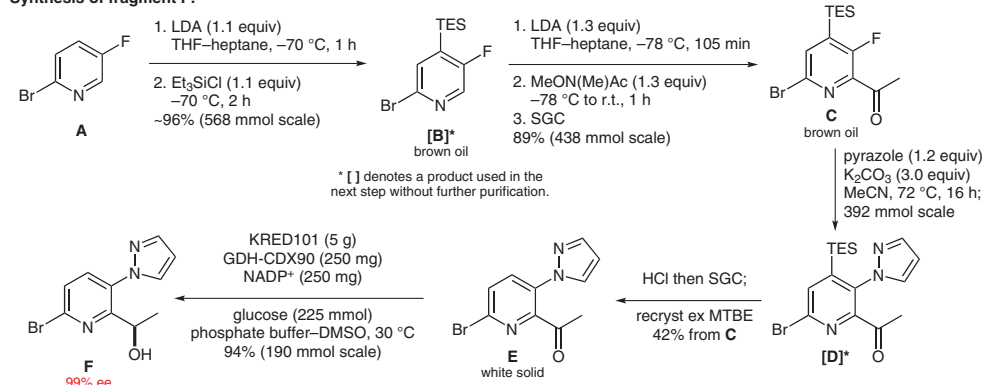
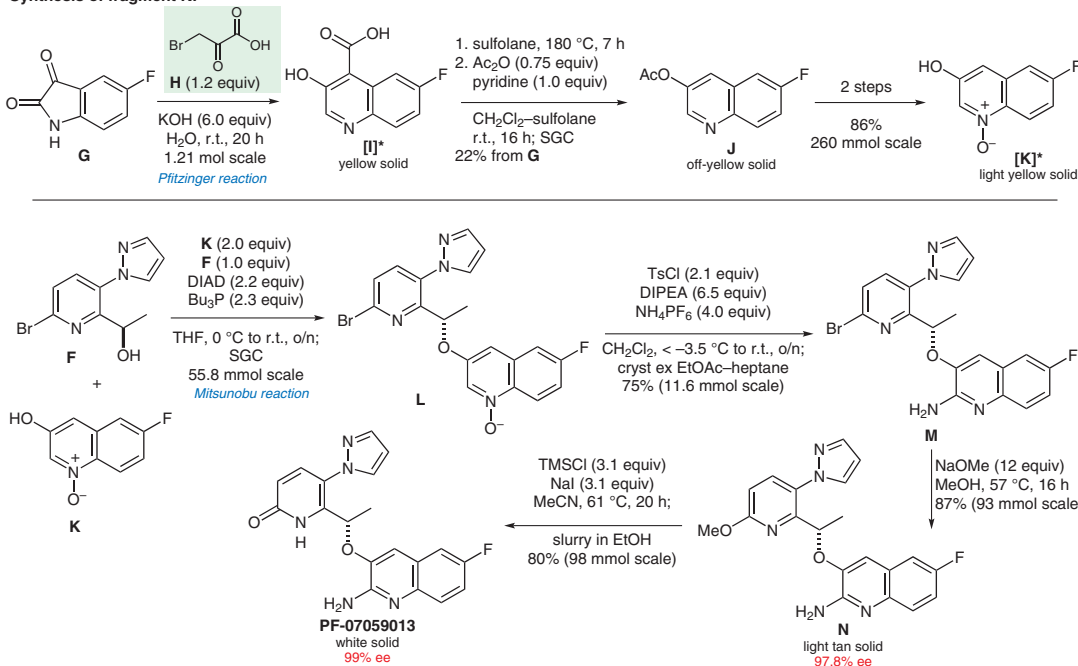


Synthesis of PF-07059013

Synthesis of fragment F:



Synthesis of fragment K:



Significance: Sickle cell disease is a common genetic disorder that affects 15 million people worldwide. It is caused by a single point mutation on the β -chain of adult hemoglobin. PF-07059013 is a noncovalent modulator of hemoglobin that has entered phase I clinical trials for the treatment of sickle cell disease.

Comment: Key steps in the synthesis depicted are (1) the asymmetric reduction of ketone **E** using the ketoreductase KRED101 from Codexis to afford enantiopure **F** in 94% yield (>99 ee), (2) the construction of quinoline **I** using a Pfitzinger reaction, and (3) a Mitsunobu reaction that links fragments **F** and **K**.