Total Synthesis of (*S*)-Cularine via Nucleophilic Substitution on a Catechol

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OL | Organic Letters

Org. Lett. 2021, 23, 236–241

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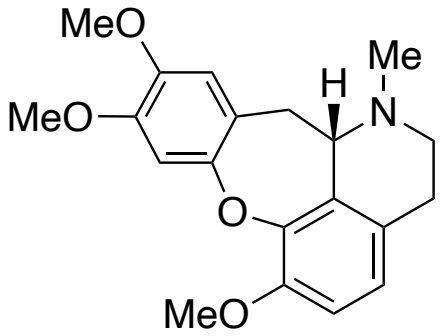
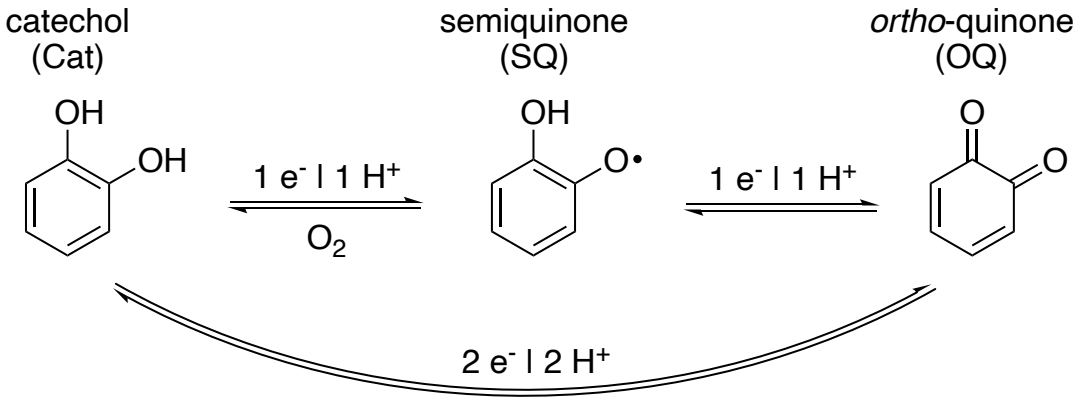
Liu Research Group
February 24th, 2021

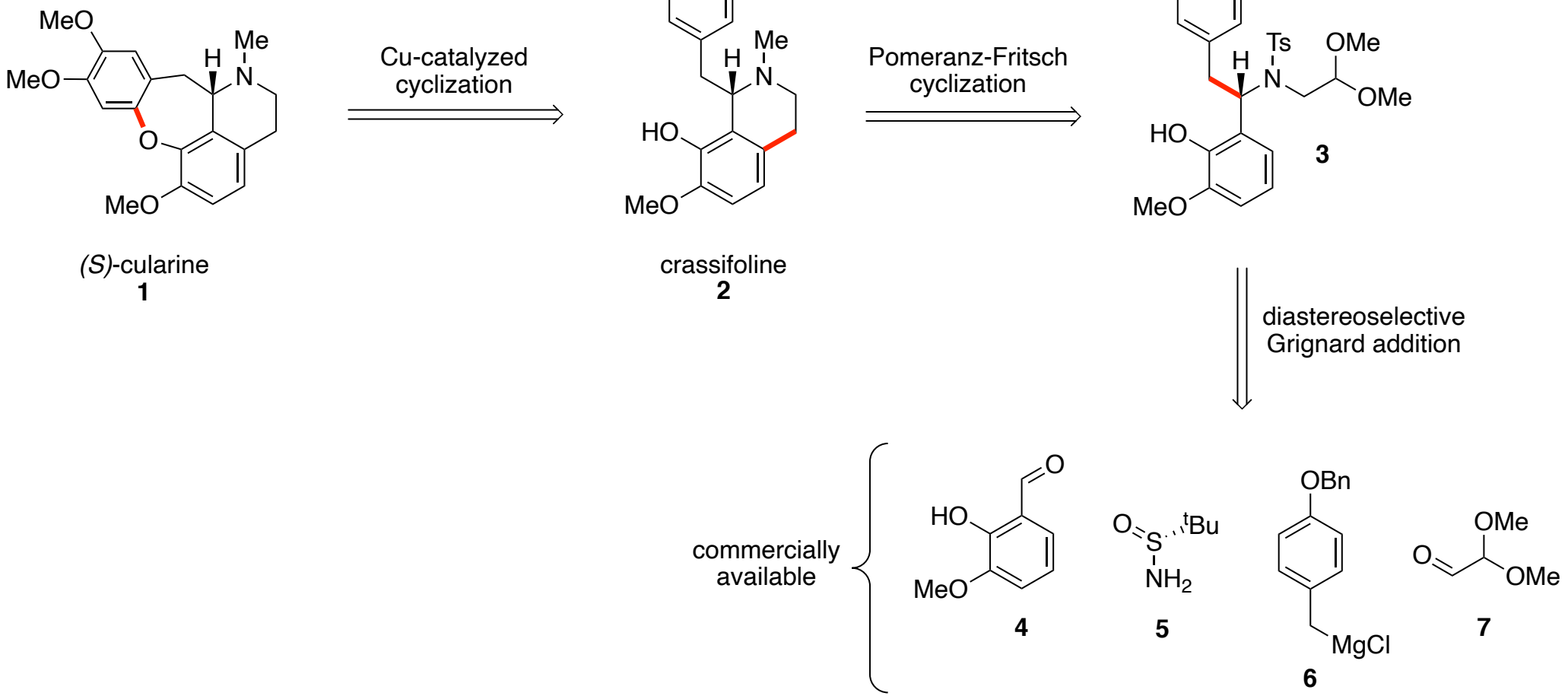
- Found in plants of the *Dicentra* and *Corydalis* families (poppies).
- Parent compound for the cularine group of isoquinoline alkaloids.
  - Biosynthesized from crassifoline by oxidative cyclization.
- Challenging due to 1,7,8-trisubstituted tetrahydroisoquinoline core and catechol moiety:
- <u>This work</u>: concise enantioselective total synthesis of *(S)*-cularine through a mild, formal S_NAr on an electron-rich catechol.

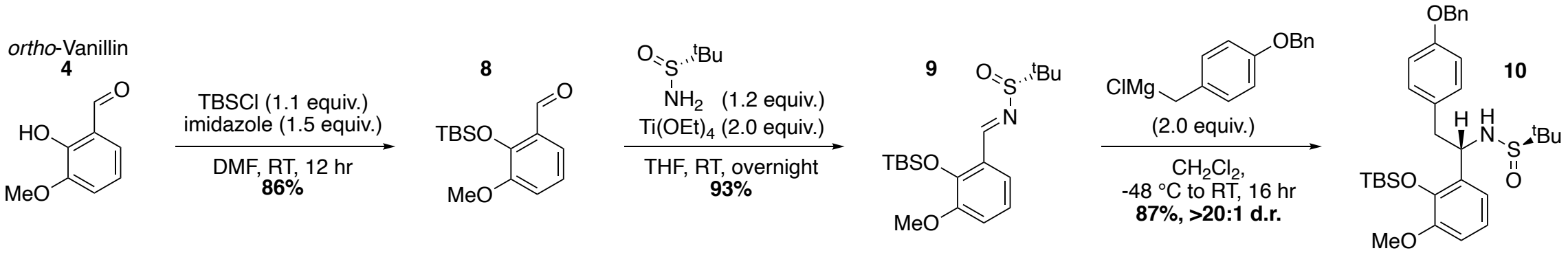


(S)-cularine

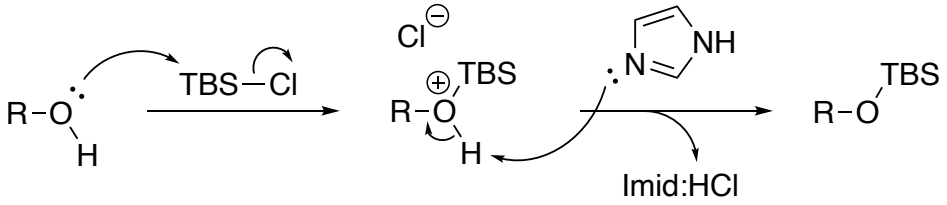


Retrosynthetic Analysis:

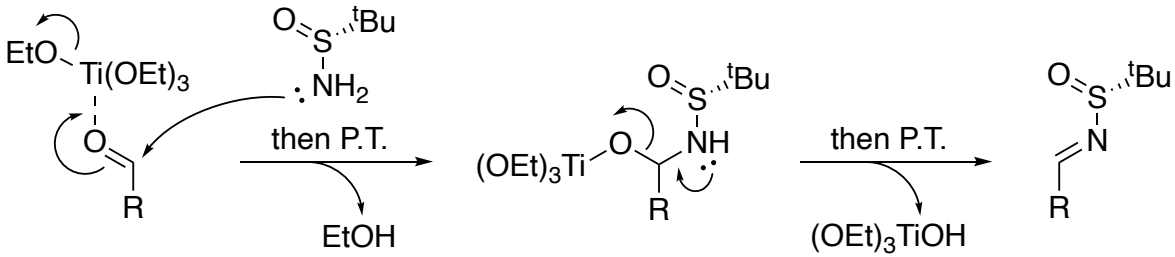




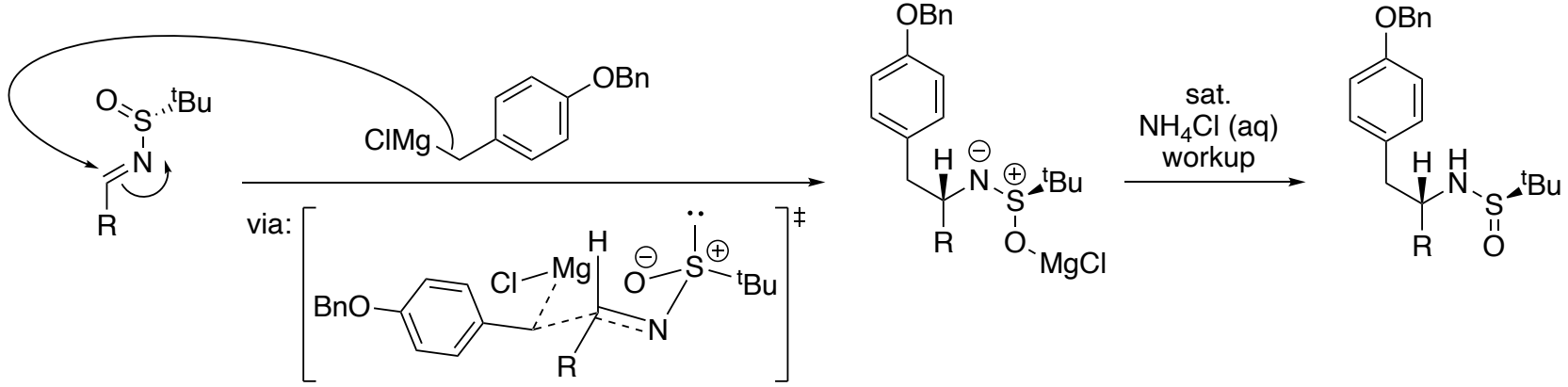
TBS Protection:

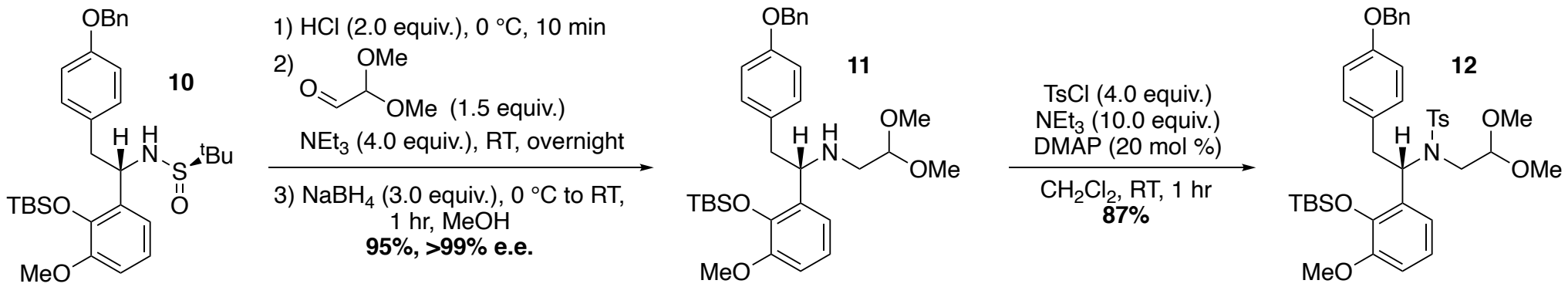


Titanium-Mediated Condensation:

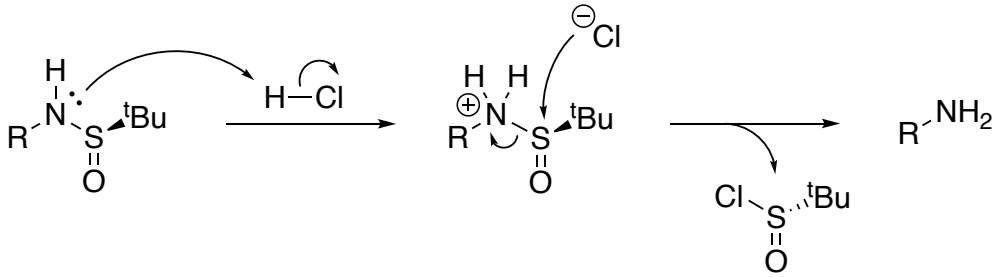


Diastereoselective Grignard Addition:

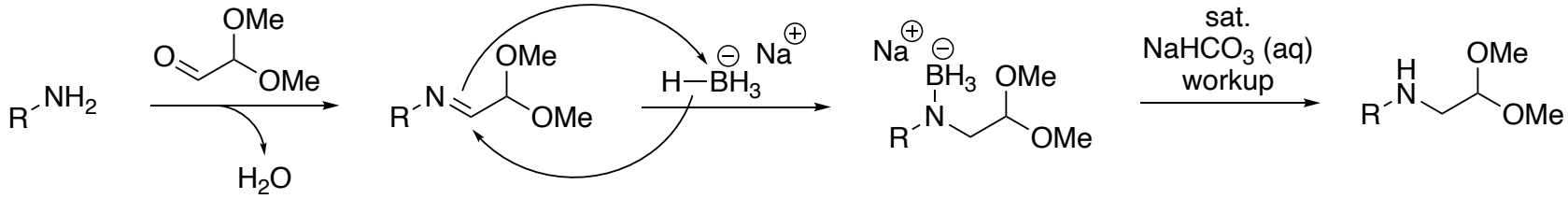




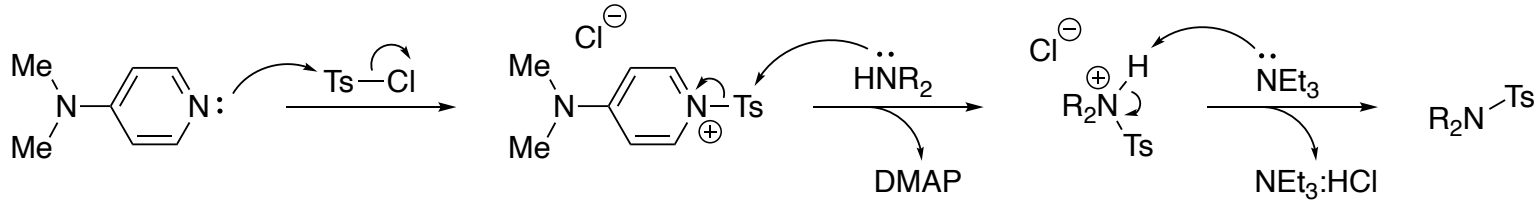
Chiral Auxiliary Removal:

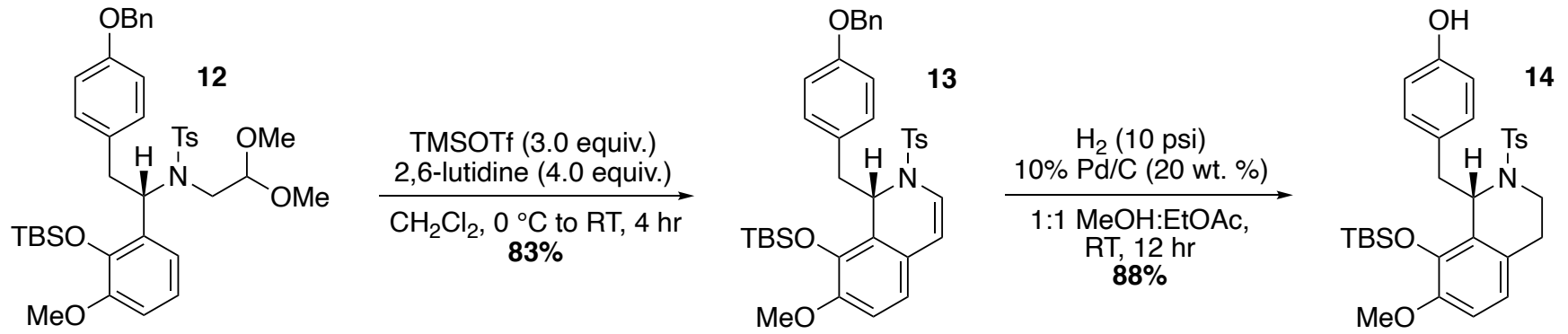


Reductive Alkylation:

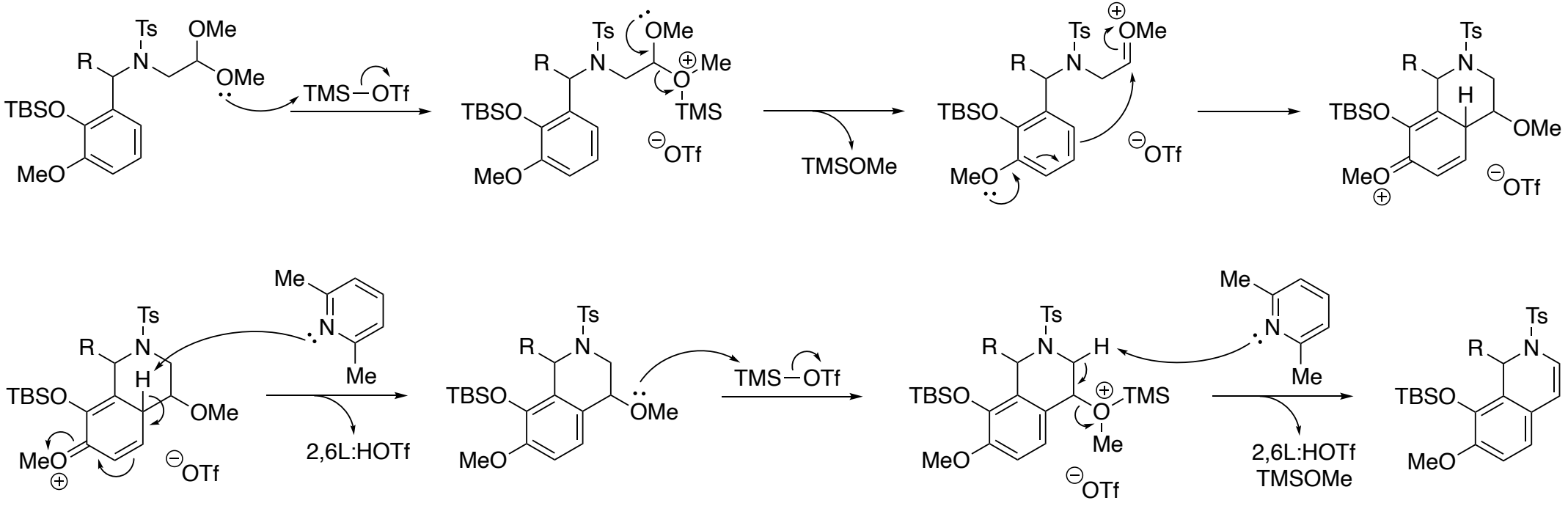


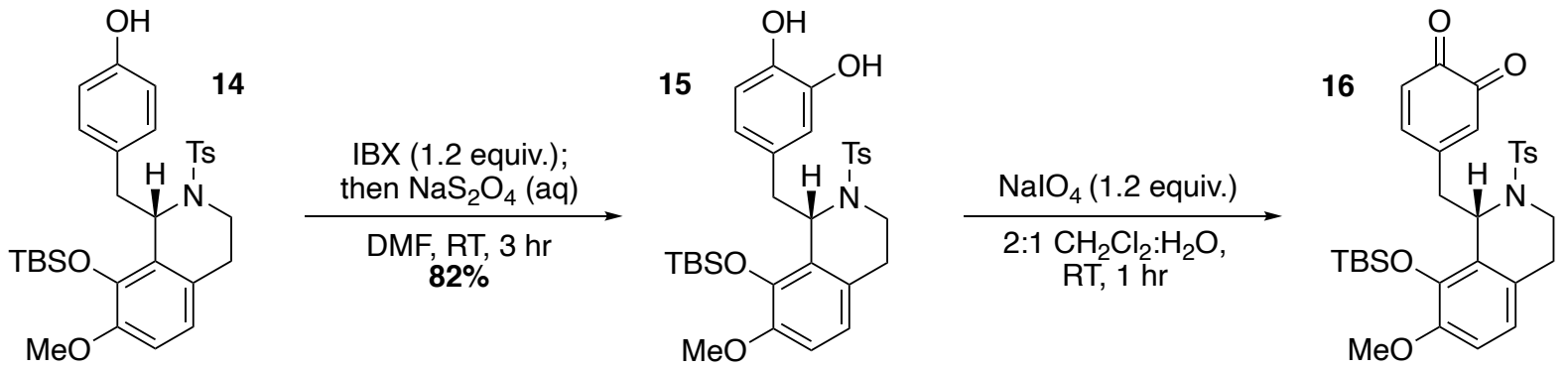
Amine Tosylation:



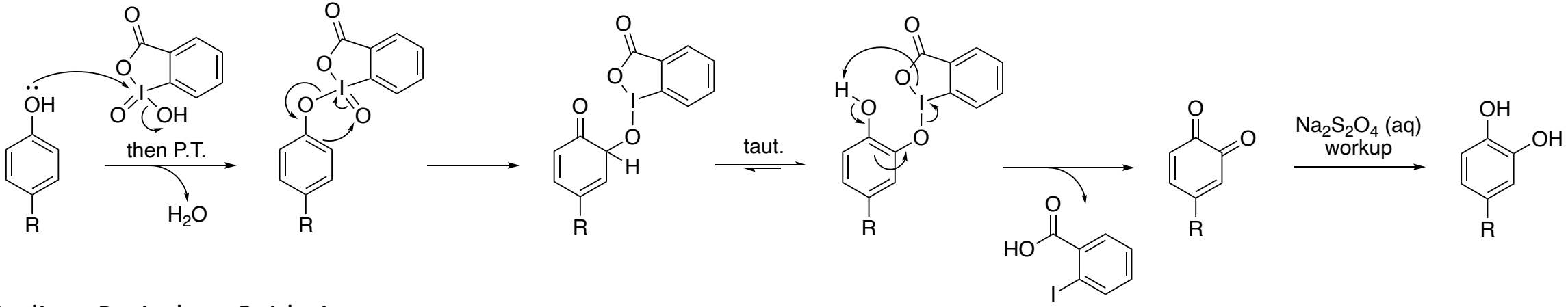


Pomeranz-Fritsch Cyclization:

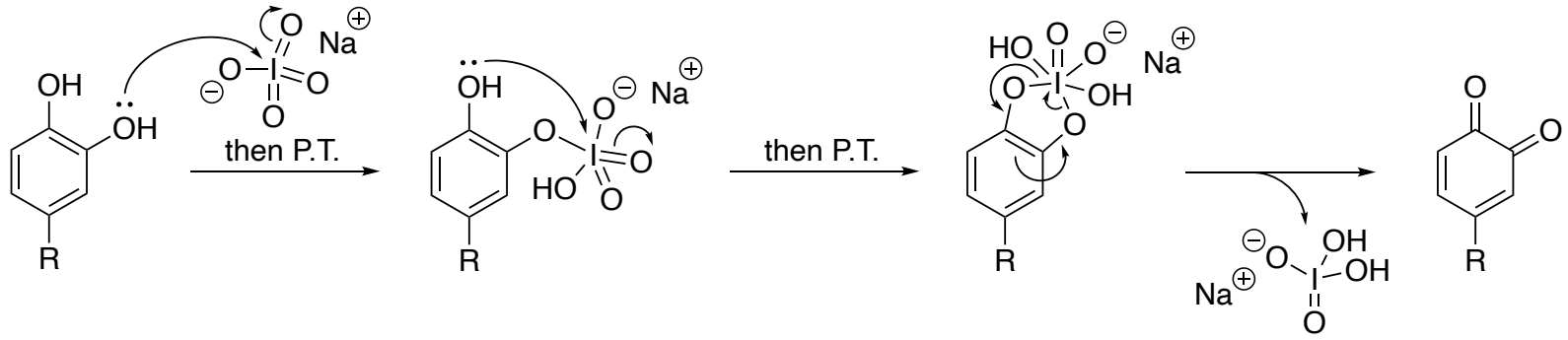


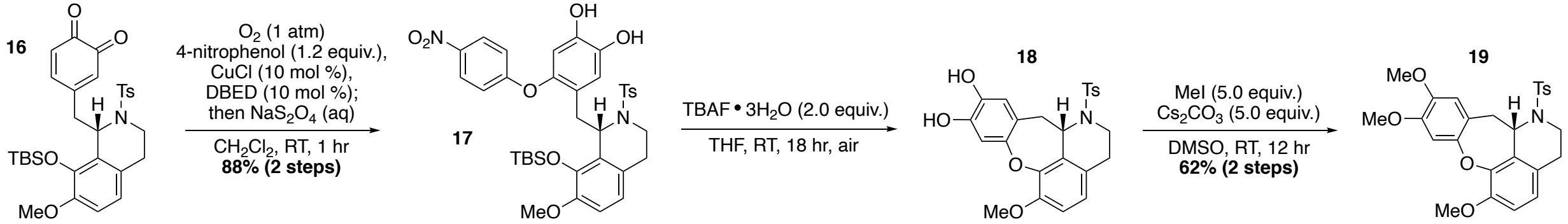


IBX Oxidation:

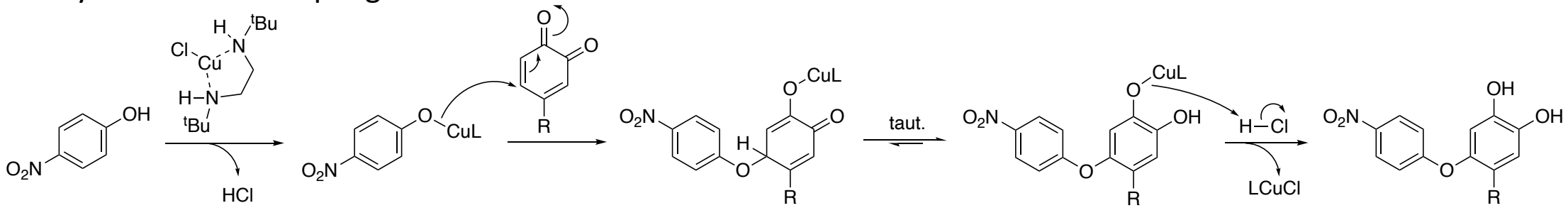


Sodium Periodate Oxidation:

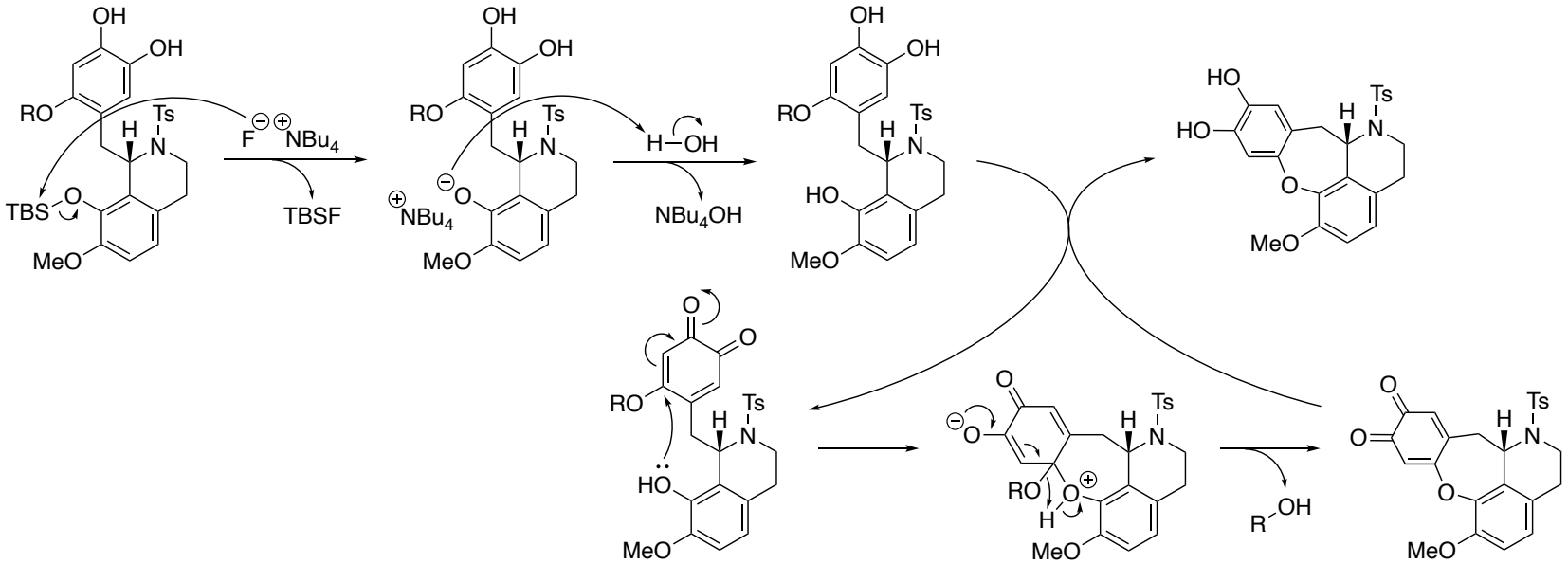




Cu-Catalyzed Aerobic Coupling:



TBAF Deprotection/Cyclization:



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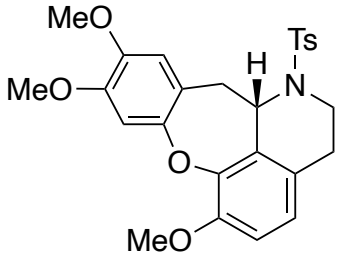
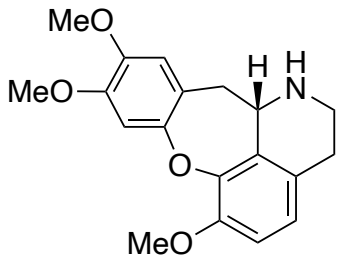


LiNap (4.0 equiv.)

THF, -78 °C, 2 hr

90%

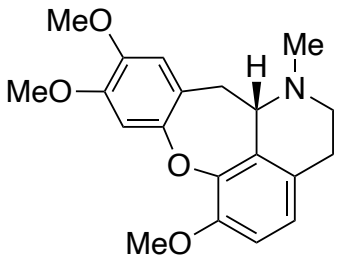
20



CH_2O (2 equiv.);
then $NaBH_4$ (5.0 equiv.)

MeOH, 0 °C to RT, 5 hr

81%



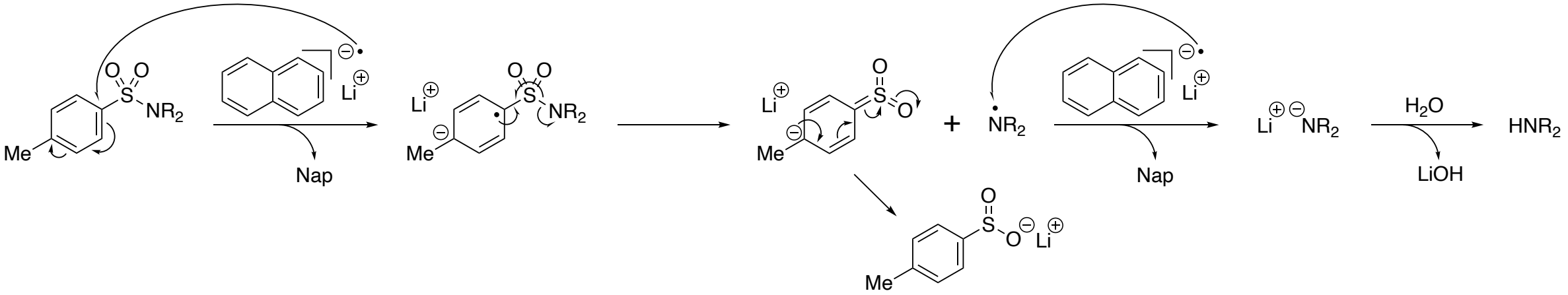
(S)-cularine

1

14 steps LLS

15% overall yield

Lithium Naphthalenide Deprotection:



Amine Methylation: