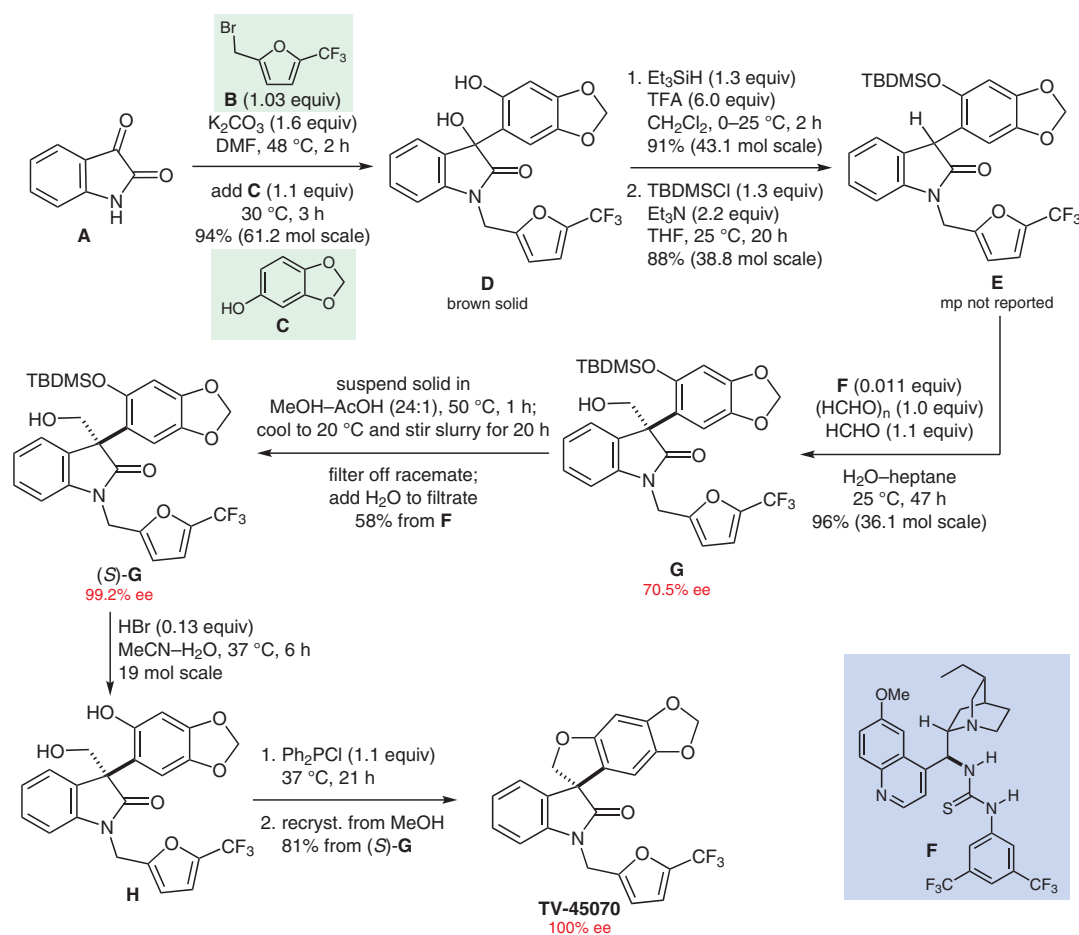


Pilot-Scale Synthesis of TV-45070



Significance: TV-45070 is an antagonist of the $\text{Na}_v1.7$ sodium ion channel protein that is of interest for the treatment of chronic pain associated with shingles. The key step in the synthesis depicted is the asymmetric aldol reaction of the enolate derived from **E** with a mixture of solid paraformaldehyde and aqueous formaldehyde using only 1.1 mol% of thiourea catalyst **F** to give adduct **G** in 96% yield and 70.5% ee. This solid product was heated in MeOH at 50 °C and cooled to 20 °C whereupon the near racemic product **G** (5% ee) precipitated. Addition of water to the supernatant afforded (S)-**H** in 99% ee and 58% yield.

Comment: Attempts to synthesize chloro or mesylate intermediates from diol **H** using conventional reagents were unsuccessful due to the congested neopentyl center. Diethyl chlorophosphate, dichlorophenyl phosphine, and diethylchlorophosphite did not provide sufficient conversion or a good impurity profile. However, chlorodiphenylphosphine completely consumed **H** when heated to 37 °C and provided the spirocycle in 81% yield. For a preceding asymmetric synthesis of TV-45070, see: S. Sun et al. US 9,487,535, **2016**. For a synthesis of catalyst **F**, see: Y. Wang et al. *Org. Process Res. Dev.* **2017**, *21*, 408.