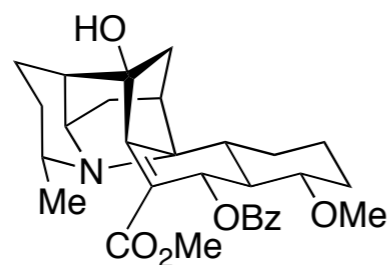


Total Synthesis of (-)- Himandrine

Movassaghi, M.; Tjandra, M.; Qi, J.
J. Am. Chem. Soc. **2009**, *131*, 9648-9650.

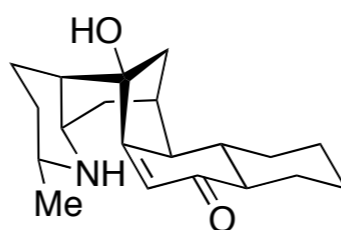
Jason M. Stevens - 07.29.2009

Galbulimima Alkaloids



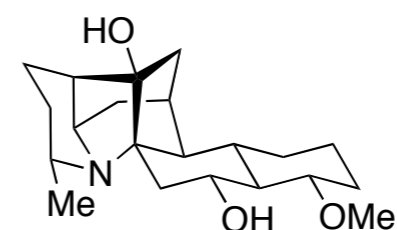
(-)-himandrine

Movassaghi



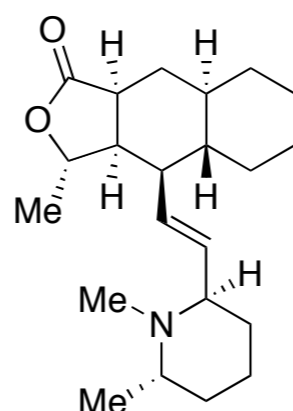
Galbulimima
Alkaloid 13

Movassaghi
Schering Plough
Evans
Mander

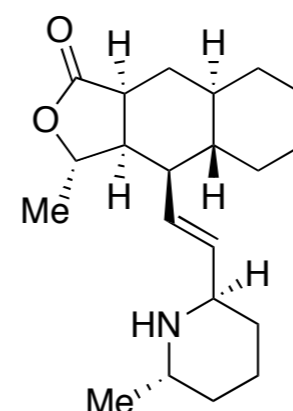


himgaline

Schering-Plough
Evans



himbacine



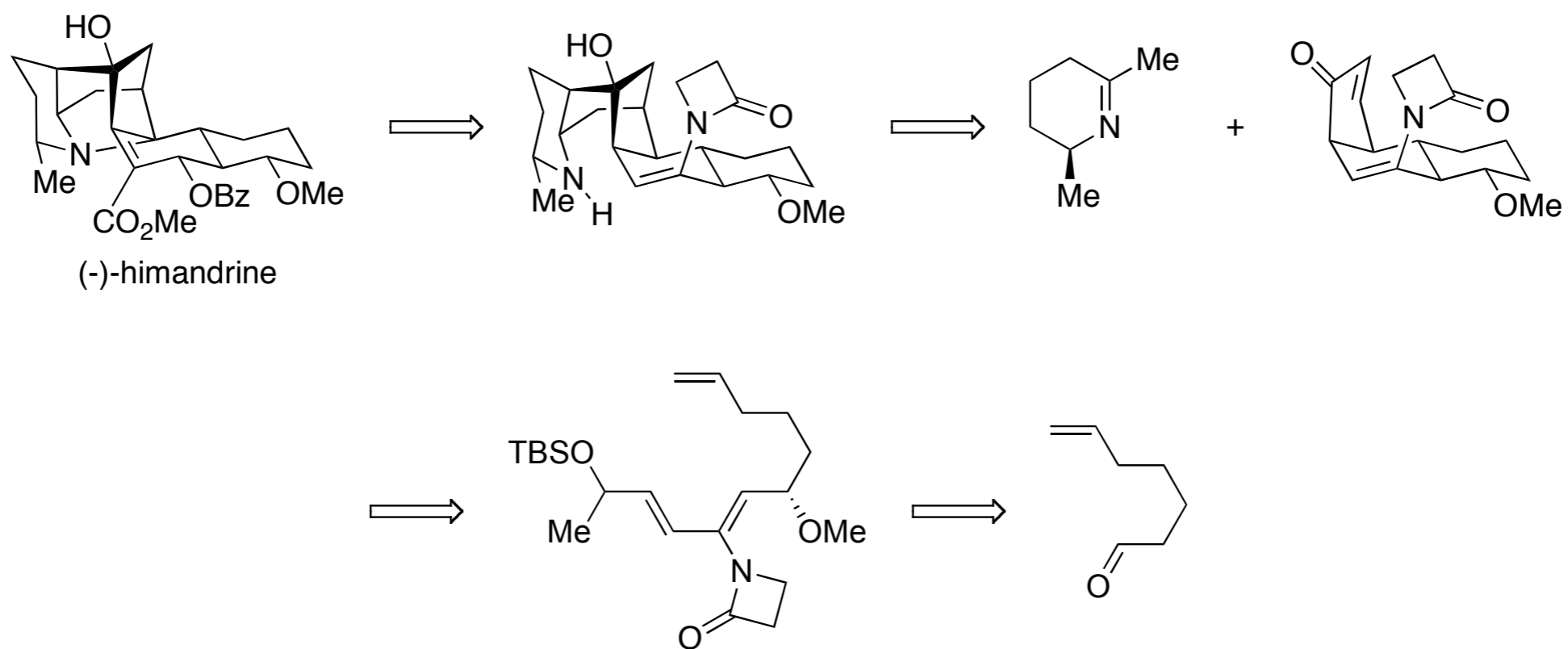
himbeline

Hart and Kozikowski

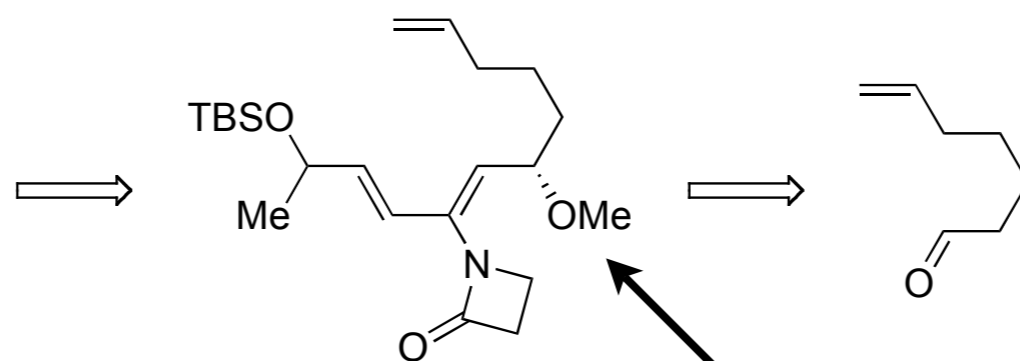
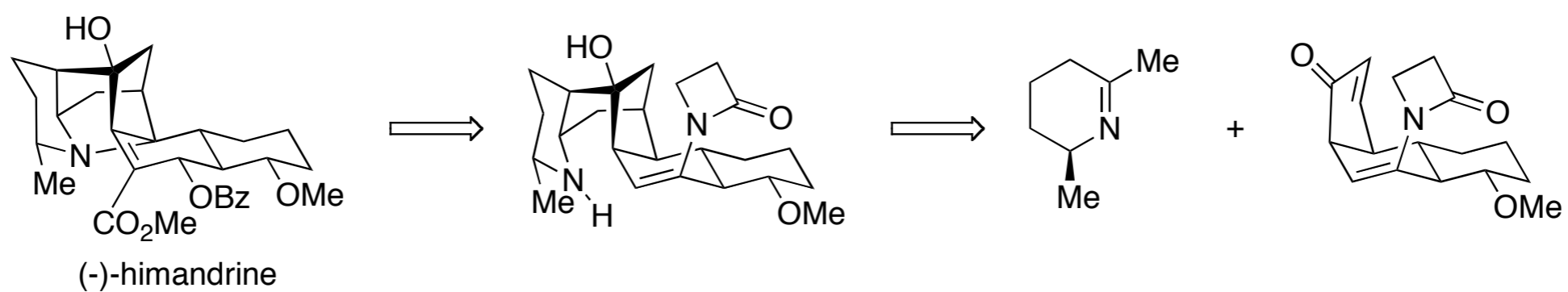
About (-)-Himandrine

- Isolated from the bark of *Galbulimima belgraveana* (New Guinea/Australia)
- Galbulimima Alkaloids have shown to be useful as antithrombotic agents and possible agents for offsetting Alzheimer's disease
- This work is ~75% the same as for GB-13

Retrosynthesis

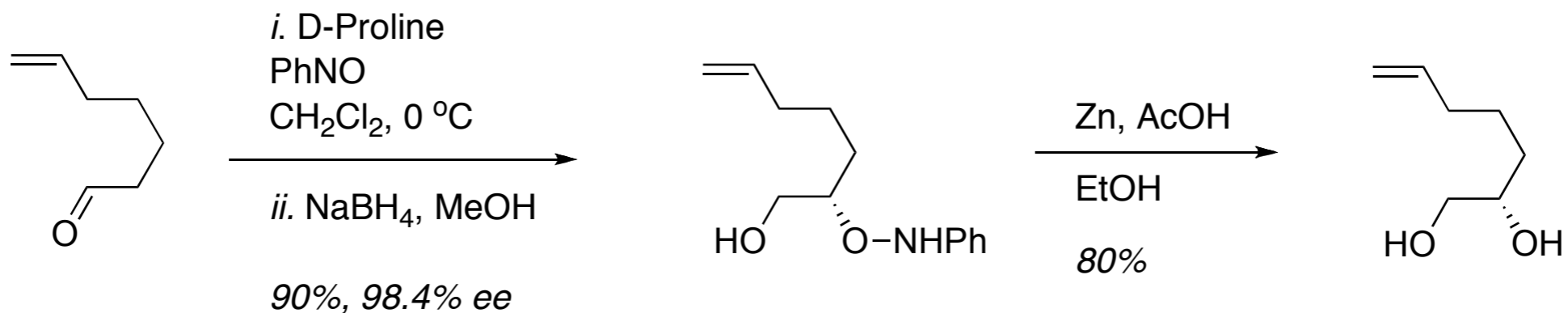


Retrosynthesis

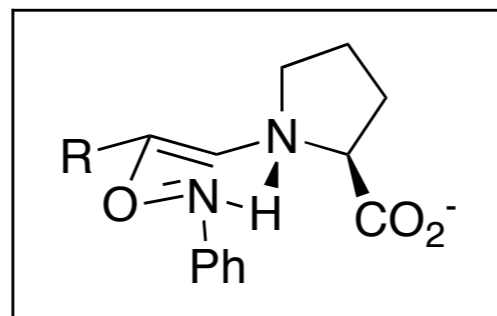
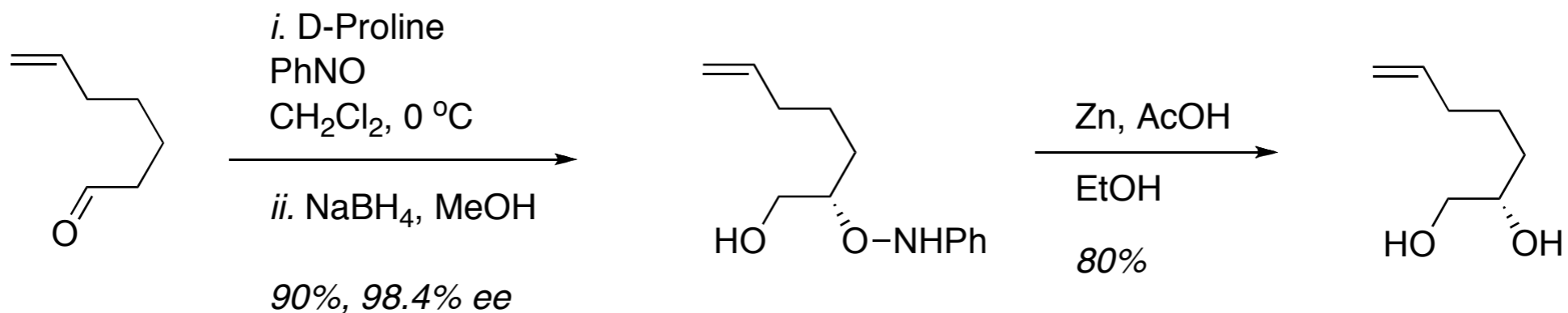


Responsible for setting every stereocenter in the molecule

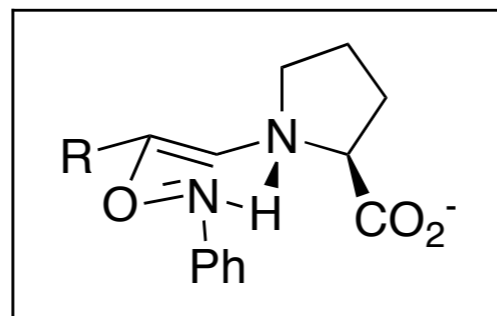
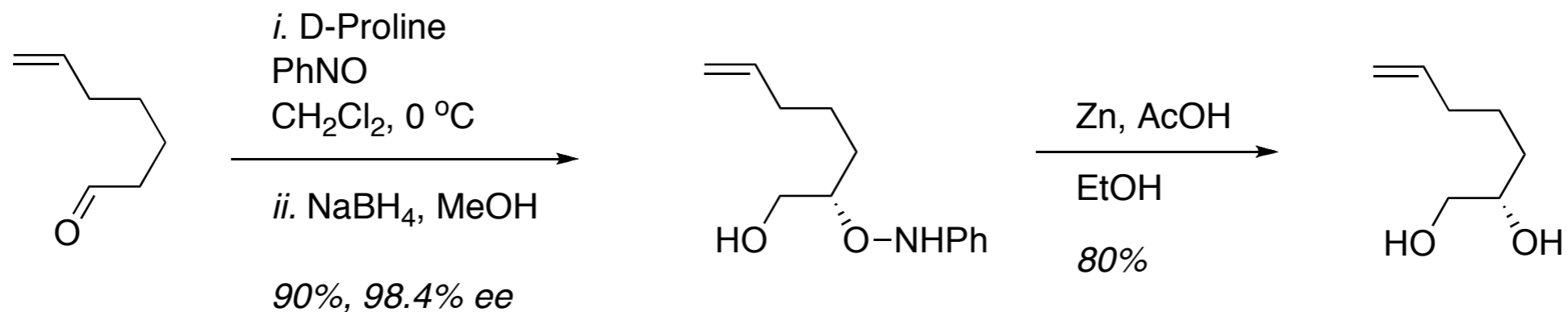
Building the *trans*-Decalin



Building the *trans*-Decalin

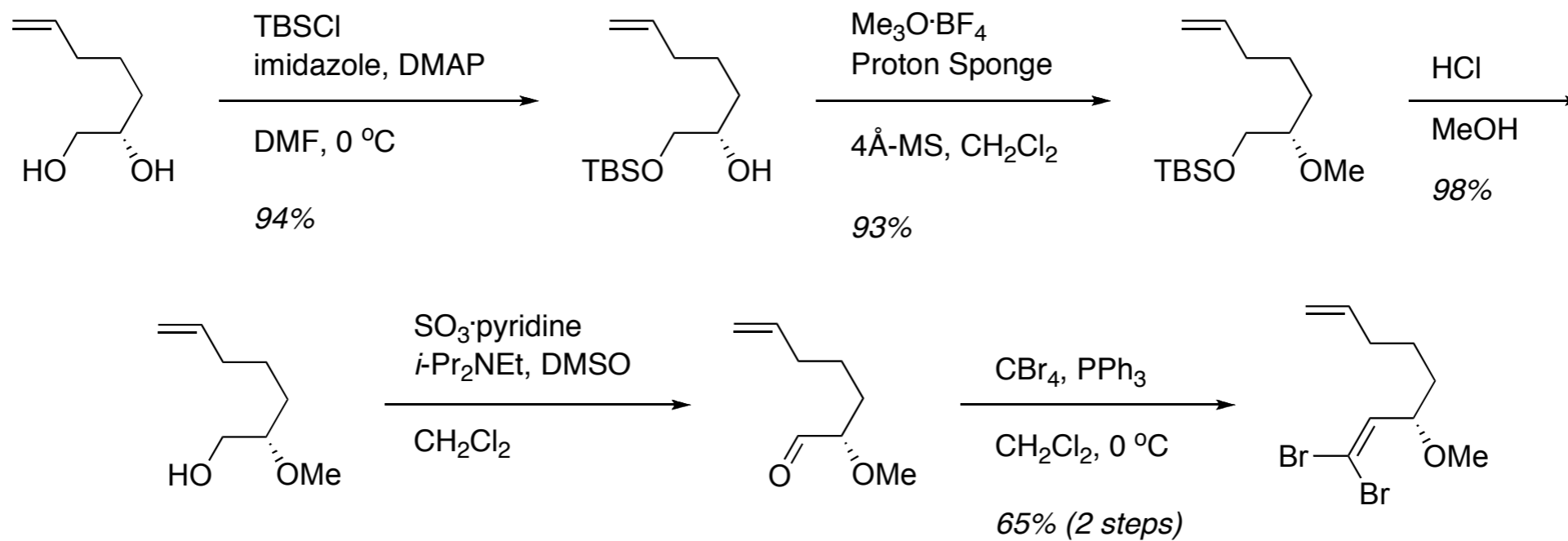


Building the *trans*-Decalin

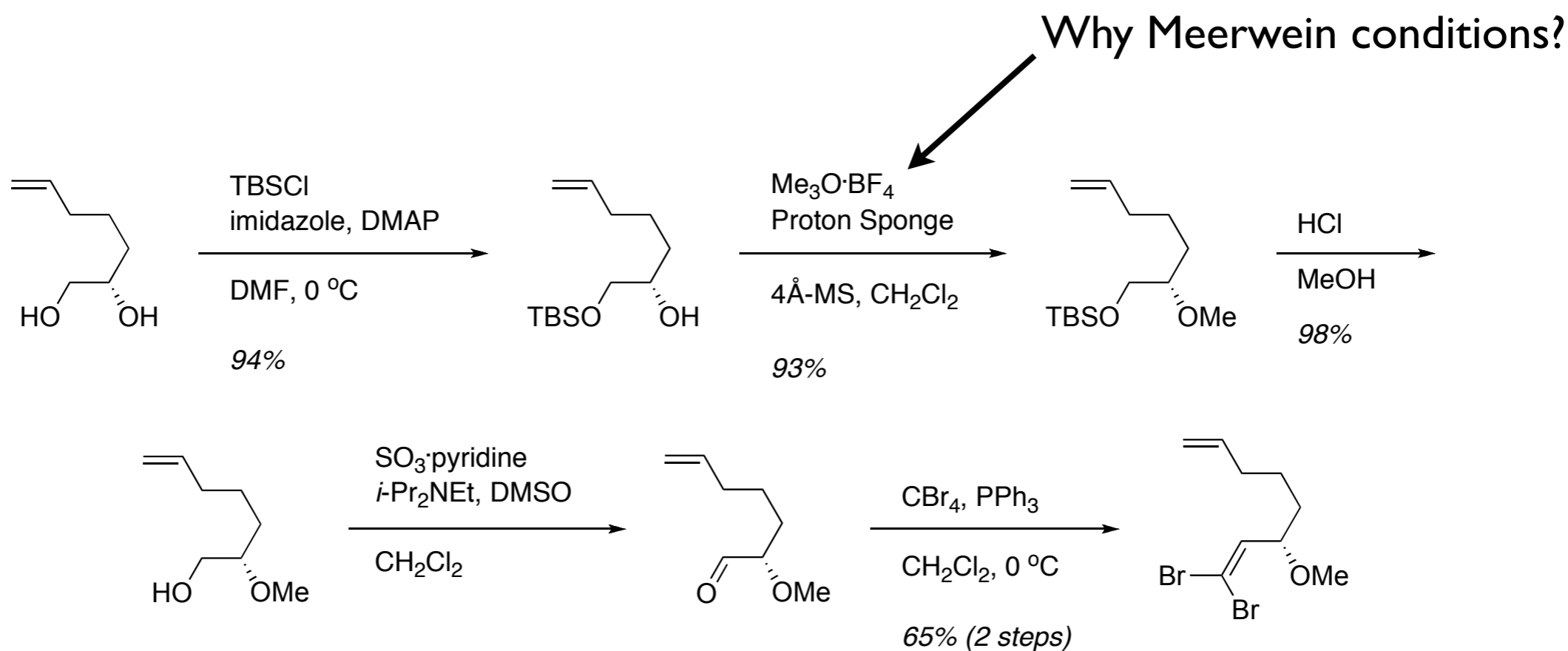


Why C-O bond formation and not C-N bond formation?

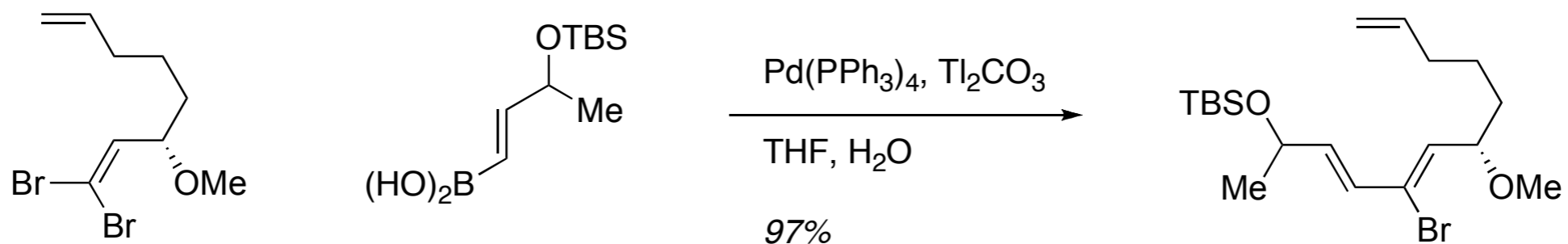
Building the *trans*-Decalin



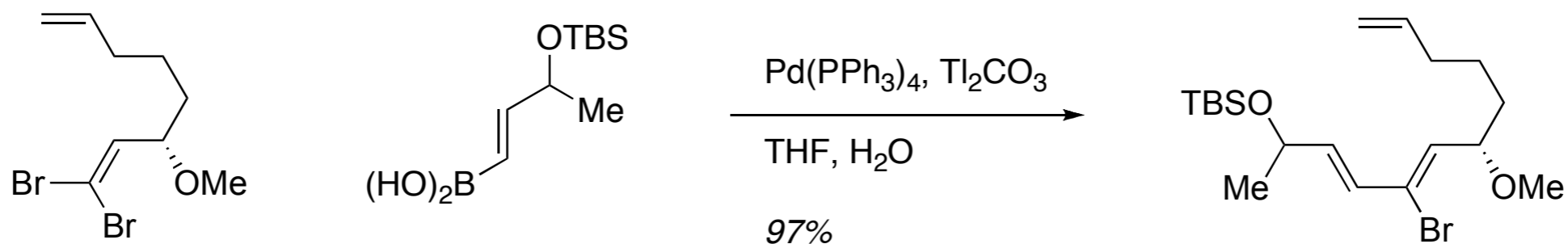
Building the *trans*-Decalin



Building the *trans*-Decalin

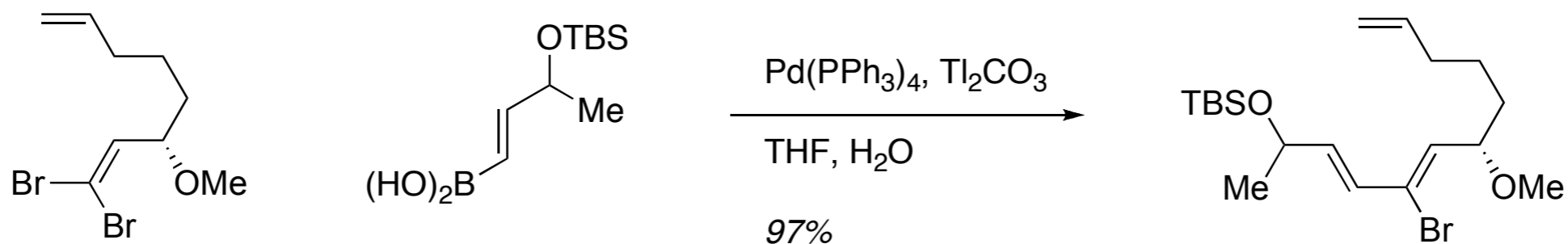


Building the *trans*-Decalin



Why is there complete selectivity for the “E”-Br?

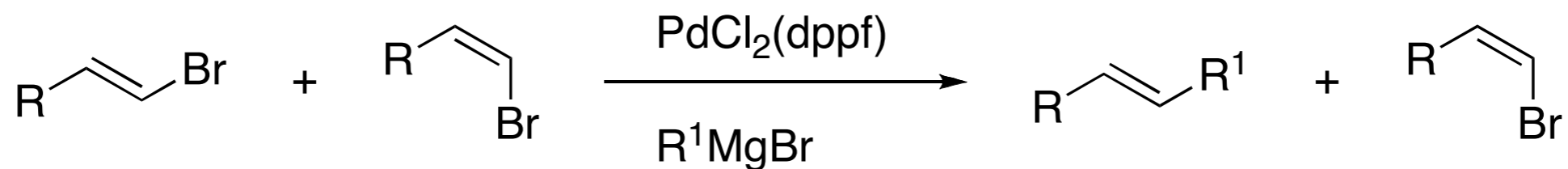
Building the *trans*-Decalin



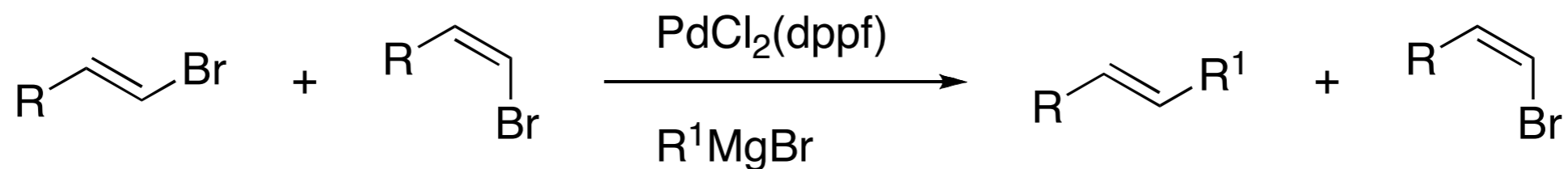
Why is there complete selectivity for the “E”-Br?

What is the role of the Ti_2CO_3 ?

Building the *trans*-Decalin

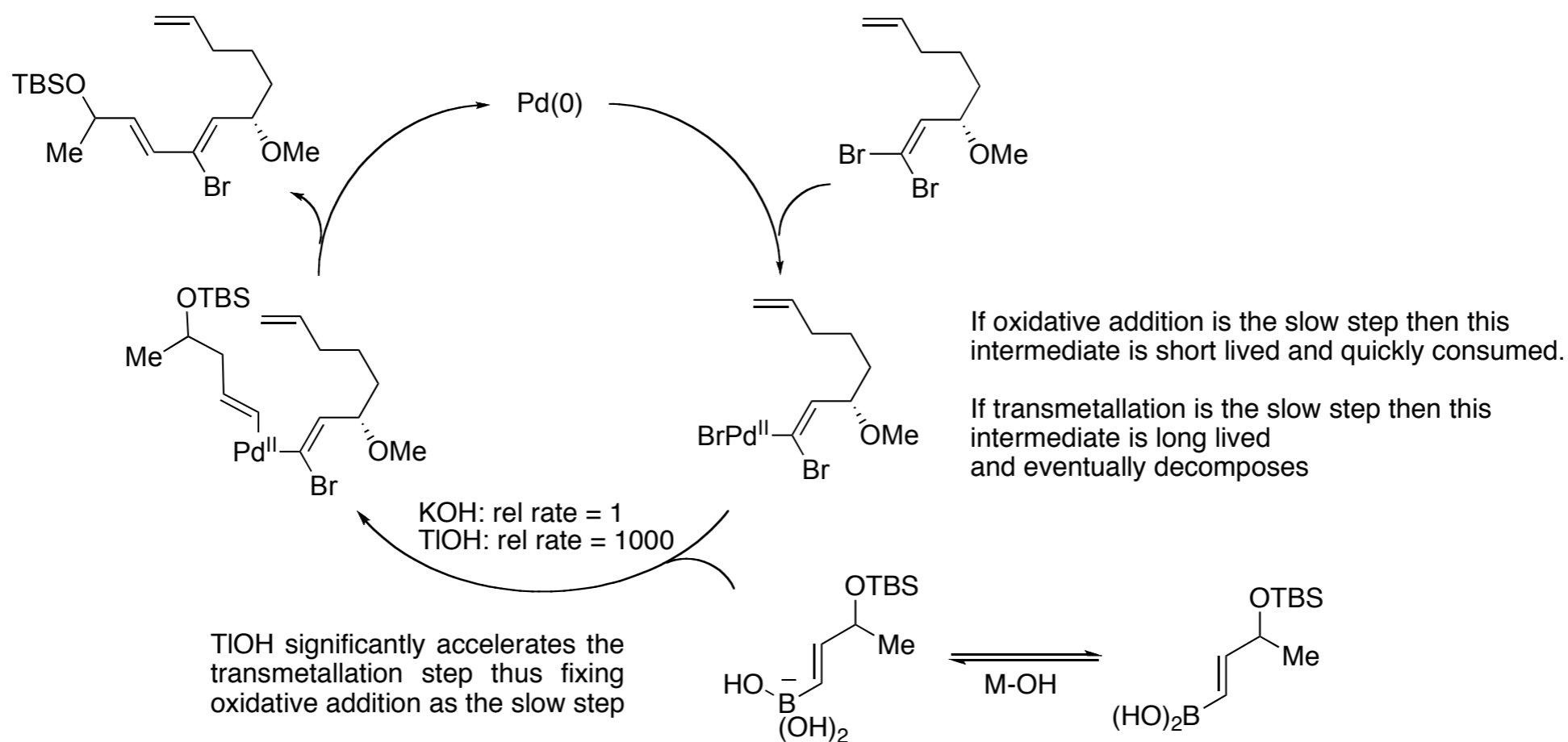


Building the *trans*-Decalin

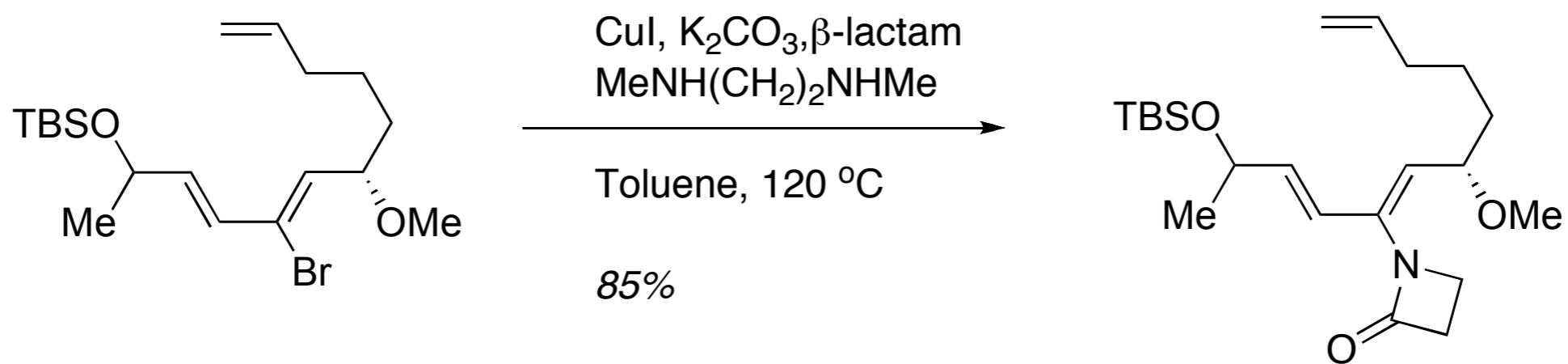


Generally, E-vinyl bromides are much more reactive than Z-vinyl bromides

Building the *trans*-Decalin

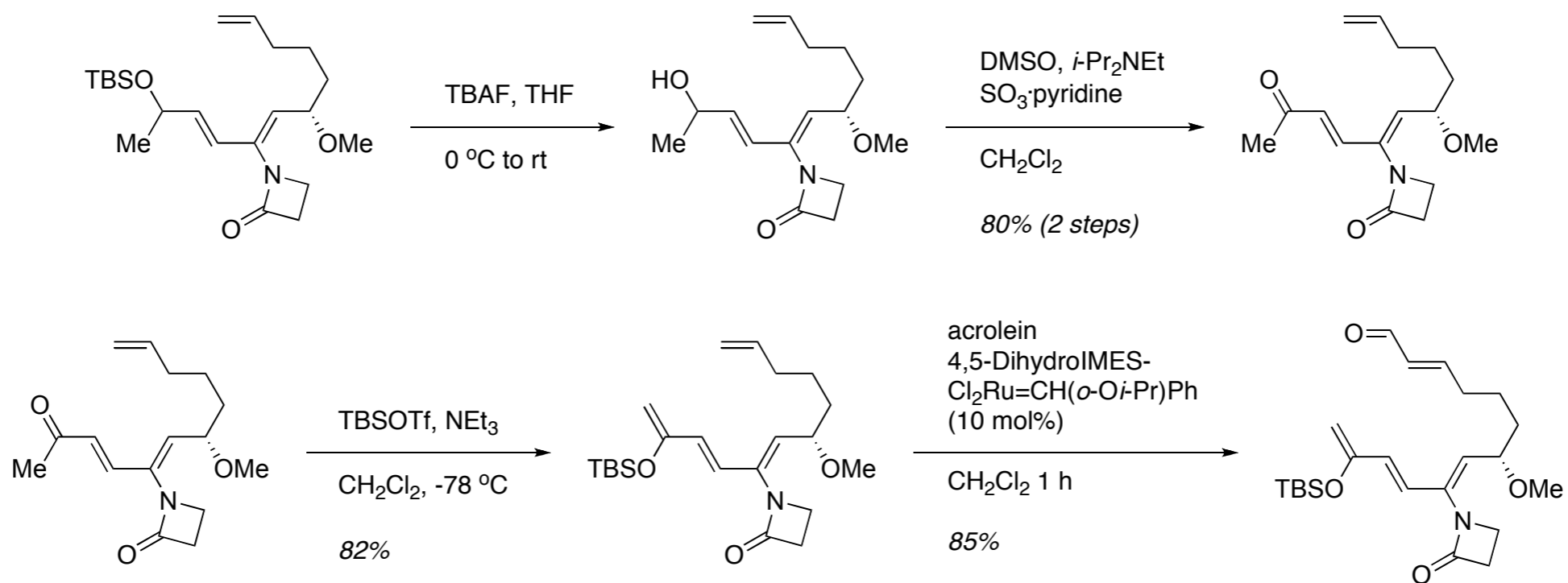


Building the *trans*-Decalin

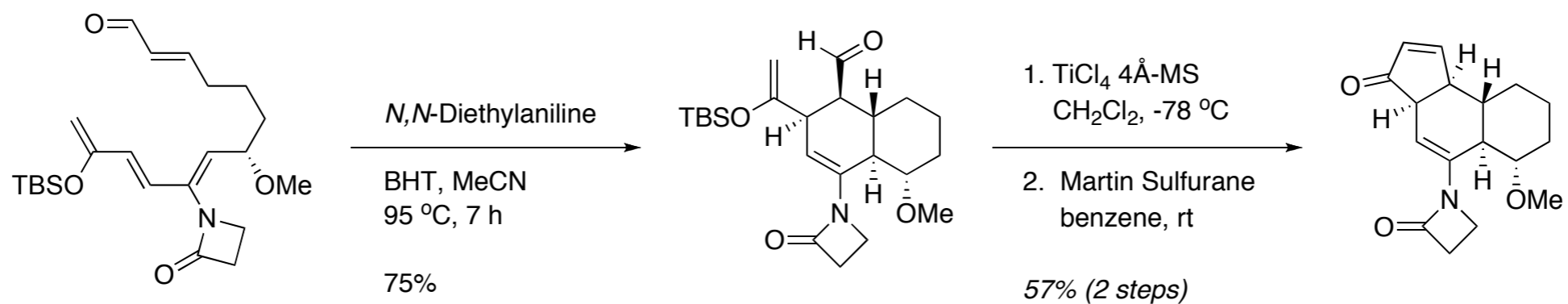


What is this even for?

Building the *trans*-Decalin

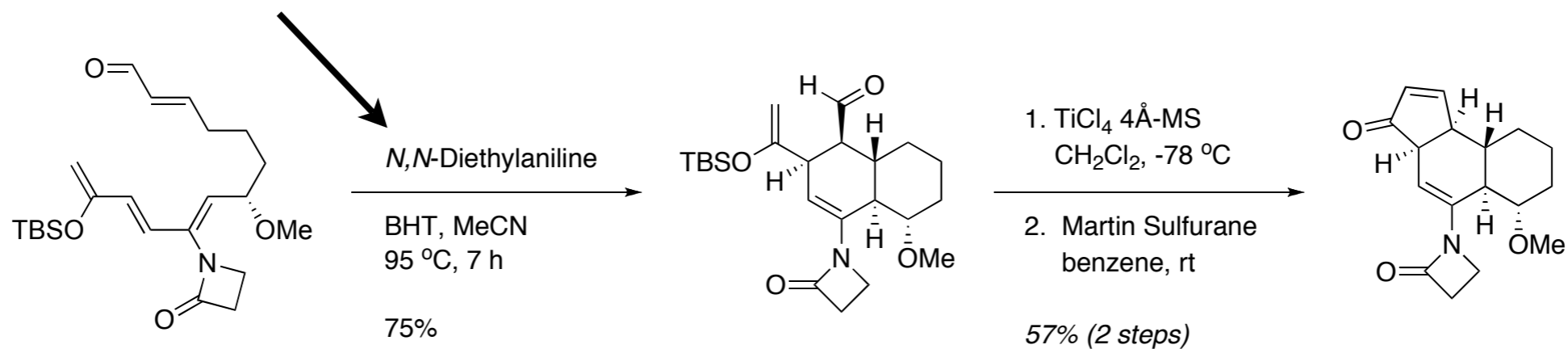


Building the *trans*-Decalin



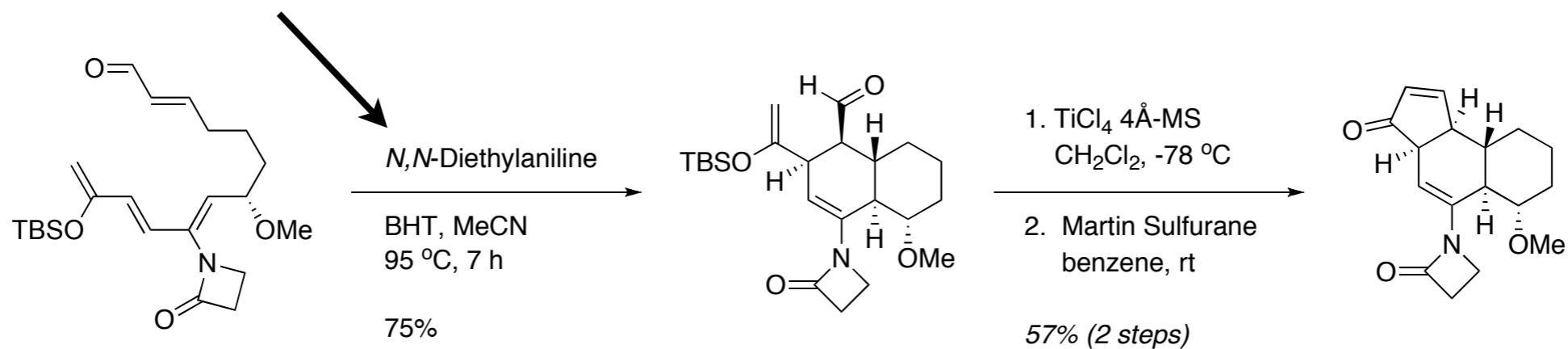
Building the *trans*-Decalin

What is this for?



Building the *trans*-Decalin

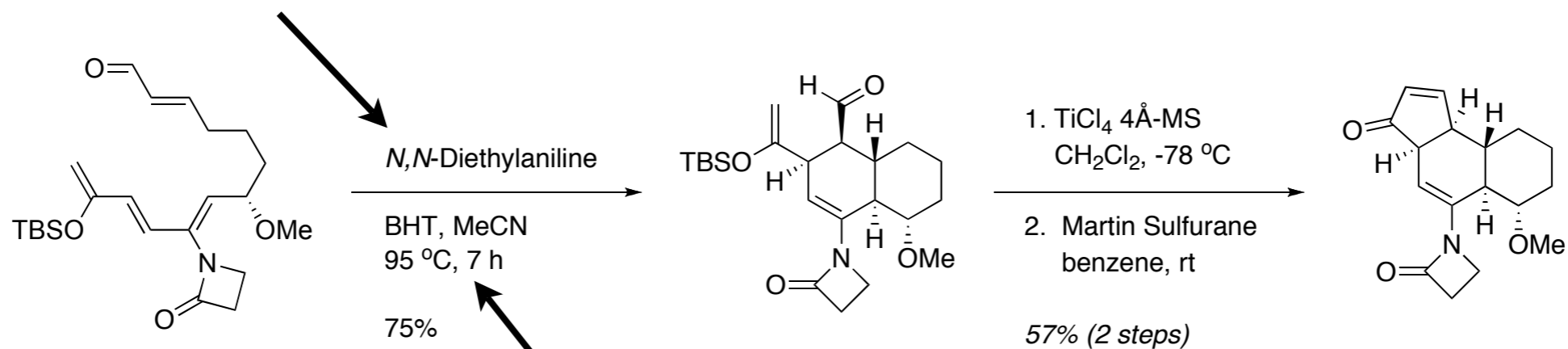
What is this for?



Enforces *s*-cis geometry

Building the *trans*-Decalin

What is this for?

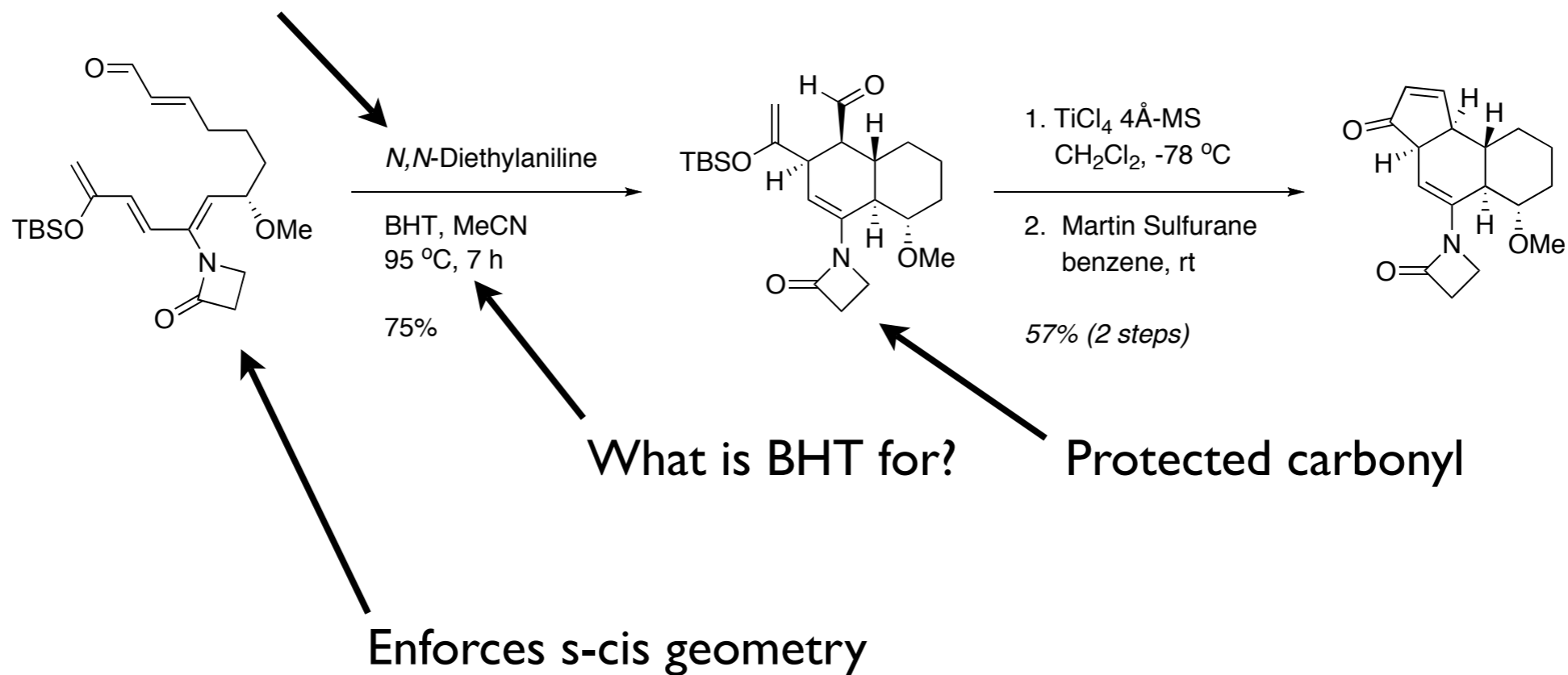


What is BHT for?

Enforces *s*-cis geometry

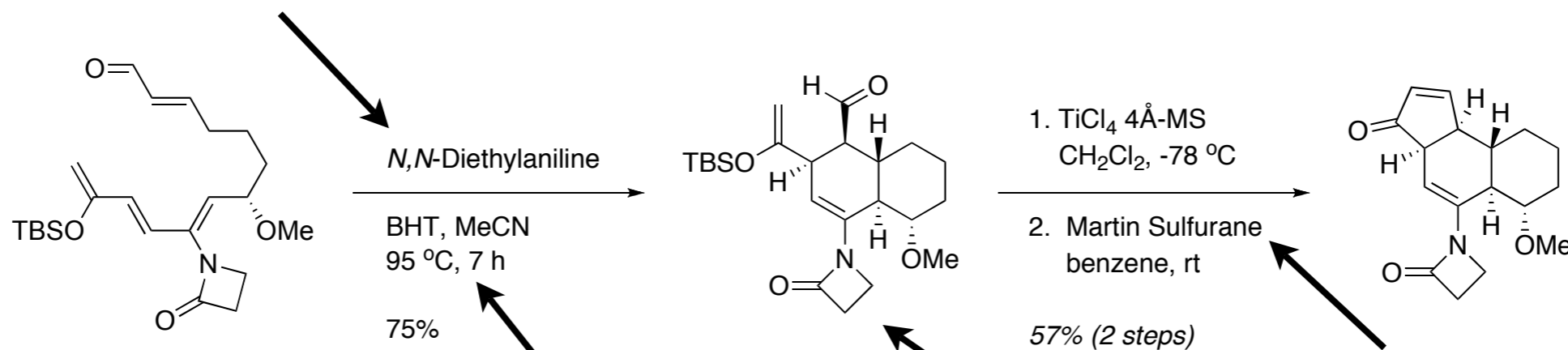
Building the *trans*-Decalin

What is this for?



Building the *trans*-Decalin

What is this for?

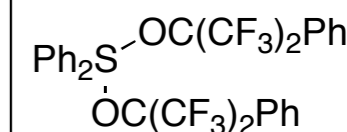


Why Martin Sulfurane?

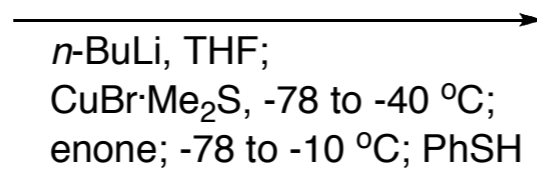
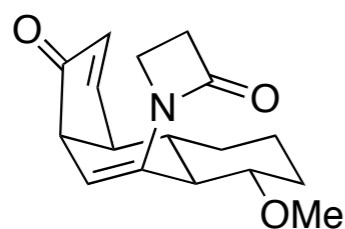
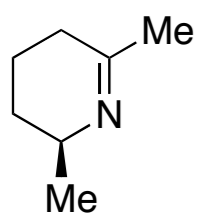
What is BHT for?

Protected carbonyl

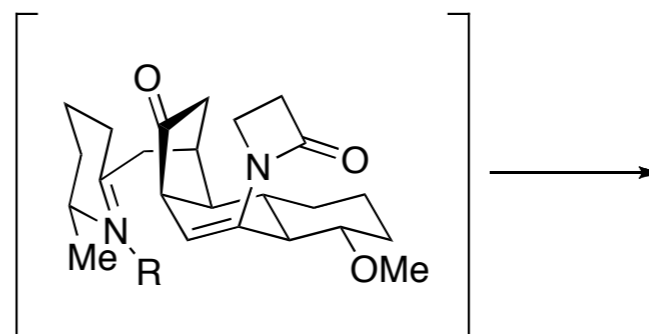
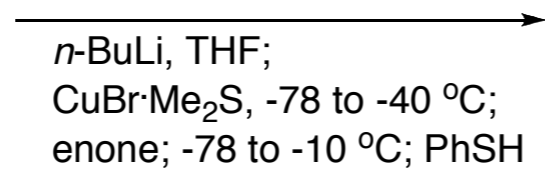
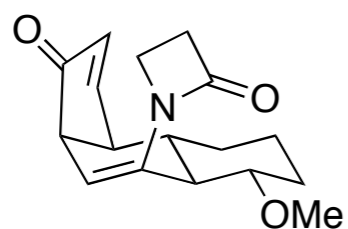
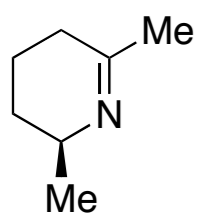
Enforces *s*-cis geometry



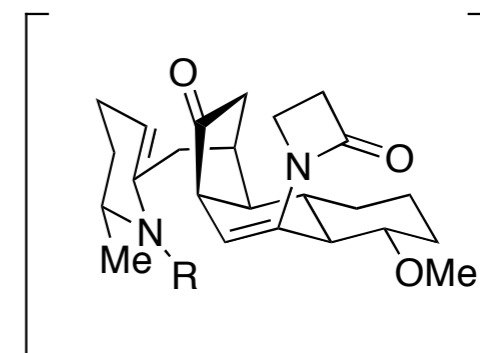
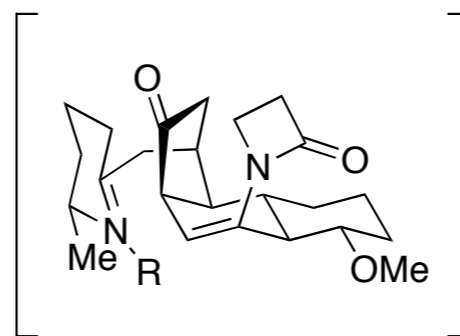
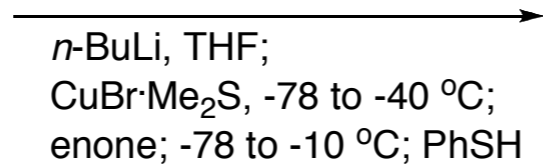
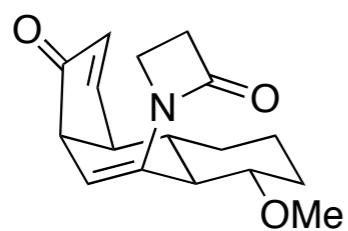
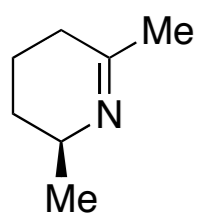
The Cyclohexylamine



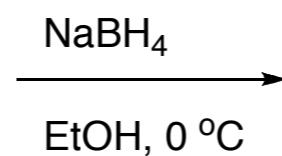
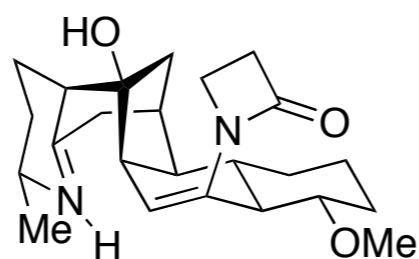
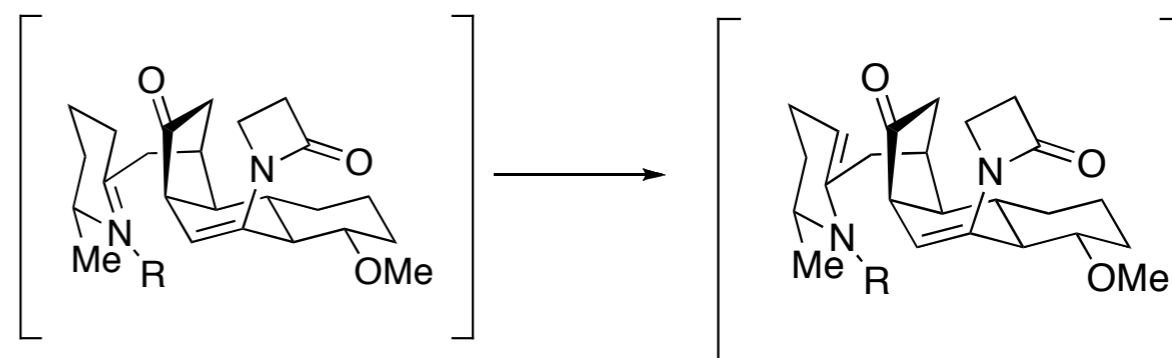
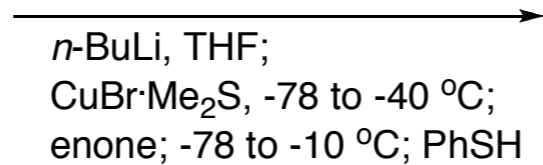
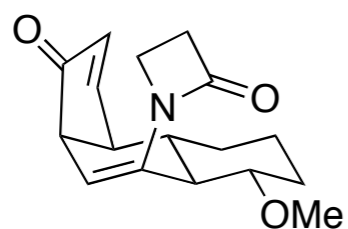
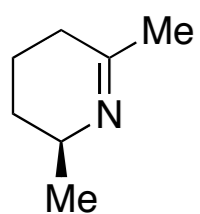
The Cyclohexylamine



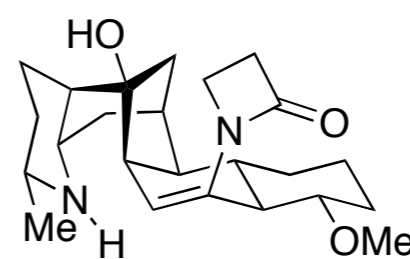
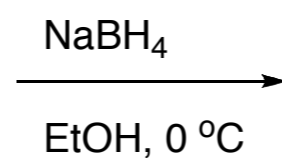
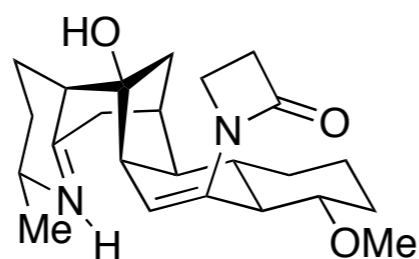
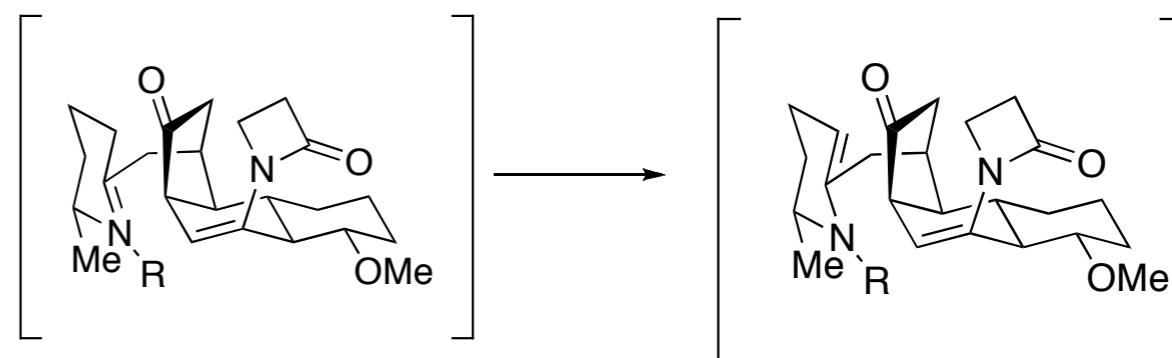
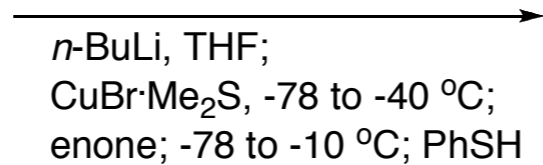
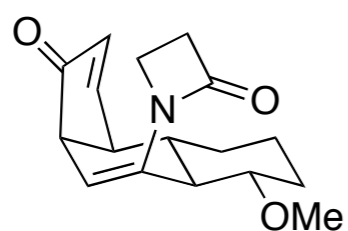
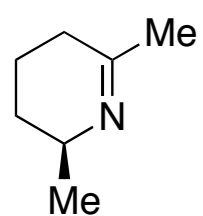
The Cyclohexylamine



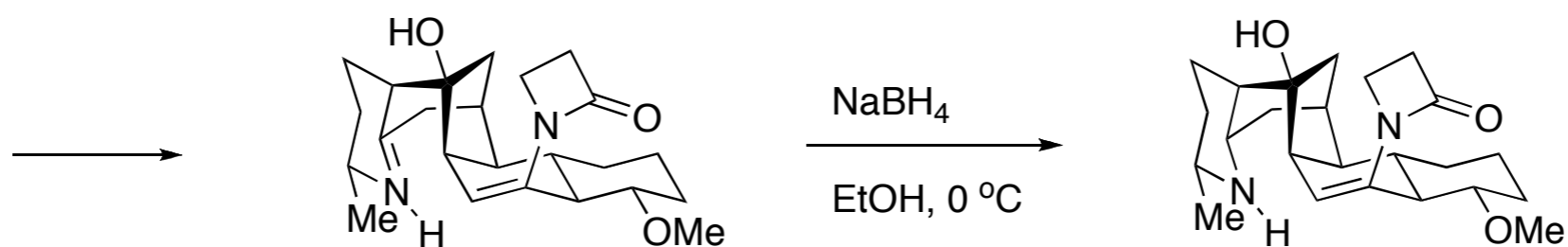
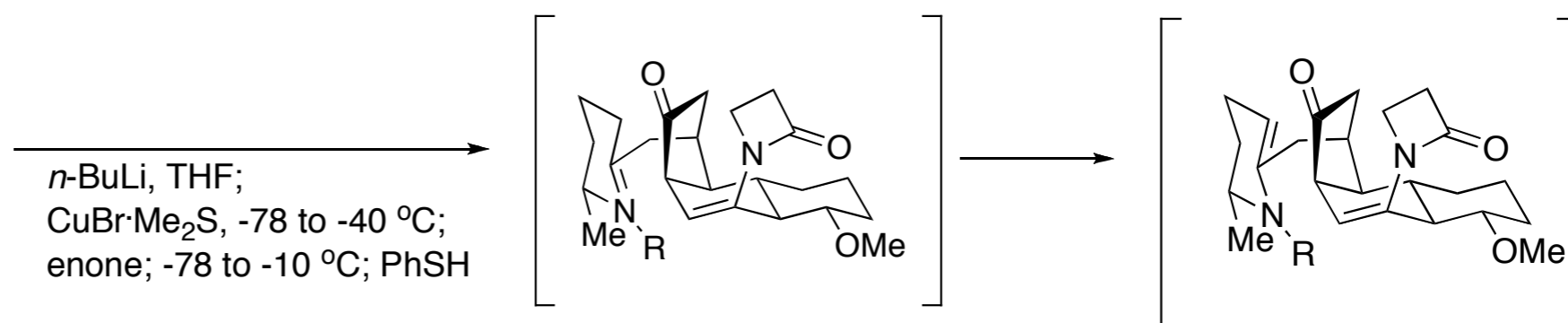
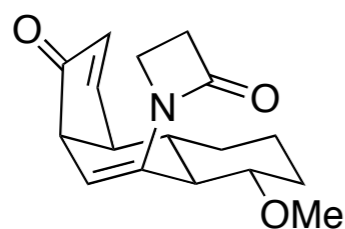
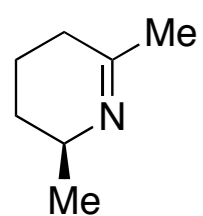
The Cyclohexylamine



The Cyclohexylamine

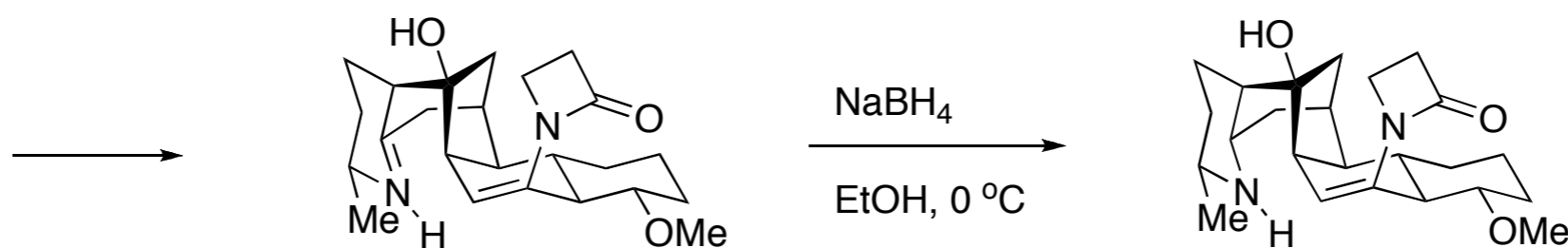
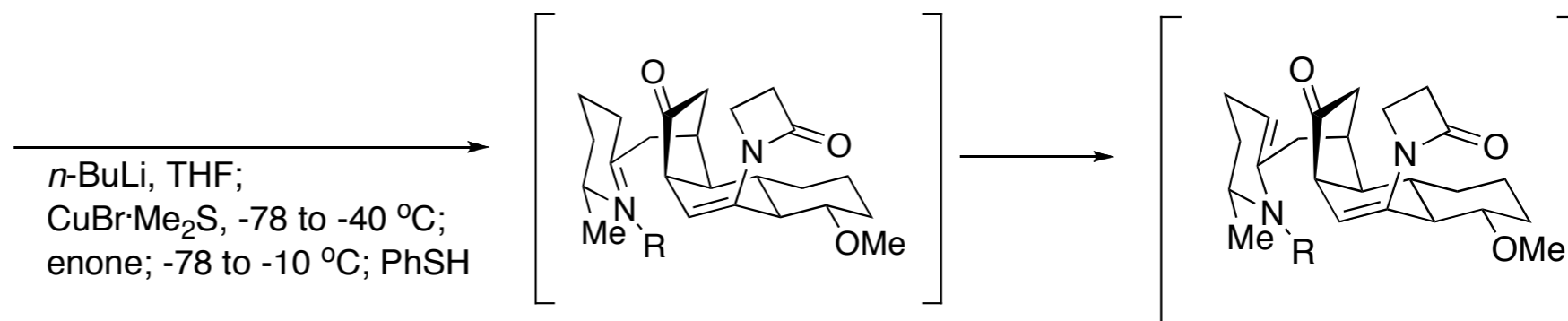
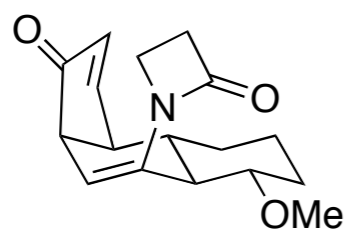
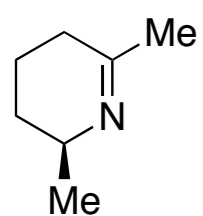


The Cyclohexylamine



complete selectivity

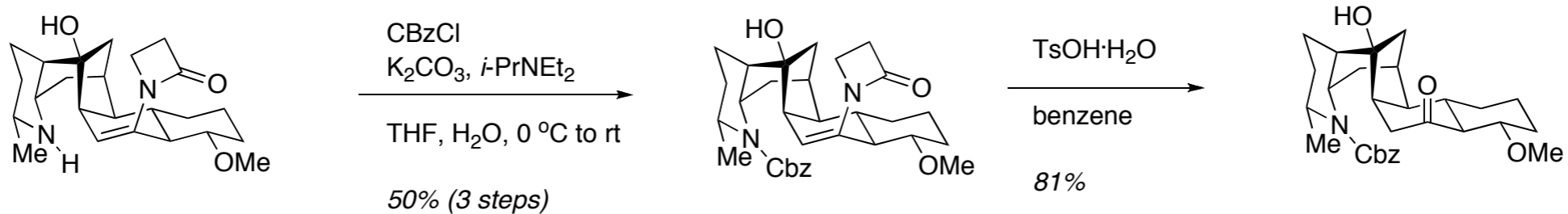
The Cyclohexylamine



complete selectivity

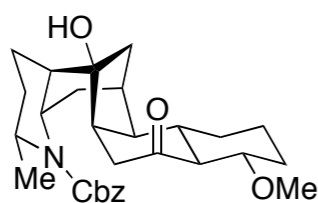
2-azetidinone still in place
to protect the carbonyl

PG Adjustments



still rockin the
2-azetidinone

Installing the Methyl Ester

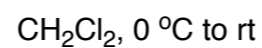
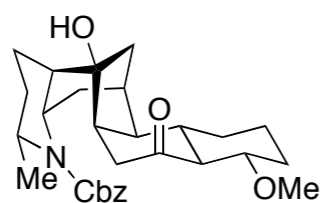


POCl₃, DMF

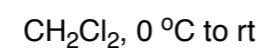
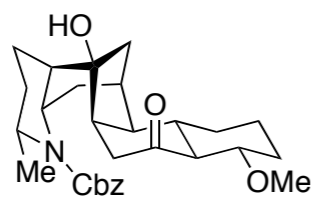
CH₂Cl₂, 0 °C to rt

71%

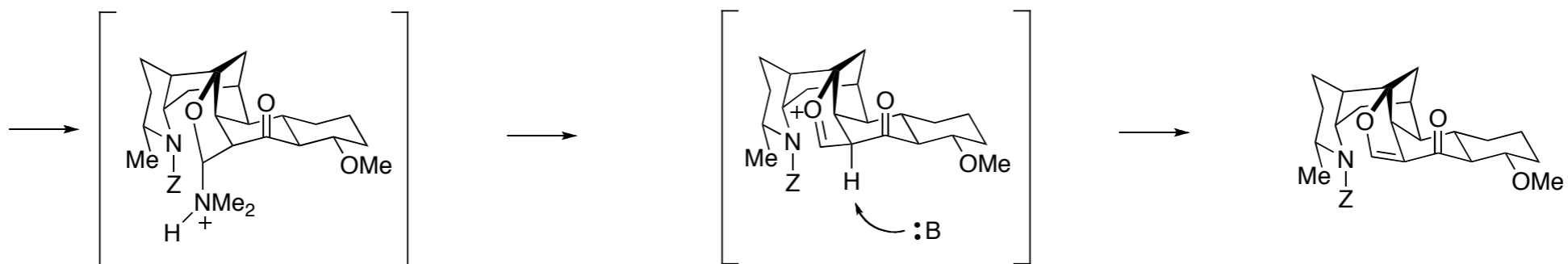
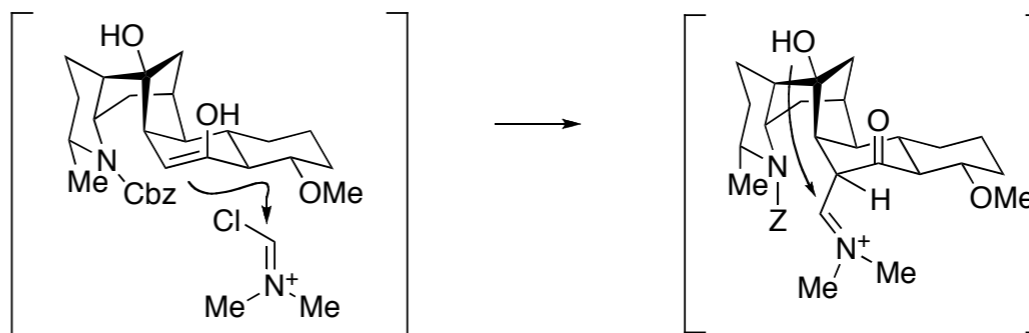
Installing the Methyl Ester



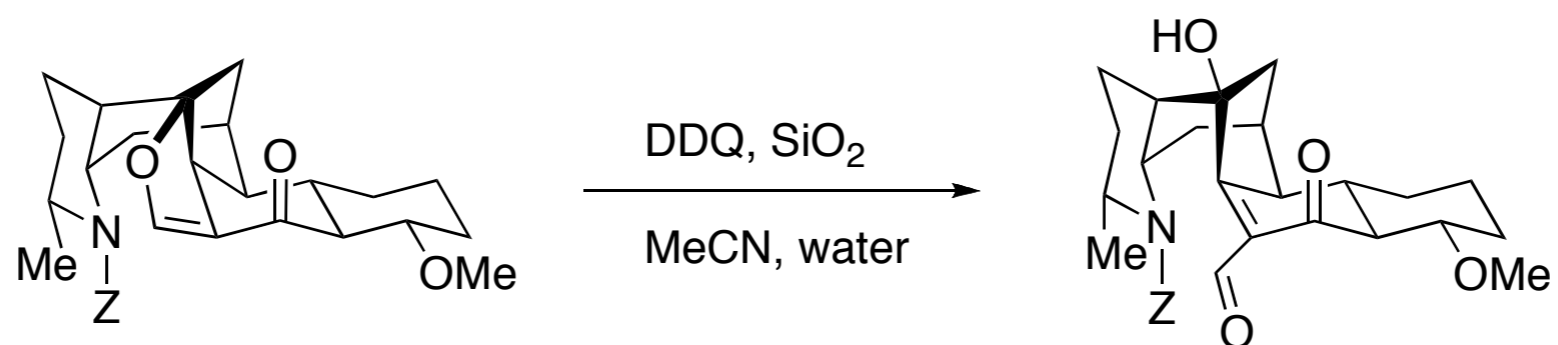
71%



71%

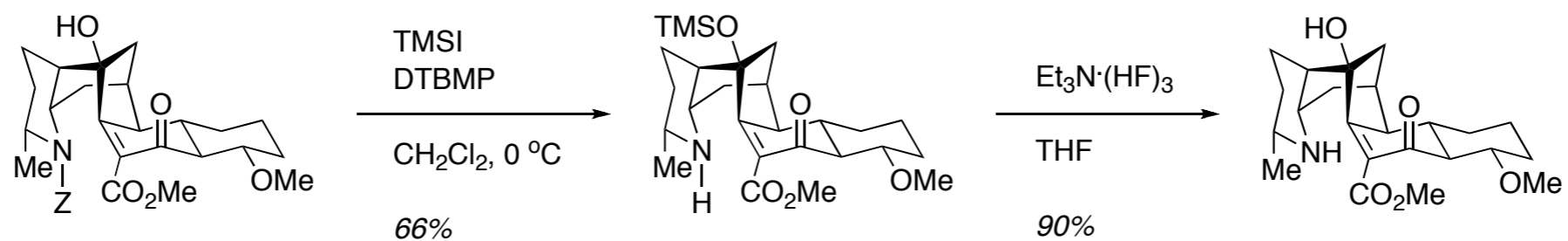
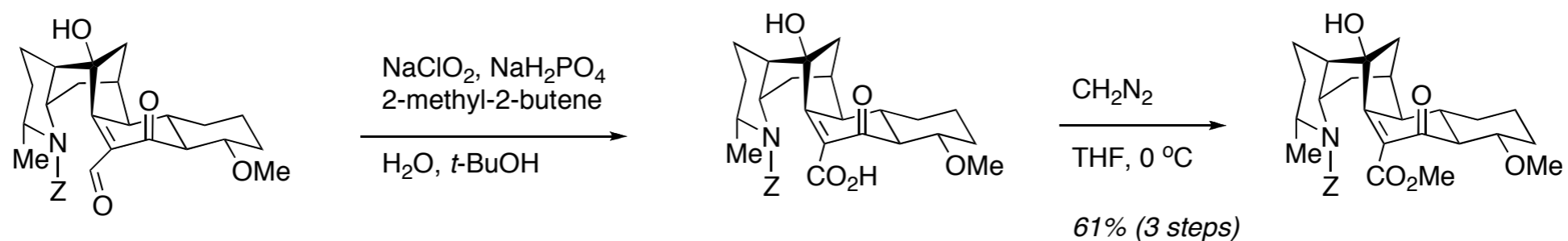


Getting Rid of the Enol

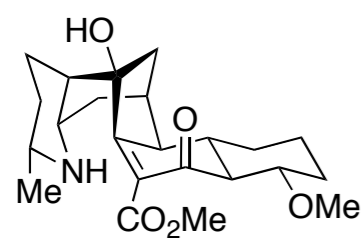


Would anyone like to suggest a mechanism?

Installing the Methyl Ester



Almost There!

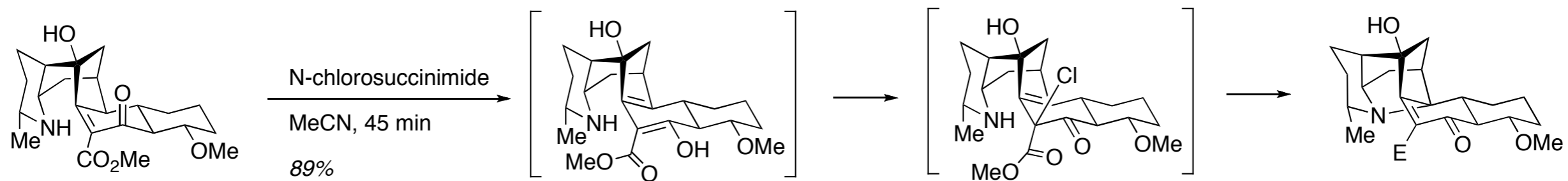
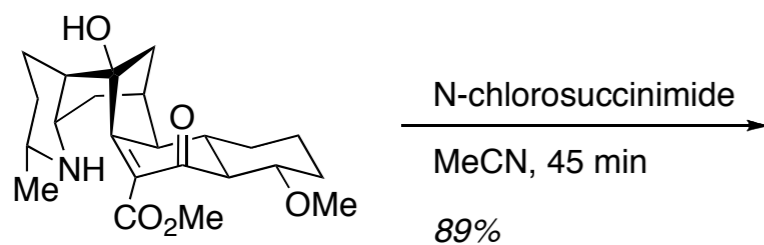


N-chlorosuccinimide

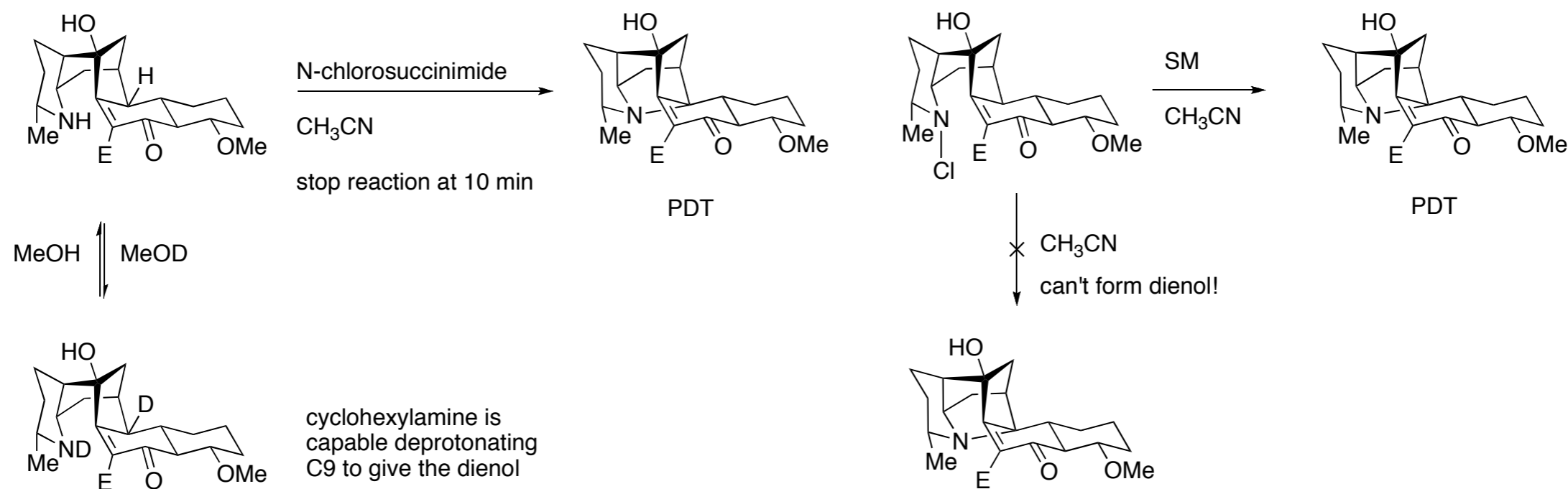
MeCN, 45 min

89%

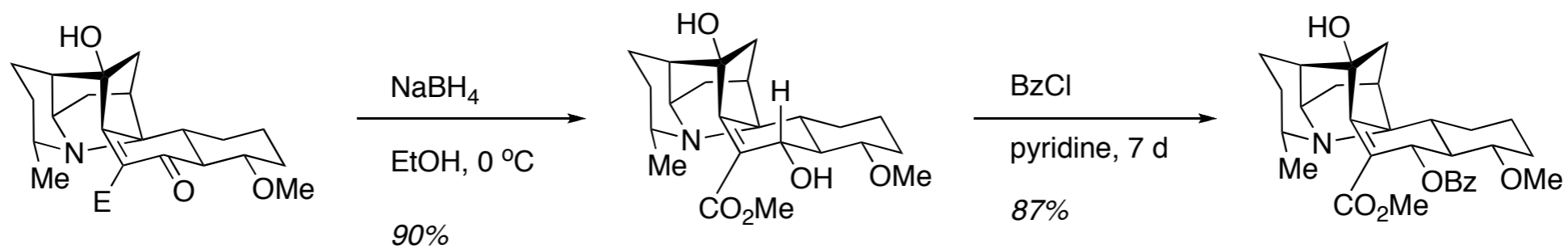
Almost There!



Also of Interest



Finished



Yet another completely
selective NaBH_4 reduction

Conclusions

- Total synthesis completed in 27 steps.
- Proline catalyzed alpha-aldehyde oxidation provided the stereocenter that lead to the formation of all other stereocenters under substrate control.
- Demonstrated sequential cross-coupling reactions from a dibromoolefin.
- Transannular IMDA.
- Conjugate addition-Mannich reaction to incorporate the cyclohexylamine.
- NCS mediated late stage ring closure.