

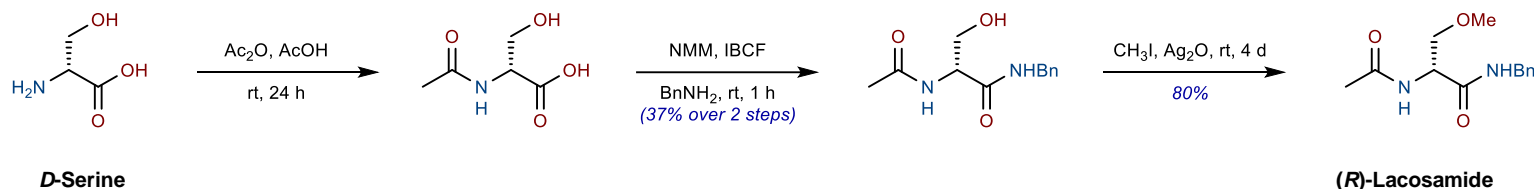
Medicinal use:



- (R)-Lacosamide treats epileptic seizures
- 70% of people could become seizure free with proper treatment.
- active ingredient in Vimpat, introduced by UCB Pharma in 2008



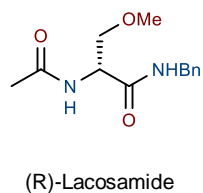
Starting point:



- Final step results in epimerization
- Solution to this problem discovered by Choi *et al.*
- However, 5 eq. and a 4 day stir time are still limiting
- 3 steps, 30% overall yield

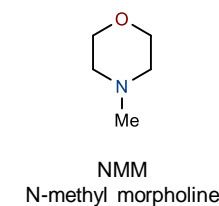
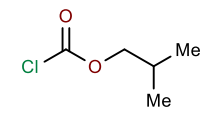
J. Med. Chem. **1996**, 39, 1907
<https://pubs.acs.org/doi/10.1021/jm9508705>

Synthesis challenge:



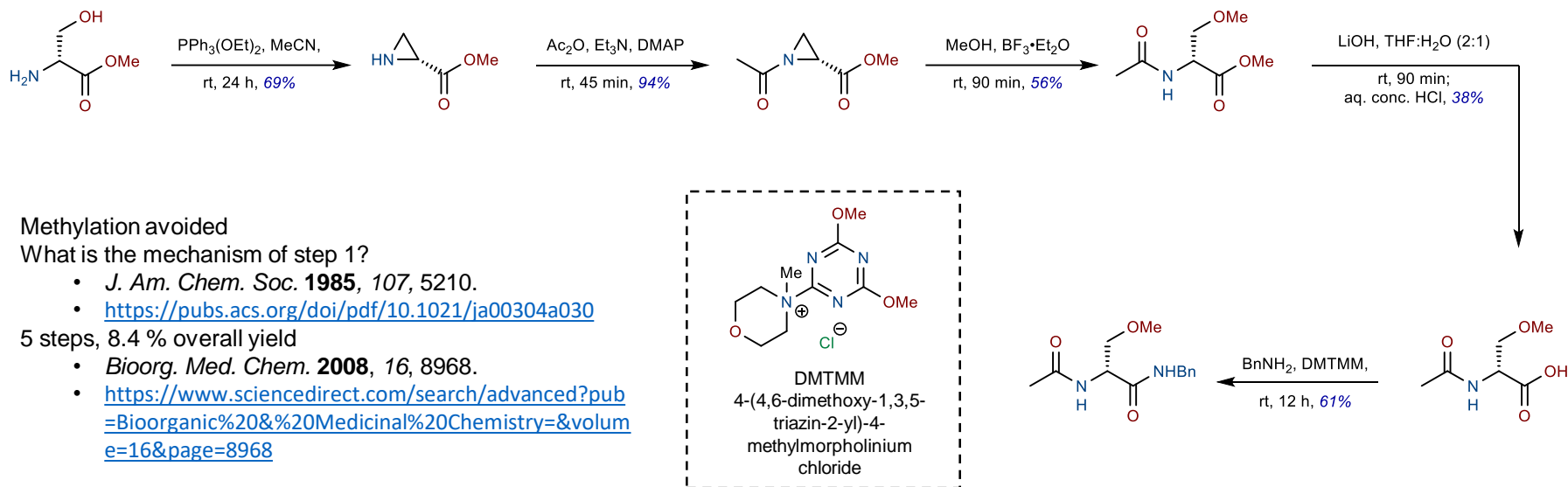
- Chiral pool
- Asymmetric Synthesis

Org. Process Res. Dev. **2020**, 24, 17
<https://pubs.acs.org/doi/10.1021/acs.oprd.9b00373>



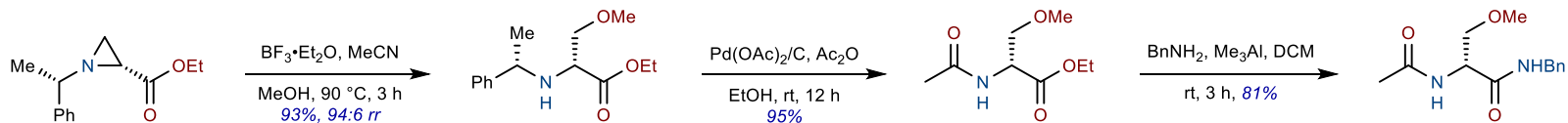
Chiral Pool:

Aziridine opening with MeOH



- Methylation avoided
- What is the mechanism of step 1?
 - J. Am. Chem. Soc.* **1985**, *107*, 5210.
 - <https://pubs.acs.org/doi/pdf/10.1021/ja00304a030>
- 5 steps, 8.4 % overall yield
 - Bioorg. Med. Chem.* **2008**, *16*, 8968.
 - <https://www.sciencedirect.com/search/advanced?pub=Bioorganic%20&%20Medicinal%20Chemistry=&volume=16&page=8968>

Aziridine opening with MeOH



- Starting material is commercially available, via enzymatic resolution.
 - Chem. Bio. Chem.* **2009**, *10*, 2213.
 - <https://chemistry-europe.onlinelibrary.wiley.com/doi/epdf/10.1002/cbic.200900343>
- Three steps, 99.9% ee and 71% overall yield
 - Synthesis* **2017**, *49*, 1264.
 - <https://www.thieme-connect.com/products/ejournals/pdf/10.1055/s-0036-1588093.pdf>

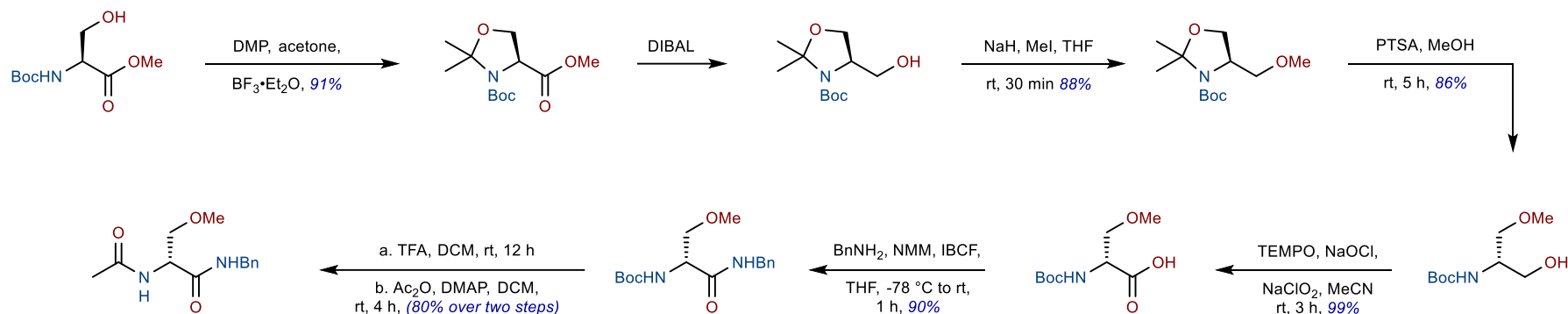
Chiral Pool (continued):

Phase transfer catalysis



- Partial racemization solved using phase transfer catalysis in the first step
- 69% overall yield, 99.91% chiral purity. *Org. Process Res. Dev.* **2019**, 23, 818. <https://pubs.acs.org/doi/pdf/10.1021/acs.oprd.8b00370>

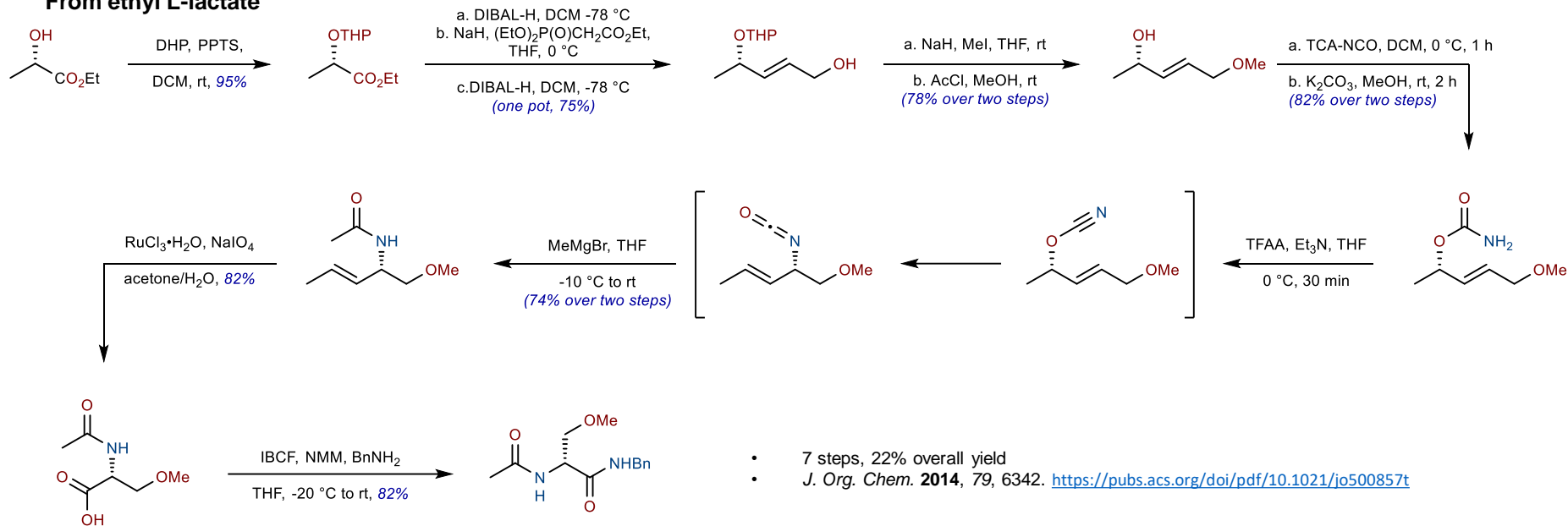
From natural amino acid L-serine



- No racemization observed during the methylation step
- *Tet. Lett.* **2015**, 56, 5802. <https://www.sciencedirect.com/search/advanced?pub=Tetrahedron%20Letters&volume=56&page=5802>

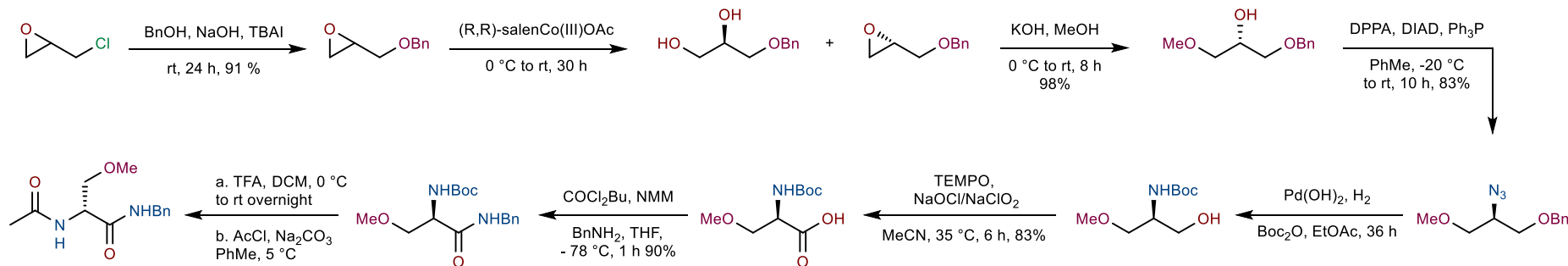
Chiral Pool (continued):

From ethyl L-lactate



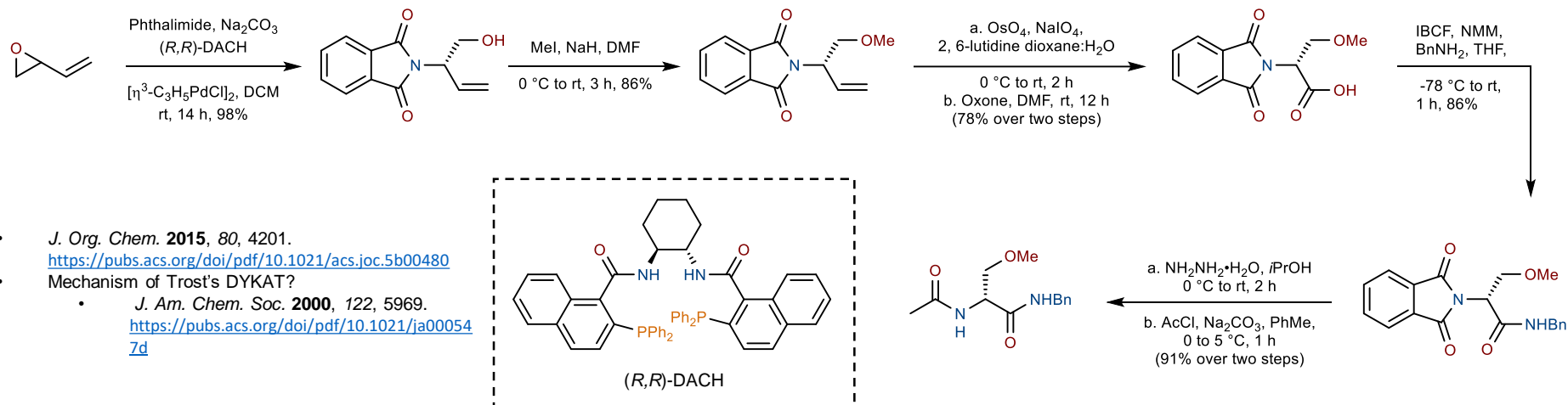
Asymmetric Methods:

Using Jacobsen's HKR

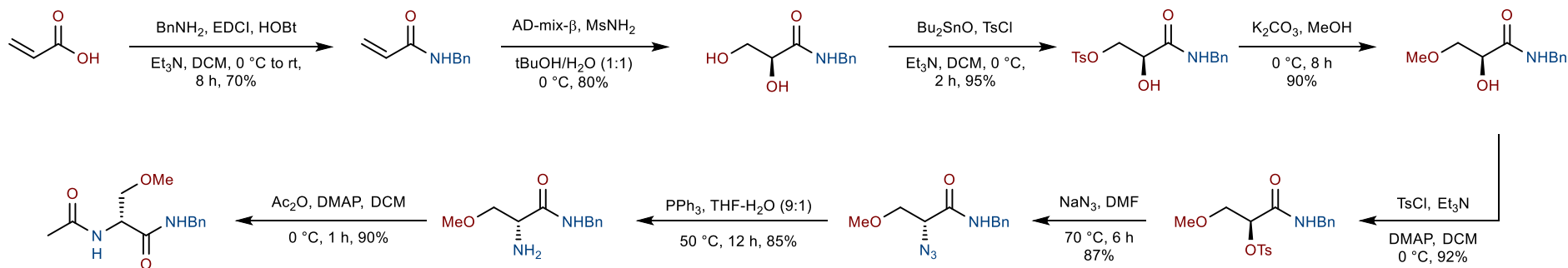


- *Tet. Asym.* **2011**, *22*, 1353. <https://www.sciencedirect.com/science/article/pii/S0957416611004277?via%3Dihub>
- Jacobsen's HKR: *J. Am. Chem. Soc.* **2004**, *126*, 1360. <https://pubs.acs.org/doi/pdf/10.1021/ja038590z>

Asymmetric Methods (continued): Using Trost's DYKAT

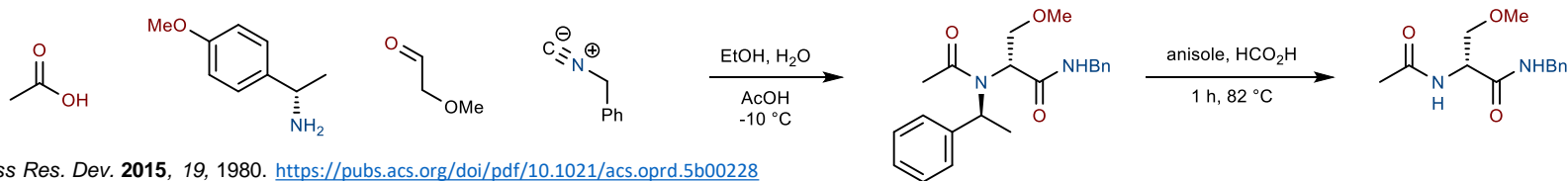


Using Sharpless Asymmetric Dihydroxylation



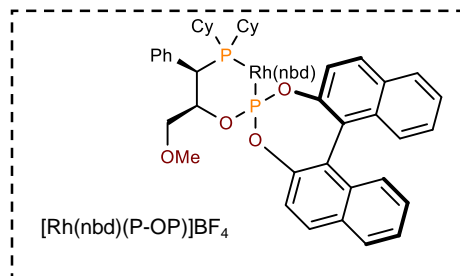
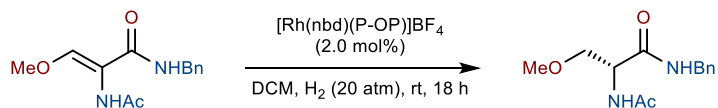
- *Synthesis* **2013**, *45*, 3383. <https://www.thieme-connect.com/products/ejournals/pdf/10.1055/s-0033-1339901.pdf>
- Mechanism of selective tosylation? *J. Am. Chem. Soc.* **2002**, *124*, 3578. <https://pubs.acs.org/doi/pdf/10.1021/ja016031r>

Asymmetric Methods (continued): Using the Ugi reaction



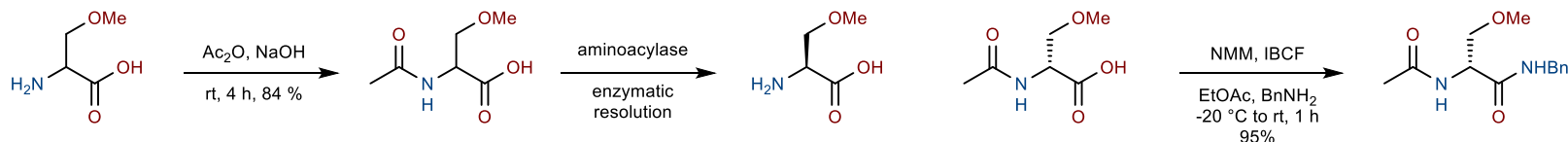
- *Org. Process Res. Dev.* **2015**, *19*, 1980. <https://pubs.acs.org/doi/pdf/10.1021/acs.oprd.5b00228>
- What is the mechanism?

Using asymmetric hydrogenation:



- *Organometallics* **2011**, *30*, 6718. <https://pubs.acs.org/doi/pdf/10.1021/om200933b>

Using chemoenzymatic resolution:



- *Chem. Res. Chin. Univ.* **2012**, *28*, 833.