Literature Report 3

Rapid Syntheses of (+)-Limaspermidine and (+)-Kopsihainanine A

Reporter: Xiao-Yong Zhai
Checker: Shubo Hu
Date: 2017-10-30

Pritchett, B. P.; Donckele, E. J.; Stoltz, B. M.
Angew. Chem. Int. Ed. **2017**, *56*, 12624.

CV of Brian M. Stoltz

Brian M. Stoltz

Education:

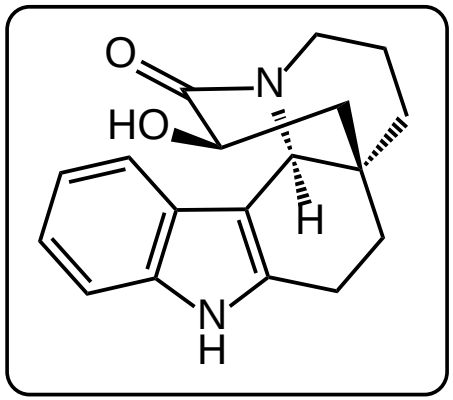
- **1989–1993** B.S., Indiana University of Pennsylvania
- **1993–1996** M.S., Yale University (John L. Wood)
- **1996–1997** Ph.D., Yale University (John L. Wood)
- **1998–2000** NIH Postdoctoral Fellow, Harvard University (Elias J. Corey)
- **2000–2006** Assistant professor, California Institute of Technology
- **2006–2017** Professor, California Institute of Technology

Research:

- Developing new methodology for synthetic chemistry, such as oxidative kinetic resolution, enantioselective allylic alkylation and aerobic oxidative annulation etc;
- Designing new strategies for the preparation of complex molecules, such as Cyanthiwigin F and Aspewentins A, B, C etc.

Contents

Introduction



(+)-Kopsihainanine A

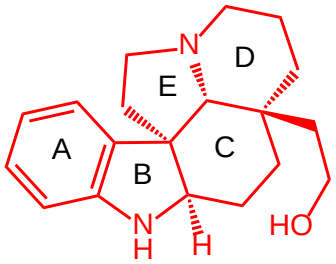
Kopsia hainanensis
(海南蕊木)

- Isolated from the *Kopsia hainanensis* in 2011;
- Possessing 6/5/6/6/6 pentacyclic ring;
- Exhibiting inhibitory activity against acetylcholine esterase (AChE) (IC_{50} 38.5 μM).

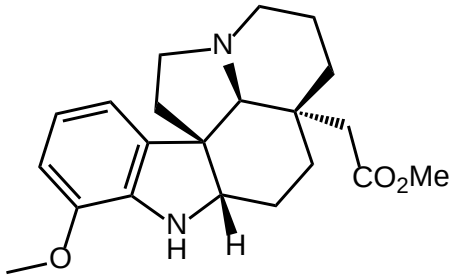
Gao, K. *et al*. *Org. Biomol. Chem.* **2011**, *9*, 5334.

Introduction

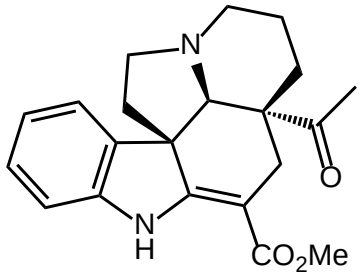
Selected Aspidosperma and Kopsia alkaloids



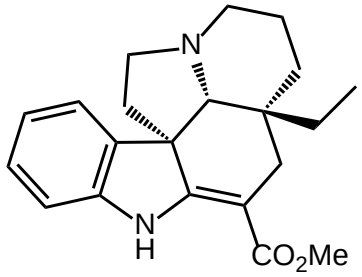
(+)-Limaspermidine



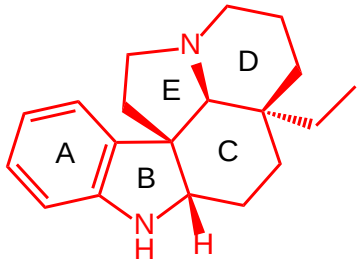
Cylindrocarine



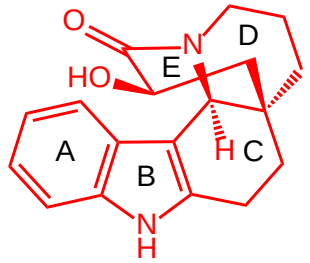
Minovincine



Vincadifformine



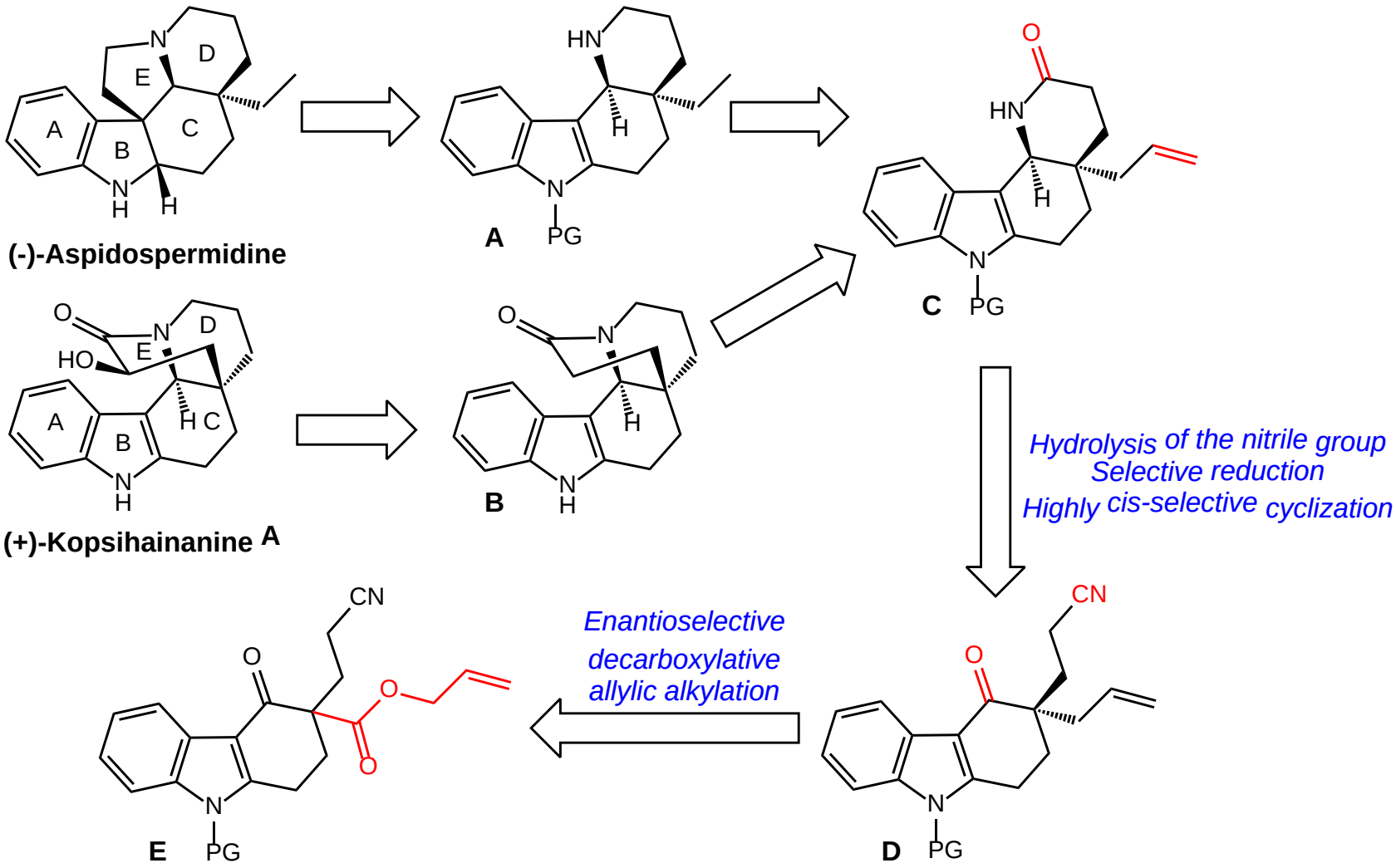
(-)-Aspidospermidine



(+)-Kopsihainanine **A**

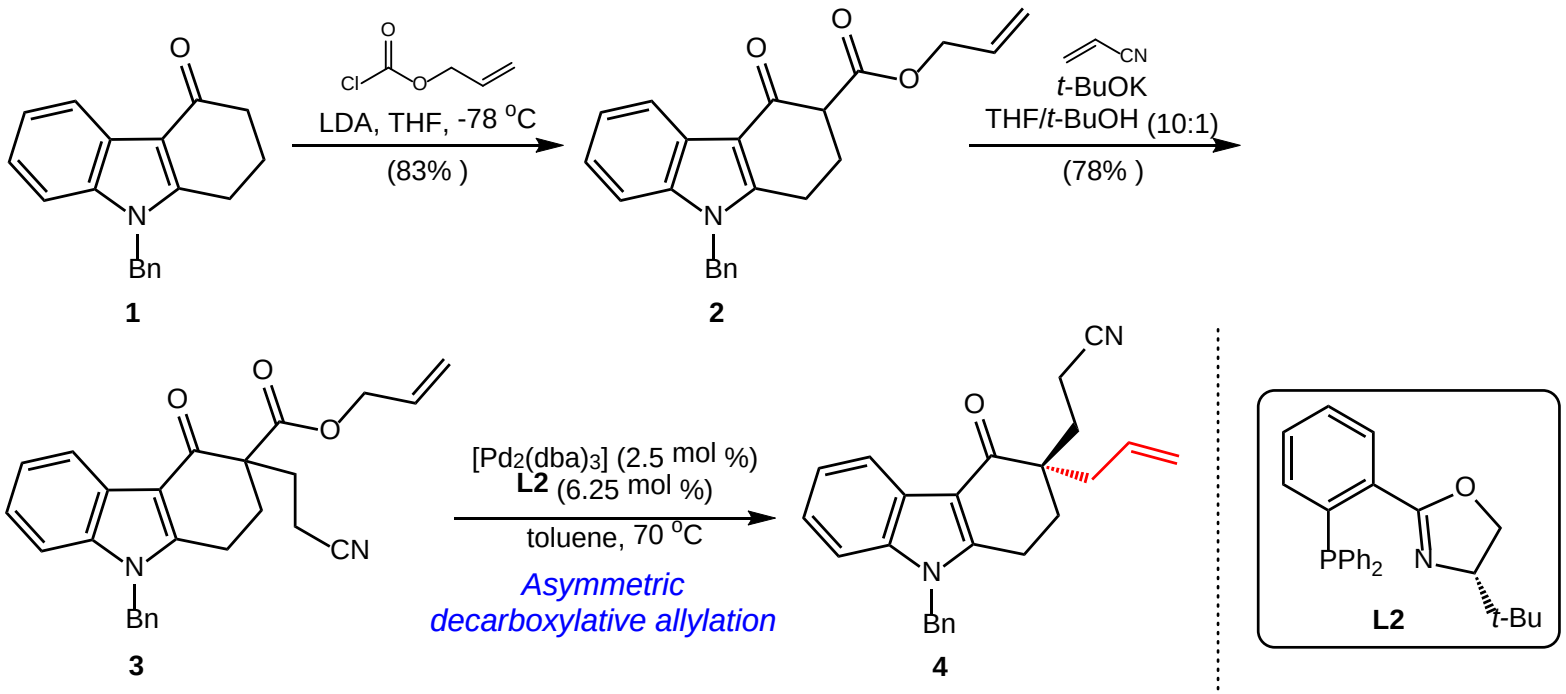
Shao, Z-H. *et al. Angew. Chem. Int. Ed.* **2013**, *52*, 4117.

Retrosynthetic analysis

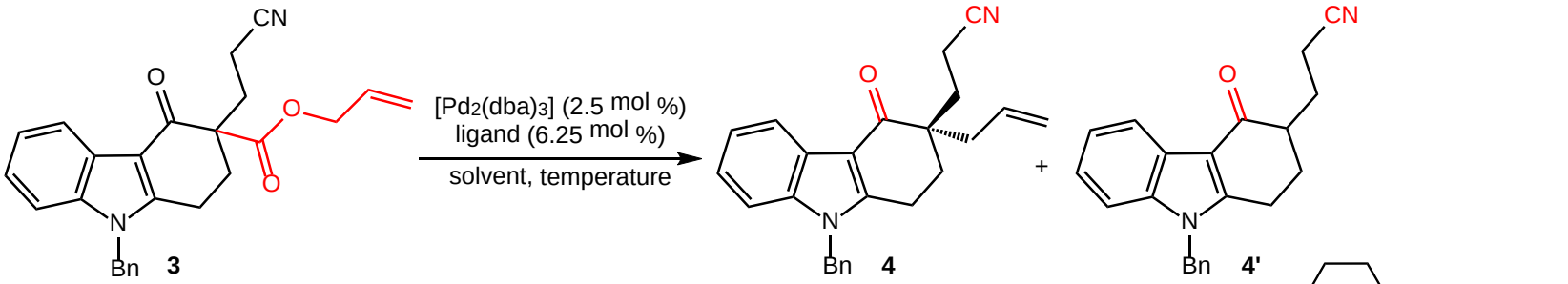


Shao, Z-H. *et al. Angew. Chem. Int. Ed.* **2013**, *52*, 4117.

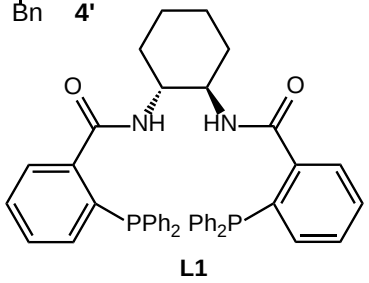
Total synthesis of (-)-Aspidospermidine



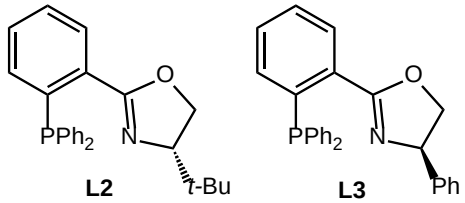
Asymmetric decarboxylative allylation



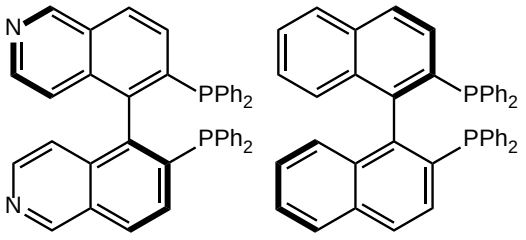
Entry	L	Solvent	T/°C	**4:4'**	Yield/%	ee of **4**
1	**L1**	toluene	70	0:100	0	-
2	**L2**	**toluene**	**70**	**19:1**	**93**	**92**
3	**L3**	toluene	70	6:1	75	-74
4	**L4**	toluene	70	6:1	80	-40
5	**L5**	toluene	70	3:1	66	22
6	**L2**	THF	70	1.6:1	51	89
7	**L2**	*m*-xylene	70	3.4:1	64	93
8	**L2**	benzene	70	4.6:1	74	76
9	**L2**	toluene	55	1.7:1	57	88
10	**L2**	toluene	80	2.7:1	67	91



L1

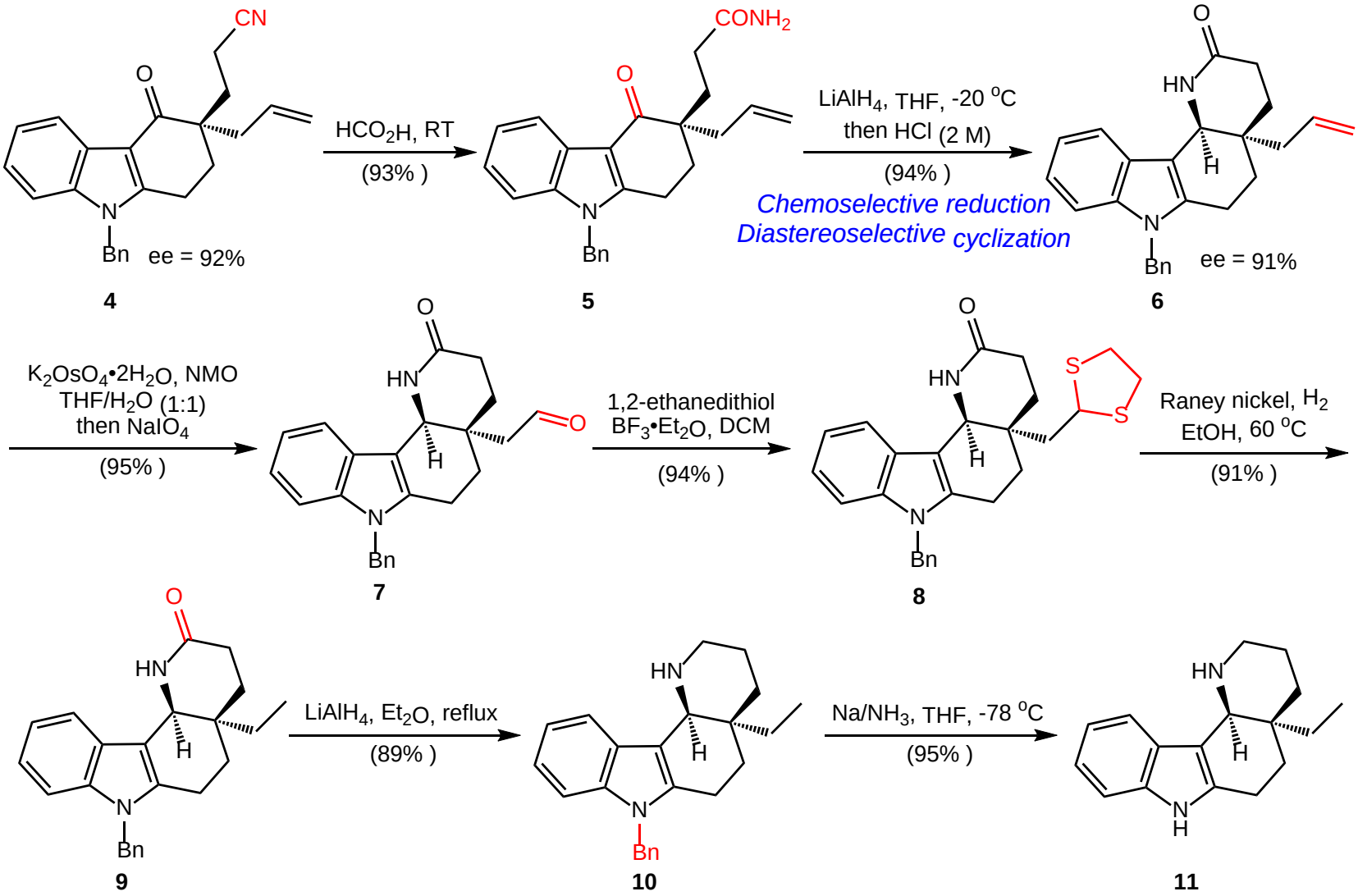


L2 **L3**

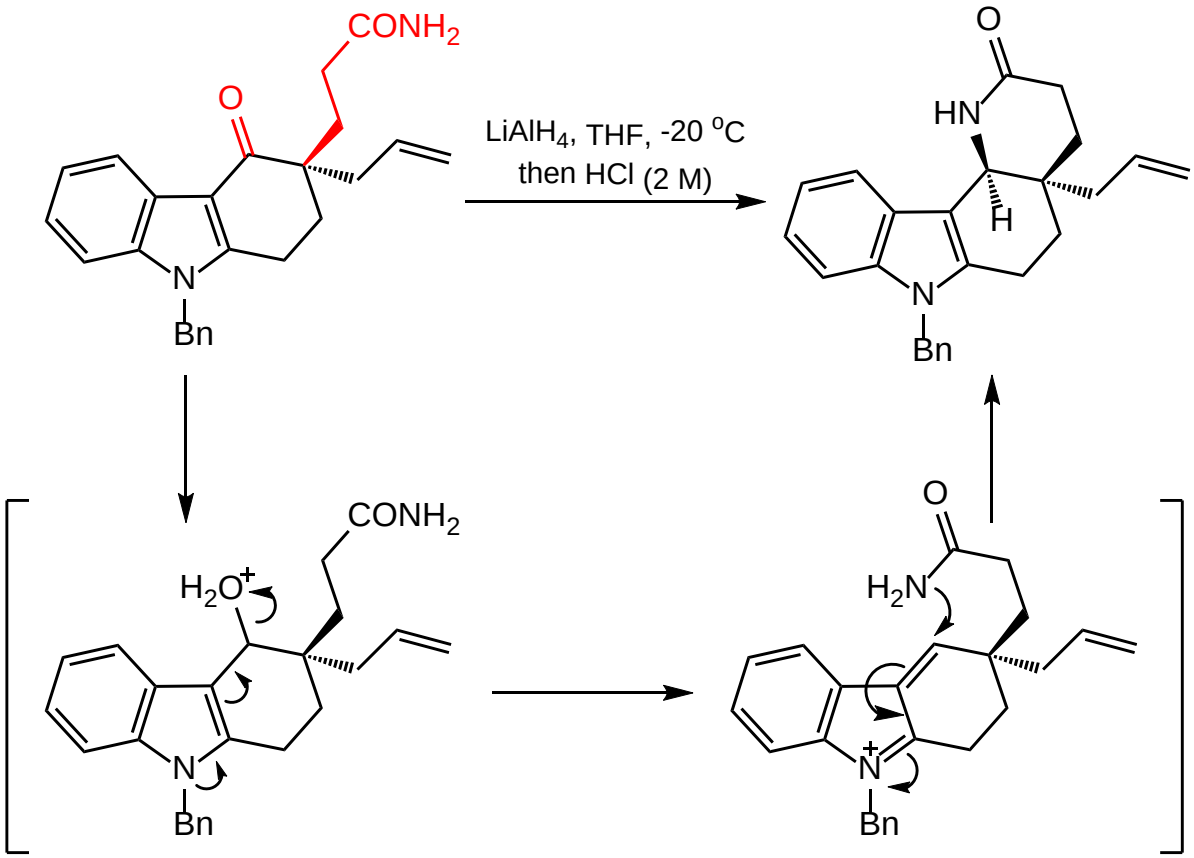


L4 **L5**

Total synthesis of (-)-Aspidospermidine

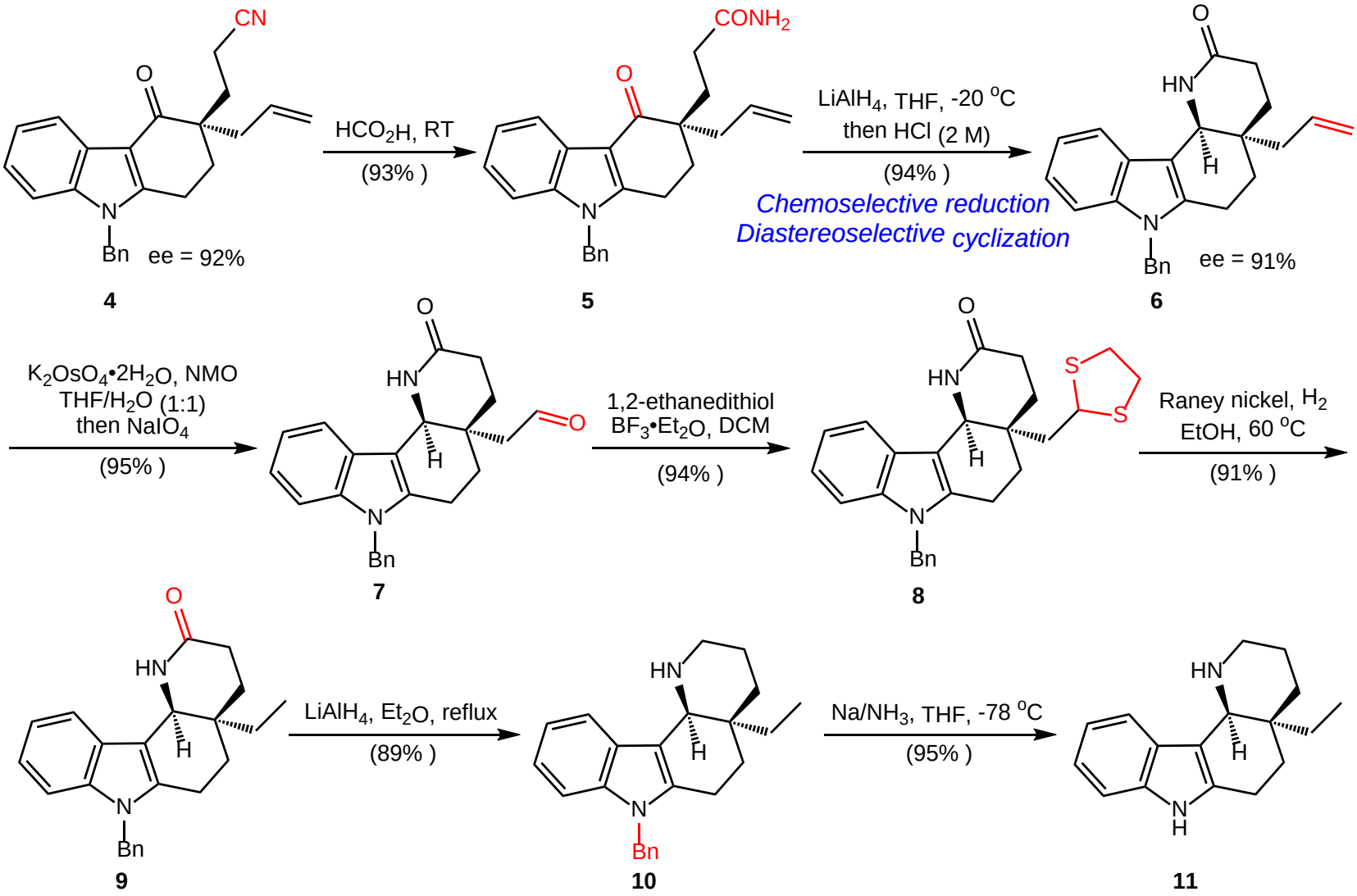


Diastereoselective cyclization

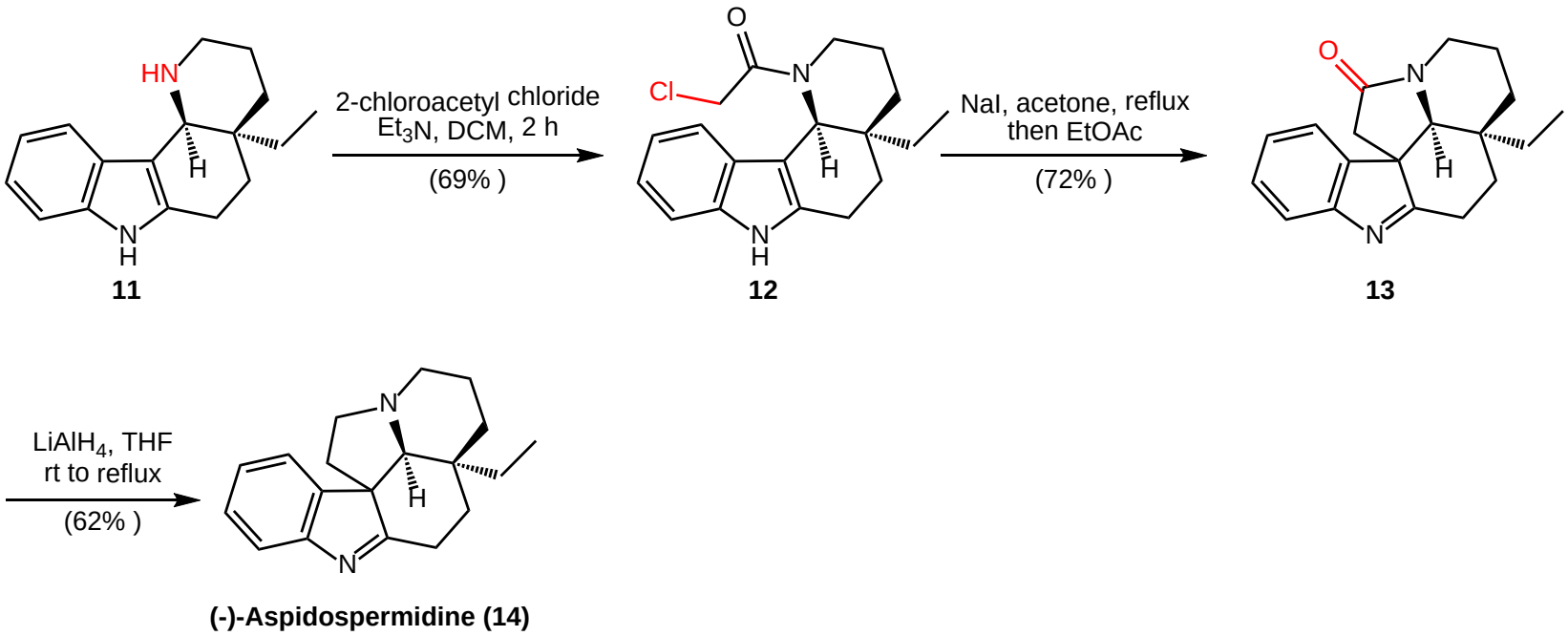


She, X. *et al*. *Chem. Eur. J*. **2012**, *18*, 6729.

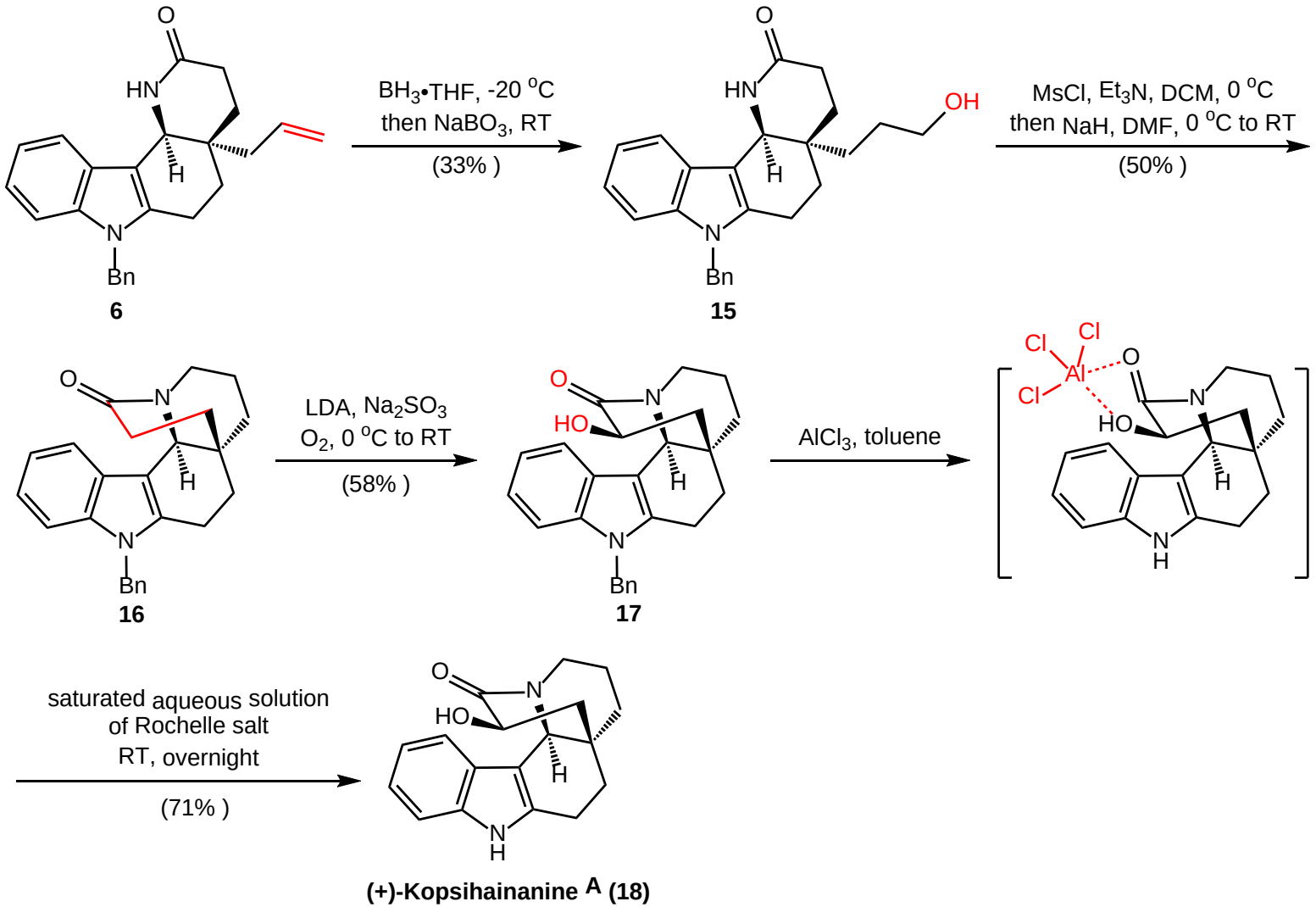
Total synthesis of (-)-Aspidospermidine



Total synthesis of (-)-Aspidospermidine

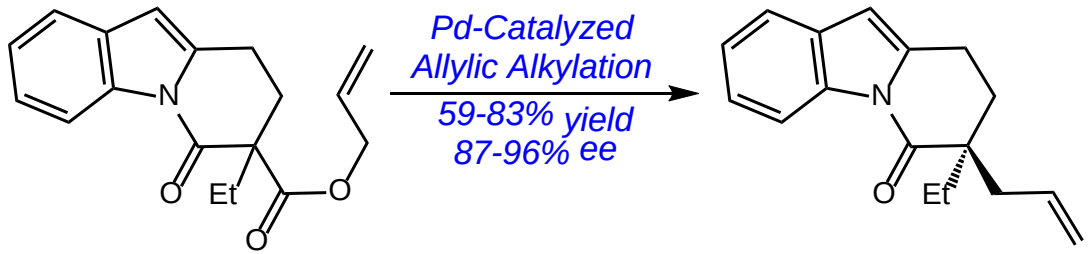


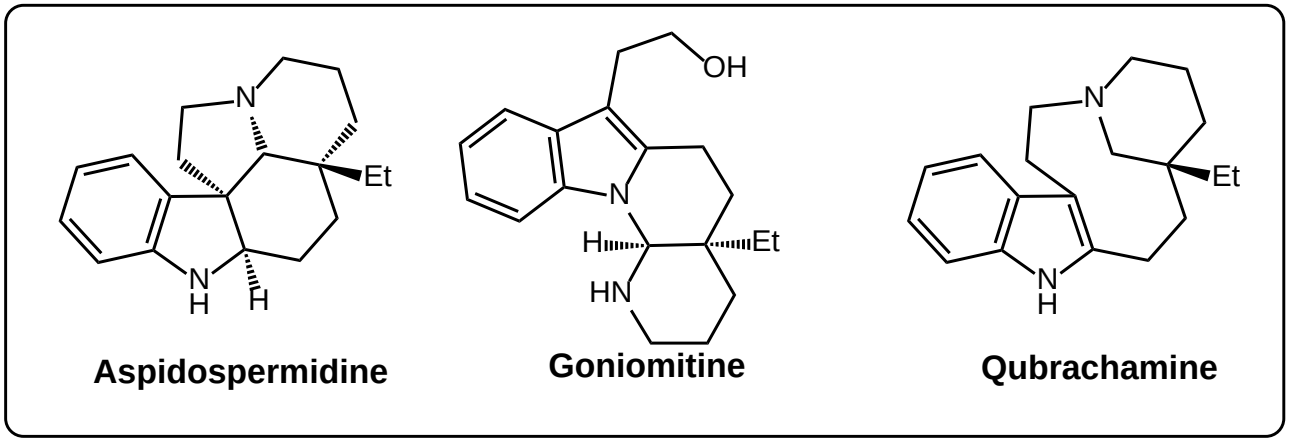
Total synthesis of (+)-Kopsihainanine A



Retrosynthetic analysis of (+)-Kopsihainanine A

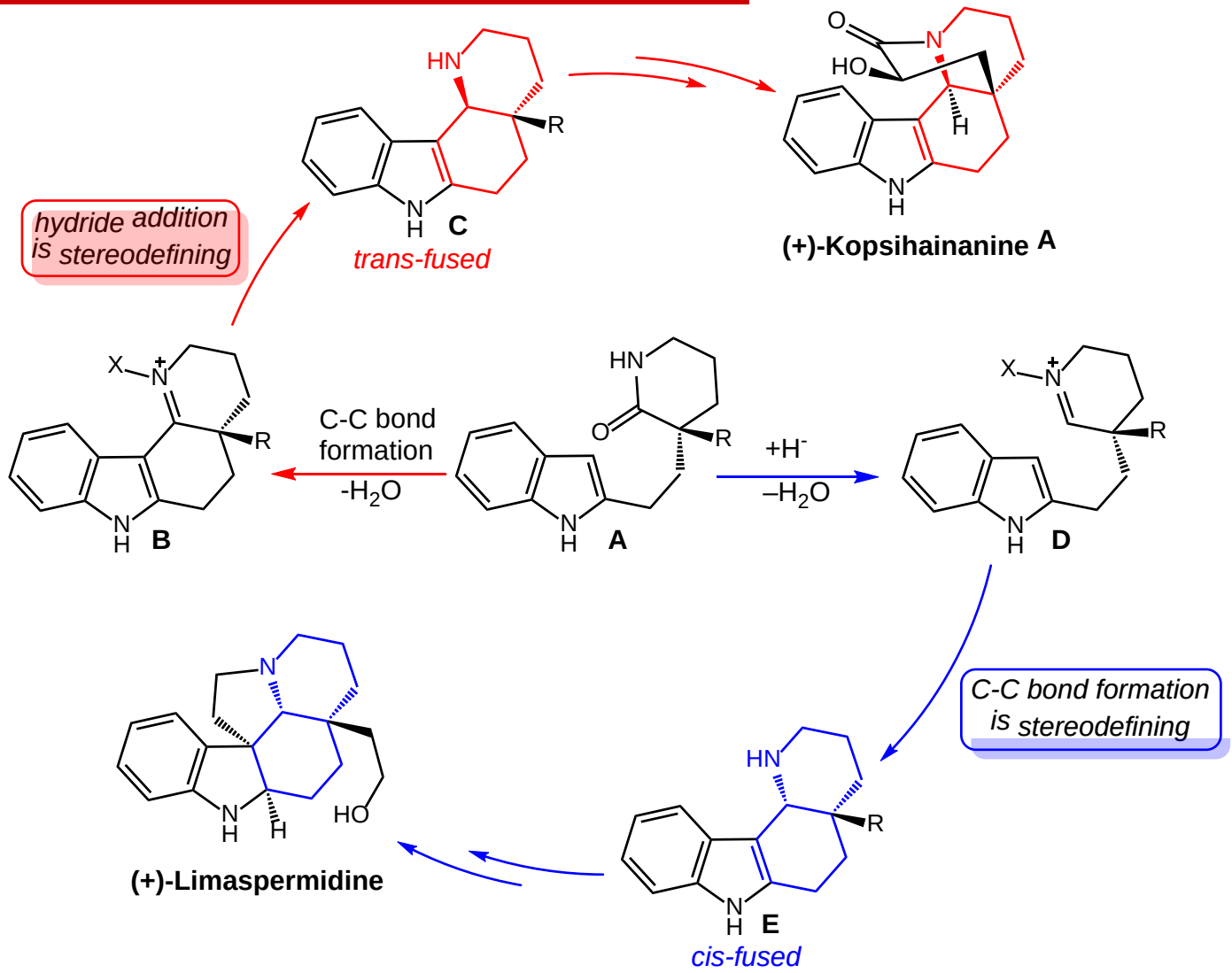
Palladium Catalysis and Regiodivergent Cyclizations (2016)





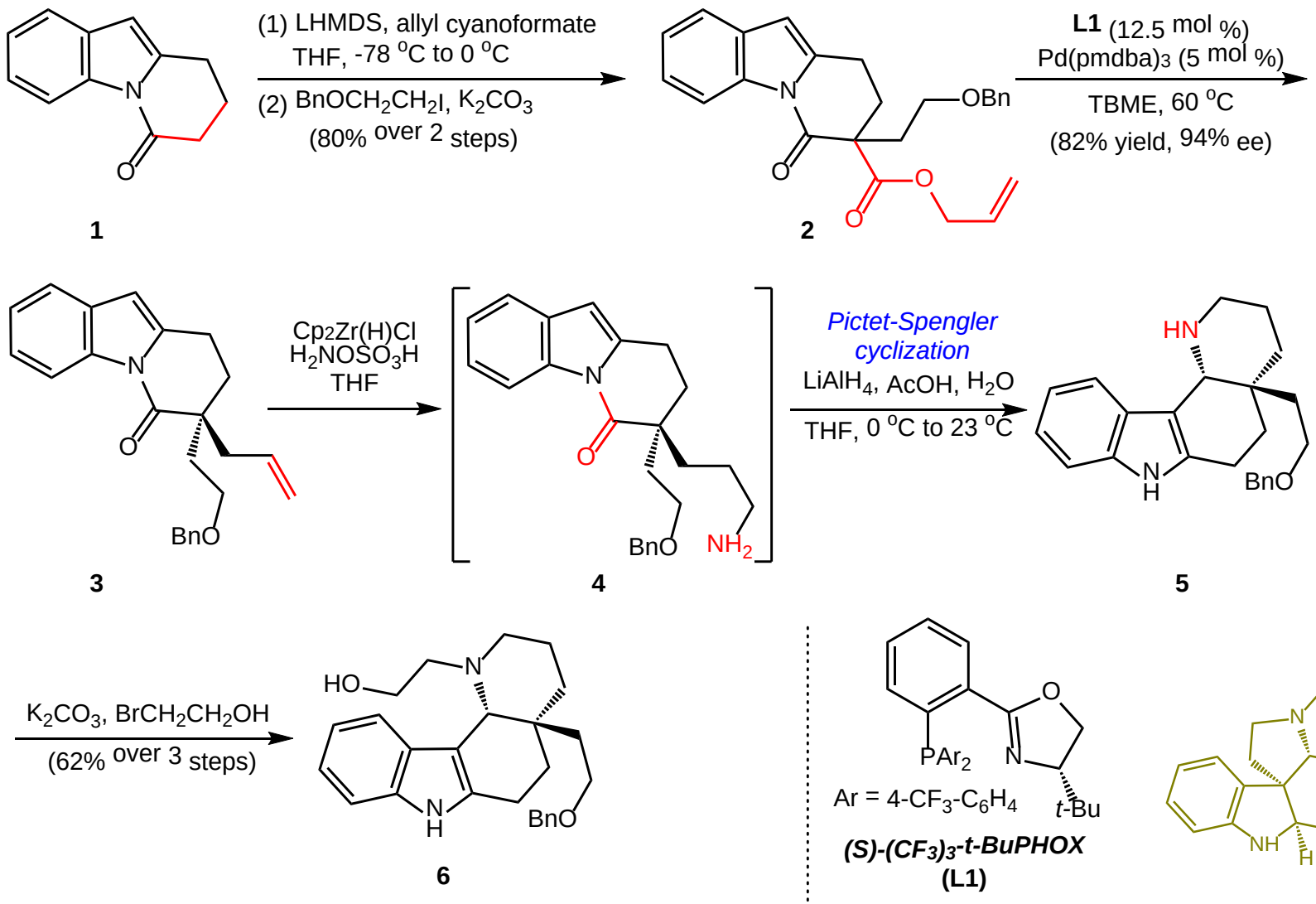
Stoltz, B. M. *et al. Angew. Chem. Int. Ed.* **2016**, *55*, 13529.

Retrosynthetic analysis of (+)-Kopsihainanine A

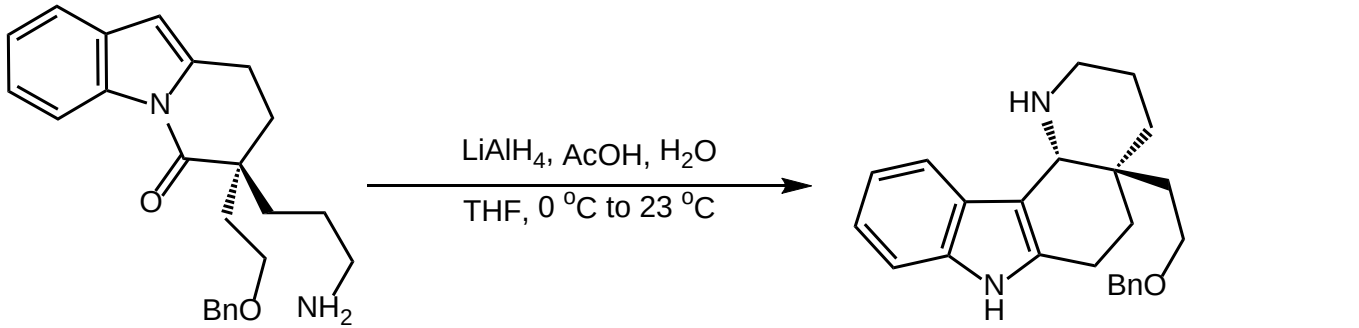


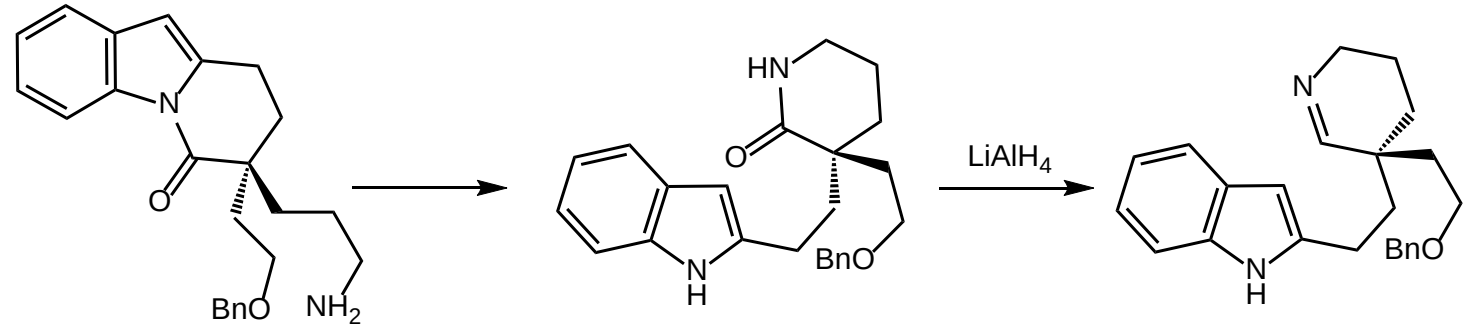
Stoltz, B. M. *et al. Angew. Chem. Int. Ed.* **2017**, *56*, 12624.

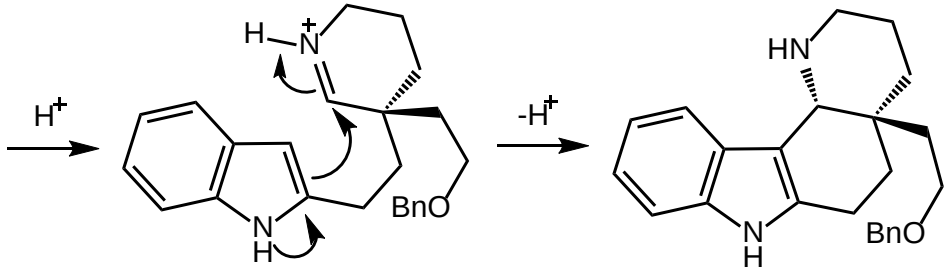
Total synthesis of (+)-Limaspermidine



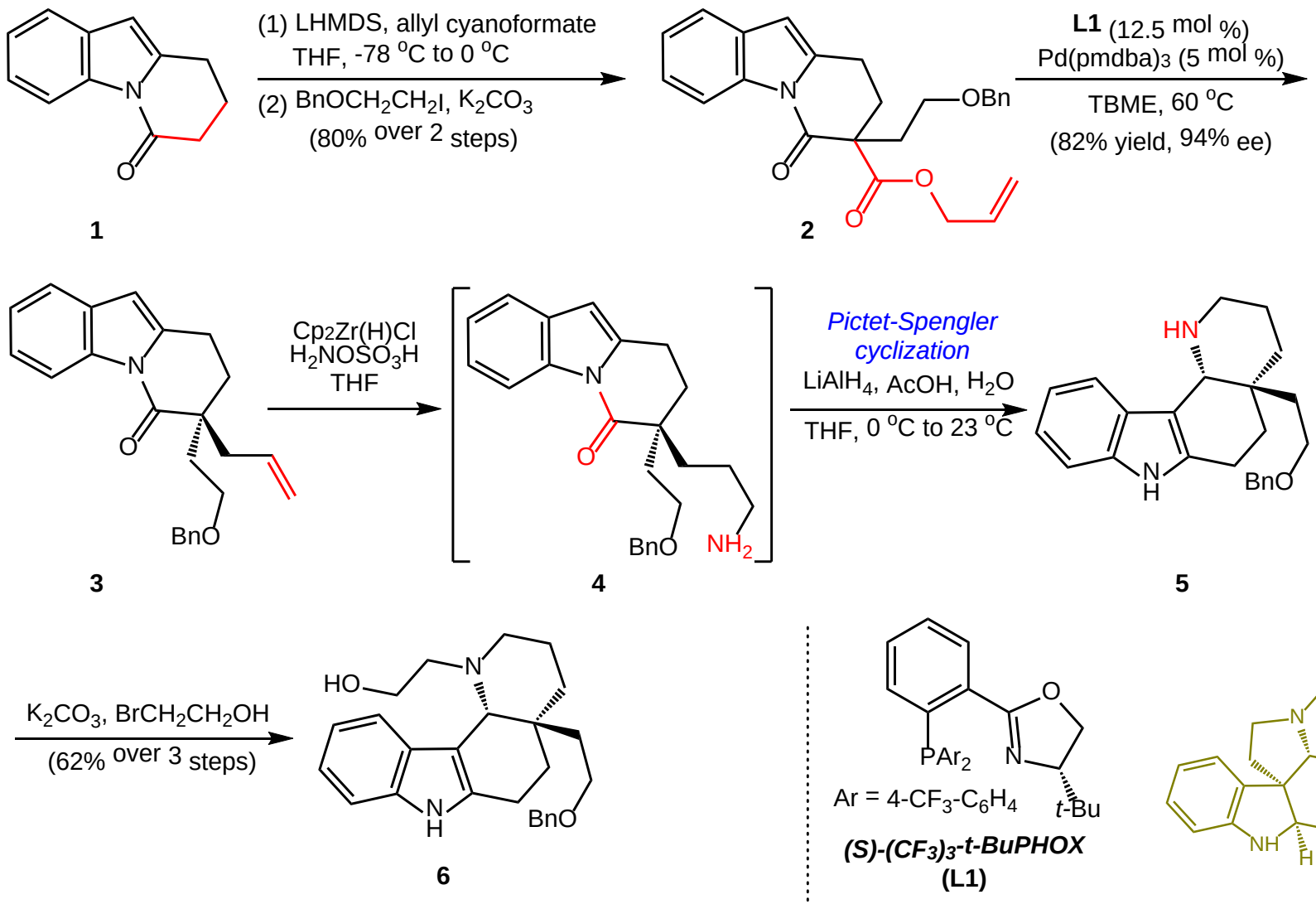
Pictet–Spengler cyclization



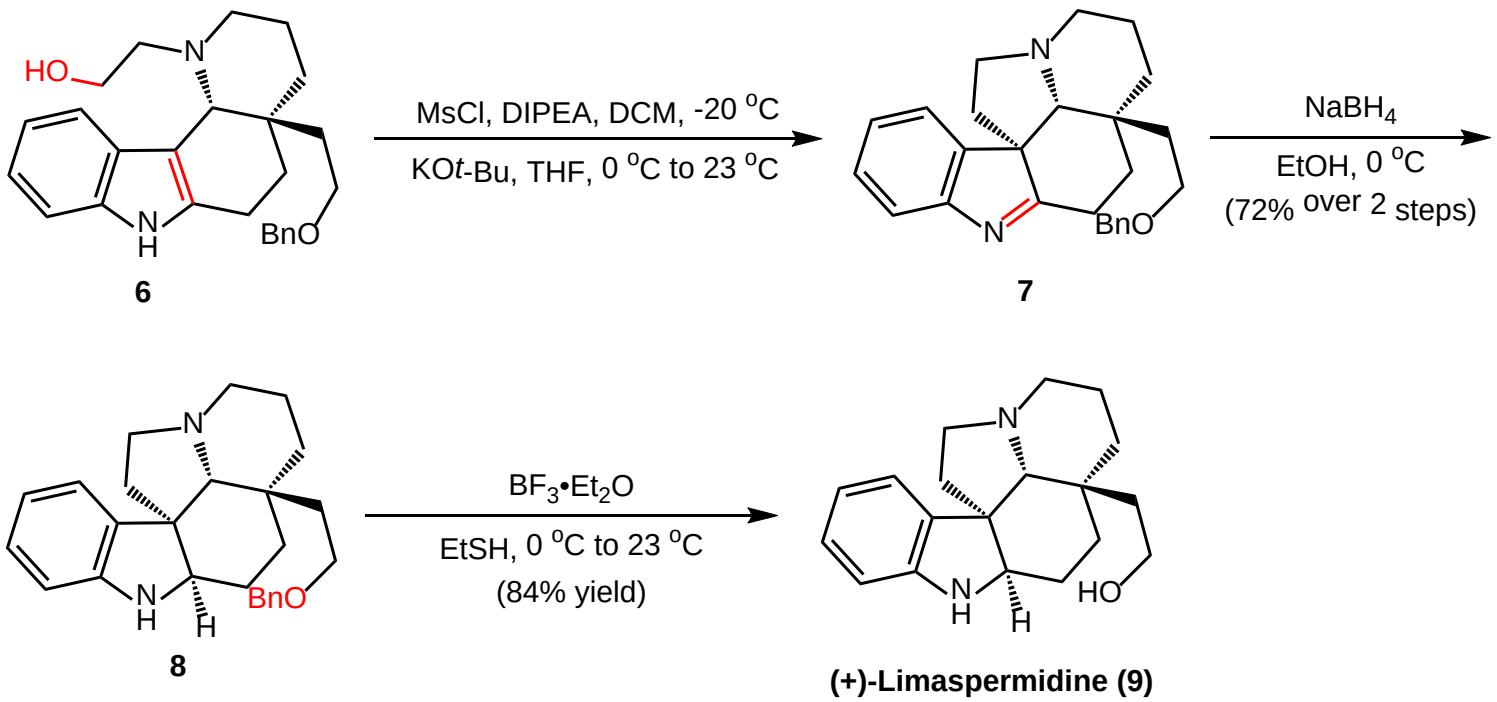




Total synthesis of (+)-Limaspermidine

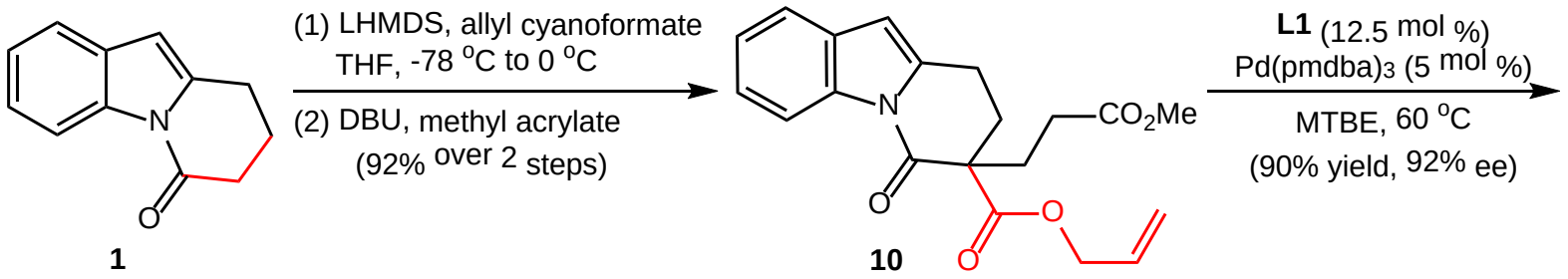


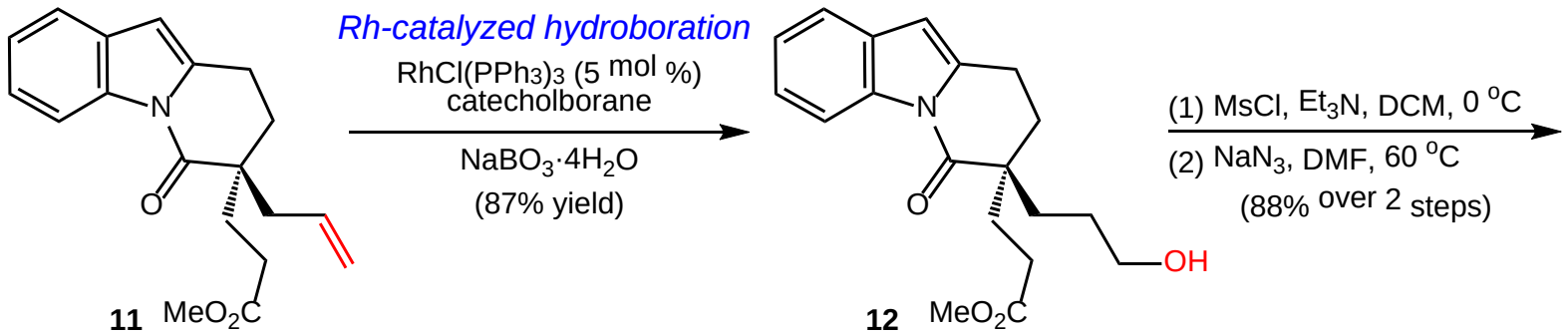
Total synthesis of (+)-Limaspermidine

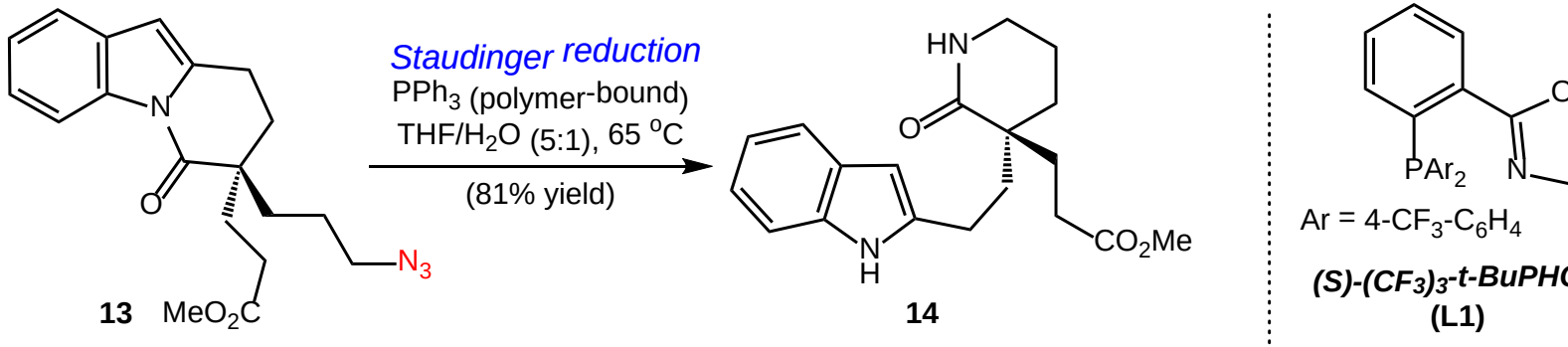


6 **7** **8** **(+)-Limaspermidine (9)**

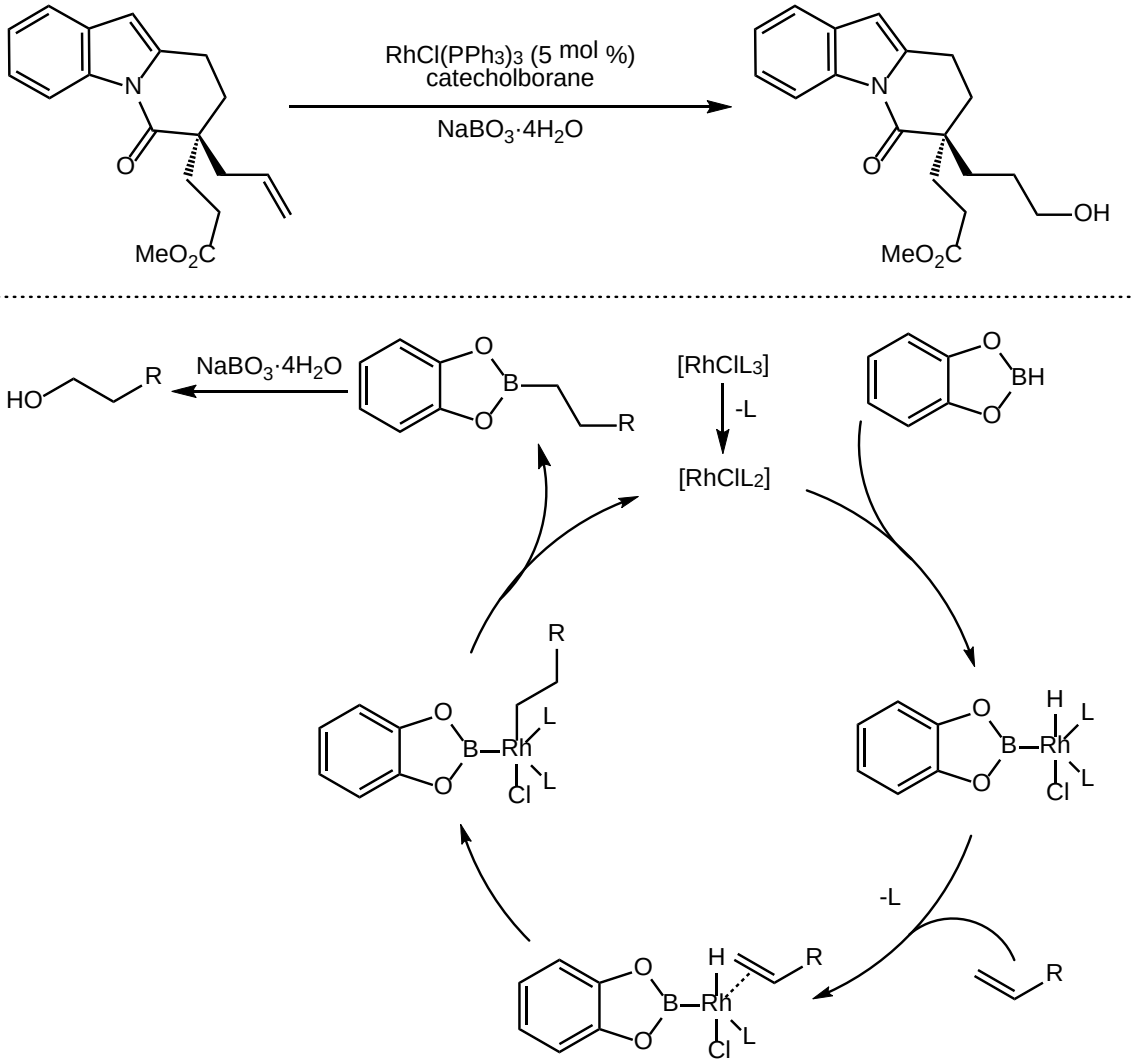
Total synthesis of (+)-Kopsihainanine A





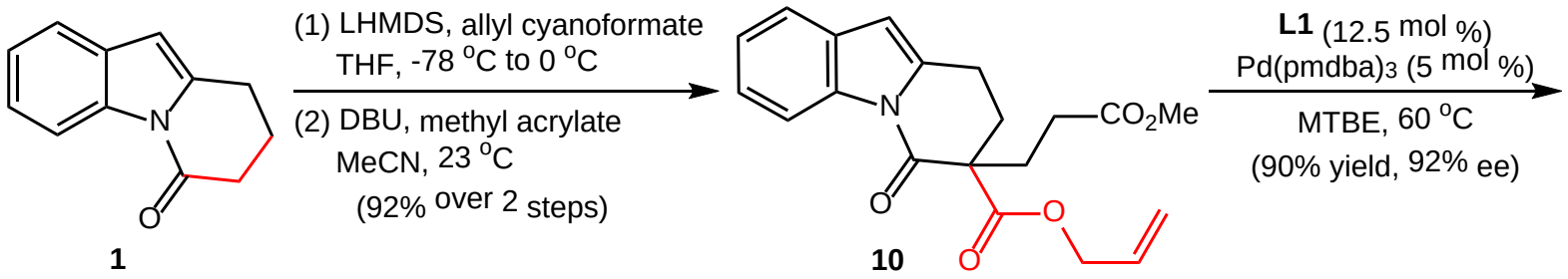


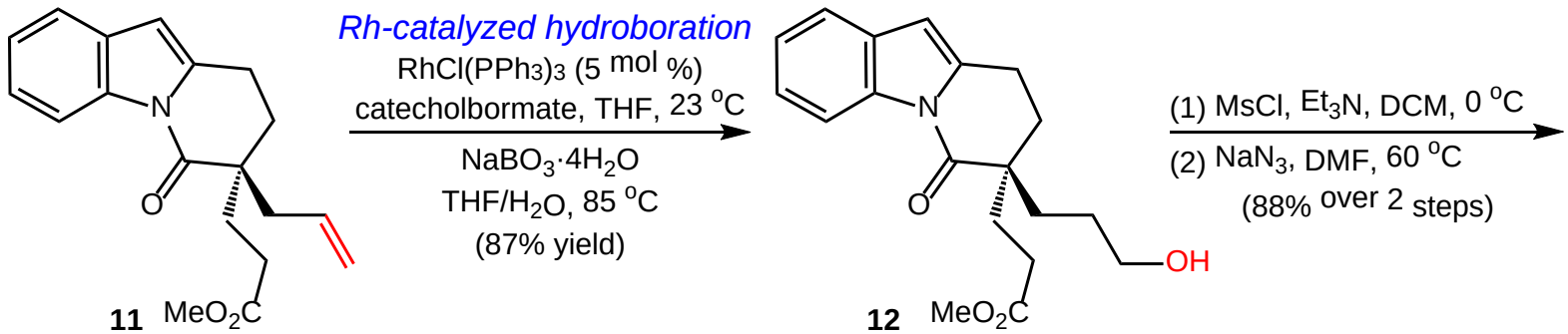
Rh-catalyzed hydroboration

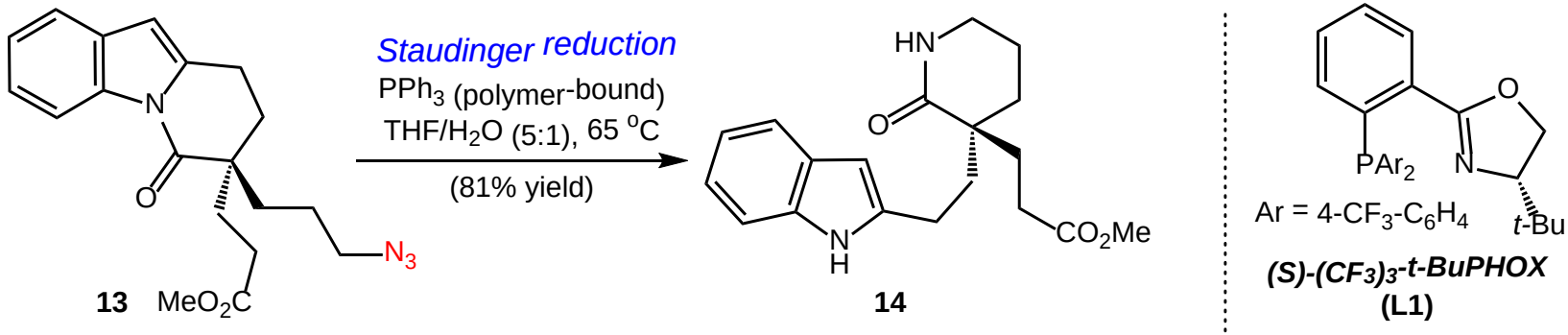


Noth, H. *et al*. *Angew. Chem. Int. Ed.* **1985**, *24*, 878.

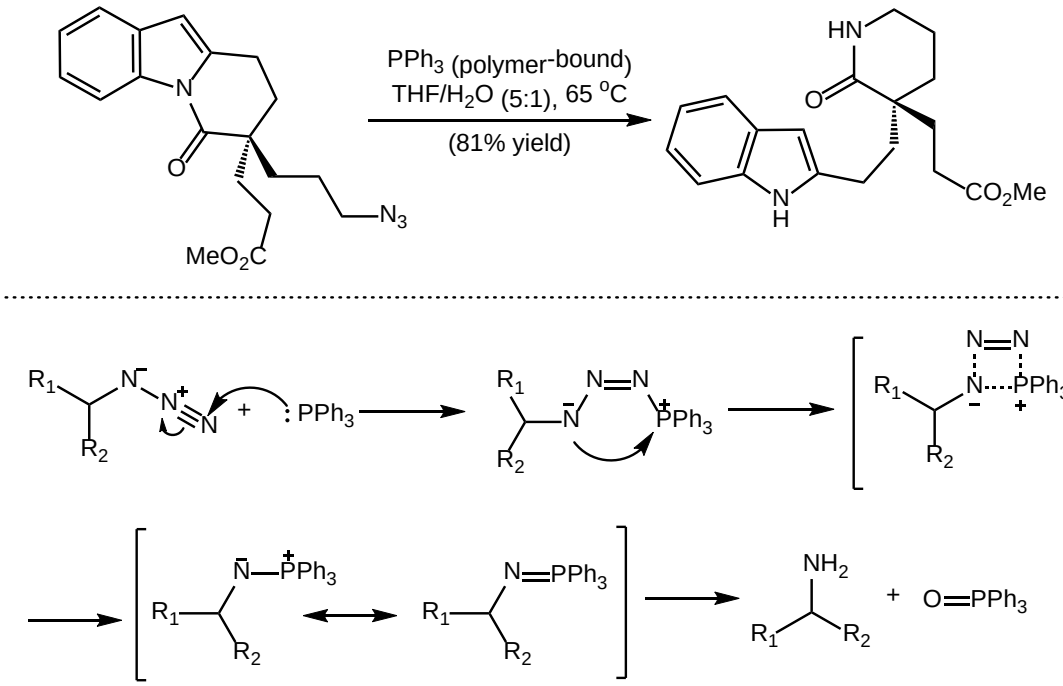
Total synthesis of (+)-Kopsihainanine A



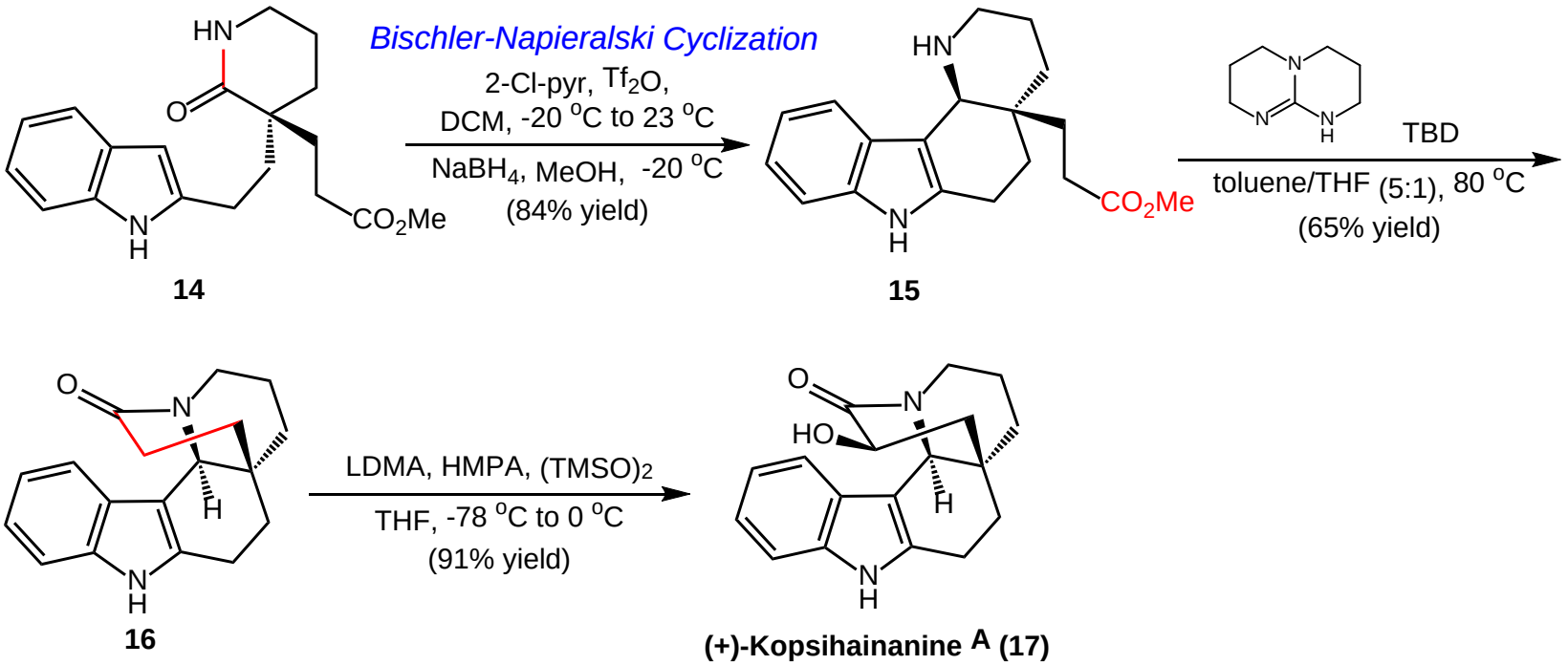




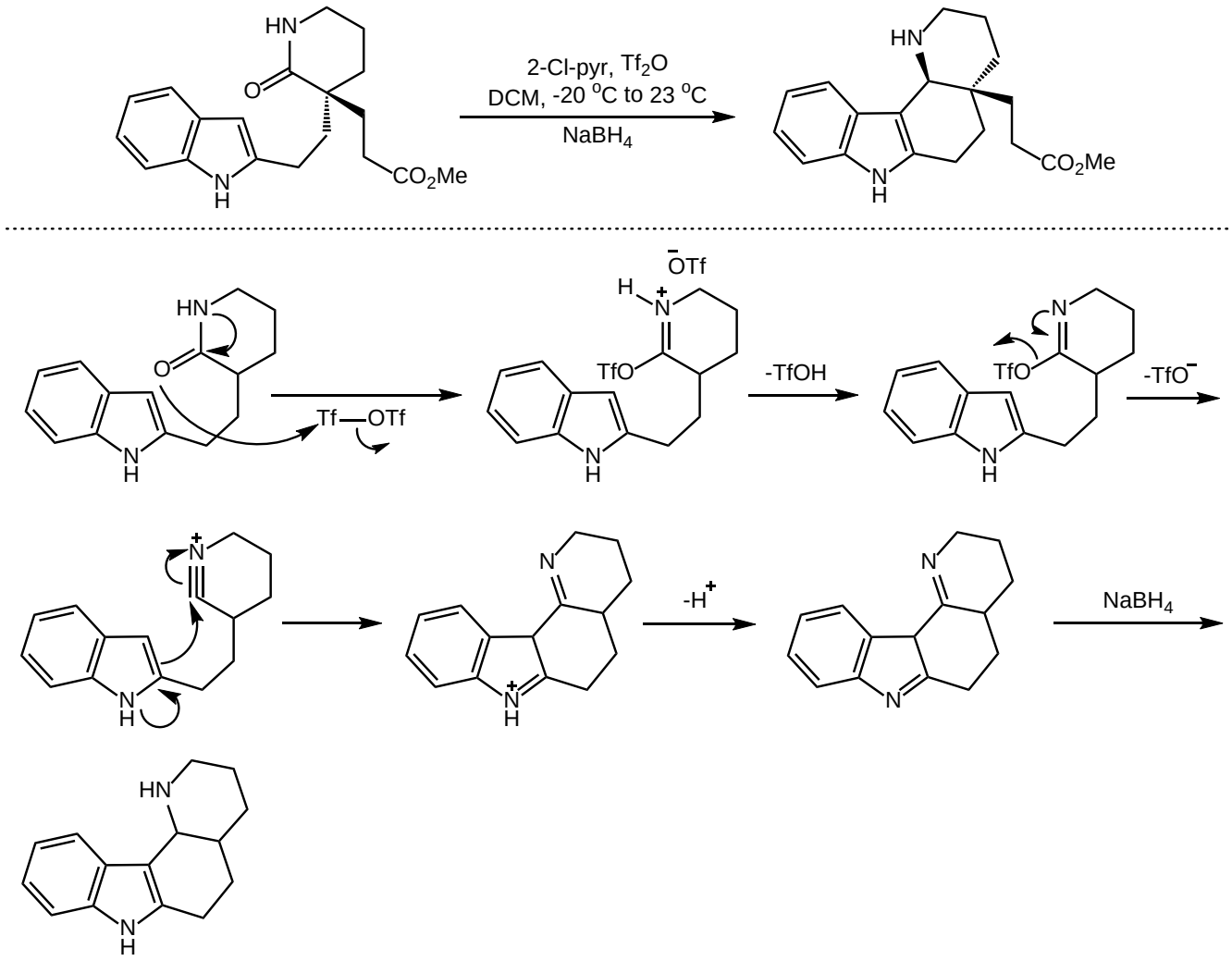
Staudinger reduction



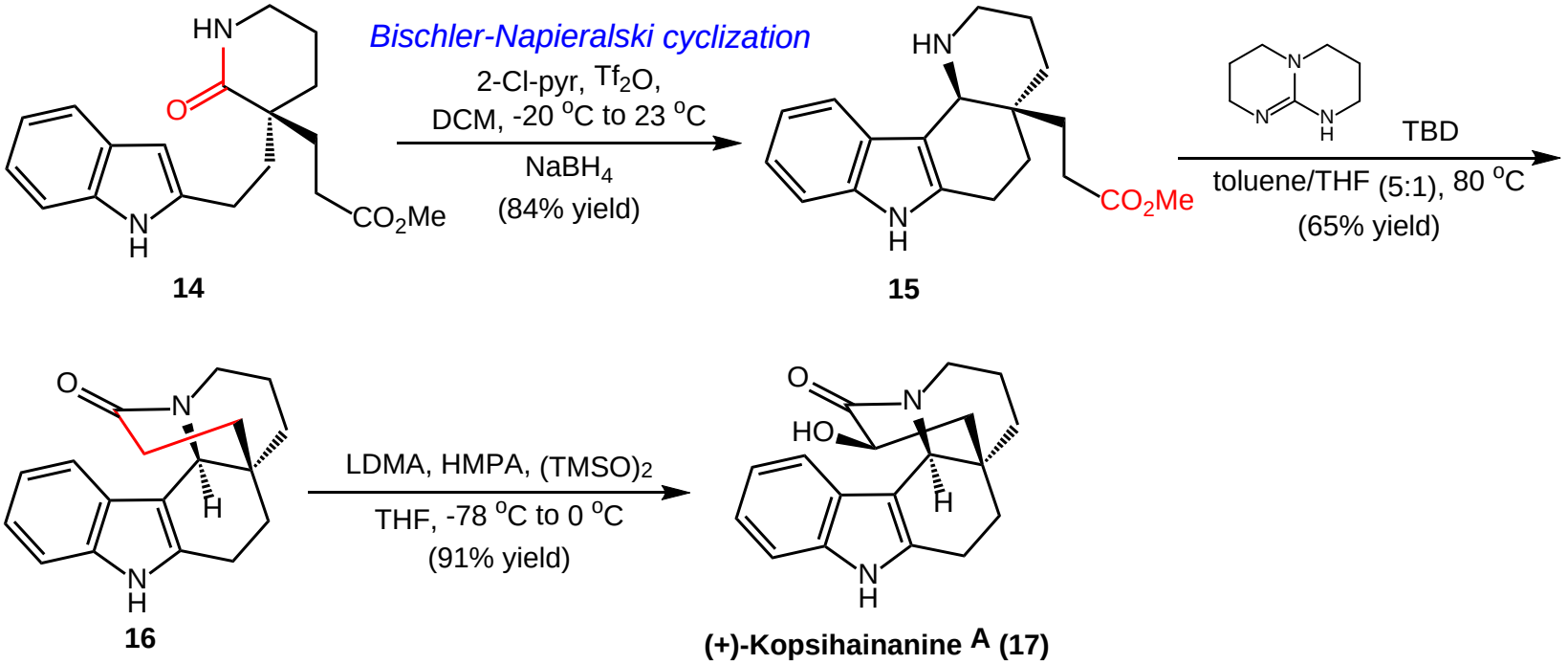
Total synthesis of (+)-Kopsihainanine A



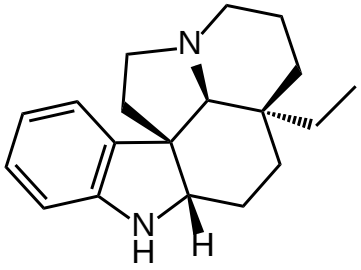
Bischler-Napieralski cyclization



Total synthesis of (+)-Kopsihainanine A



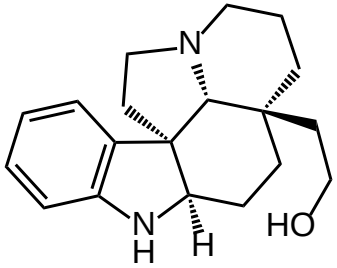
Summary



(-)-Aspidospermidine

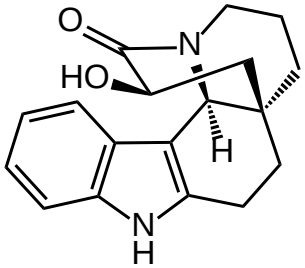
- (-)-Aspidospermidine: 13 Steps, 11.1% overall yield;
- (+)-Kopsihainanine A: 9 Steps, 3.6% overall yield;
- The first catalytic enantioselective total synthesis of (+)-Kopsihainanine A;
- The first Pd-catalyzed enantioselective decarboxylative allylic alkylation of carbazolone enolates.

Shao, Z-H. *et al. Angew. Chem. Int. Ed.* **2013**, *52*, 4117.



(+)-Limaspermidine

- (+)-Limaspermidine: 8 Steps, 25.0% overall yield;
- (+)-Kopsihainanine A: 10 Steps, 16.0% overall yield;
- Enantioselective Pd-catalyzed allylic alkylations of DHPI;
- One-pot hydroamination/reduction/Pictet–Spengler sequence;
- Bischler–Napieralski cyclization.



(+)-Kopsihainanine A

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The first paragraph

Monoterpene indole alkaloids from the structurally related Aspidosperma and Kopsia families have been studied for more than half a century owing to their intricate polycyclic structures and broad biological activities. One significant structural difference between these families is the ring-fusion geometry of the octa- or decahydroquinoline moiety contained within the polycyclic core. Aspidosperma alkaloids typically possess a cis-fused azadecalin motif. Conversely, members of the Kopsia family often contain a trans-fused azadecalin substructure.

The last paragraph

In conclusion, the combination of enantioselective Pd-catalyzed allylic alkylations of dihydropyrido[1,2-a]indolone (DHPI) substrates with stereodivergent indole–iminium cyclization strategies is a powerful tool for the synthesis of monoterpene indole alkaloids. The Aspidosperma family of alkaloids can be accessed through stereodefining C-C bond formation, as highlighted herein by our synthesis of (+)-limaspermidine in eight linear steps and in 25% overall yield from tricyclic DHPI. Critically, a highly productive one-pot hydroamination/reduction/Pictet–Spengler sequence enabled the synthesis of the cis-fused decahydroquinoline moiety present in (+)-Limaspermidine.

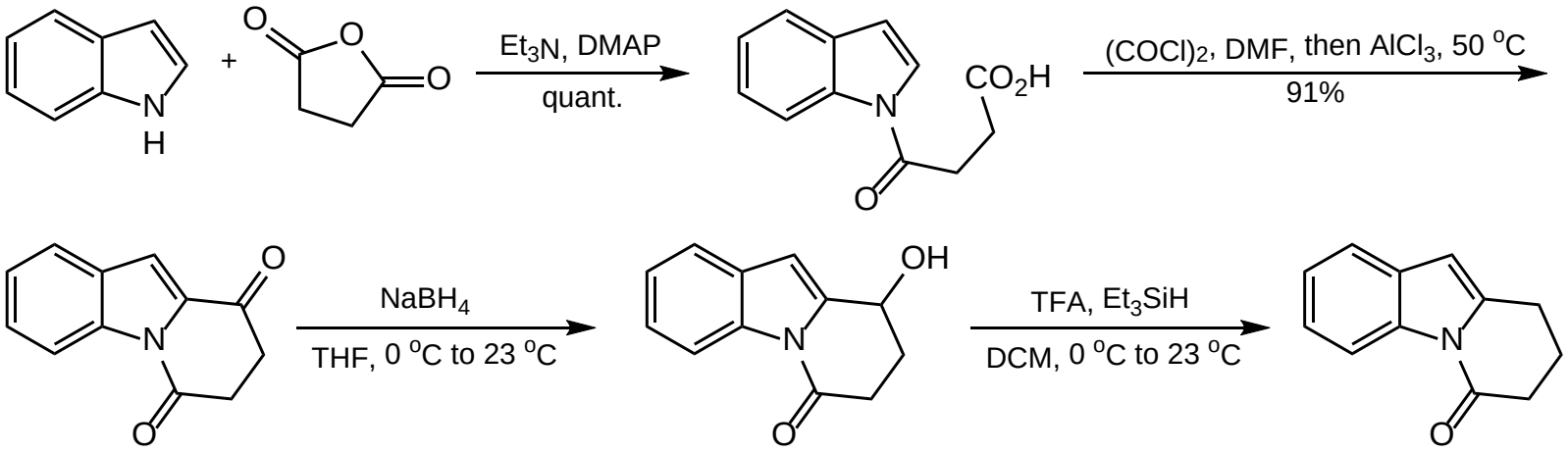
The last paragraph

Furthermore, the Kopsia family of alkaloids can be accessed using a Bischler–Napieralski cyclization, followed by stereodefining hydride addition to furnish the opposite diastereomeric series. This capability was demonstrated through a nine-step synthesis (28% overall yield) of strained lactam 29, thereby completing a formal synthesis of (+)-kopsihainanine A. Efforts to further exploit the synthetic utility conferred by the DHPI substrate class, particularly in the synthesis of more highly caged Kopsia alkaloids, will be reported in due course.

Acknowledgement

Thanks
for your attention

The formation of DHPI



Formal anti-Markovnikov hydroamination