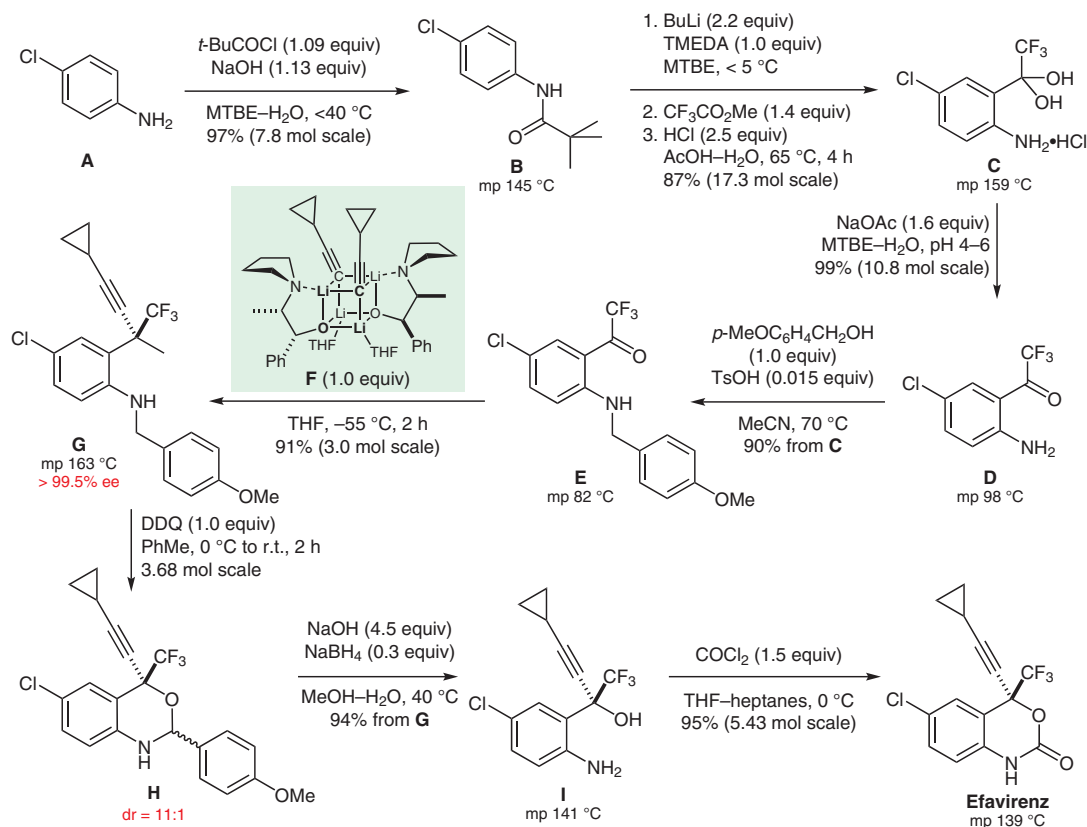
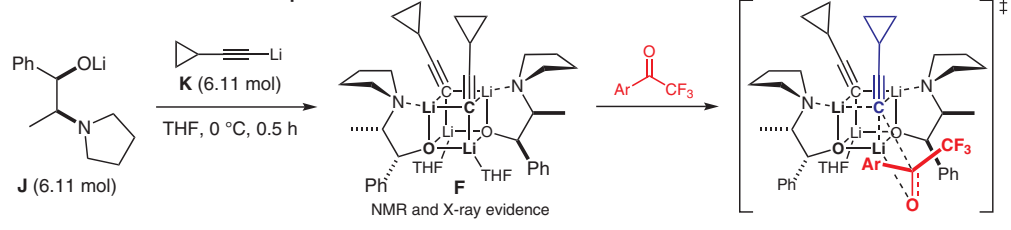


M. E. PIERCE*, C.-Y. CHEN*, R. D. TILLYER* ET AL. (THE DUPONT PHARMACEUTICALS COMPANY, DEEPWATER AND MERCK RESEARCH LABORATORIES, RAHWAY, USA)
 Practical Asymmetric Synthesis of Efavirenz (DMP 266), an HIV-1 Reverse Transcriptase Inhibitor
J. Org. Chem. **1998**, *63*, 8536–8543.

Synthesis of Efavirenz via Asymmetric Alkynylation



Formation of the tetrameric complex F:



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

2019 © Georg Thieme Verlag Stuttgart · New York

Category

Synthesis of Natural Products and Potential Drugs

Key words

efavirenz

reverse transcriptase inhibitor

asymmetric alkynylation

chiral chaperone

Synfact Classic

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.