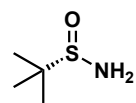
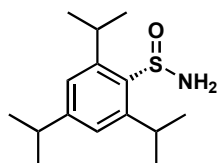


Process of the Week: Ellman's auxiliary



(S)-TBSA
"Ellman's auxiliary"

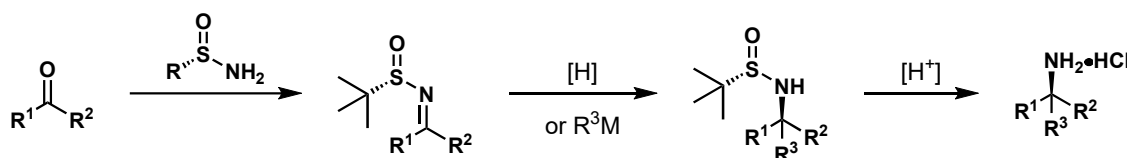


(S)-TIPPSA

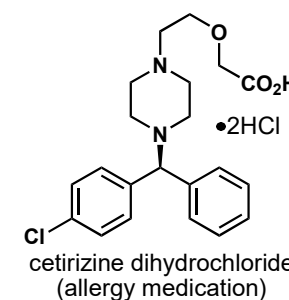
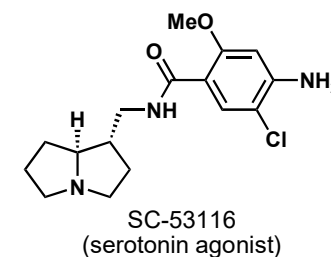
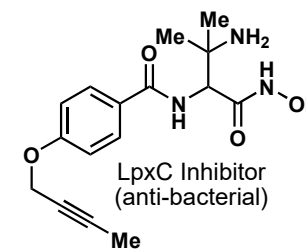
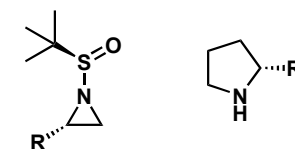
- Chiral sulfonylamides are a powerful tool in organic synthesis commonly used as auxiliaries for the synthesis of chiral amines.
- large and bulky sulfonylamides provide higher stereoselectivities, such as Ellman's tertbutanesulfinamide (TBSA) and Senanayake's trisopropylbenzenesulfinamide (TIPPSA)
- Ellman's auxiliary in particular is frequently used in large-scale production of drugs and other bioactive compounds such as cetirizine, SC-53116 and a LpxC Inhibitor
- These chiral auxiliaries can also be used to asymmetrically synthesize important building blocks such as aziridines and pyrrolidines.



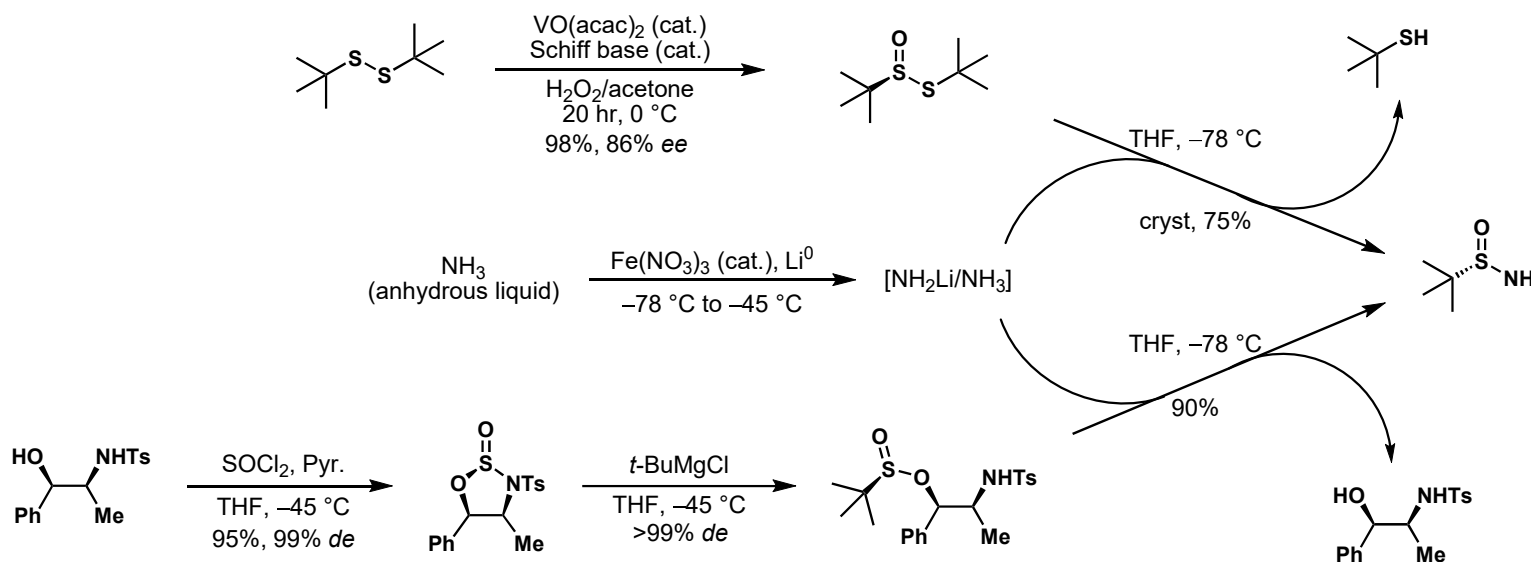
Asymmetric reductive amination



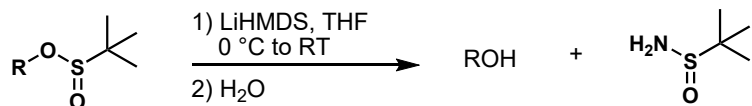
Other Examples



Previous routes

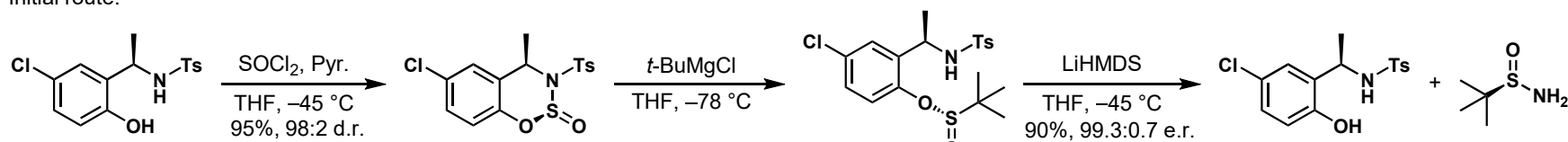


Leaving groups



Entry	R	pKa	Time [Hr]	Yield
1	Et	16	>12	0%
2	PHCH ₂	15.4	>12	0%
3	Ph	9.95	1.5	99%
4	4-MeOC ₆ H ₄	10.2	5	95%
5	4-ClC ₆ H ₄	9.38	<1	99%

Initial route:

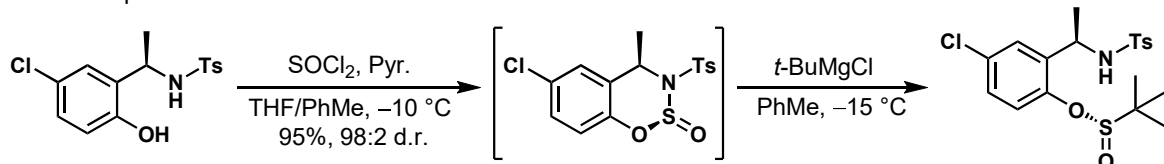


- 1.3 eq of SOCl₂ lead to NaHCO₃ quench. Exothermic, gas evolution, pH 6 solution.
- Extraction of pH 6 solution lead to left over Pyr.
- Removal of residual H₂O by azeotropic distillation lead to 5-10% racemization

- NaHCO₃ quench lead to Mg salts that were difficult to filter.
- Cryogenic temperatures

- Four DCM extractions only lead to 75% recovery of the sulfonamide
- Cryogenic temperatures

Final scale up route:

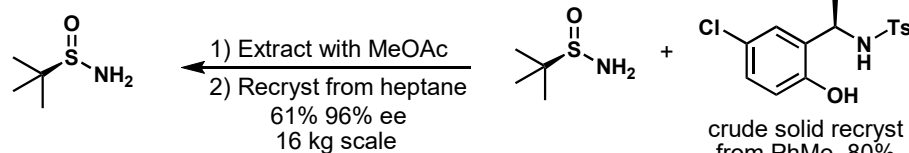


- 1.02 eq of SOCl₂ lead to H₂O quench, pH 3 - 4 solution.
- Extraction of pH 3 - 4 solution lead to no Pyr.
- Subsequent Na₂HPO₄ wash lead to pH 7 solution and no excess H₂O to distill.

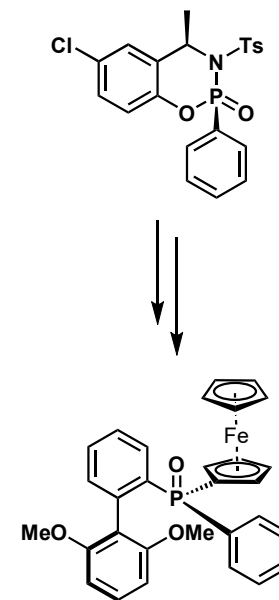
- Citric acid quench lead to clean phase separation.
- PhMe as a solvent allowed higher temperatures

- 1) LiHMDS, THF, -10 °C
- 2) H₂O
- 3) Distillation
- 4) H₃PO₄ solution

- MeOAc extraction lead to 90% recovery of sulfonamide.
- H₃PO₄ precipitated template
- Run on large scale



P-Chiral phosphines



Amine synthesis

