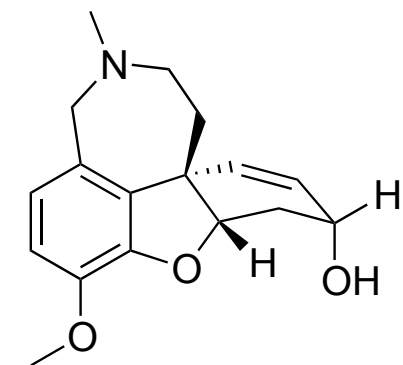
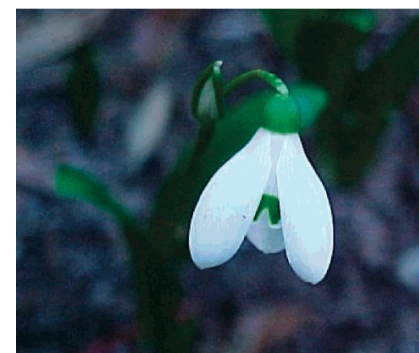
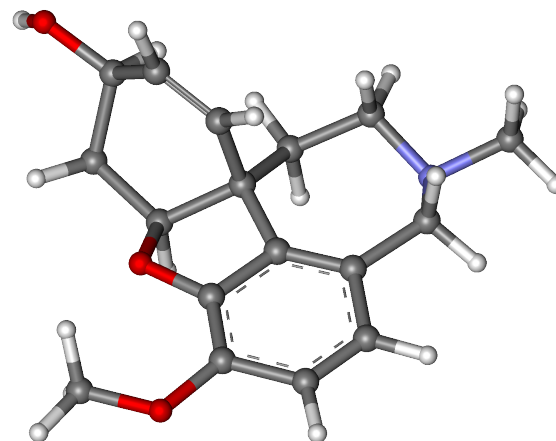


Catalytic Asymmetric Total Syntheses of (-)-Galanthamine and (-)-Lycoramine

Li, L.; Yang, Q.; Wang, Y.; Jia, Y. *Angew. Chem. Int. Ed.*, **2015**, *54*, 6255-6259.

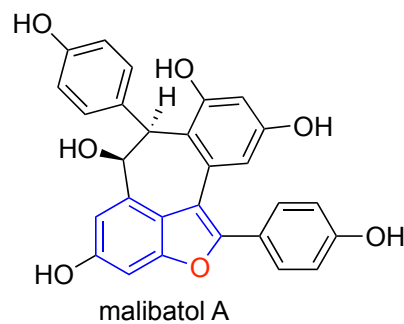
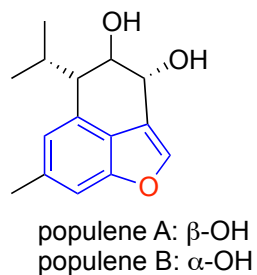
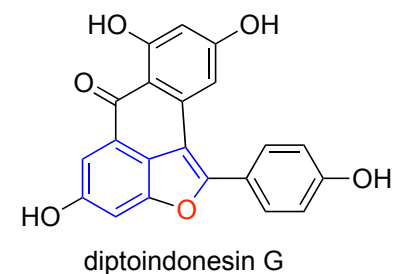
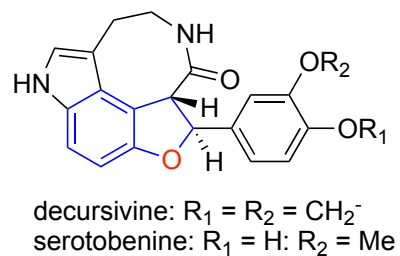
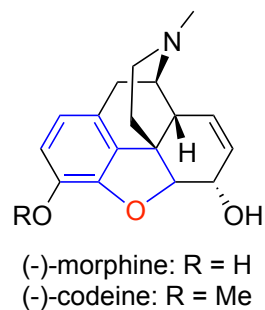
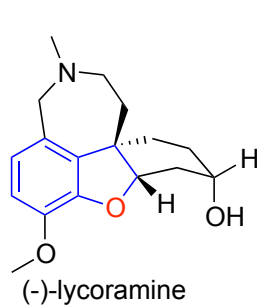


(-)-Galanthamine

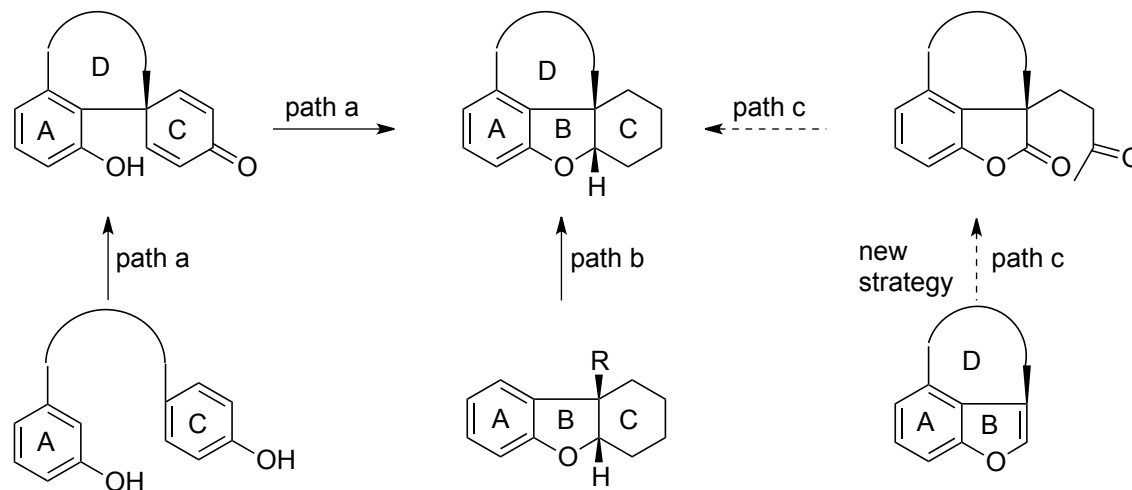


- An alkaloid isolated form:
 - **Caucasian Snow Drop** (*Galanthus woronowii*)
 - Bulbs of different species of family *Amaryllidaceae*
- An **acetylcholinesterase inhibitor**, treatment for **Alzheimer's disease** and **other memory impairments**
- Available as Nivalin, Razadyne, Razadyne ER, Reminyl, Lycoremine
- Isolated form daffodils: **0.1-0.2% dry weight**
cost: **\$ 50 000.00/1Kg**

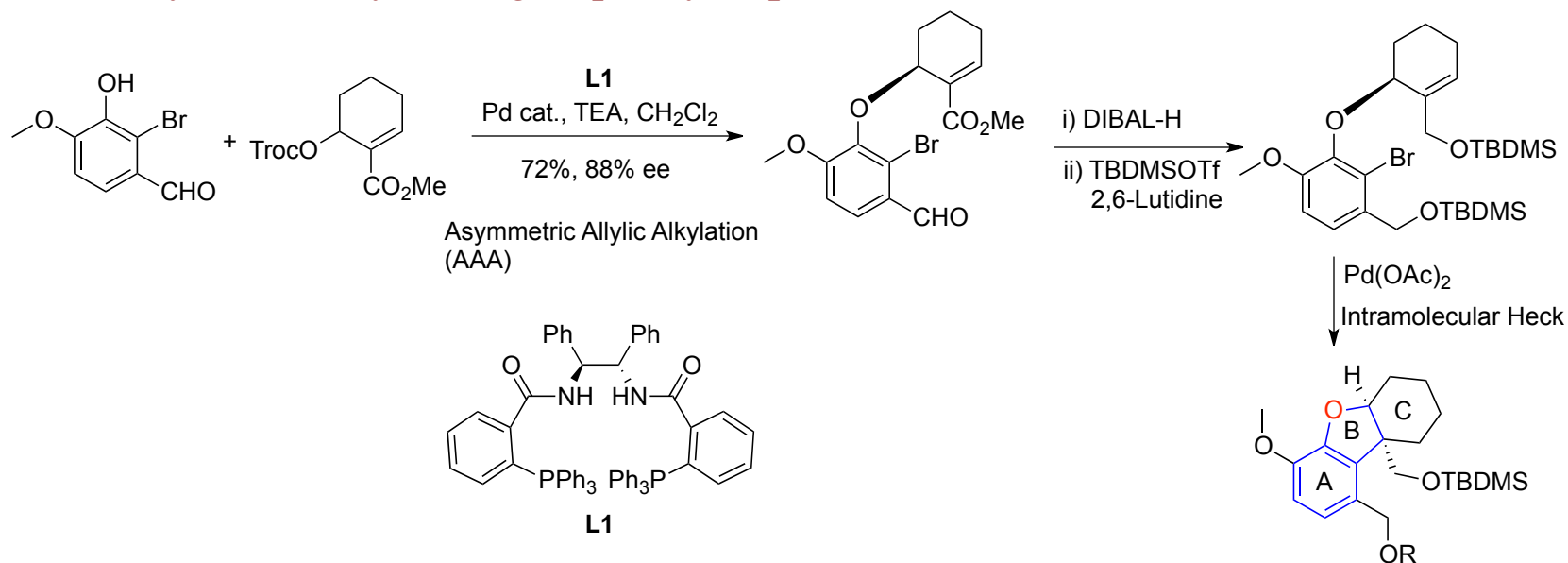
Representative Natural Products with a Fused Benzofuran Core Structure



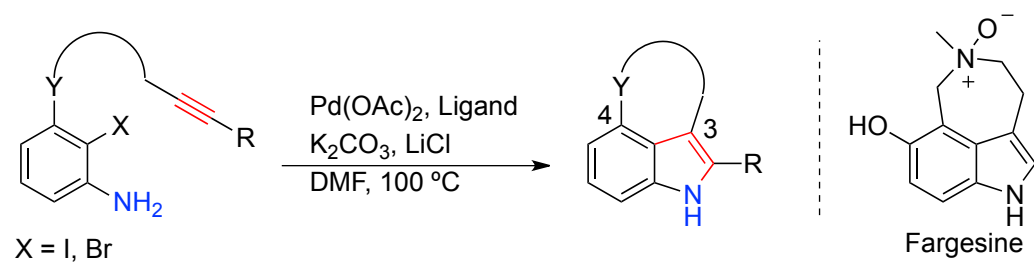
Different Strategies



Previous Syntheses: by Trost group (key steps)

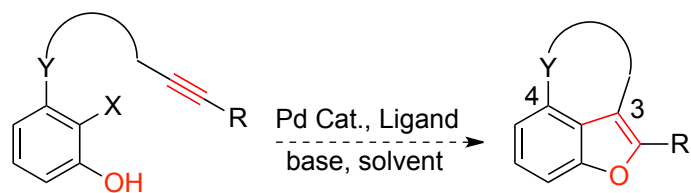


Previous work



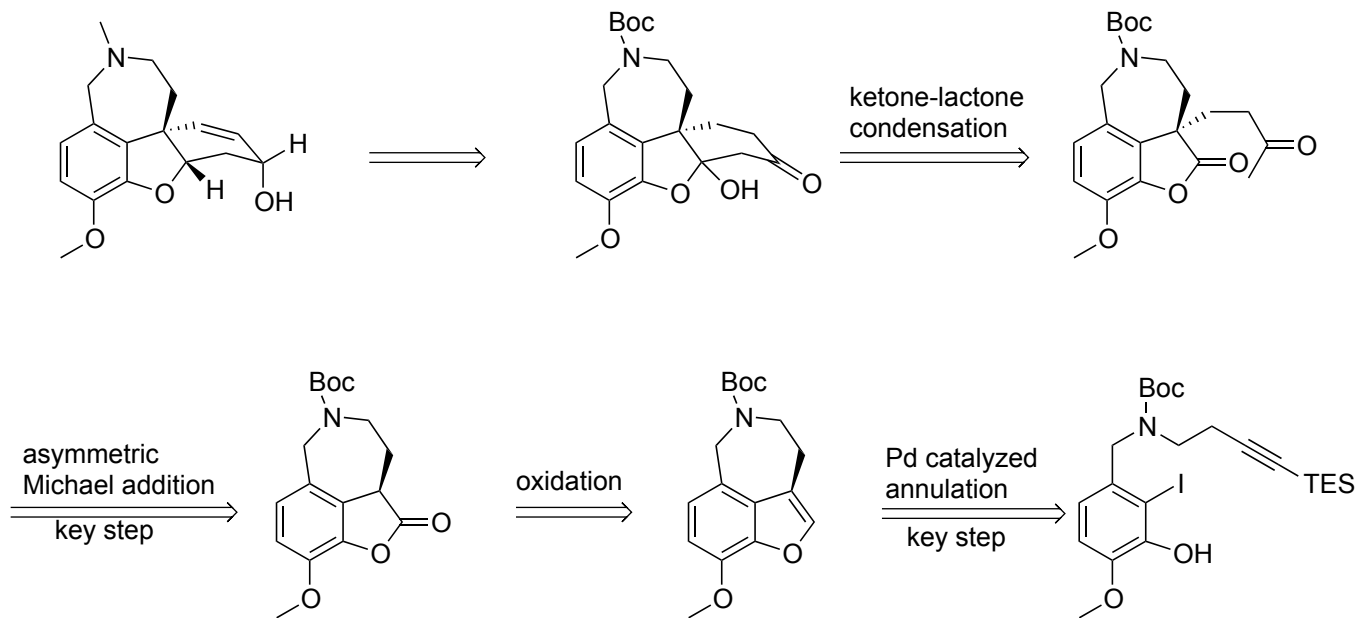
Shan, D.; Gao, Y.; Jia, Y. *Angew. Chem. Int. Ed.*, **2013**, 52, 4902-4905.

Current work

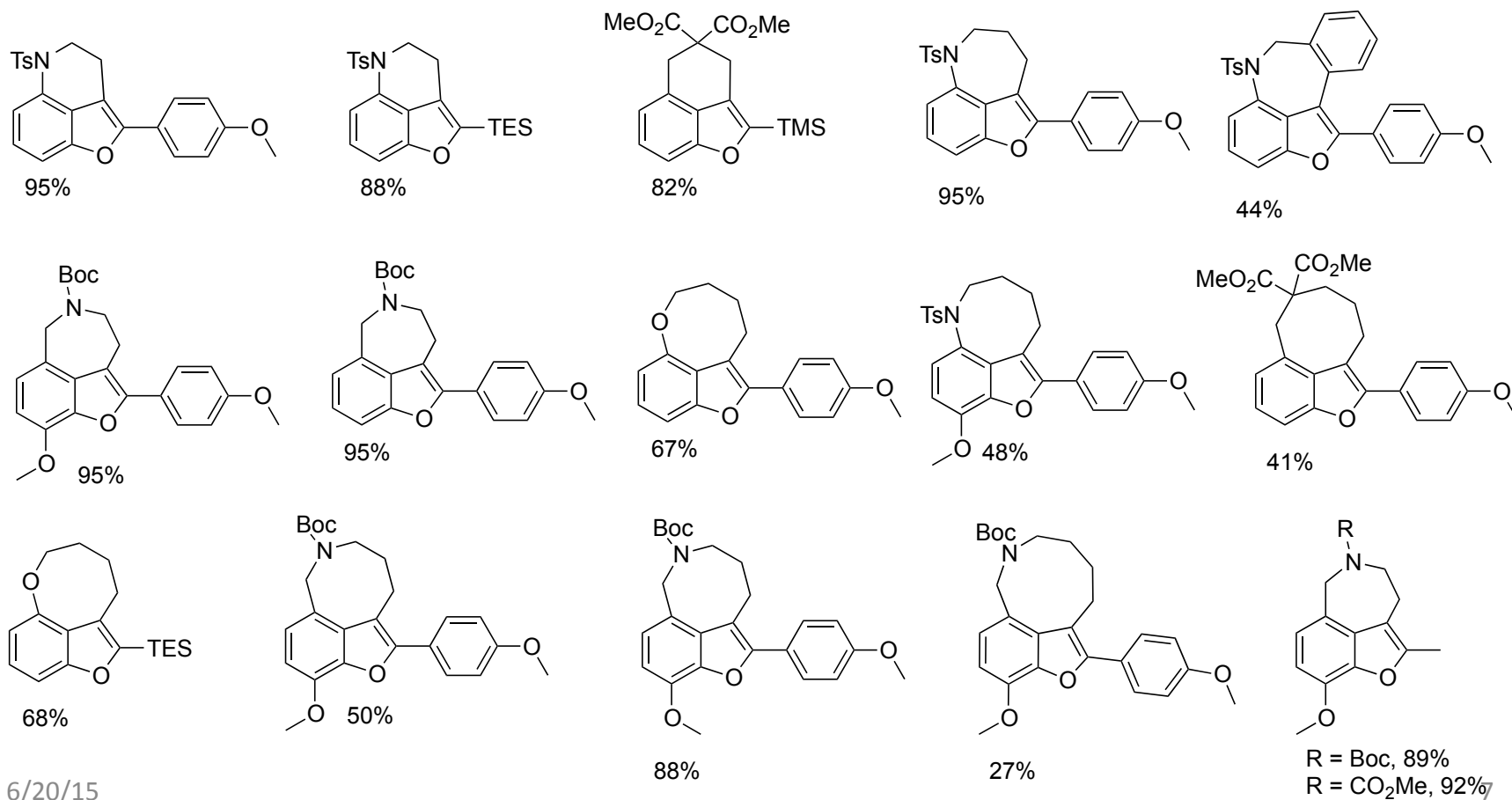
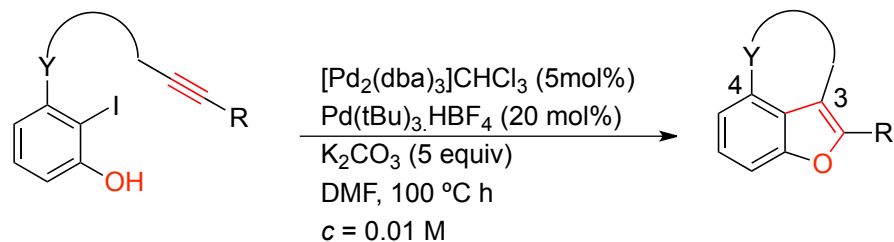


Li, L.; Yang, Q.; Wang, Y.; Jia, Y. *Angew. Chem. Int. Ed.*, **2015**, 54, 6255-6259.

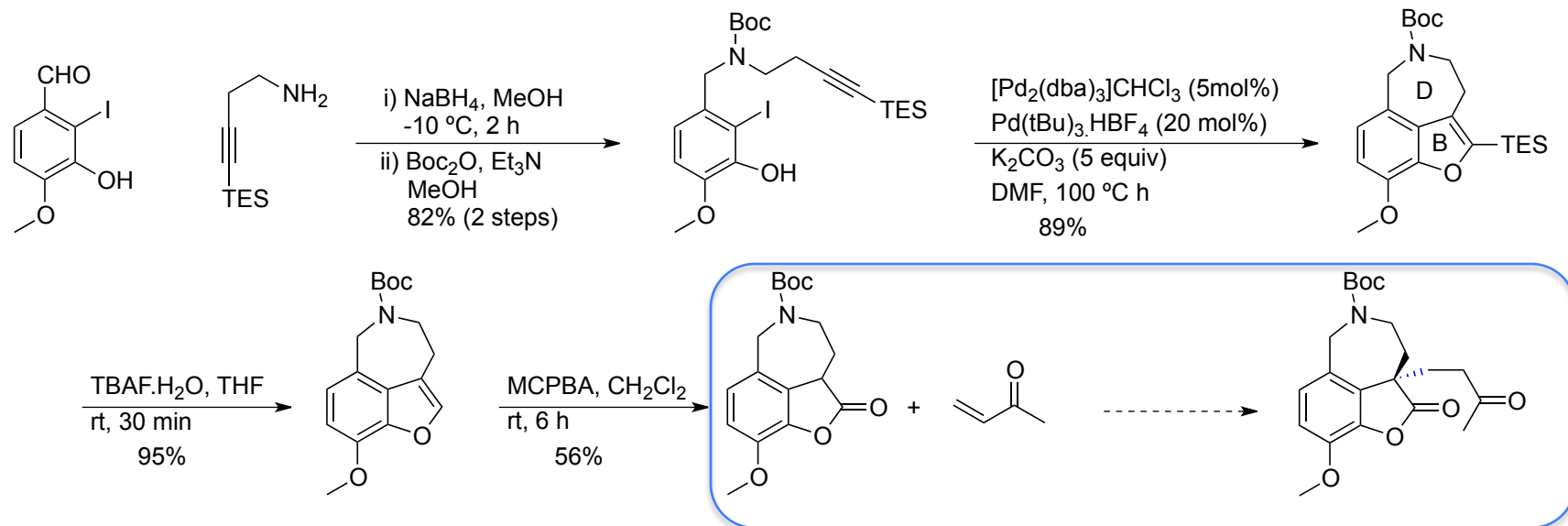
Retrosynthetic Analysis

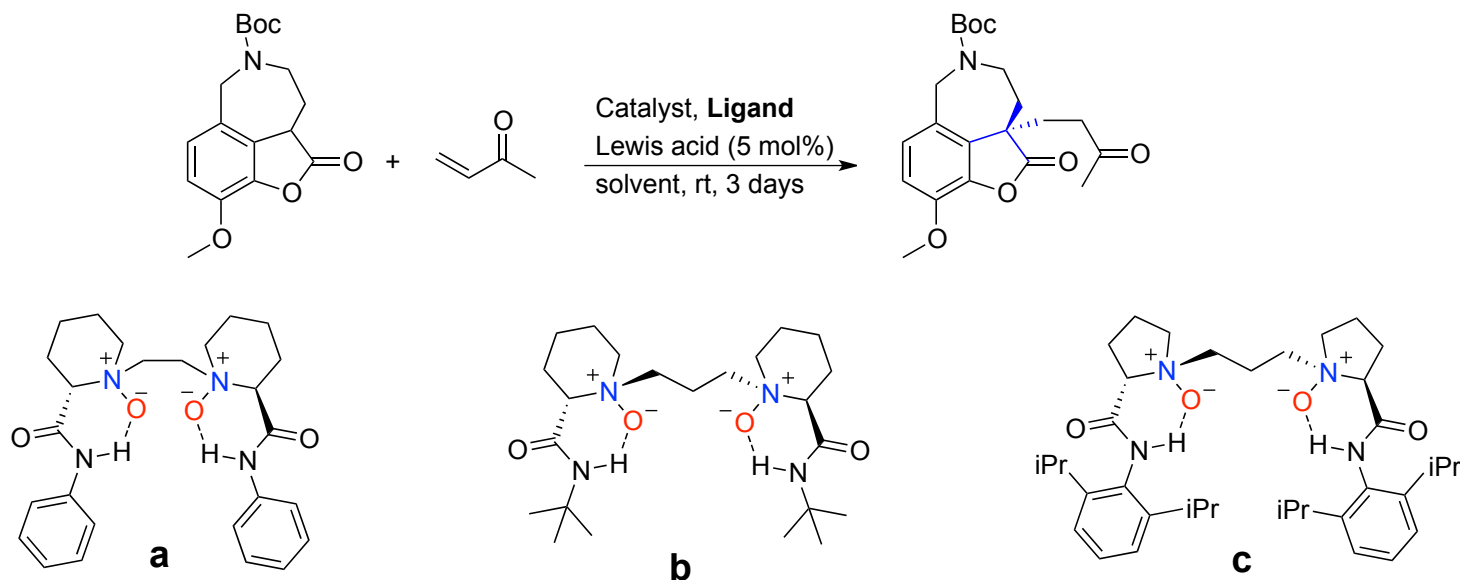


Development of the Proposed Strategy



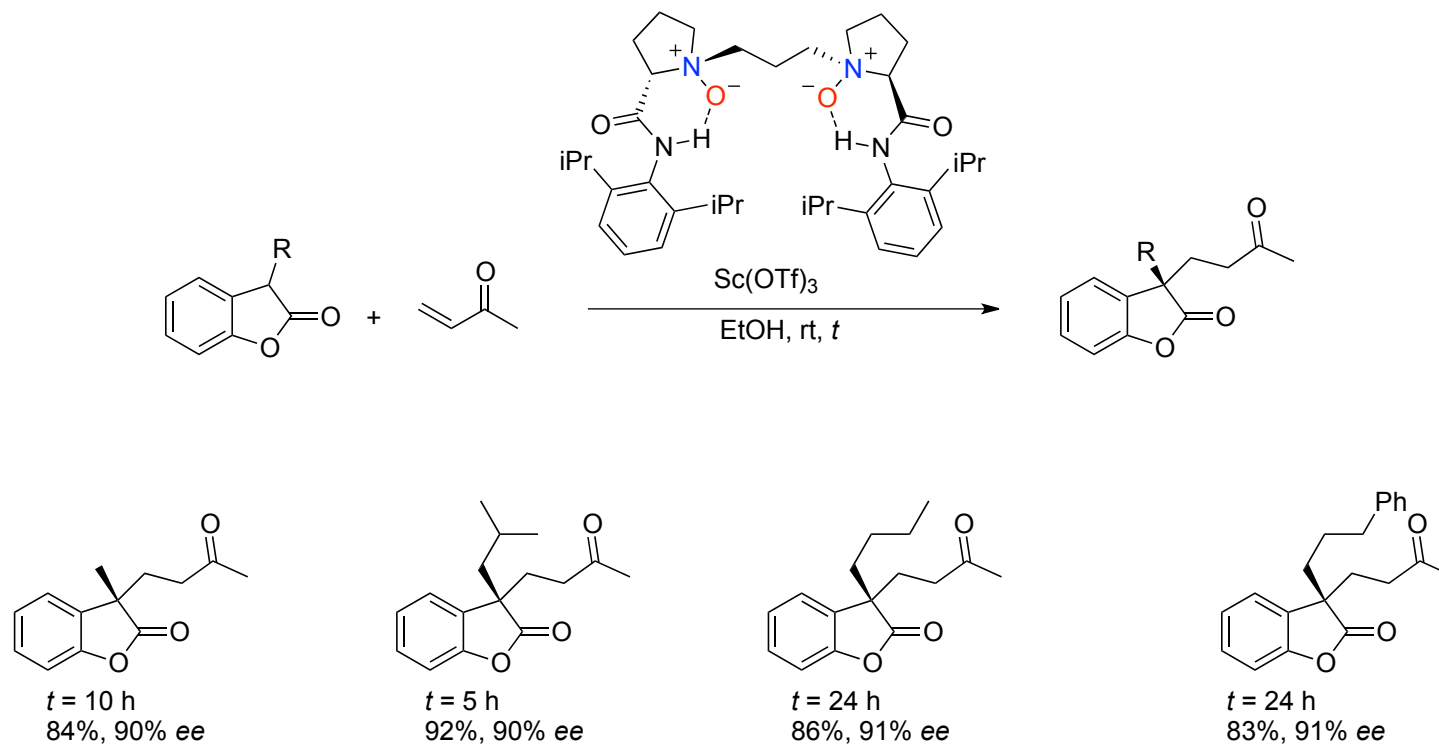
Synthesis of (-)-Galanthamine



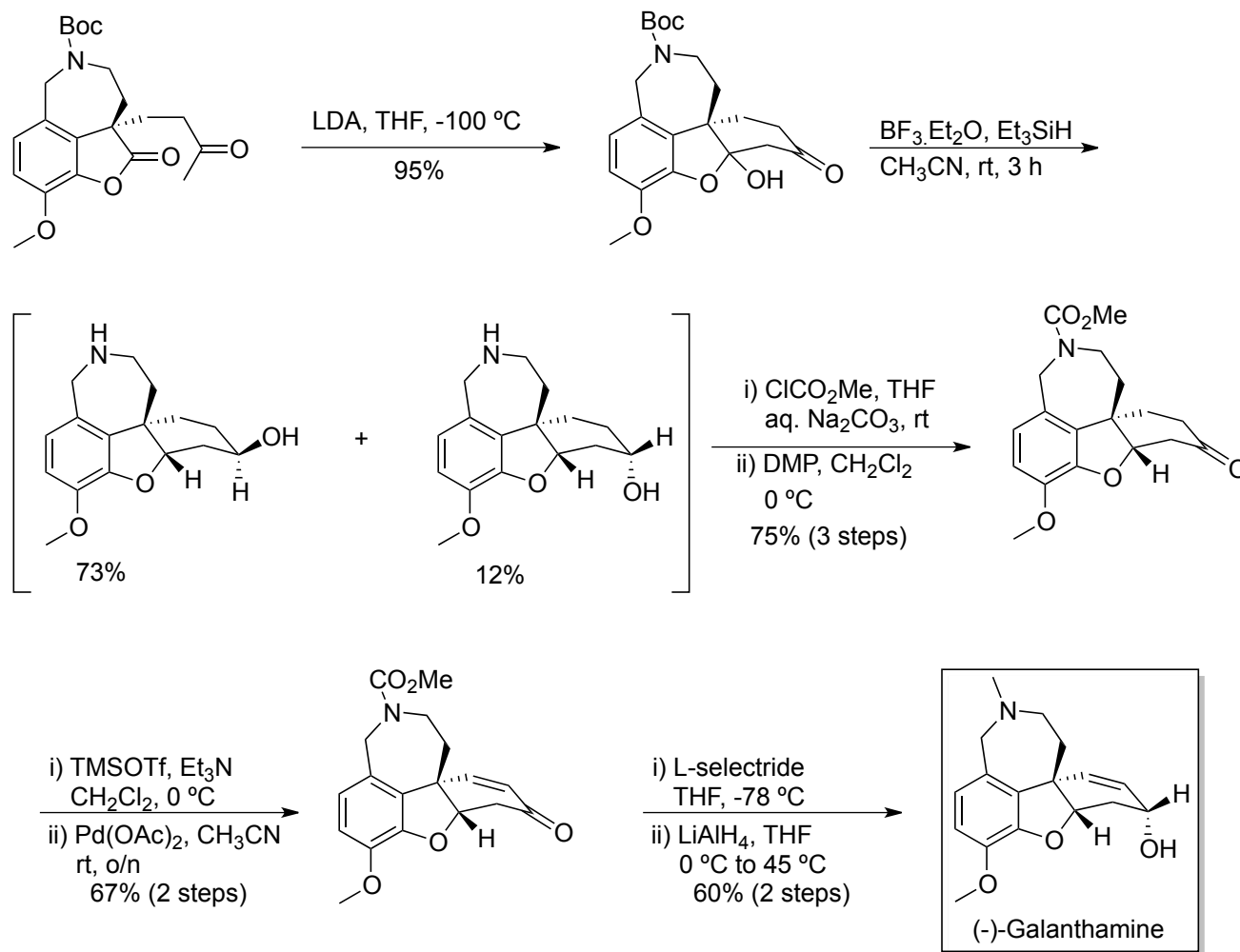
Chiral *N,N'*-oxide ligands for asymmetric catalysis

| Entry | Lewis acid | Ligand | Solvent | Yield [%] ^[b] | <i>ee</i> [%] ^[c] |
|------------------|----------------------|----------|---------------------------------|--------------------------|------------------------------|
| 1 | Yb(OTf) ₃ | a | CH ₂ Cl ₂ | n.r. | – |
| 2 | Yb(OTf) ₃ | b | CH ₂ Cl ₂ | n.r. | – |
| 3 | Yb(OTf) ₃ | c | CH ₂ Cl ₂ | 10 | 42 |
| 4 | Yb(OTf) ₃ | c | EtOH | 33 | 38 |
| 5 | Sc(OTf) ₃ | c | EtOH | 85 | 93 |
| 6 ^[d] | Sc(OTf) ₃ | c | EtOH | 85 | 94 |

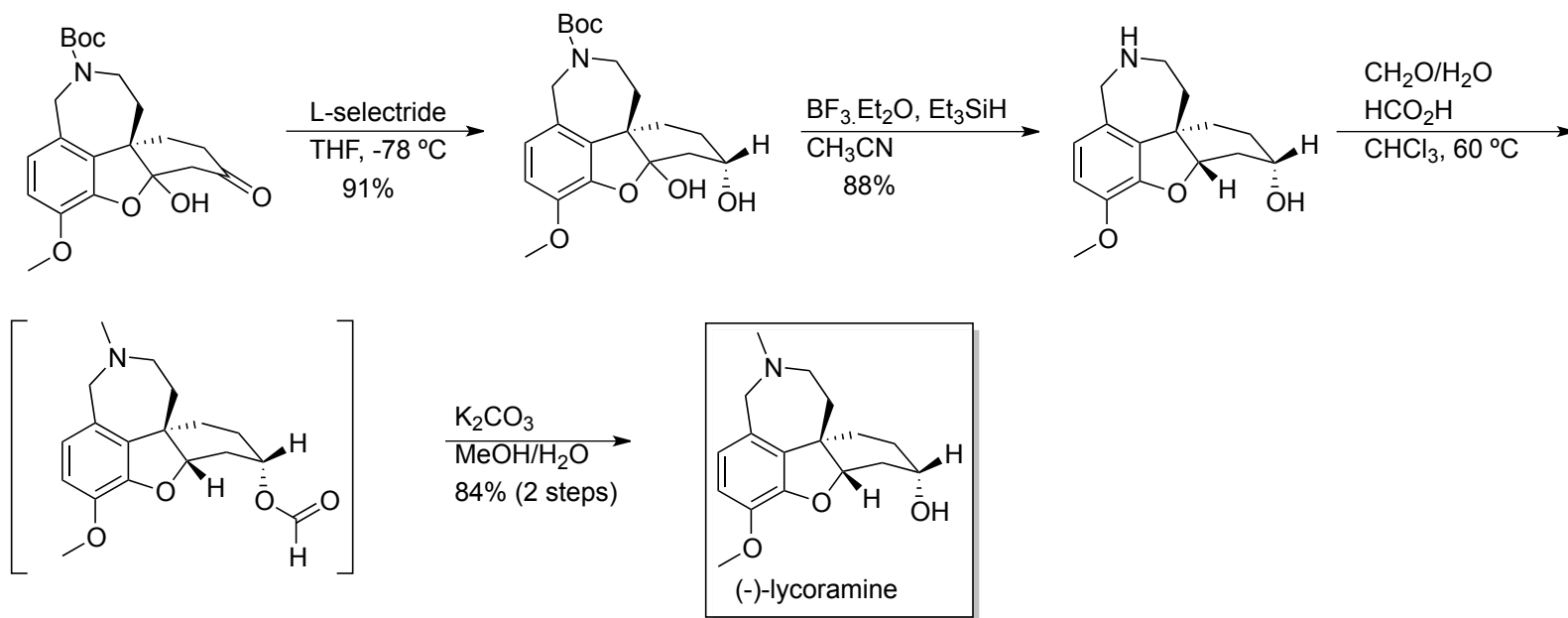
Studying the substrate scope



Synthesis of (-)-Galanthamine contd.



Synthesis of (-)-Lycoramine



Conclusions:

- Asymmetric Total syntheses of **(-)-Galanthamine** and **(-)-Lycoramine** based on two metal catalyzed reactions
 - a. Pd-catalyzed **intramolecular Larock annulation** to construct **3,4-fused tricyclic benzofurans**
 - b. **Enantioselective conjugate addition** of 3-alkyl substituted **benzofuranone to MVK**; catalyzed by $\text{Sc}^{\text{III}}/\text{N,N}'\text{-dioxide}$ complex

Thank you!