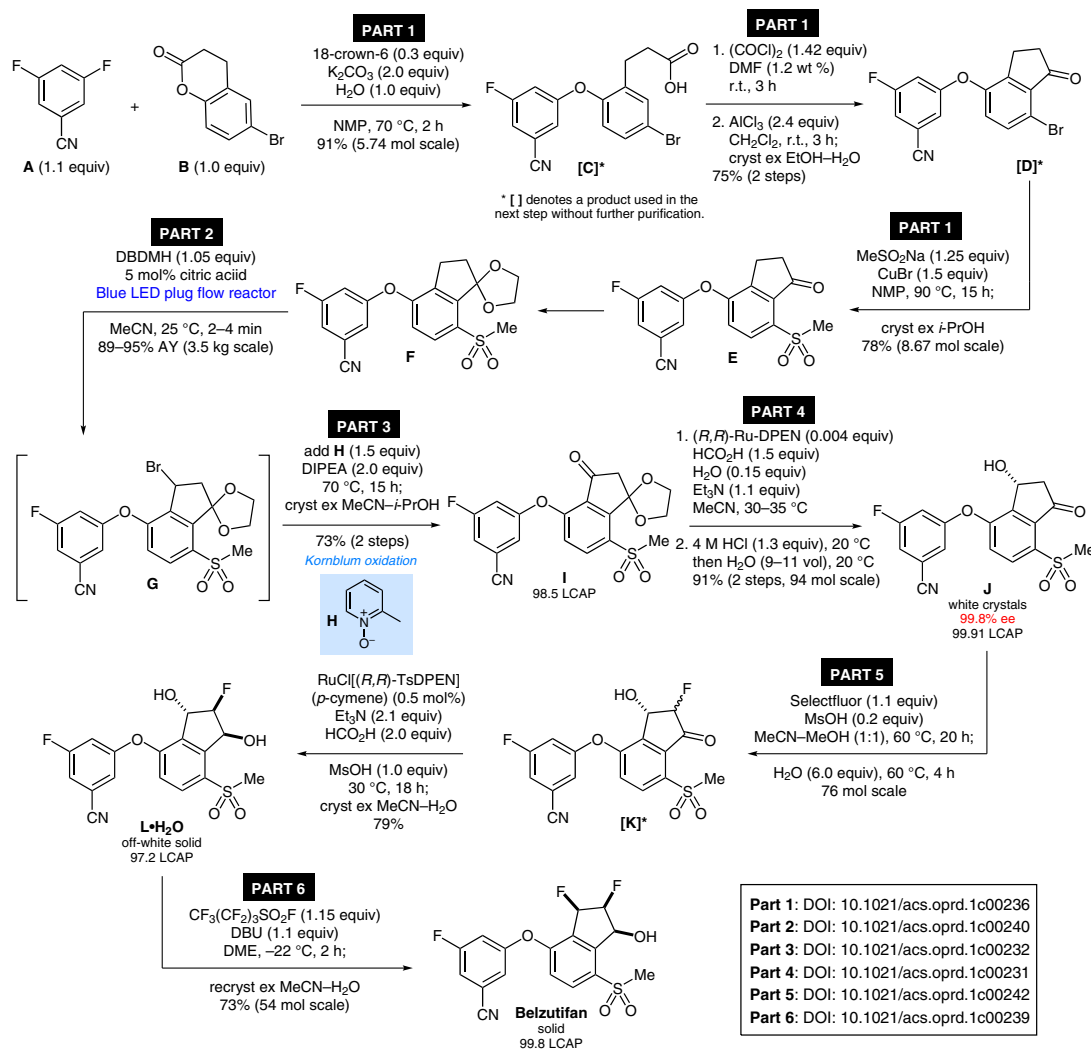


# Synthesis of Belzutifan



**Significance:** Belzutifan (MK-6482) is a selective hypoxia-inducible factor-2 alpha (HIF-2 $\alpha$ ) inhibitor that was approved by the FDA in 2021 as a first-in-class treatment for renal-cell carcinoma. A manufacturing process for belzutifan is described in forensic detail in six back-to-back papers that have been conflated in the single scheme shown above.

**Comment:** Especially innovative steps in the synthesis are (1) the copper-catalyzed C,S-coupling, leading to sulfone **E** (Part 1); (2) the continuous-flow photochemical bromination of **F** under mild conditions (Part 2); (3) a Kornblum oxidation mediated by picoline *N*-oxide (Part 3); (4) a fluorination–DKR sequence that installs three contiguous stereogenic centers (Part 5).