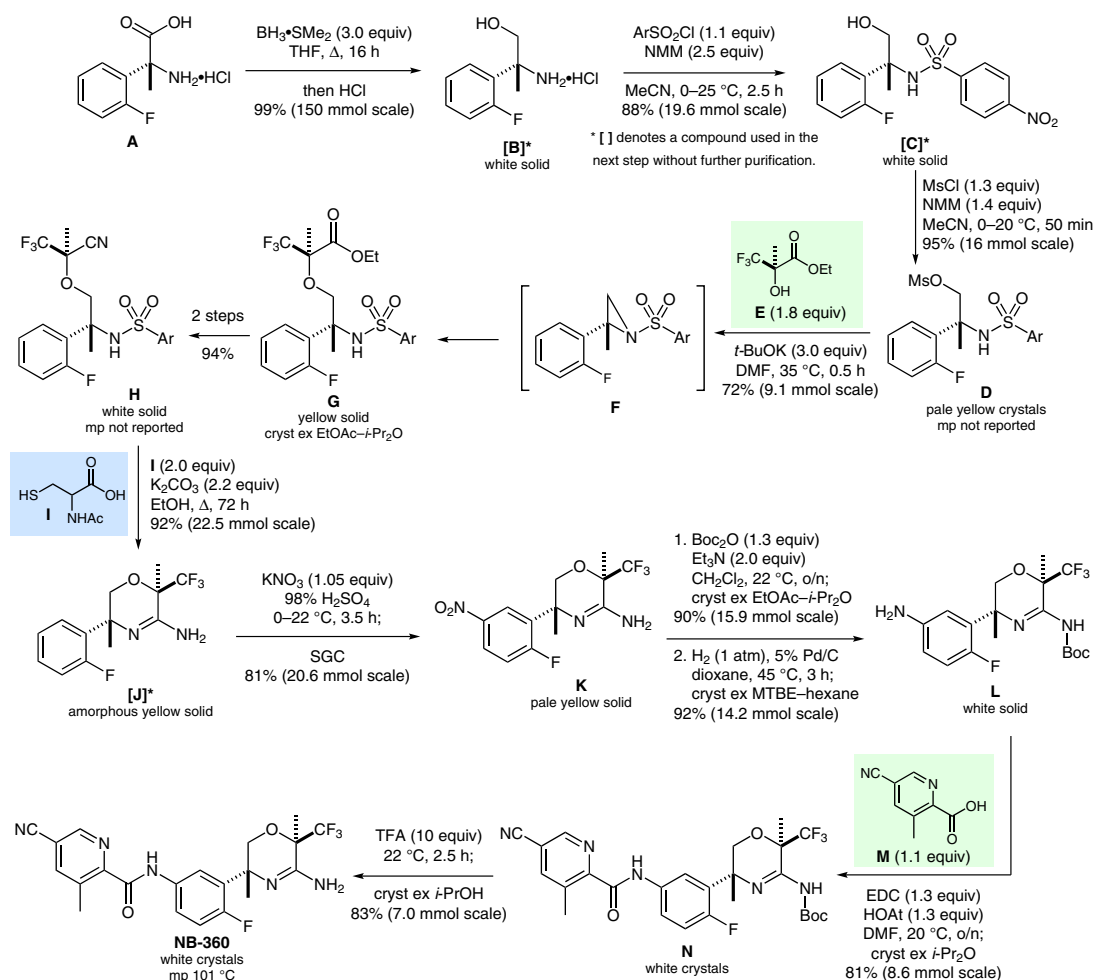


# Synthesis of $\beta$ -Secretase Inhibitor NB-360



**Significance:**  $\beta$ -Secretase 1 (BACE1) is an aspartic acid protease located primarily in neurons. It is the major  $\beta$ -secretase involved in the generation of amyloid- $\beta$  peptides (A $\beta$ ) and their subsequent aggregation to form plaques associated with the onset of Alzheimer's disease. NB-360 is the latest in a long line of similar amidine-based BACE1 inhibitors that have hitherto failed in phase II/III clinical trials.

**Comment:** The two quaternary centers in NB-360 shielded the amidine and ether oxygen from undesired chemical and metabolic transformations. The key step in the most practical route to the 1,4-oxazine **K** entailed the nucleophilic opening of the chiral *N*-sulfonylaziridine **F** with the chiral alkoxide derived from **E** in the presence of potassium *tert*-butoxide in DMF at 35 °C.