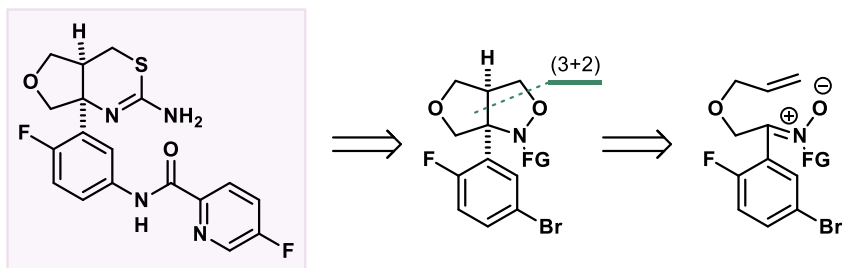


LY2886721



Lilly LY2886721

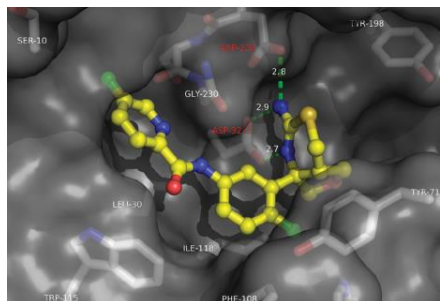
- Potent and selective inhibitor of β -amyloid cleaving enzyme (BACE)
- BACE1 IC_{50} = 20.3 nM
- Phase II studies were terminated voluntarily by Lilly due to abnormal liver enzyme elevations in 4 patients out of 70. [1]

Problems associated with the Gen 1 synthesis:

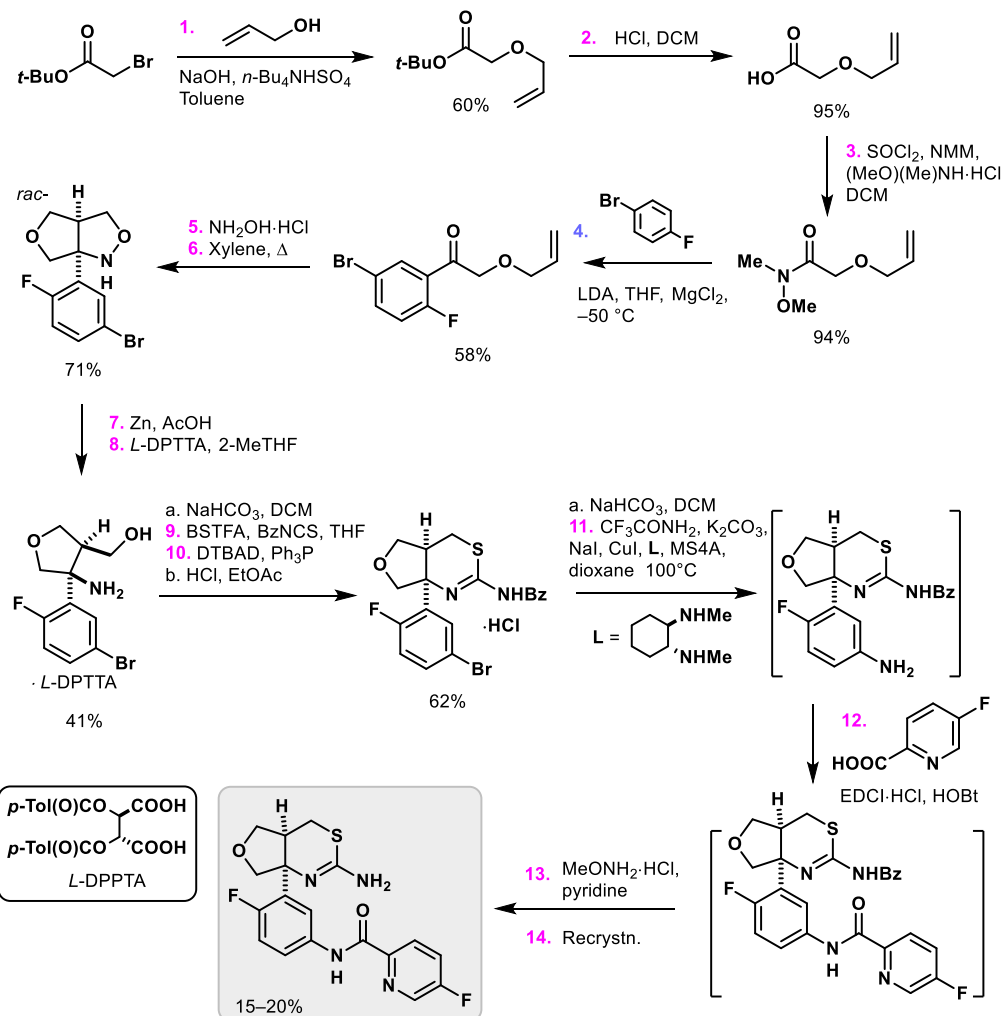
- Long synthesis and poor overall yield (~1%)
- Moderate yield on step 4 after optimization
- Stoichiometric Zn reduction in step 7 + waste disposal problem
- Resolution at step 8
- Expensive ring closure at step 10
- Low and inconsistent yields at step 11

References:

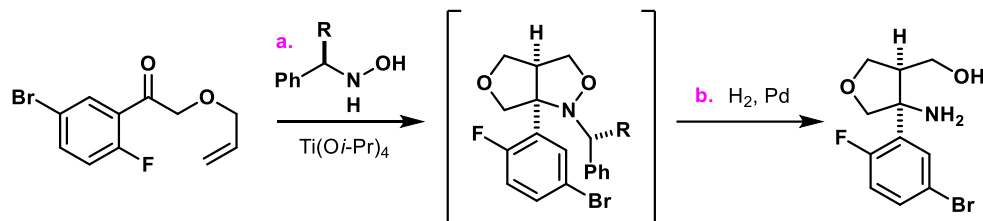
- 1 *J. Neurosci.* **2015**, 35, 1199
- 2 *Org. Process Res. Dev.* **2015**, 19, 1203
- 3 *Org. Process Res. Dev.* **2015**, 19, 1214
- 4 *Org. Process Res. Dev.* **2015**, 19, 1231
- 5 *Org. Process Res. Dev.* **2015**, 19, 1244



First generation route [2]

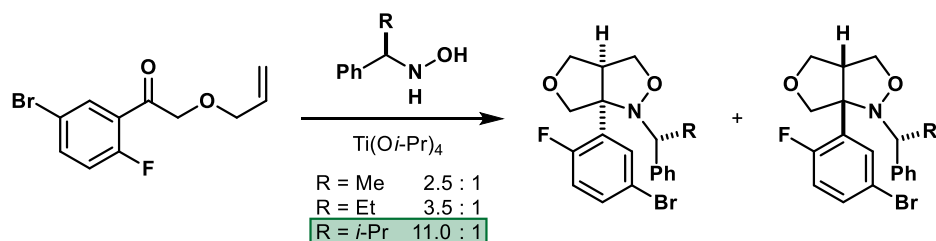


Optimization goal:



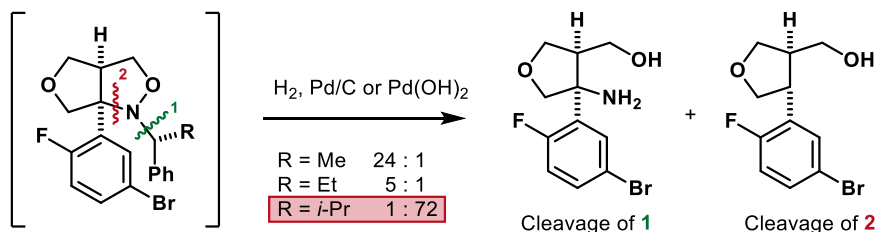
- Avoids throwing out 50% of material at the resolution step
- Avoids using stoichiometric amounts of Zn

Diastereoselectivity optimization



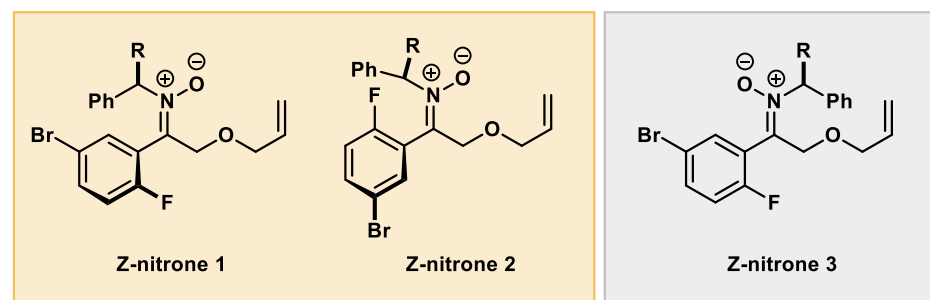
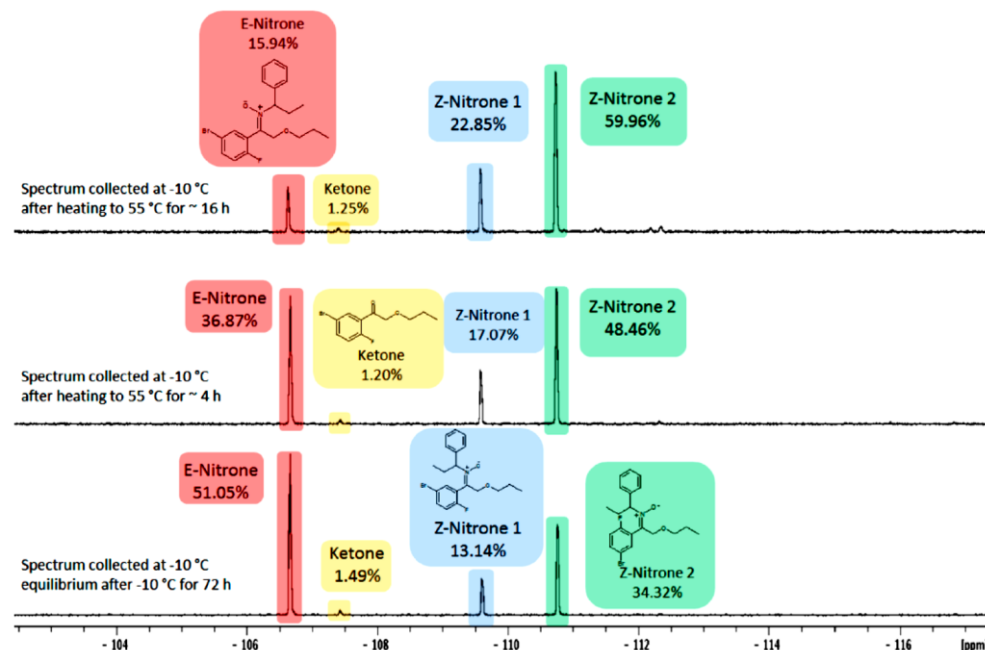
- No evidence of titanium assistance in the cycloaddition
- Primary role of $\text{Ti}(\text{O}i\text{-Pr})_4$ is efficient condensation with hydroxylamine. Other alkoxides (Zr, Hf, Sc, Si) proved inefficient
- Increased steric bulk around the stereogenic center results in increased *dr*...

Hydrogenolysis optimization



- ... but drastically decreases selectivity for the hydrogenolysis

Mechanistic investigation [2]

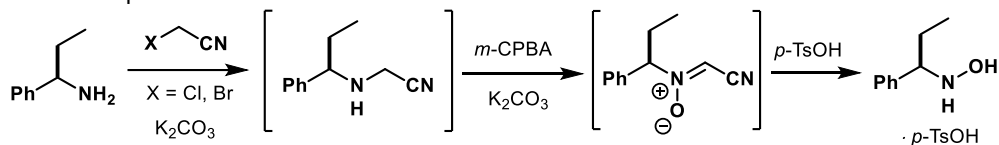


Competent in the cycloaddition

Geometrically restricted, possible, but no evidence of reactivity

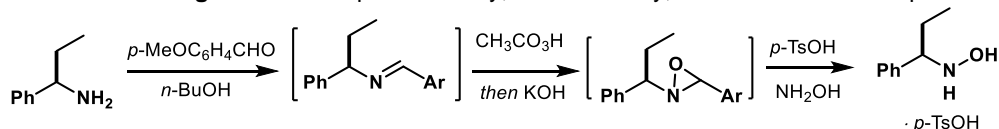
Synthesis of the hydroxylamine

- First generation:** potentially hazardous (HCN 4.5 g / kg product was released), expensive bromoacetonitrile



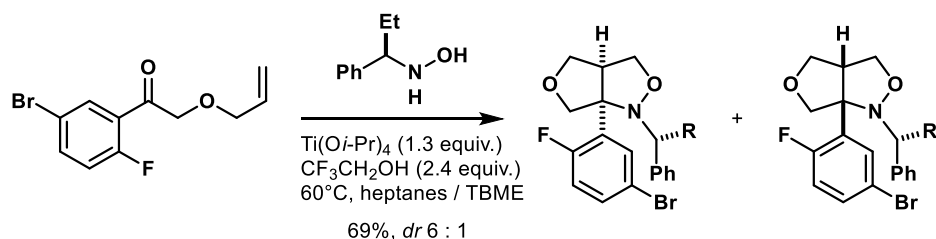
Avg. yield 80%, 1.6 kmol scale, total of 1227 kg / 3 batches

- Second generation:** improved safety, cost efficiency, lower solvent consumption



Avg. yield 84%, 2.1 kmol scale, 2296 kg / 4 batches

Optimal conditions

Optimized 2nd generation route