

Pyrone Involved Inverse-Electron-Demand Diels–Alder Reaction (IEDDA) in Natural Product Synthesis

Group Seminar

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Laboratory of Synthesis and Natural Products (LSPN)

Ecole Polytechnique Fédérale de Lausanne (EPFL)

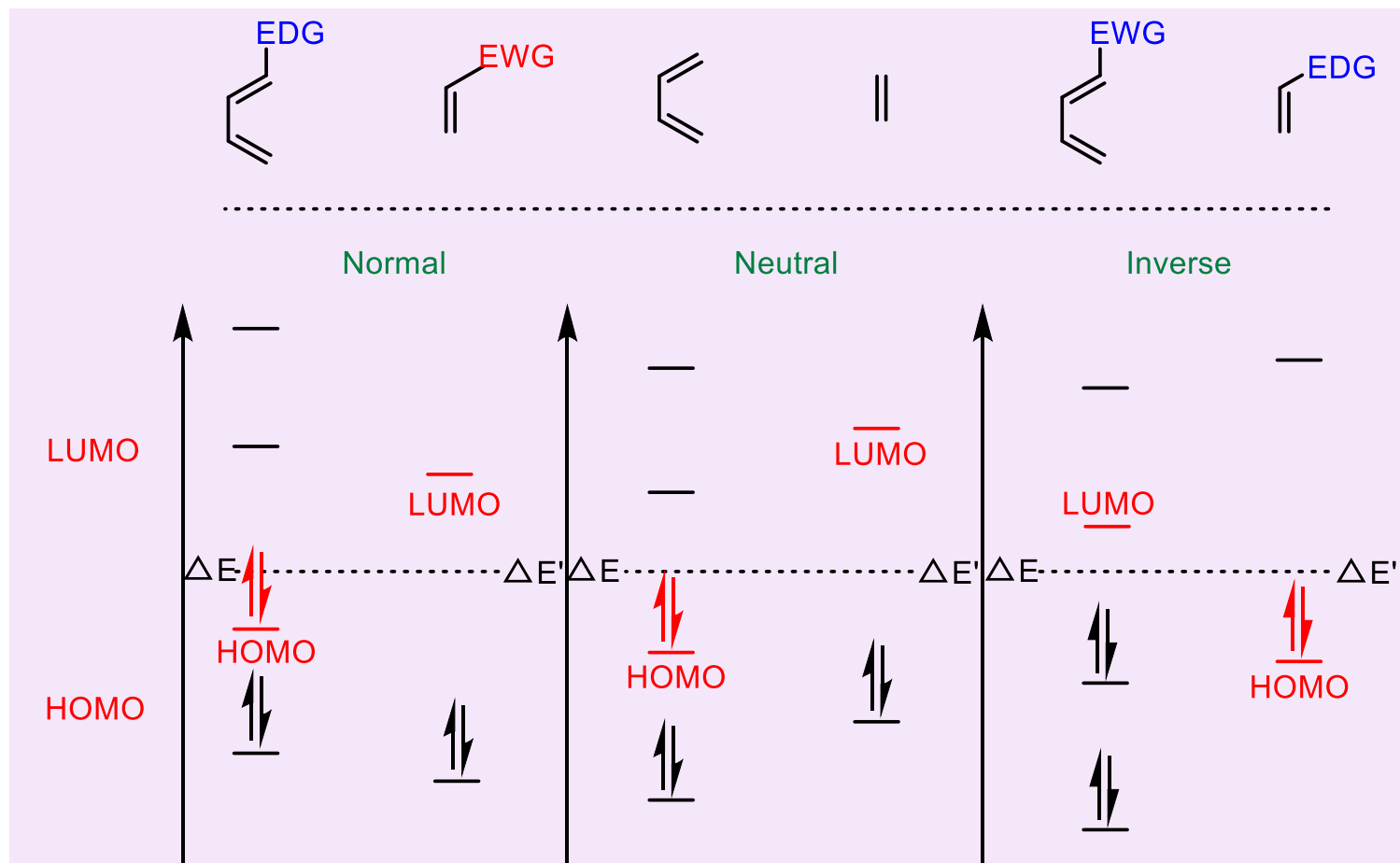
➤ **Introduction**

➤ **Application of Pyrone Involved IEDDA Reaction in Total Synthesis**

- Total Synthesis of Cephanolides A-D (R. Sarpong, et al. *JACS*, **2021**, *143*, 2710-2715)
- Total Synthesis of Cephanolides A-B (Q. Cai, et al. *ACIE*, **2021**, *60*, 26610-26615)
- Total Synthesis of Lucidumone (A. de la Torre. *JACS*, **2022**, *144*, 17803-17807)

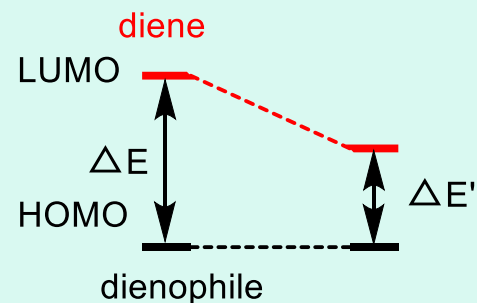
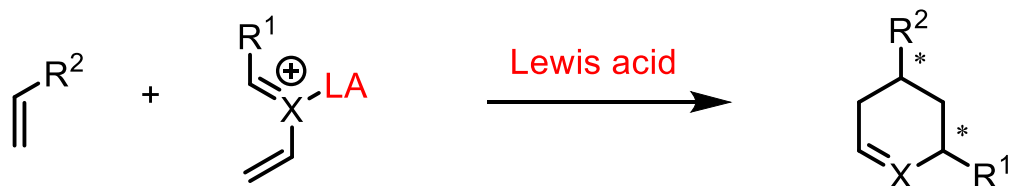
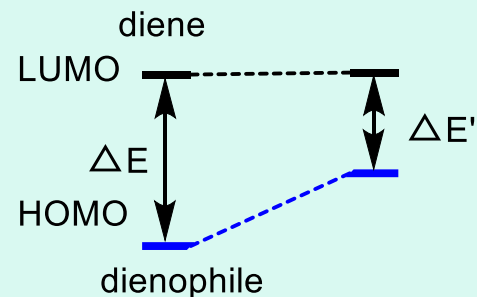
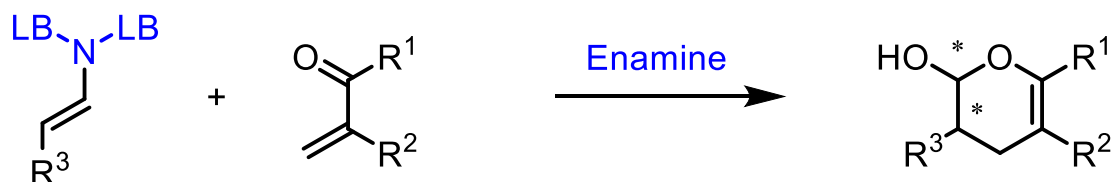
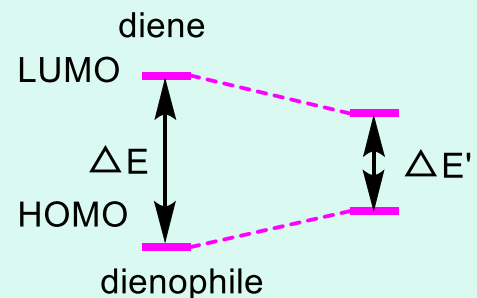
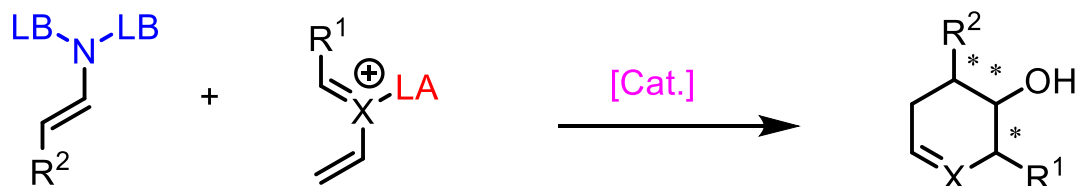
➤ **Summary**

Classification of Diels-Alder Reaction

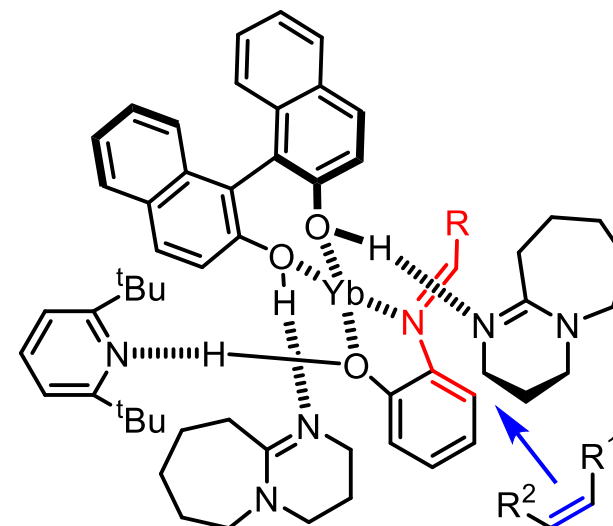
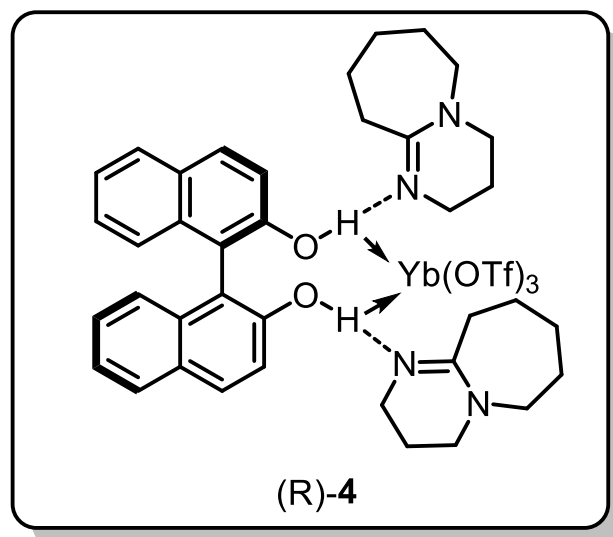
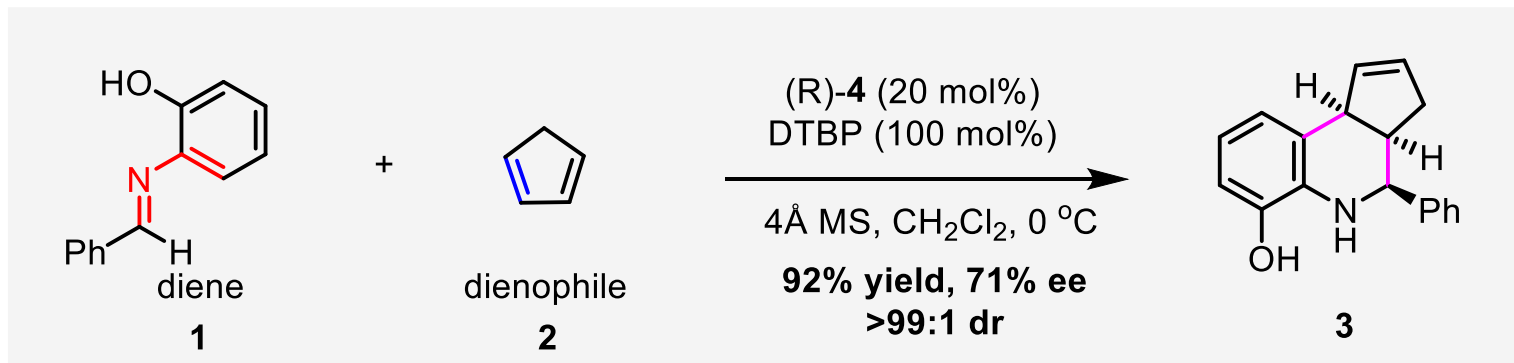


EDG: Electron-donating groups; EWG: Electron-withdrawing groups

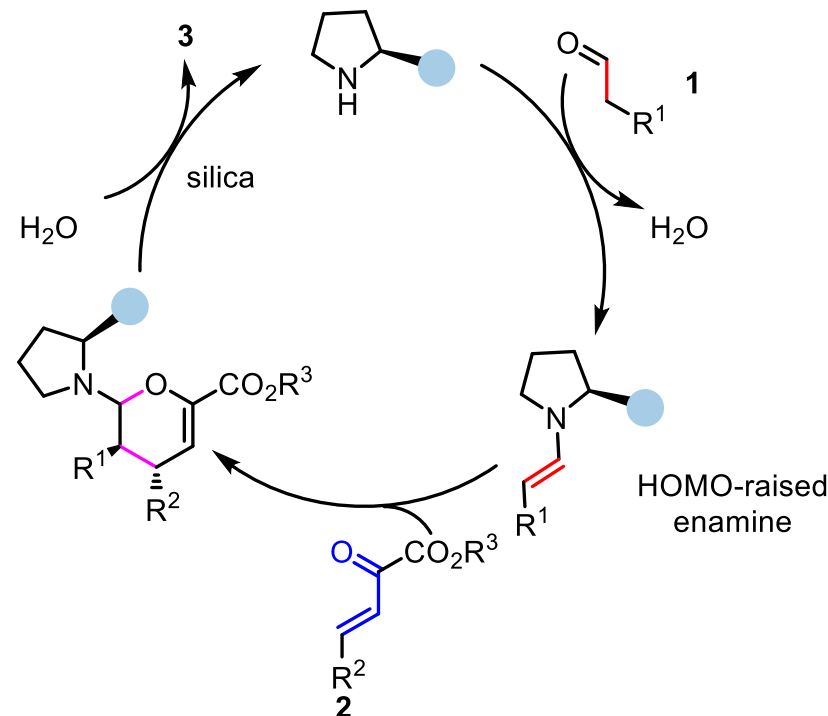
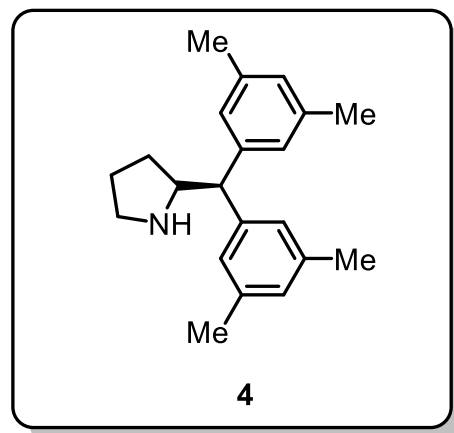
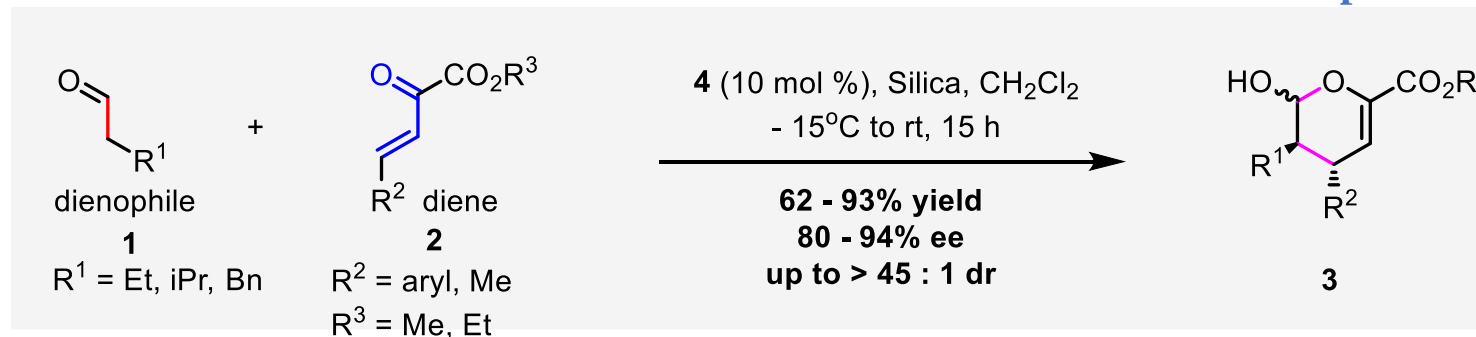
Three strategies to facilitate IEDDA reaction

LUMO_{dienes} - activation:LUMO_{dienes}-lowering
strategyHOMO_{dienophiles} - activation:HOMO_{dienophiles}-raising
strategyHOMO_{dienophiles} and LUMO_{dienes} - activation:Bifunctional HOMO_{dienophiles}
and LUMO_{dienes} activation
strategy

Chiral Lewis acid metal complexes-catalyzed asymmetric **IEDDA** based on **LUMO_{dienes}** lowering strategy

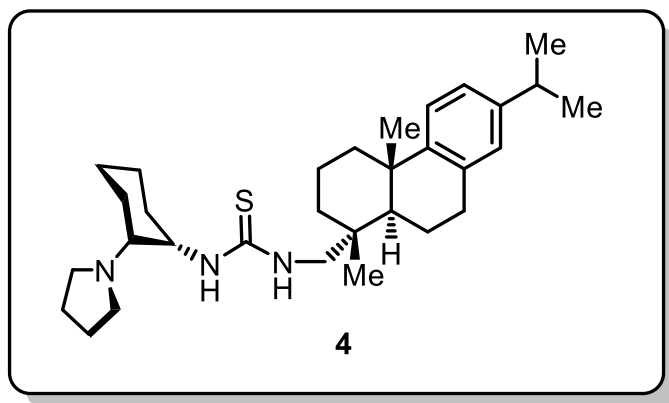
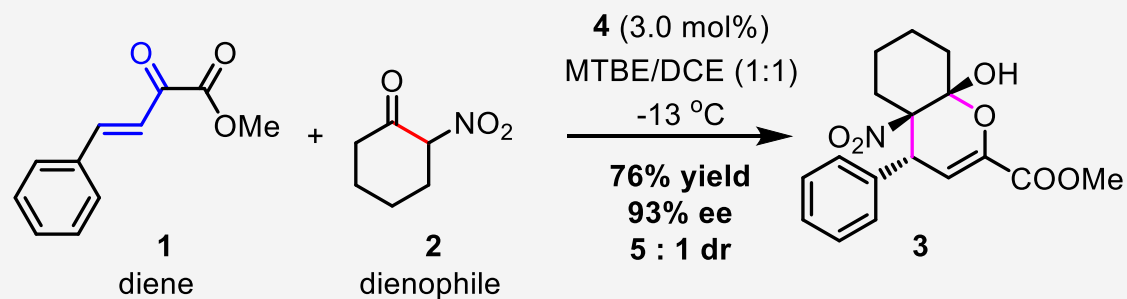


Chiral amines-catalyzed asymmetric **IEDDA** based on **HOMO_{dienophiles}-raising** strategy

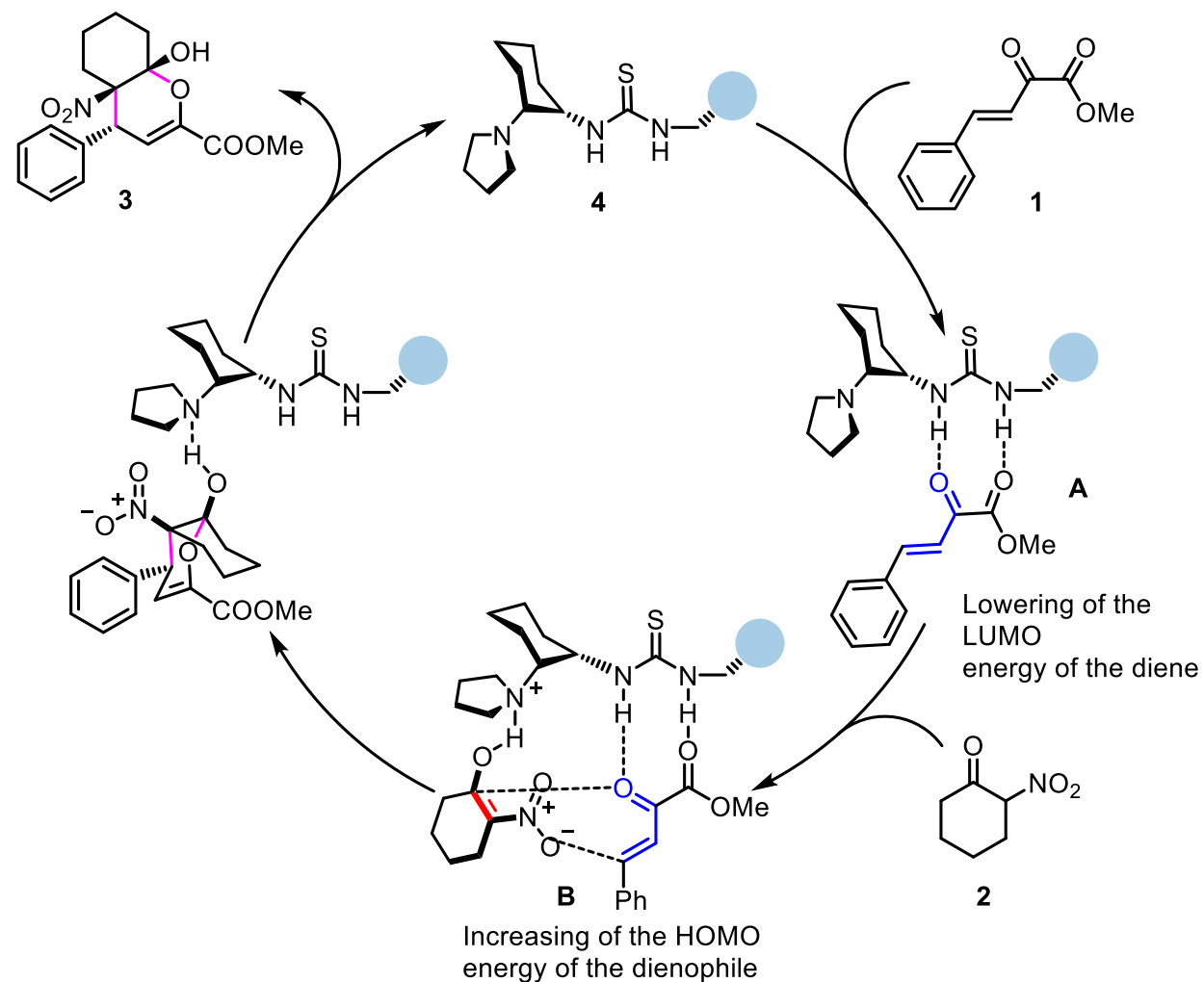


The first organocatalytic enantioselective inverse-electron-demand hetero-Diels–Alder reaction
 K. Juhl, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2003**, *42*, 1498-1501.

Bifunctional HOMO_{dienophiles} and LUMO_{dienes} strategies for catalytic asymmetric IEDDA reaction



chiral amine-thiourea



➤ Introduction

➤ **Application of Pyrone Involved IEDDA Reaction in Total Synthesis**

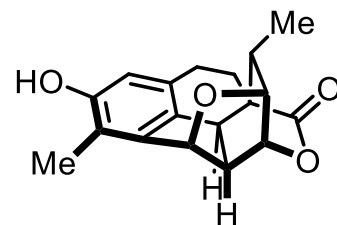
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➤ Summary

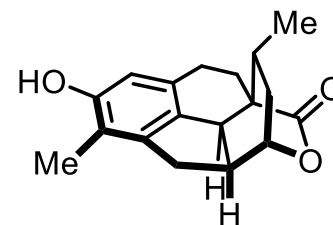
Background



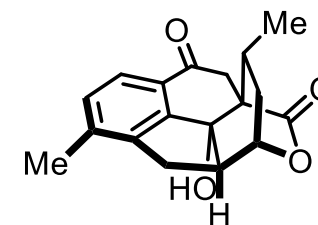
Cephalotaxus plants
三尖杉属植物



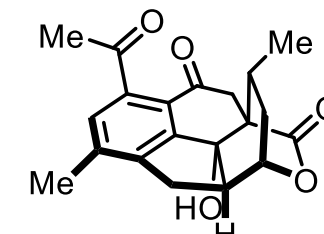
cephanolide A



cephanolide B



cephanolide C



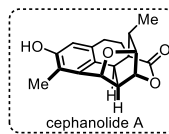
cephanolide D

Isolation and biological activity:

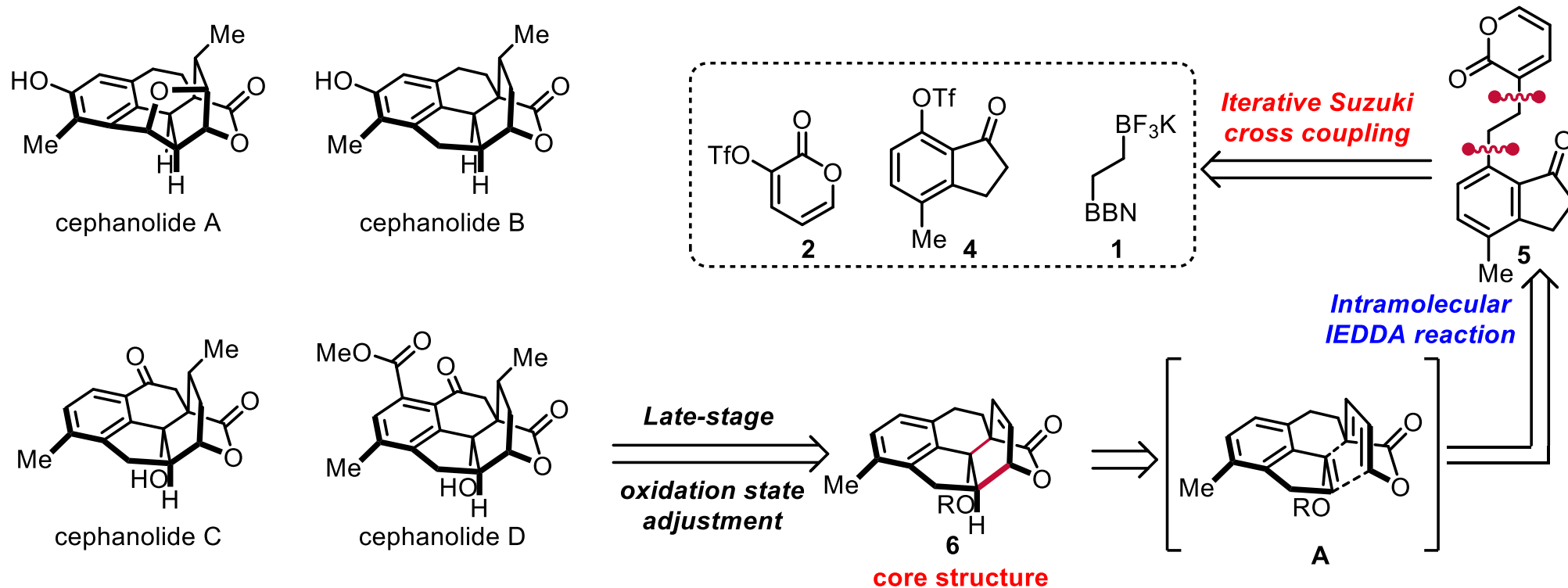
- Isolated in 2017 from Chinese *Cephalotaxus* plants by Yue and co-workers
- The larger family of *Cephalotaxus* diterpenoids have shown a broad range of bioactivity that includes plant growth inhibition as well as antineoplastic, antiviral, and antitumor properties.

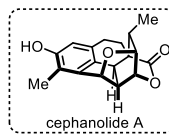
Structure Characters:

- C₁₈ norditerpenoids
- a cage-like six-membered rings
- a bridged lactone and a THF ring
- seven contiguous stereogenic centers involving an all-carbon quaternary center

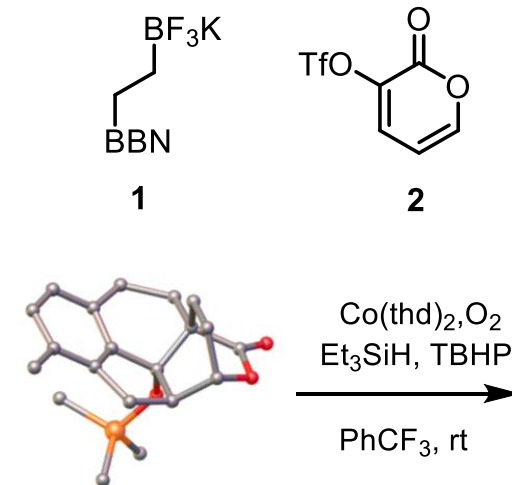
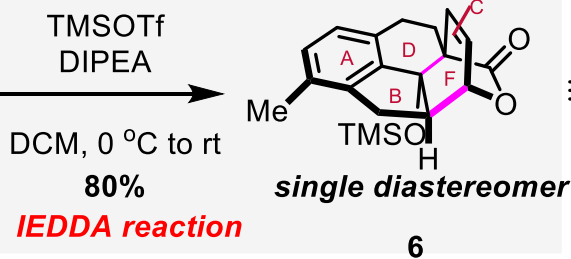
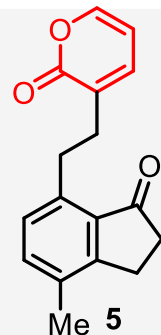
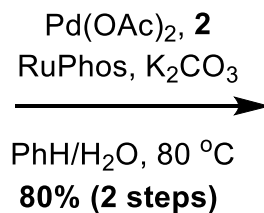
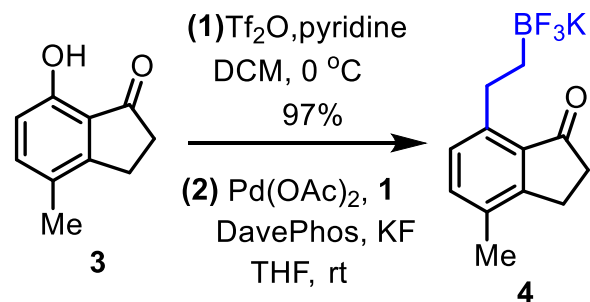


Retrosynthetic analysis of cephanolides A-D

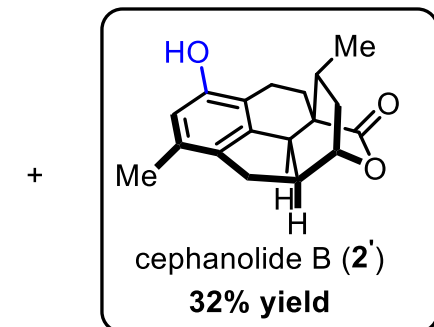
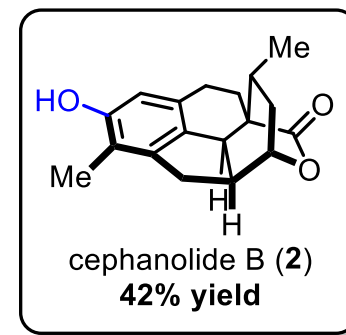
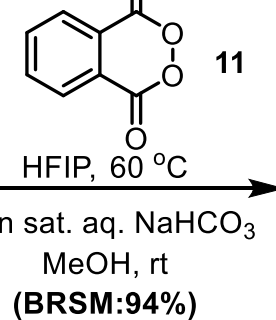
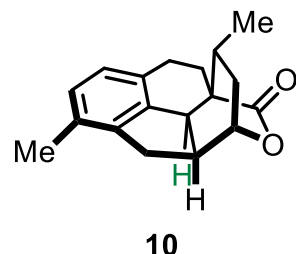
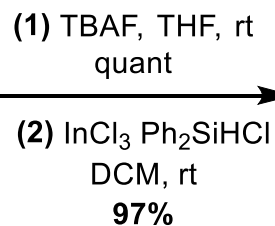
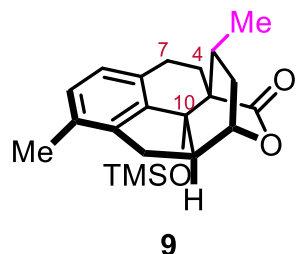
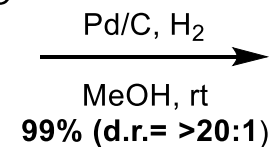
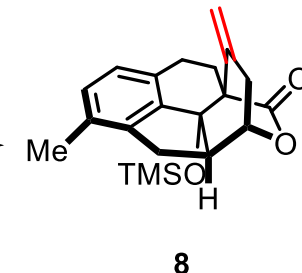
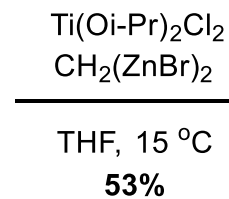
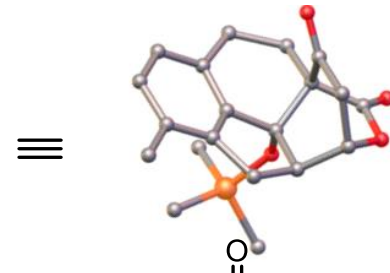
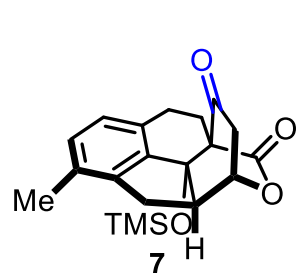
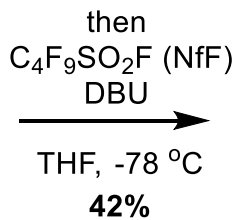
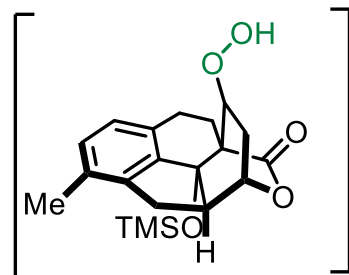




◆ Total Synthesis of Cephanolides B



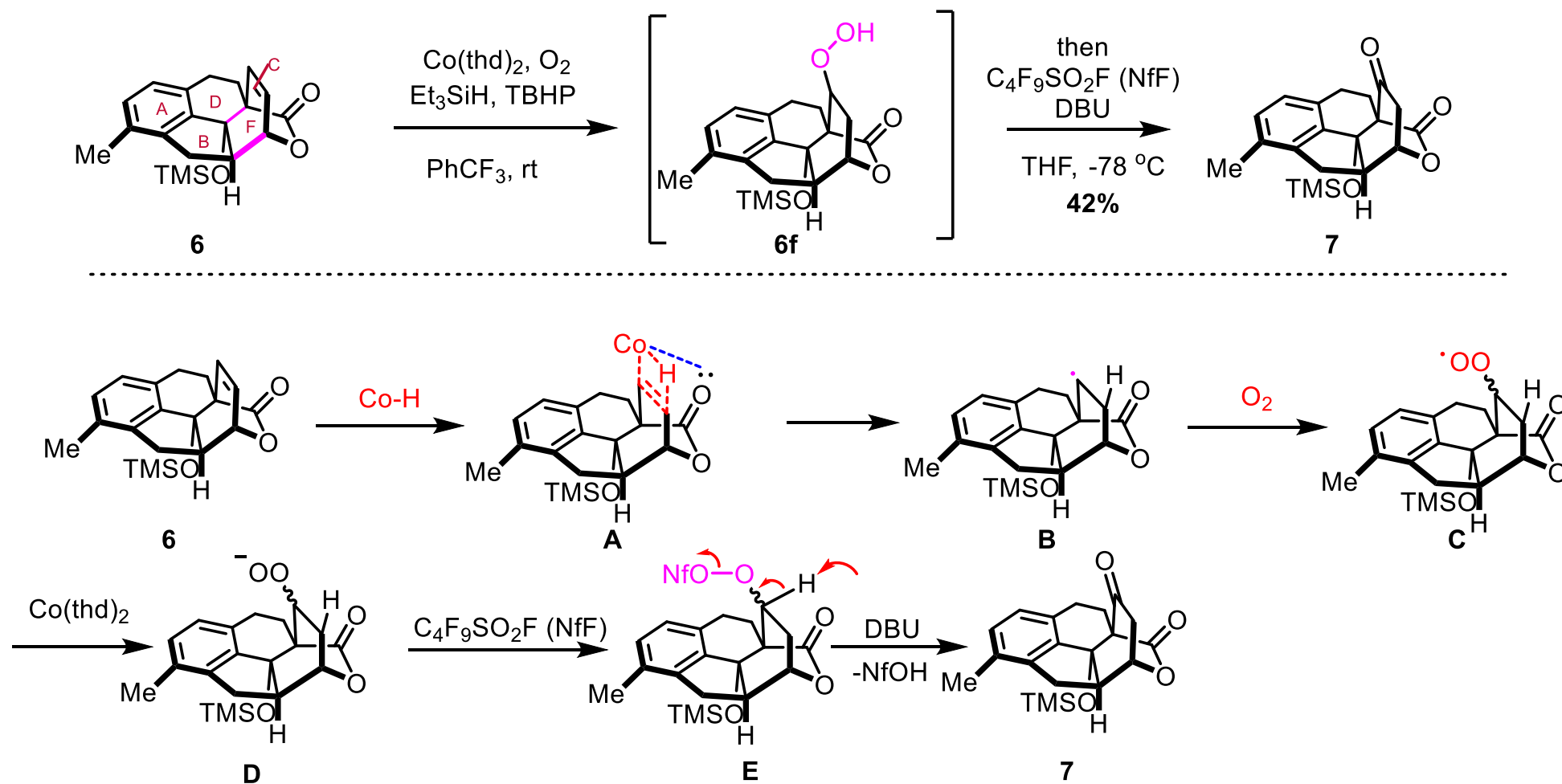
Mukaiyama hydration reaction



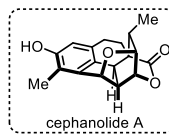
common intermediate

10 steps, 12.5% overall yield

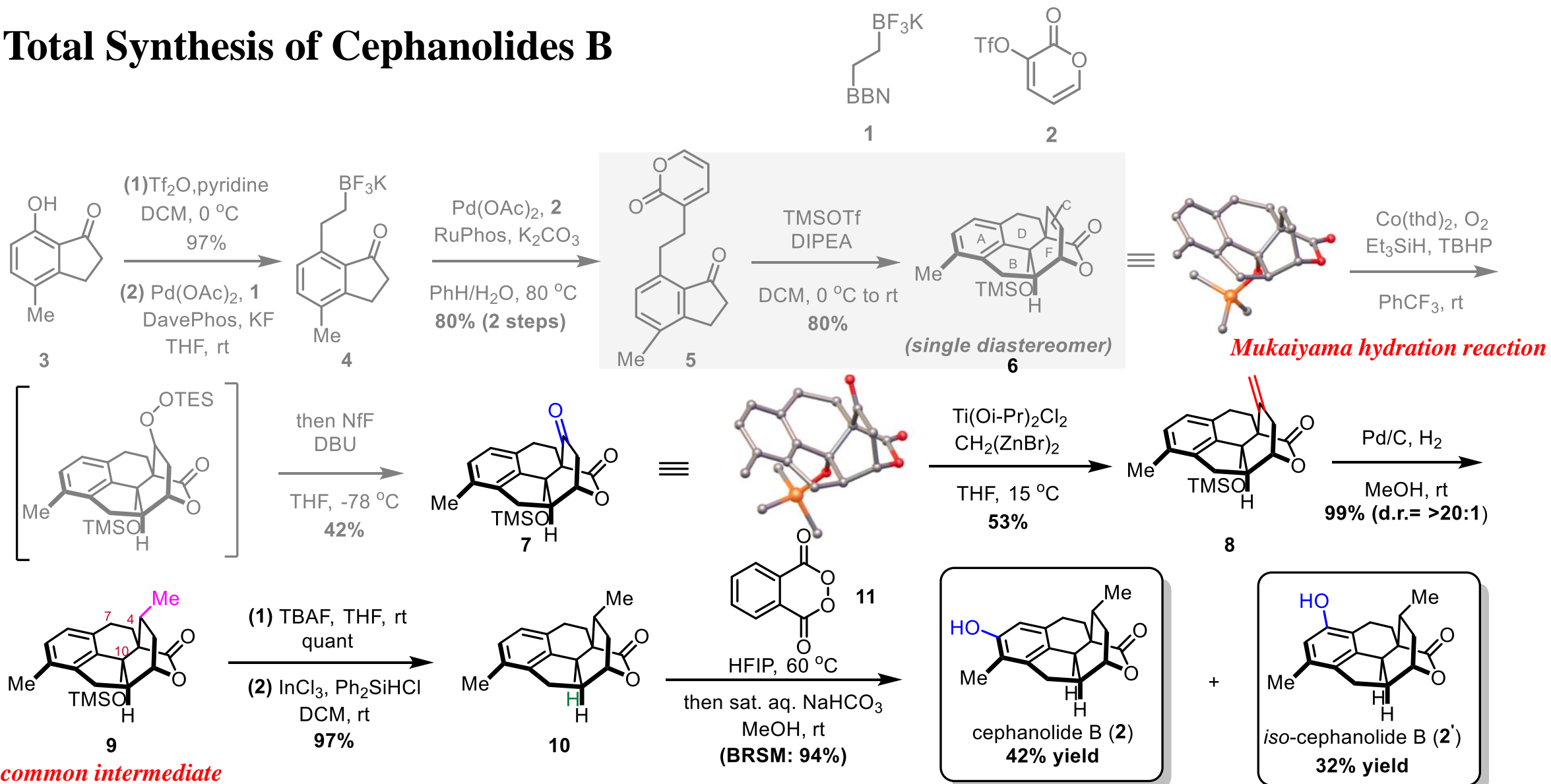
◆ Co-catalyzed Mukaiyama hydration reaction

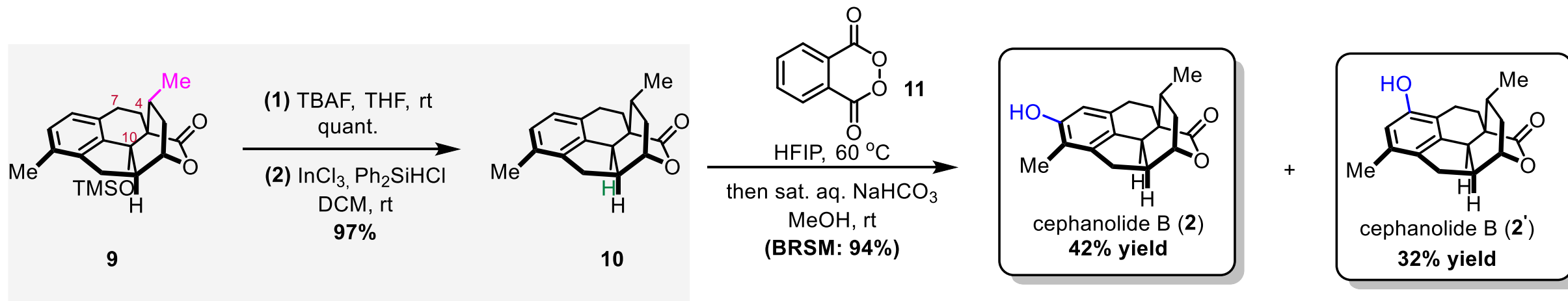
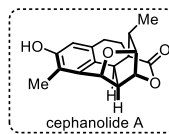
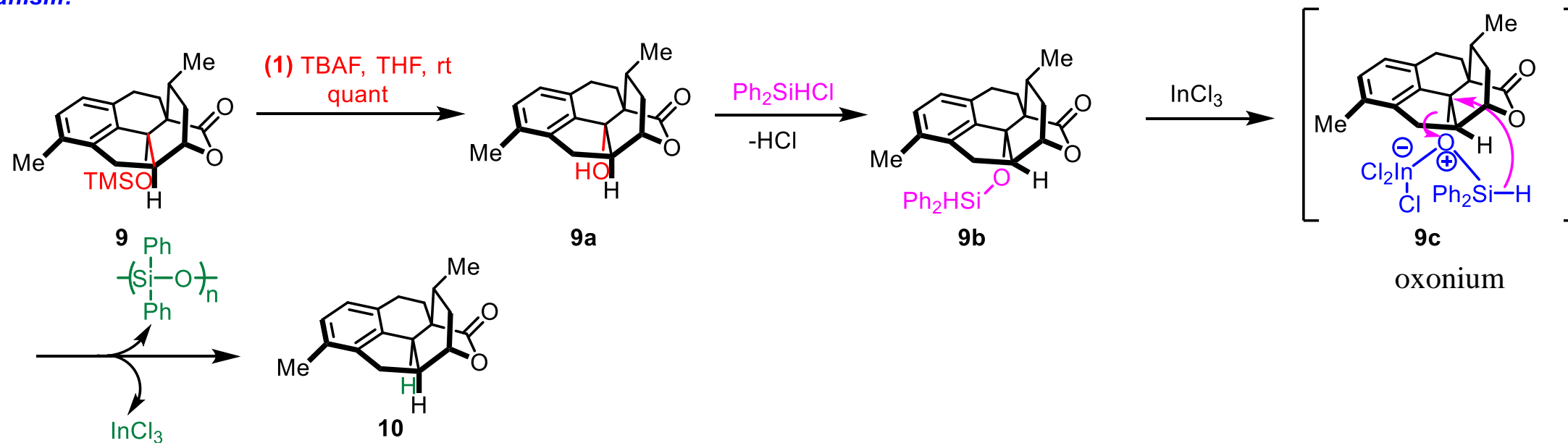


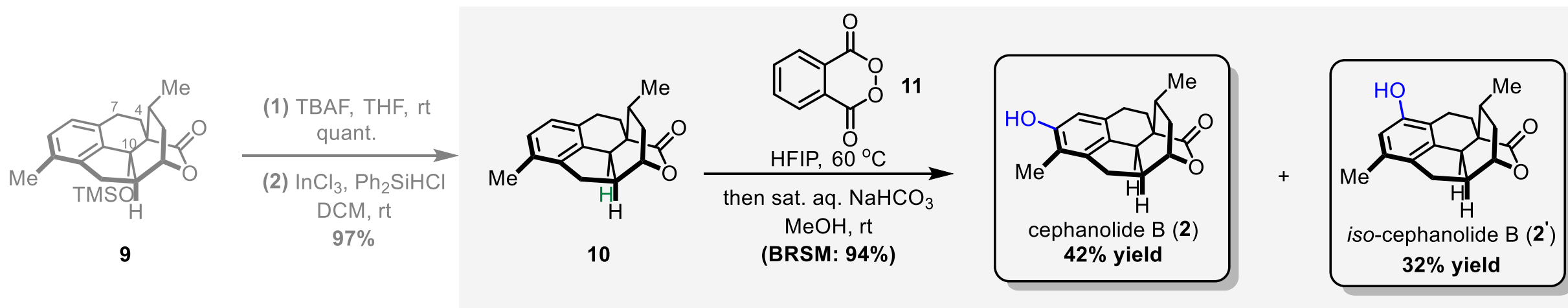
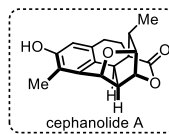
The regioselective hydrocobaltation could be attributed to a directing effect by the oxygen lone pair of the lactone



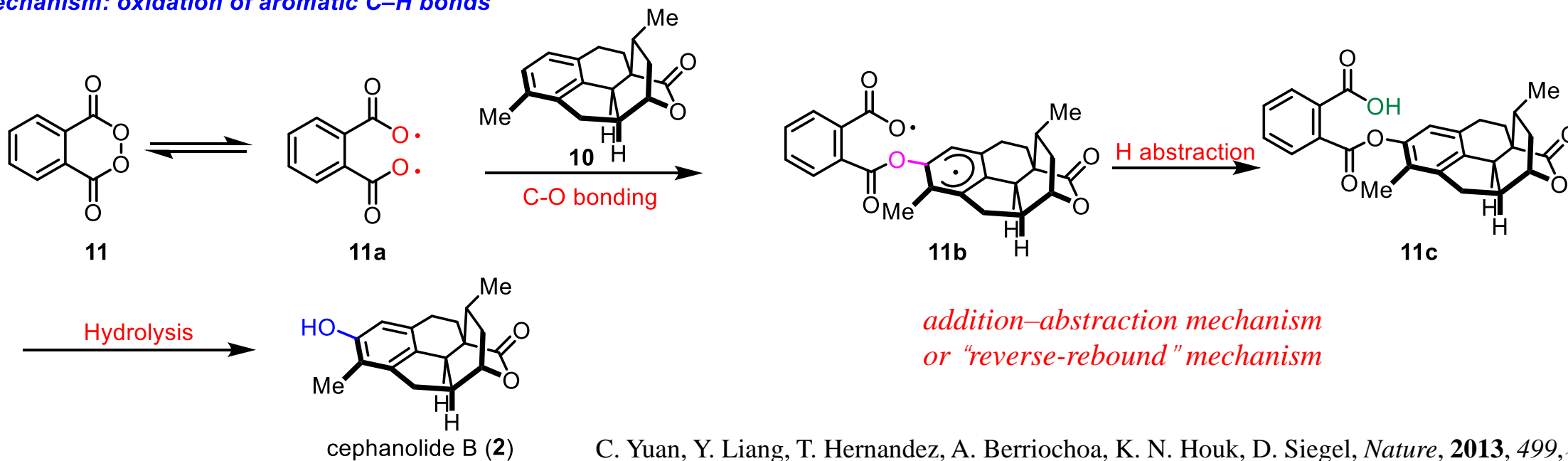
◆ Total Synthesis of Cephanolides B

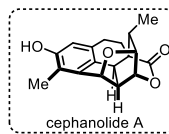


**Mechanism:**



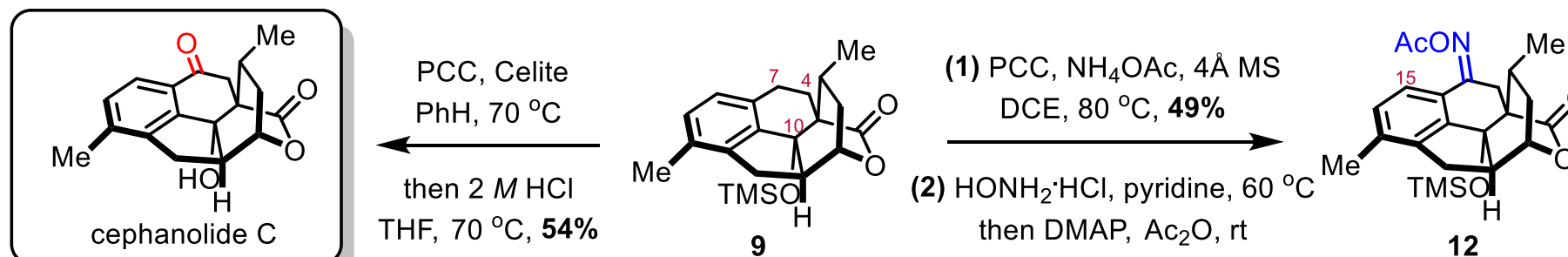
Mechanism: oxidation of aromatic C–H bonds



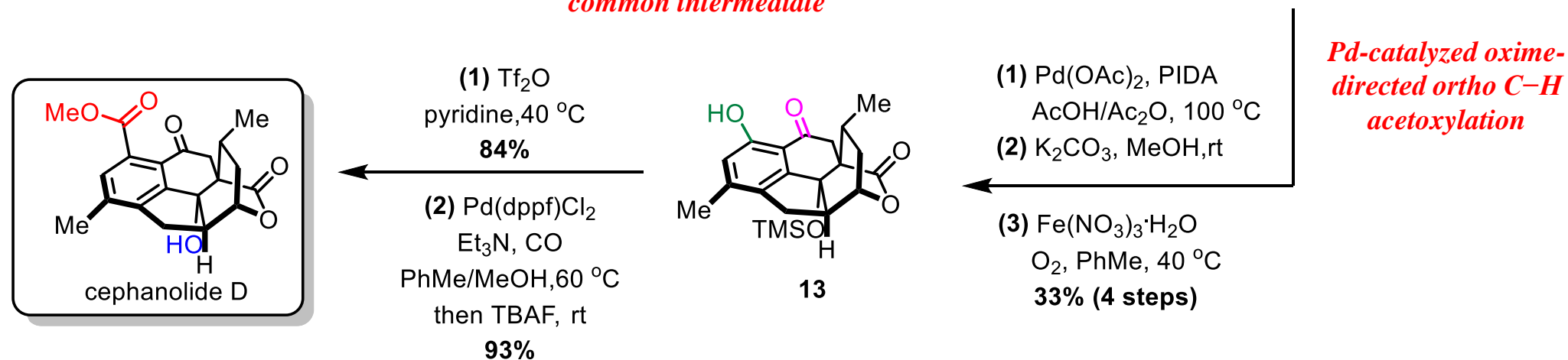


◆ Complete the Total Synthesis of Cephanolides C-D

8 steps

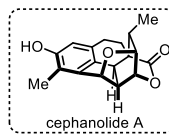
*common intermediate*

14 steps

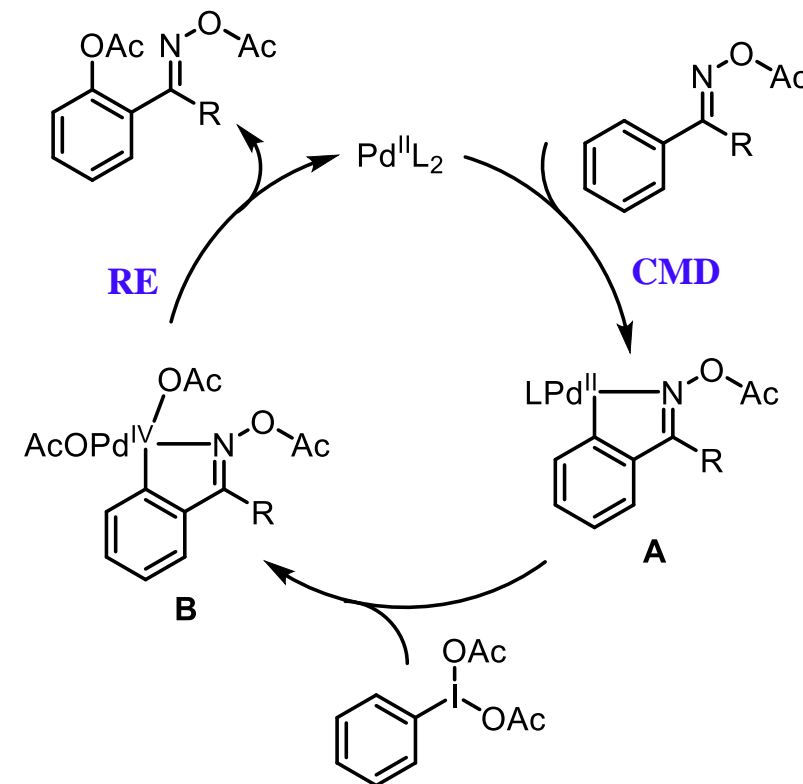
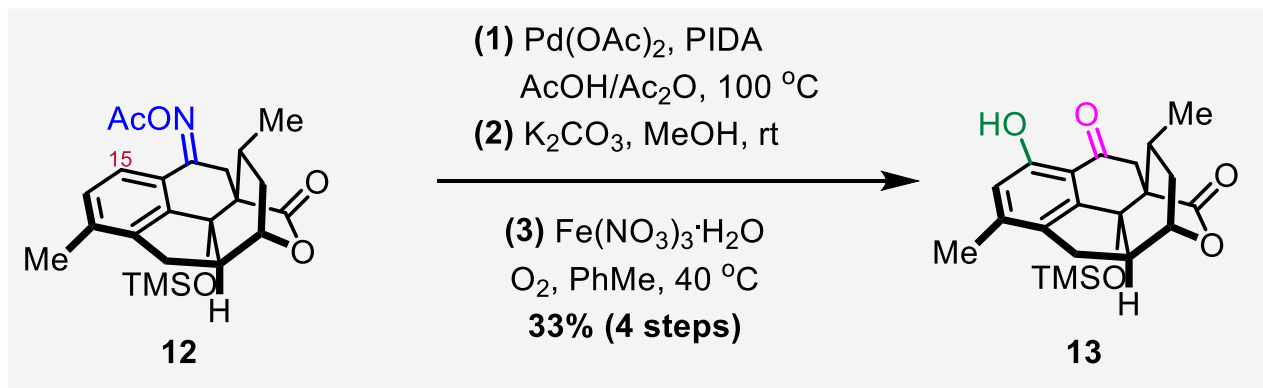


Acetoxylation: S. R. Neufeldt, M. S. Sanford, *Org. Lett.* **2010**, *12*, 532-535.

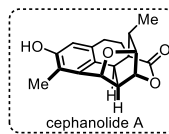
Oxidative removal of the oxime: Y. Li, N. Xu, G. Mei, Y. Zhao, Y. Zhao, J. Lyu, G. Zhang, C. Ding, *Can. J. Chem.* **2018**, *96*, 810-814.¹⁶



Pd-catalyzed oxime directed ortho C–H acetoxylation

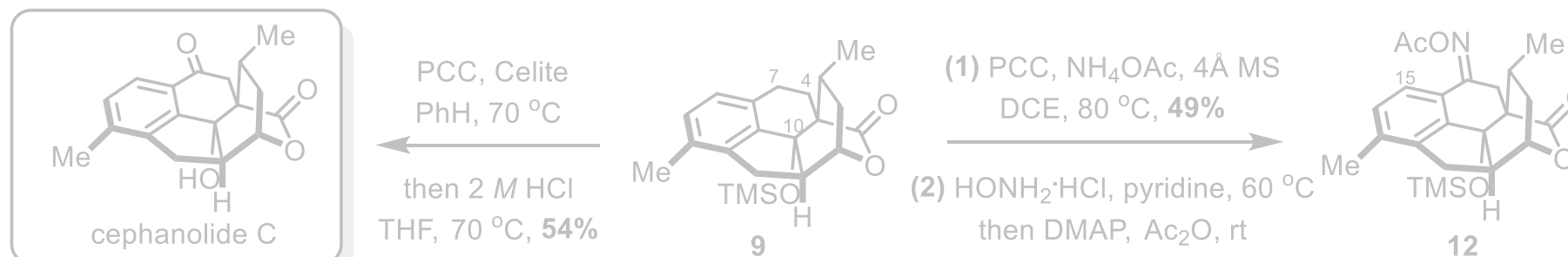


CMD: concerted metalation deprotonation

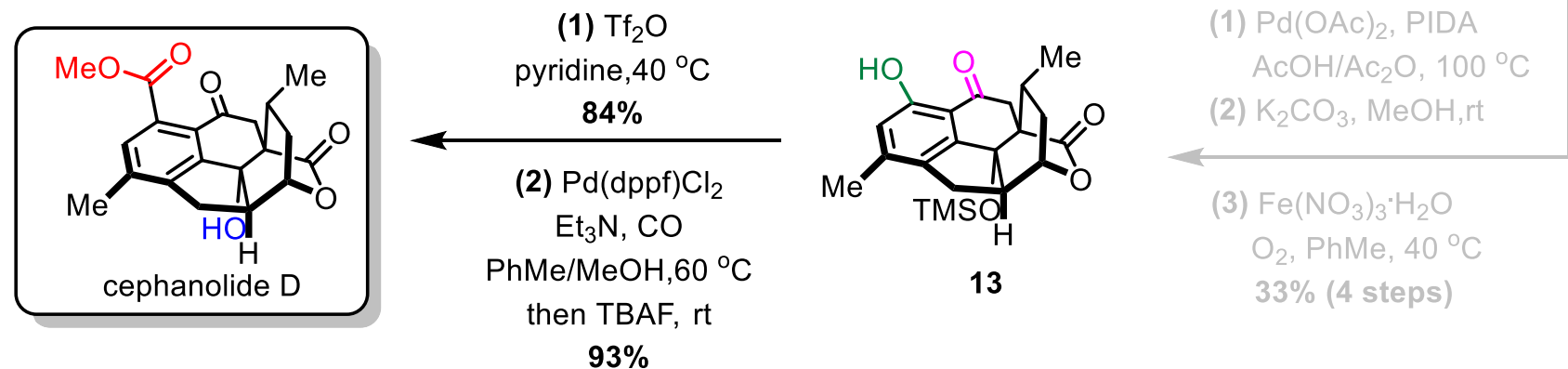
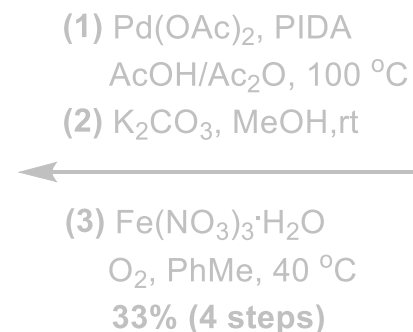


◆ Complete the Total Synthesis of Cephanolides C-D

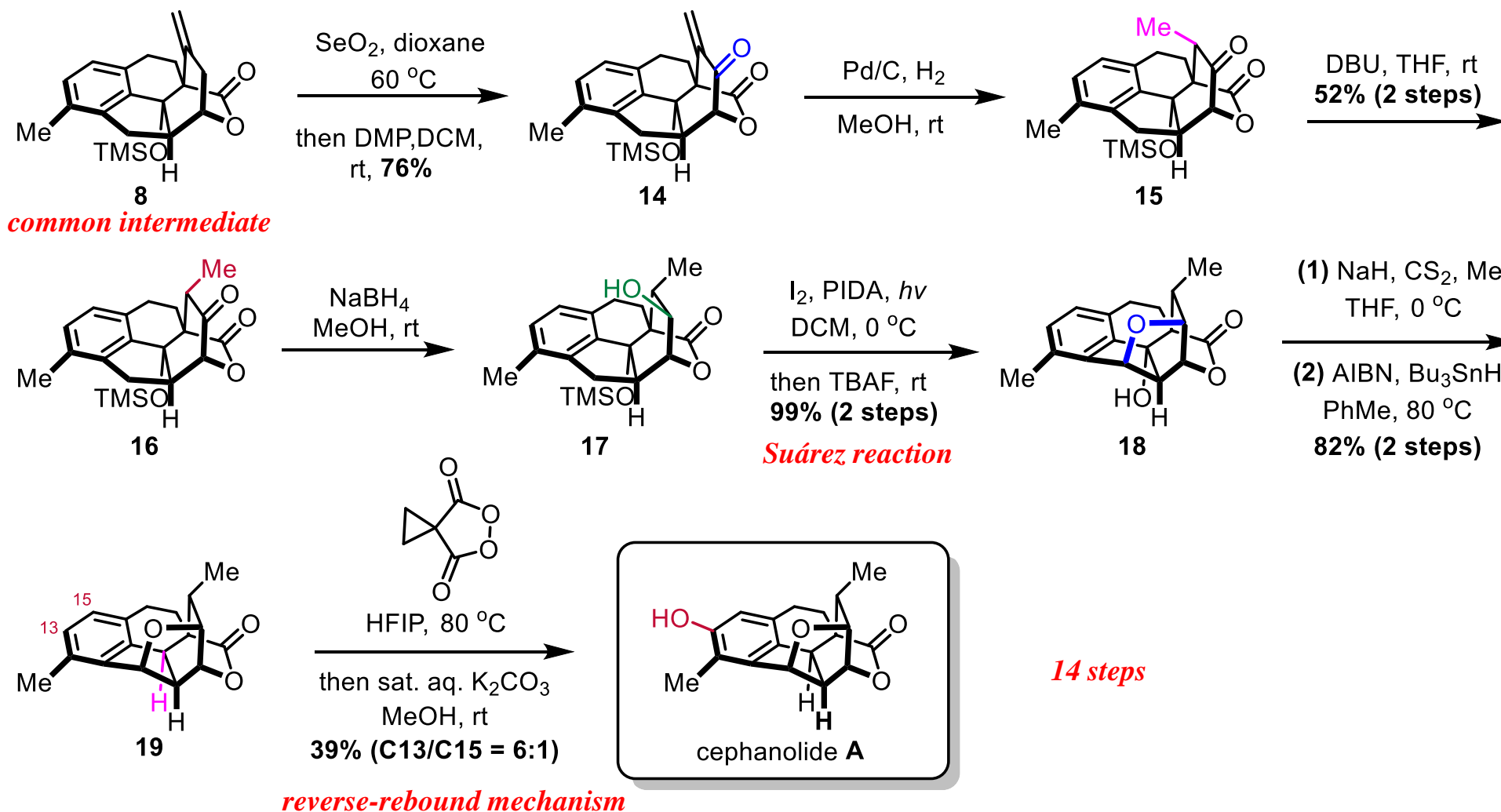
8 steps

*common intermediate*

14 steps

*Pd-catalyzed methoxy carbonylation**Oxime-directed ortho C-H acetoxylation*

◆ Complete the Total Synthesis of Cephanolide A



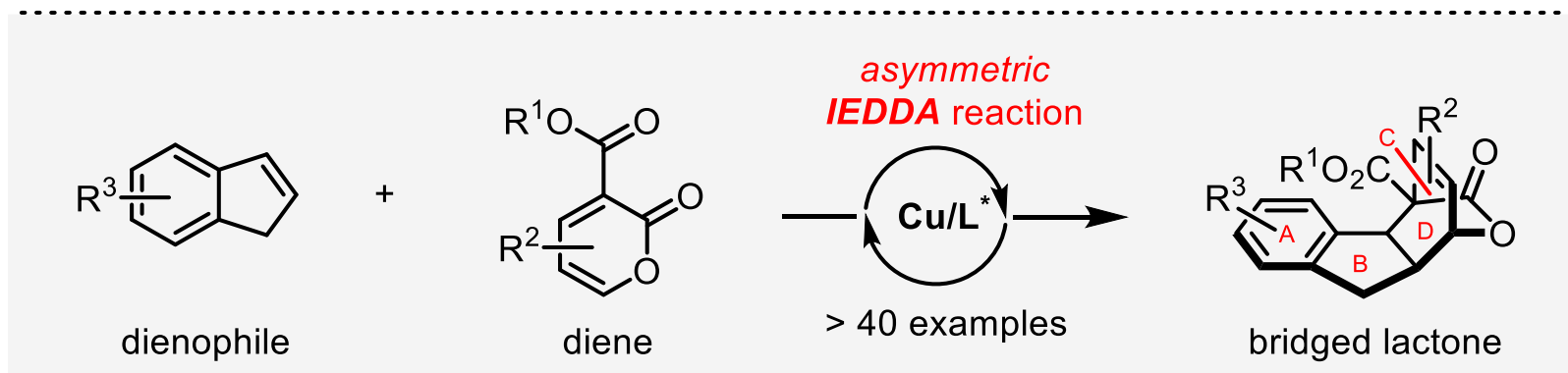
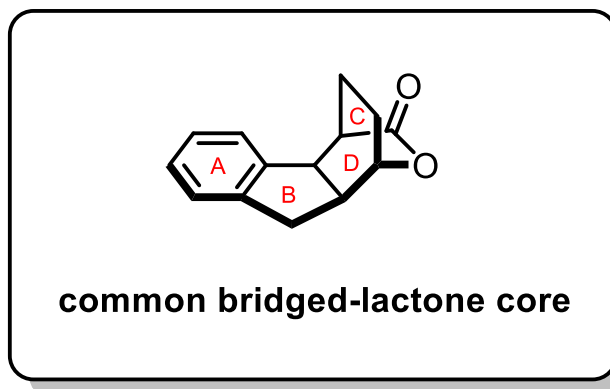
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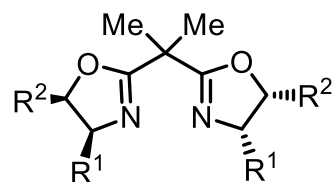
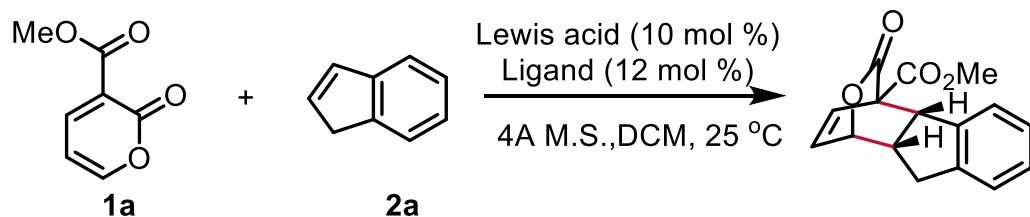
➤ Summary

Catalytic asymmetric **IEDDA** reaction of 2-pyrones with indenenes



- ◆ Electron-deficient 2-pyrones
- ◆ Highly functionalized hexahydrofluorenyl lactones
- ◆ Asymmetric total synthesis of cephanolides A and B
- ◆ Electronically unbiased indenenes
- ◆ High yield, high dr, high ee

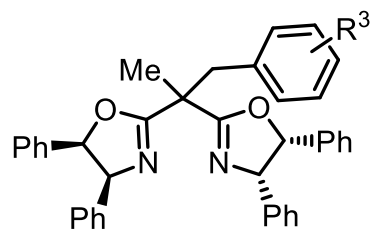
Optimization of IEDDA reaction condition



L1, $R^1 = \text{Ph}$, $R^2 = \text{H}$

L2, $R^1 = \text{Bn}$, $R^2 = \text{H}$

L3, $R^1 = \text{Ph}$, $R^2 = \text{Ph}$



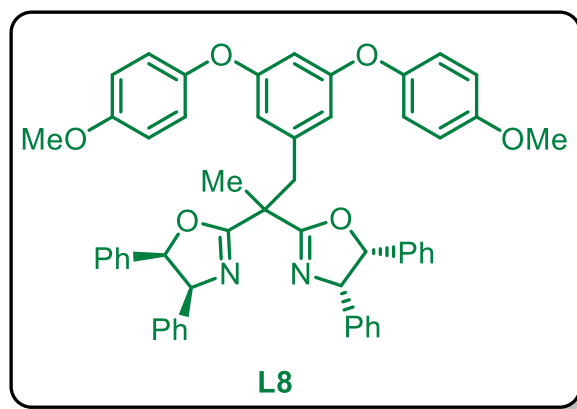
L4, $R^3 = 3,5\text{-(OMe)}_2$

L5, $R^3 = 3,5\text{-(OEt)}_2$

L6, $R^3 = 3,5\text{-(OiPr)}_2$

L7, $R^3 = 3,5\text{-(OPh)}_2$

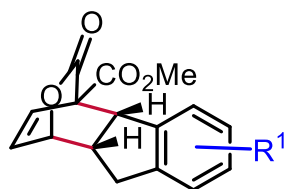
With Large Side Arm



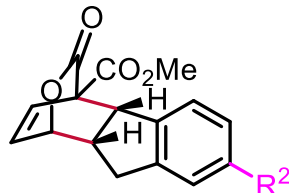
Entry	Lewis acid	Ligand	Yield [%]	ee [%]
1	$\text{Cu}(\text{OTf})_2$	L1	99	62
2	$\text{Cu}(\text{ClO}_4)_2 \cdot 6 \text{H}_2\text{O}$	L1	98	59
3	$\text{Cu}(\text{NTf}_2)$	L1	99	49
4	$\text{Cu}(\text{OTf})_2$	L2	98	32
5	$\text{Cu}(\text{OTf})_2$	L3	98	69
6	$\text{Cu}(\text{OTf})_2$	L4	97	81
7	$\text{Cu}(\text{OTf})_2$	L5	98	85
8	$\text{Cu}(\text{OTf})_2$	L6	99	87
9	$\text{Cu}(\text{OTf})_2$	L7	99	92
10	$\text{Cu}(\text{OTf})_2$	L8	93	94
11	$\text{Cu}(\text{OTf})_2$	L8	99	94

Reaction condition: **1a** (0.2 mmol), **2a** (0.3 mmol), Lewis acid (10 mol%), ligand (12 mol%), 4Å M.S. (50 mg) in DCM (1.0 mL) at 25 °C.

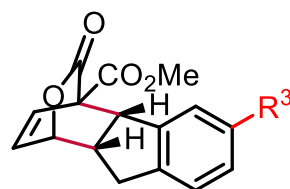
Entry 11: **1a** (0.2 mmol), **2a** (0.3mmol), $\text{Cu}(\text{OTf})_2$ (5 mol%), **L8** (6 mol%), 4Å M.S. (50 mg) in DCM (1.0 mL) at 25 °C.

Scope of **indenes** (yield > 89%, ee > 92%)

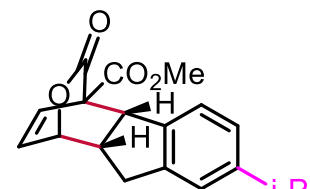
R¹ = Me, OMe, Br



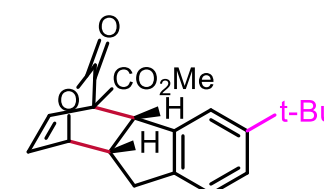
R² = Cl, F, CO₂Me



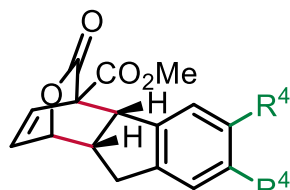
R³ = Cl, Et



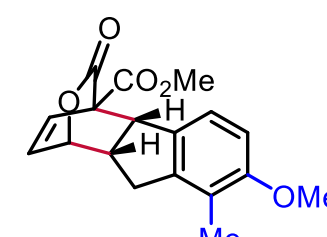
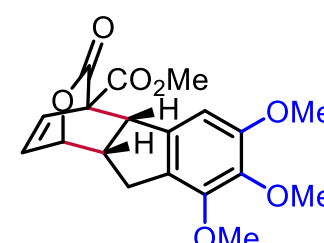
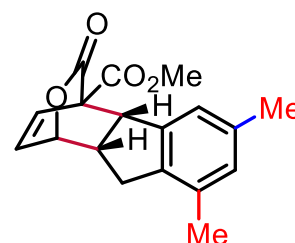
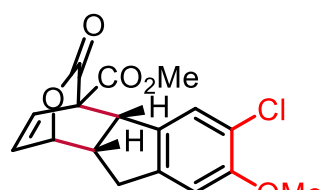
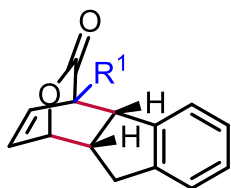
i-Pr



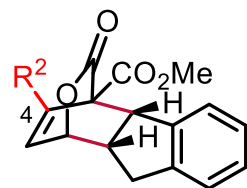
t-Bu



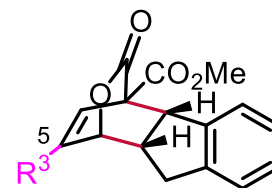
R⁴ = Me, OMe

Scope of **2-pyrones**

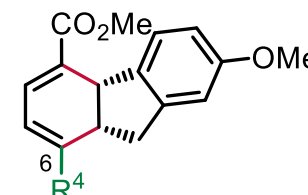
R¹ = CO₂Me, CO₂Et,
CO₂Bn, CO₂C₂H₄Ph
90–99% yield
92–94% ee



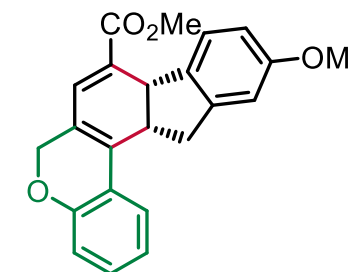
R² = Me, Et, Ph,
p-chlorophenyl
93–99% yield
71–85% ee



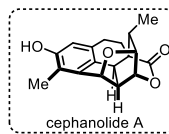
R³ = Br, *p*-methylphenyl,
p-chlorophenyl, Ph
46–99% yield
88–90% ee



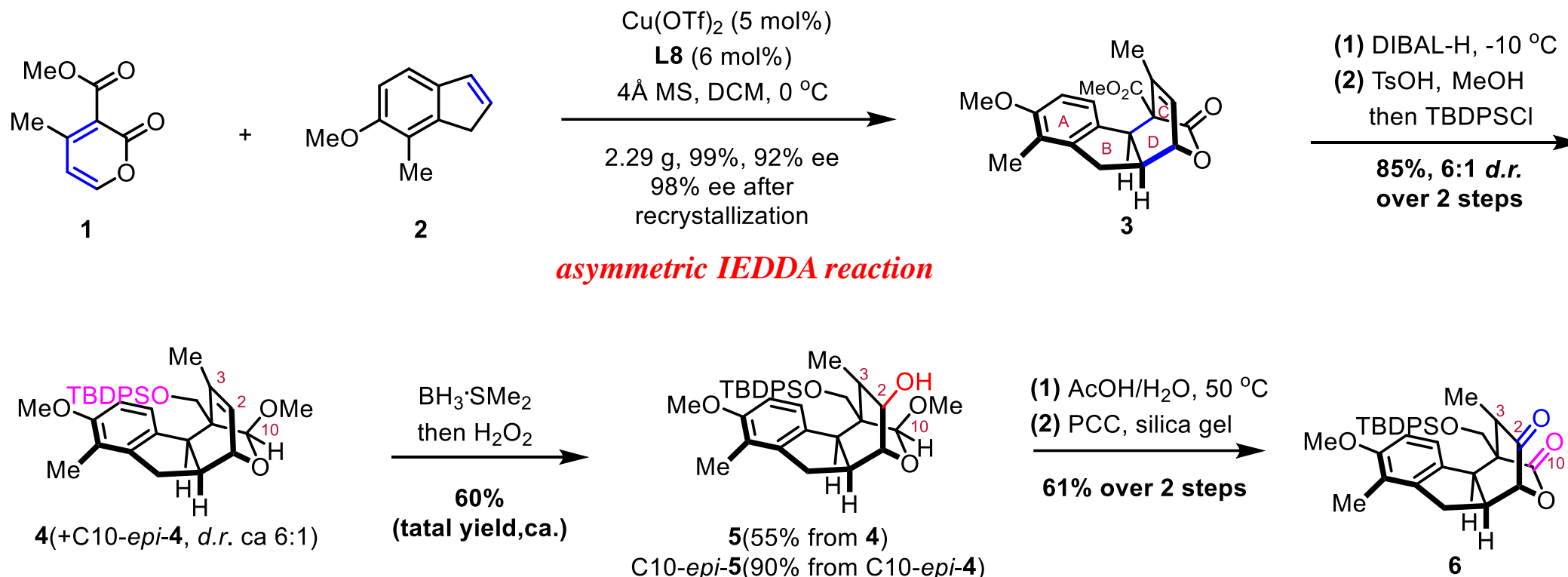
R⁴ = Ph, *p*-methylphenyl,
p-chlorophenyl, *p*-bromophenyl
70–97% yield
93–95% ee



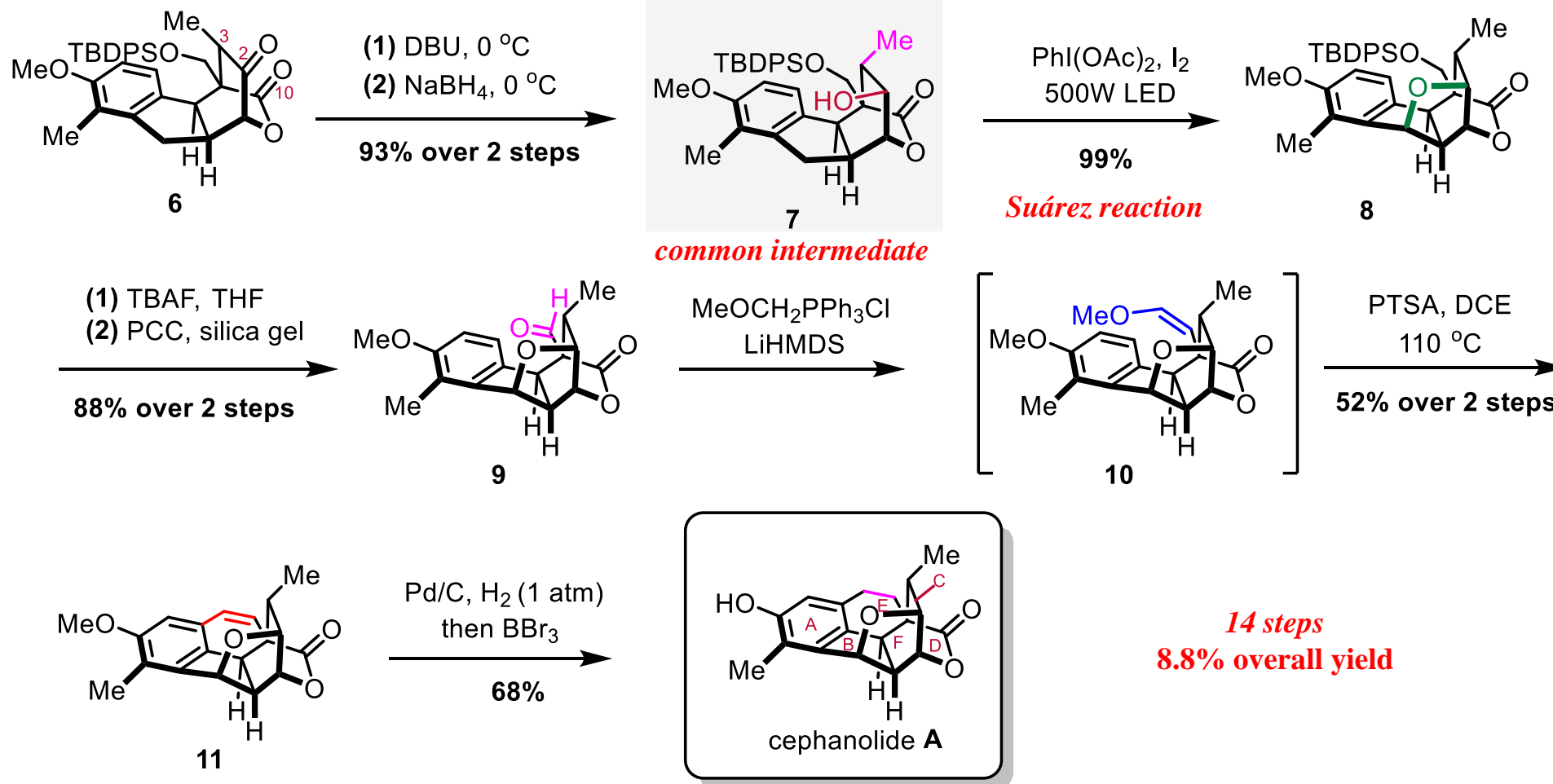
95% yield
95% ee

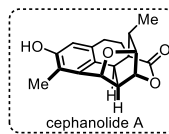


Total Synthesis of Cephanolide A

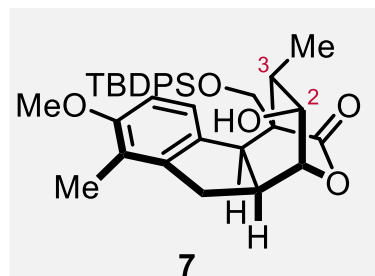


Total Synthesis of Cephanolide A





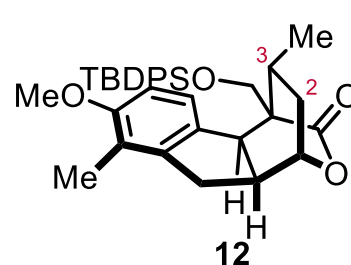
Total Synthesis of Cephanolide B



common intermediate

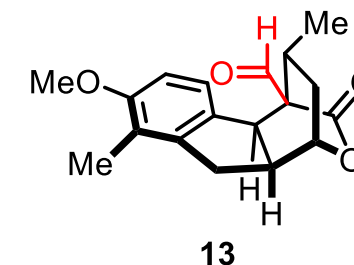
(1) NaH, CS₂, MeI
(2) AIBN, Bu₃SnH

92% over 2 steps

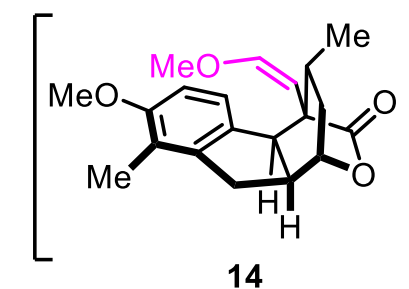


(1) TBAF, THF
(2) PCC, silica gel

89% over 2 steps

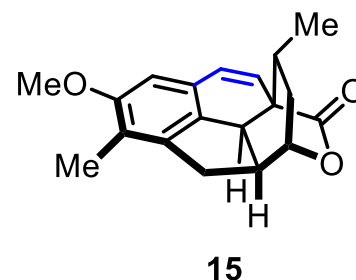


MeOCH₂PPh₃Cl
LiHMDS



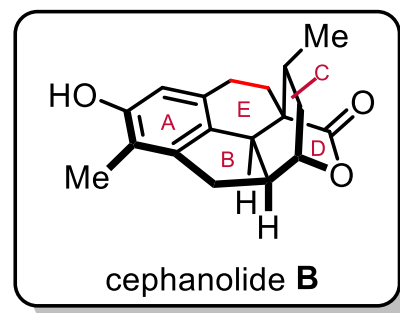
PTSA, DCE
100 °C

50% over 2 steps



Pd/C, H₂(1 atm)
then BBr₃

83%



15 steps

9.7% overall yield

➤ Introduction

➤ **Application of Pyrone Involved IEDDA Reaction in Total Synthesis**

- Total Synthesis of Cephanolides A-D (R. Sarpong, et al. *JACS*, **2021**, *143*, 2710-2715)
- Total Synthesis of Cephanolides A-B (Q. Cai, et al. *ACIE*, **2021**, *60*, 26610-26615)
- Total Synthesis of Lucidumone (A. de la Torre. *JACS*, **2022**, *144*, 17803-17807)

➤ Summary

Background



Ganoderma lucidum (灵芝)

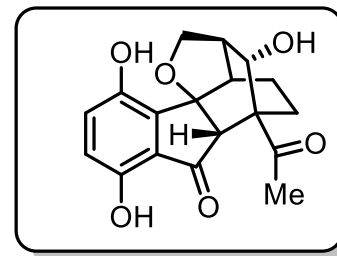
Isolation:

Isolated from *Ganoderma lucidum*, a mushroom commonly used as traditional medicine in China

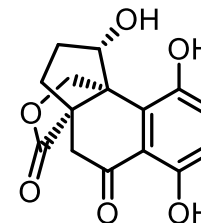
Biological activity:

Preliminary studies indicate that lucidumone selectively inhibits COX-2 by directly binding with Tyr385 and Ser530 residues to provide it with an interesting therapeutic **potential for the treatment of inflammation**

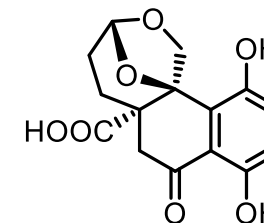
Selected meroterpenoids isolated from *Ganoderma*:



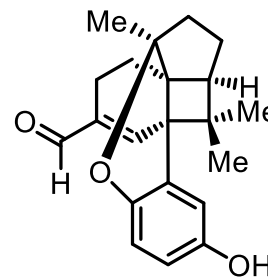
lucidumone



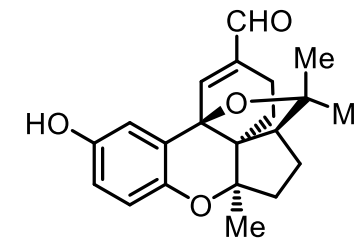
lingzhiol



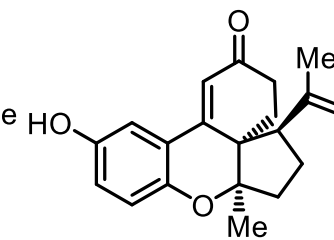
cochlearol A



cochlearol B



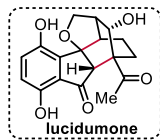
ganocin A



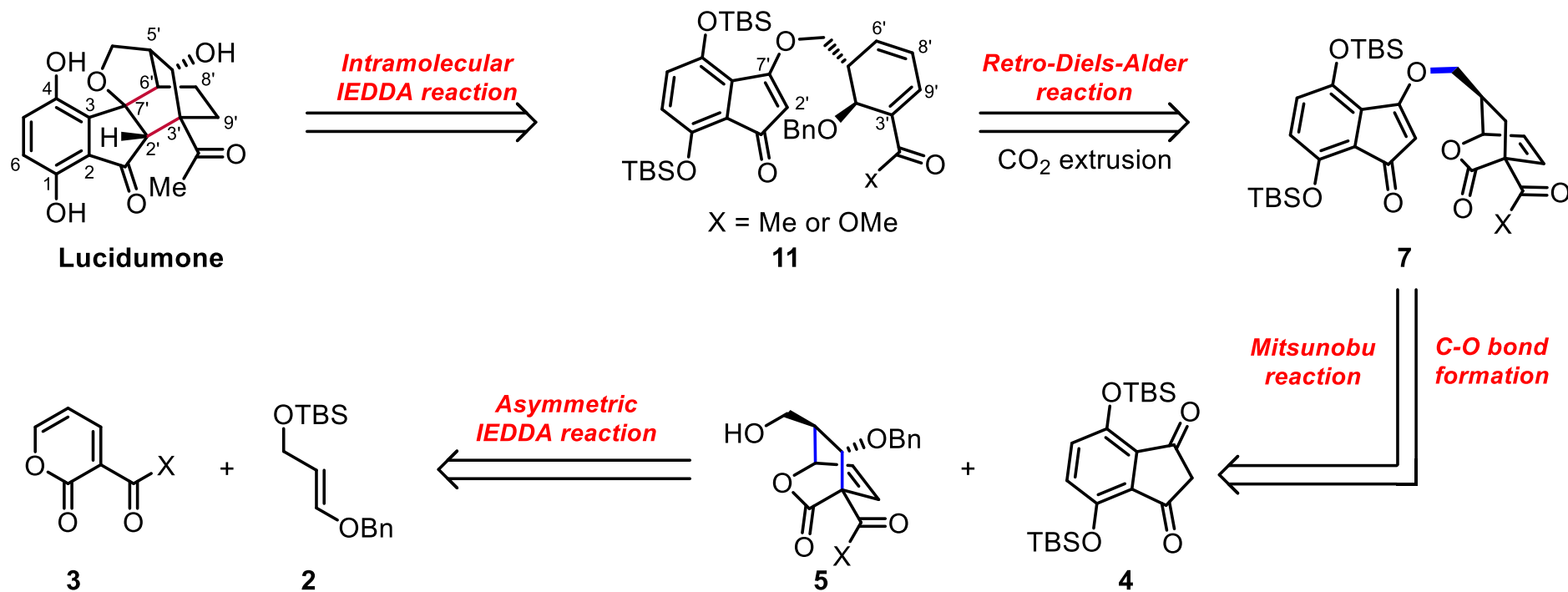
ganocin B

Structure:

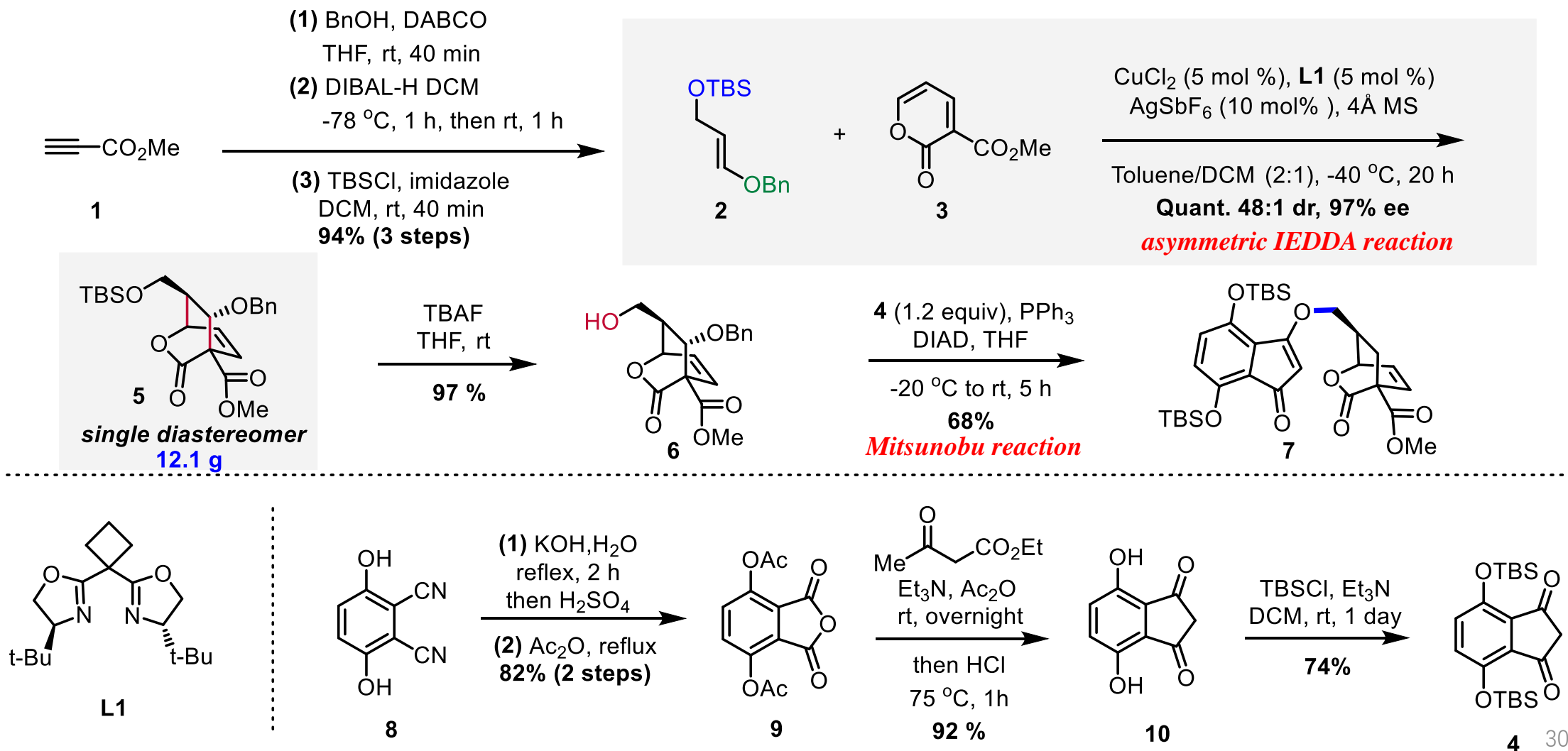
- meroterpenoid
- unprecedented 6/5/6/6/5 caged pentacyclic structure
- a fused indanone motif with a hydroquinone
- six contiguous stereocenters on the bicyclo[2.2.2]octane unit

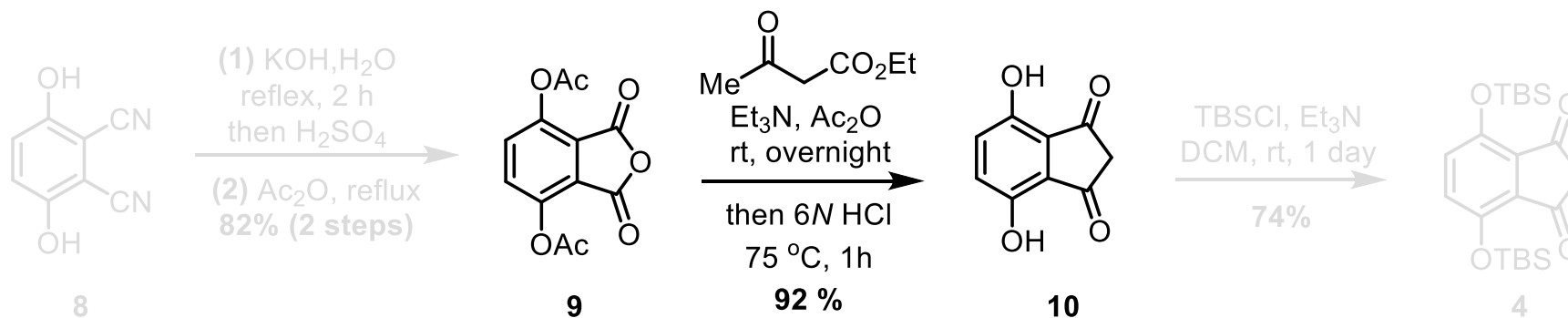
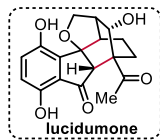


Retrosynthetic analysis of Lucidumone

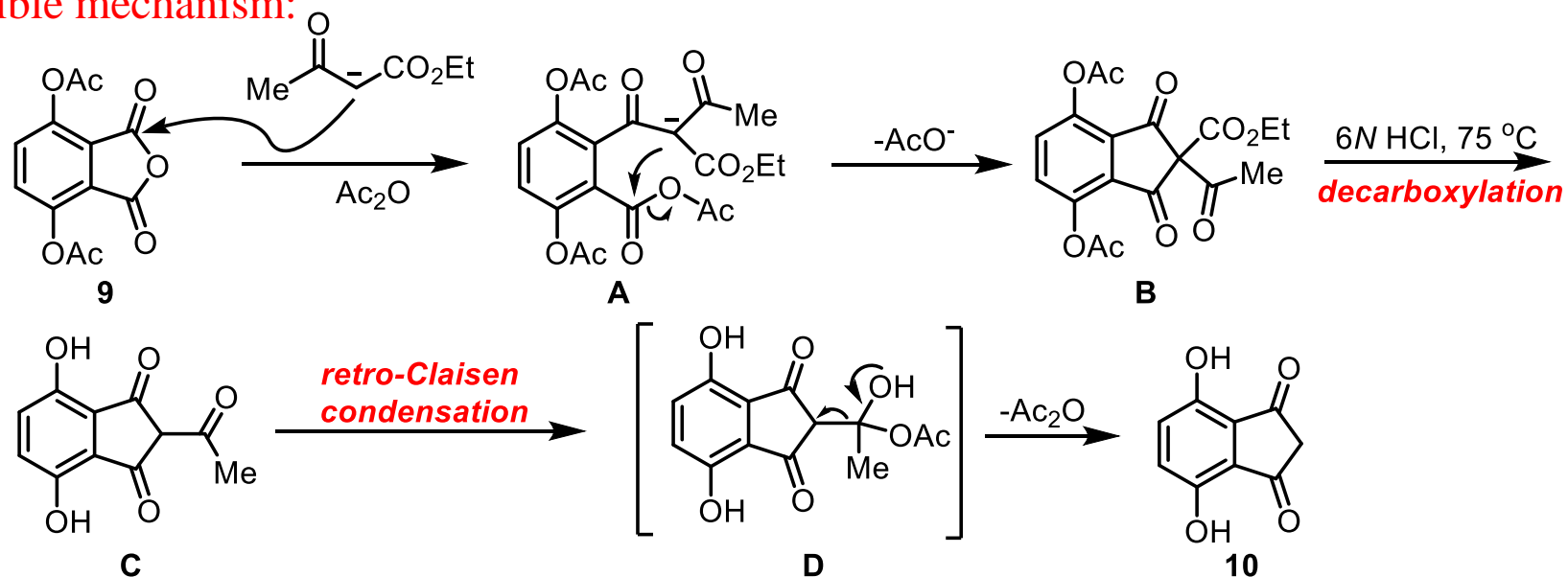


Synthesis of bridged lactone by using asymmetric IEDDA reaction

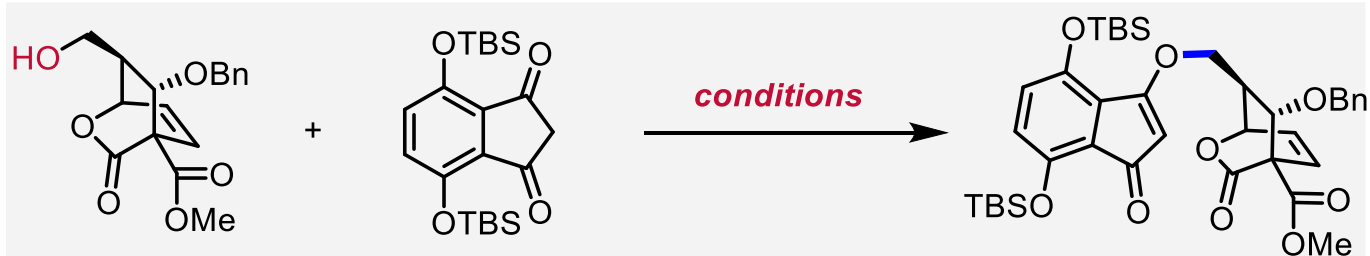




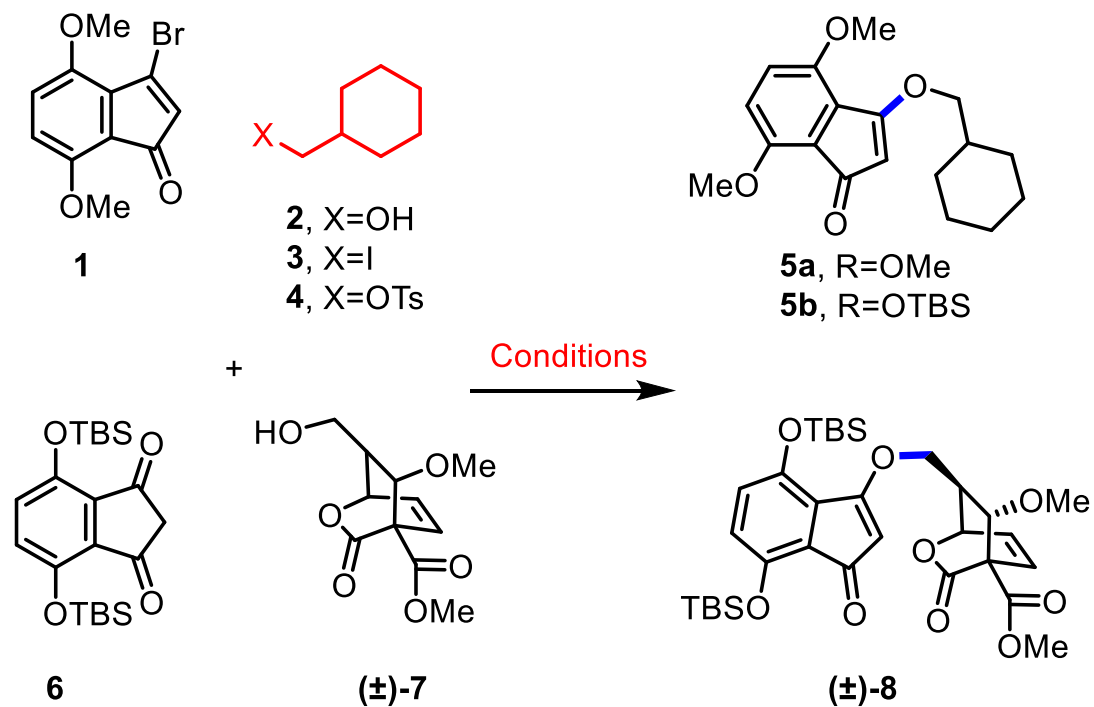
Plausible mechanism:



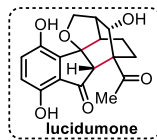
Study of the C-O Bond formation



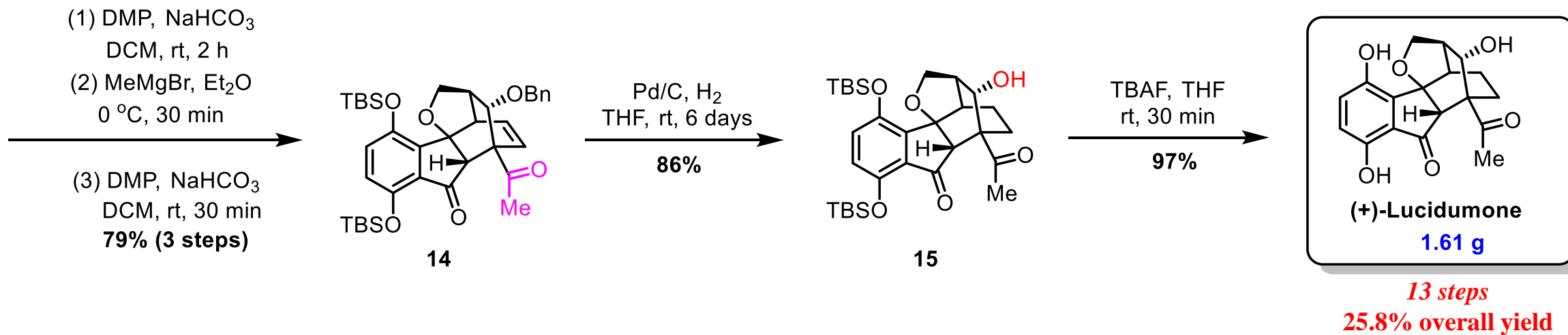
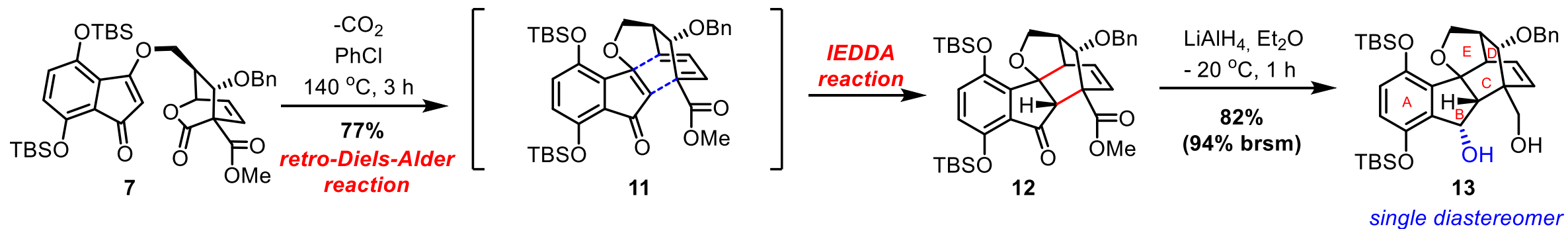
Model reactions



entry	conditions	result
1	1, 2, CuI, 1,10-Phen, Cs ₂ CO ₃ , toluene, 100 °C	N.R
2	1, 2, CuCl, EtOAc, NaH, toluene, 120 °C	decomposition
3	1, 2, <i>n</i> -BuLi, THF, 0 to 65 °C	decomposition
4	1, 2, K ₂ CO ₃ , DMF, 80 °C	decomposition
5	6, 3, K ₂ CO ₃ , DMF, 70 °C	C-alkylation
6	6, 4, K ₂ CO ₃ , DMF, 0 °C	decomposition
7	6, 2, TsOH, toluene, reflux	no reaction
8	6, 2, TiCl ₄ , toluene, rt to 60 °C	decomposition
9	6, (±)-7, PPh ₃ , DEAD, THF, -20 °C to rt	(±)-8 (51%)



Complete the Total Synthesis of Lucidumone

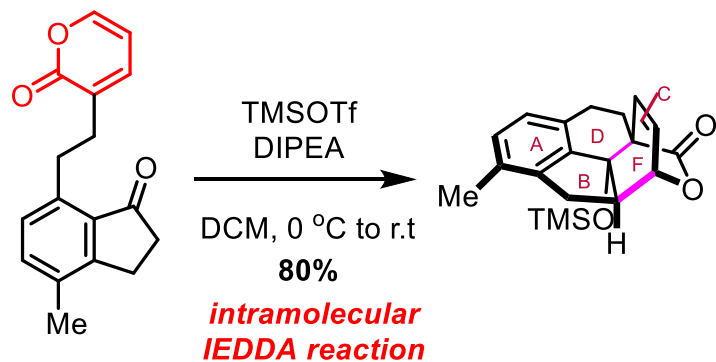
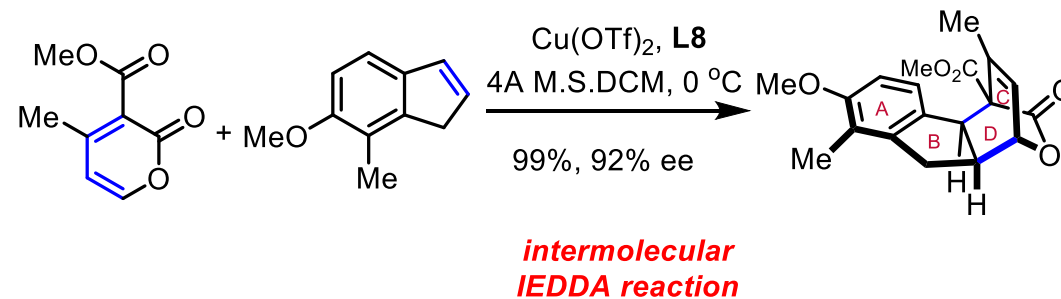
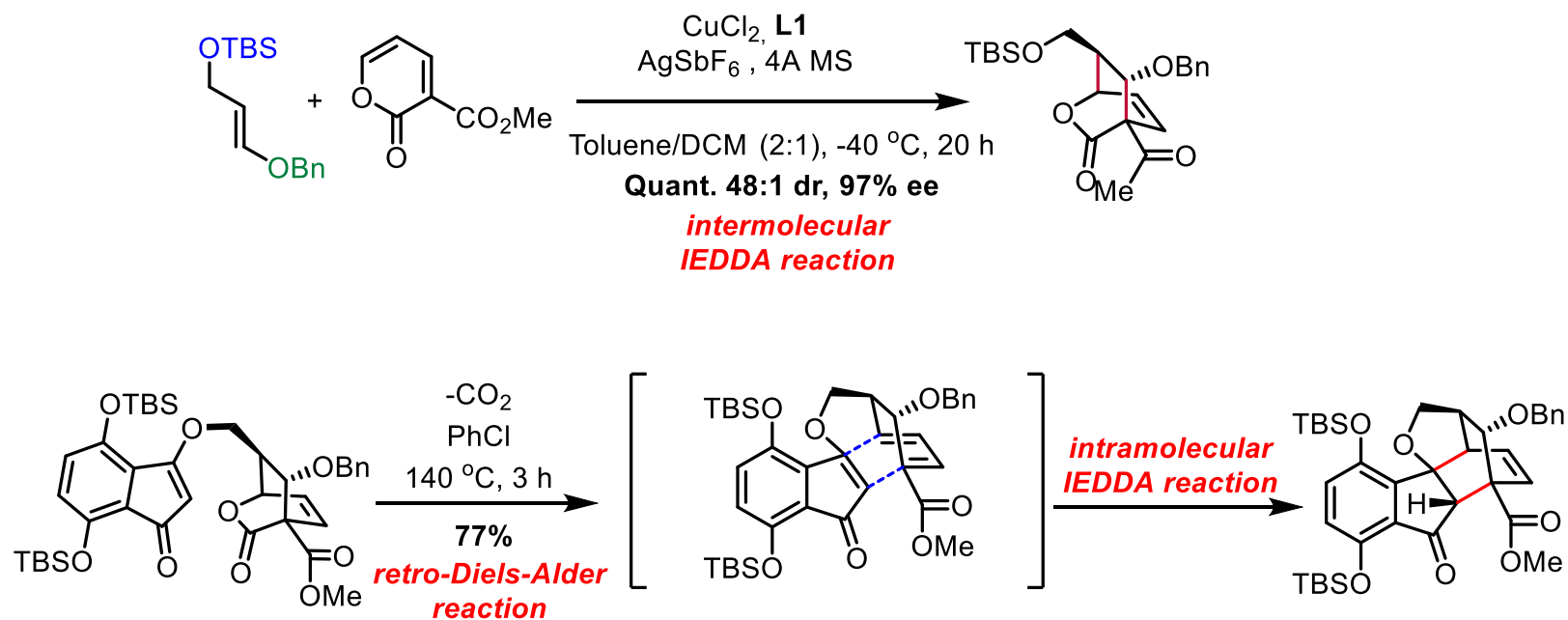


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➤ Summary

Cephanolides A-D by **Sarpong** *et al.*Cephanolides A and B by **Cai** *et al.*(+)-Lucidumone by **Torre** *et al.*

Thanks for your attention !