Total Synthesis of (−)-Himalensine A

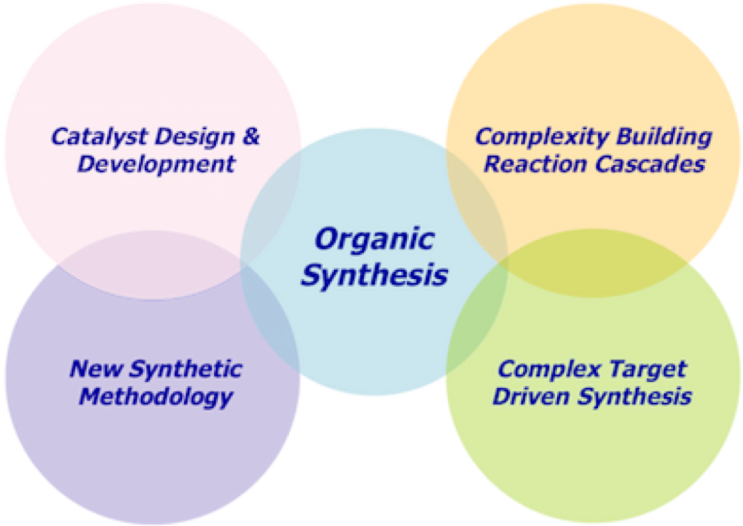
Heyao Shi, Iacovos N. Michaelides, Benjamin Darses, Pavol Jakubec, Quynh Nhu N. Nguyen, Robert S. Paton,* and Darren J. Dixon*

J. Am. Chem. Soc. 2017, 139, 17755−17758

Journal Club
Renaud Group
Department of Chemistry and Biochemistry
University of Bern

By Komba Thomas
March 1, 2018

Darren J. Dixon



2014 to date: Director, EPSRC CDT in Synthesis for Biology and Medicine, University of Oxford, UK

2008 to date: Professor of Chemistry, University of Oxford, UK

Knowles-Williams Fellow in Organic Chemistry, Wadham College, Oxford, UK

2007 – 2008: Reader in Organic Chemistry, University of Manchester, UK

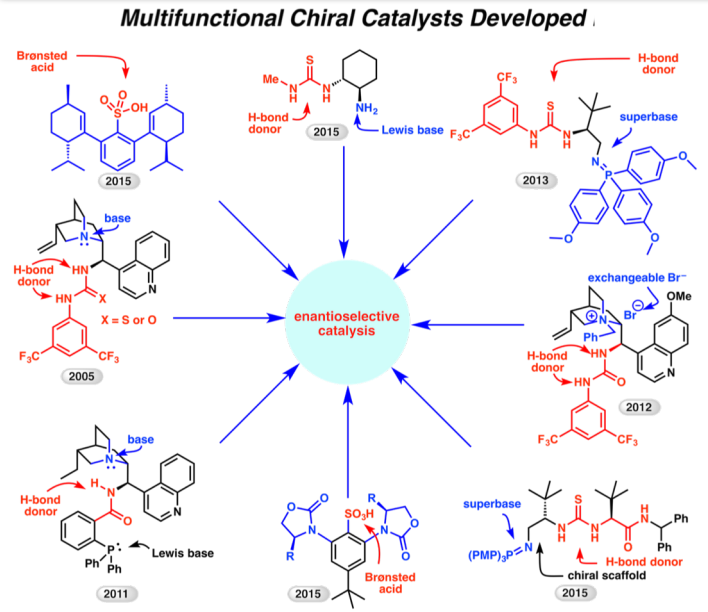
2004 – 2007: Senior Lecturer in Organic Chemistry, University of Manchester, UK

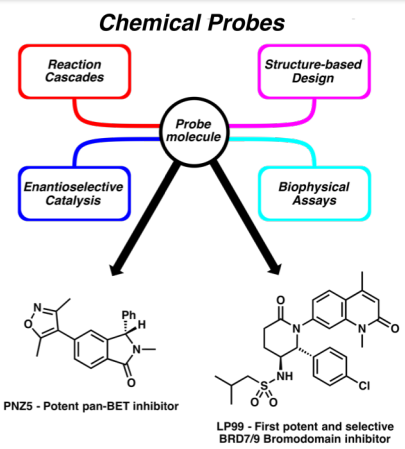
2000 – 2004: Senior Assistant in Research in Organic Chemistry, University of Cambridge, UK

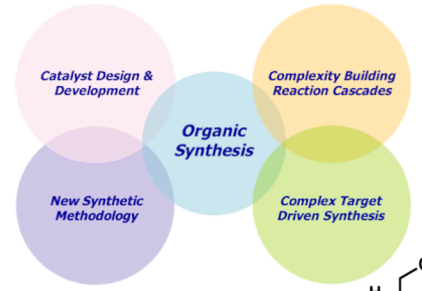
1997 – 2000: Postdoctoral Research Position, Prof. S. V. Ley, FRS, University of Cambridge, UK

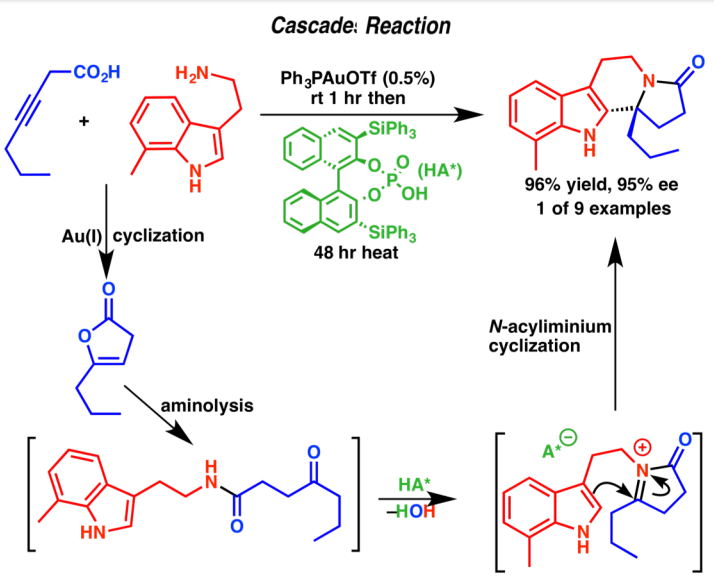
http://dixon.chem.ox.ac.uk/research.html

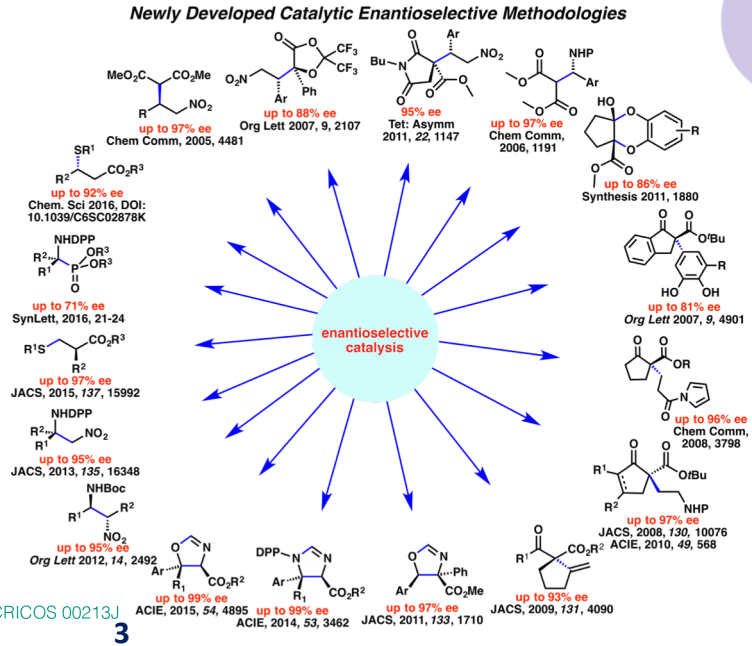
Darren J. Dixon: Research

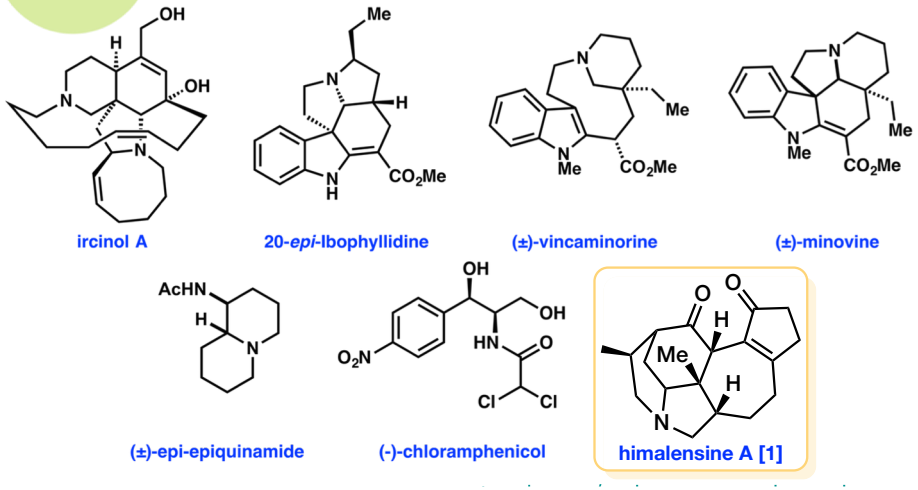








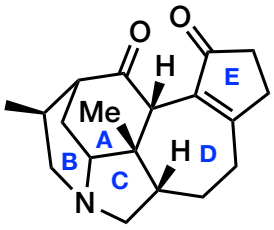




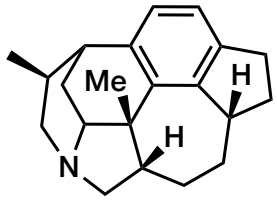
Himalensine A: Synthetic Strategy

- *Daphniphyllum himalense* alkaloid: only grows in the southern Himalaya Mountains.
- Potential biological activity (cytotoxic, antioxidant, vasorelaxant).
- Complex structural architecture (features a trinorcalyciphylline A-type backbone).

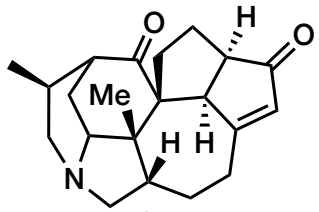
Calyciphlline A-type family



1
himalensine A



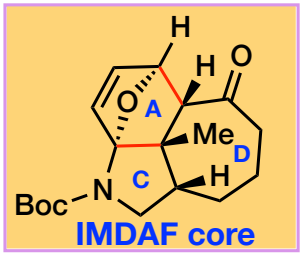
2
daphenylline



3
longeracinphyllin A

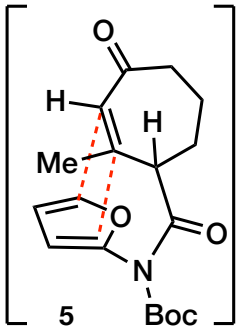
Intramolecular amidofuran Diels–Alder (IMDAF

Key step to tricyclic core

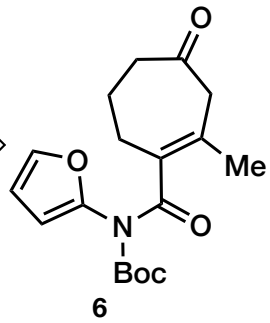


4

Diels-Alder

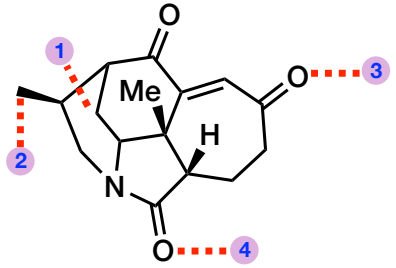


prototropic shift



6

catalytic, enantioselective
2 C-C bonds, 5 stereocentres

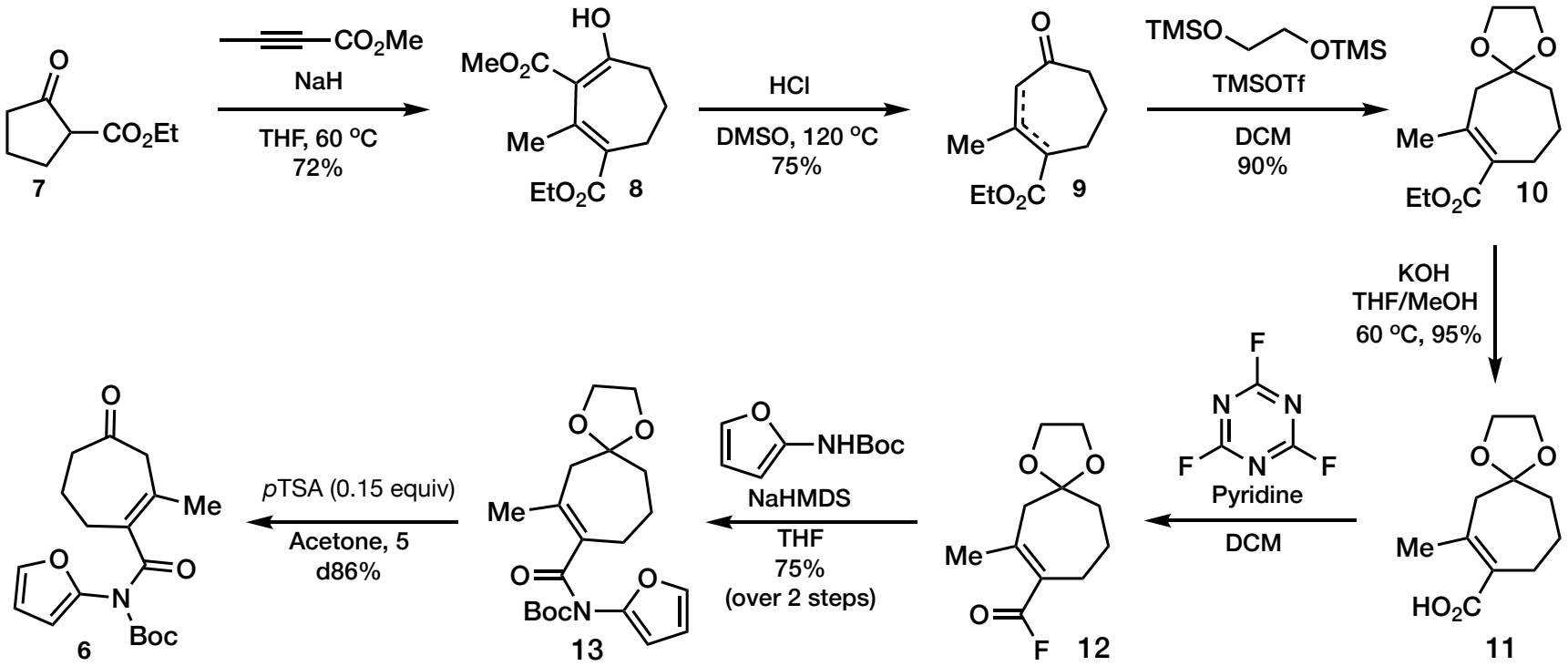


Key transformations

1. radical cyclisation
2. diastereoselective hydrogenation
3. O_2-mediated C-H oxidation
4. chemoselective lactam reduction

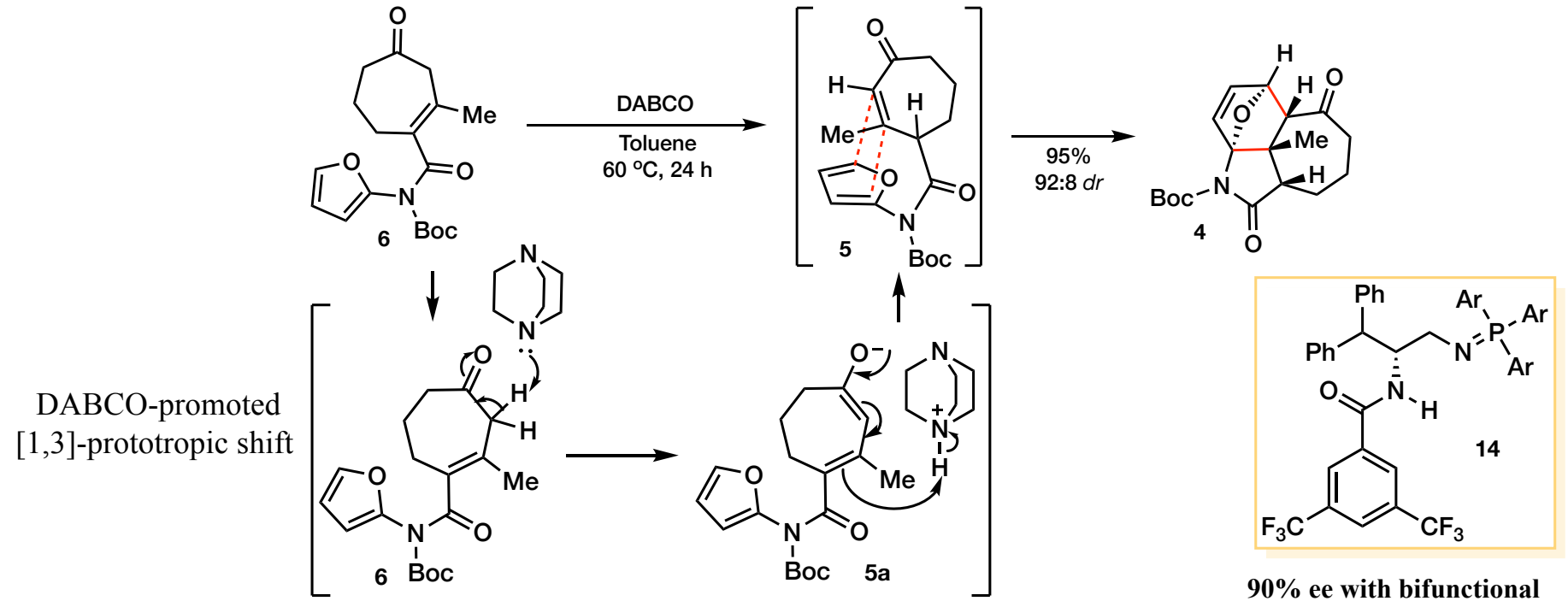
Planta Med. 2013, 79, 1589; Org. Lett. 2016, 18, 1202; Org. Lett. 2017, 19, 4648;

Synthesis of IMDAF precursor **6**

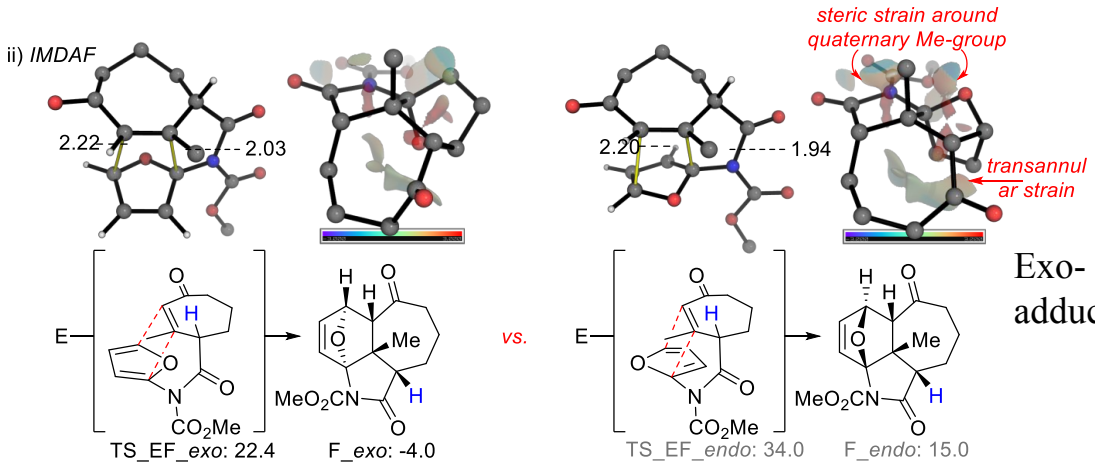


Lennon, M.; McLean, A.; McWatt, I.; Proctor, G. R. J. Chem. Soc., Perkin Trans. 1 1974, 1828; Frew, A. J.; Proctor, G. R. J. Chem. Soc., Perkin Trans. 1 1980, 1245; Frew, A. J.; Proctor, G. R.; Silverton, J. V. J. Chem. Soc., Perkin Trans. 1 1980, 1251.

➢ Enantio- and diastereoselective IMDAF reaction

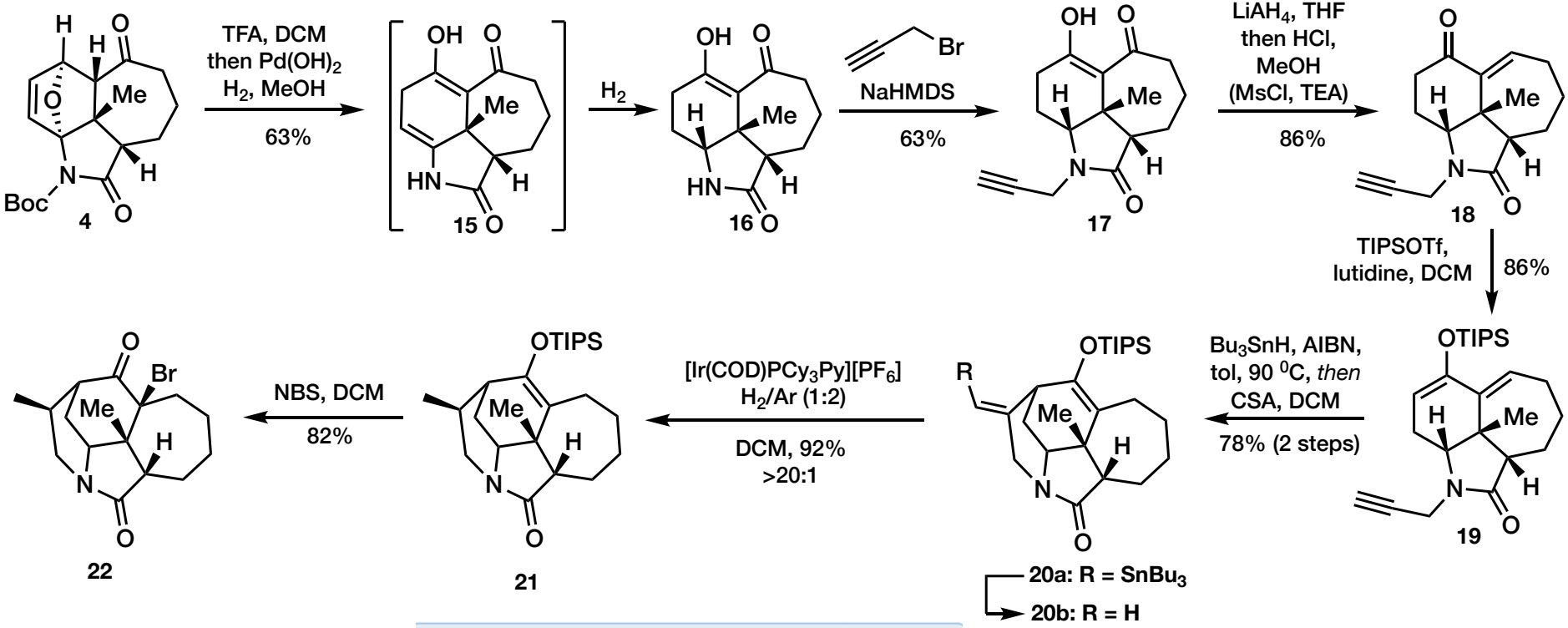


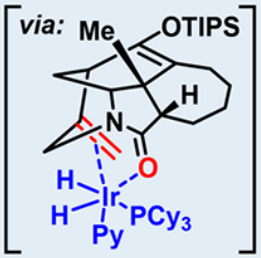
90% ee with bifunctional iminophosphorane



Exo- and endo-transition structures and adducts

Synthesis of Himalensine A

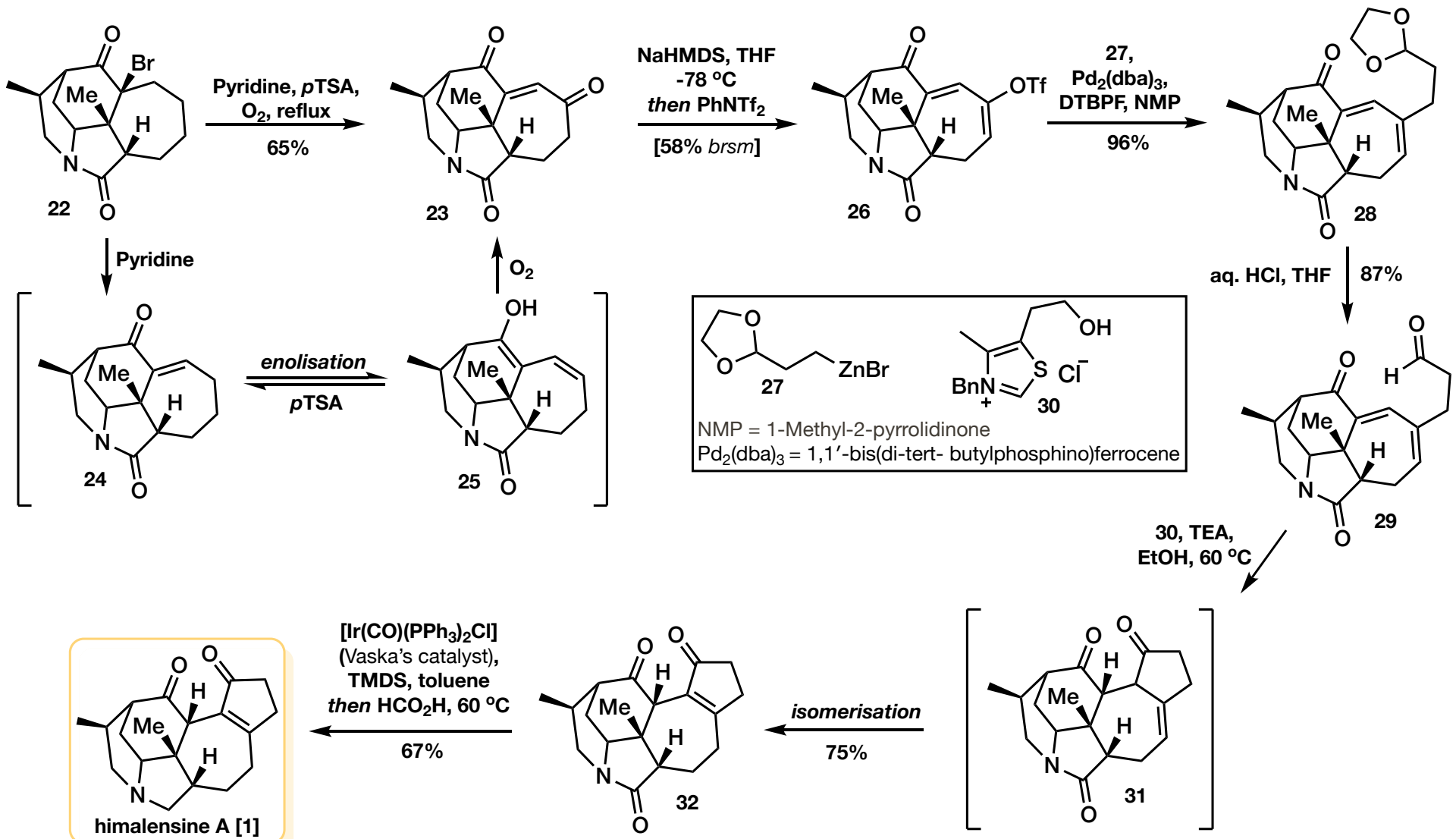




pressure / mbar	dr
1086[a)]	2.2:1
1055[b)]	2.8:1
1029[c)]	3.4:1
1029[c)] (50% Ar)	6.8:1
1029[c)] (66% Ar)	**>20:1**

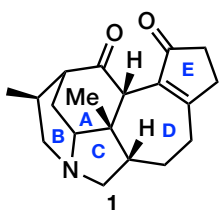
Crabtree's catalyst

Synthesis of Himalensine A: end-game manipulations

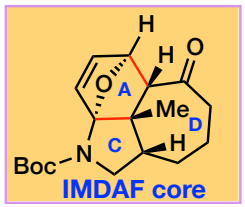


Summary

- The first enantioselective synthesis of (−)-himalensine A in 22 steps.
- The **ACD** tricyclic core constructed via a catalytic, enantioselective prototropic shift/IMDAF reaction.
- The **B** ring accessed via reductive radical cyclization.
- End-game manipulations include: a molecular oxygen mediated γ-CH oxidation, a Stetter cyclization and a highly chemoselective lactam reduction.



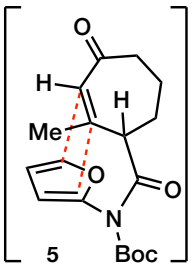
1
himalensine A



4

Key step to tricyclic core

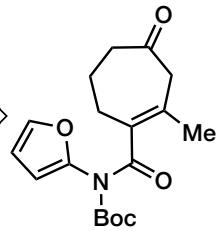
Diels-Alder



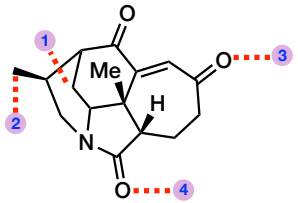
5

catalytic, enantioselective
2 C-C bonds, 5 stereocentres

prototropic shift



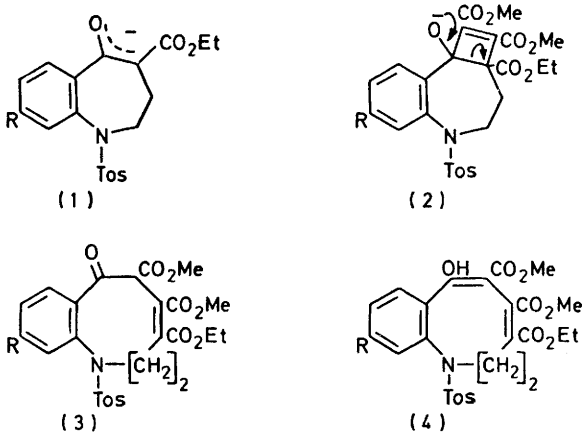
6

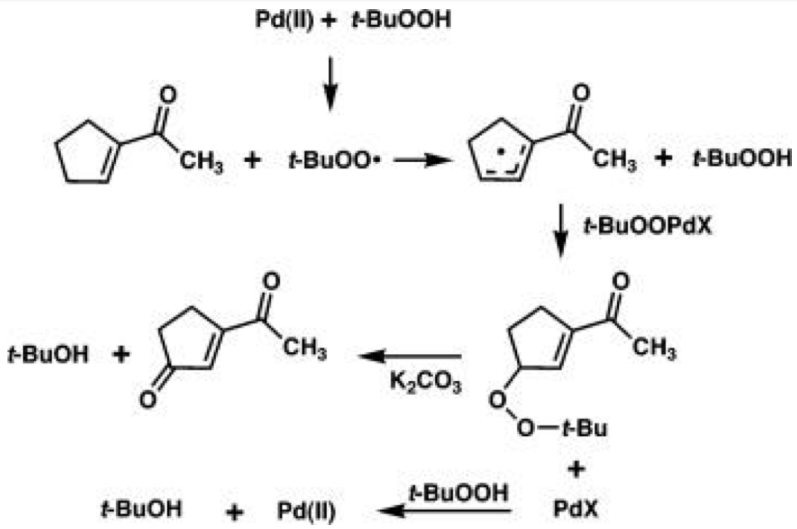


Key transformations
1. radical cyclisation
2. diastereoselective hydrogenation
3. O_2-mediated C-H oxidation
4. chemoselective lactam reduction

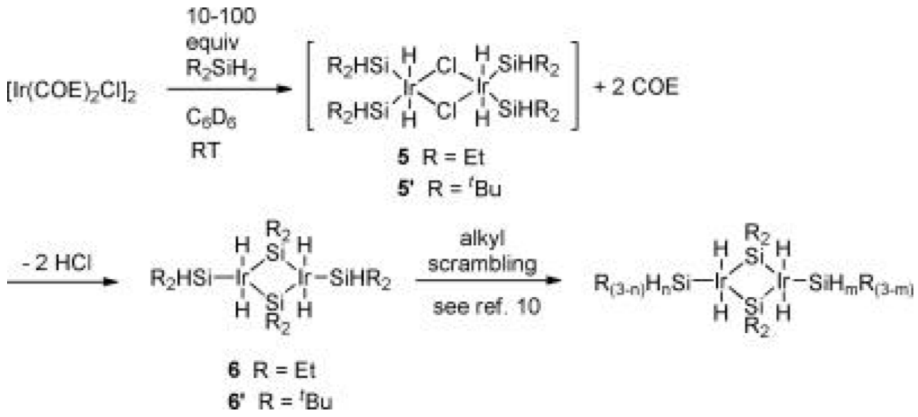
Mechanism

Formation of 8





Formation of the Proposed Catalyst Resting State



Proposed Mechanism for Iridium-Catalyzed Reduction of Secondary Amides to N-Silylamines