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Asymmetric Fluorination Approach to the Scalable Synthesis of a SYK Inhibitor
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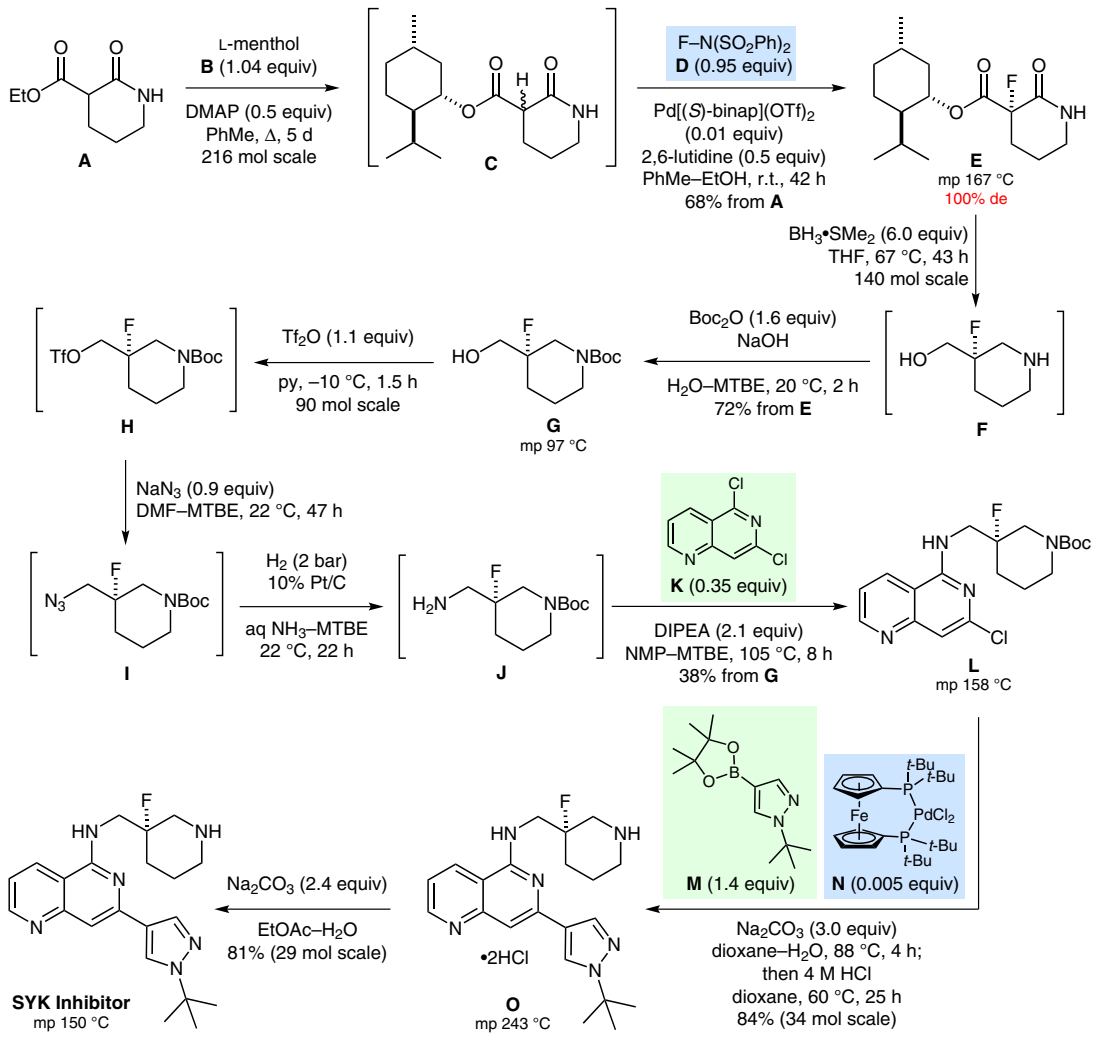
Asymmetric Fluorination Approach to an SYK Inhibitor



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 diastereoselective fluorination (**C** + **D** → **E**) mediated by Pd[(*S*)-binap](OTf)$_2$.

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Category

Synthesis of Natural Products and Potential Drugs

Key words

SYK inhibitor

asymmetric fluorination

***N*-fluorobenzenesulfonimide**

palladium catalysis

Suzuki–Miyaura cross-coupling

Synfact of the month