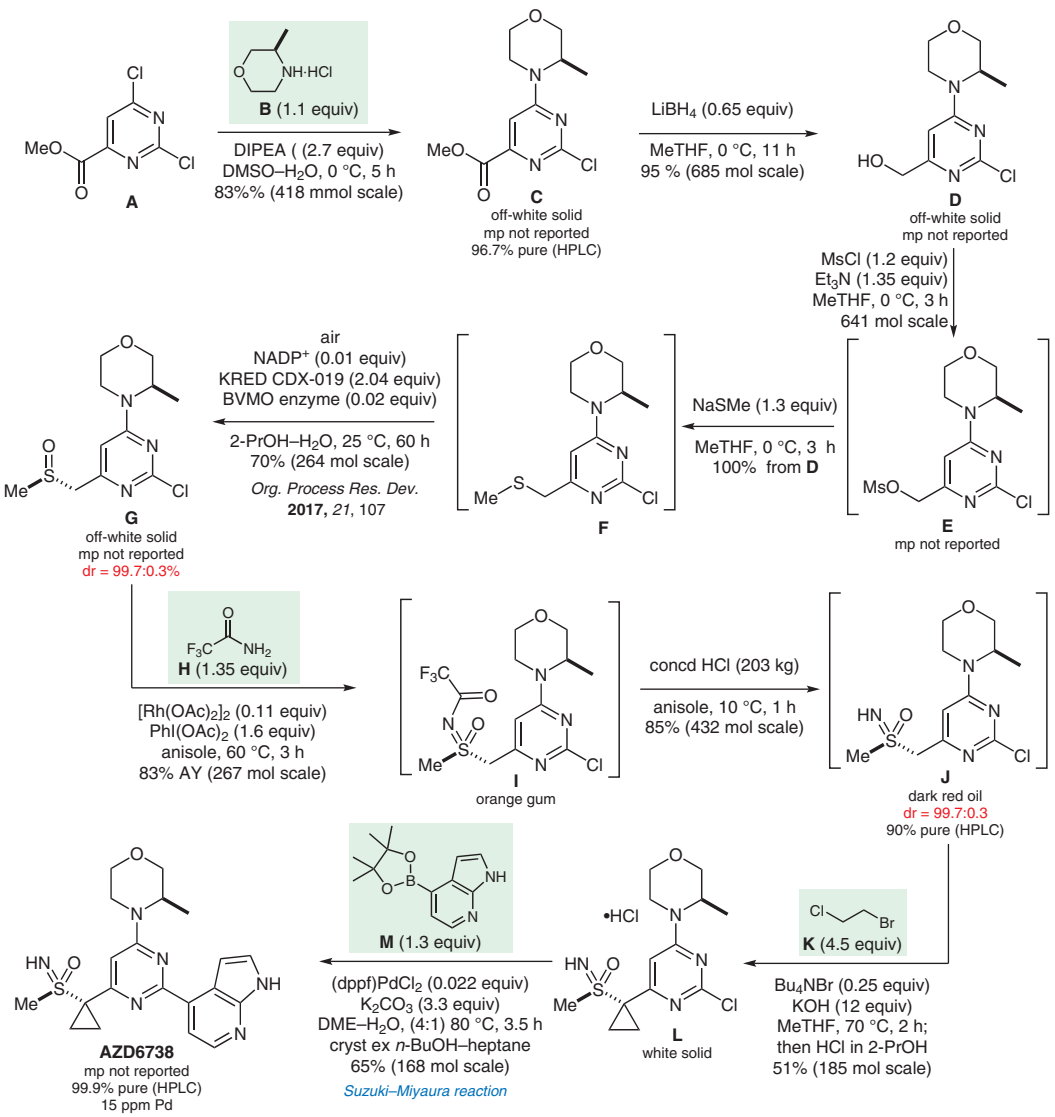
W. R. F. GOUNDRY*, K. DAI, M. GONZALEZ, D. LEGG, A. O'KEARNEY-MCMULLAN, J. MORRISON, A. STARK, P. SIEDLECKI, P. TOMLIN, J. YANG (ASTRAZENECA, MACCLESFIELD, UK; CHANGZHOU SYNTHEALL PHARMACEUTICAL CO., LTD., CHANGZHOU AND ASYMCHEM LABORATORIES CO. LTD., TIANJIN, P. R. OF CHINA)

Development and Scale-up of a Route to ATR Inhibitor AZD6738
Org. Process Res. Dev. **2019**, *23*, 1333–1342.

Synthesis of AZD6738



Significance: Workers at AstraZeneca recently reported a mol-scale synthesis of ATR inhibitor AZD6738 based on the use of chiral HPLC to access the chiral sulfoxide intermediate **G** (*J. Med. Chem.* **2018**, *61*, 9889). A plant scale synthesis of AZD6738 is now reported that features a biocatalytic asymmetric sulfoxidation reaction (**F** → **G**) and a cyclopropanation (**J** → **L**) in continuous stirred tank reactors.

Comment: The sulfoxidation reaction uses a Baeyer–Villiger monooxygenase in tandem with nicotinamide adenine dinucleotide phosphate (NADPH), which is oxidized to $NADP^+$. NADPH is then regenerated through reduction of $NADP^+$ by a ketoreductase (KRED) enzyme, which in turn oxidizes the co-solvent isopropanol to acetone. Efficient gas–liquid mass transfer of oxygen is key to obtaining a high yield.

SYNFACTS Contributors: Philip Kocienski
Synfacts 2019, 15(10), 1091 Published online: 17.09.2019
DOI: 10.1055/s-0039-1690625; **Reg-No.:** K05819SF

Category
Synthesis of Natural Products and Potential Drugs

Key words
AZD6738
asymmetric sulfoxidation
sulfoximines
biocatalysis
rhodium catalysis