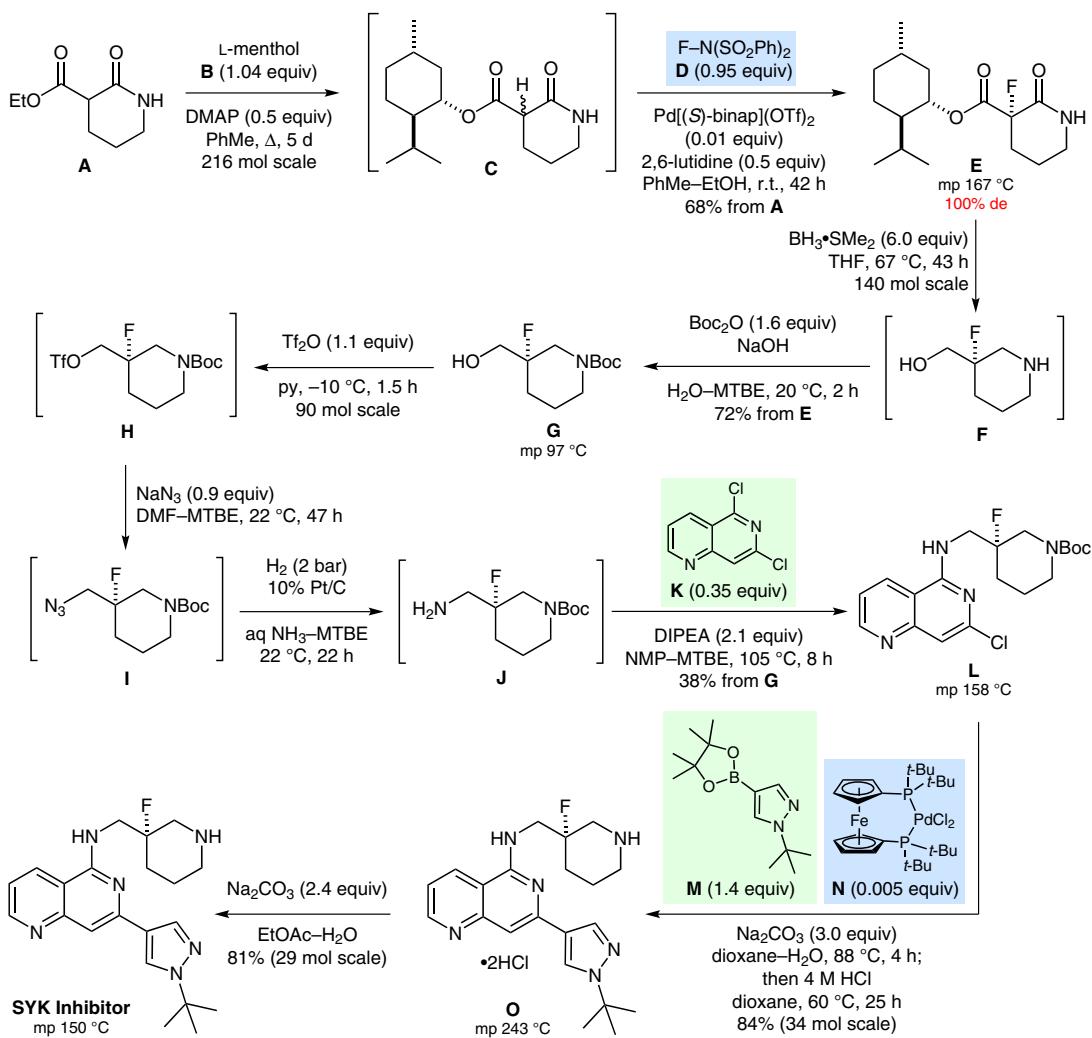


Asymmetric Fluorination Approach to an SYK Inhibitor



Significance: Spleen tyrosine kinase (SYK) is implicated in diverse cellular responses such as proliferation, differentiation, and phagocytosis. The target molecule is a SYK inhibitor that is of interest for the treatment of rheumatoid arthritis, B-cell lymphoma, and asthma. The highly telescoped, large-scale synthesis depicted delivered eight kilograms of API.

Comment: The asymmetric fluorination of β -keto ester A using (S)-BINAP as the chiral ligand gave a modest 44% ee but this improved to 72% ee with the bulkier DTBM-SEGPHOS ligand. The best results were obtained by the combined use of a chiral auxiliary (L-menthol) and an enantio- and dia stereoselective fluorination (C + D → E) mediated by Pd[(S)-binap](OTf)₂.