北京大学
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ASAP Report

Reporter: Yangyang Jiang

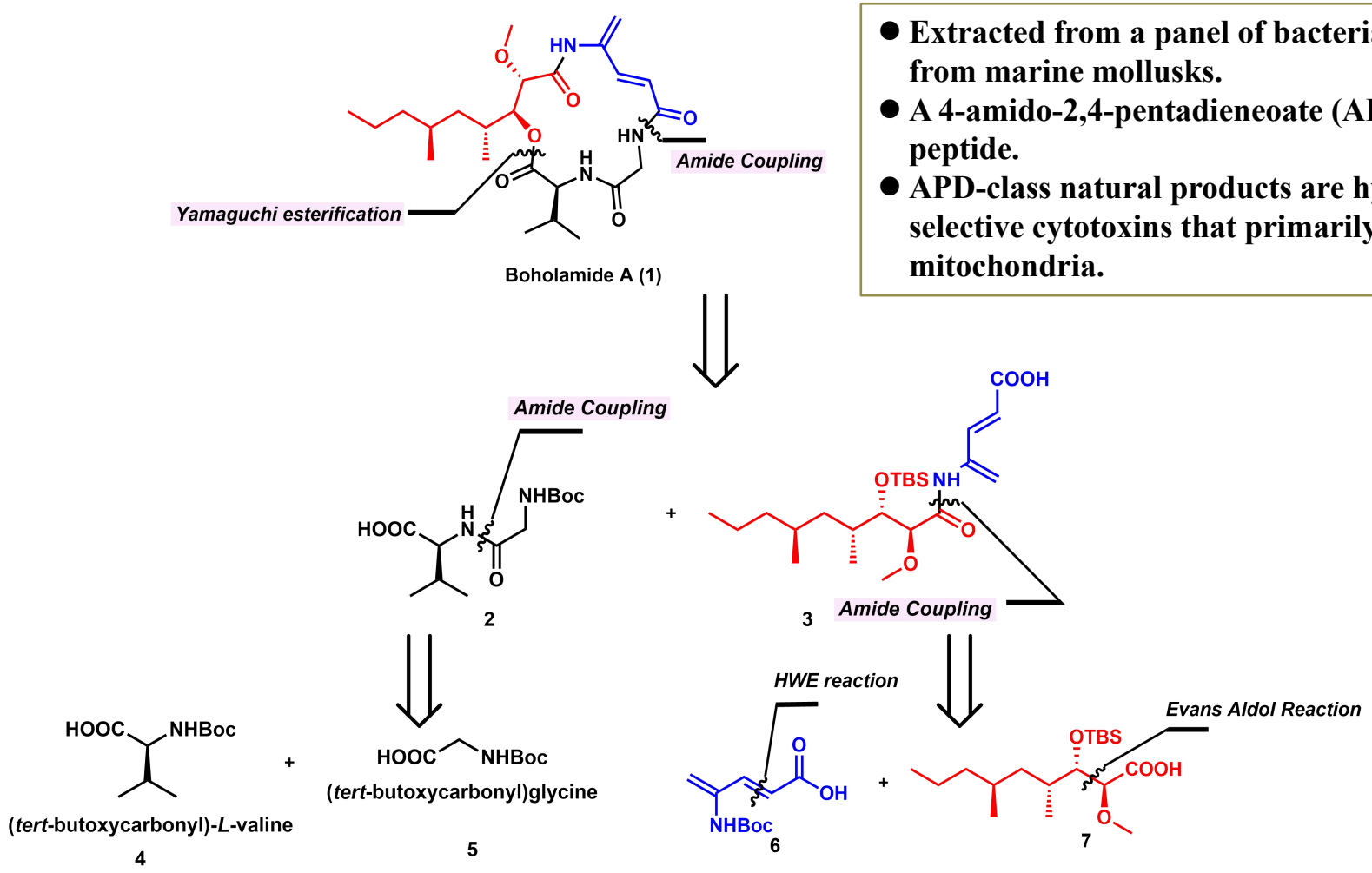
Supervisors: *Prof.* Tao Ye

***Dr.* Yian Guo**

October 5, 2020

Introduction

Part I :Retrosynthetic analysis of Boholamide A

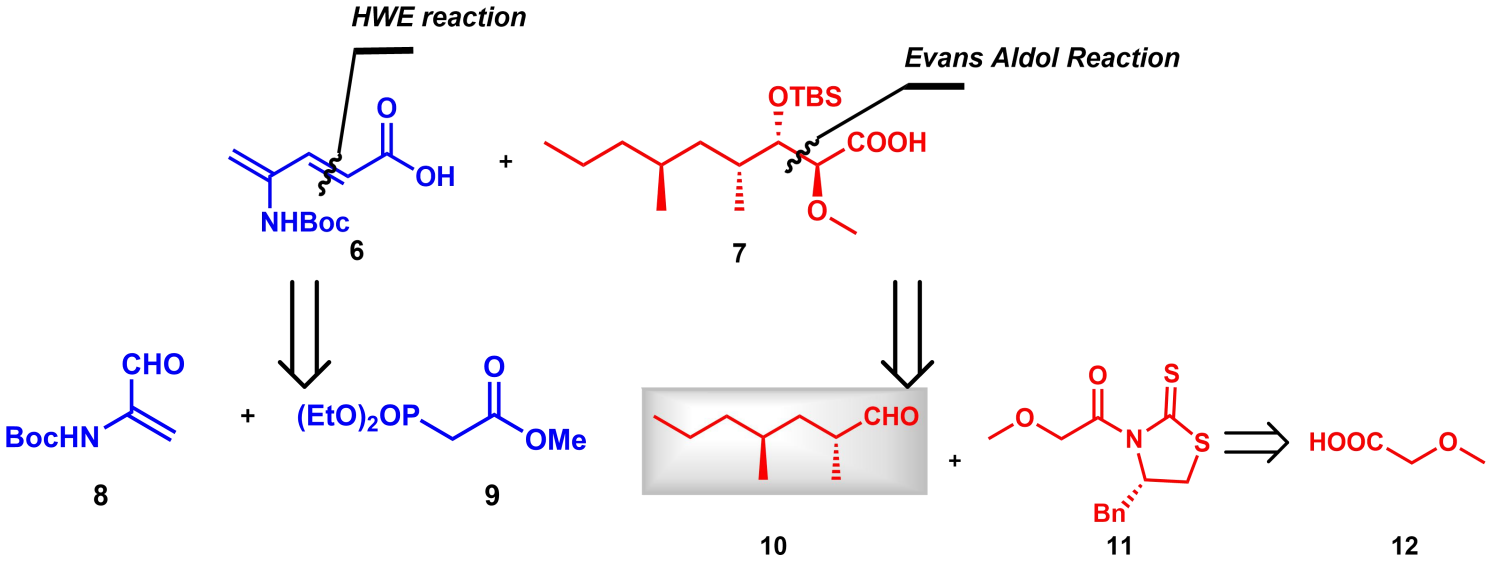


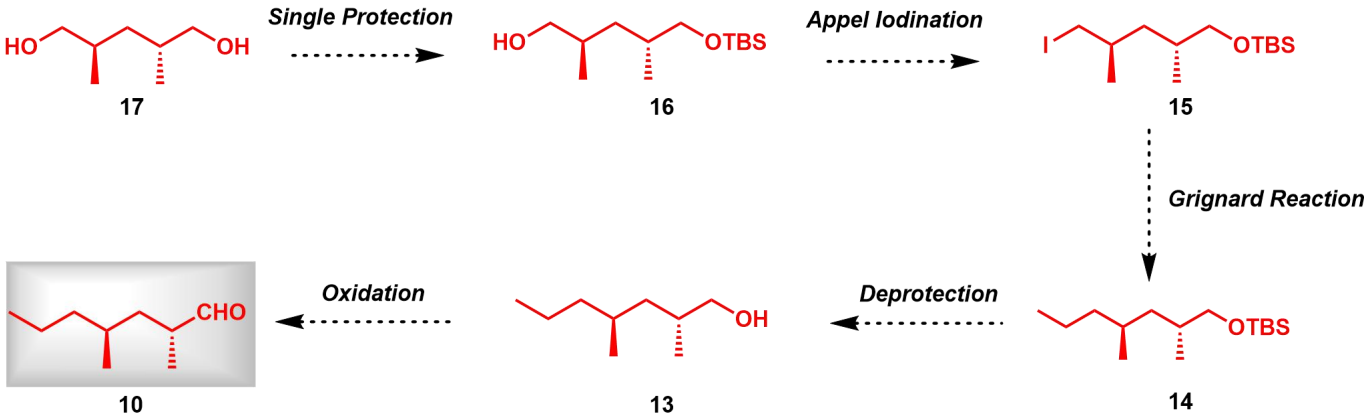
- Extracted from a panel of bacteria isolated from marine mollusks.
- A 4-amido-2,4-pentadieneoate (APD)-class peptide.
- APD-class natural products are hypoxia-selective cytotoxins that primarily target mitochondria.

Torres, Joshua P. et al, *J. Nat. Prod.* **2020**, *83,* 1249-1257.

Introduction

Part I :Retrosynthetic analysis of Boholamide A

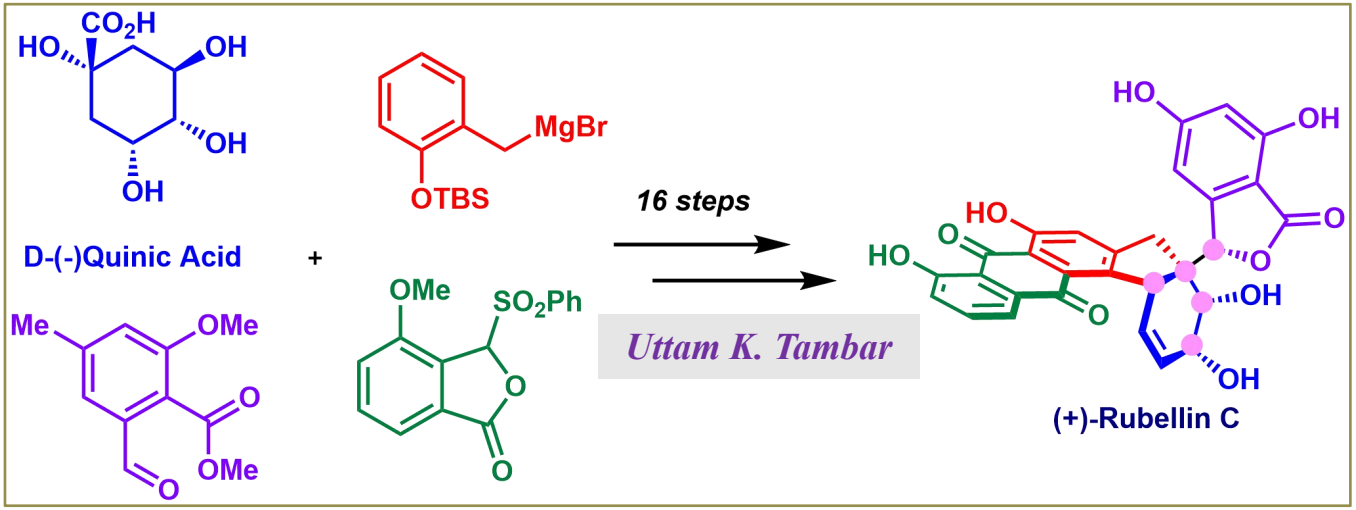




Torres, Joshua P. et al, *J. Nat. Prod.* **2020**, *83,* 1249-1257.
Evans D.A. et al, *J. Am. Chem. Soc*. **2002**, *124*, 392-393.

Introduction

Part II:Total synthesis of (+)-Rubellin C



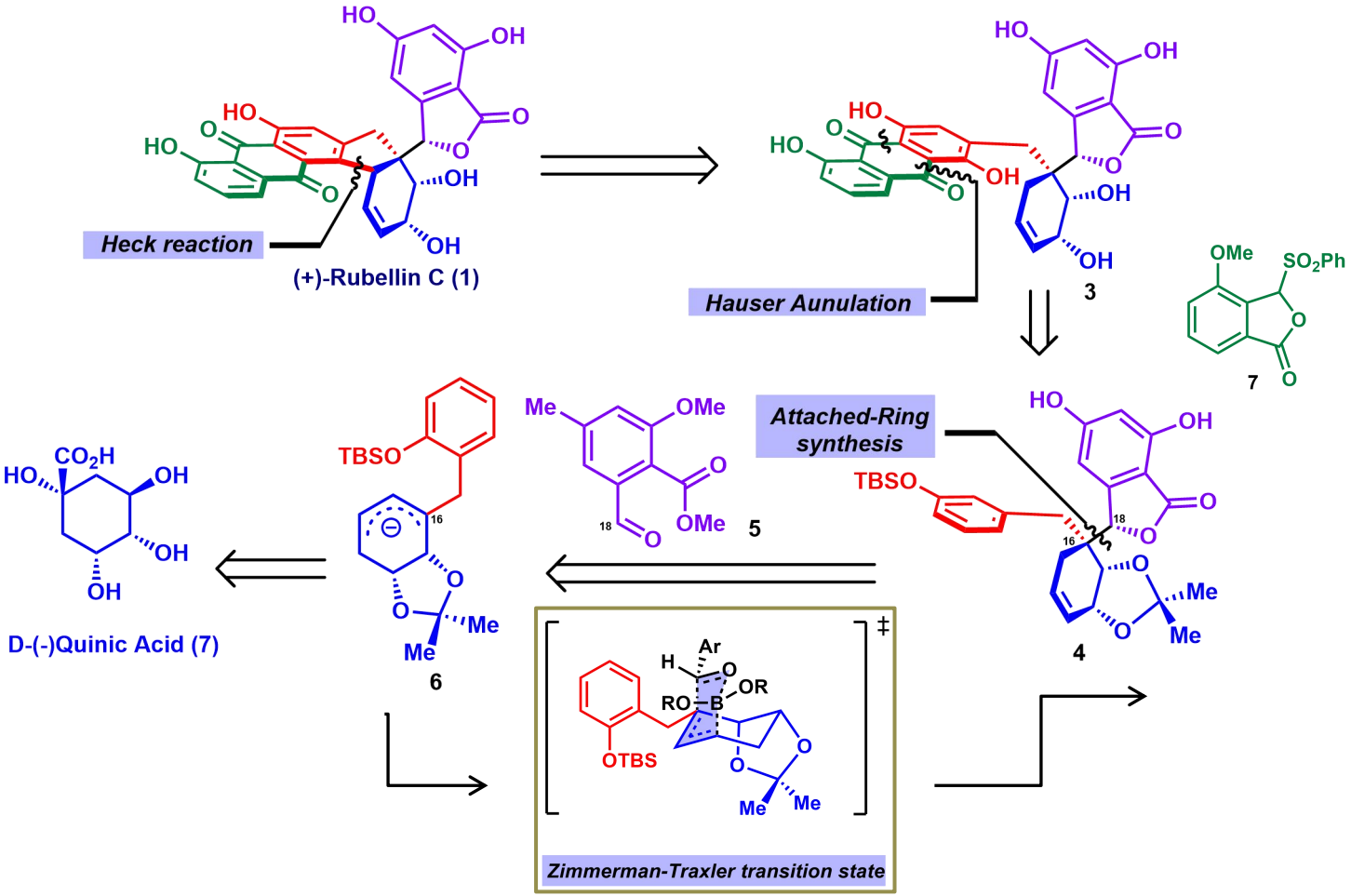
Synthetic Challenge:

- **-unprecedented topplogy**
- **-5 contiguous stereocenters**
- **-quaternary carbon stereocenter**
- **-functionalized anthraquinone**

Uttam K. Tambar. et al, *Org. Lett.* **2020**, *6*, 2954−2963.

Introduction

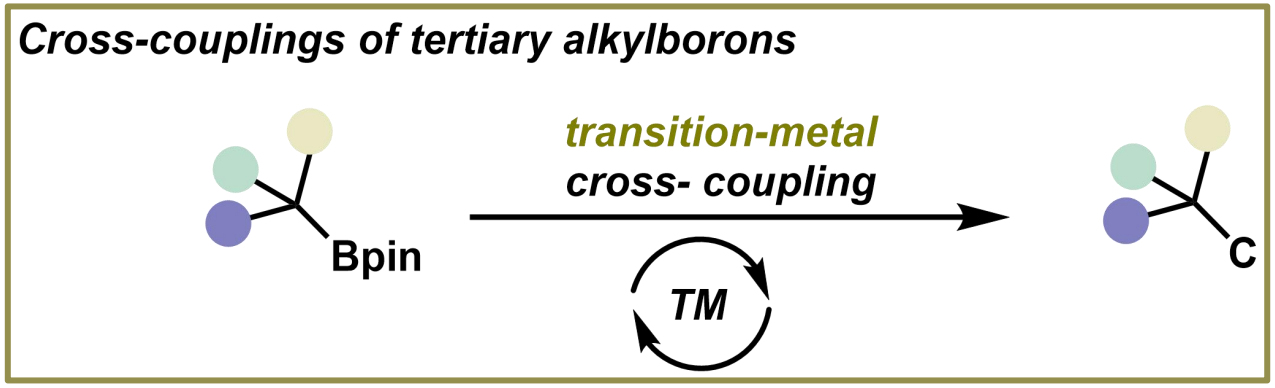
Part II:Total synthesis of (+)-Rubellin C



Uttam K. Tambar. et al, *Org. Lett.* **2020**, *6*, 2954−2963.

Introduction

Part III :Transition-Metal-Free Cross-Coupling Using Tertiary Benzylic Organoboronates



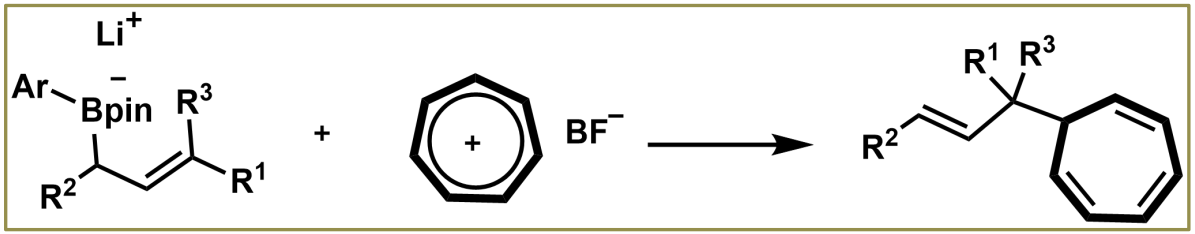
Problemematic steps

- **transmetalation： the slow transmetalation from sterically encumbered nucleophiles**
- **reductive elimination： β-hydride elimination**

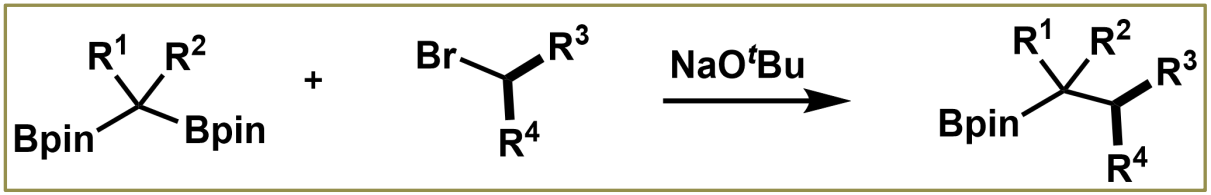
Hirohisa Ohmiya. et al, *Angew. Chem. Int. Ed.* **2020**

Introduction

Aggarwarl's work（2011）



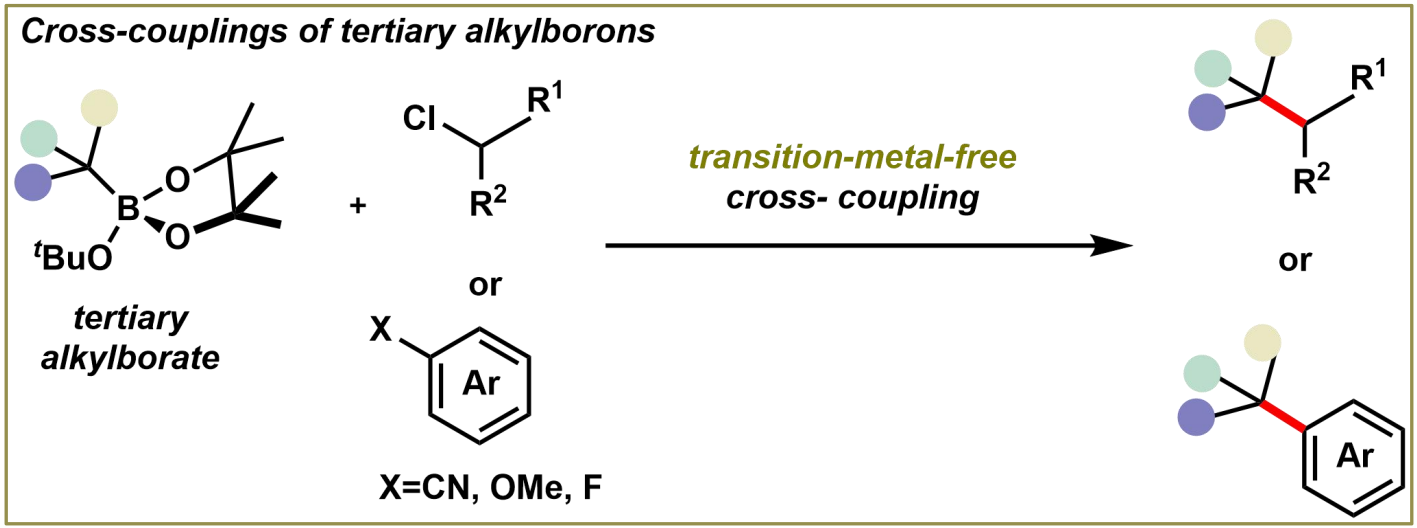
Morken's work（2014）



Hirohisa Ohmiya. et al, *Angew. Chem. Int. Ed.* **2020**

Introduction

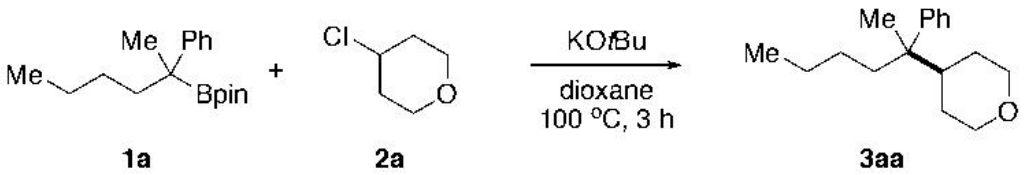
Tertiary alkylative cross-coupling of alkyl or aryl electrophiles (this work)



Hirohisa Ohmiya. et al, *Angew. Chem. Int. Ed.* **2020**

Introduction

Screening of conditions for cross-coupling between 1a and 2a.



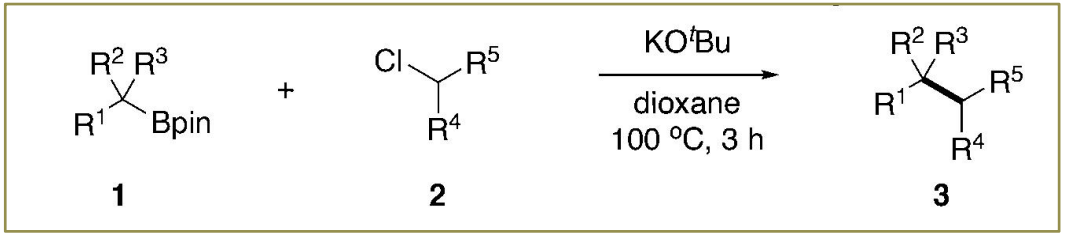
1a **2a** **3aa**

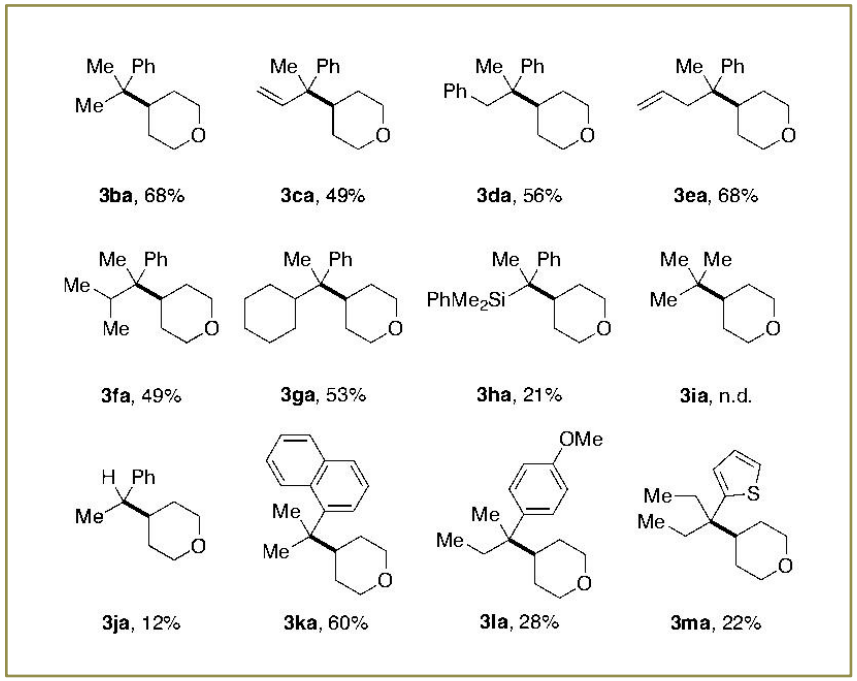
Entry	Change from standard conditions	Yield (%) of **3aa**[b]
1	none	97 (87)
2	NaO*t*Bu instead of KO*t*Bu	53
3	LiO*t*Bu instead of KO*t*Bu	0
4	KHMDS instead of KO*t*Bu	47
5	KOMe instead of KO*t*Bu	60
6	PhLi instead of KO*t*Bu	51
7	F as leaving group instead of Cl	0
8	Br as leaving group instead of Cl	0
9	I as leaving group instead of Cl	3
10	OTs as leaving group instead of Cl	31
11	OMs as leaving group instead of Cl	0

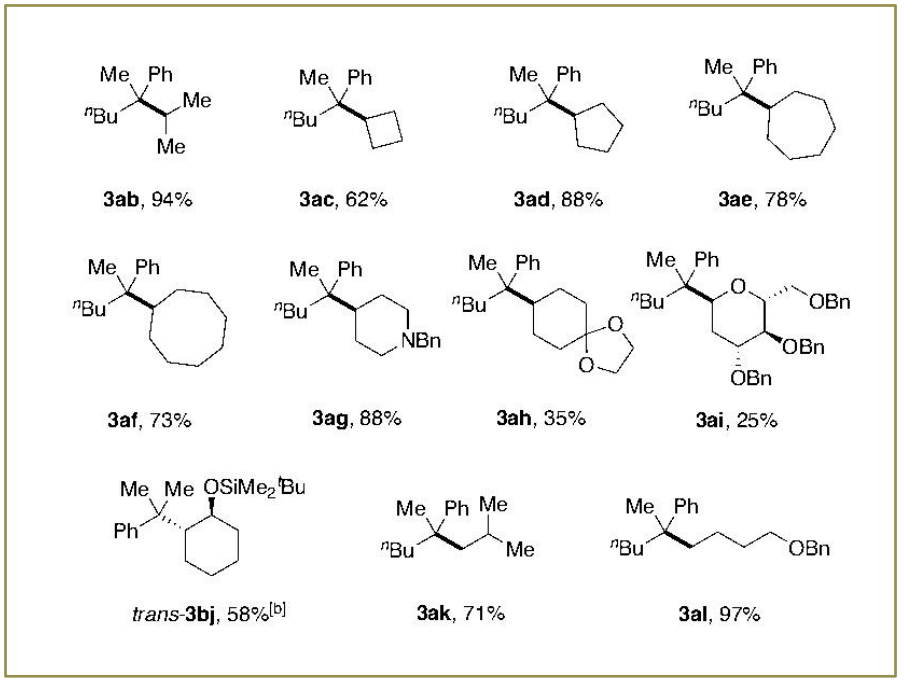
Hirohisa Ohmiya. et al, *Angew. Chem. Int. Ed.* **2020**

Introduction

Substrate scope of C(sp3)–C(sp3) cross-coupling



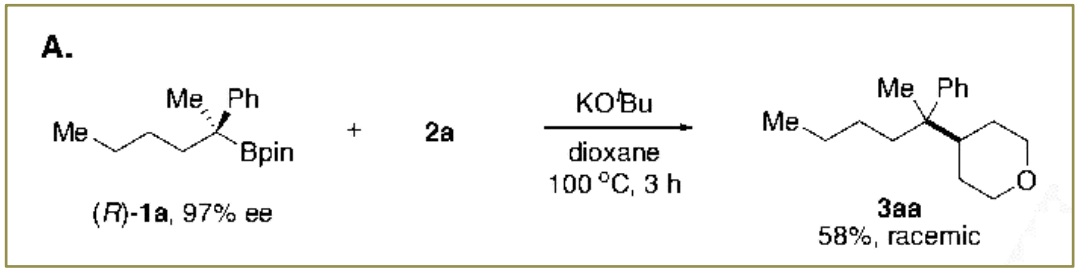


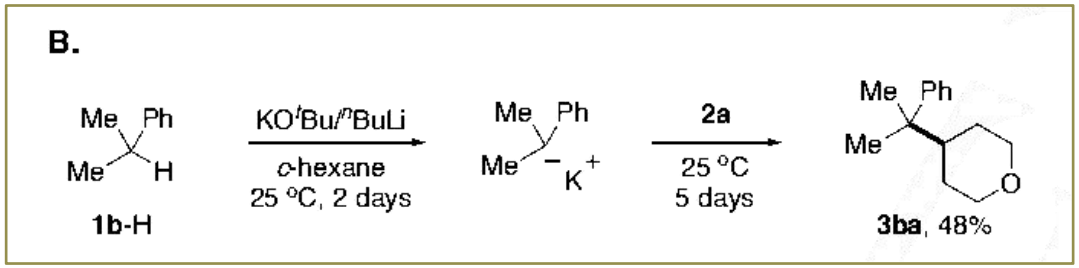


Hirohisa Ohmiya. et al, *Angew. Chem. Int. Ed.* **2020**

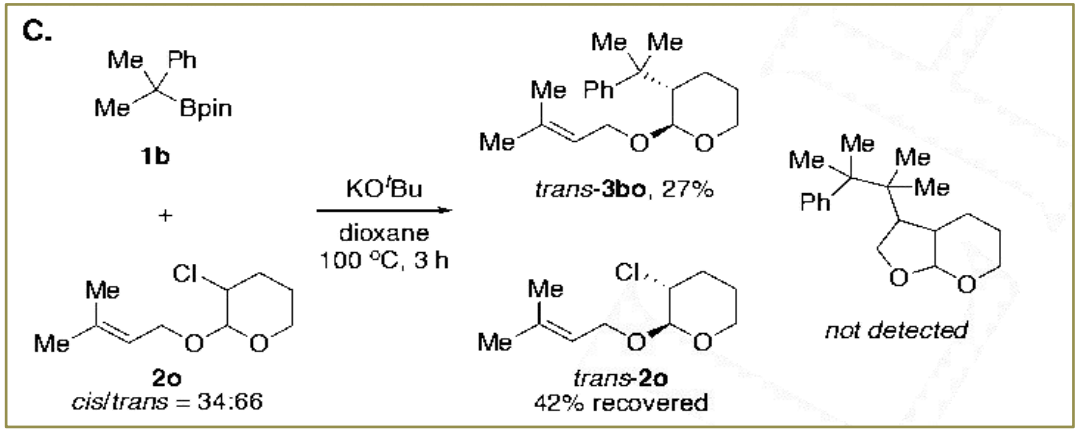
Introduction

Mechanistic studies





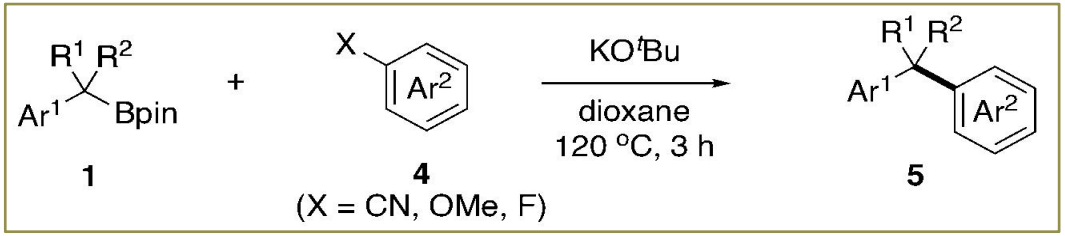
Radical clock experiments

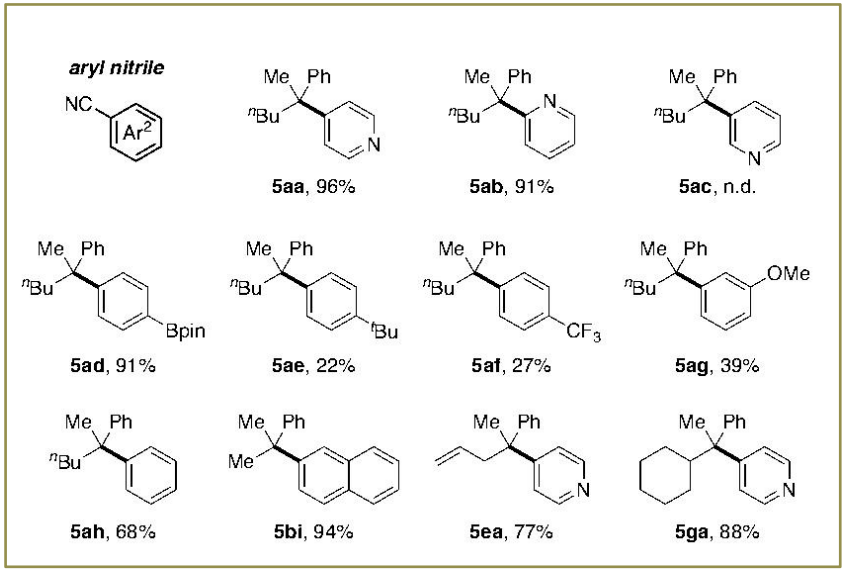


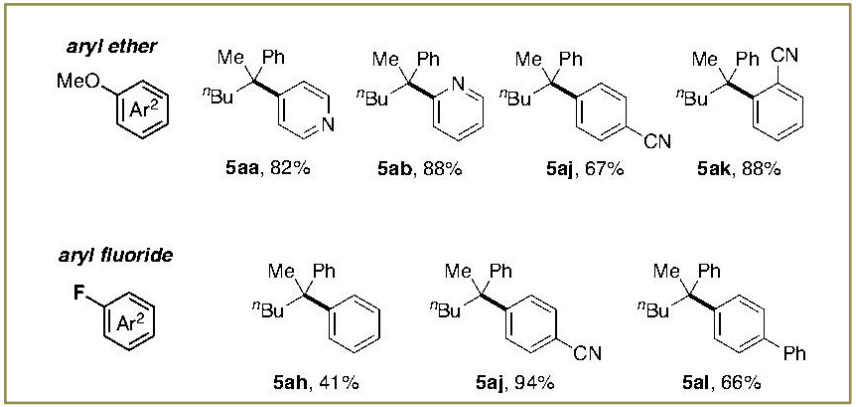
Hirohisa Ohmiya. et al, *Angew. Chem. Int. Ed.* **2020**

Introduction

Substrate scope of C(sp3)–C(sp2) cross-coupling



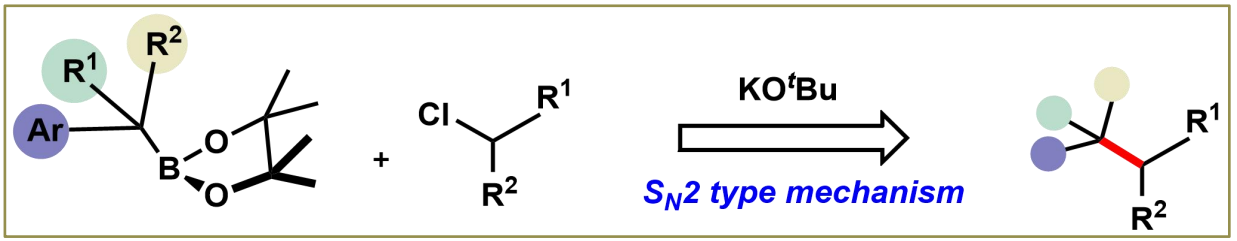




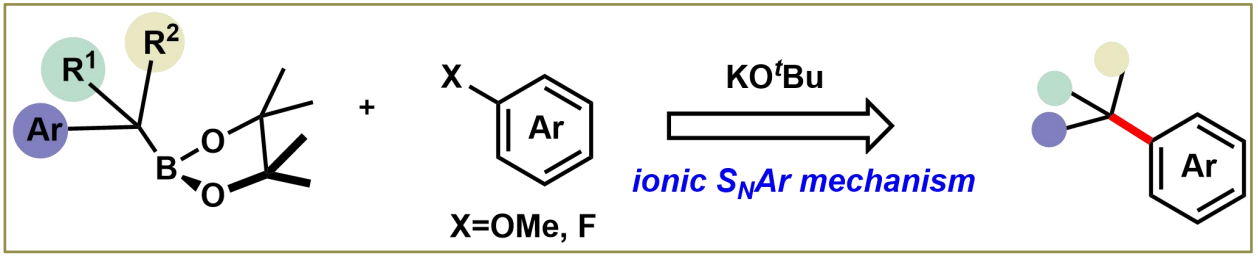
Hirohisa Ohmiya. et al, *Angew. Chem. Int. Ed.* **2020**

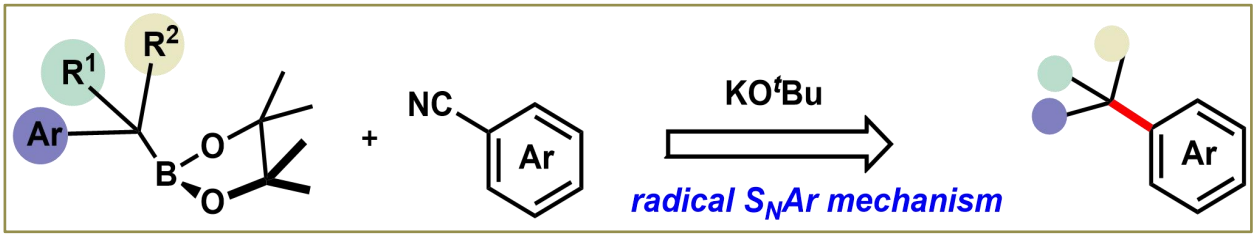
Introduction

C(sp3)–C(sp3) cross-coupling mechanism



C(sp3)–C(sp2) cross-coupling mechanism





Hirohisa Ohmiya. et al, *Angew. Chem. Int. Ed.* **2020**

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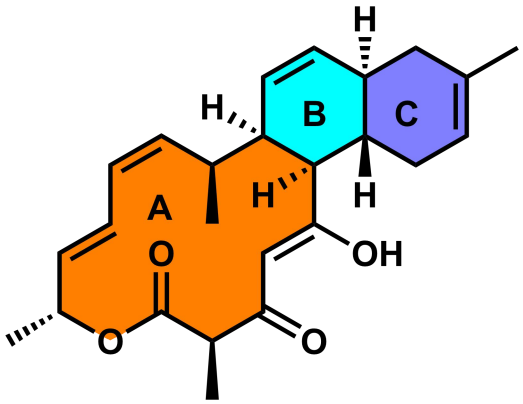
Asymmetric Total Synthesis of the Naturally Occurring Antibiotic Anthracimycin



(-)-anthracimycin

Reporter: Yangyang Jiang

Supervisors: *Prof.* Tao Ye

***Dr.* Yian Guo**

October 5, 2020

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PEKING UNIVERSITY

- 1.Introduction
- 2.Retrosynthetic Analysis
- 3.Synthetic Route
- 4. Summary

Introduction

Margaret A. Brimble

Education

- 1983 to 1985 PhD in Chemistry, The University of Southampton, UK
- 1982 to 1983 MSc in Chemistry with First Class Honours, The University of Auckland, NZ
- 1979 to 1981 BSc in Chemistry, The University of Auckland, NZ

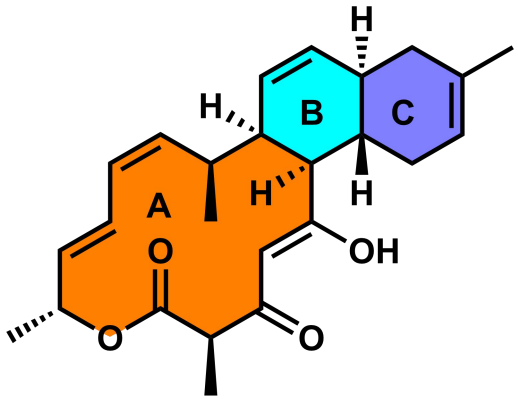
Fellowship

- 2019 Damehood
- 2018 Fellow of the Royal Society (FRS)
- 2005 Fellow of the Royal Society of Chemistry, UK (FRSC)
- 2001 Fellow of the Royal Society of New Zealand (FRSNZ)
- 1999 Fellow of the New Zealand Institute of Chemistry (FNZIC)
- 1998 Fellow of the Royal Australian Chemical Institute (FRACI)

Research interests

- Asymmetric synthesis, heterocyclic chemistry and organocatalysis to synthesise complex bioactive natural products.
- Synthesis of glycopeptides, lipopeptides, peptidomimetics and peptide natural products.

Introduction



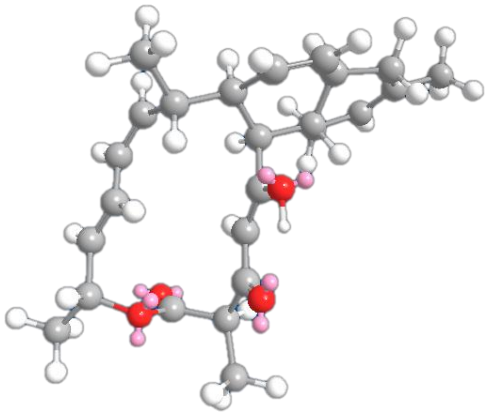
(-)-anthracimycin

Isolation:

- **(−)-Anthracimycin was isolated from the marine sediment derived *Streptomyces* sp. CNH365, collected off the coast of Santa Barbara, USA.**

Structural features:

- **14-membered macrolide natural product;**
- **7 asymmetric carbon centers;**
- **Trans-decalin framework.**



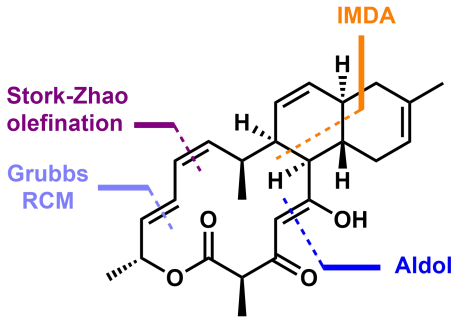
Biology activity:

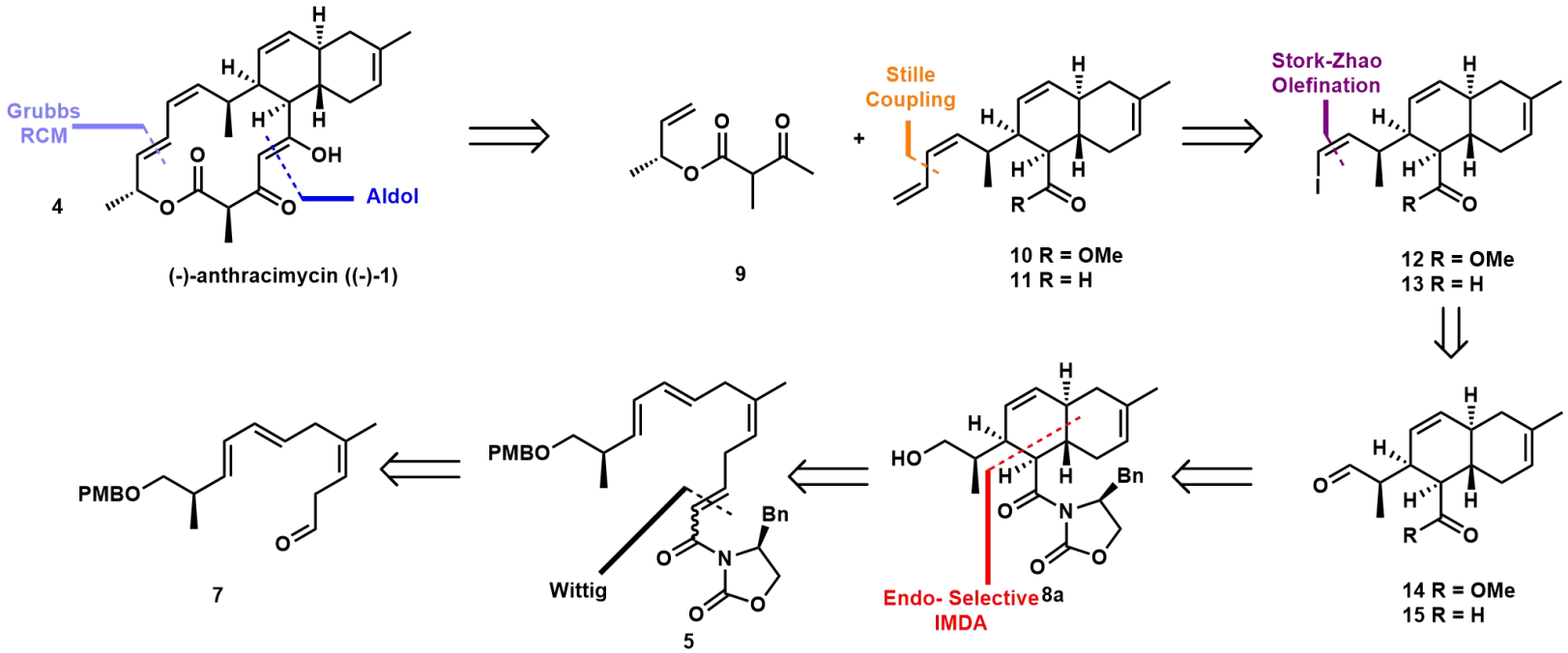
- **(−)-Anthracimycin exhibited potent in vitro antibacterial activity against several MRSA strains (MIC 0.03−0.0625 μg/mL) alongside *Bacillus anthracis*, and *M. tuberculosis* (H37Ra, MIC 1−2 μg/mL).**

Margaret A. Brimble. et al, *Org. Lett.* **2020**, *22* , 5550-5554.

Retrosynthetic Analysis

Retrosynthesis

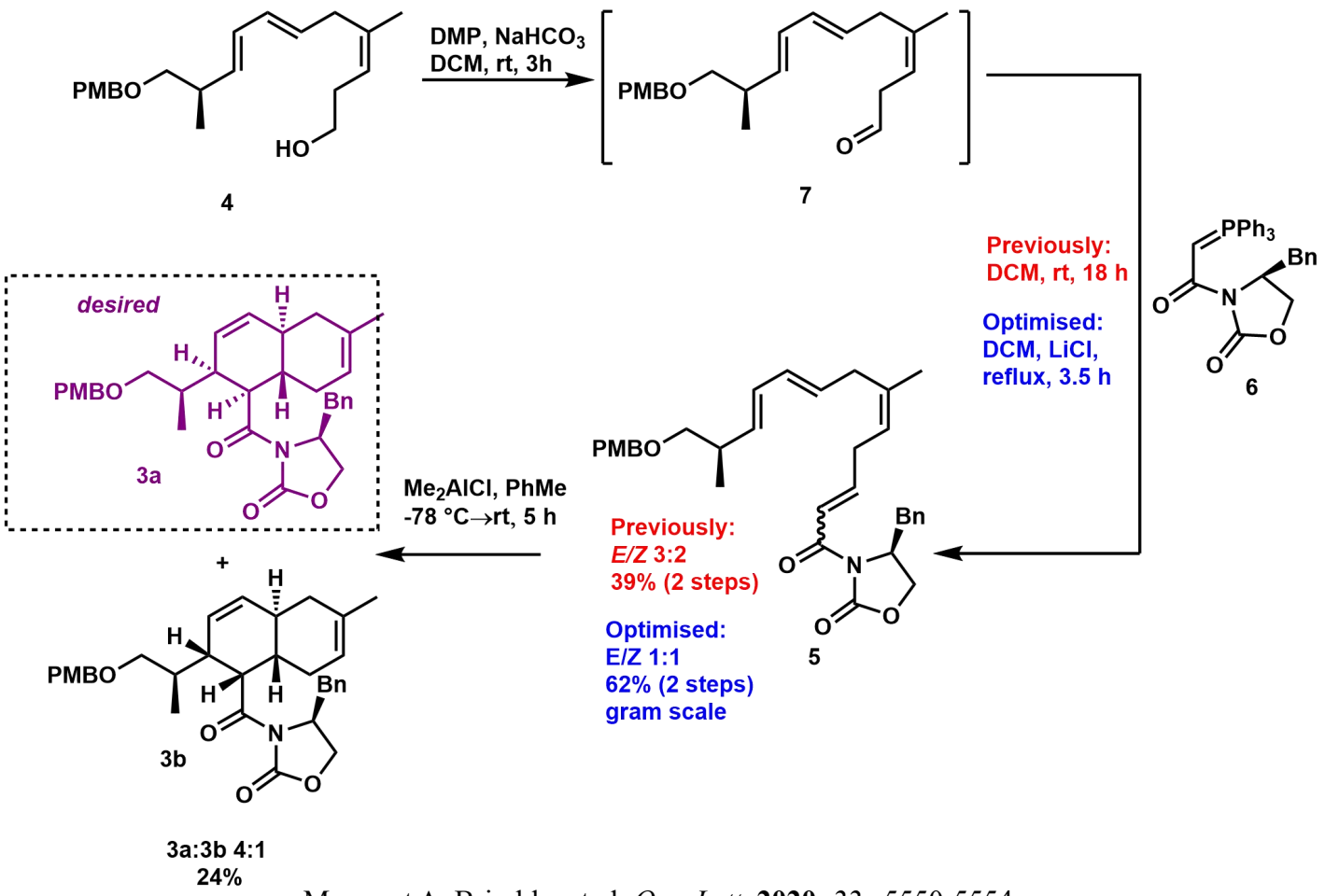




Margaret A. Brimble. et al, *Org. Lett.* **2020**, *22* , 5550-5554.

Synthetic Route

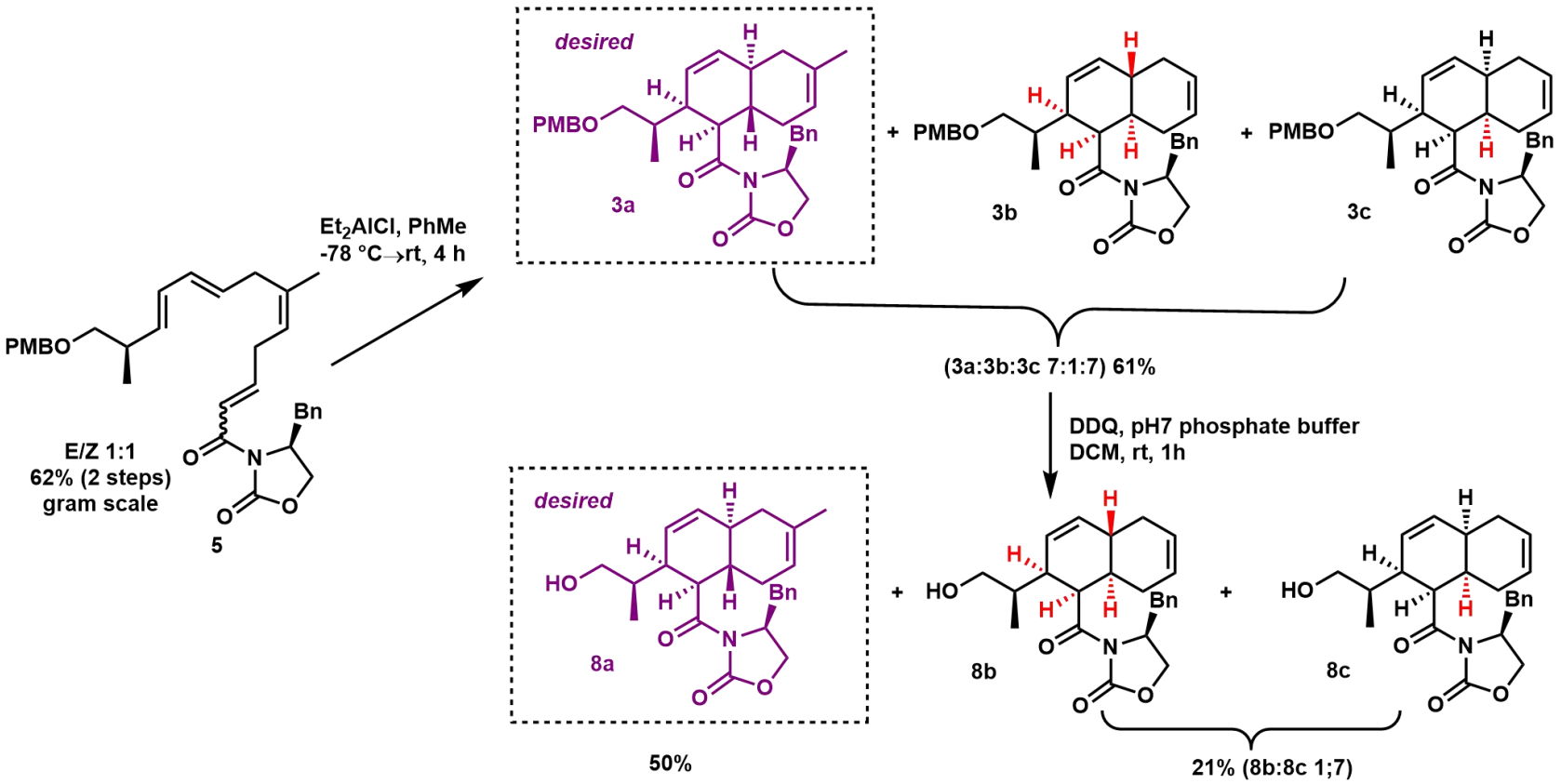
Previously Reported Wittig-IMDA Sequence to trans-Decalin Fragment 3a



Margaret A. Brimble. et al, *Org. Lett.* **2020**, *22* , 5550-5554.

Synthetic Route

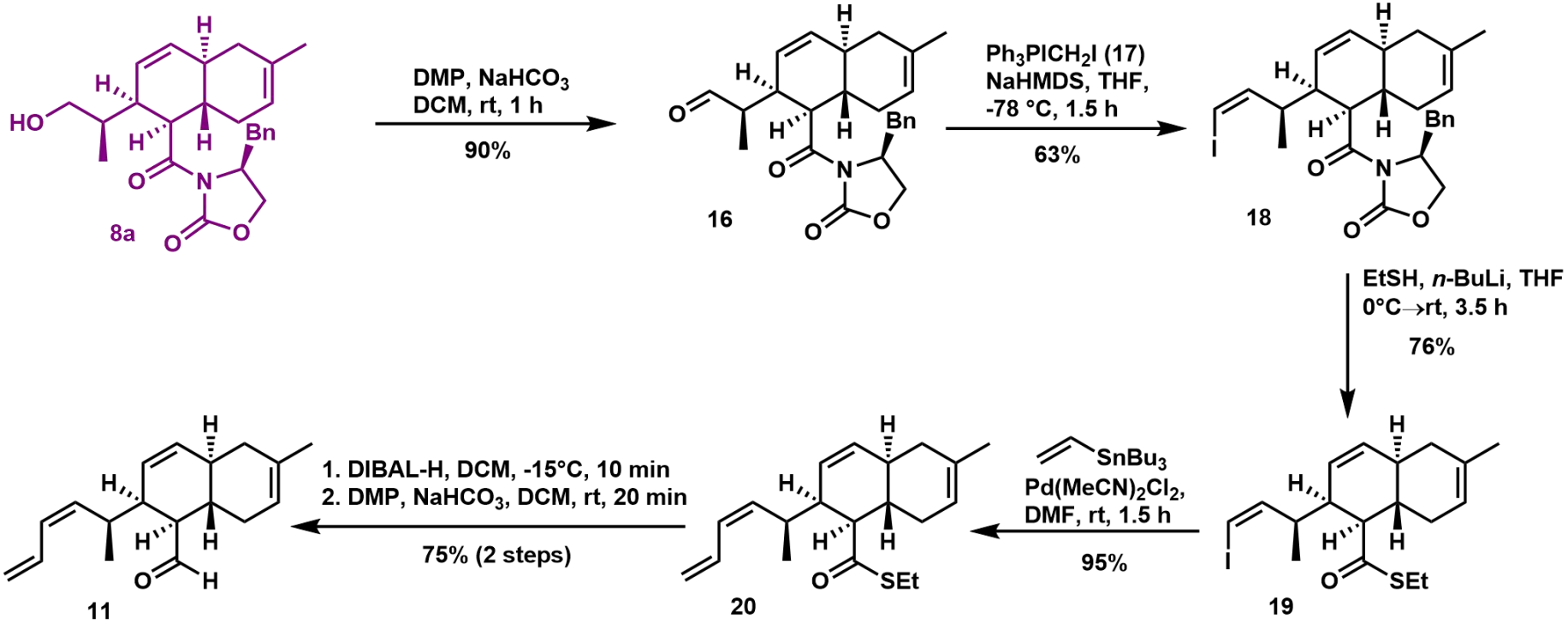
Preparation of Alcohol 8a



Margaret A. Brimble. et al, *Org. Lett.* **2020**, *22* , 5550-5554.

Synthetic Route

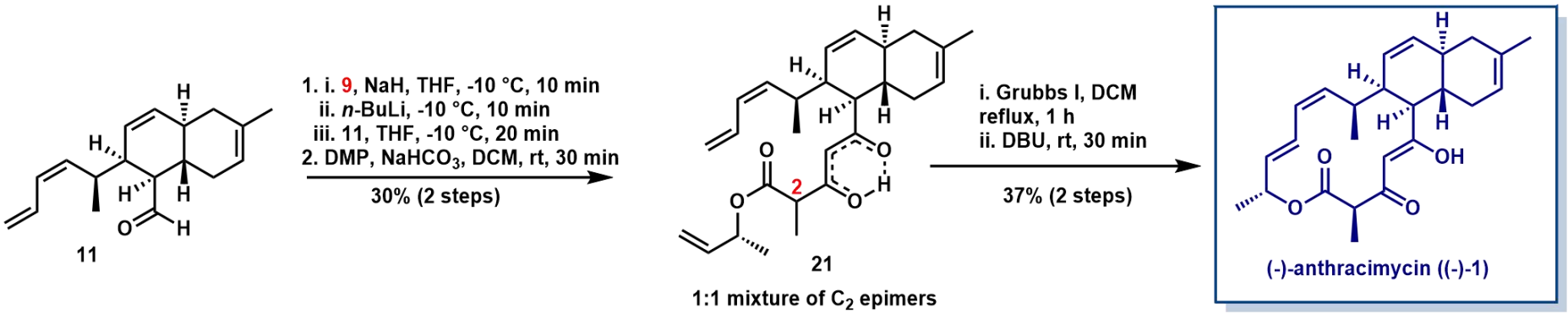
Preparation of Aldehyde 11

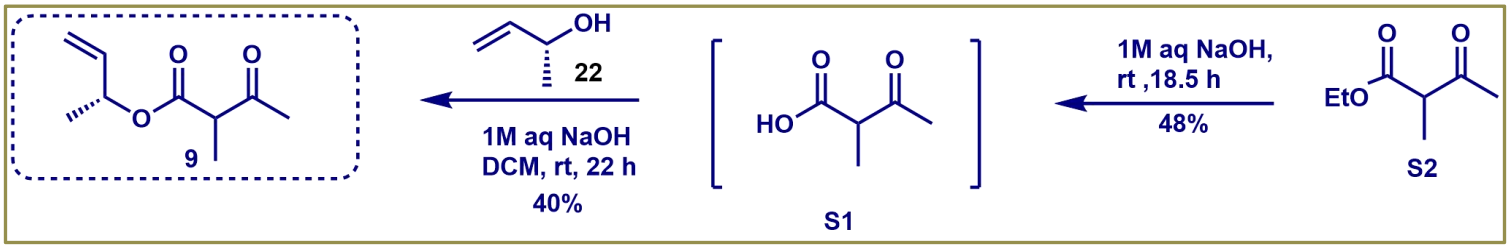


Margaret A. Brimble. et al, *Org. Lett.* **2020**, *22* , 5550-5554.

Synthetic Route

Synthesis of Scabrolide A





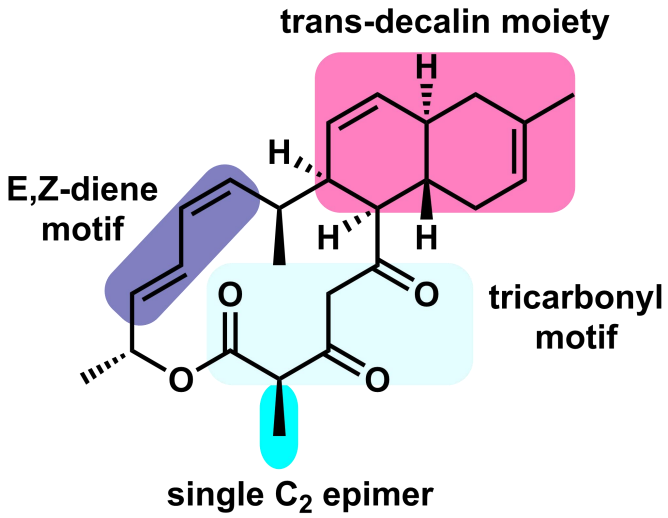
Margaret A. Brimble. et al, *Org. Lett.* **2020**, *22* , 5550-5554.

Summary

Take-home message

IMDA reaction

Stork–Zhao olefination / Grubbs ring closing metathesis



Aldol reaction using a complex β-ketoester

Base-mediated epimerization

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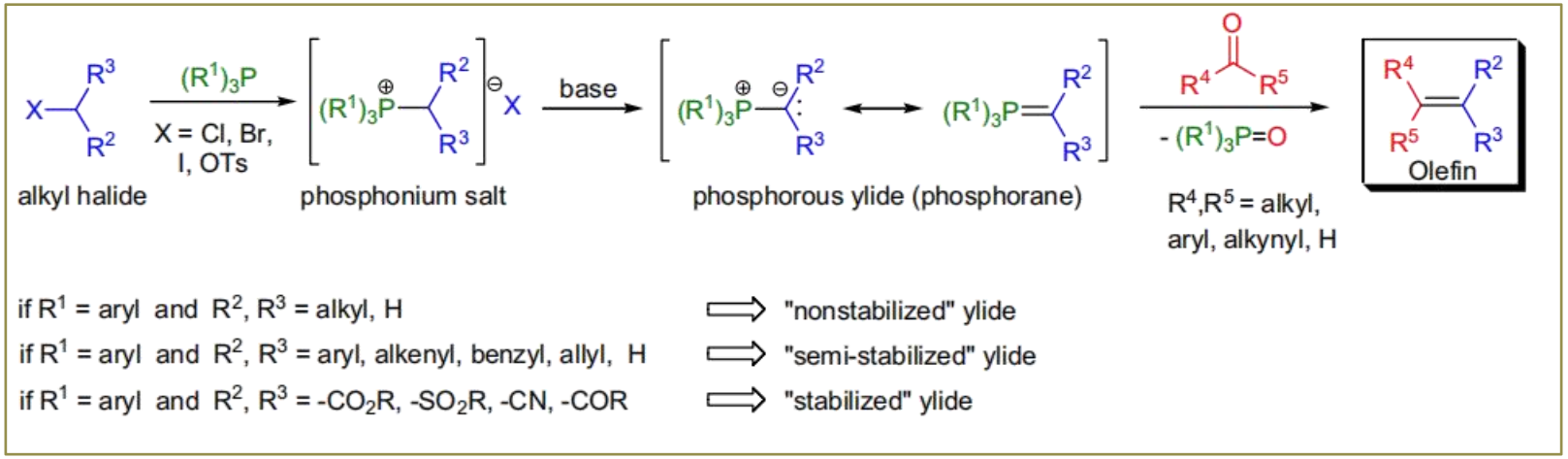
THANKS
FOR YOUR ATTENTION!

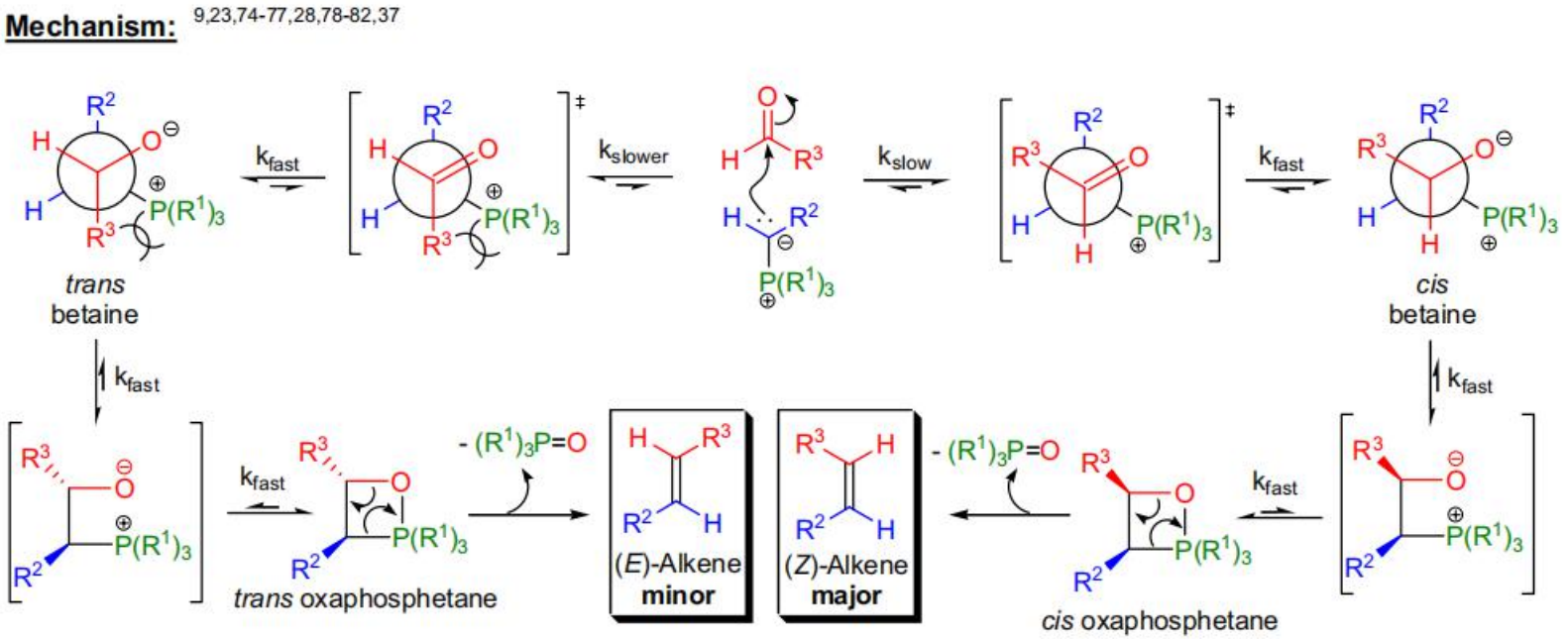
Supporting Materials

Wittig reaction



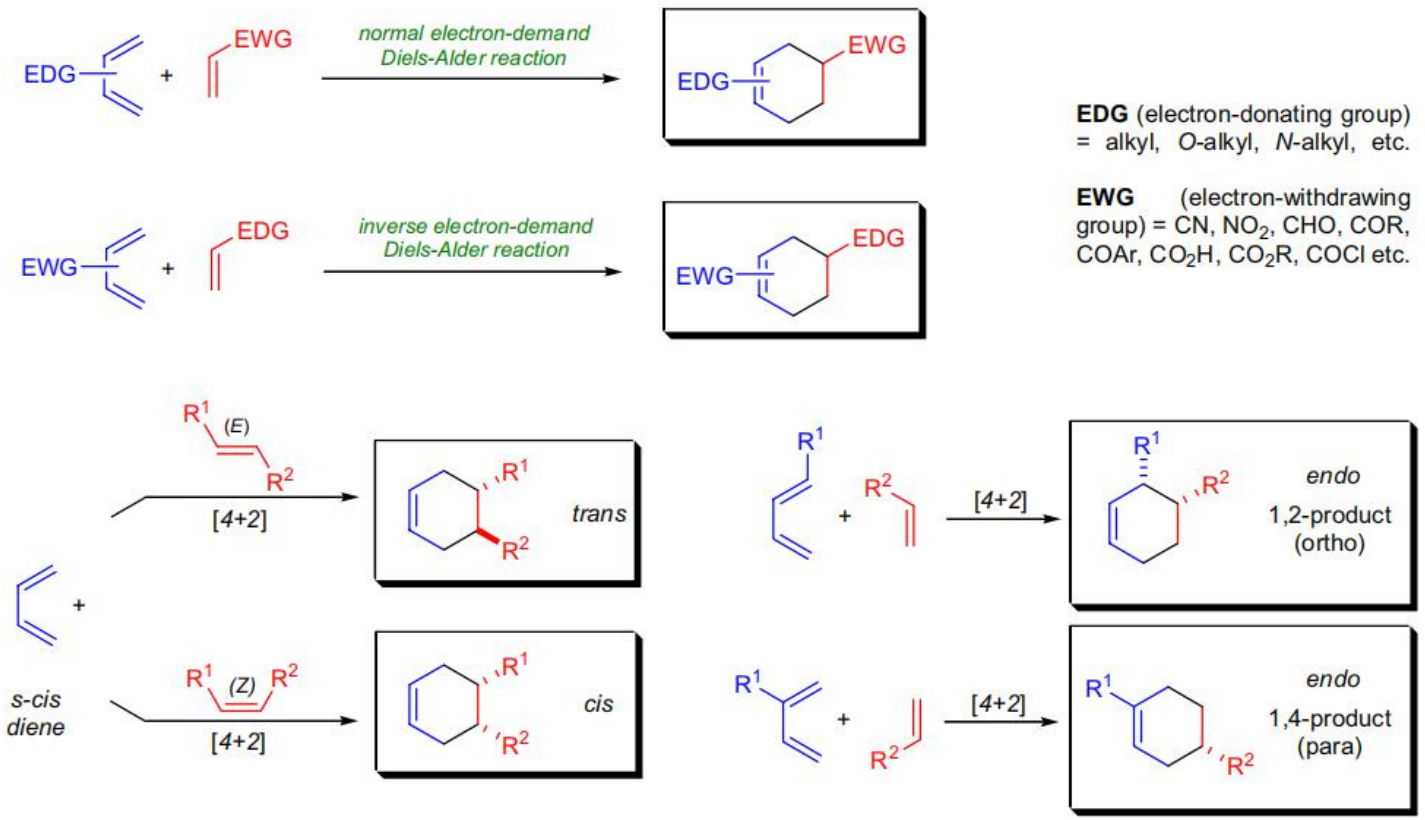
Supporting Materials

Wittig reaction



Supporting Materials

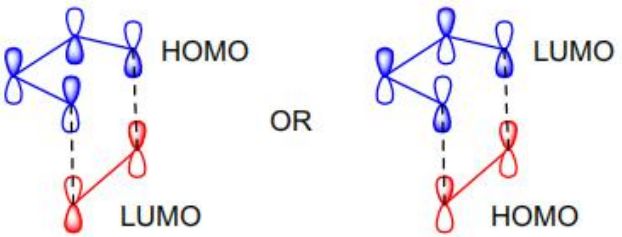
Diels–Alder reaction

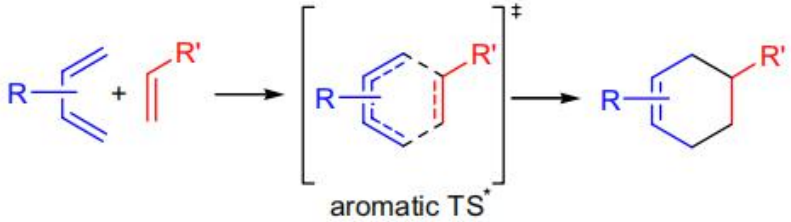


Supporting Materials

Diels–Alder reaction

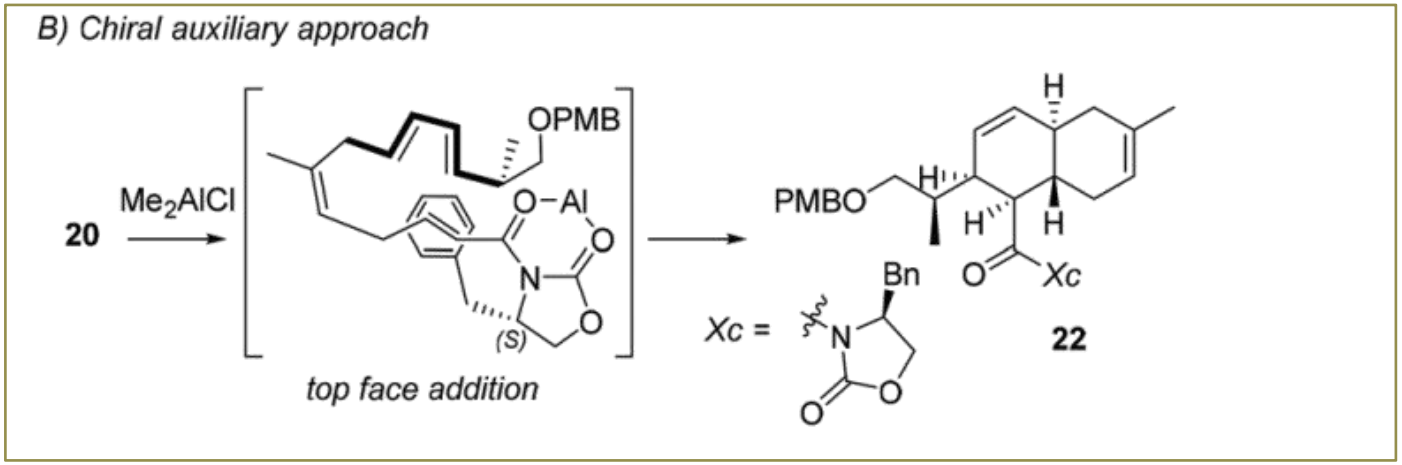
Mechanistically the D-A reaction is considered a concerted, pericyclic reaction with an aromatic transition state. The driving force is the formation of two new σ-bonds. The *endo* product is the kinetic product and its formation is explained by *secondary orbital interactions*.[80] Some of the mechanistic studies suggested that a diradical[79] or a di-ion mechanism may be operational in certain cases.[82] It was also shown that solvents and salts can influence reaction kinetics.[38]





Supporting Materials

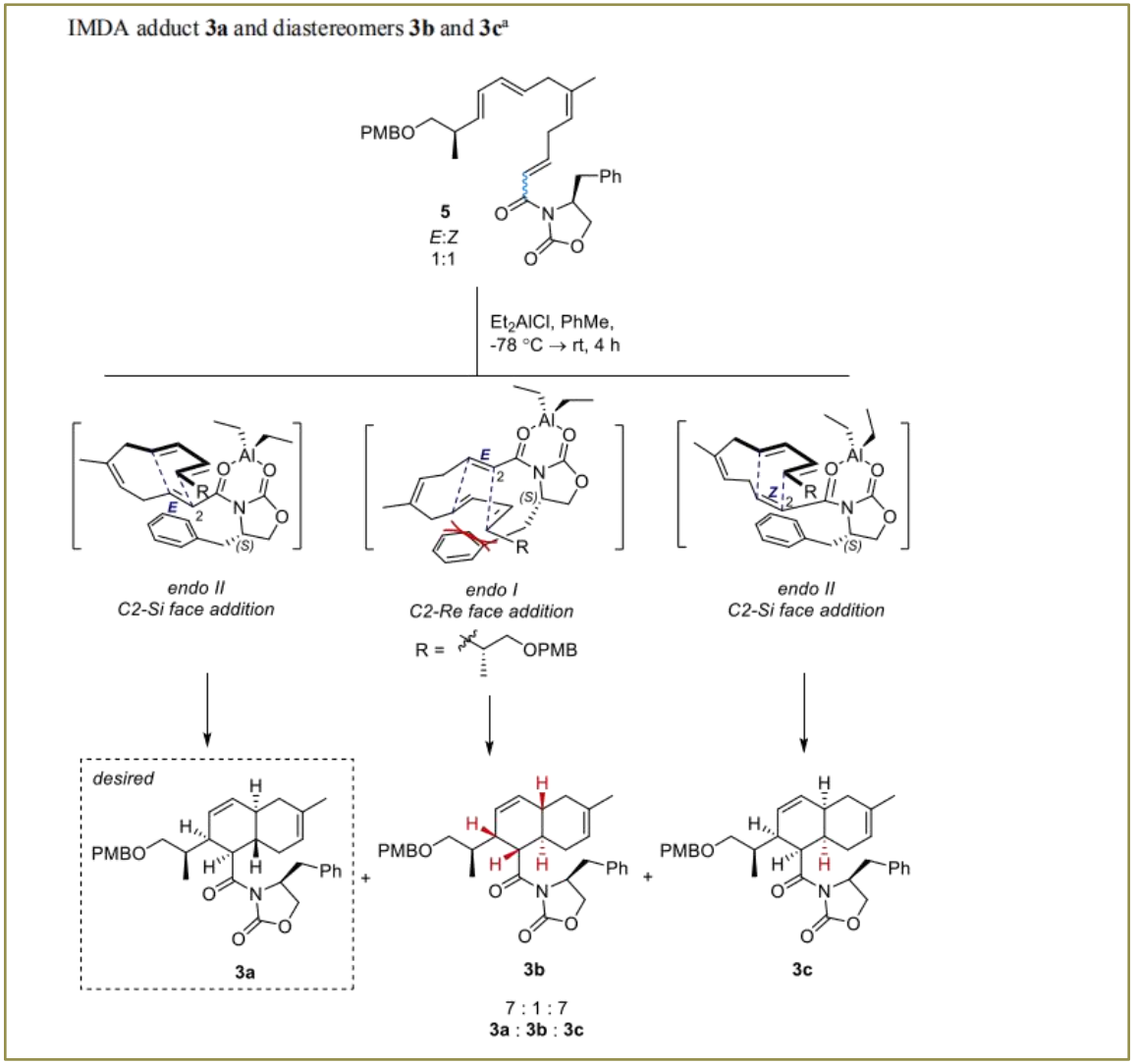
Diels–Alder reaction



degree of facial control. Evans' benzyl oxazolidinones reinforce facial selectivity of cycloadditions through postulated π-stacking of the benzyl substituent preferentially on one face of the dienophile olefin. In our case, the C4′-*S* oxazolidinone sterically disfavours cycloaddition to the bottom face of the dienophile, promoting top-face attack to afford the desired stereochemical outcome (Scheme 5B). Therefore, this approach can be used to override the inherent stereoselectivity of the cycloaddition to afford the desired stereoisomer.

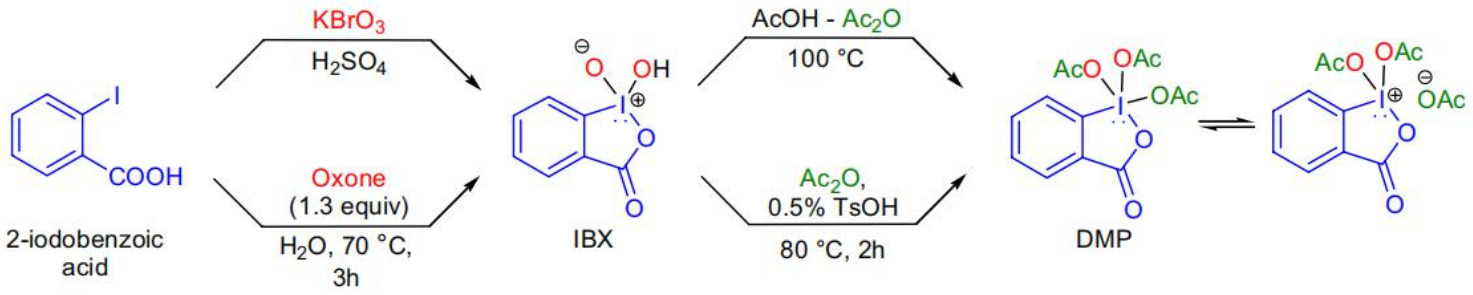
Supporting Materials

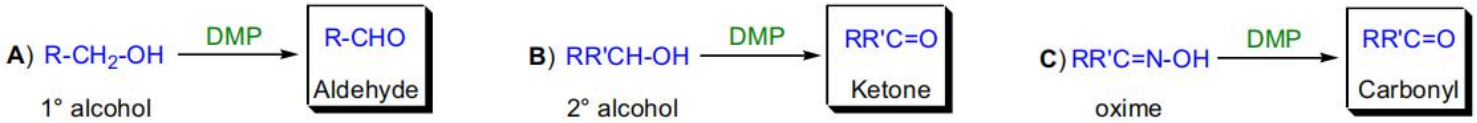
Diels–Alder reaction



Supporting Materials

Dess-Martin Periodinane

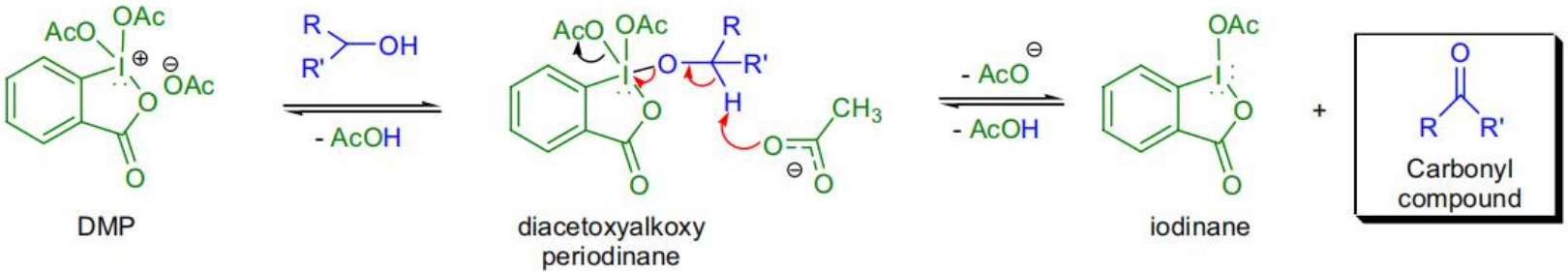




Supporting Materials

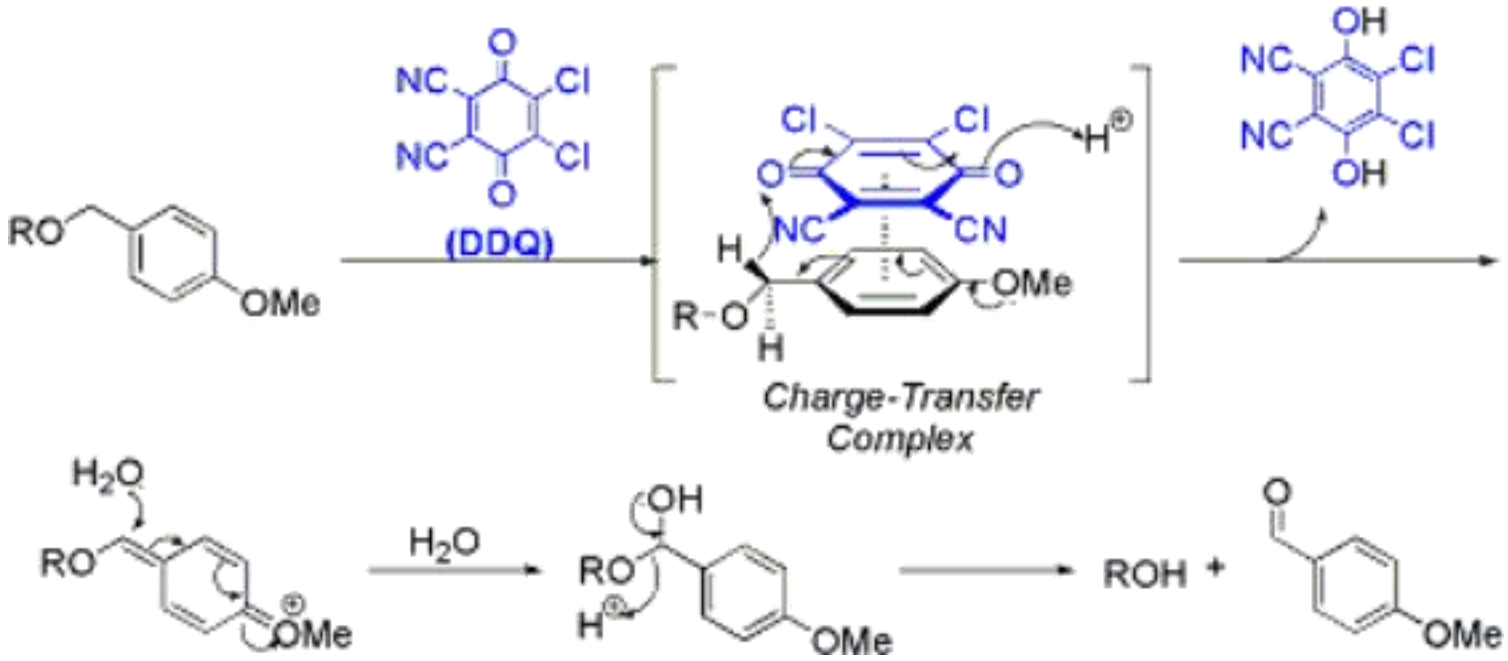
Dess-Martin Periodinane

It has been shown by ^{1}H-NMR that DMP reacts rapidly with 1 equivalent of alcohol (1° or 2°) to give diacetoxyalkoxyperiodinanes, while in the presence of 2 equivalents of alcohol (or diol) a double displacement takes place to produce acetoxydialkoxyperiodinanes. Next, the α-proton of the alcohol is removed by a base (acetate), and the carbonyl compound is released along with a molecule of iodinane. When excess alcohol is present, the oxidation is much faster due to the especially labile nature of acetoxydialkoxyperiodinanes.[9] It has also been shown that added water accelerates DMP oxidations.[11]



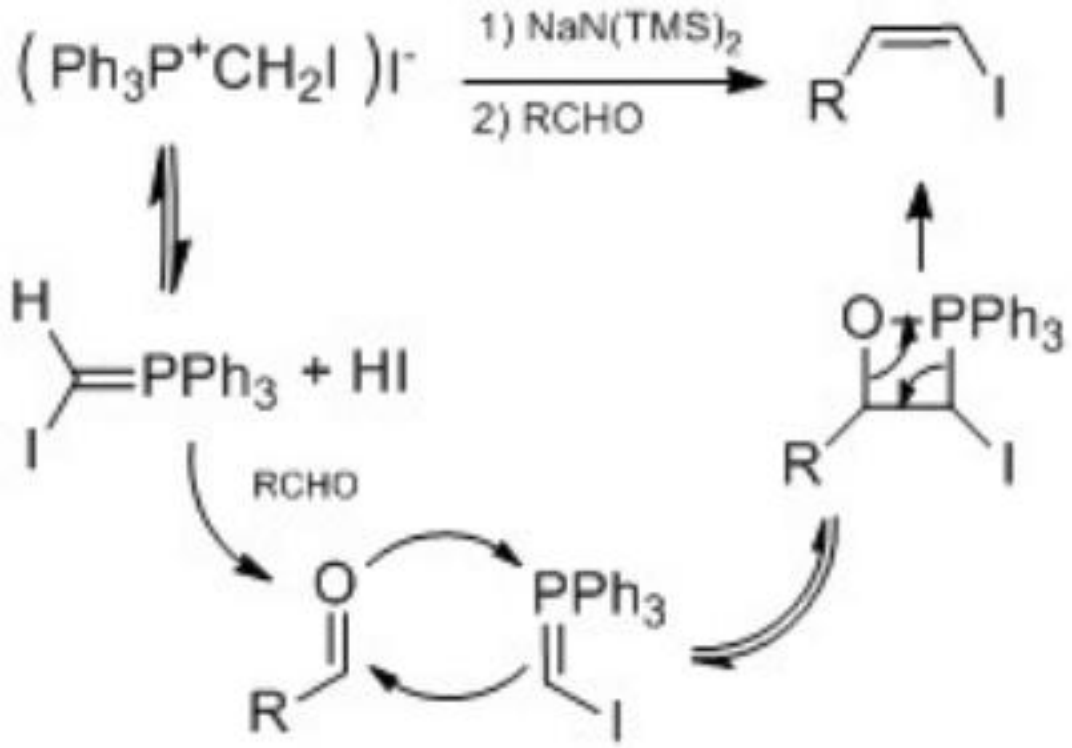
Supporting Materials

PMB Deprotection with DDQ



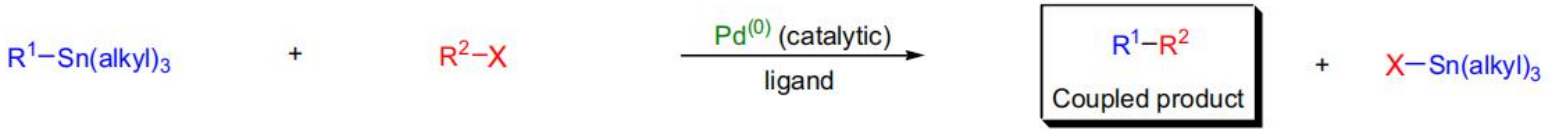
Supporting Materials

Stork-Zhao-Wittig Olefination

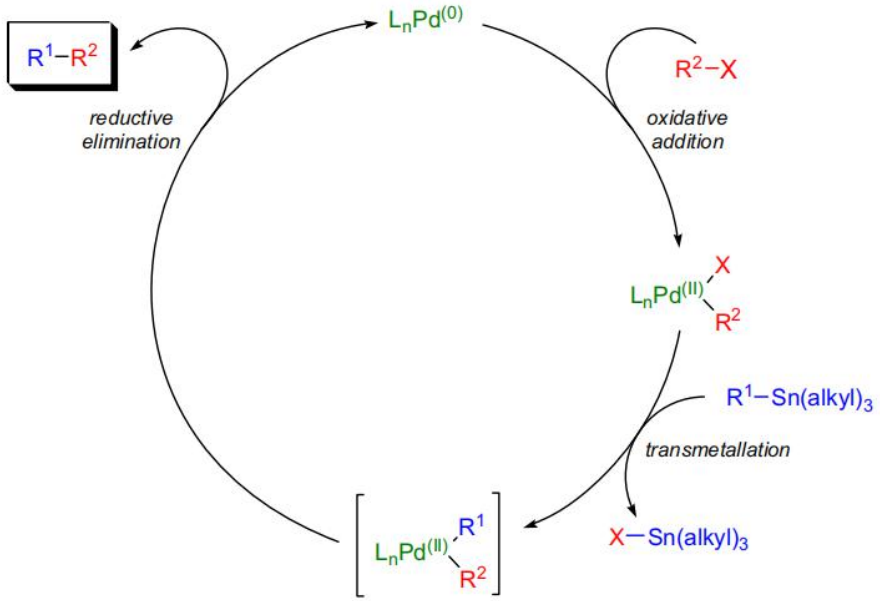


Supporting Materials

Stille coupling

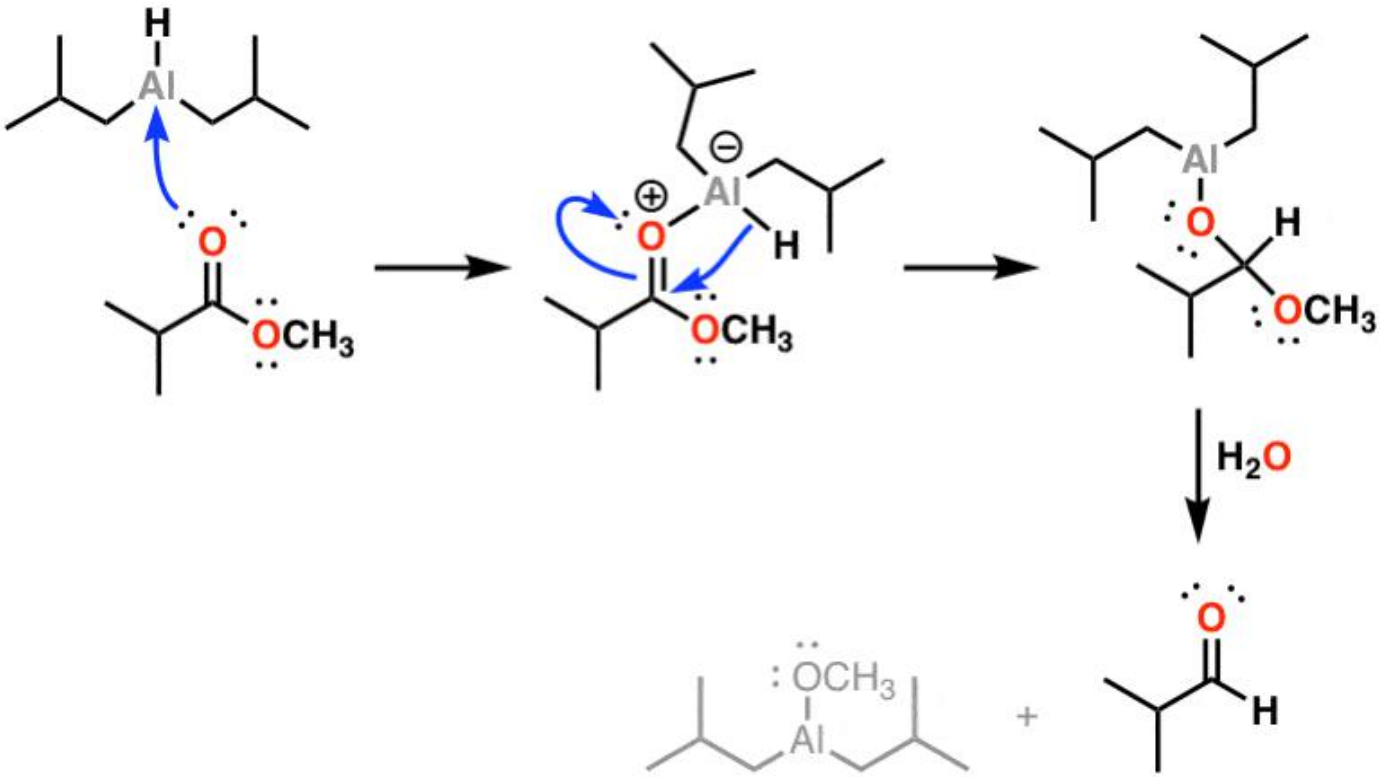


R^1 = allyl, alkenyl, aryl; R^2 = alkenyl, aryl, acyl; X = Cl, Br, I, OTf, $OPO(OR)_2$



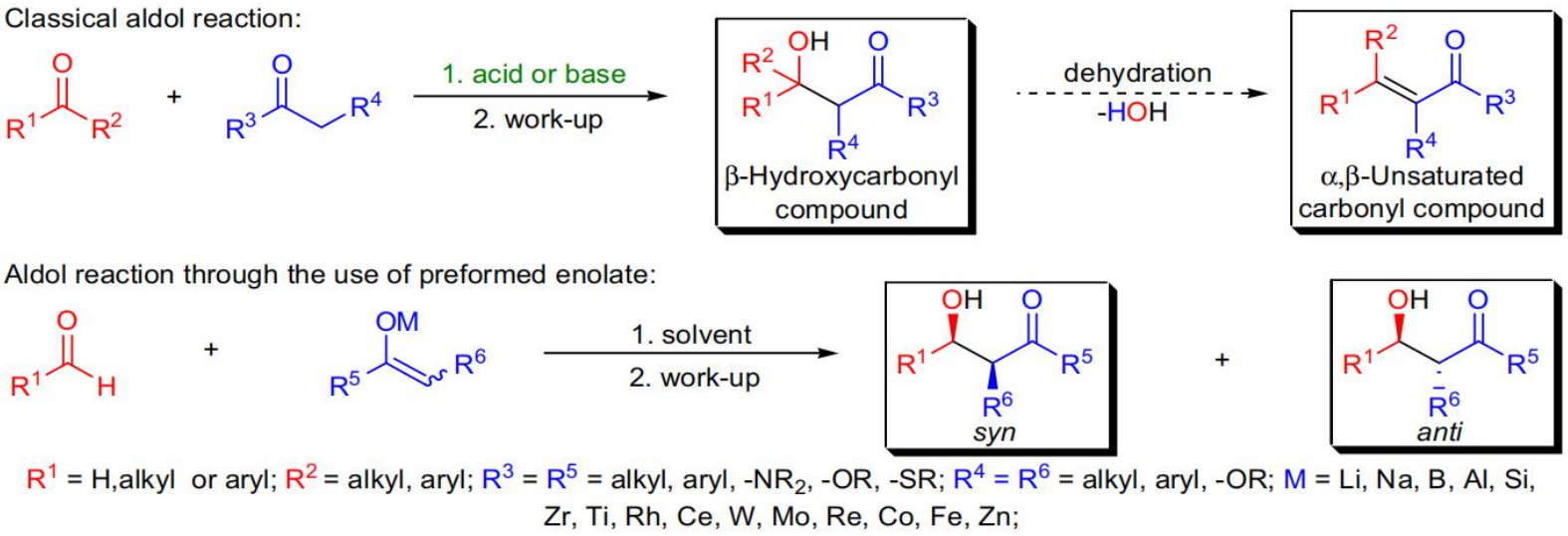
Supporting Materials

Reduction to aldehydes [DIBAL]



Supporting Materials

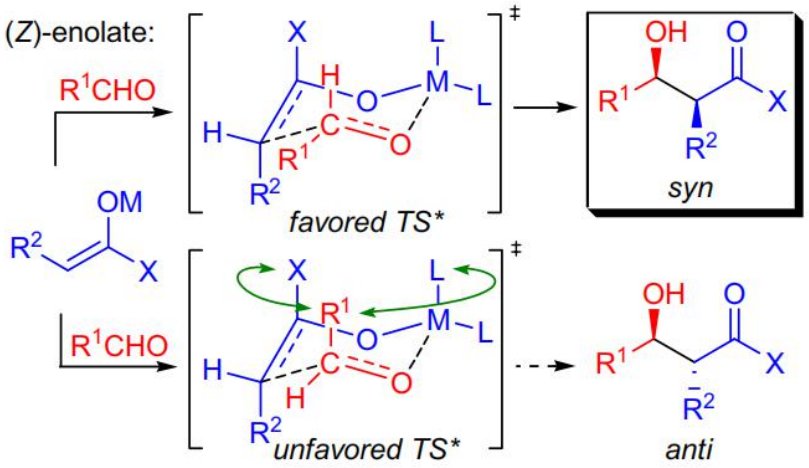
Aldol condensation



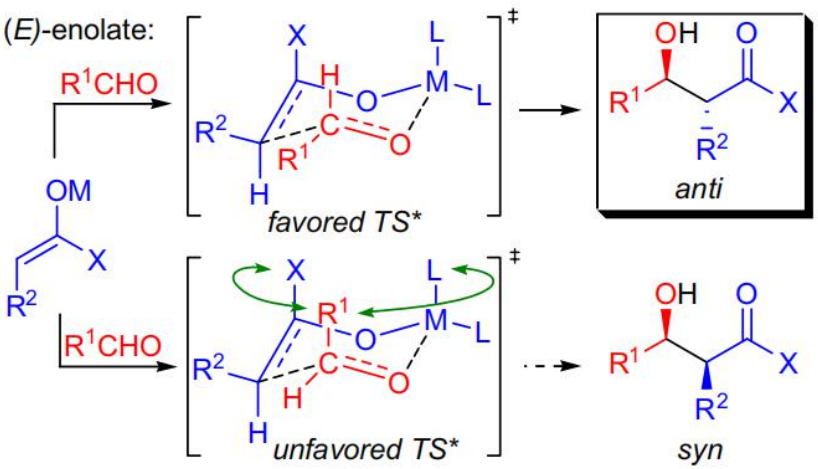
R^1 = H,alkyl or aryl; R^2 = alkyl, aryl; R^3 = R^5 = alkyl, aryl, -NR_2, -OR, -SR; R^4 = R^6 = alkyl, aryl, -OR; M = Li, Na, B, Al, Si, Zr, Ti, Rh, Ce, W, Mo, Re, Co, Fe, Zn;

Supporting Materials

Aldol condensation



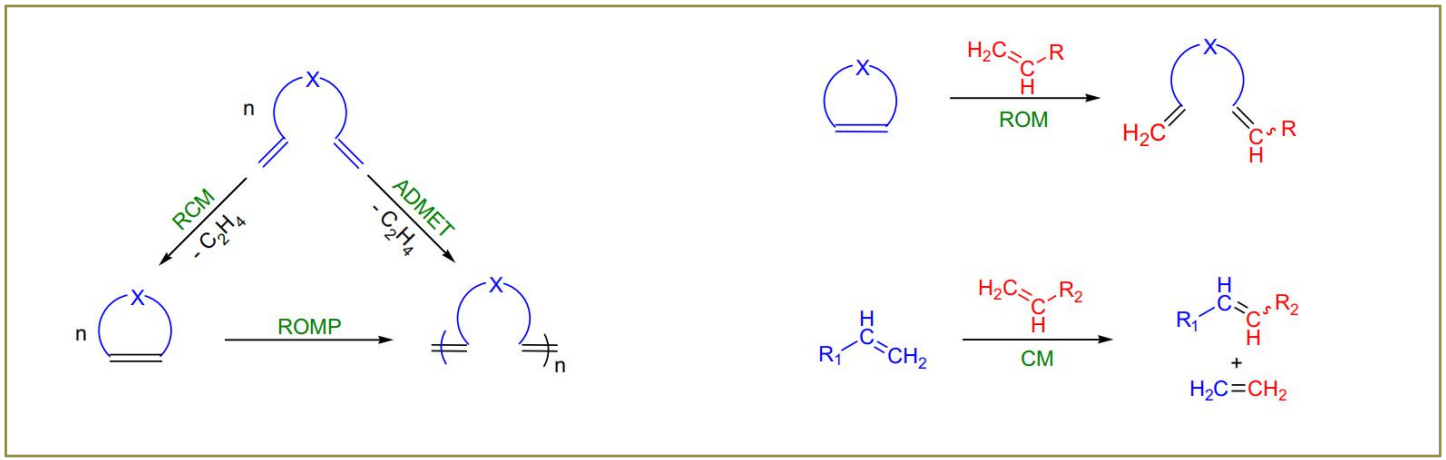
Zimmerman-Traxler model for (Z)- enolate



Zimmerman-Traxler model for (E)- enolate

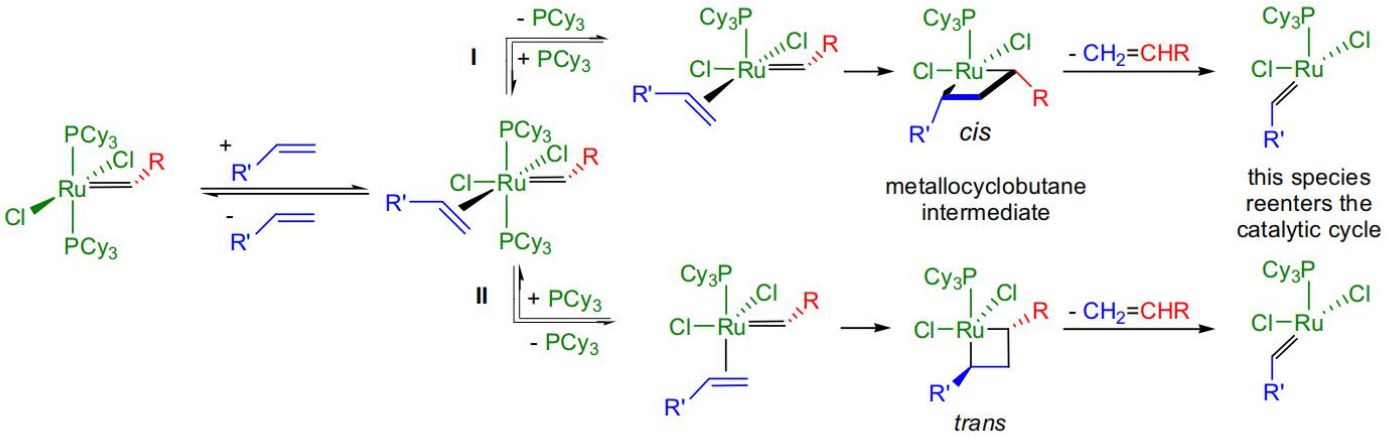
Supporting Materials

alkene (olefin) mechansim

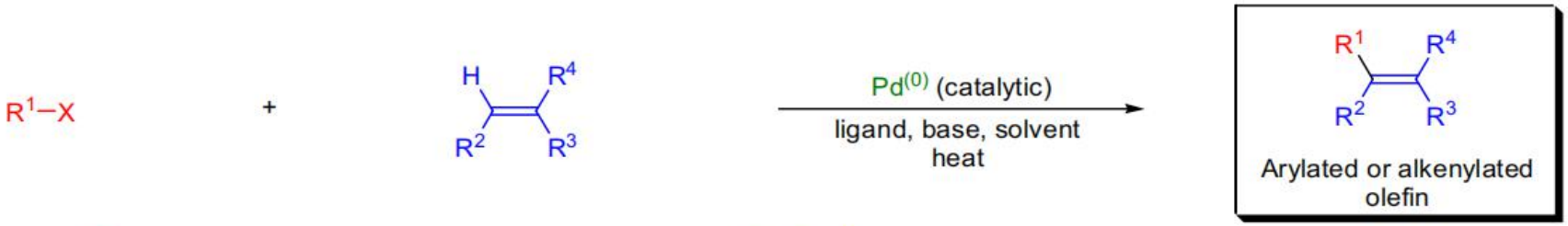


Supporting Materials

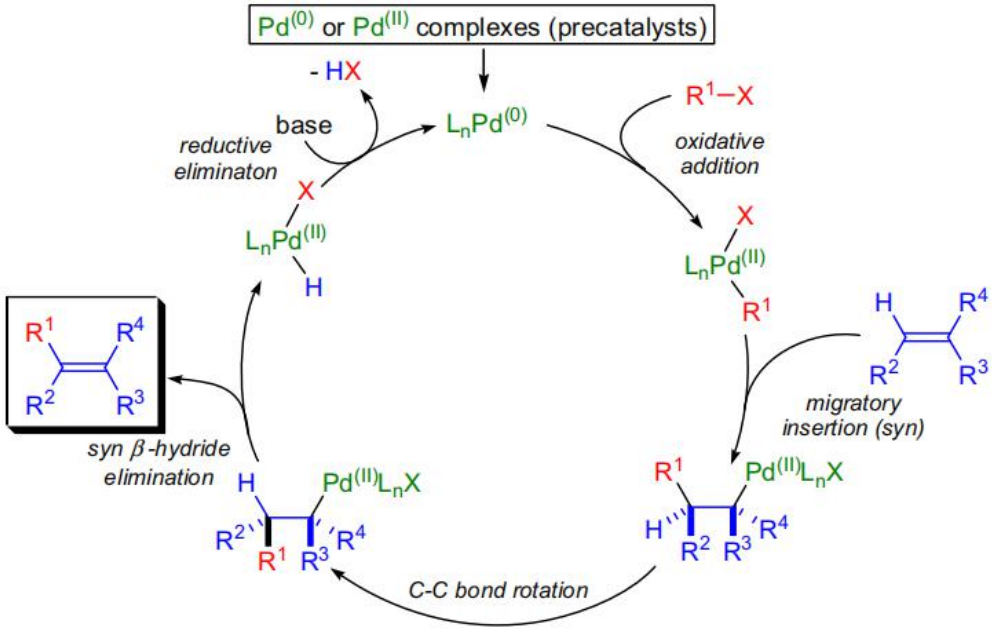
alkene (olefin) mechansim



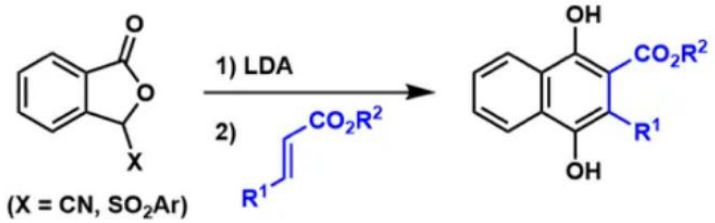
Heck reaction

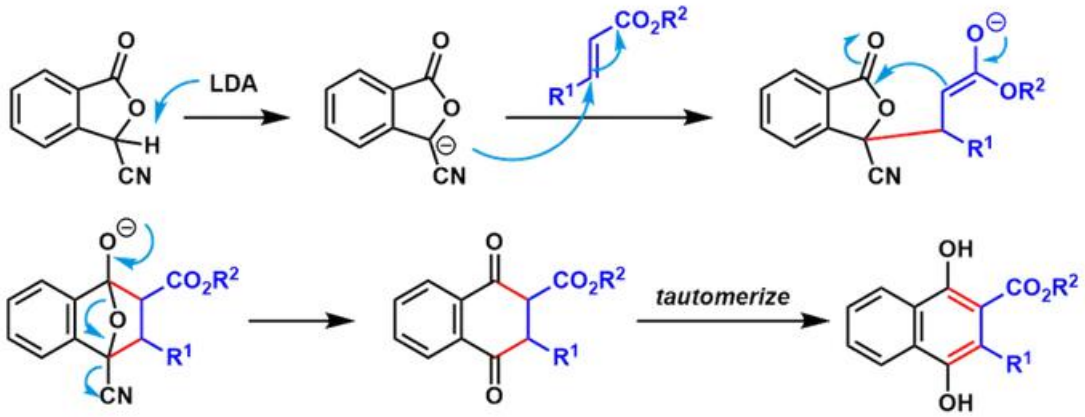


R^1 = aryl, benzyl, vinyl (alkenyl), alkyl (no β hydrogen); R^2, R^3, R^4 = alkyl, aryl, alkenyl; X = Cl, Br, I, OTf, OTs, N_2^+;
ligand = trialkylphosphines, triarylphosphines, chiral phosphines; base = 2° or 3° amine, KOAc, NaOAc, $NaHCO_3$

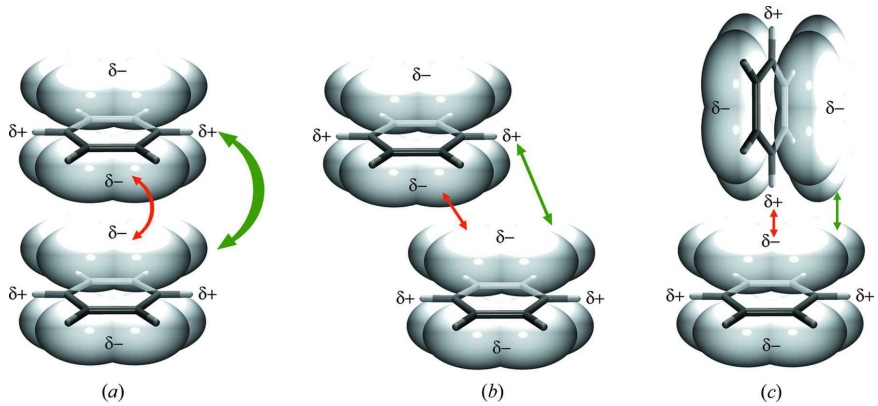


Hauser–Kraus annulation





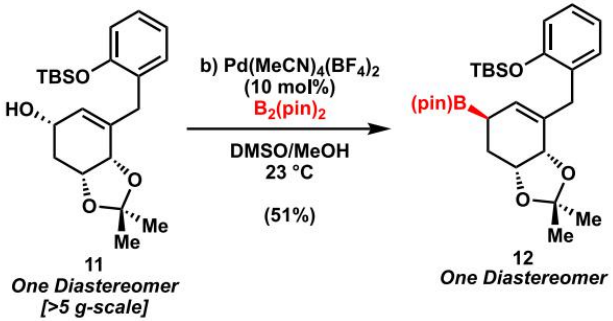
π-stacking



π-π堆积是芳香化合物的一种特殊空间排布，指一种常常发生在芳香环之间的弱相互作用，通常存在于相对富电子和缺电子的两个分子之间，是一种与氢键同样重要的非共价键相互作用。

Introduction

Part II:Total synthesis of (+)-Rubellin C



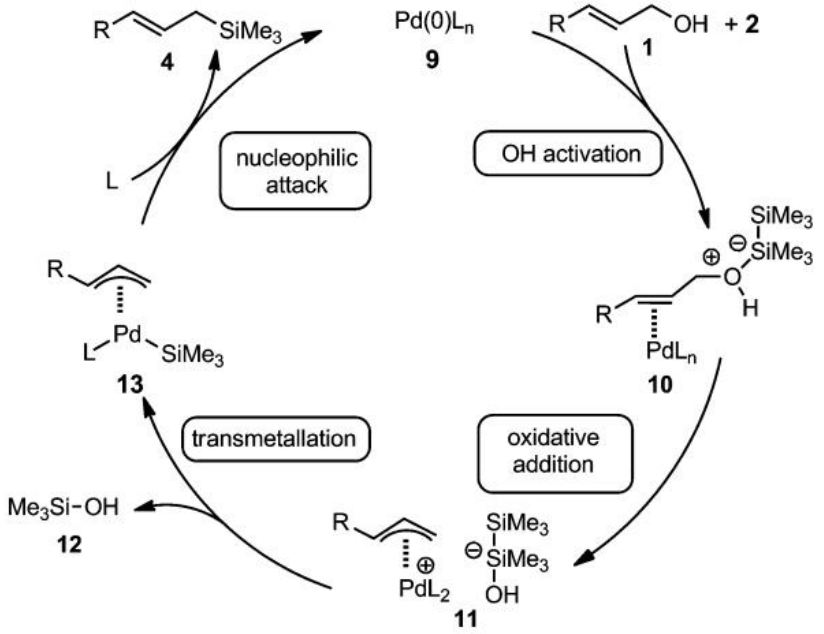


Figure 2. Proposed catalytic cycle for silylation of allylic alcohols.

Selander, N. et al. *J. Am. Chem. Soc* . **2011**, *133* , 409-411.