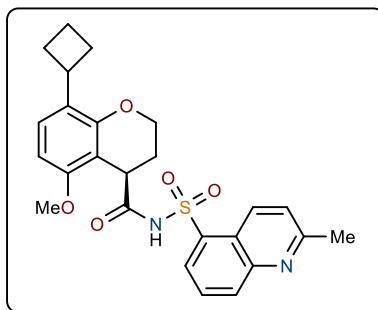
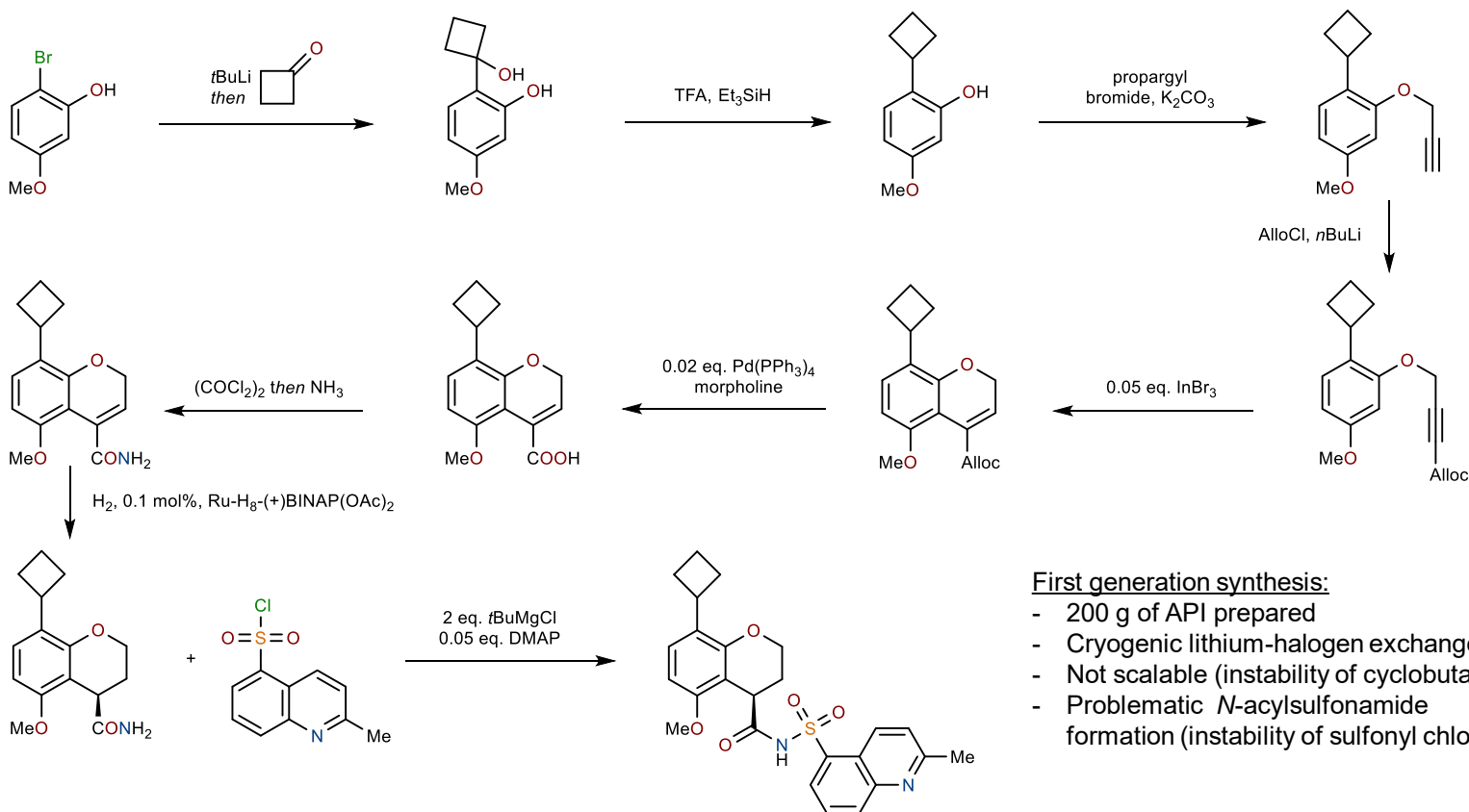


**Cystic fibrosis**

- Genetic disease
- Mutation of CF transmembrane conductance regulator (CFTR) protein
- > 100,000 people affected worldwide
- CFTR modulators (small molecule drugs)

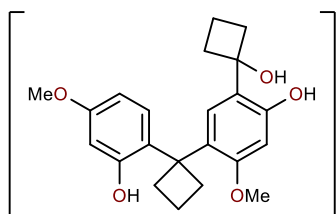
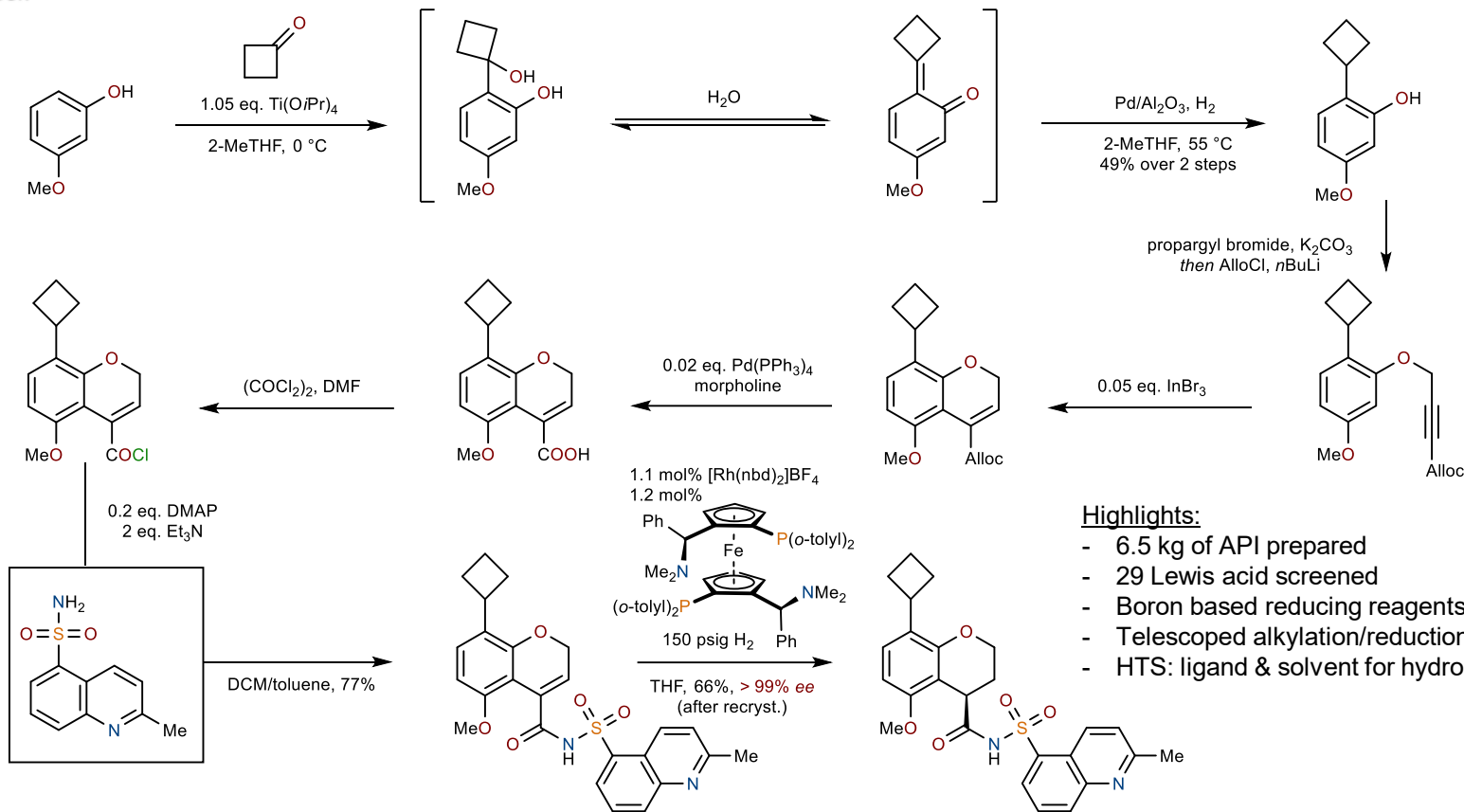


abbvie

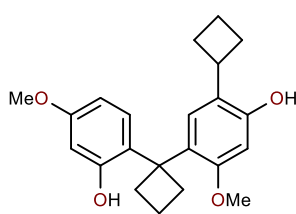


First generation synthesis:

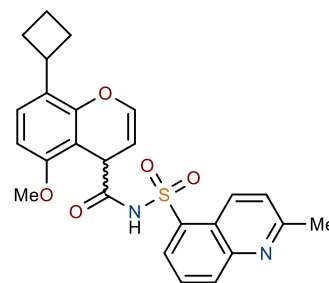
- 200 g of API prepared
- Cryogenic lithium-halogen exchange
- Not scalable (instability of cyclobutanol)
- Problematic *N*-acylsulfonamide formation (instability of sulfonyl chloride)



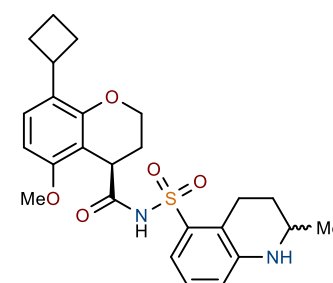
Alkylation  
Observed with LCMS



Alkylation  
Isolated after reduction



N-Acylsulfonamide formation  
Up to 10% (area) in toluene



Asymmetric hydrogenation  
Up to 1.5% (area) in THF