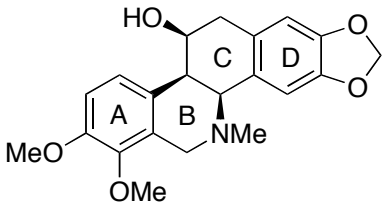
Enantioselective Total Synthesis of (+)-Homochelidonine by a Pd^{II}-Catalyzed Asymmetric Ring-Opening Reaction of a *meso*-Azabicyclic Alkene with an Aryl Boronic Acid

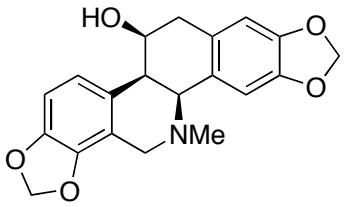
*Helen A. McManus, Matthew J. Fleming and Mark Lautens**

Angew. Chem. Int. Ed. **2007**, *46*, 433

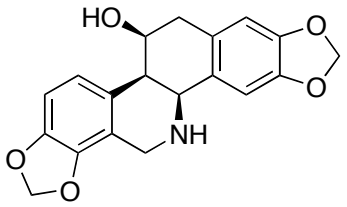
Introduction



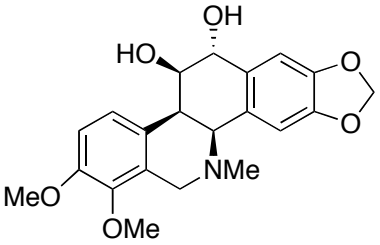
(+)-homochelidonine (**1**)



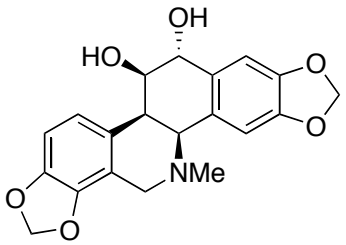
(+)-chelidonine (**2**)



(-)-norchelidonine (**3**)



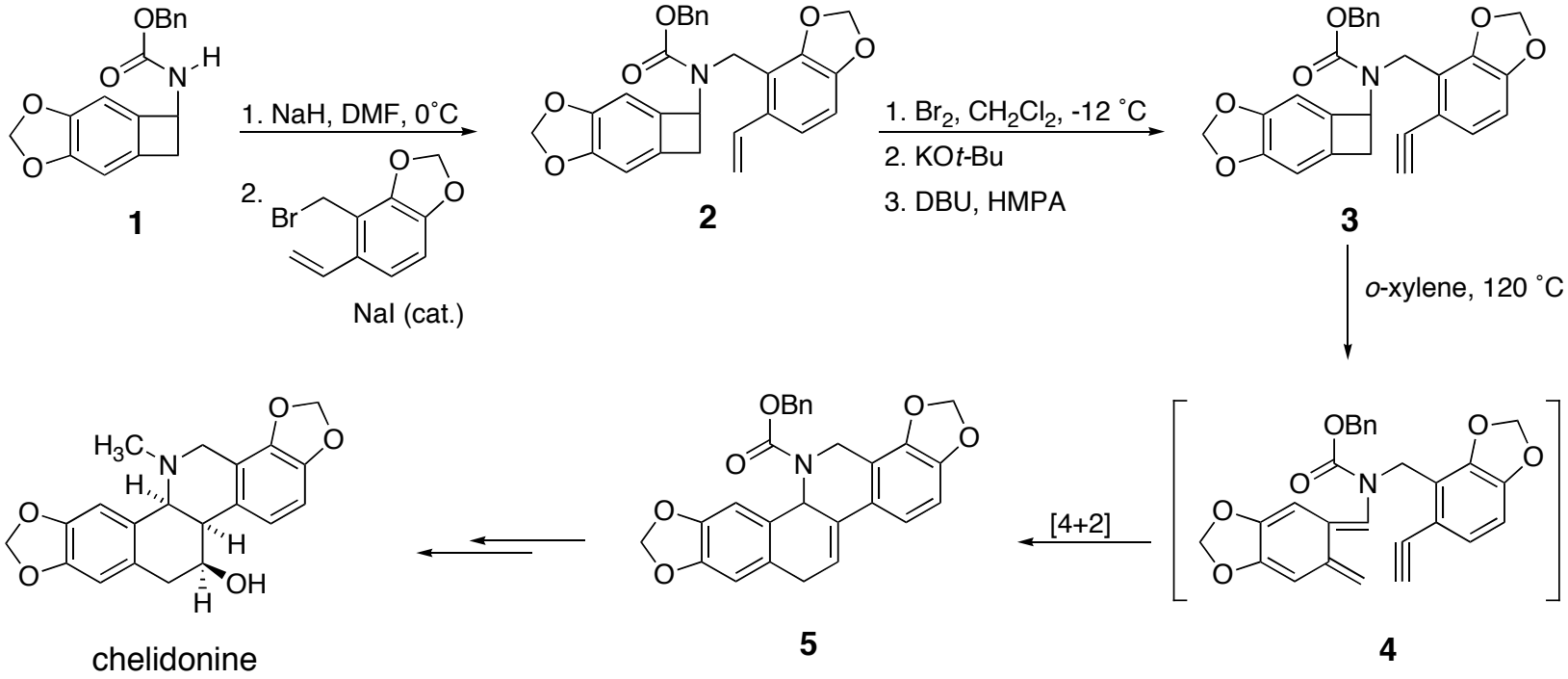
(+)-chelamidine (**4**)



(+)-chelamine (**5**)

- Hexahydrobenzo[*c*]phenanthridine class of alkaloids
- **1** and **2** isolated from the roots of *Chelidonium majus*
- Cytotoxic, inhibits tubulin polymerization
- Major component of the drug Ukrain, a semisynthetic preparation from *C. majus* alkaloids
- Fully aromatic A and D rings, partially hydrogenated B and C rings, C11-hydroxy group and 3-contiguous *syn*-stereocenters

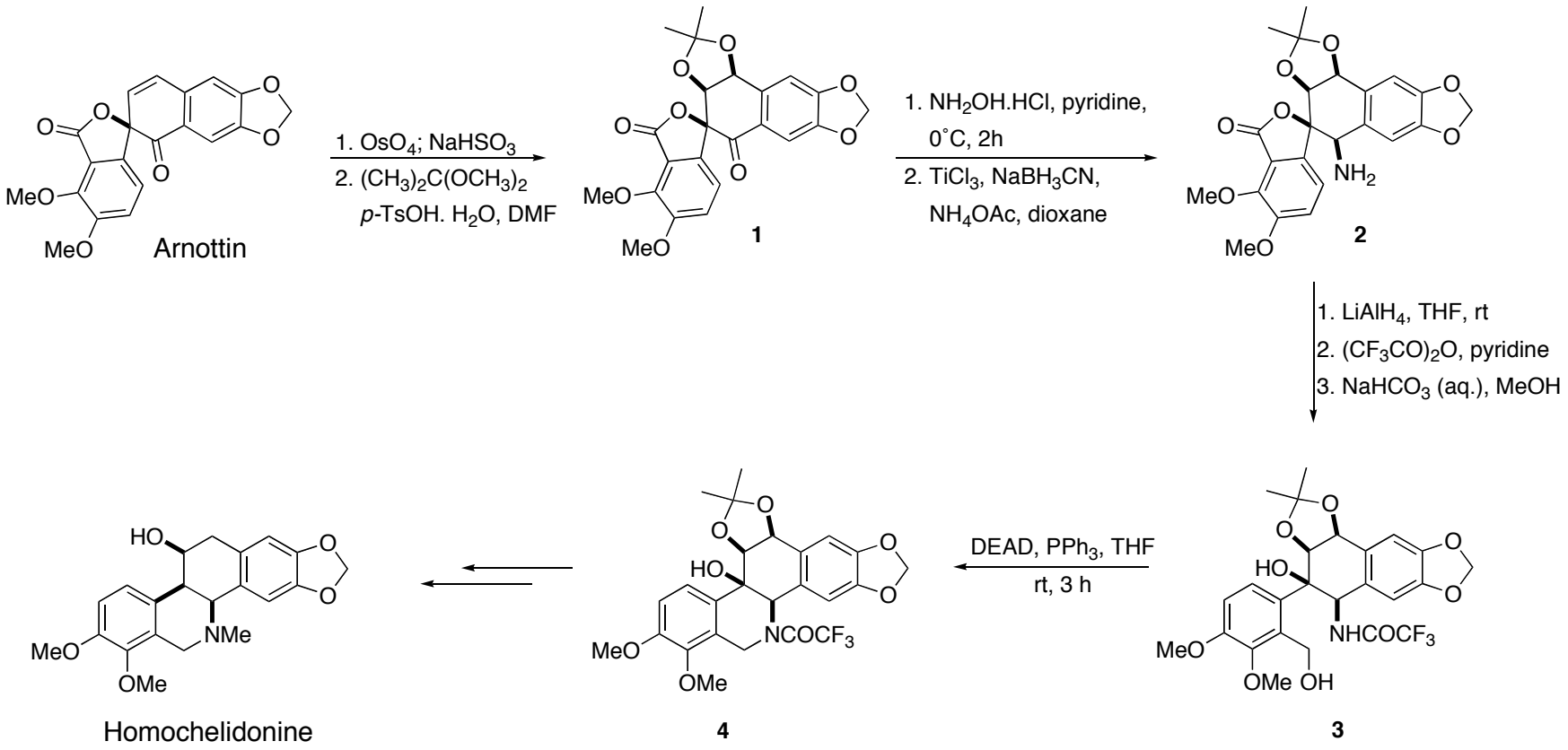
Total Synthesis of Chelidonine



- First total synthesis of *dl*-chelidonine using intramolecular [4+2] cycloaddition strategy

Oppolzer, W. and Keller, K. *J. Am. Chem. Soc.* **1971**, *93*, 3836

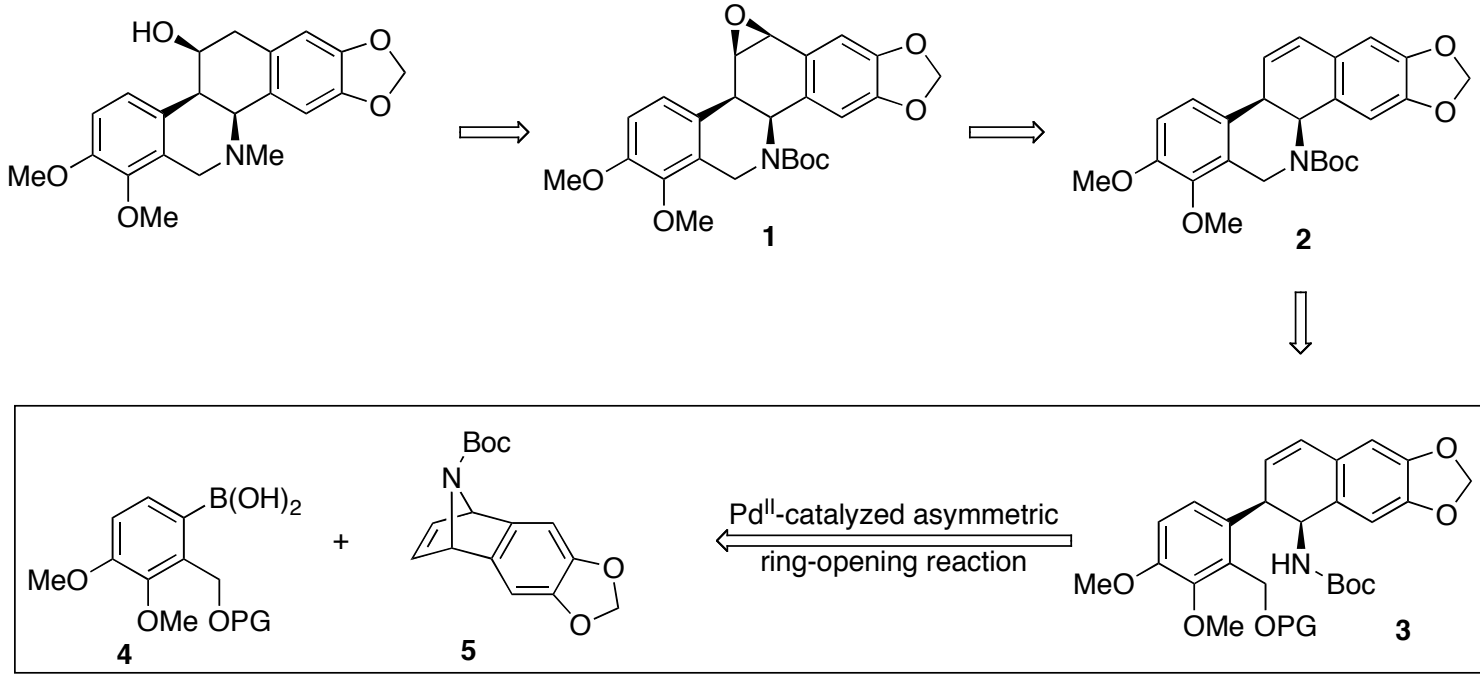
Total Synthesis of Homochelidonine



- 15 linear steps, 11 % overall yield

Yoshida, M.; Watanabe, T; Ishikawa, T. *Tetrahedron Lett.* **2002**, *43*, 6751

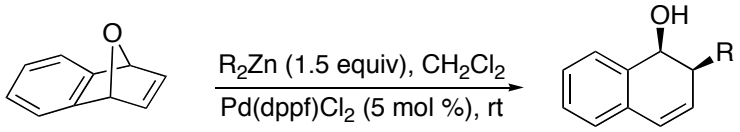
Homochelidonine: Retrosynthetic Analysis



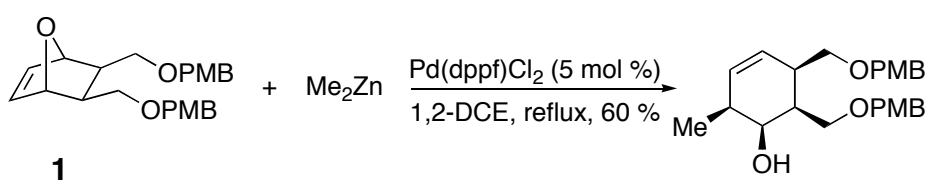
- Ring-opening of azabicyclo-alkene with aryl boronic acid as the key step in synthesis

McManus, H.; Flemming, M.J.; Lautens, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 433

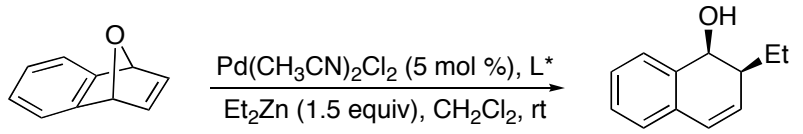
Pd-Catalyzed Alkylative Ring Opening



R	yield (%)	de (%)
Me	80	> 98
Et	92	> 98
t-Bu	72	> 98
vinyl	55	> 98
$TMSCH_2$	67	> 98



1 **2**



3

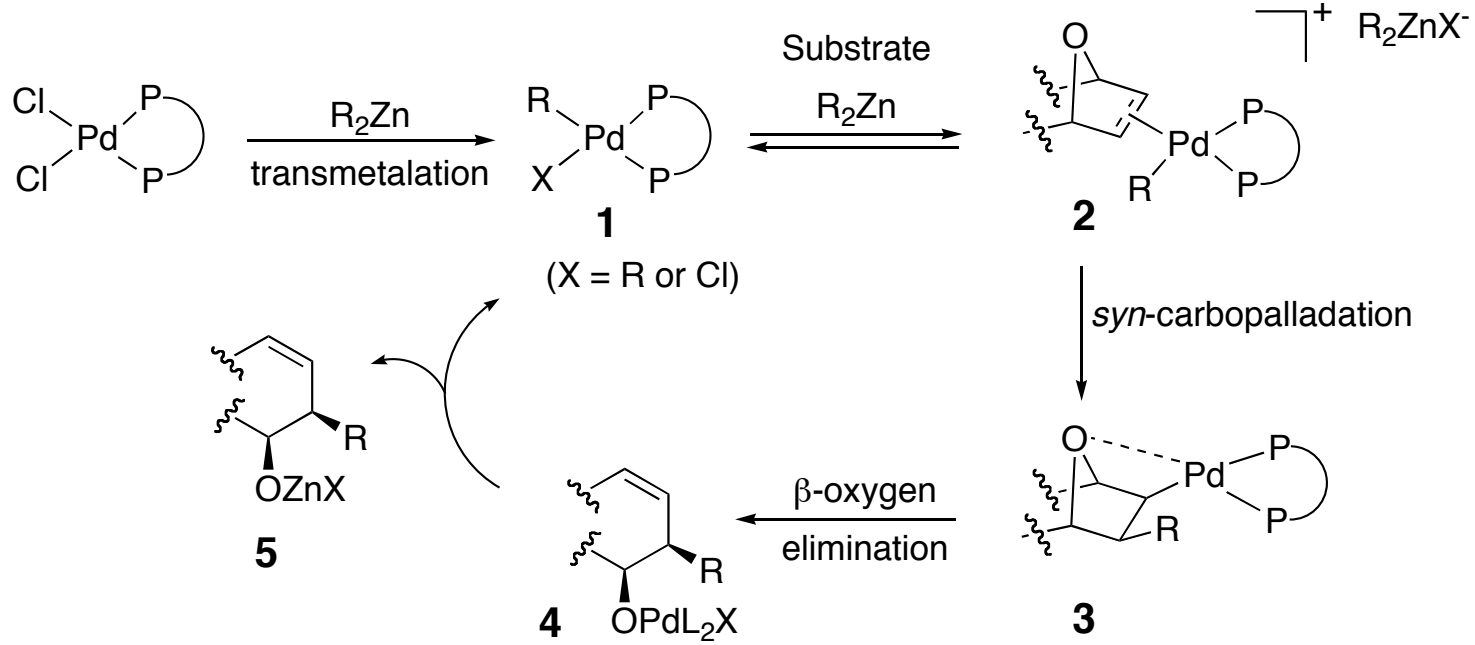
L = (*R*)-*tol*-BINAP

4, 98 % yield
96 % *ee*

- The product was obtained in good yield and as a single diastereomer

Lautens, M.; Renaud, J.-L.; Hibbert, S. *J. Am. Chem. Soc.* **2000**, *122*, 1804

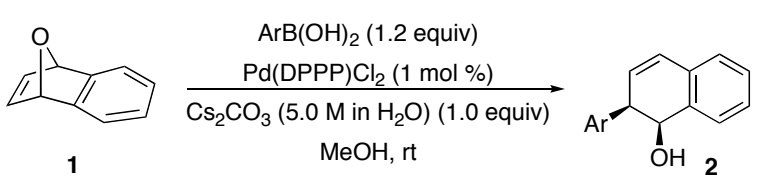
Proposed Mechanism



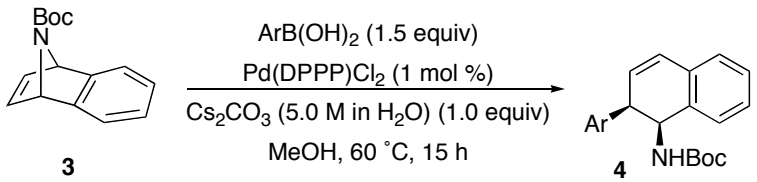
- Carbopalladation: rate-limiting step

Lautens, M.; Hibbert, S.; Renaud, J.-L. *J. Am. Chem. Soc.* **2001**, *123*, 6834

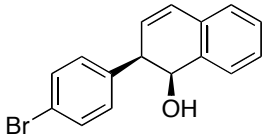
Addition of Aryl Boronic Acids to Bicyclic Alkenes



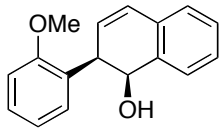
1 2



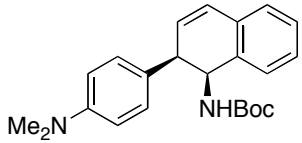
3 4



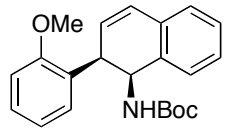
83 %



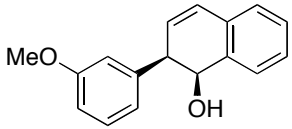
74 %



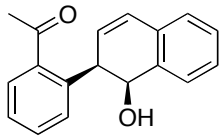
71 %



93 %



86 %



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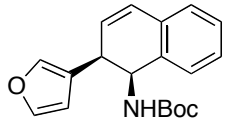
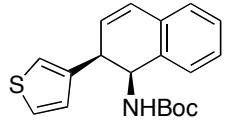


86 %

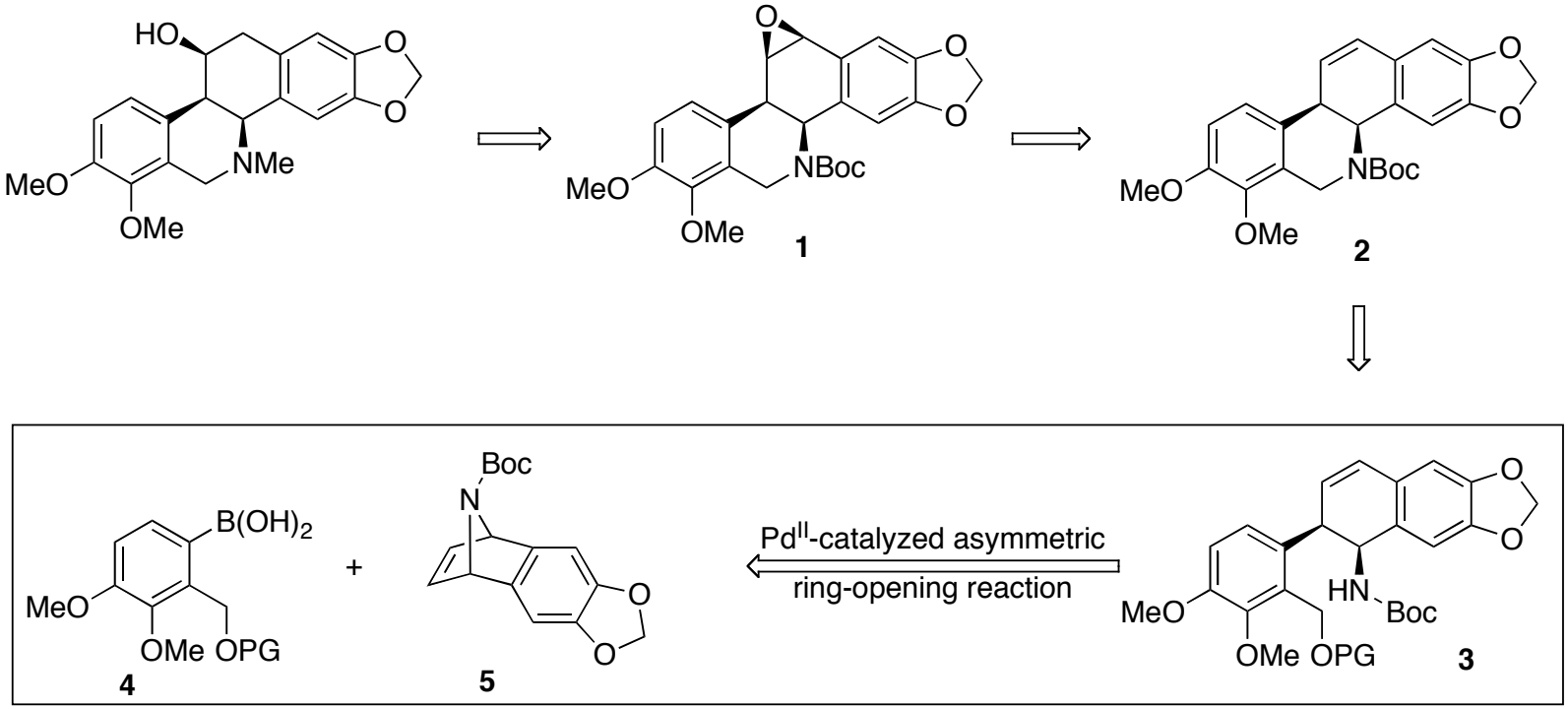


99 %

- Addition of heteroaryl boronic acids to oxa- and aza-bicyclic alkenes

Lautens, M.; Dockendorff, C. *Org. Lett.* **2003**, *5*, 3695

Homochelidonine: Retrosynthetic Analysis



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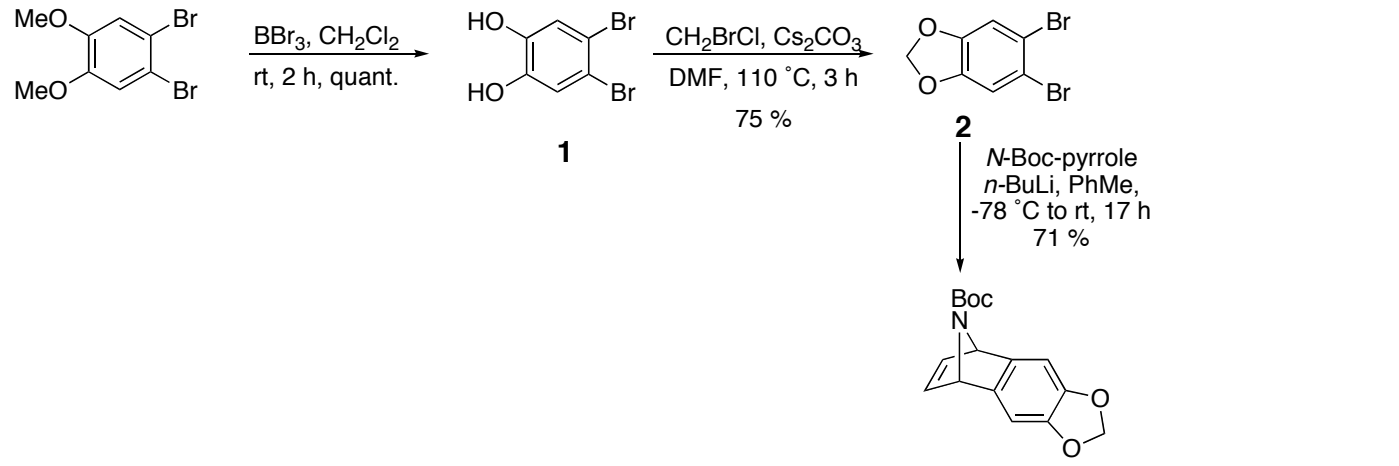
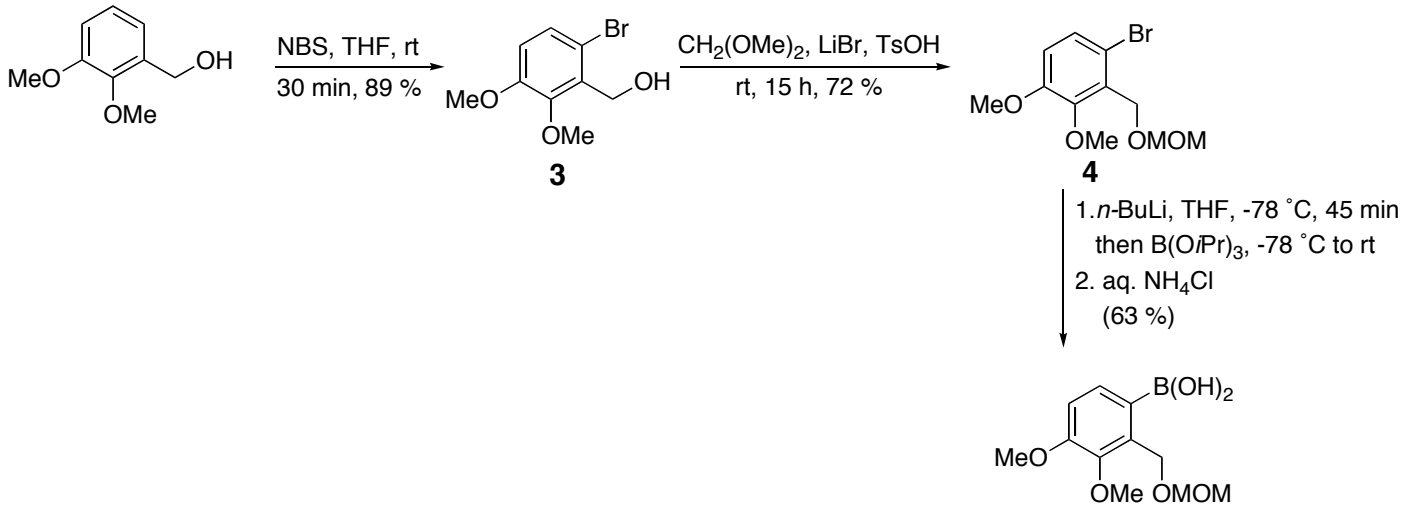
Synthesis of the Intermediates





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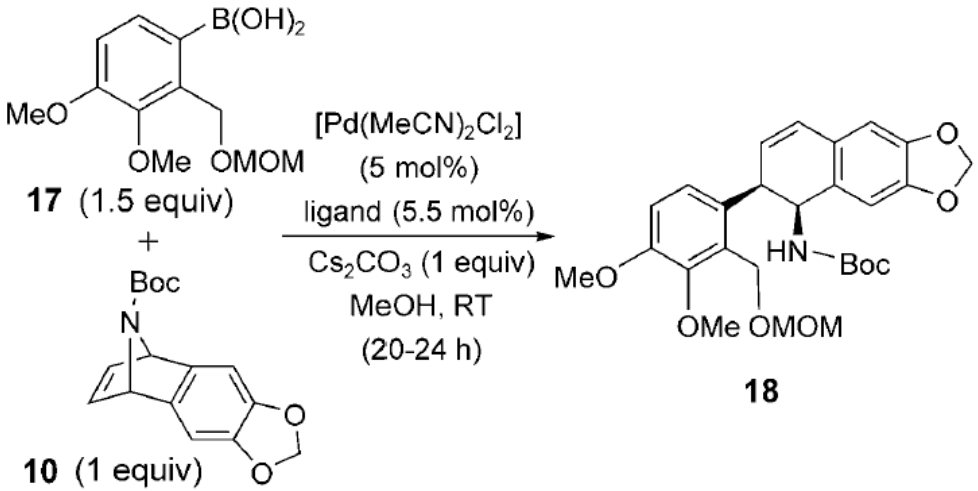
Asymmetric Ring-Opening Reaction



Entry	Ligand[a]	Yield [%][b]	*ee* [%][c]
1[d]	dppp	82	–
2	(*S*)-binap	48	87
3	(S,S)-chiraphos	66	40
4	(*R*)-monophos	25	14
5	(*R*)-segphos	61	77
6	(*R*,*R*)-Me-duphos	92	37
7	(S)-tol-binap	90	91

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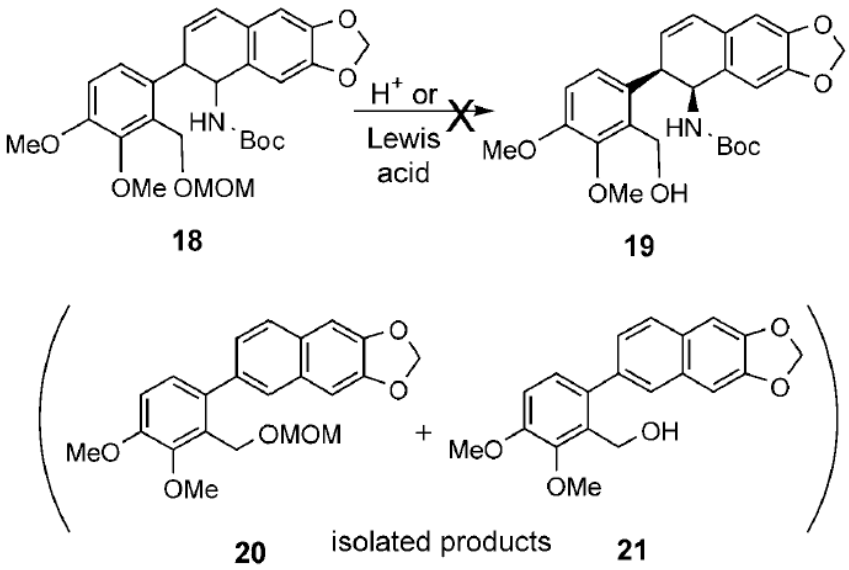
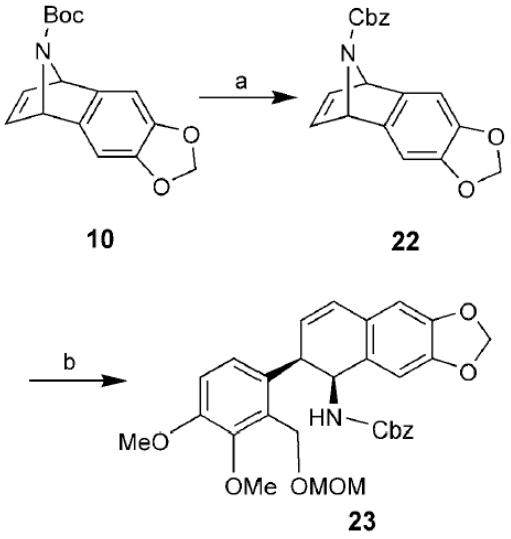
Protecting Group Manipulations





Scheme 6. Synthesis of dihydronaphthalene **23**: a) TMSI, NEt_3, CH_2Cl_2, reflux, 15 min; then CbzCl, RT, 3 h, 80%; b) $[Pd(MeCN_2)Cl_2]$ (5 mol%), (*S*)-binap (5.5 mol%), **17**, Cs_2CO_3, MeOH, RT, 6 h, 89%, 90% *ee* (80%, 99% *ee* after one recrystallization). Cbz = benzyloxycarbonyl, TMS = trimethylsilyl.

- Acid-stable protecting group on the Nitrogen

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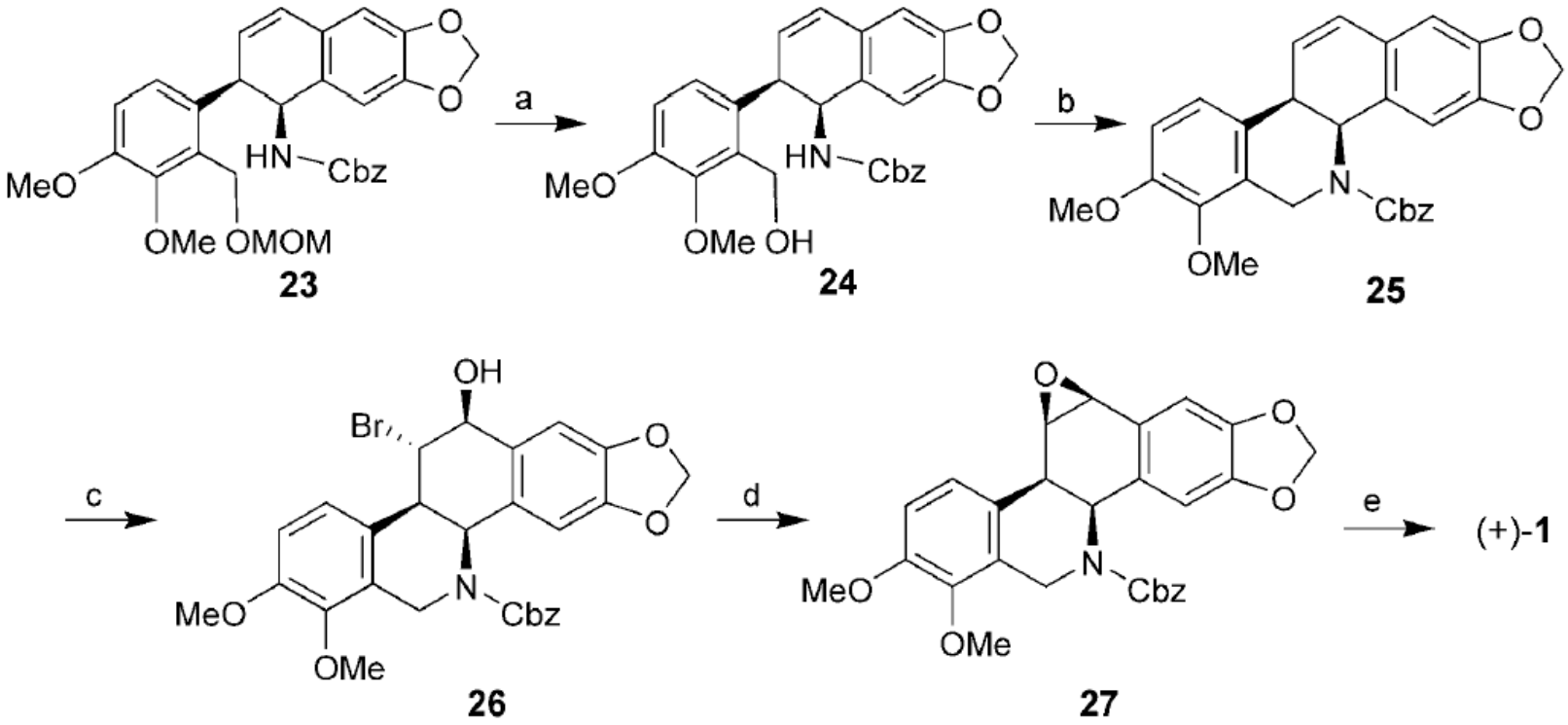
Completion of the Synthesis



Scheme 7. Completion of the synthesis of (+)-**1**: a) HCl, *i*PrOH/THF, RT, 8 h, 75%; b) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 1 h; then NaH, DMF, 0 °C, 3 h, 90%; c) NBS, THF/H_2O, RT, 90 min, 75%; d) KO*t*Bu, THF, −78 °C, 30 min, quant.; e) $LiAlH_4$, 1,4-dioxane, reflux, 12 h, 87%.

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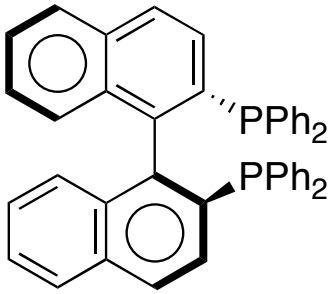
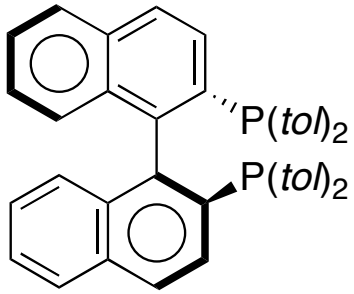
Conclusion

- Enantioselective total synthesis of (+)-Homochelidonine was achieved in 14 steps with 15 % overall yield from 4,5-dibromovertrole.
- A new and general strategy for the synthesis of hexahydrobenzo[*c*]phenanthridine alkaloids using highly enantioselective Pd(II)-catalyzed ring-opening reaction of a *meso*-azabicycle with aryl boronic acid has been established.
- Application of this methodology to the synthesis of other alkaloids is under investigation.

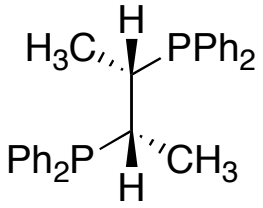
Phosphine Ligands



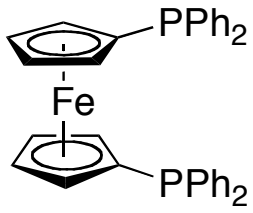
(*S*)-BINAP



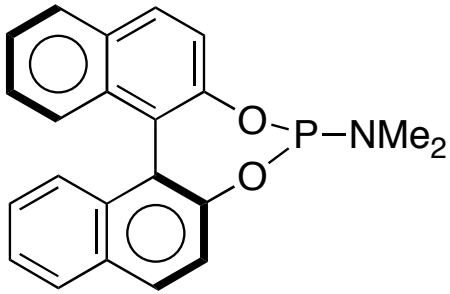
(*S*)-*tol*-BINAP



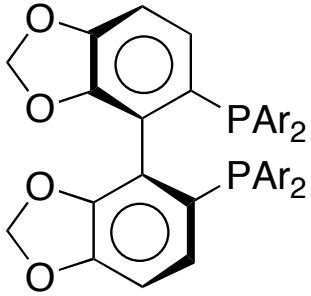
(*S,S*)-chiraphos



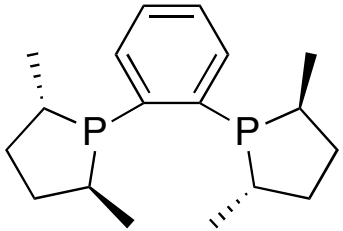
dppf



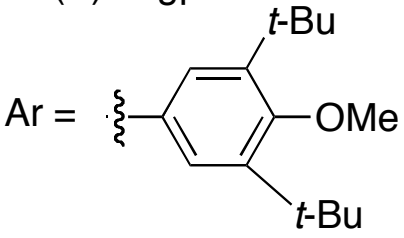
(*S*)-monophos

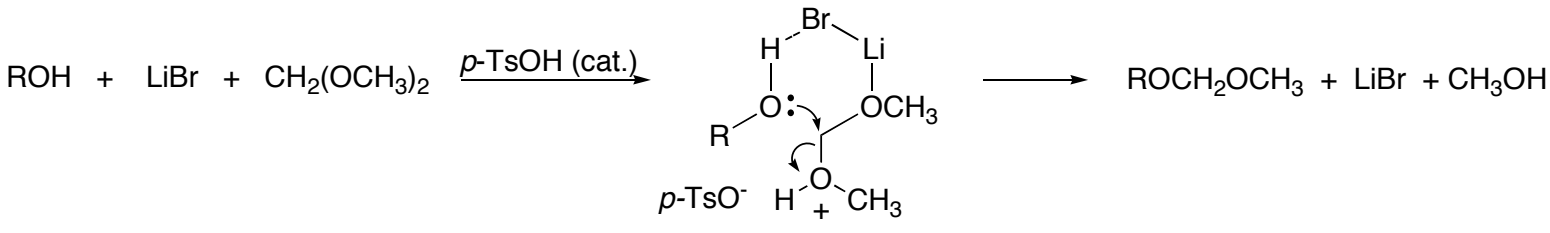


(*S*)-segphos



Me-duphos





Gras, J.-L. *et al.*, *Synthesis* **1985**, 74-75.