ASAP Report

Reporter: Jing Chen

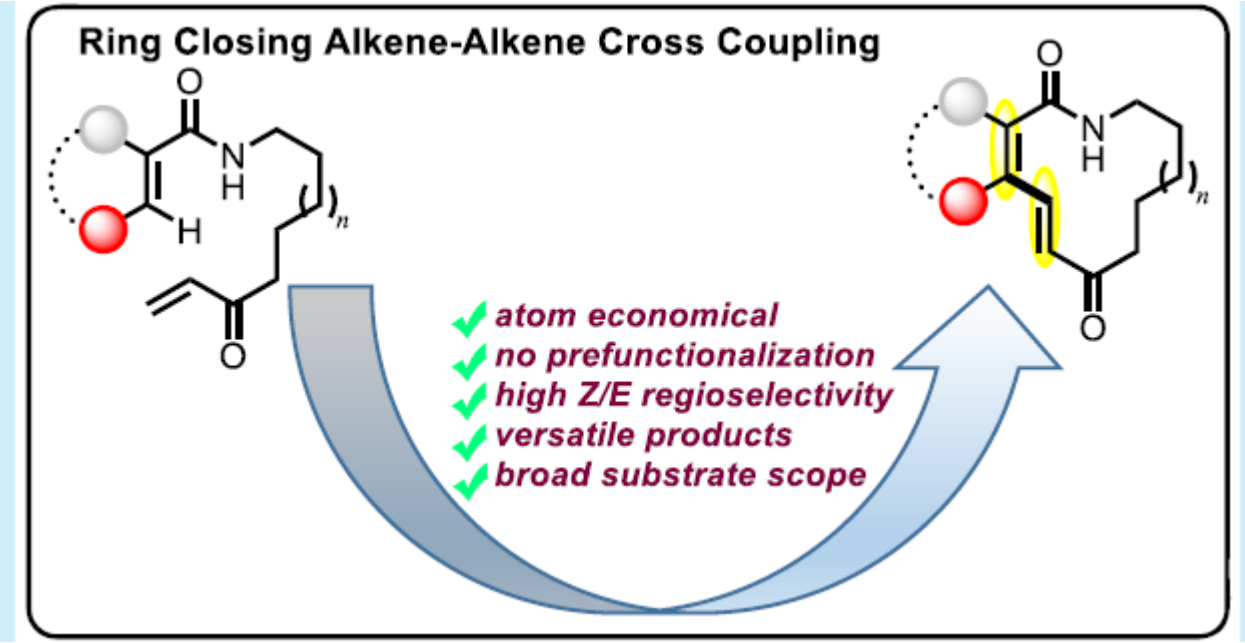
Supervisors: *Prof.* Tao Ye

***Dr.* Yian Guo**

Dec. 7st, 2020

Introduction

Part I : **Macrolactam Synthesis via Ring-Closing Alkene−Alkene Cross-Coupling Reactions**



T. P. Loh. et al, *Org. Lett.* **2020**, *10.1021/acs.orglett.0c03801.*

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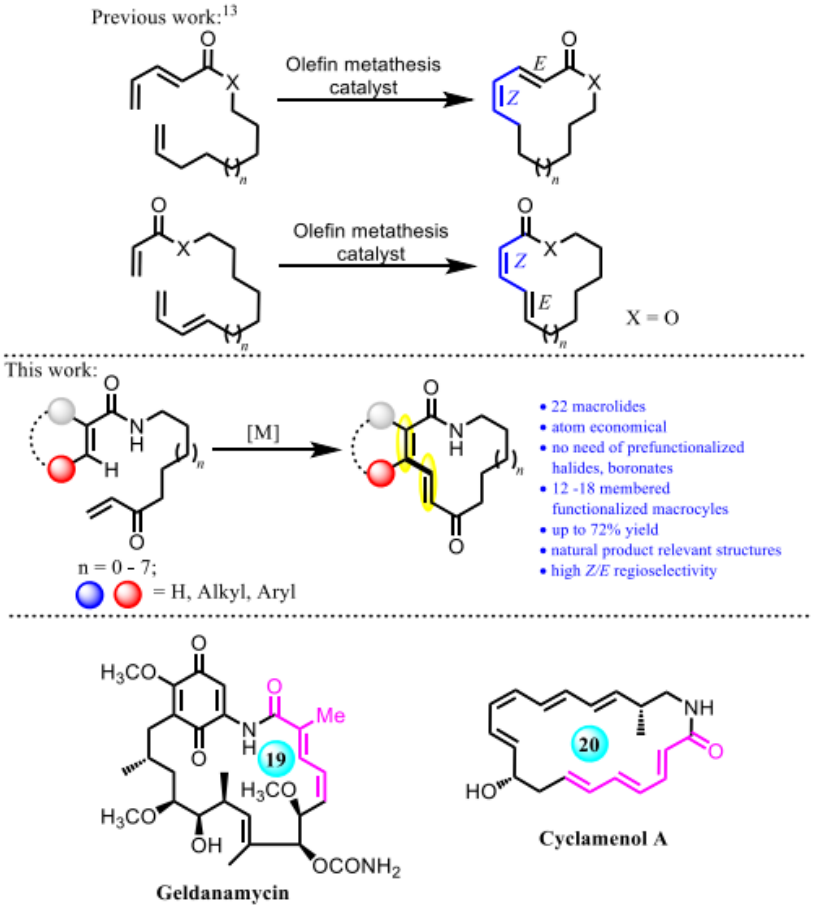

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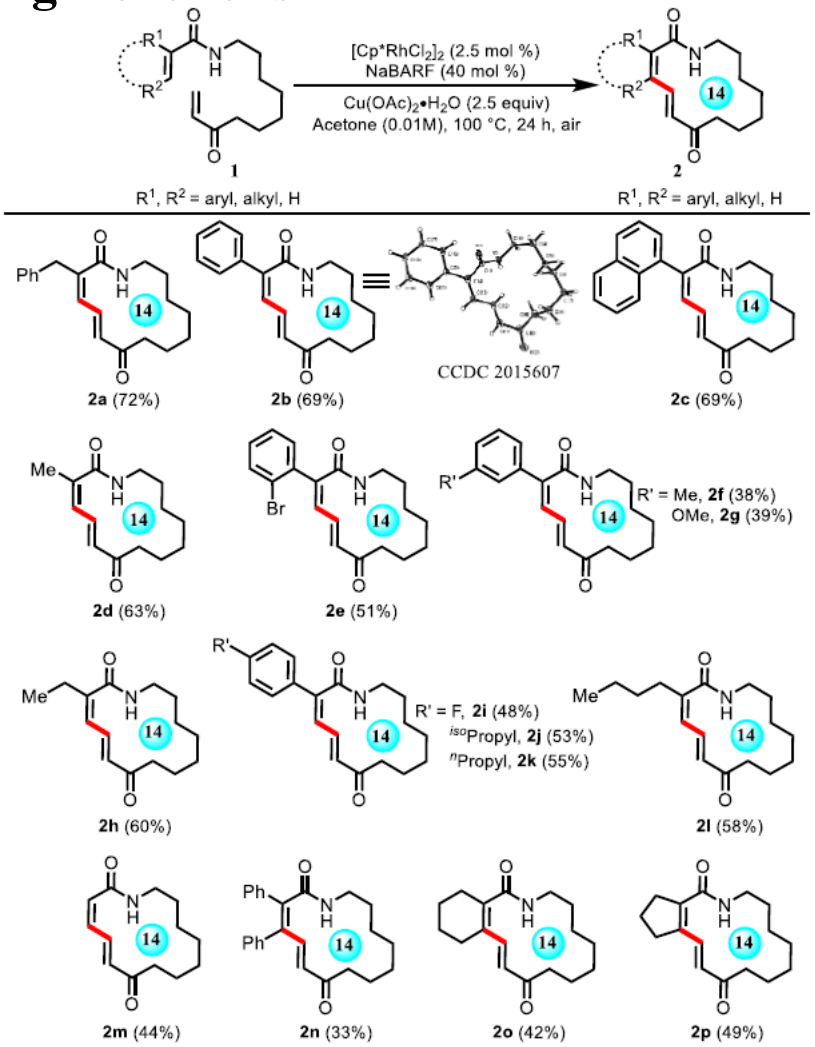

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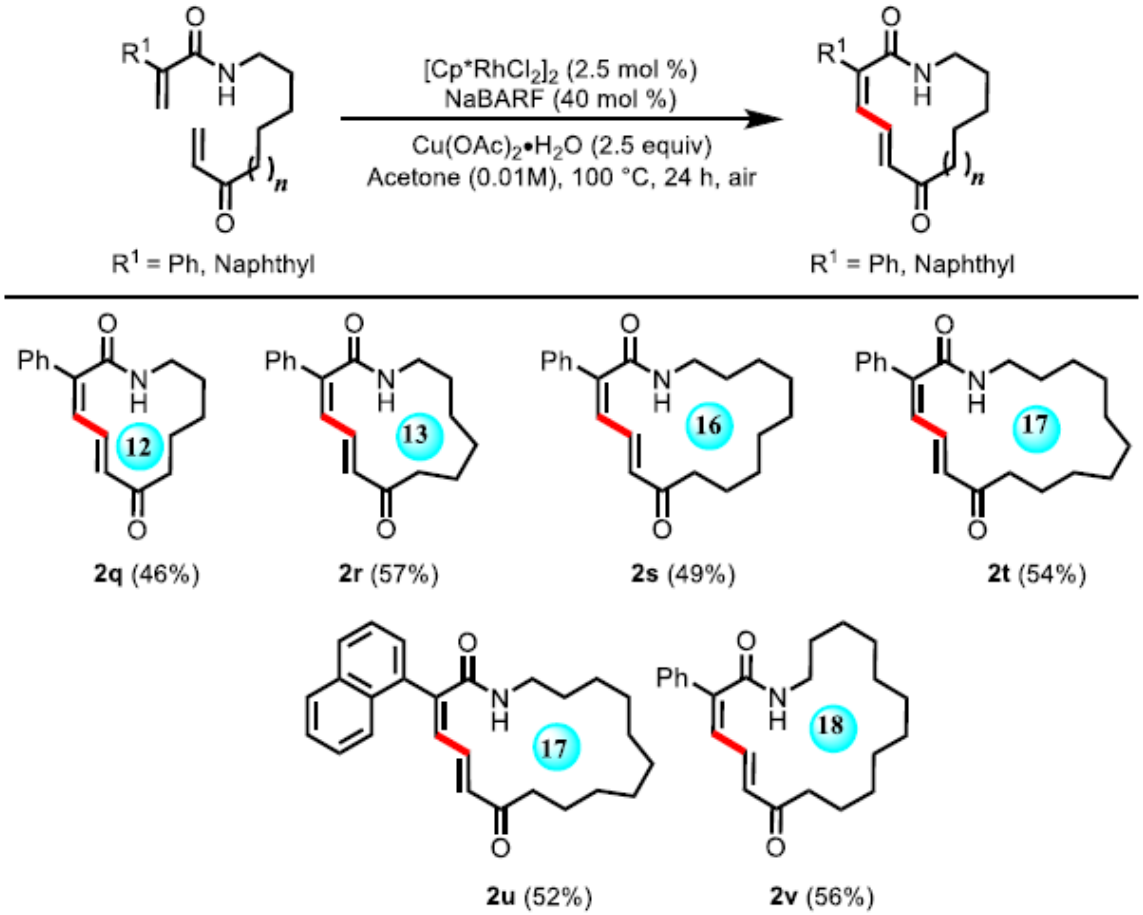
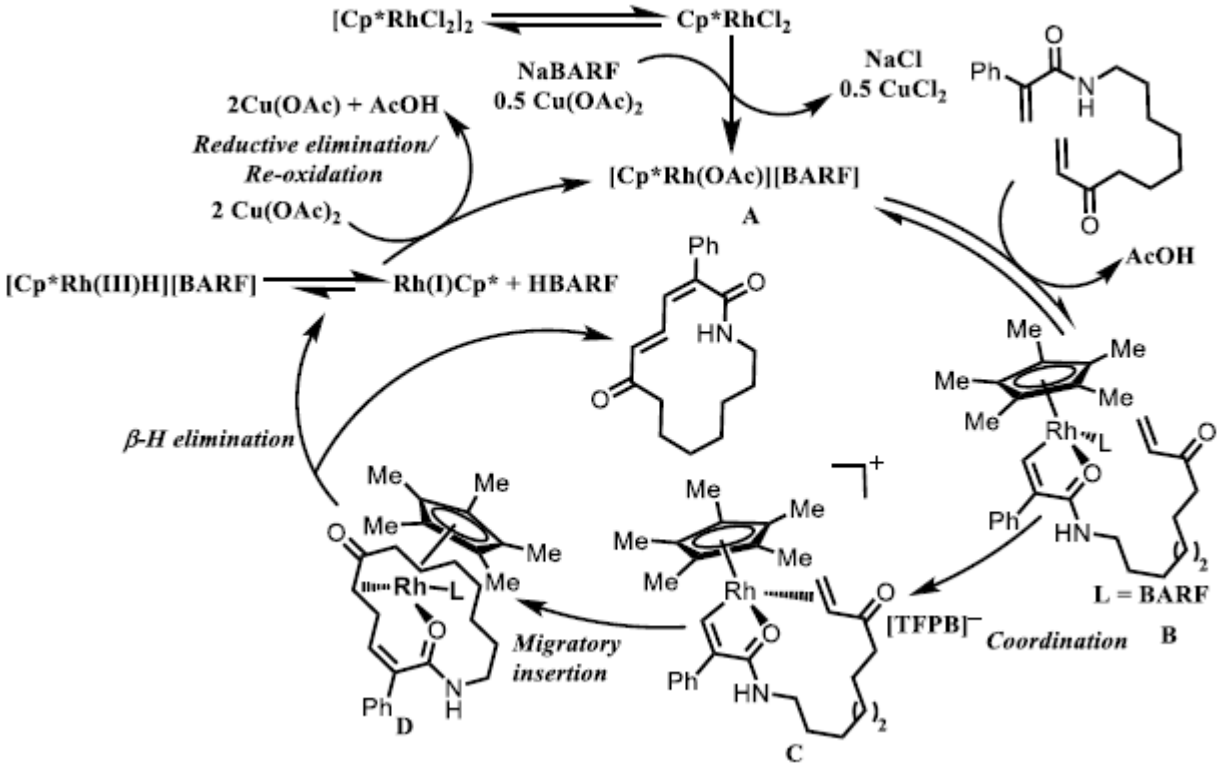


Introduction

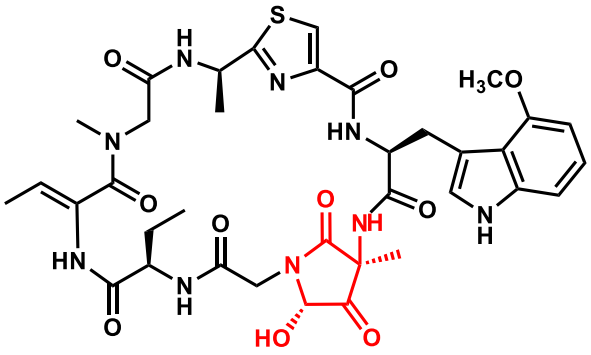
Part I : **Macrolactam Synthesis via Ring-Closing Alkene−Alkene Cross-Coupling Reactions**

Scheme 5. Proposed Mechanism

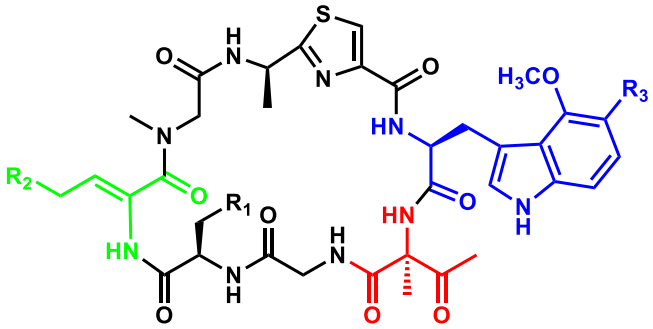


Introduction

Part II: **Zelkovamycins B−E, Cyclic Octapeptides Containing Rare Amio Acid Residues from an Endophytic *Kitasatospora sp.***



Zelkovamycin B



Zelkovamycin C, $R_1 = CH_3$, $R_2 = H$, $R_3 = OH$
Zelkovamycin D, $R_1 = CH_3$, $R_2 = OH$, $R_3 = H$
Zelkovamycin E, $R_1 = R_2 = R_3 = H$

Isolation

- Four novel Cyclic Octapeptides were isolated from an endophytic ***Kitasatospora sp.***

Biological activities:

- Zelkovamycin E displayed potent inhibitory a ctivity against H1N1 influenza A virus.

	H1N1		
Compounds	EC_{50}(μM)	CC_{50}(μM)	SI
Zelkovamycin B	Not tested	>100	Not tested
Zelkovamycin C	Not tested	>100	Not tested
Zelkovamycin D	34.8±0.1	>100	>2.9
Zelkovamycin E	0.3±0.05	44.8±2.0	149
ribavirin	15.4±0.9	>100	>6.5

M. L. Gan. et al, *Org. Lett.* **2020**, *22*, 9346–9350.

Introduction

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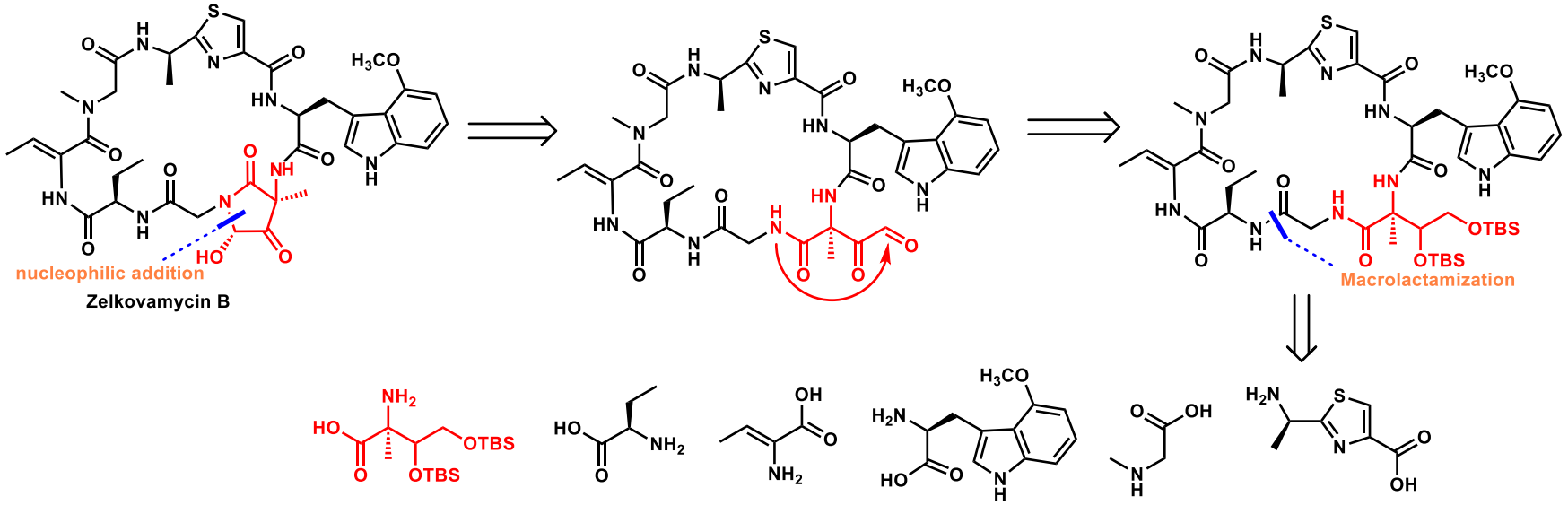
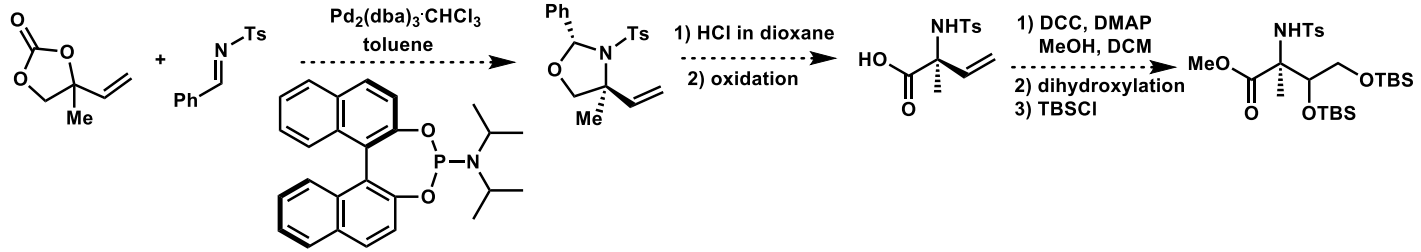
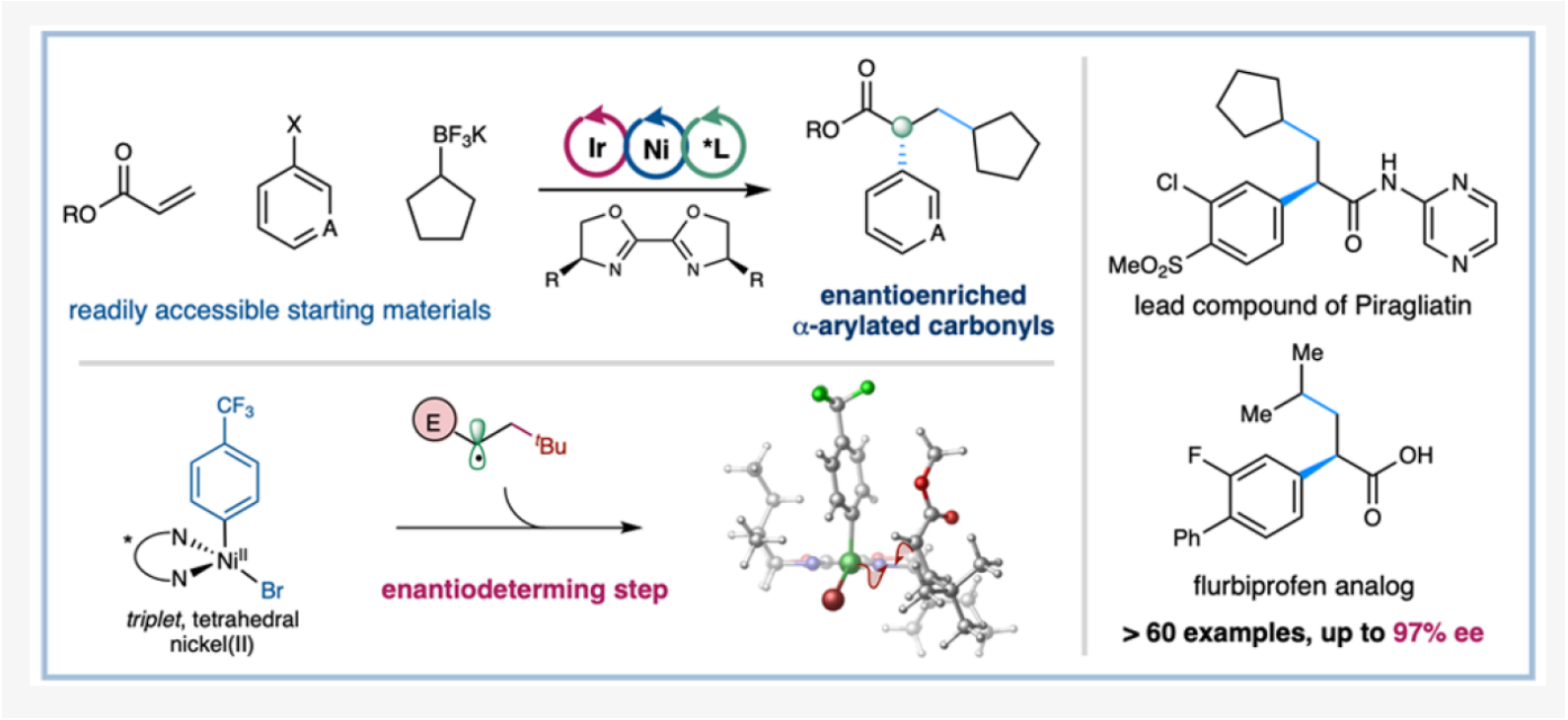




Y. J. Zhang. et al, *Org. Lett.* **2015**, *17*, 6230−6233.

Introduction

Part III: **General Method for Enantioselective Three-Component Carboarylation of Alkenes Enabled by Visible-Light Dual Photoredox/Nickel Catalysis**



L. L. Chu. et al, *J. Am. Chem. Soc.* **2020**, *142*, 20390−20399.

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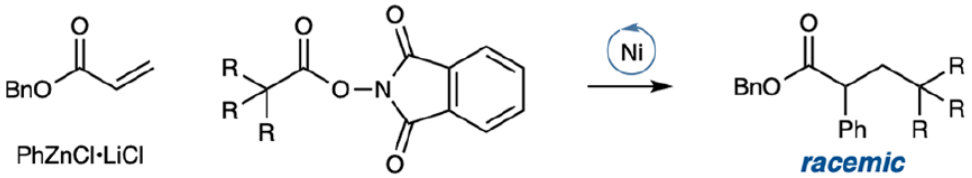
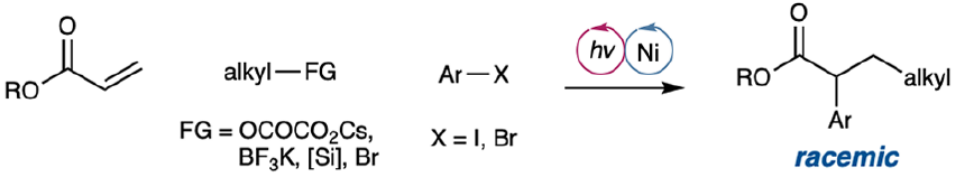
Part III: **General Method for Enantioselective Three-Component Carboarylation of Alkenes Enabled by Visible-Light Dual Photoredox/Nickel Catalysis**

B) Prior work on Ni-catalyzed three-component alkylarylation of acrylates

Baran (2015)

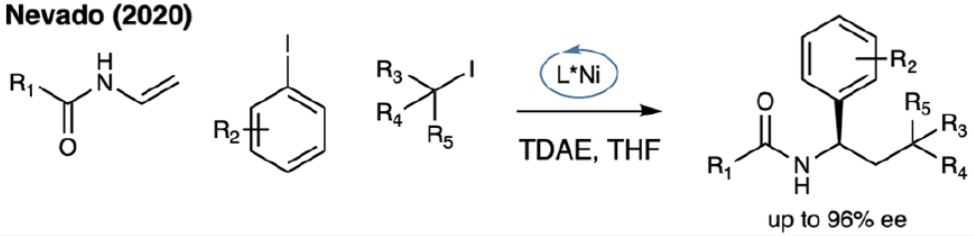


Molander, Nevado, Martin, Chu (2019-2020)



C) Prior work on enantioselective three-componet alkylarylation of alkenes via Ni-catalyzed reductive coupling (Chu and Nevado)

Nevado (2020)



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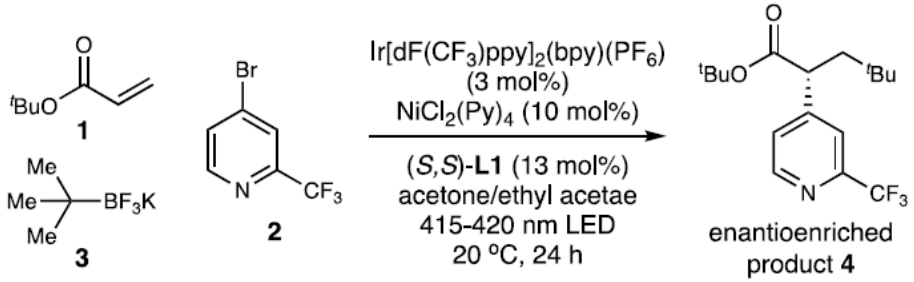
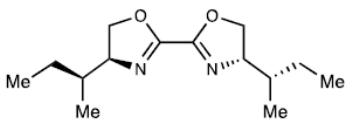
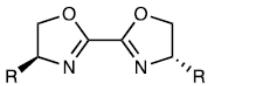
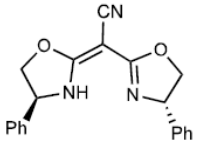


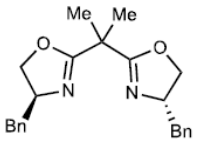
Entry	Chiral ligand	Yield	ee
1	(*S*,*S*)-**L1**	82%	95%
2	(*S*,*S*)-**L2**	21%	7%
3	(*S*,*S*)-**L3**	60%	86%
4	(*S*,*S*)-**L4**	76%	72%
5	(*S*,*S*)-**L5**	60%	82%
6	(*S*,*S*)-**L6**	83%	88%
7	(*S*,*S*)-**L7**	87%	88%
8	(***R***,***R***)-**L8**	74%	-88%
9	(*S*,*S*)-**L9**, (*S*,*S*)-**L10**, (*S*)-**L11**	5%~ 78%	3%~ 24%

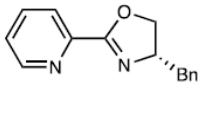




L2 R = ^{t}Bu; **L3** R = Ph; **L4** R = Bn;
L5 R = ^{i}Pr; **L6** R = Cp; **L7** R = Cy;
(*R*,*R*)-**L8** R = *i*-heptyl







L. L. Chu. et al, *J. Am. Chem. Soc.* **2020**, *142*, 20390−20399.

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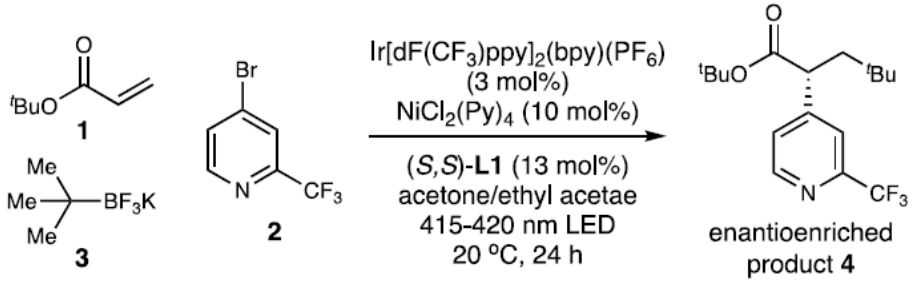

Entry	Variations from the "standard conditions"	Yield	ee
10	10 °C, instead of 20 °C	80%	95%
11	w/o [Ir], [Ni], (*S*,*S*)-**L1**, or light	0%	--
12	^{t}BuOCOCO$_2$Cs, instead of **3**	trace	--

L. L. Chu. et al, *J. Am. Chem. Soc.* **2020**, *142*, 20390−20399.

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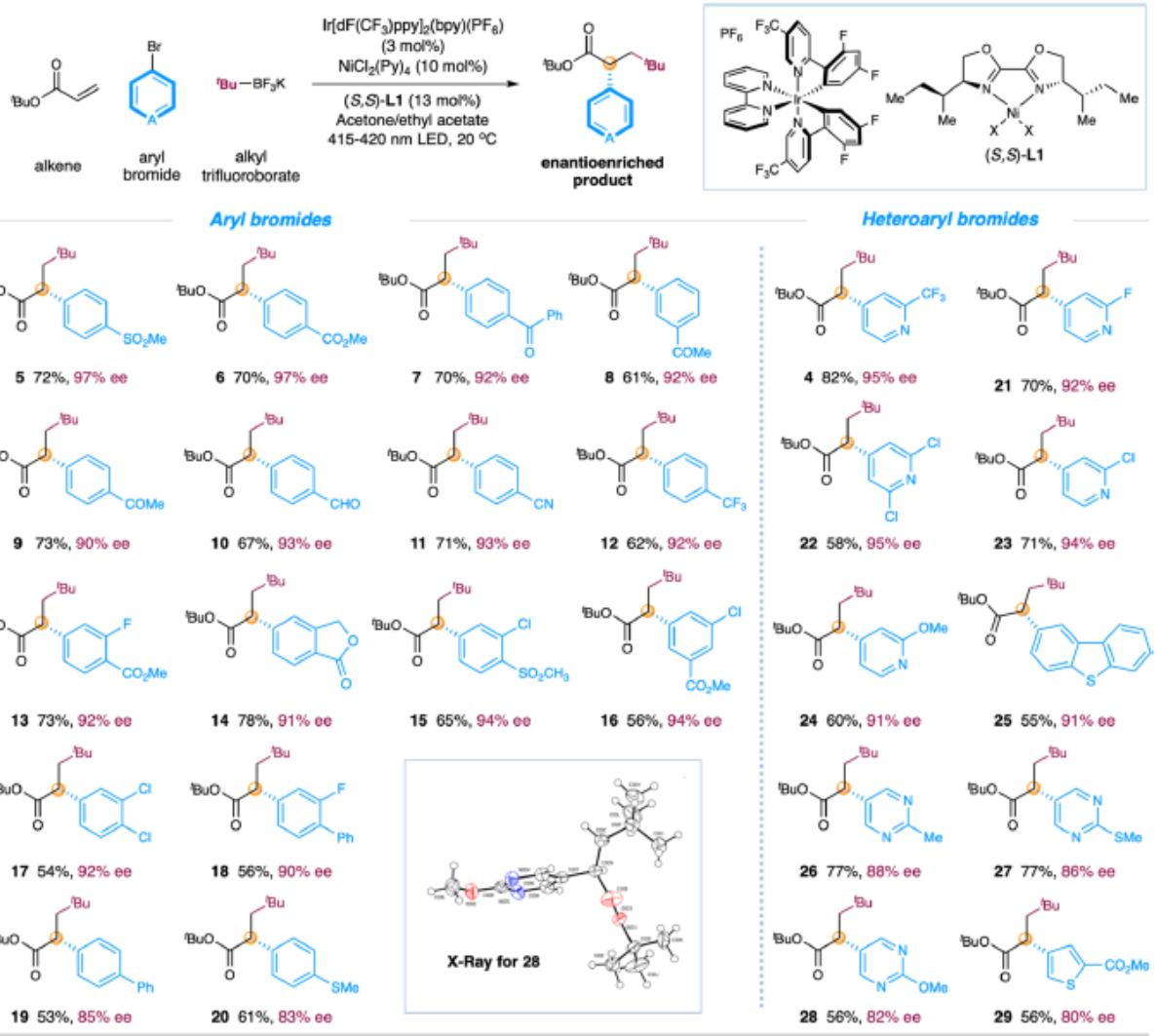

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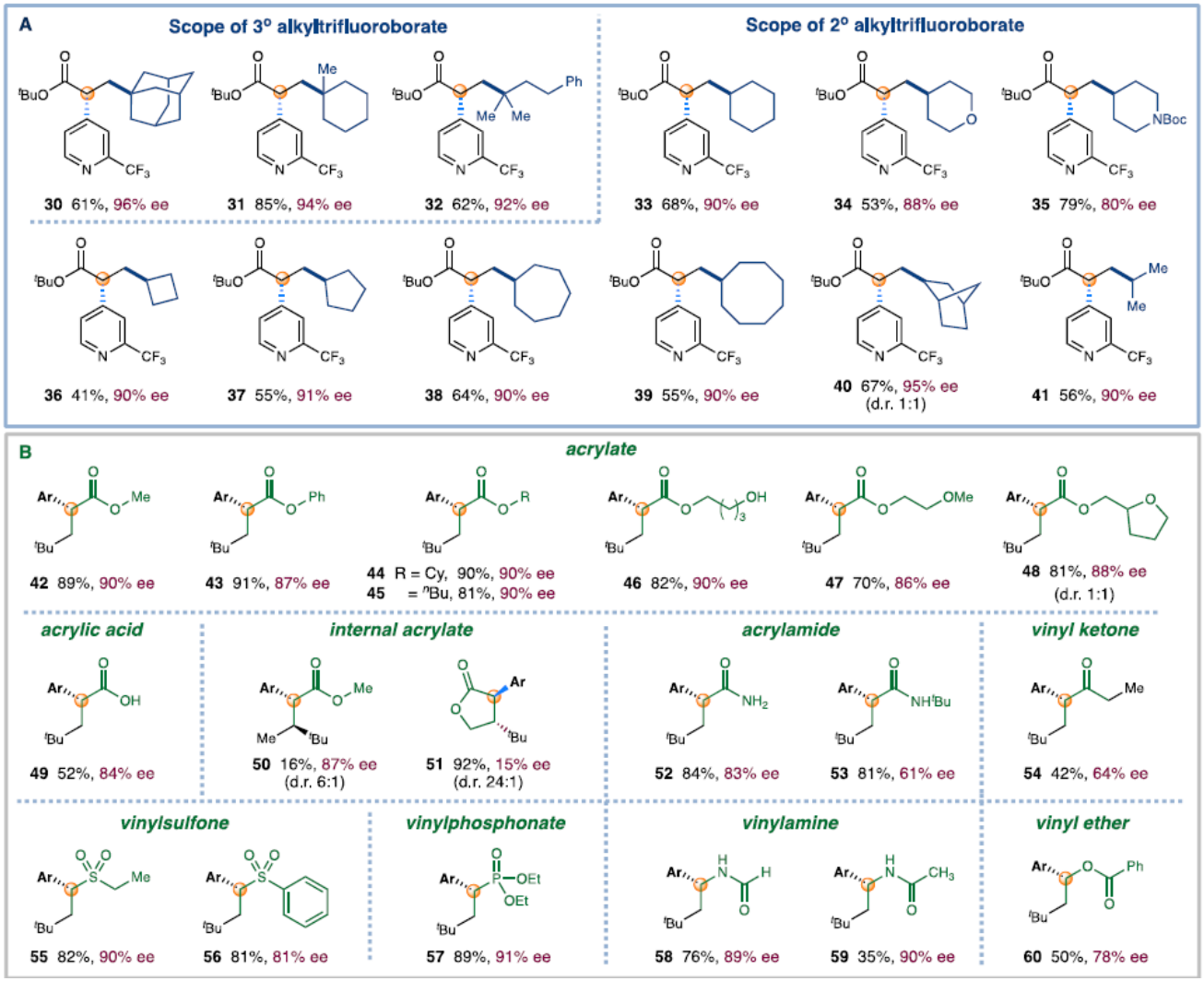

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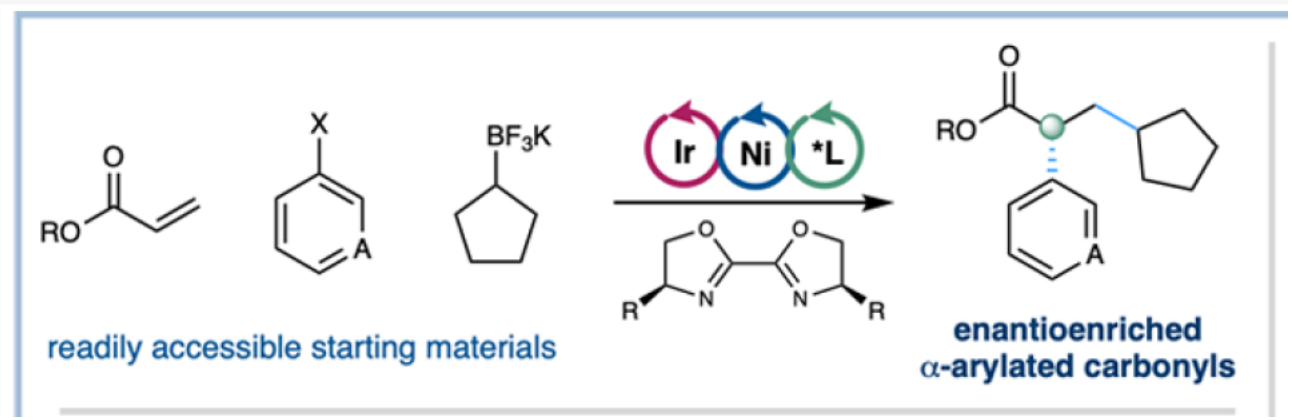

- the factors controlling the regioselectivity;
- the factors controlling the **enantioselectivity**;
- the preference of the three-component carboarylation over the direct arylation of the generated alkyl radical(**chemselectivity**).

L. L. Chu. et al, *J. Am. Chem. Soc.* **2020**, *142*, 20390−20399.

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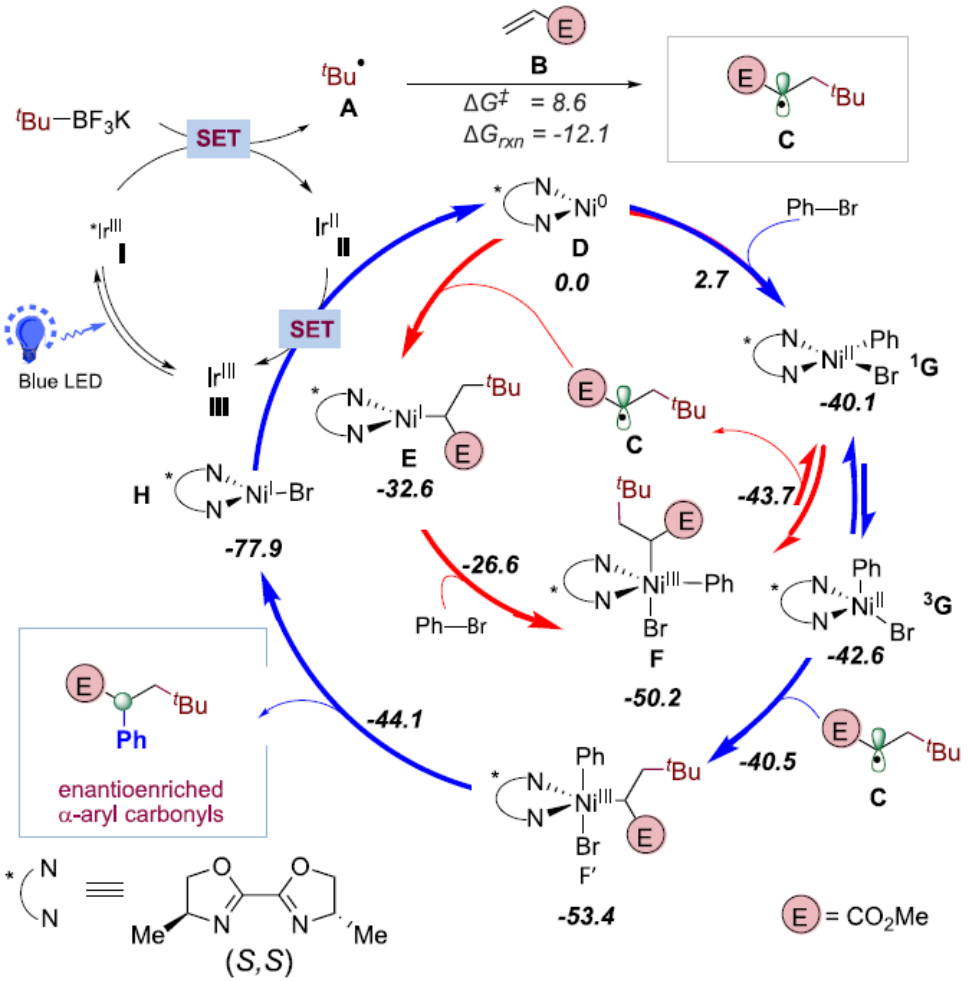

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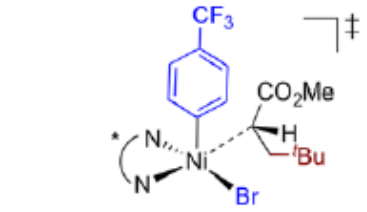
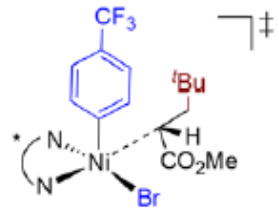
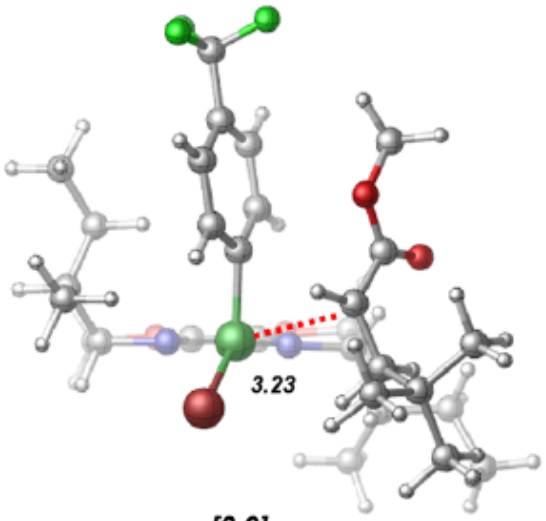


^{2}G-TS-F'^{R}-B^{CF3}



^{2}G-TS-F'^{S}-B^{CF3}



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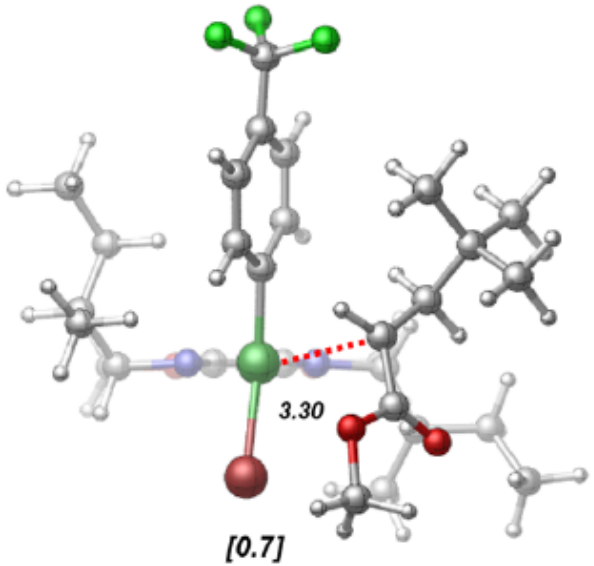

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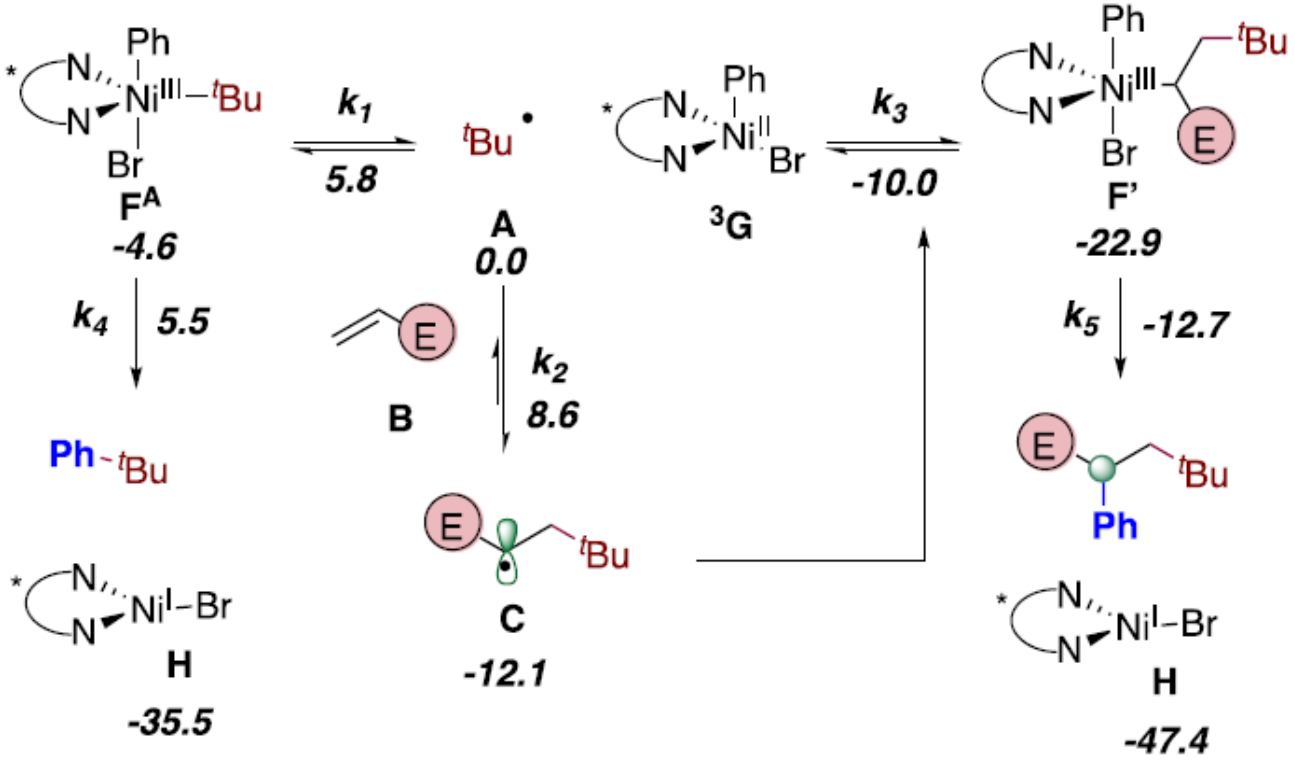
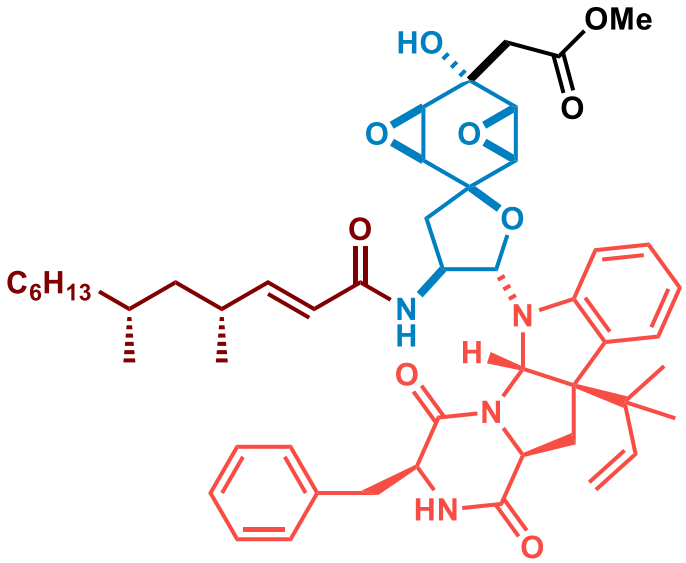


Origin of Chemoselectivity of the Model System

Total synthesis of (-)-penicimutanin A and Related congeners



penicimutanin A

T. Xu et al, *Chem. Sci.* **2020**, *11*, 656–660.

Contents

Introduction

Tao Xu

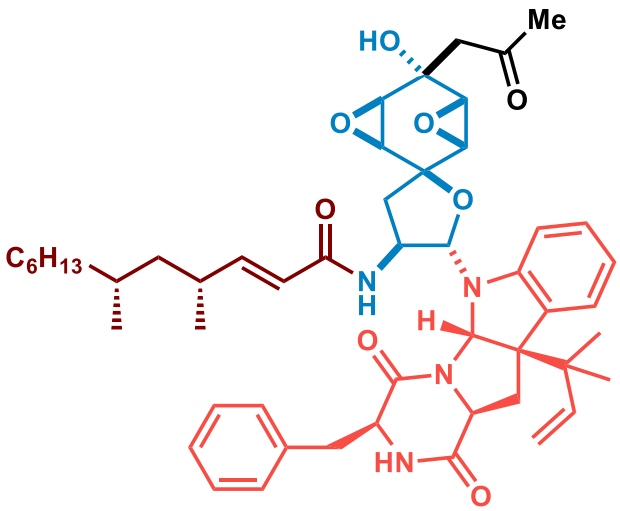
Education & Current job:

-Ph.D.: 2011, Peking University
-Postdoctoral Fellow: 2015, University of Texas at Austin
-Professor: 2015-now, Ocean University of China

Research Interests & Areas:

- Natural Product Synthesis
- Complex ring system structure methodology

Introduction



penicimutanin A

Isolation

- Penicimutanin A, isolated from a marine-derived fungal strain identied as Penicillium purpurogenm G59 in 2018.

Biological activities:

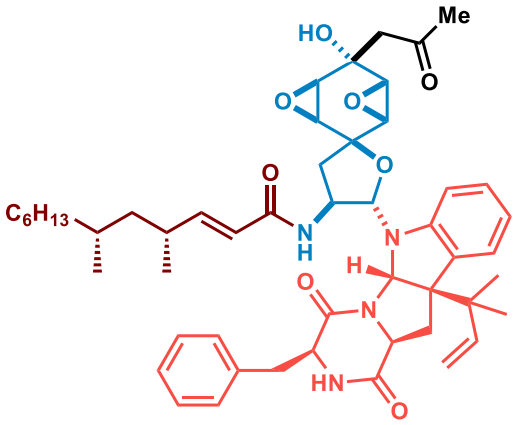
- Penicimutanin A demonstrated in vivo antitum or activity in murine sarcoma HCT116 tumor-bearing Kunming mice.

Structural features

- Labile C2 hemi-aminal ether.
- Diketopiperazine fused hexapyrroloindoline.
- Fully oxygenated cyclohexane ring contains an acid/base-sensitive cis-bisoxirane moiety.

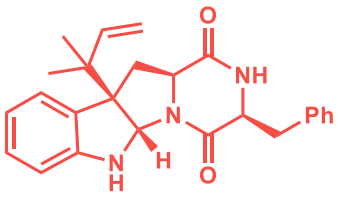
H. J. Zhu. et al, *Eur. J. Med. Chem.*, **2018**, *158*, 548.

Retrosynthetic Analysis



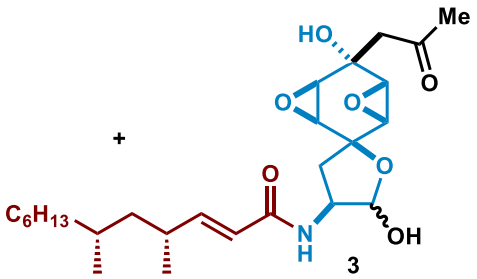
penicimutanin A (1)

hemi-aminal ether formation



2

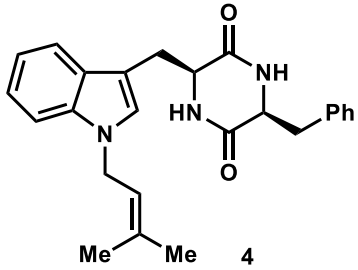
+



3

aza-Claisen/ cyclization

diastereo selective addition



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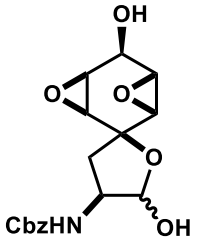
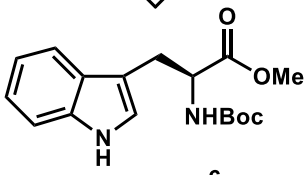
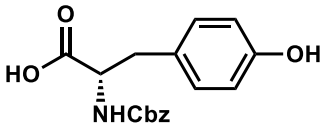


5

oxidative dearomatization



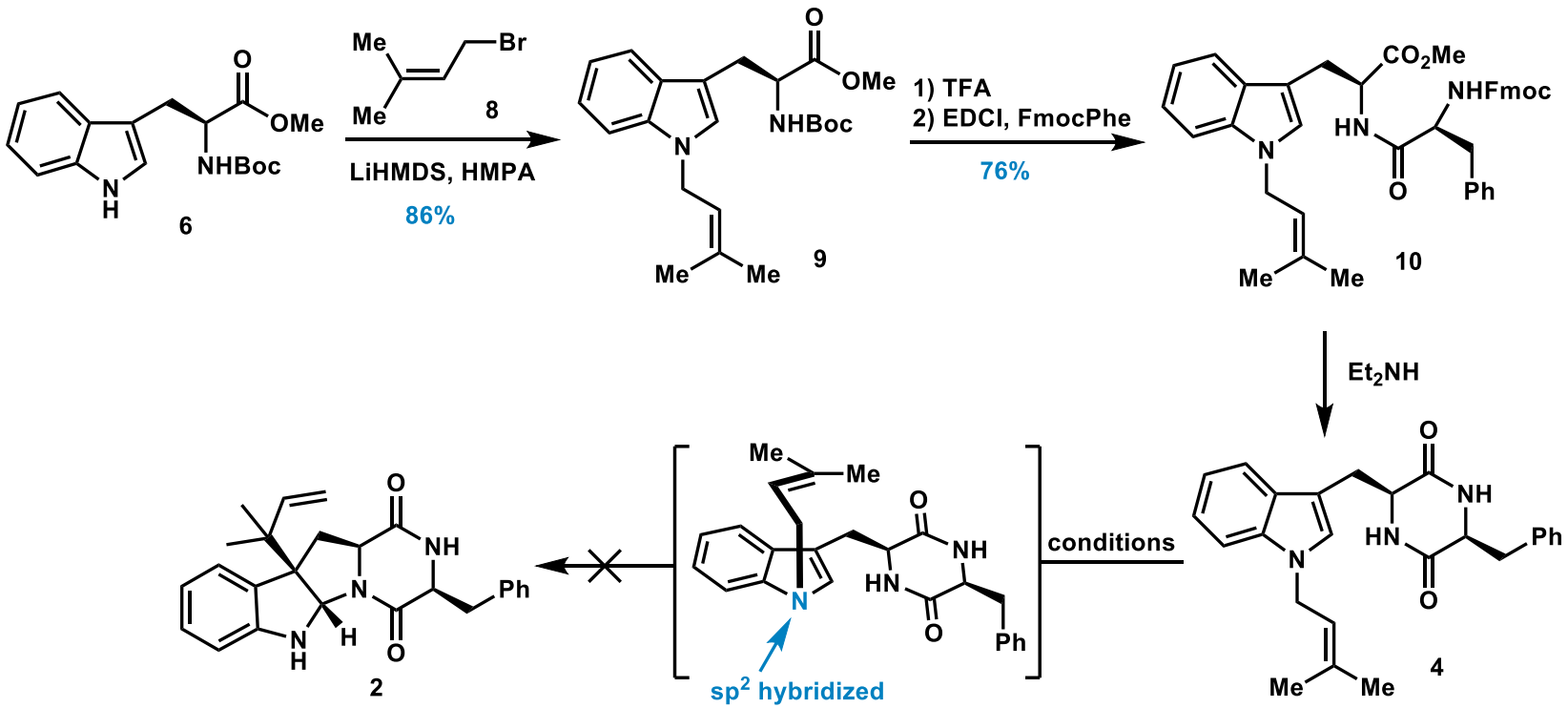
6



7

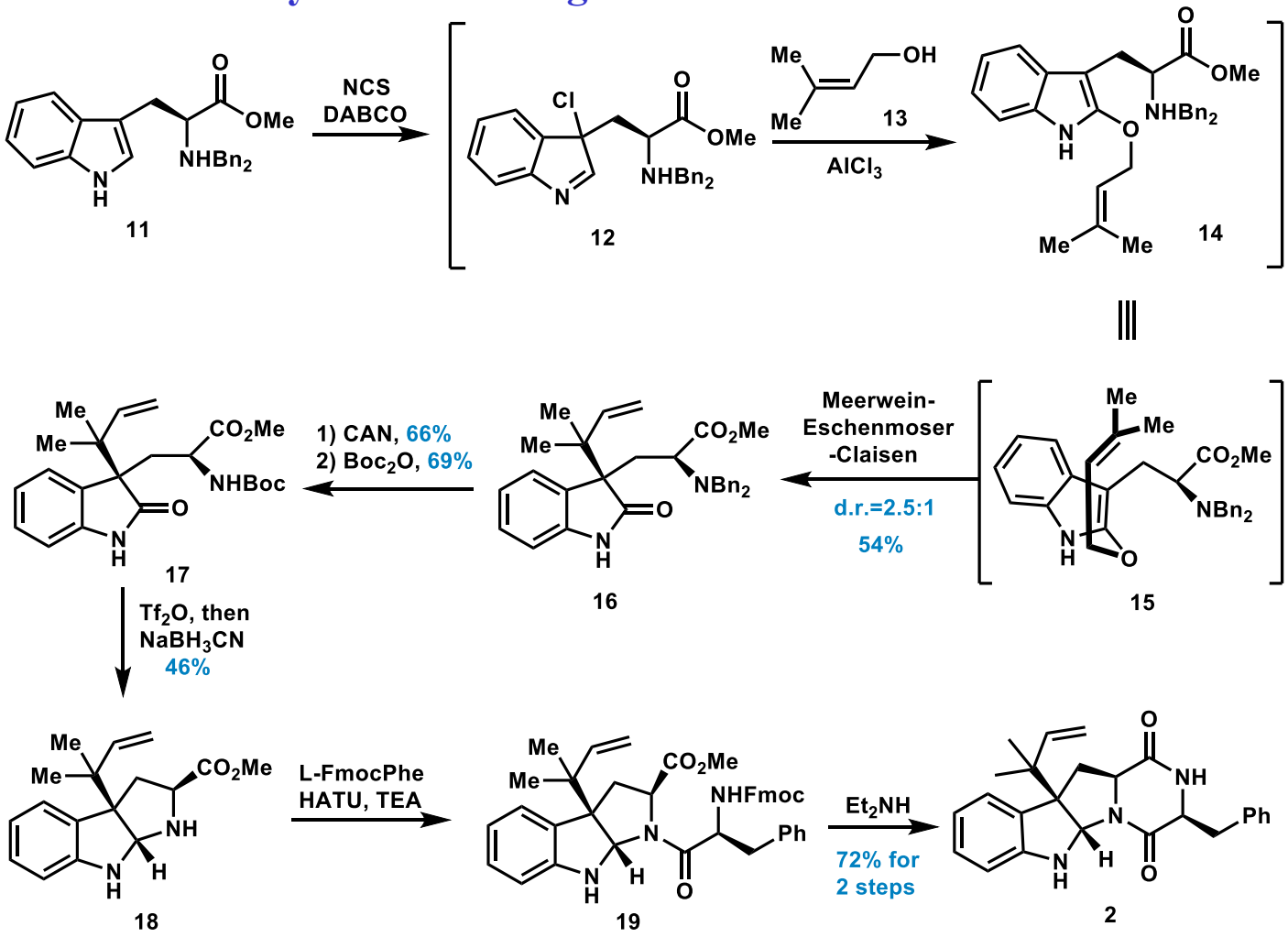
Synthetic Route

1st generation Route of Synthesis of Fragment 2



Synthetic Route

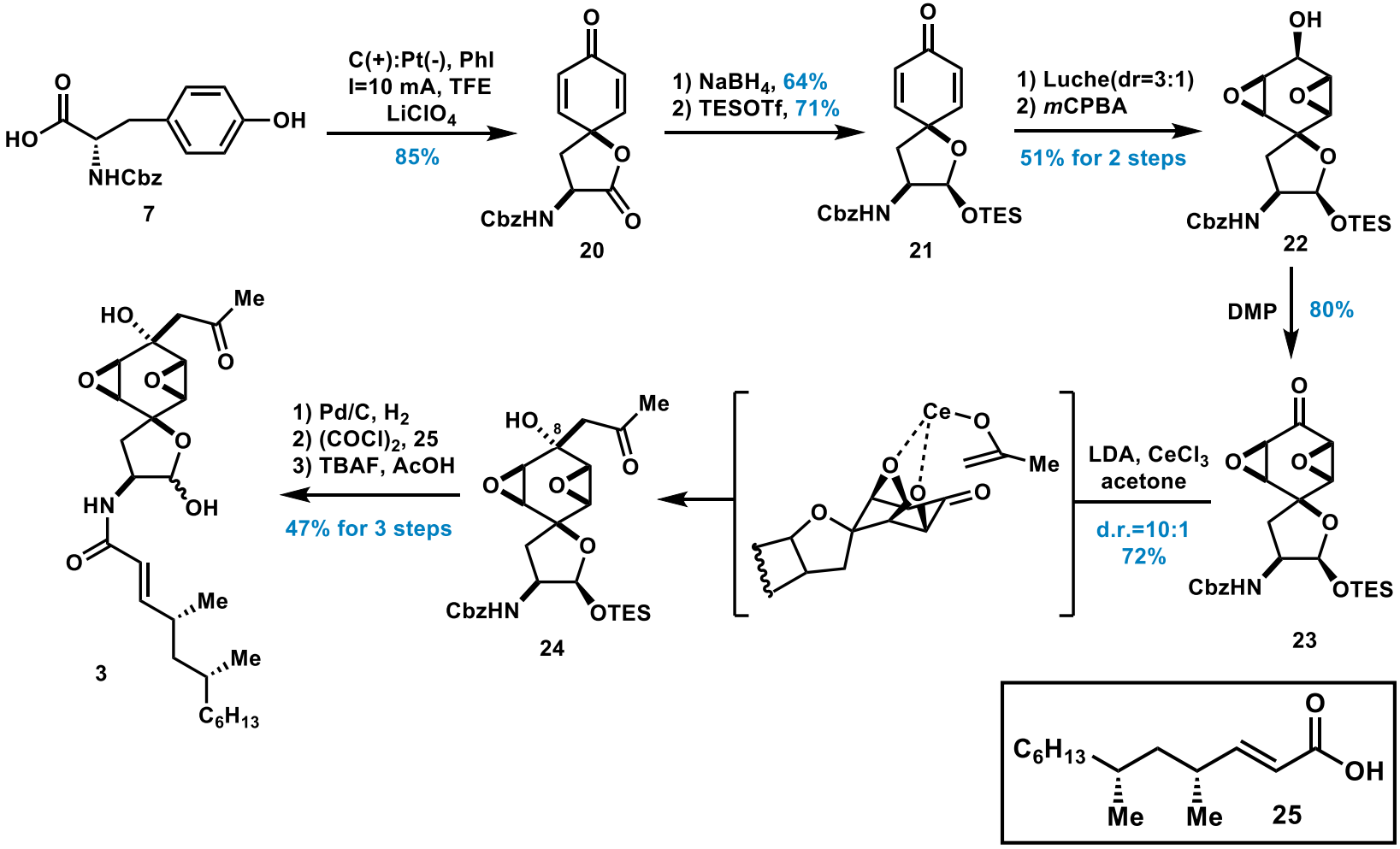
2st generation Route of Synthesis of Fragment 2



M. Voyle. et al, *Tetrahedron Lett.* **2000**, *41*, 4657.

Synthetic Route

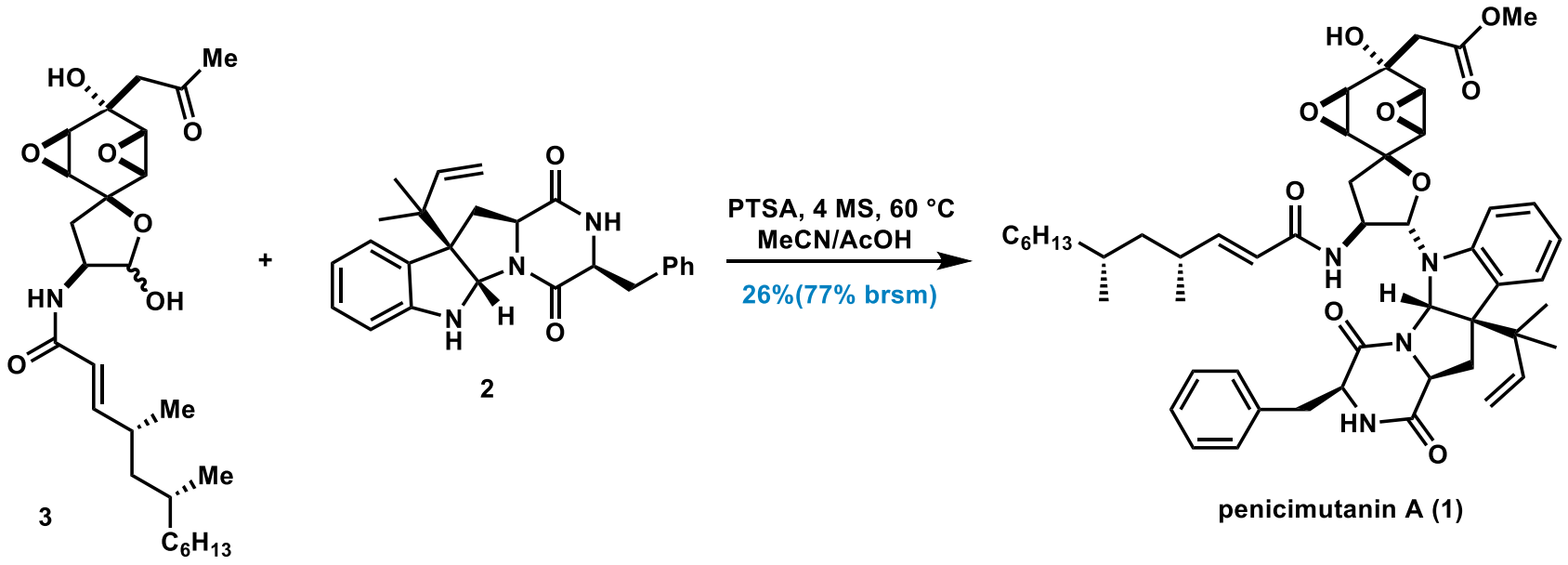
Synthesis of Fragment 3



M. B. Meyers. et al, *J. Am. Chem. Soc.* **1963**, *85*, 3702.

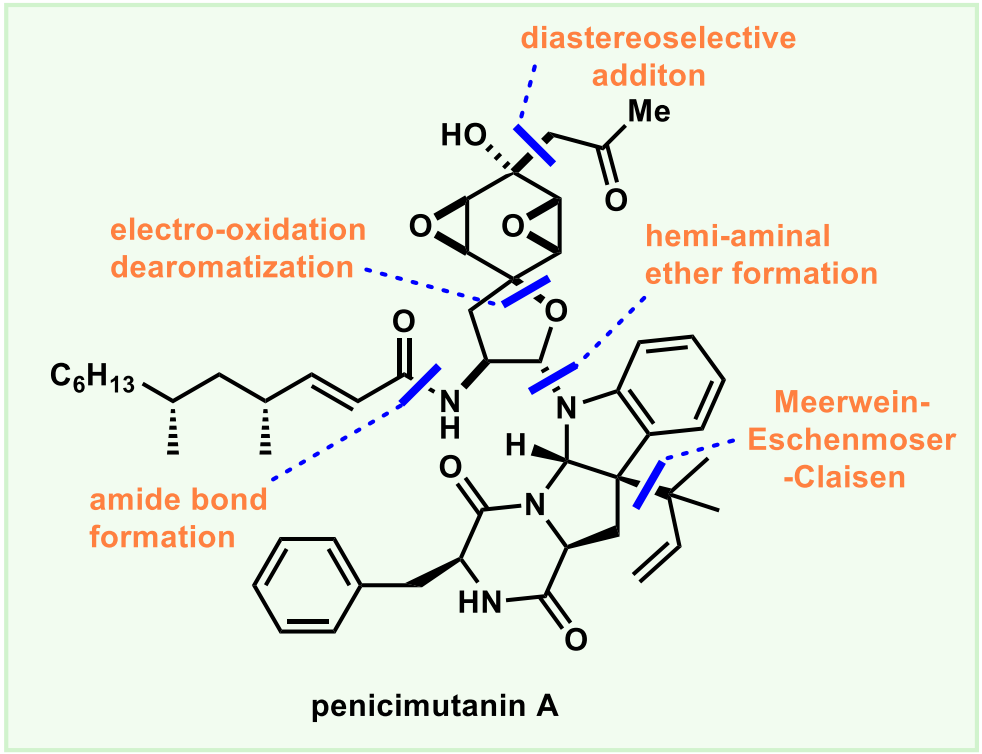
Synthetic Route

Completed total Synthesis of penicimutanin A



M. J. Dai et al, *Curr. Org. Chem.* **2016**, *20,* 1850.

Summary



penicimutanin A

longest liner 10 steps

The End

Thanks for your attention!

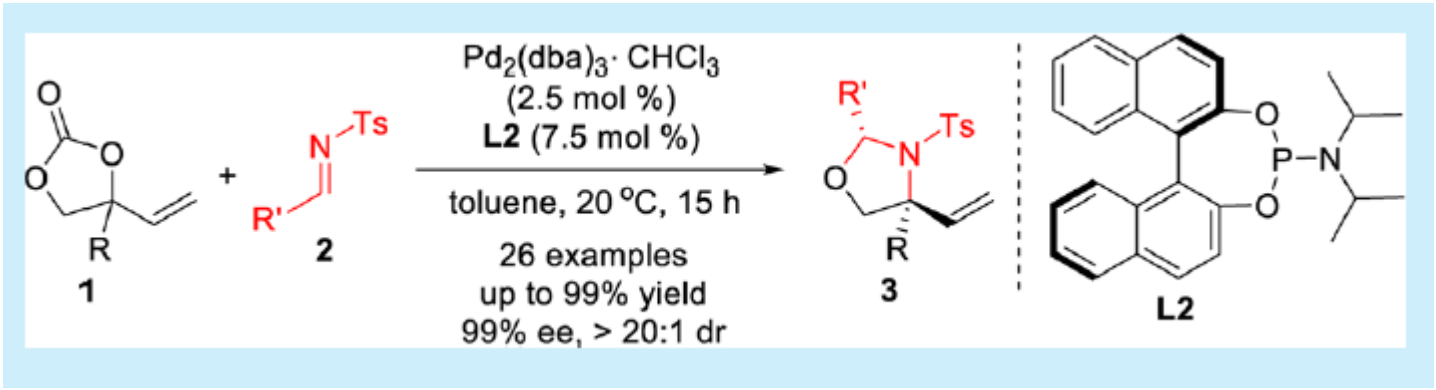
Acknowledgement

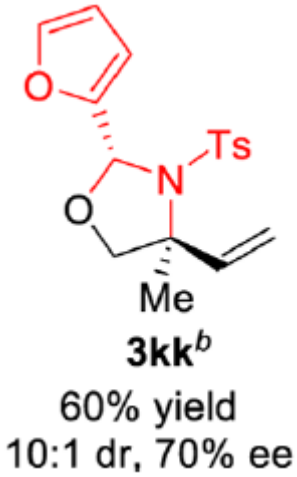
Prof. Tao Ye and Dr. Yi-an Guo;

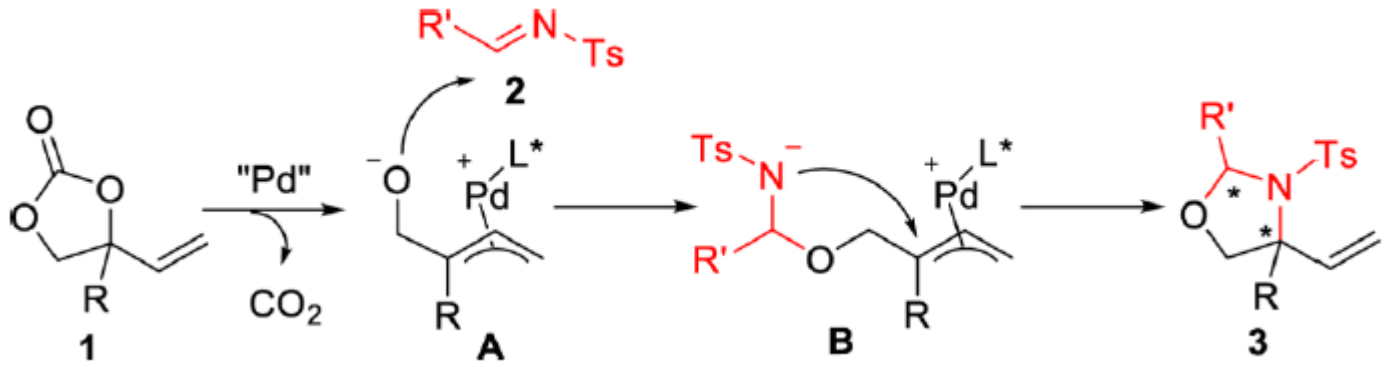
All professors and faculties in SCBB;

All my labmates in F211!

Synthetic Route







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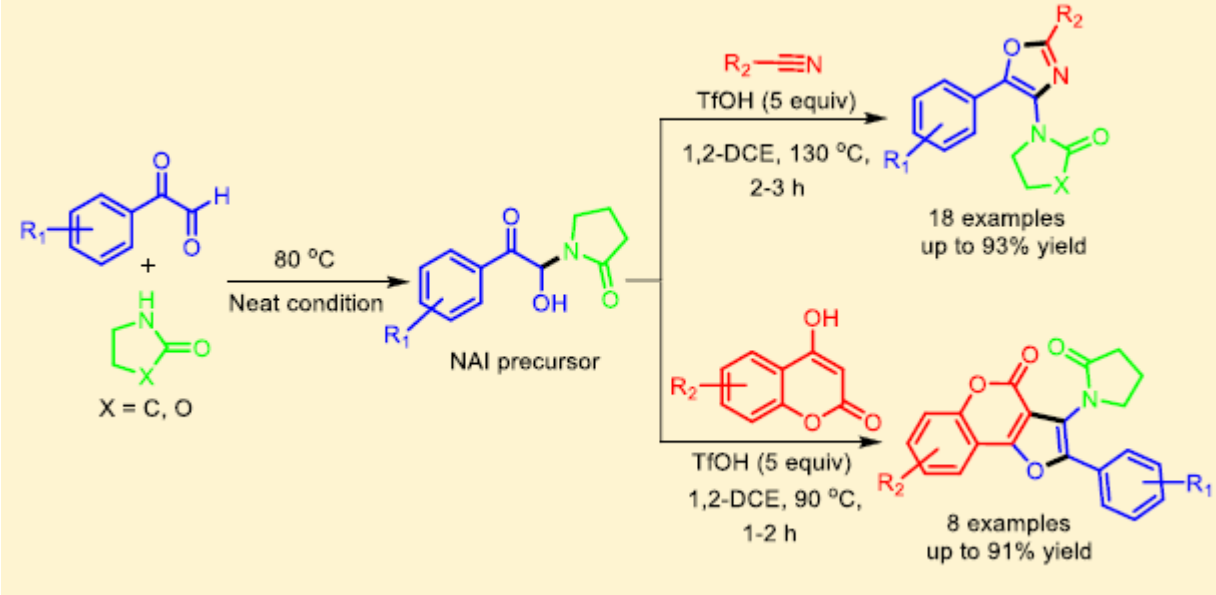

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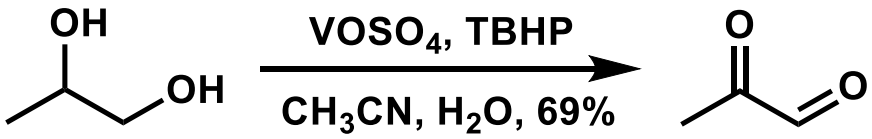
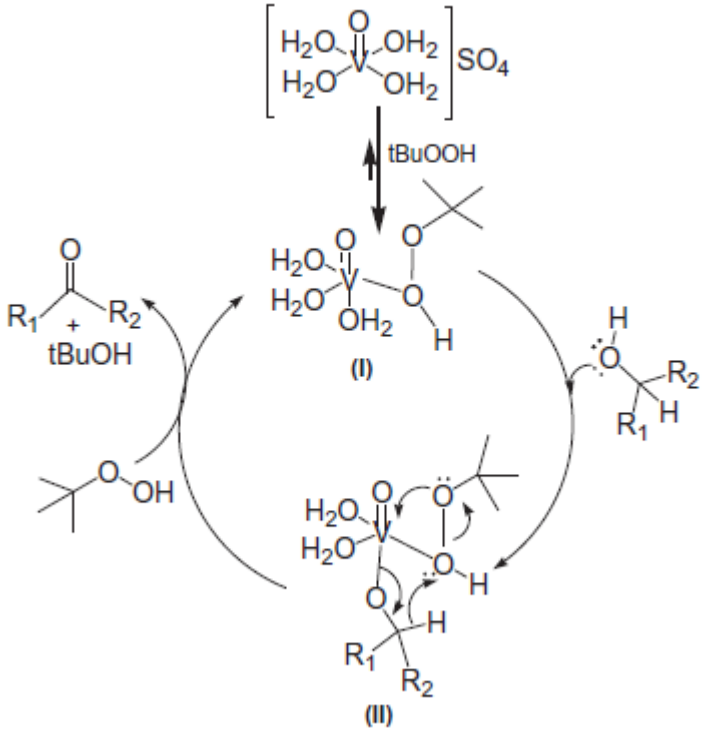
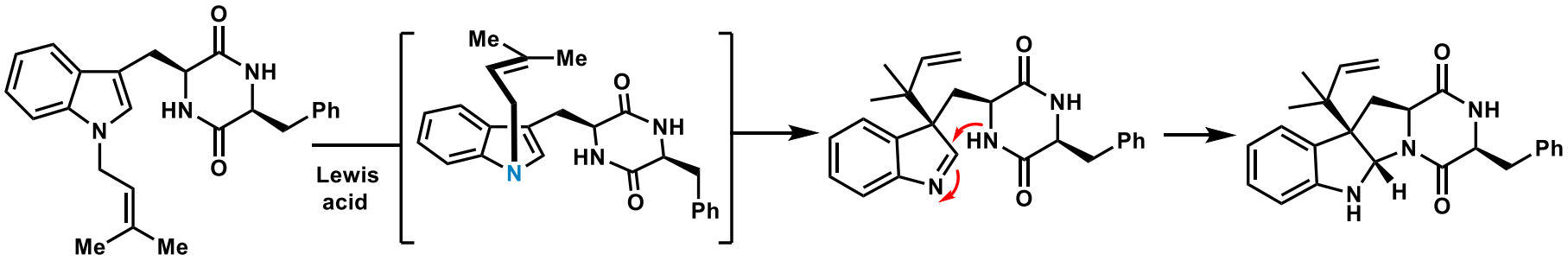


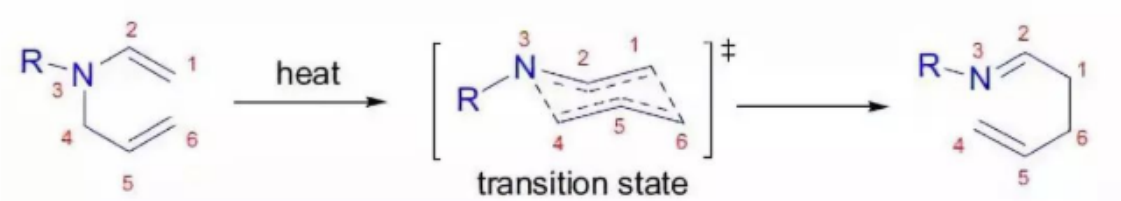


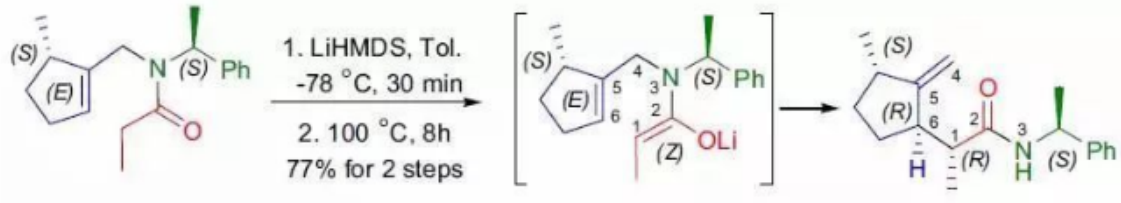
Supporting Materials

Aza-Claisen/cyclization



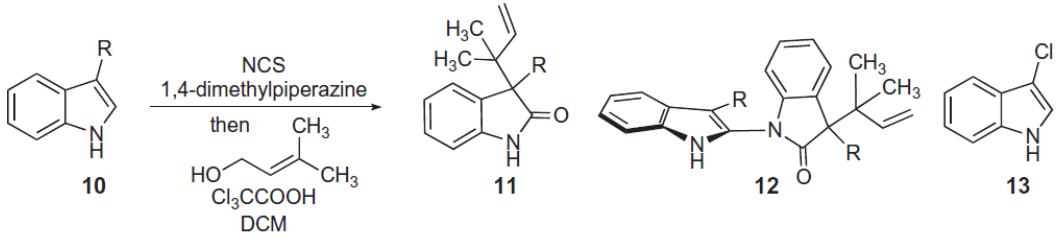
底物通过一个椅式过渡态（胺上的取代基处于平伏键），进行[3,3]-σ迁移得到产物。



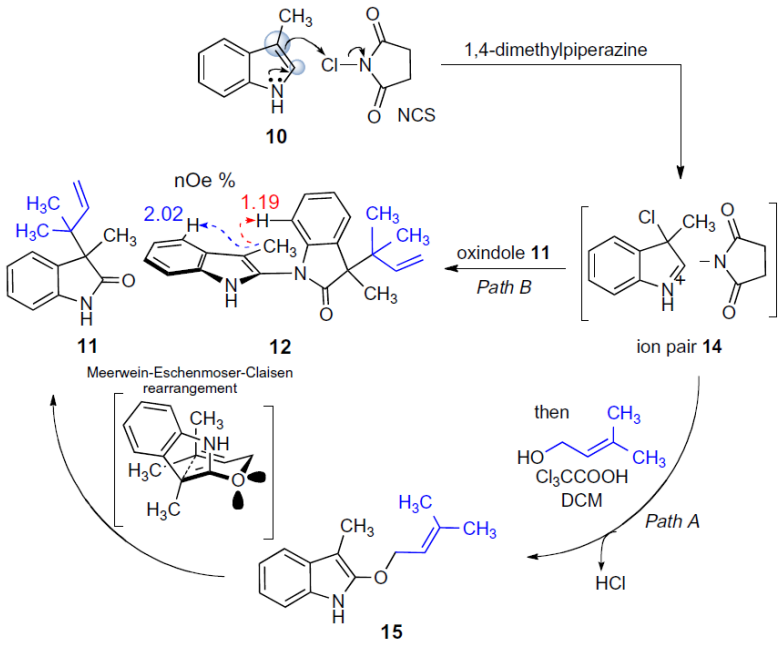


Supporting Materials

Meerwein–Eschenmoser–Claisen rearrangement

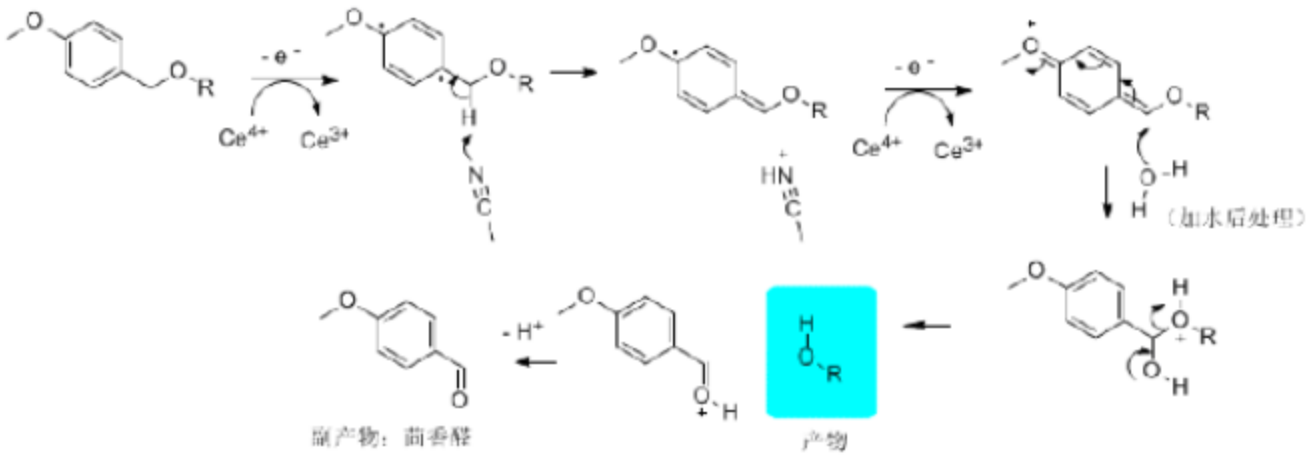


Entry	C3 substitution	% Yield of **11**[a]	% Yield of **12**[a]	% Yield of **13**[a]
1	R = H only 3-chloroindole formed	nd[b]	nd	Quant.
2	R = CH_3	37.7	2.6	nd
3	R = CH_2CH_2NPhth[c]	85	nd	nd
4	R = $CH_2CH_2N(CH_3)Nos$[d]	74	nd	nd



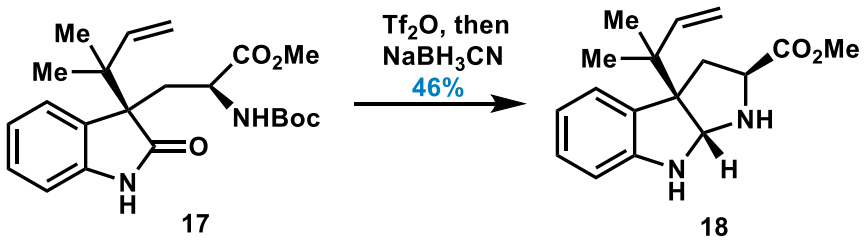
were replaced by a hydrogen, which can be lost as a proton to the media, the corresponding ion pair will result in 3-chloroindole **13**. However, in the absence of a C3 proton, dimethylallyl alcohol reacted with this ion pair and caused an addition to occur, leading to, a precursor for an ensuing Meerwein-Eschnmoser-Claisen rearrangement, after the loss of an equivalent of HCl (*path A*). In our experience and of others, this allyloxyimidate **15** was transforming immediately even at ambient temperature into its corresponding rearranged oxindole product **11**. The primary driving force for this thermodynamically driven downhill process is accountable based on the fact that an amide bond is generated in the event. In contrast, if the ion pair **14** is encountering the oxindole **11** itself as a nucleophile, especially promoted in the presence of basic components in the reaction mixture, the mechanistic cascade is projected to lead to formation of a different oxindole **12**.[12] In the case of C3 methyl substitution, this dimeric adduct was indeed observed, albeit in low conversion, and was structurally characterized using

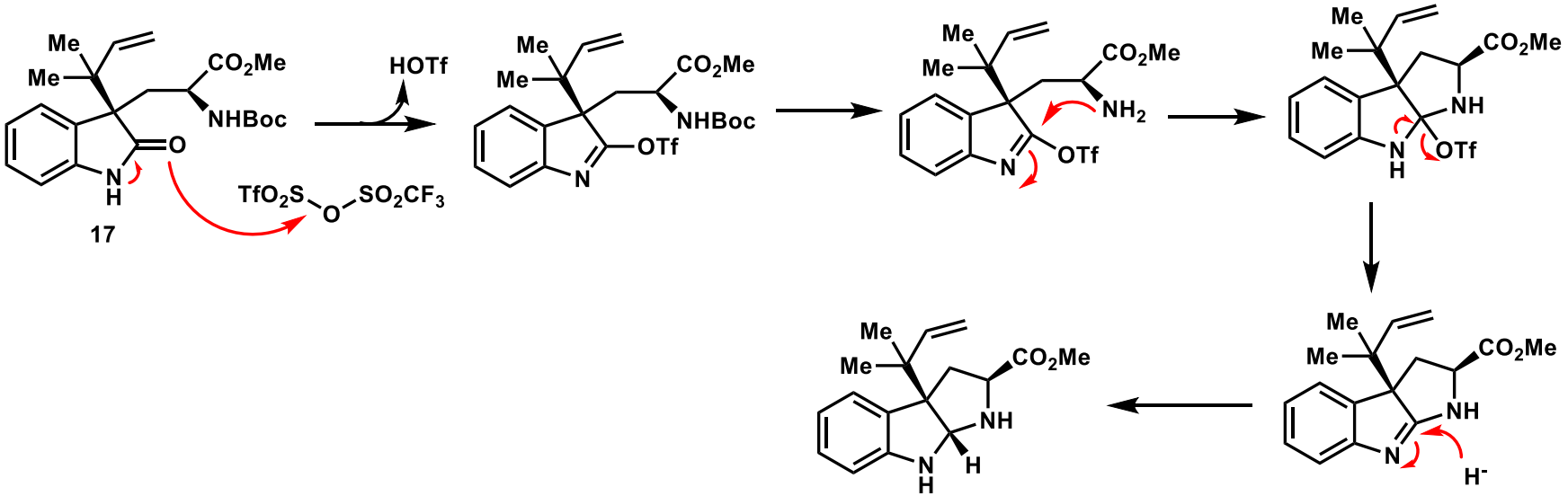
Supporting Materials



Supporting Materials

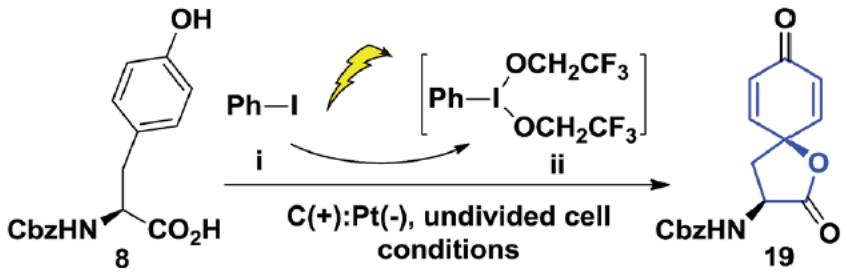
reductive amination





Supporting Materials

oxidative dearomatization

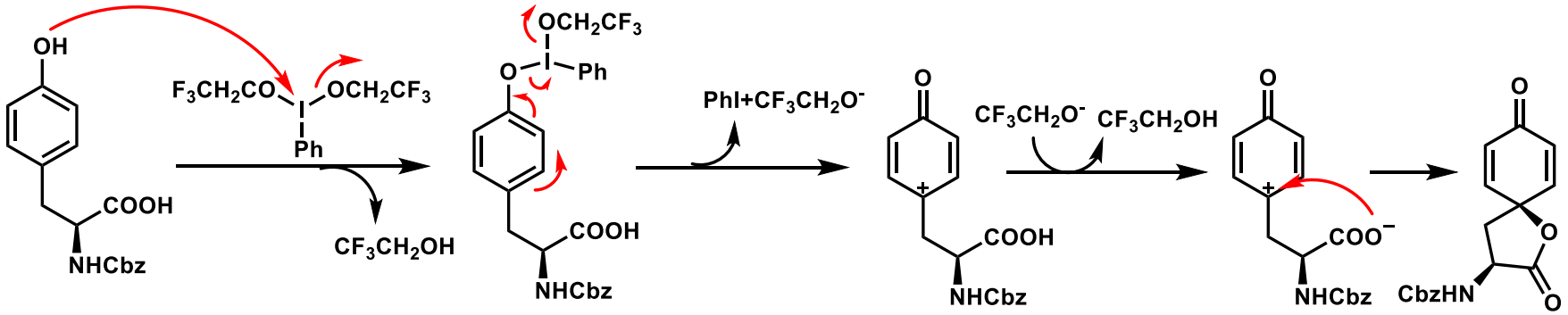


Entry[a]	Conditions	Time	Yield[b] (%)
1	$LiClO_4$ (1 eq.), I = 2.1 mA, PhI (1 eq.)	8 h	38
2	$LiClO_4$ (10 eq.), I = 6.1 mA, PhI (4 eq.)	4 h	64
3	$LiClO_4$ (10 eq.), I = 6.1 mA, PhI (4 eq.)	6 h	65
4	$LiClO_4$ (13 eq.), I = 10 mA, PhI (5 eq.)	6 h	65
5	$LiClO_4$ (15.6 eq.), I = 10 mA, PhI (6 eq.)	3 h	65
6[c]	$LiClO_4$ (13 eq.), I = 10 mA, PhI (5 eq.)	4 + 6 h	82
7[d]	**$LiClO_4$ (15.6 eq.), I = 10 mA, PhI (6 eq.)**	**5 + 5 h**	**85**

[a] All reactions were run with $LiClO_4$ as the electrolyte, PhI as the additive and a C(+)/Pt(−) anode in an undivided cell on a 0.31 mmol scale using 2,2,2-trifluoromethylethanol (TFE) as the solvent at a concentration of 0.04 M at ambient temperature for indicated hours with a constant electrical current unless otherwise noted. [b] Isolated yields. [c] The electrical current was stopped after 4 h but stirring was continued for 6 h. [d] The electrical current was stopped after 5 h but stirring was continued for 5 h.

Supporting Materials

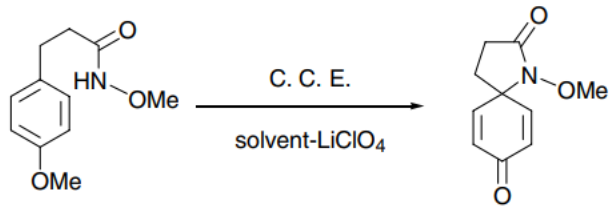
oxidative dearomatization



Supporting Materials

oxidative dearomatization

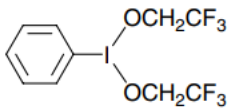
Table 1. Direct anodic oxidation of methoxyamide **1a**



1a **2a**

Entry	Solvent	Product (%)
1	MeOH	12
2	TFE	67
3	$MeNO_2$	32
4	MeCN	16

Anode: glassy carbon beaker, cathode: platinum wire, CCE, 2.5 F/mol.

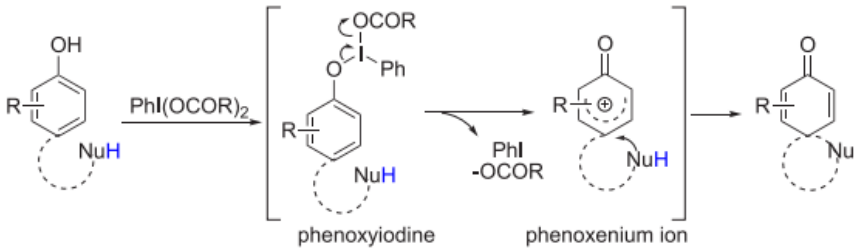


D

Figure 1. A plausible structure of the oxidant **D**.

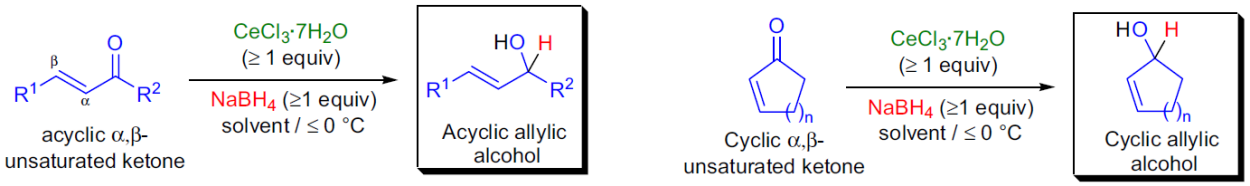
unidentified; however, the hypervalent structure [**D**] was conceivable, based on the report of similar iodobenzene derivatives generated under electrolytic conditions[5] (Fig. 1). In addition, the mixture was submitted to EI mass spectroscopy, which revealed a fragment ion at *m/z* 303 ($PhIOCH_2CF_3^+$). A similar ion, *m/z* 317 ($PhIO_2CCF_3^+$), was also observed in the EI mass of PIFA.

A. mechanism of spirocyclization



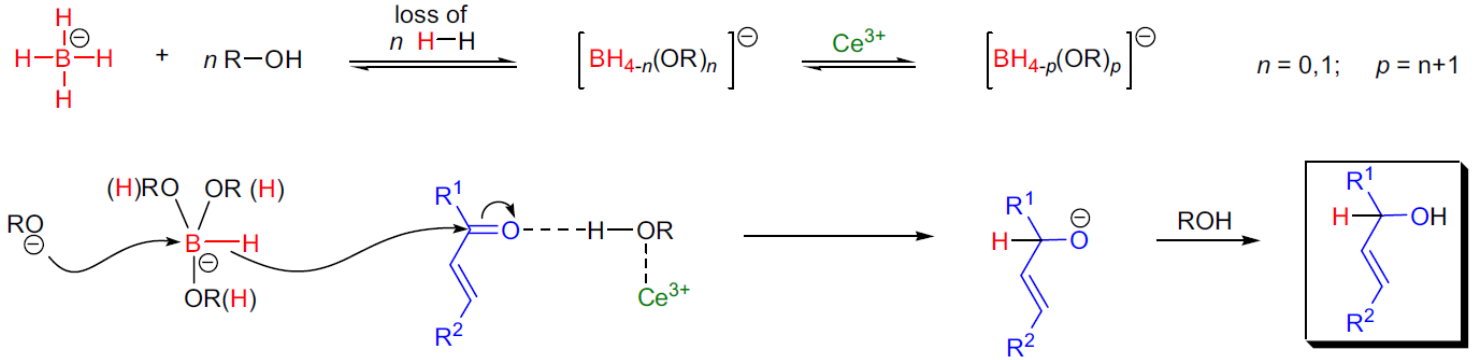
Supporting Materials

LUCHE REDUCTION



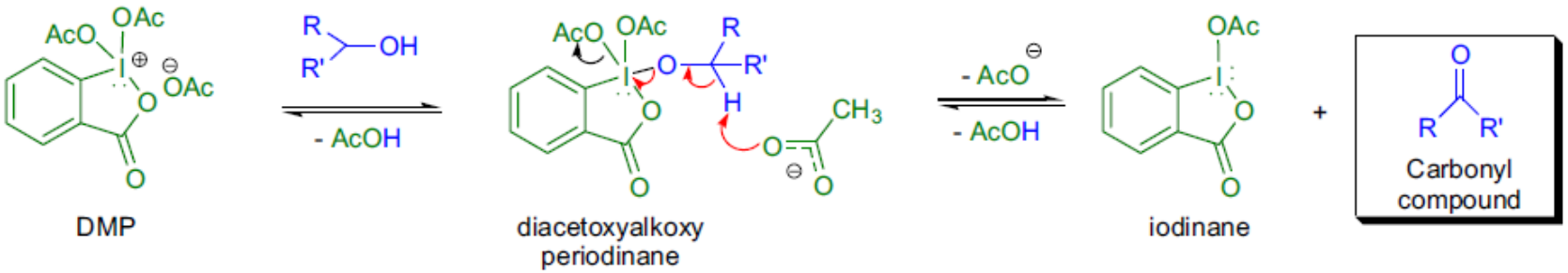
R^{1-2} = H, alkyl, aryl; n = 1-3; solvent = methanol, ethanol, isopropanol

Formation of alkoxyborohydrides:



Supporting Materials

DESS-MARTIN OXIDATION



Supporting Materials

Removal of the PMB ether