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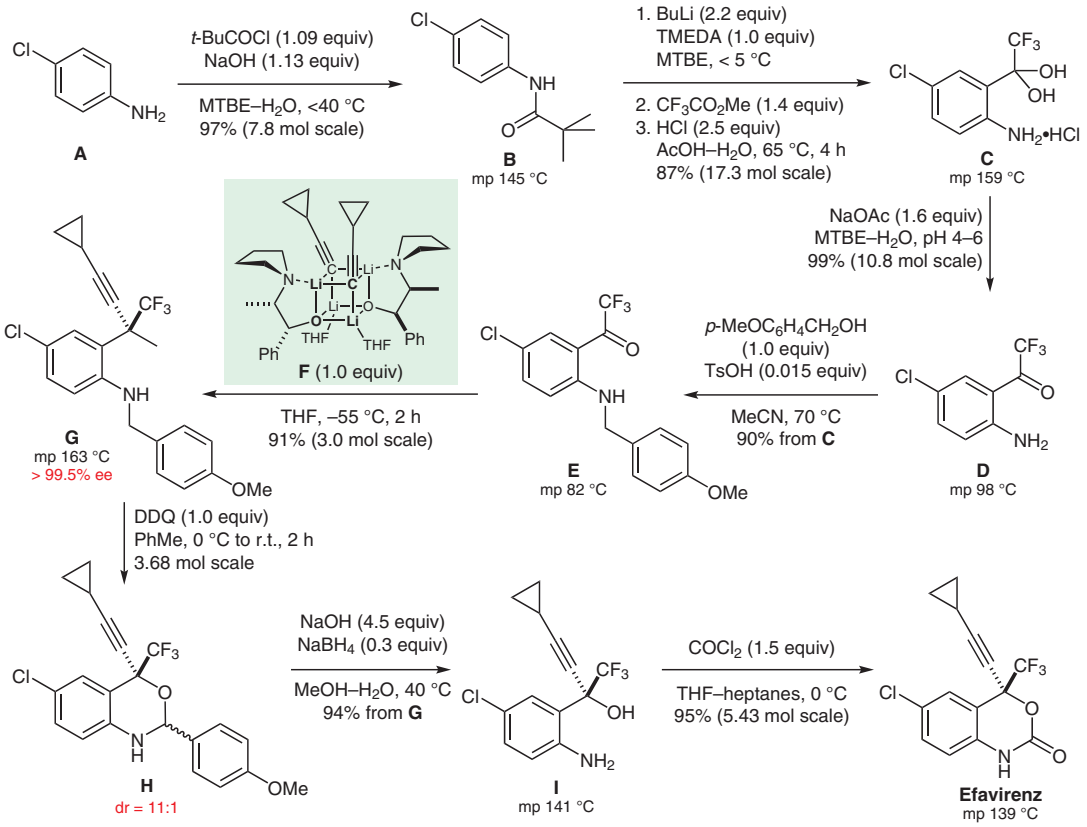
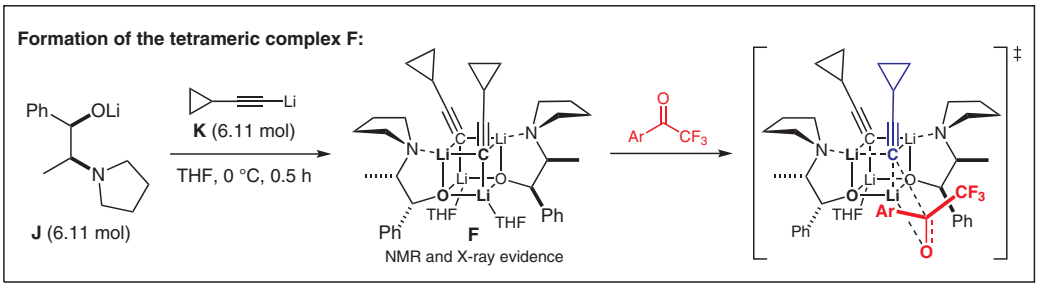
Practical Asymmetric Synthesis of Efavirenz (DMP 266), an HIV-1 Reverse Transcriptase Inhibitor
J. Org. Chem. **1998**, *63*, 8536–8543.

Synthesis of Efavirenz via Asymmetric Alkynylation





Significance: Efavirenz (Sustiva®) is an HIV-1 reverse transcriptase inhibitor that was approved by the FDA in 1998 for the treatment of HIV/AIDS. The classic DuPont–Merck synthesis depicted incorporates a highly enantioselective addition of lithium acetylide **K** (as the tetrameric complex **F**) to ketone **E** mediated by chiral chaperone **J**. The synthesis proceeds in 62% overall yield in just seven steps. Since all intermediates were crystalline, no chromatography was required.

Comment: For the mechanism of the acetylide addition, see: A. Thompson et al. *J. Am. Chem. Soc.* **1998**, *120*, 2028. For further practical refinements in the nucleophilic addition, see: A. Choudhury et al. *Org. Process Res. Dev.* **2003**, *7*, 324. A large scale enantioselective alkynylation of ketone **D** mediated by chiral chaperone **J** gave adduct **I** directly in 95% yield (er > 99:1) on a 4.5 mol scale: WO 1998 51676.

SYNFACTS Contributors: Philip Kocienski
Synfacts 2019, 15(01), 0005 Published online: 14.12.2018
DOI: 10.1055/s-0037-1611443; **Reg-No.:** K07318SF

Category

Synthesis of Natural Products and Potential Drugs

Key words

efavirenz

reverse transcriptase inhibitor

asymmetric alkynylation

chiral chaperone