

Literature Report VIII

Enantioselective Total Synthesis of (-)-Himalensine A *via* a Palladium and 4-Hydroxyproline Co-catalyzed Desymmetrization of Vinyl-bromide-tethered Cyclohexanones

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Checker: Gao-Wei Wang

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Hamlin, T. A.; Dixon, D. J. *et al. J. Am. Chem. Soc.* **2023**, *145*, 5422

CV of Professor Darren J. Dixon



Research:

- ◆ Catalytic stereoselective synthesis;
- ◆ New cooperative catalyst designs;
- ◆ New cascade reactions;
- ◆ Total synthesis of complex natural products.

Background:

- **1989-1993** MA Chemistry, St. Peter's College, University of Oxford;
- **1993-1997** D. Phil, University of Oxford;
- **1997-2000** Postdoc., University of Cambridge;
- **2000-2008** Senior Assistant, Senior Lecturer, Reader, University of Cambridge;
- **2008-Now** Professor, University of Oxford.

Contents

1 Introduction

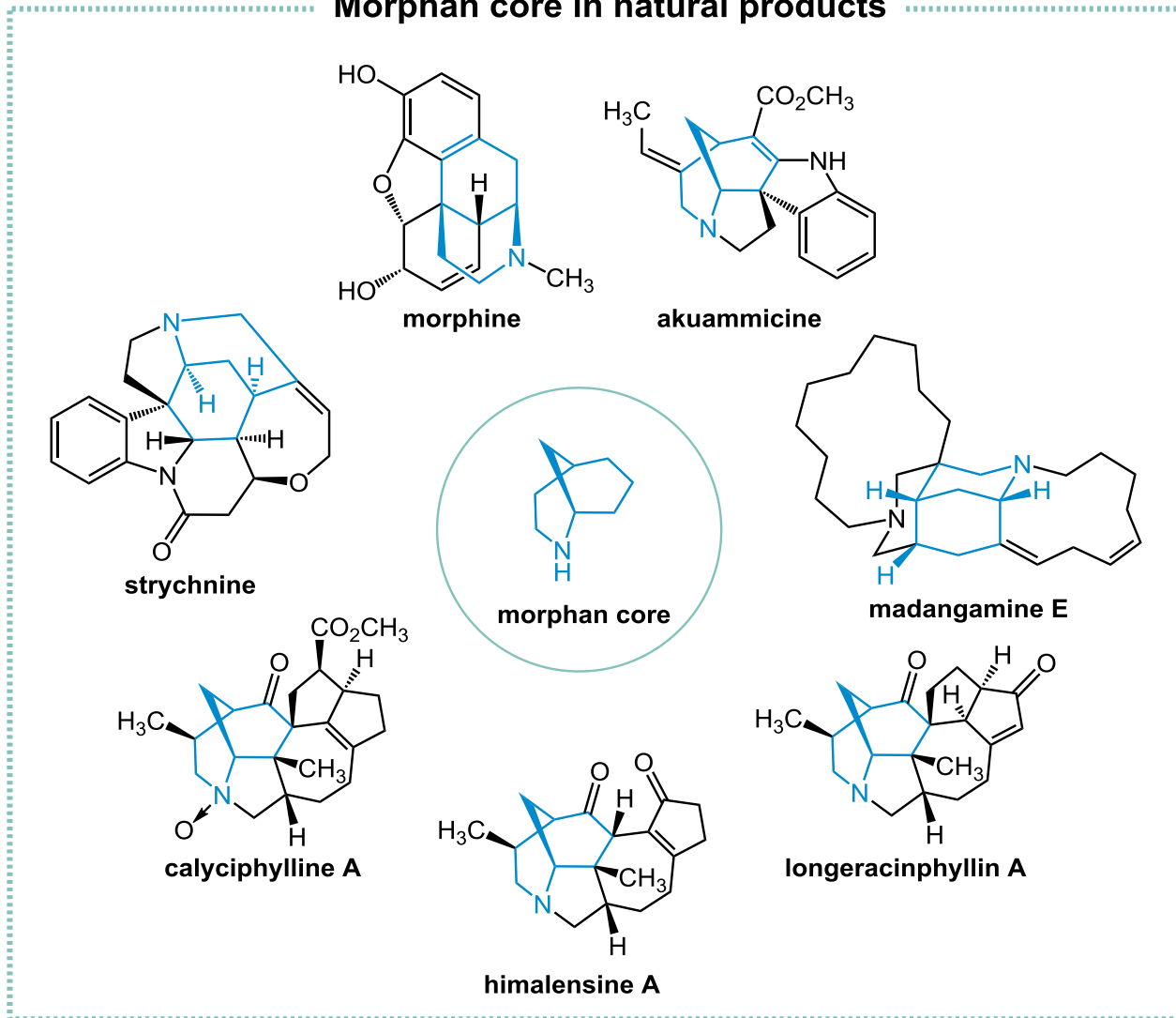
2 Pd and 4-Hydroxyproline Co-catalyzed Desymmetrization

3 Total Synthesis of (–)-Himalensine A

4 Summary

Introduction

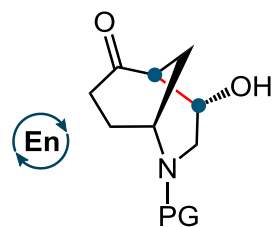
Morphan core in natural products



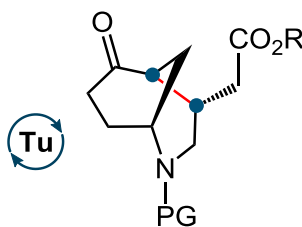
Introduction

Synthesis of morphan core by desymmetrization

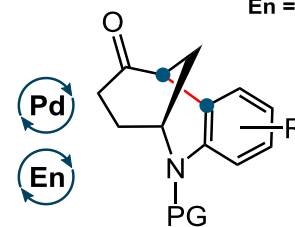
Tu = Thiourea Catalysis
En = Enamine Catalysis



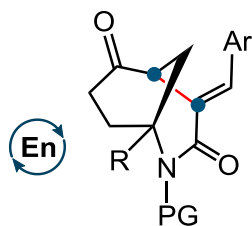
aldol reaction
Bonjoch (2009)



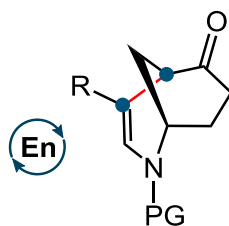
Michael add.
Dixon (2015)



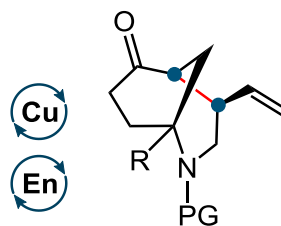
ketone arylation
Jia (2016)



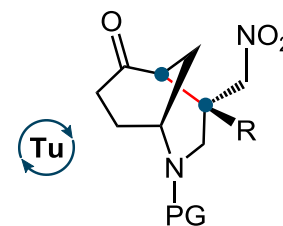
α-addition
Jia (2019)



Conia-Ene
Ye (2019)



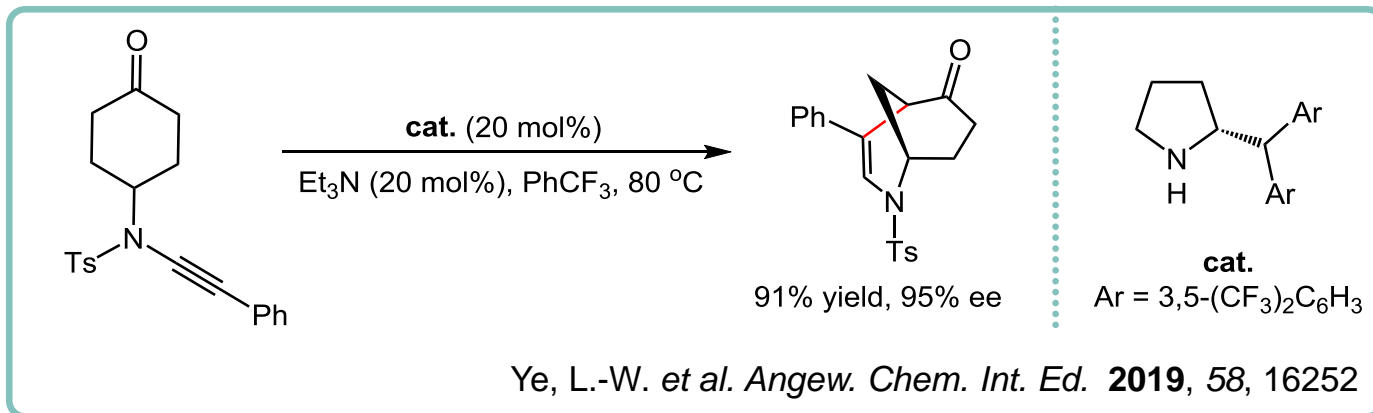
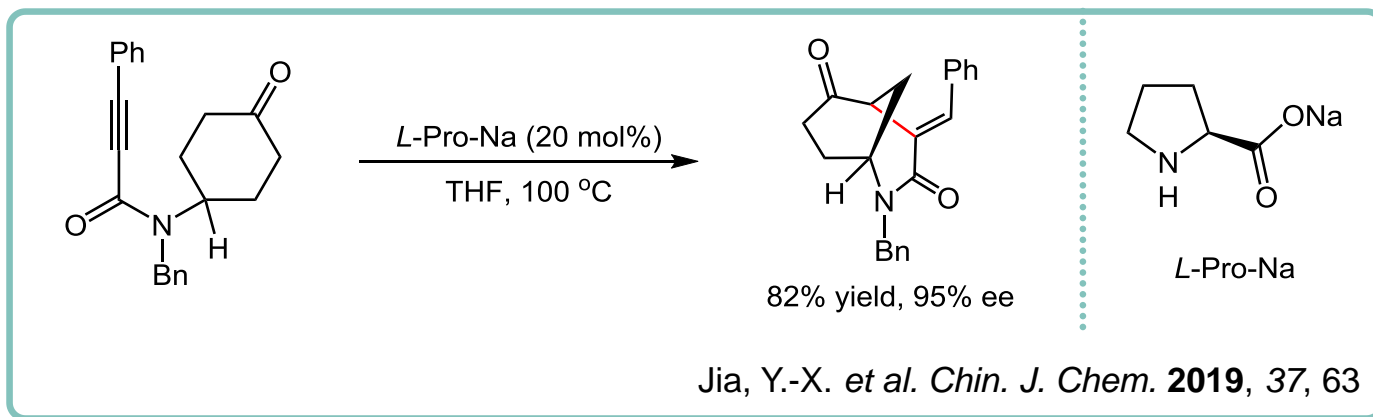
ketone allylation
Dixon (2020)



Michael add.
Dixon (2022)

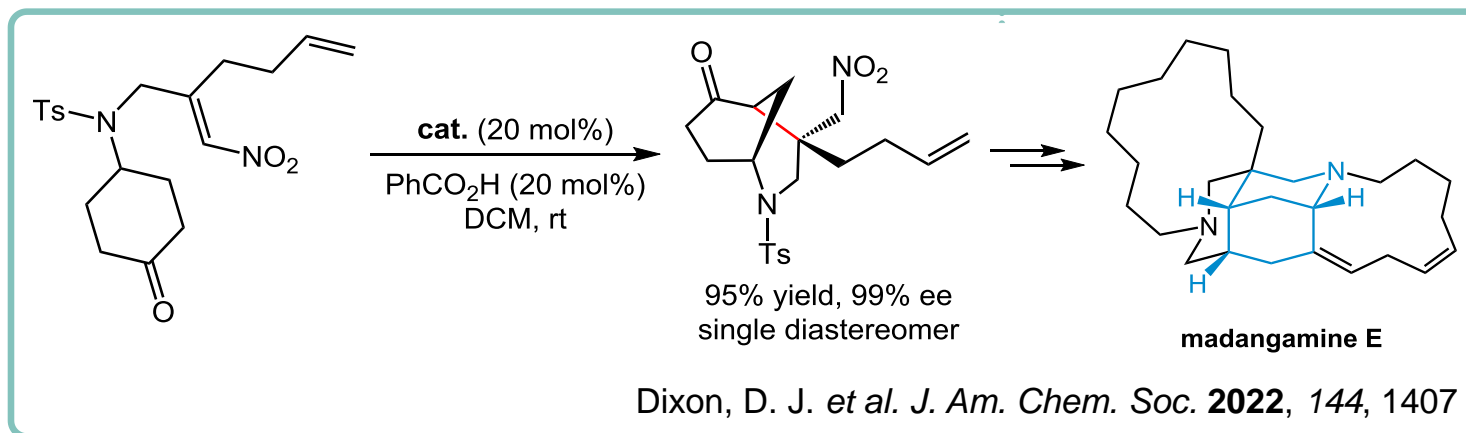
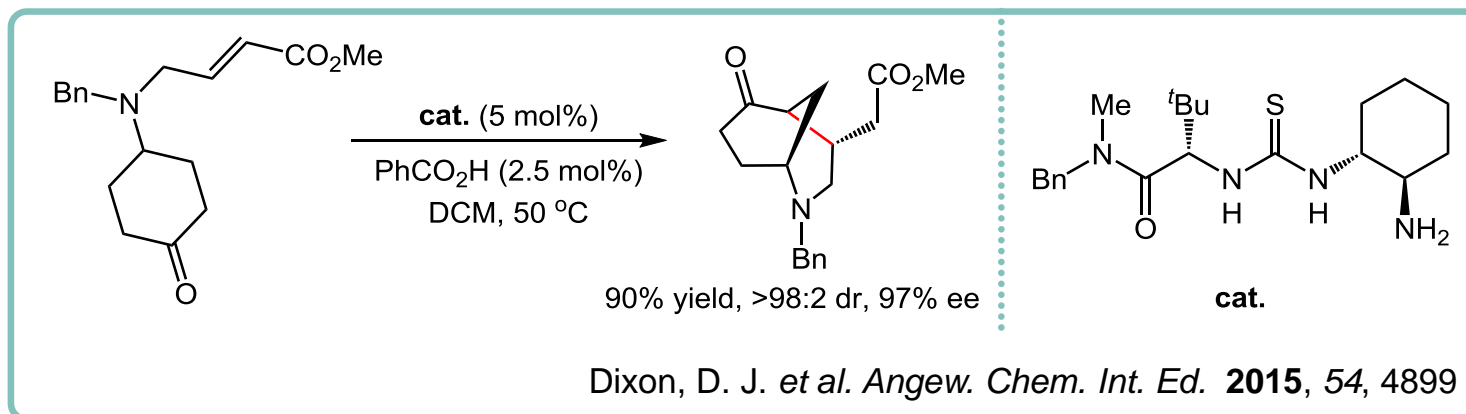
Introduction

◆ Enamine Catalytic Enantioselective Desymmetrization



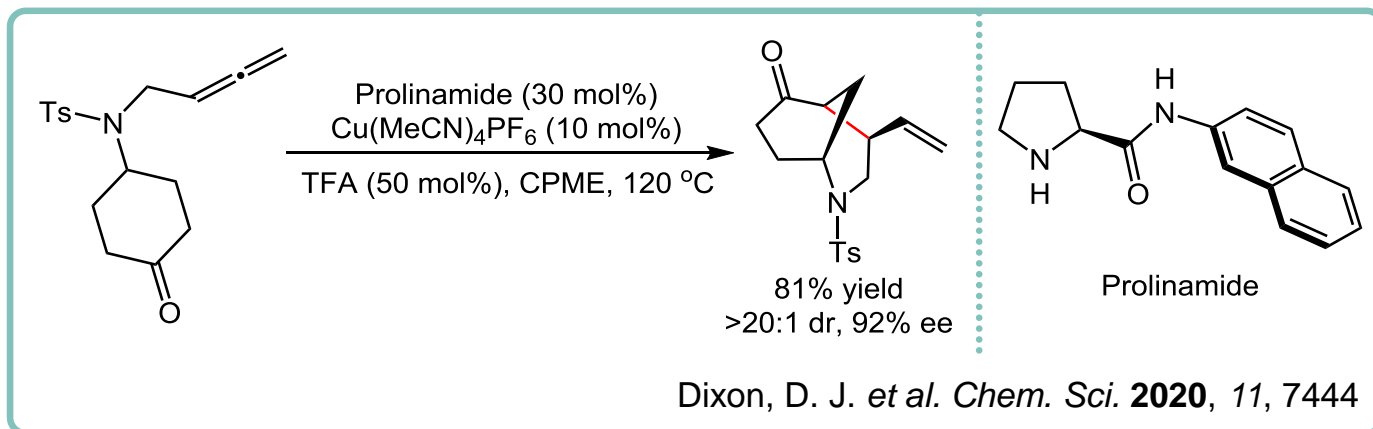
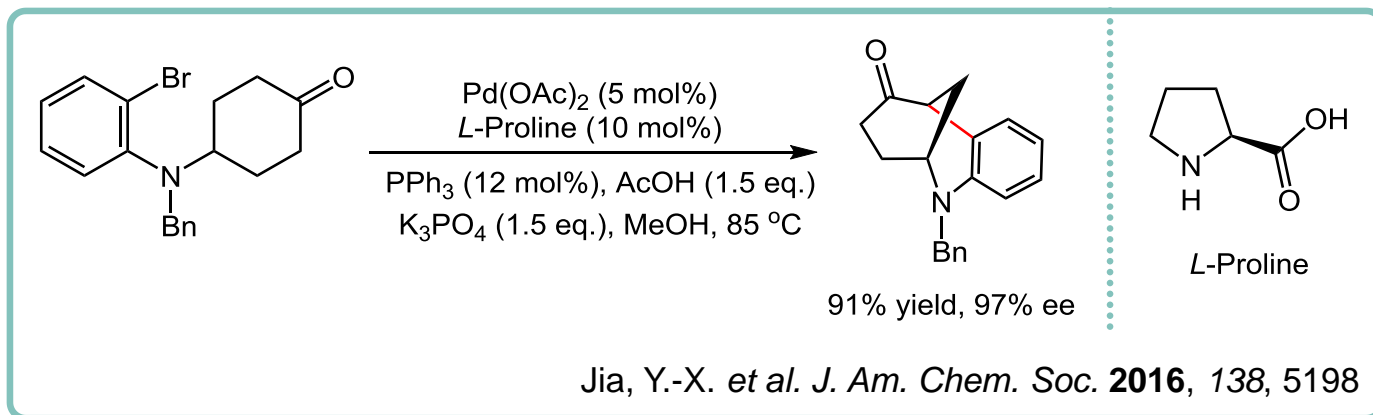
Introduction

◆ Thiourea Catalytic Enantioselective Desymmetrization



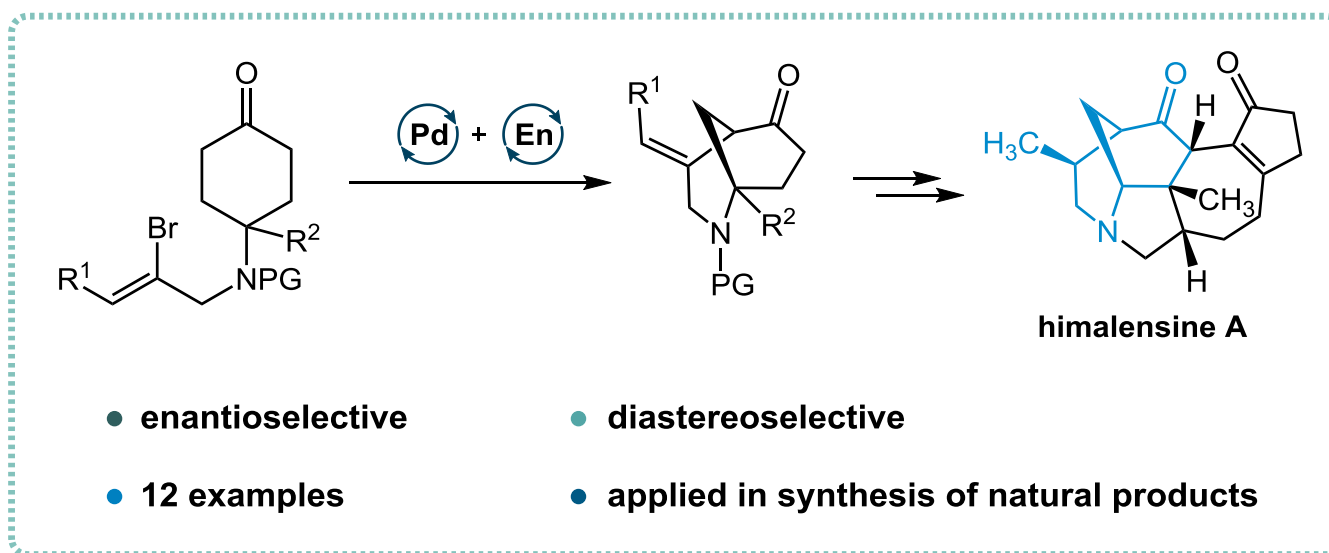
Introduction

◆ Dual Catalytic Enantioselective Desymmetrization

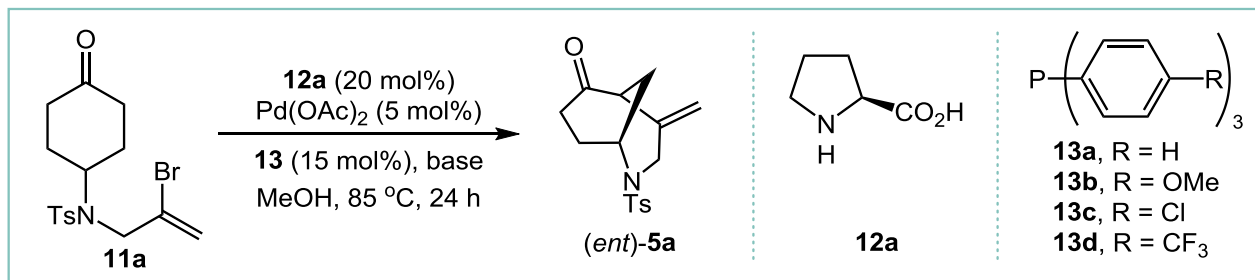


Introduction

◆ Dual Palladium/Chiral Amine Catalyst System



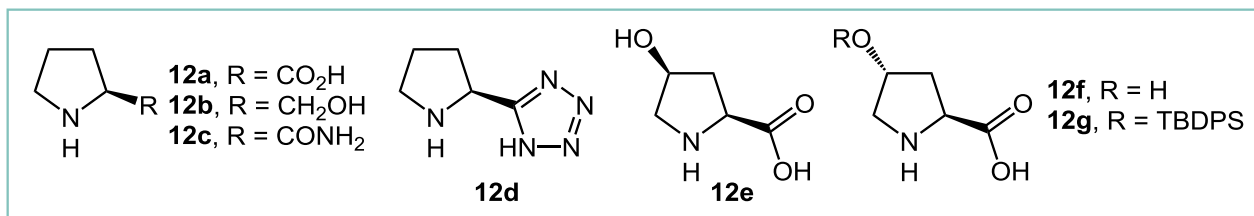
Optimization of the Reaction Conditions



entry	base	ligand	yield (%) ^b	ee (%) ^c
1	K ₂ CO ₃	13a	0	n/a
2	Cs ₂ CO ₃	13a	16	29
3	NaOAc	13a	15	68
4	K ₃ PO ₄	13a	17	42
5	K ₂ HPO ₄	13a	27	82
6	KH ₂ PO ₄	13a	0	n/a
7 ^d	K ₂ HPO ₄	13a	40	86
8 ^d	K ₂ HPO ₄	13b	22	66
9 ^d	K ₂ HPO ₄	13c	68	94
10 ^d	K ₂ HPO ₄	13d	81	93

^aReaction Conditions: **11a** (0.10 mmol), **12a** (20 mol%), Pd(OAc)₂ (5 mol%), **13** (15 mol%), base (1.5 equiv), MeOH (0.10 M), 85 °C, 24 h. ^bDetermined by ¹H NMR analysis of crude reaction mixtures using mesitylene as an internal standard. ^cDetermined by chiral HPLC analysis. ^dConcentration of 0.05 M.

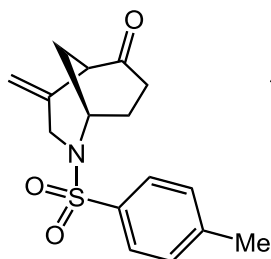
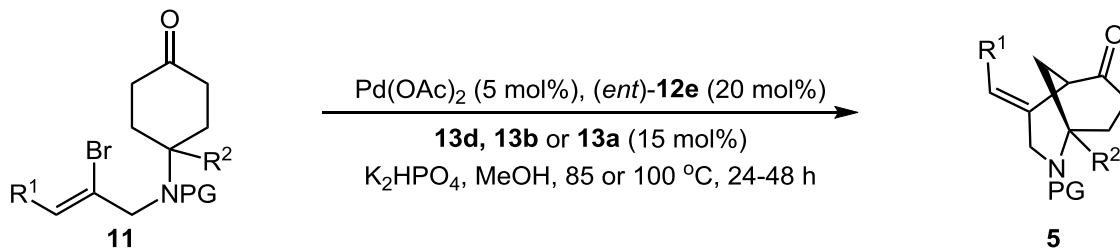
Optimization of the Reaction Conditions



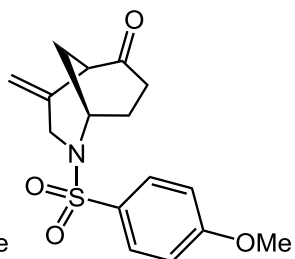
entry	base	amine	ligand	yield (%) ^b	ee (%) ^c
11	K ₂ HPO ₄	12b	13c	16	n.d.
12	K ₂ HPO ₄	12c	13c	7	n.d.
13	K ₂ HPO ₄	12d	13c	0	n/a
14	K ₂ HPO ₄	12e	13c	95	92
15	K ₂ HPO ₄	12f	13c	95	91
16	K ₂ HPO ₄	12g	13c	66	96
17^d	K₂HPO₄	12e	13d	95	94
18^d	K₂HPO₄	(ent)-12e	13d	95 (ent)	94 (ent)
19 ^{d,e}	K ₂ HPO ₄	(ent)-12e	13d	0	n/a
20 ^d	-	(ent)-12e	13d	0	n/a
21 ^d	K ₂ HPO ₄	-	13d	0	n/a

^aReaction Conditions: **11a** (0.10 mmol), **12** (20 mol%), Pd(OAc)₂ (5 mol%), **13** (15 mol%), base (1.5 equiv), MeOH (0.10 M), 85 °C, 24 h. ^bDetermined by ¹H NMR analysis of crude reaction mixtures using mesitylene as an internal standard. ^cDetermined by chiral HPLC analysis. ^dConcentration of 0.05 M. ^eNo Pd(OAc)₂.

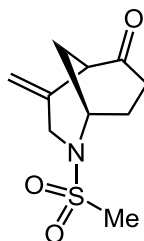
Substrate Scope



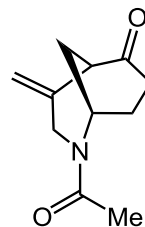
5a, 95%, 94% ee



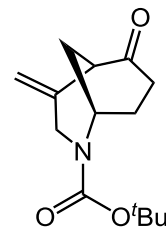
5b, 81%, 92% ee



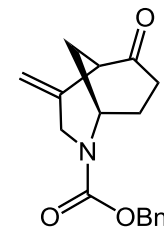
5c, 58%, 94% ee



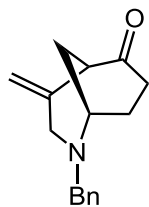
5d, 98%, 89% ee



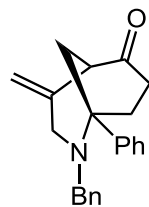
5e, 88%, 93% ee



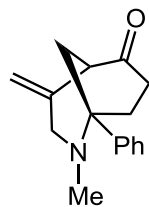
5f, 99%, 96% ee



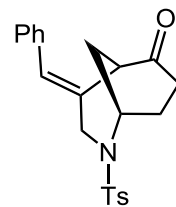
5g, 76%, 98% ee



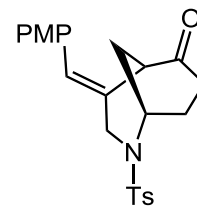
5h, 89%, 86% ee



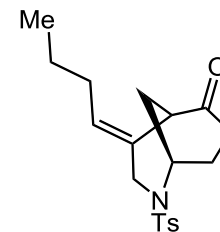
5i, 91%, 99% ee



5j, 77%, 95% ee

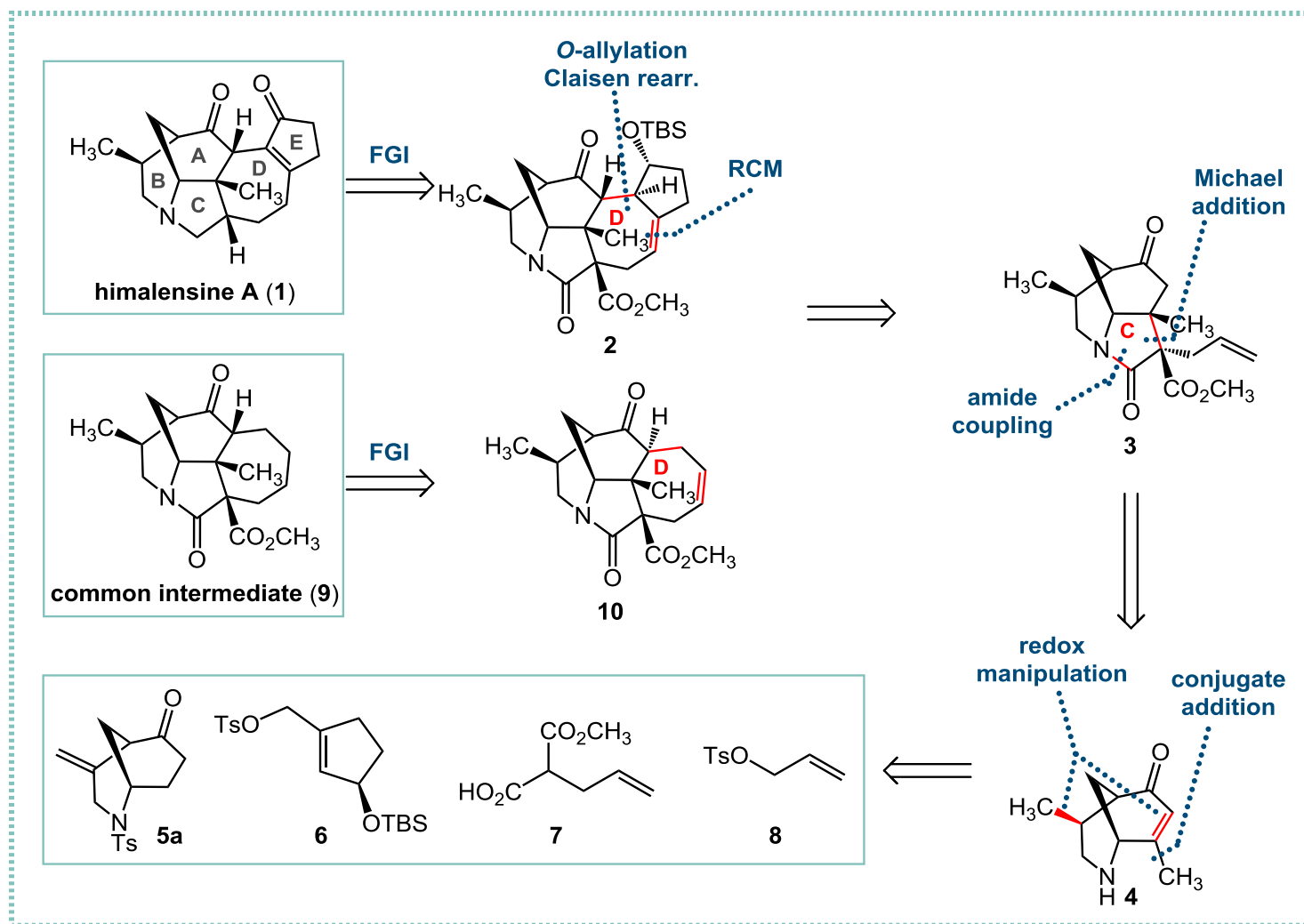


5k, 72%, 96% ee

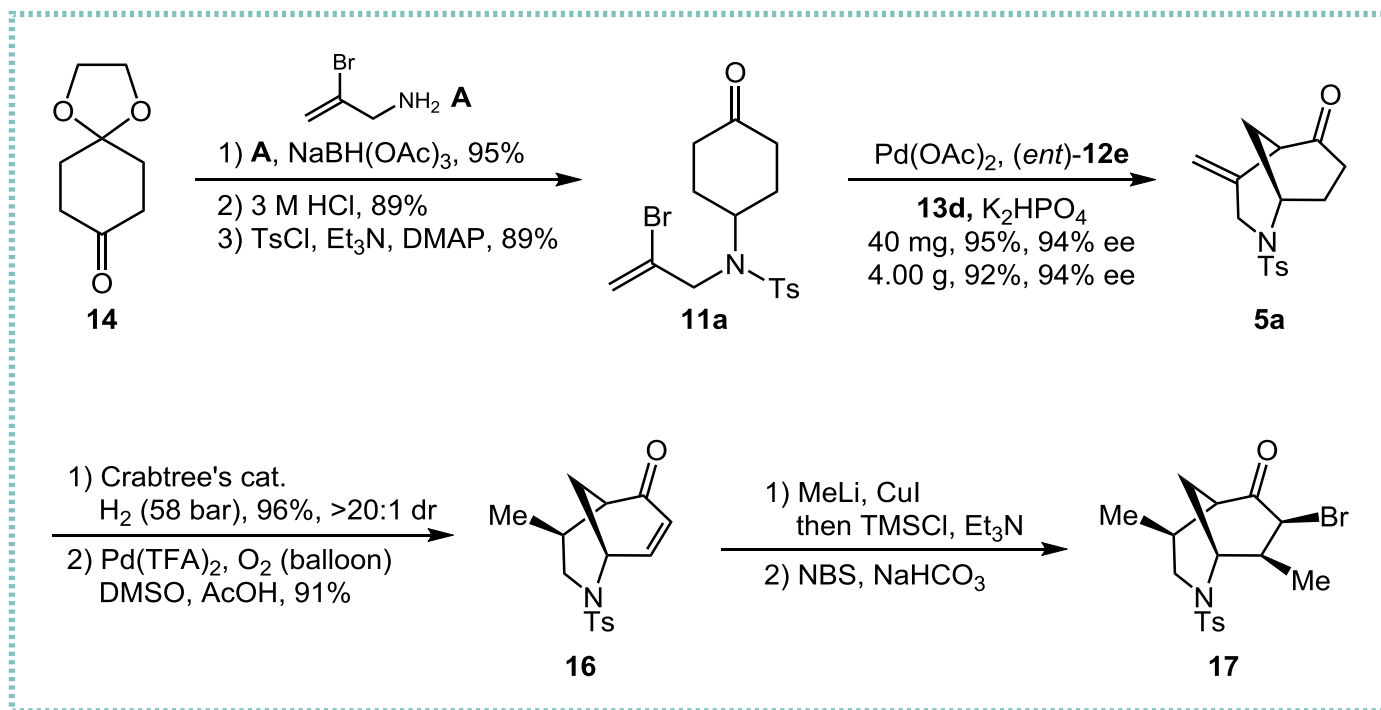


5l, 59%, 95% ee

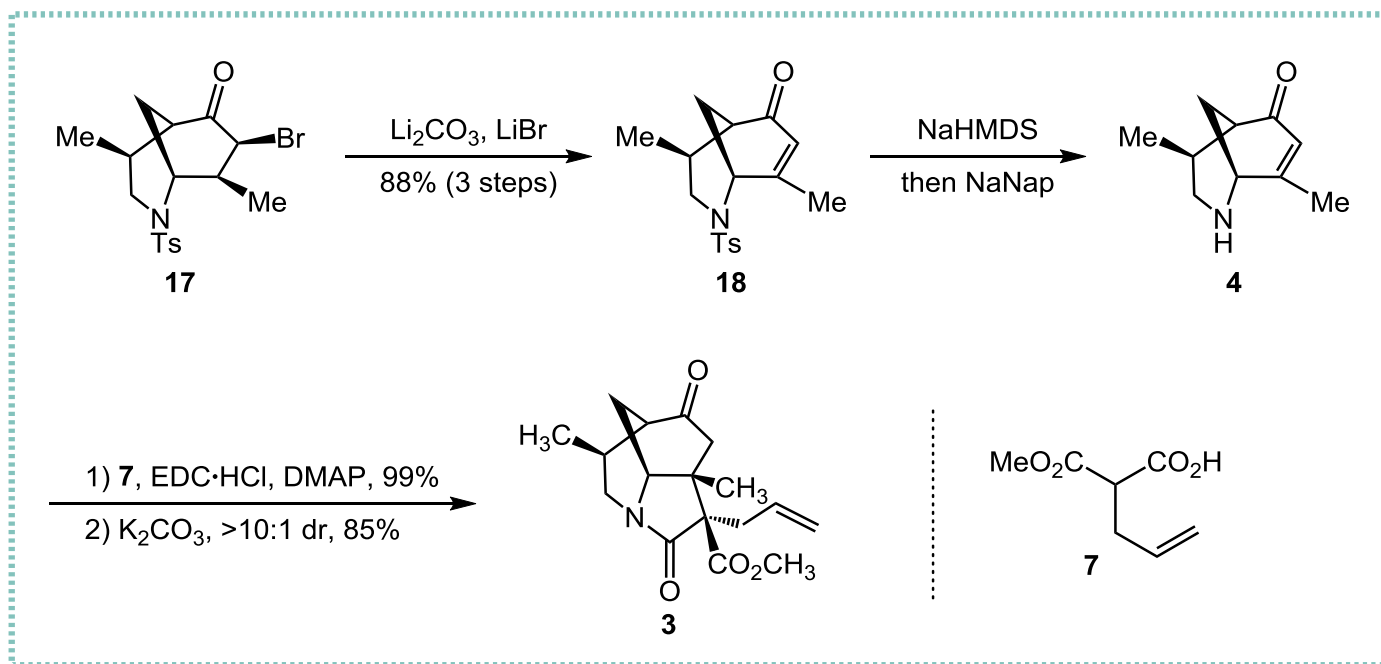
Retrosynthetic Analysis



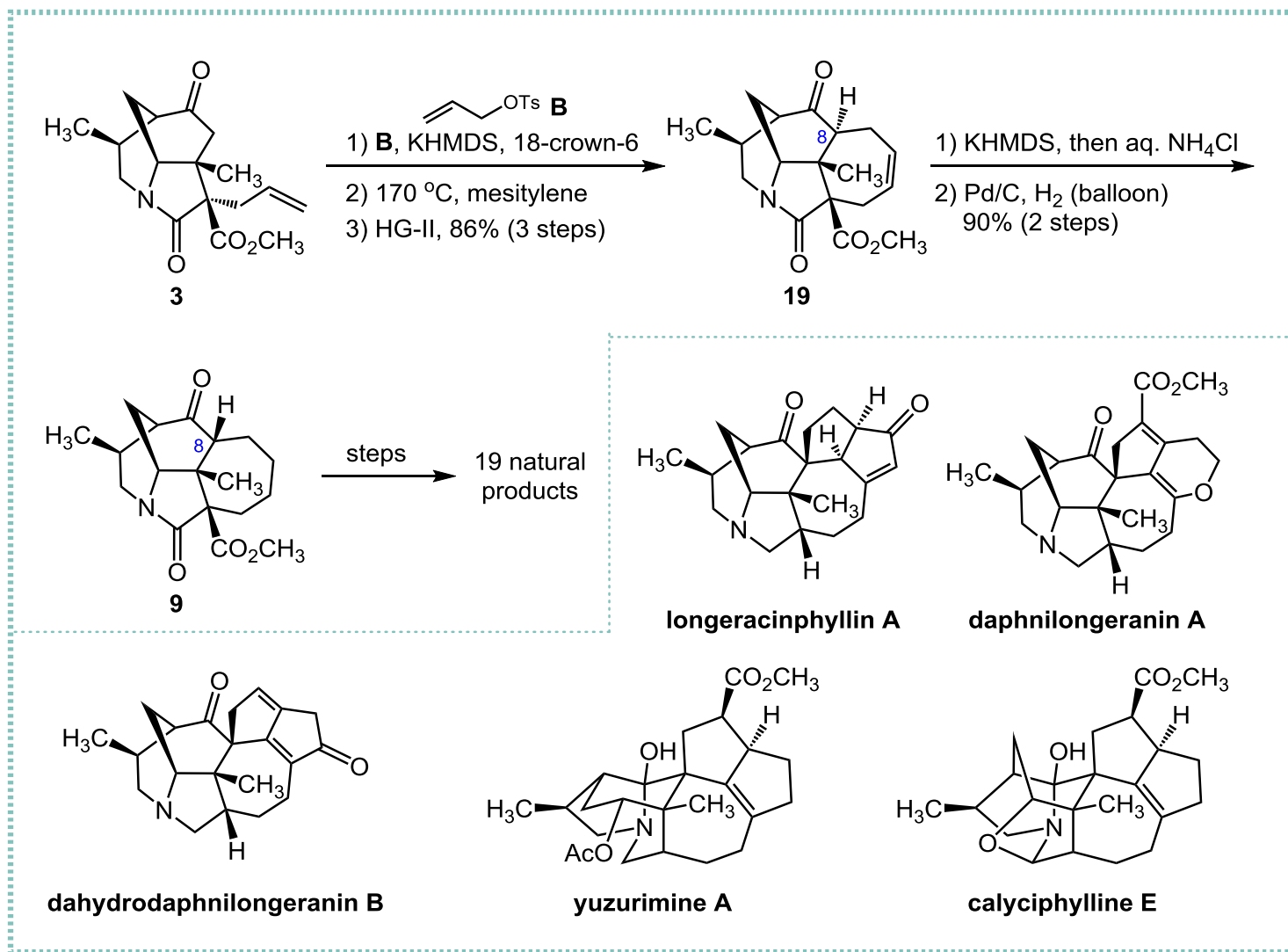
Synthesis of Intermediate 17



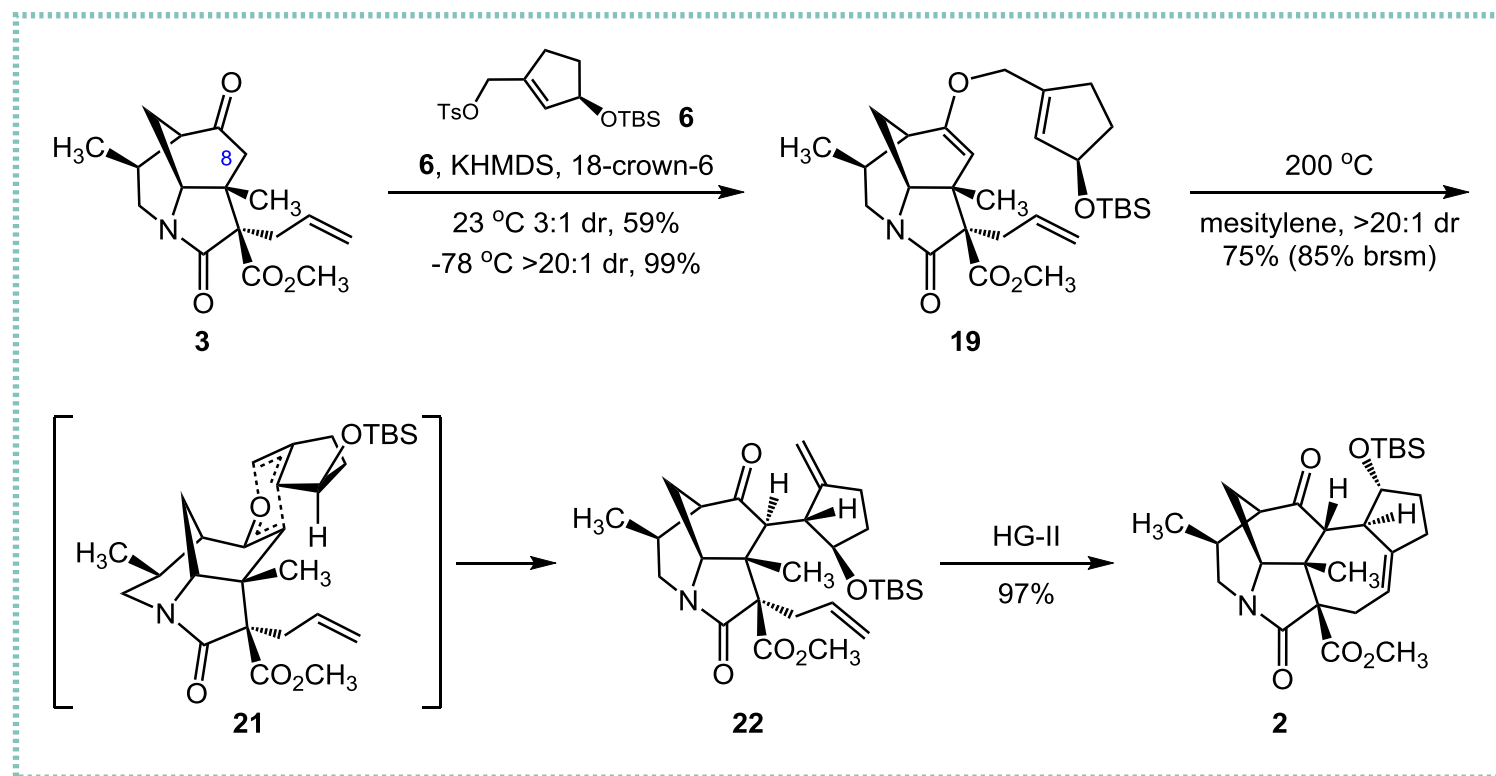
Synthesis of Tricyclic Intermediate 3



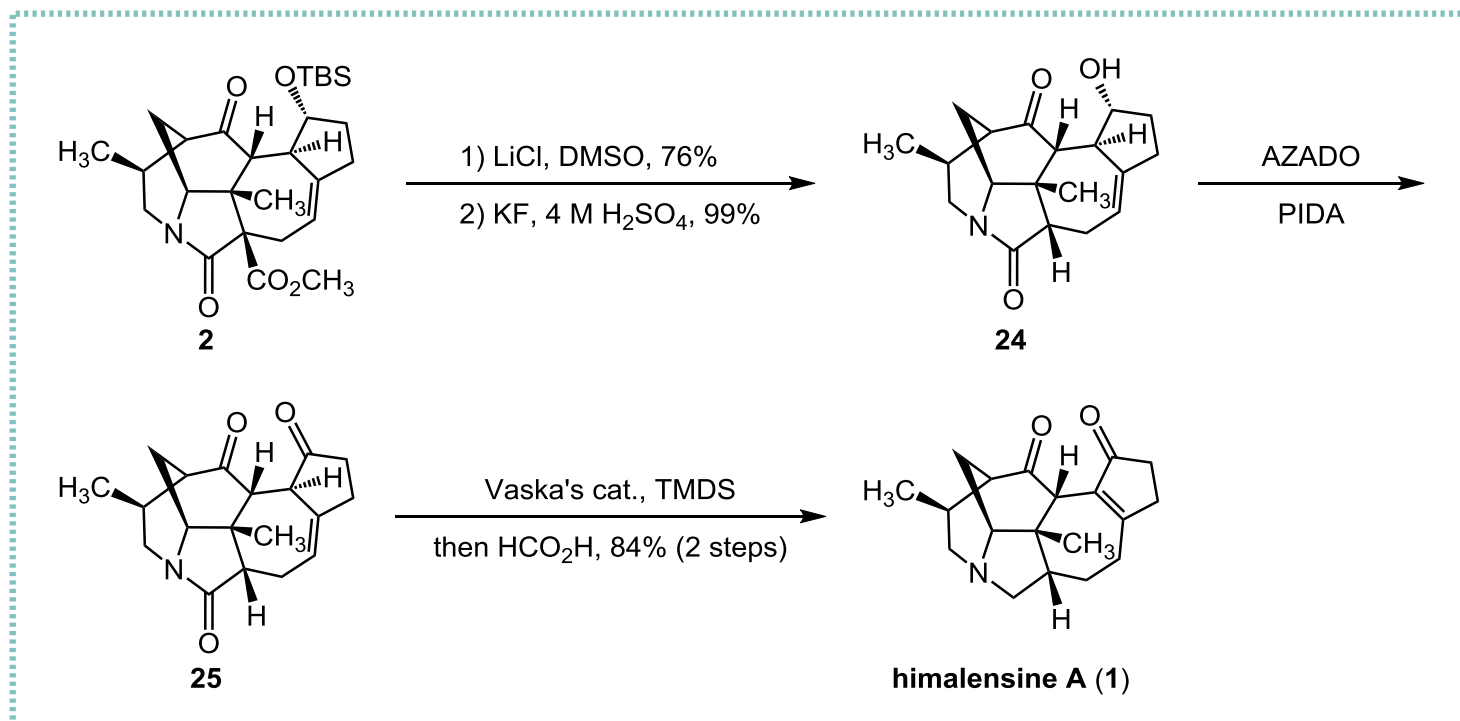
Formal Synthesis of *Daphniphyllum* Alkaloids



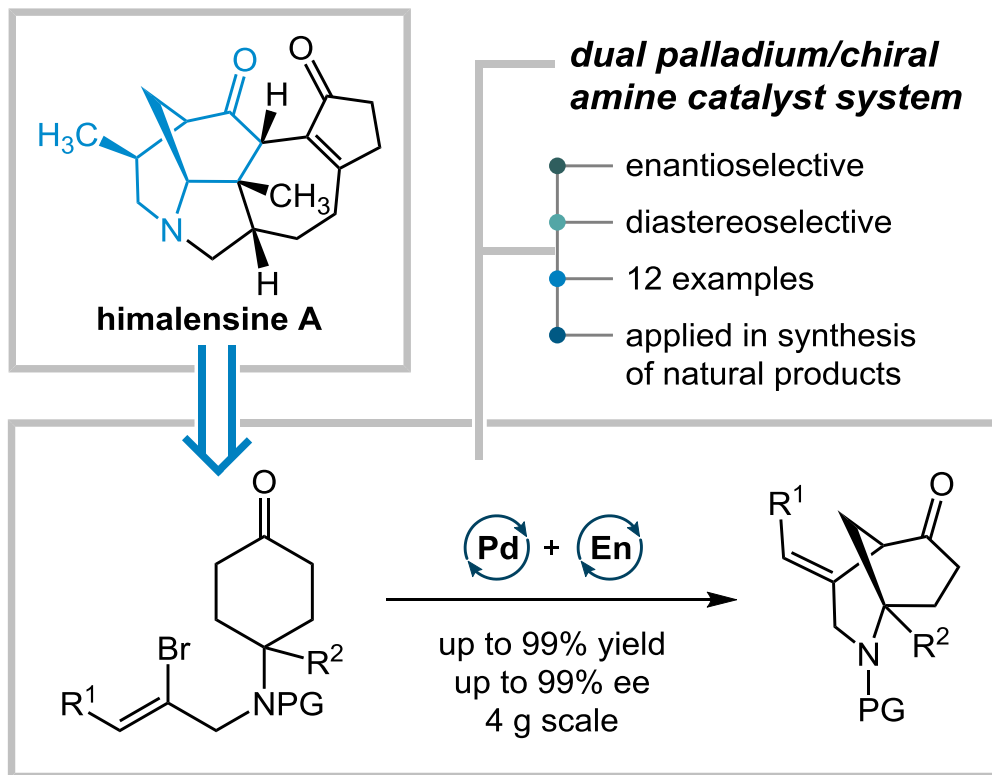
Synthesis of Intermediate 2



Total Synthesis of Himalensine A



Summary




Writing Strategy

➤ Introduction

The importance
of morphan core



Enantioselective
synthesis of the
morphan core by
desymmetrization




The necessity
to develop synthetic
strategy of enantio-
selective morphan core

- ♪ The 2-azabicyclo[3.3.1]nonane motif, known as the morphan core, is found in over 300 natural products across a variety of families, including the Strychnos, Morphine, Madangamine, and Daphniphyllum. Many of these compounds, such as strychnine and morphine, exhibit potent biological effects.
- ♪ In terms of enantioselective approaches, the desymmetrization of structurally simple molecules to rapidly access more architecturally complex and stereochemically defined products is widely considered as one of the most powerful and elegant synthetic strategies.
- ♪ Despite these advances, the application of enantioselective morphan core-generating desymmetrizing technology as a key complexity-building step in natural product synthesis is still in its infancy. To the best of our knowledge, ...


Writing Strategy

➤ The Last Paragraph

Summary of
the work



Significant steps
in total synthesis



Reaction proceeds
revealed by DFT
computations

- ♪ In conclusion, we have developed a new enantioselective synthesis of himalensine A.
- ♪ Key to the rapid construction of this natural product was a highly convergent strategy based on an amide coupling/Michael addition/allylation/RCM sequence, which allowed for the introduction of three of the five rings in only five synthetic steps (three steps after telescoping)...
- ♪ DFT computations revealed that the reaction proceeds via an intramolecular Heck reaction of an enamine intermediate formed *in situ* by condensation of the hydroxyproline catalyst with the cyclohexanone, where exquisite enantioselectivity arises from carboxylate coordination to the vinyl palladium species in the rate- and enantio-determining carbopalladation step.

Representative Examples

- Despite these advances, the application of enantioselective morphan core-generating desymmetrizing technology as a key complexity-building step in natural product synthesis is still **in its infancy**. (在起步期)
- **With the intention of** broadening this concept to other complex natural product targets, **we were drawn toward** developing a desymmetrizing vinylation methodology for ... (为了..., 我们被吸引到...)
- Pleasingly, **upscaling** of the key vinylation reaction from 40 mg to 4.0 g was straightforward, and the desired cyclized product **5a** was obtained in 92% yield and 94% ee. (扩大规模)

Acknowledgement

Thanks for your attention !