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 \( (\text{F} \rightarrow \text{G}) \) and a cyclopropanation \( (\text{J} \rightarrow \text{L}) \) 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.