harvard
-Professor: 1976, University of Pennsylvania
-Professor: 2013-now, Rice University

Research Interests & Areas:

- Natural Product Synthesis
- Designed Molecules for Biology and Medicine Synthesis
- Select Synthetic Methods

Introduction



disorazole B_1

Isolation

- Disorazoles, isolated from myxobacterium *Sorangium cellulosum* So ce12 in 1994.

Biological activities:

- Disorazoles, was proved to an antibiotics with high activity against Gram-positive and Gram-negative bacteria.

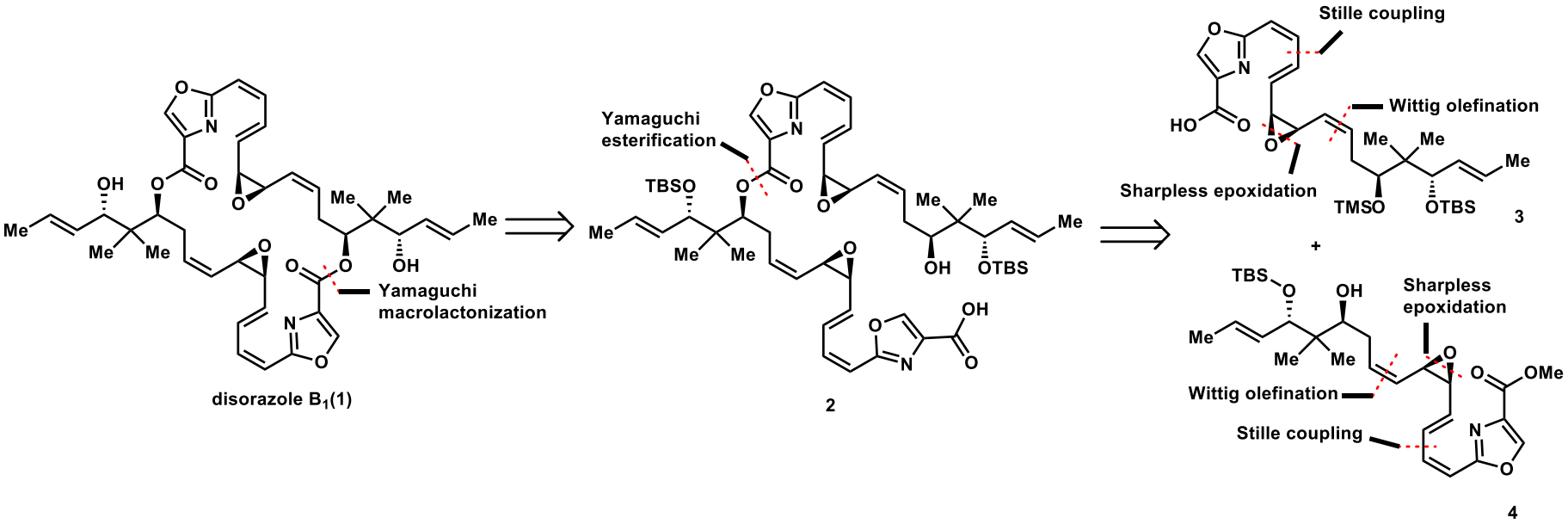
Structural features

- C2-symmetrical macrocyclic dilactones
- Two 2-pentadecyloxazol-4-carboxylic acids
- Two epoxide and two hydroxyl groups

Gerhard Hofle. et al, *Liebigs Ann. Chem.* **1994**,759-773.

Introduction

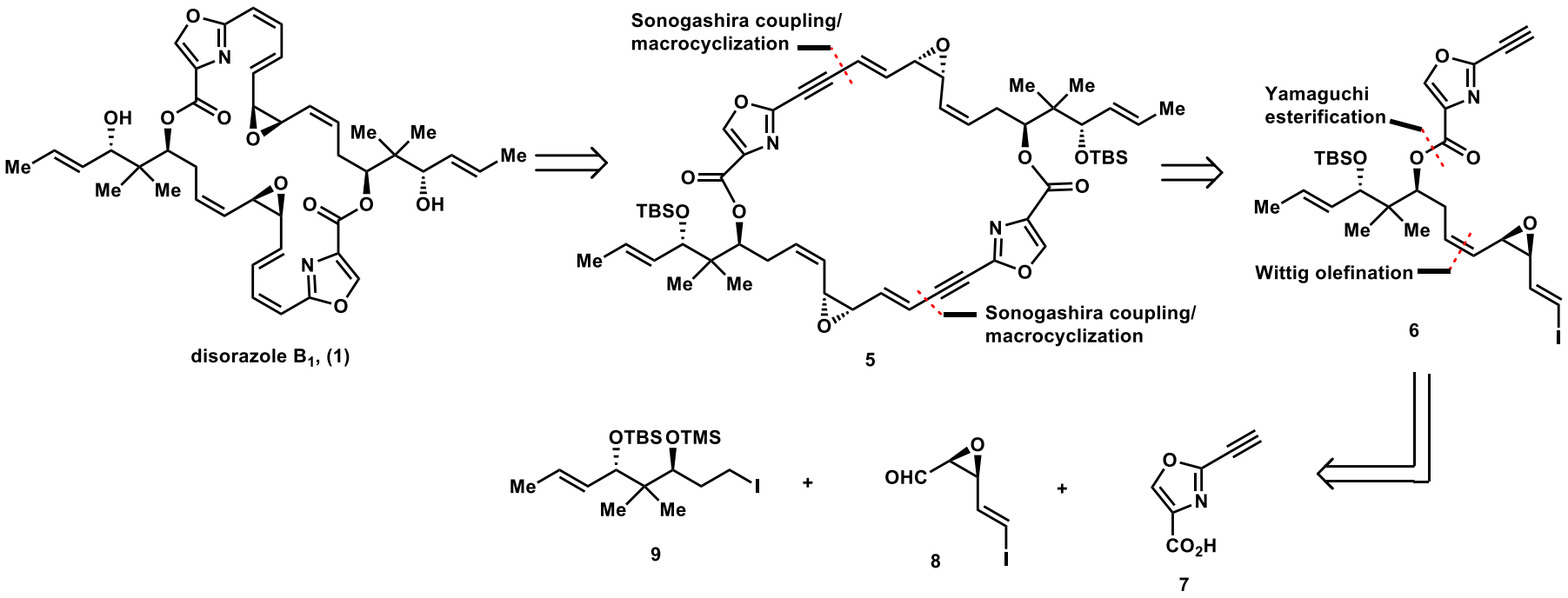
Previous stepwise total synthesis of Disorazole B1(K. C. Nicolaou, 2017):



K. C. Nicolaou et al, *J. Am. Chem. Soc.* **2017**, *139*, 15636-15639

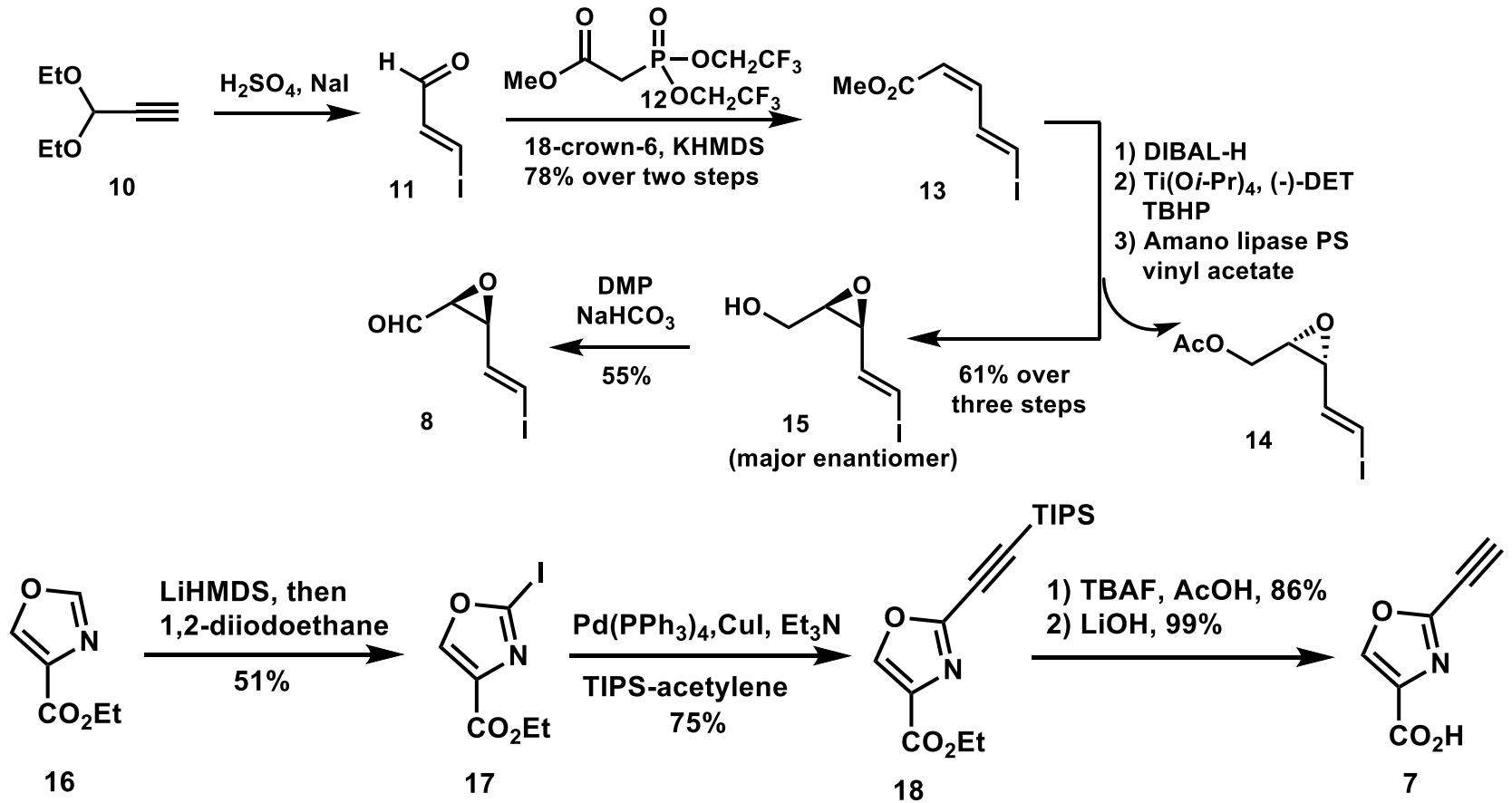
Retrosynthetic Analysis

Proposed dimerization-based total synthesis of Disorazole B1(*This work*):



Synthetic Route

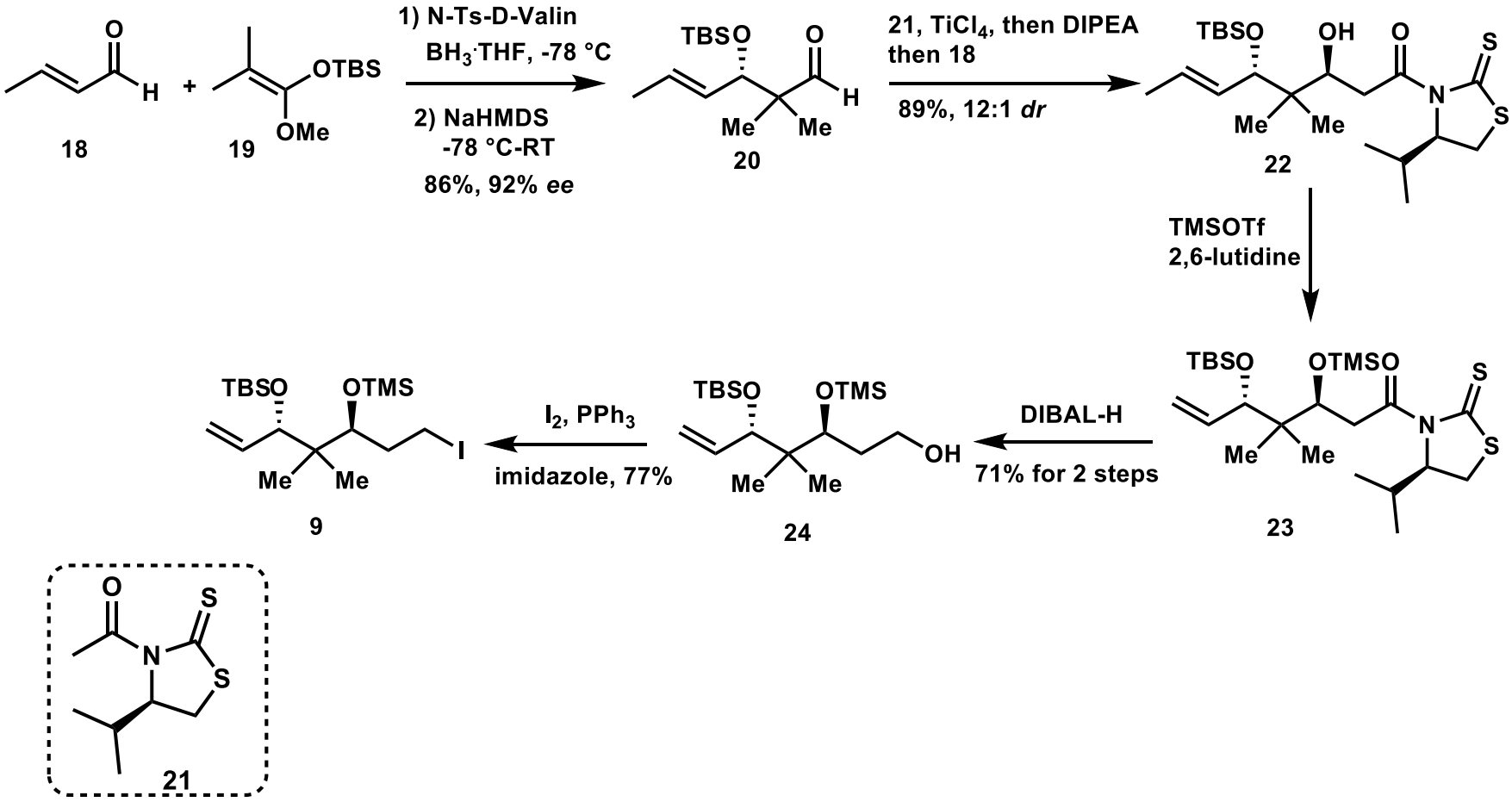
Synthesis of Fragment 7 and Fragment 8



Hong, R. et al, *J. Am. Chem. Soc.* **2017**, *139*, 12939–12942.
Aboul-Enein, H. Y. et al, *Chirality*, **2005**, *17*, 1–15.

Synthetic Route

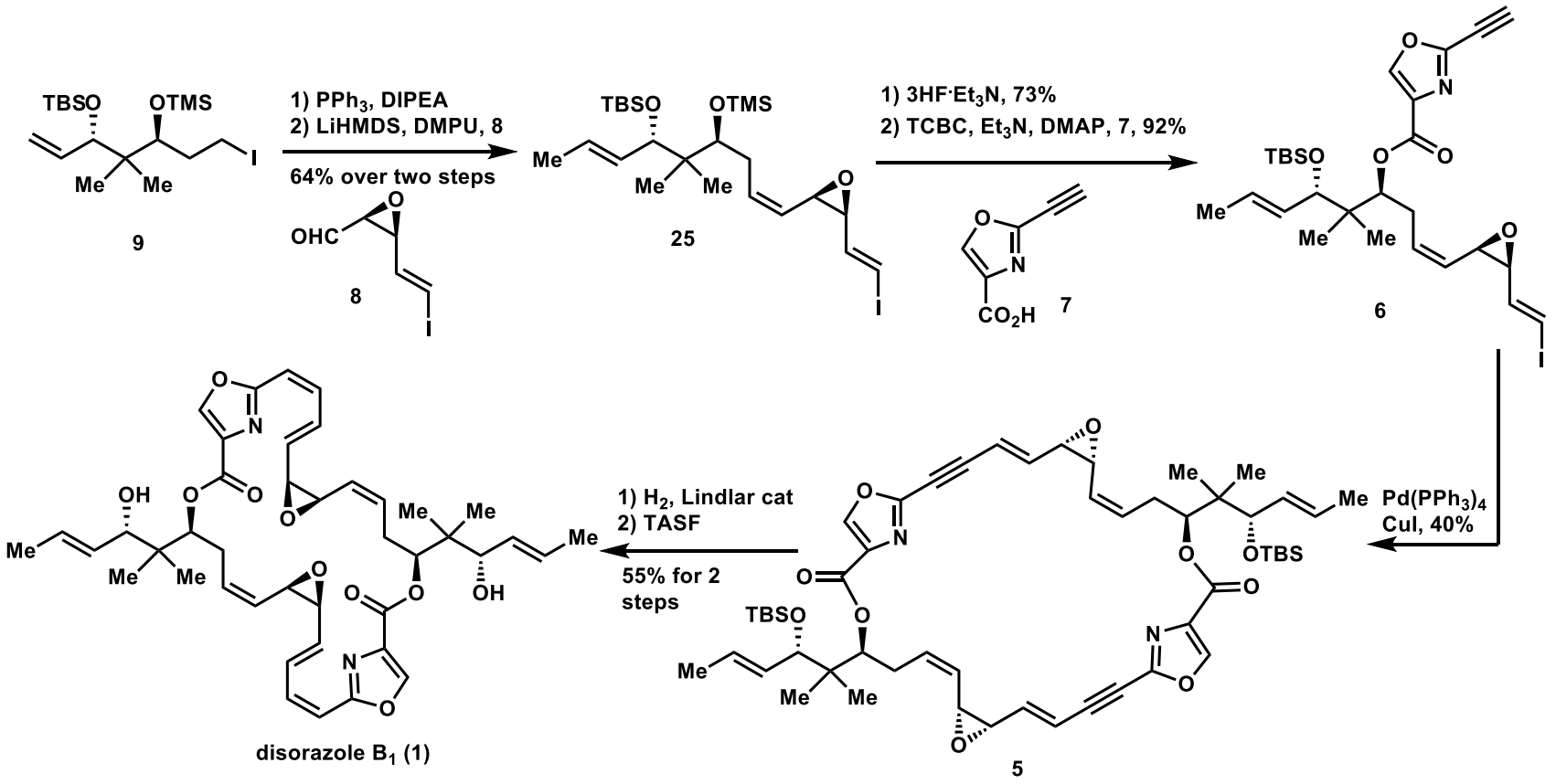
Synthesis of Fragment 9



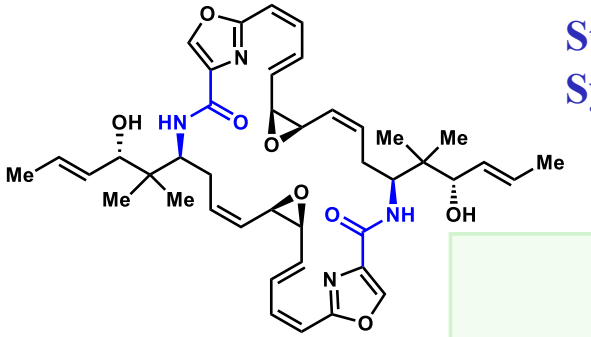
Masahito Nakano et al, *J. Org. Chem. 56*, 1991.

Synthetic Route

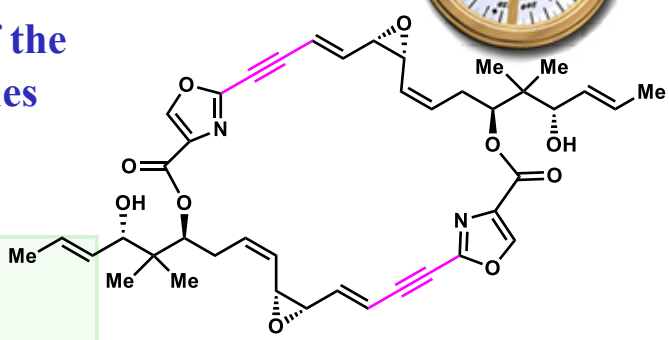
Completed total Synthesis of Disorazole B_1

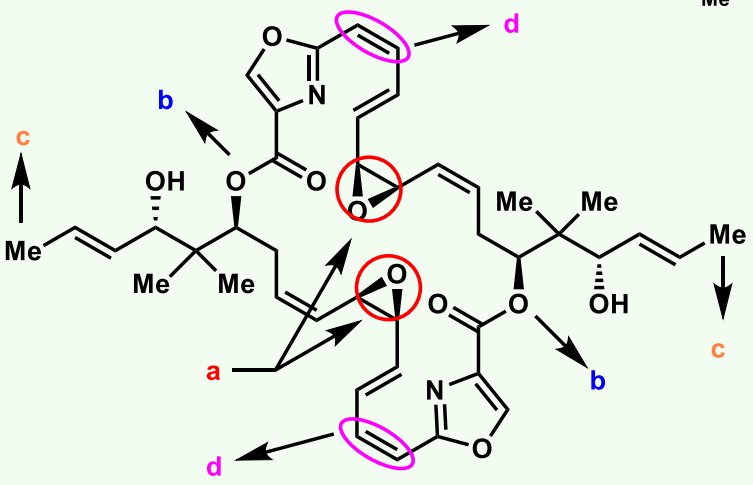


Summary

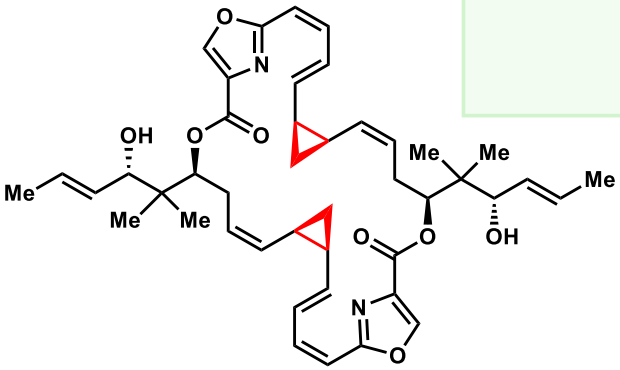


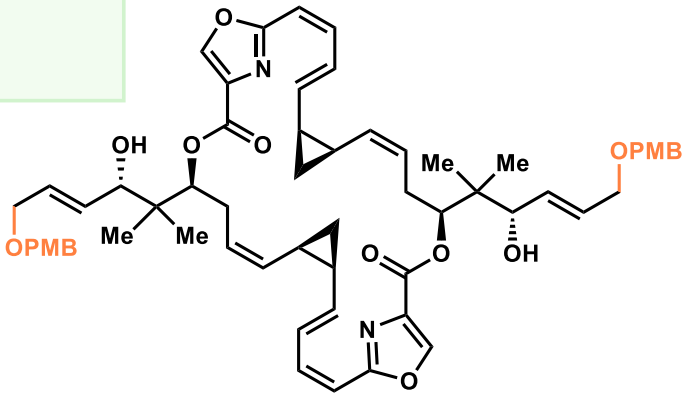
Structure–activity relationships of the Synthesized Disorazole B1 analogues





Disorazole B_1





The End

Thanks for your attention!

Acknowledgement

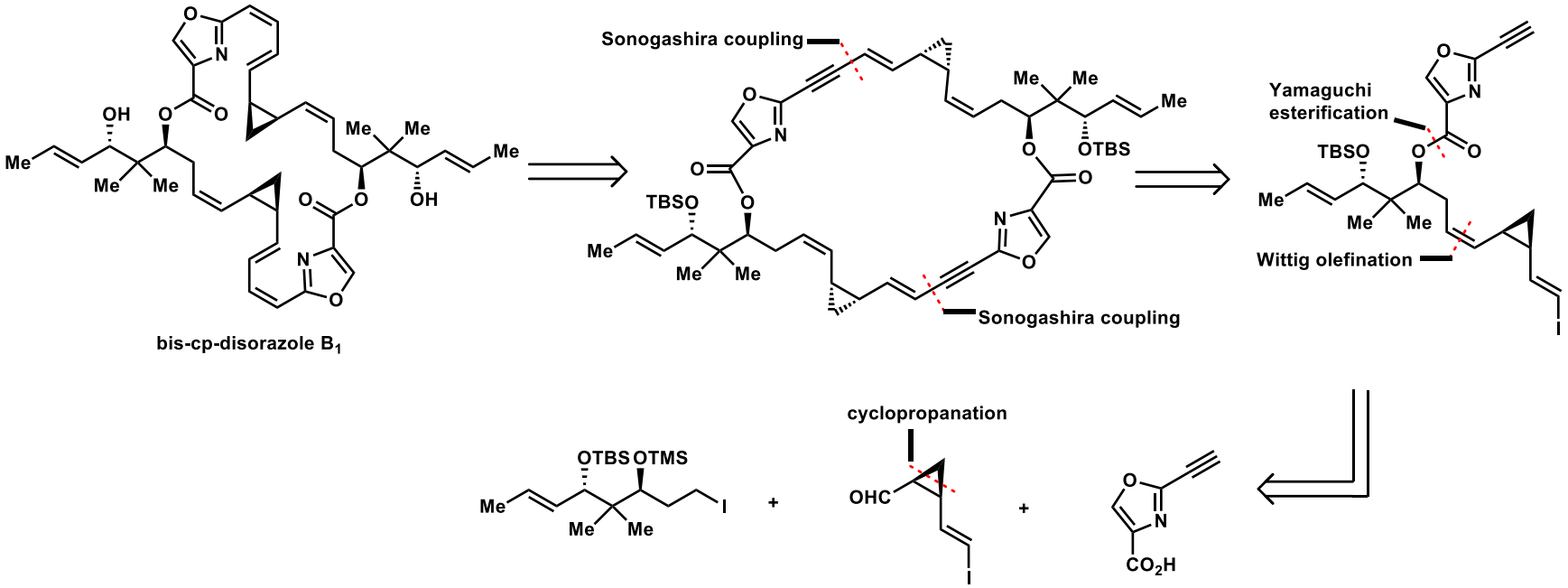
Prof. Tao Ye and Dr. Yi-an Guo;

All professors and faculties in SCBB;

All my labmates in F211!

Synthetic Route

Completed synthesis of Anhydroryanodol and formal total synthesis of Ryanodol

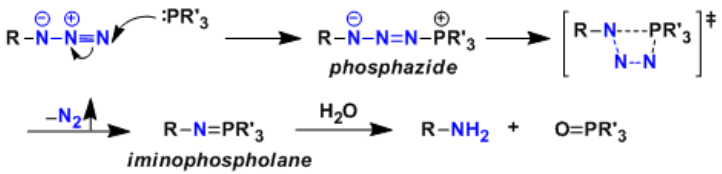


Hoveyda, A. H. et al, *J. Am. Chem. Soc.* **2000**, *122,* 8168−8179.

Supporting Materials

Staudinger Reaction

参考：*J. Org. Chem.* **2004**, *69* , 4299. *J. Am. Chem. Soc.* **2005**, 127, 2686.



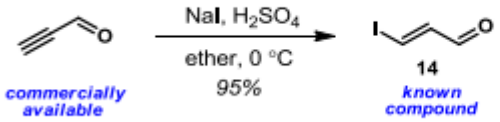
- 反应实例

Staudinger-Bertozzi配合[1]：Bertozzi等将叠氮化物与以下的膦试剂反应，成功将荧光试剂与强固的酰胺连接。这一化学修饰法以高收率、高化学选择性进行、能用于多种生物化学研究

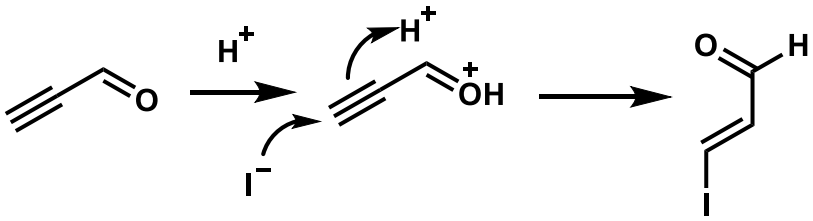
Traceless Staudinger Ligation[2]：需要Cys残基组Native Chemical Ligation没有特别的制约。

Supporting Materials

Synthesis vinyl iodide aldehyde

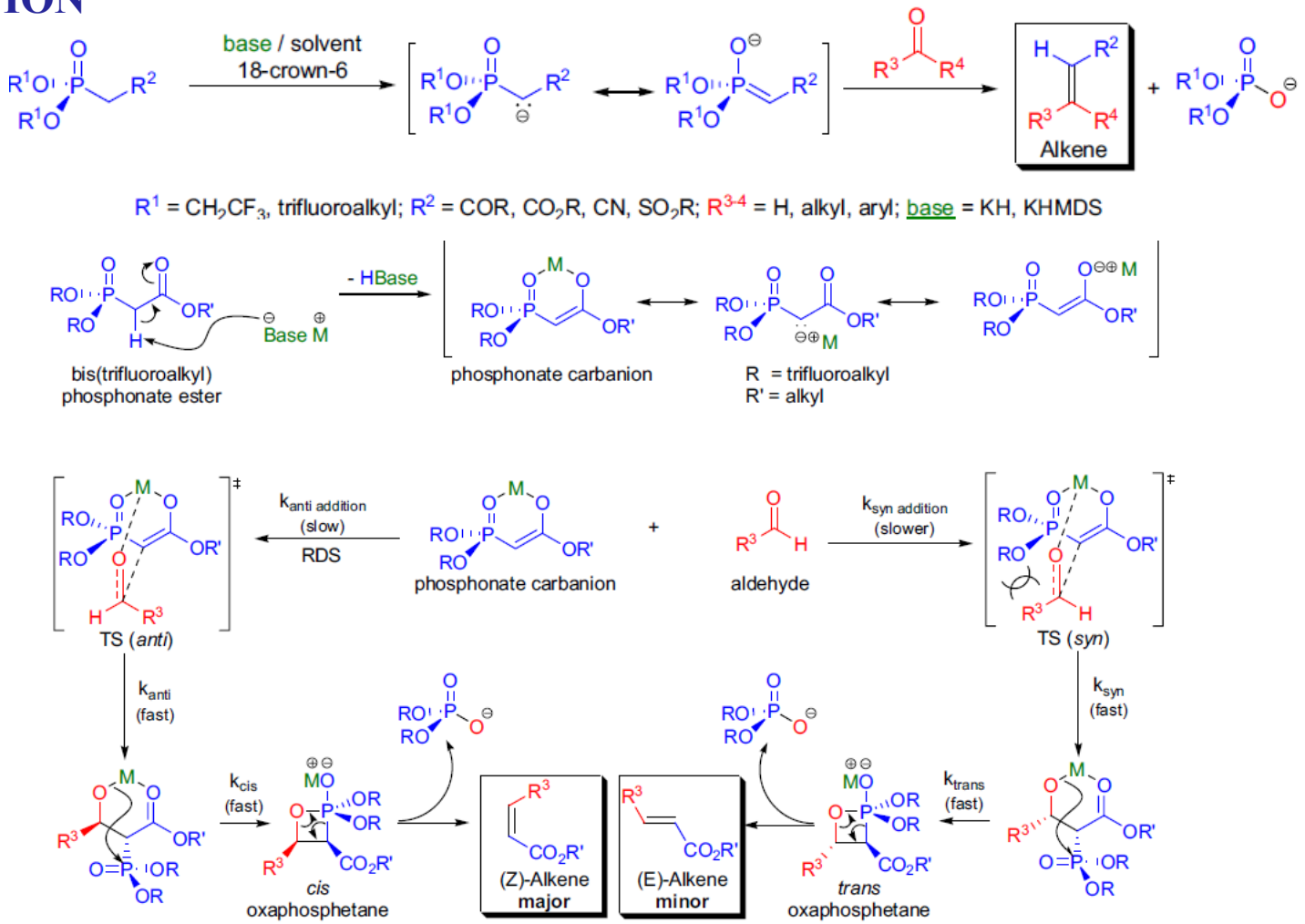


[The reaction can be readily run in decagram scale if needed.]



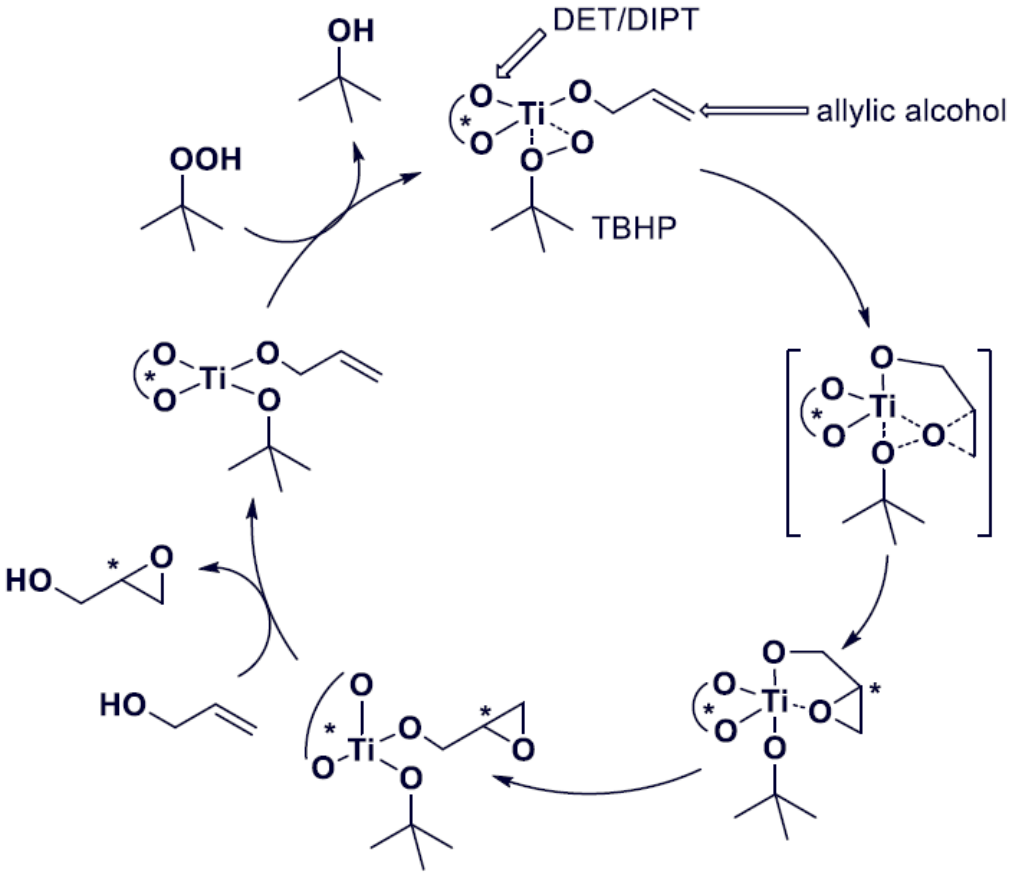
Supporting Materials

HORNER-WADSWORTH-EMMONS OLEFINATION – STILL-GENNARI MODIFICATION

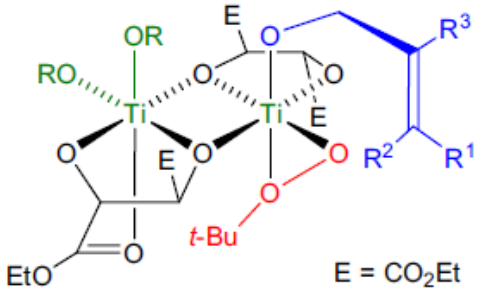


Supporting Materials

SHARPLESS ASYMMETRIC EPOXIDATION



Transition state of epoxidation:



$$\text{Rate} = \frac{[\text{Ti}(\text{O}i\text{-Pr})_2(\text{DET})]\,[\text{TBHP}]\,[\text{ROH}]}{[i\text{-PrOH}]^2}$$

Supporting Materials

Chiral Recognition by Lipases

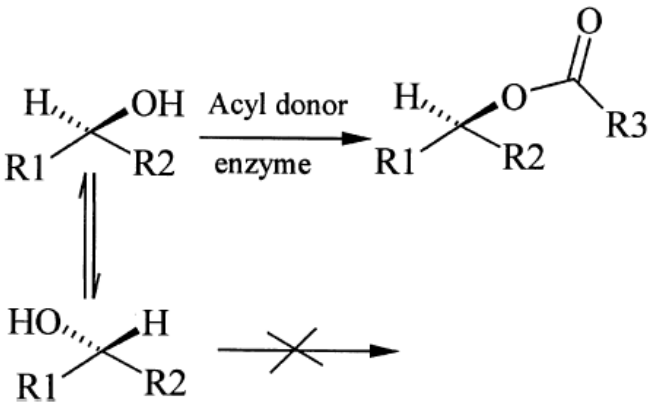


Fig. 5. Dynamic kinetic resolution of secondary alcohols.

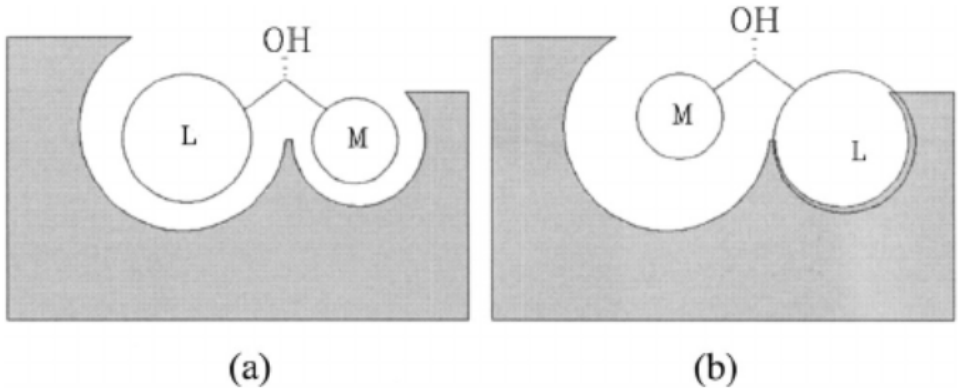
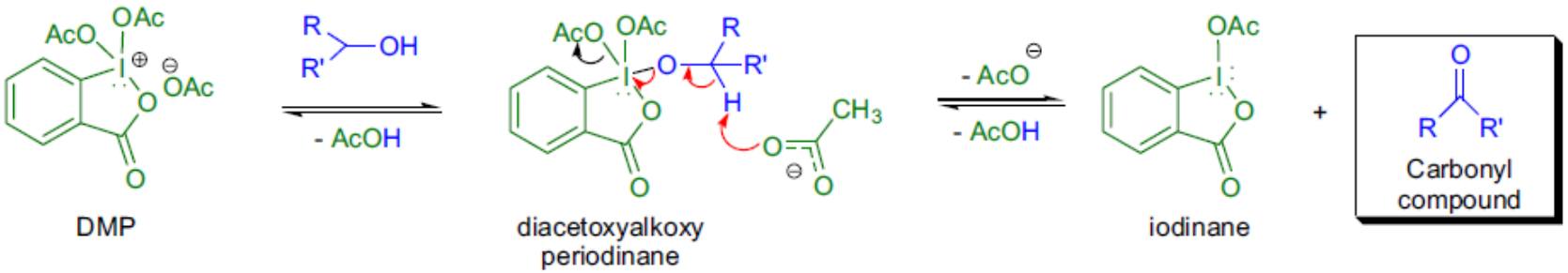


Fig. 6. The fast reacting enantiomer (**a**) and the slow reacting one (**b**) in the active side model for lipases derived from Kazlauskas' rule.

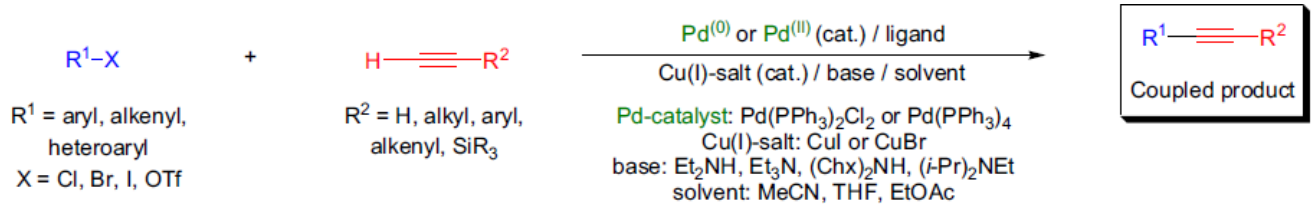
Supporting Materials

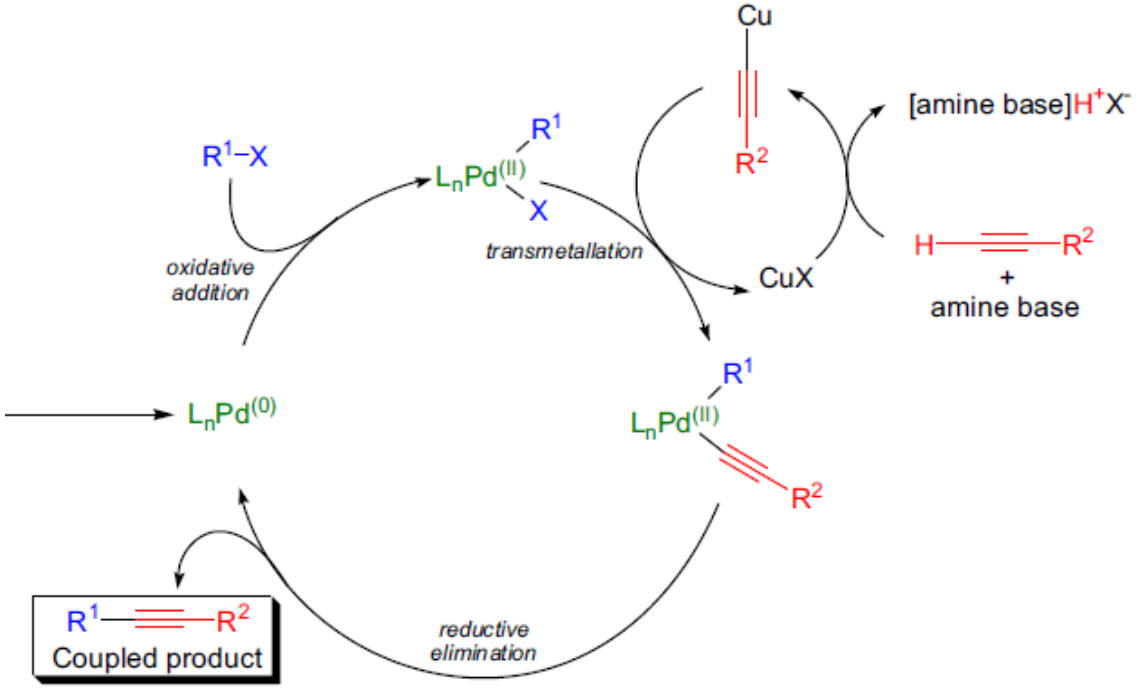
DESS-MARTIN OXIDATION



Supporting Materials

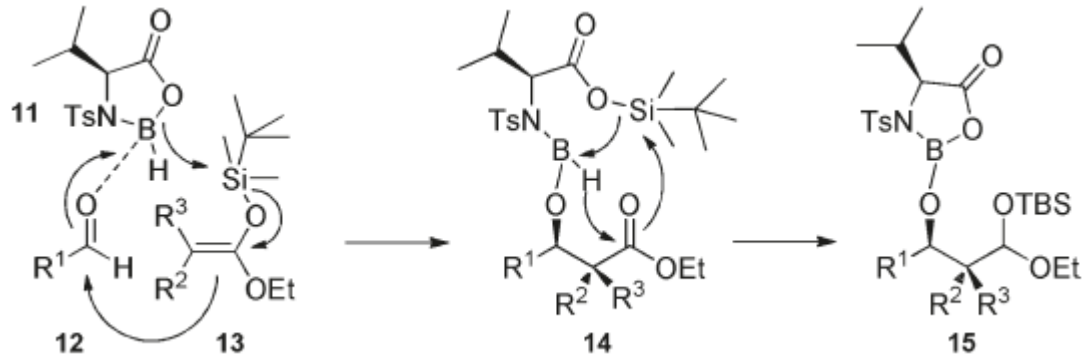
SONOGASHIRA CROSS-COUPLING

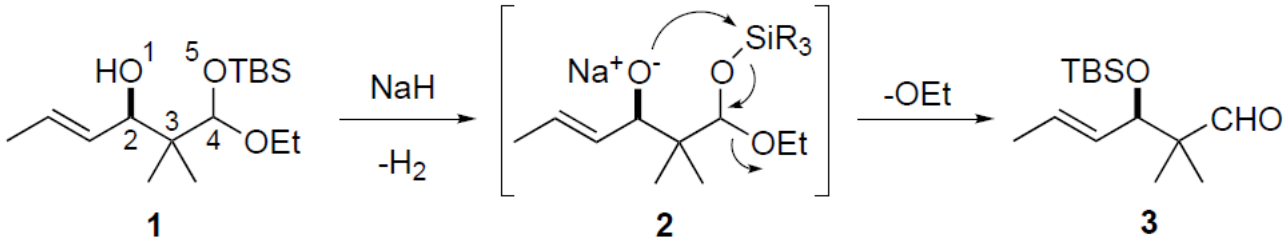




Supporting Materials

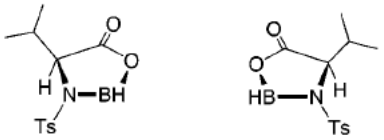
Kiyooka Aldol Reaction

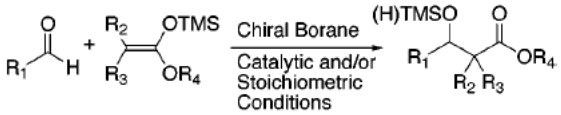


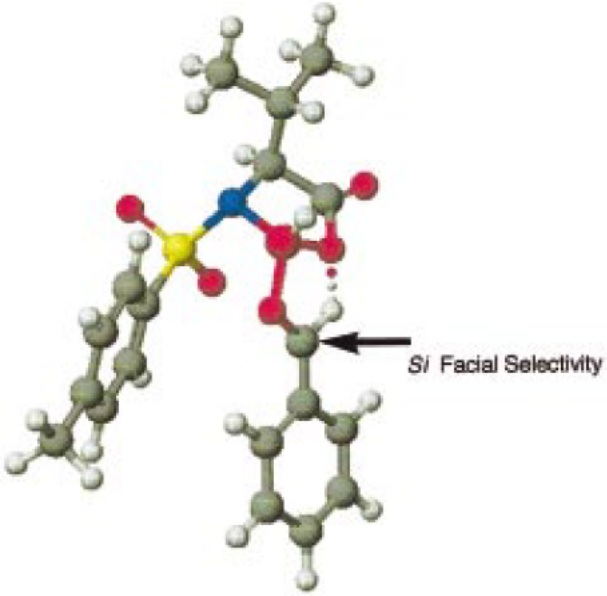


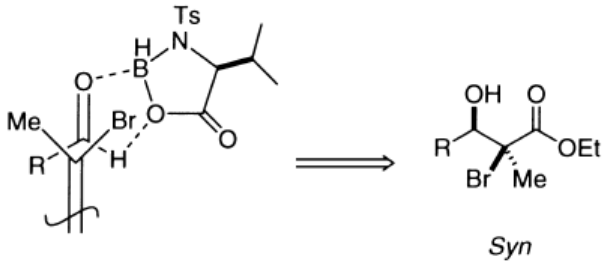
Supporting Materials

Kiyooka Aldol Reaction

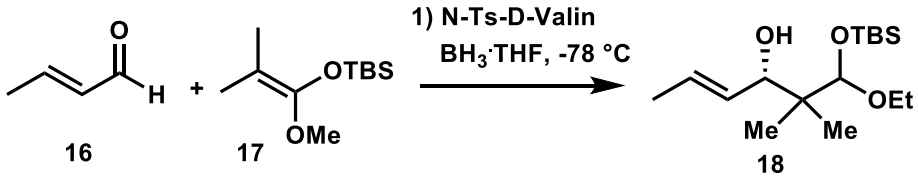






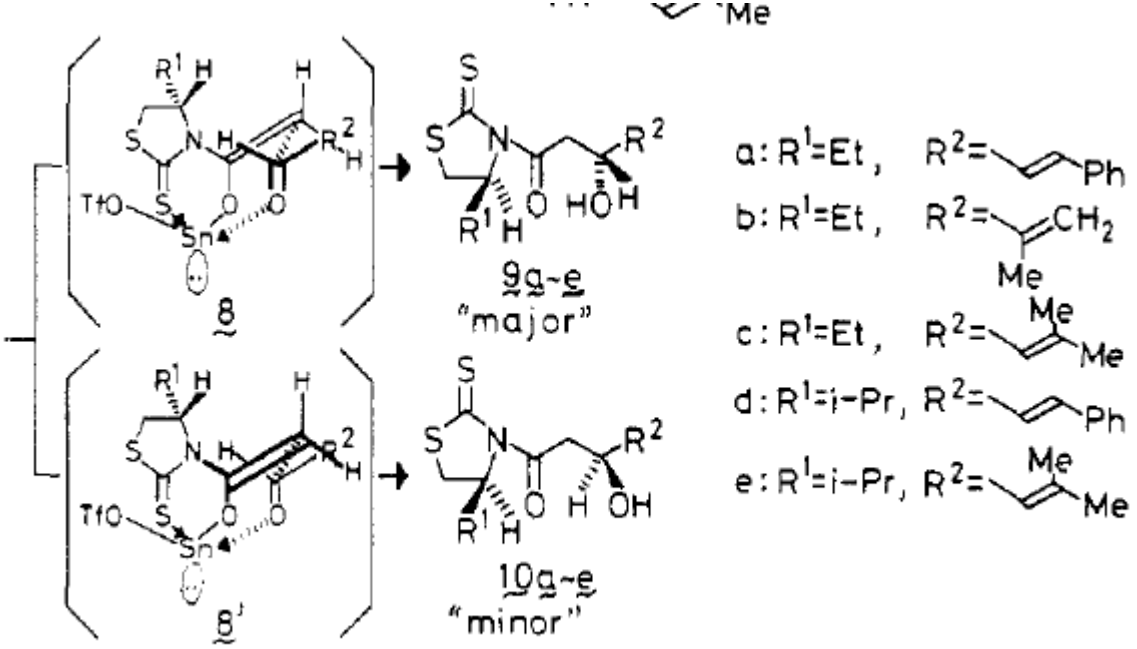


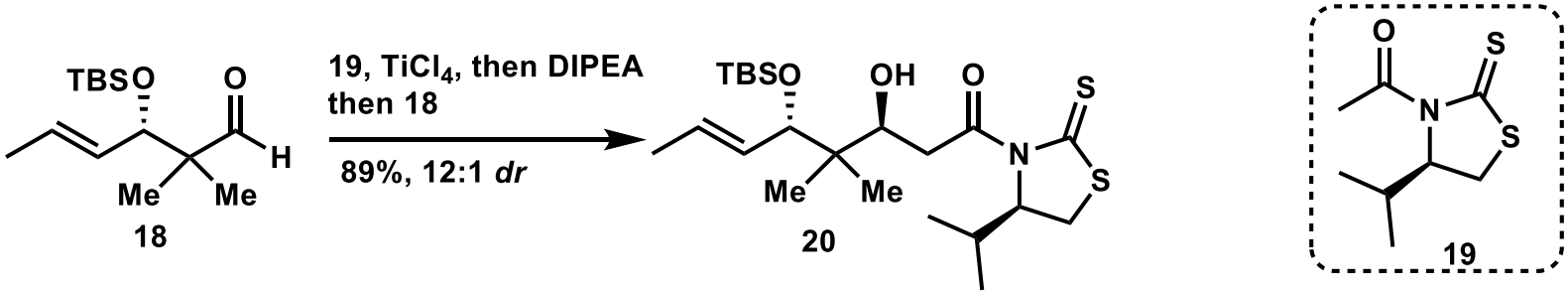
Scheme 2. A transition state assembly to *syn*



Supporting Materials

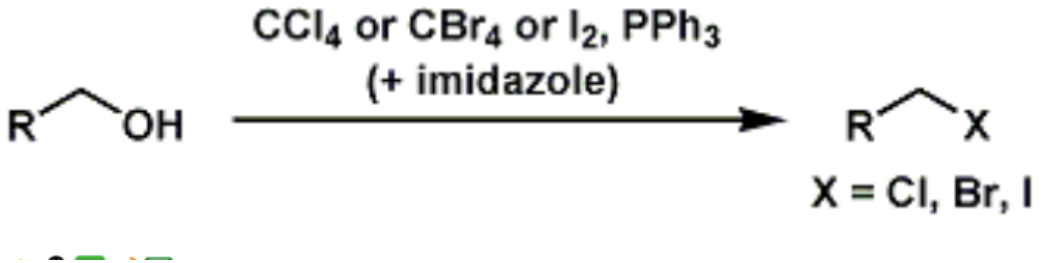
Nagao-Aldol Reaction





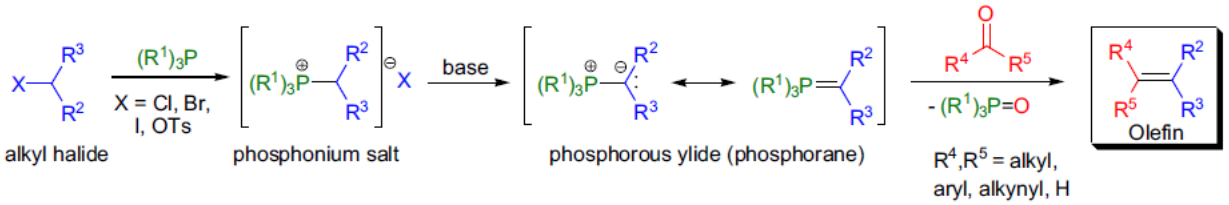
Supporting Materials

Appel reaction



Supporting Materials

WITTIG REACTION

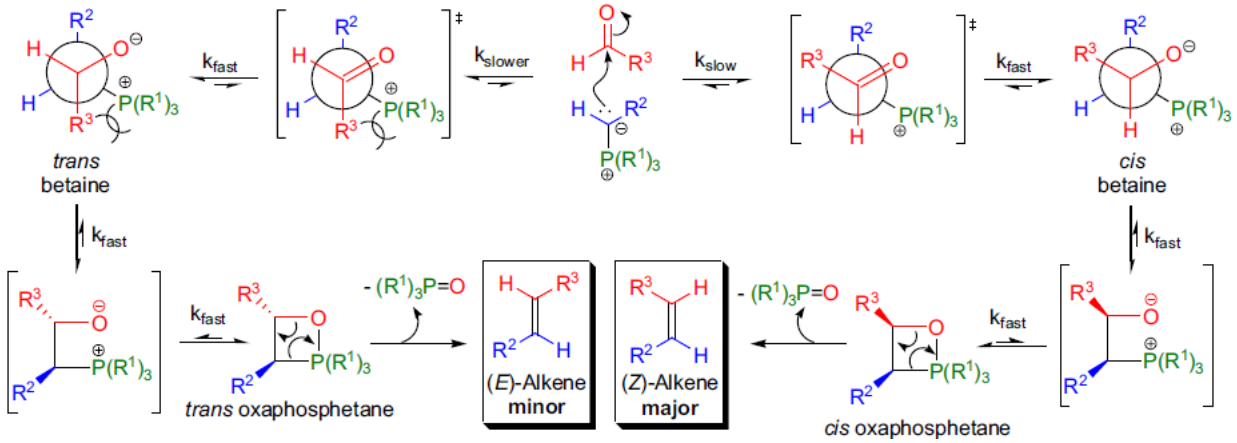


if R^1 = aryl and R^2, R^3 = alkyl, H ⟹ "nonstabilized" ylide

if R^1 = aryl and R^2, R^3 = aryl, alkenyl, benzyl, allyl, H ⟹ "semi-stabilized" ylide

if R^1 = aryl and R^2, R^3 = $-CO_2R$, $-SO_2R$, -CN, -COR ⟹ "stabilized" ylide

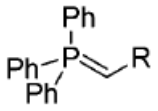
Mechanism: [9,23,74-77,28,78-82,37]



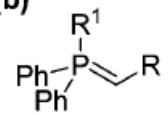
Supporting Materials

WITTIG REACTION

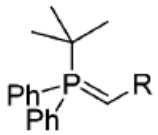
Non-stabilised ylides

(a) 

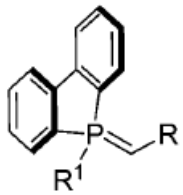
Very high *Z*

(b) 

Moderate *Z*-selectivity

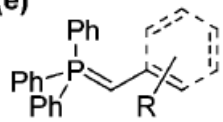
(c) 

Very high *Z*

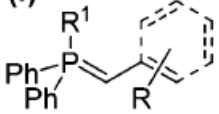
(d) 

Very high *E*

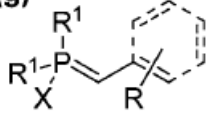
Semi-stabilised ylides

(e) 

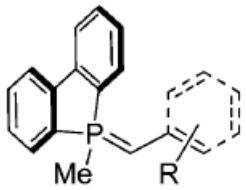
Minor selectivity for *E* or *Z*

(f) 

Moderate to high *E*

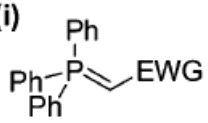
(g) 

Very high *E*

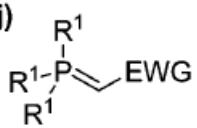
(h) 

Very high *E*

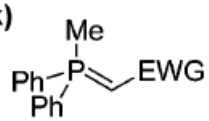
Stabilised ylides

(i) 

Very high *E*

(j) 

Very high *E*

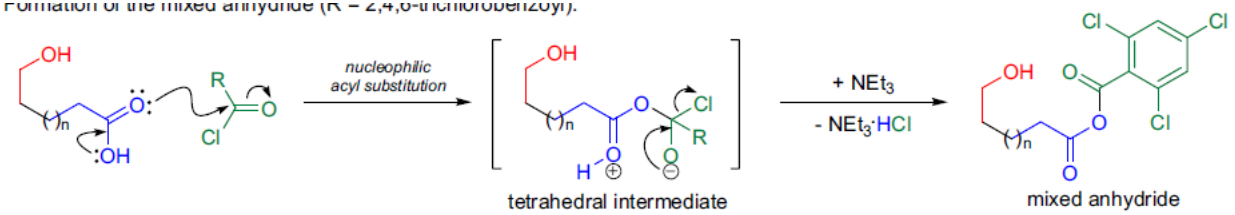
(k) 

High *E*

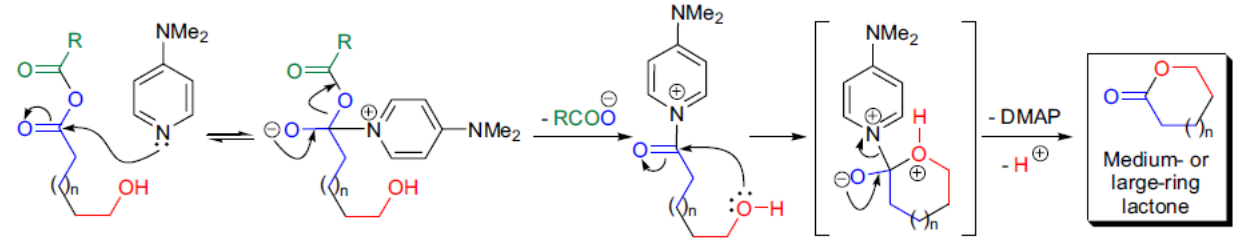
Declan G. Gilheany et al, *Chem. Soc. Rev.*, **2013**, *42*, 6670-6696.

Supporting Materials

YAMAGUCHI MACROLACTONIZATION



Formation of the macrolactone (R = 2,4,6-trichlorobenzoyl):



Supporting Materials

Removal of the PMB ether