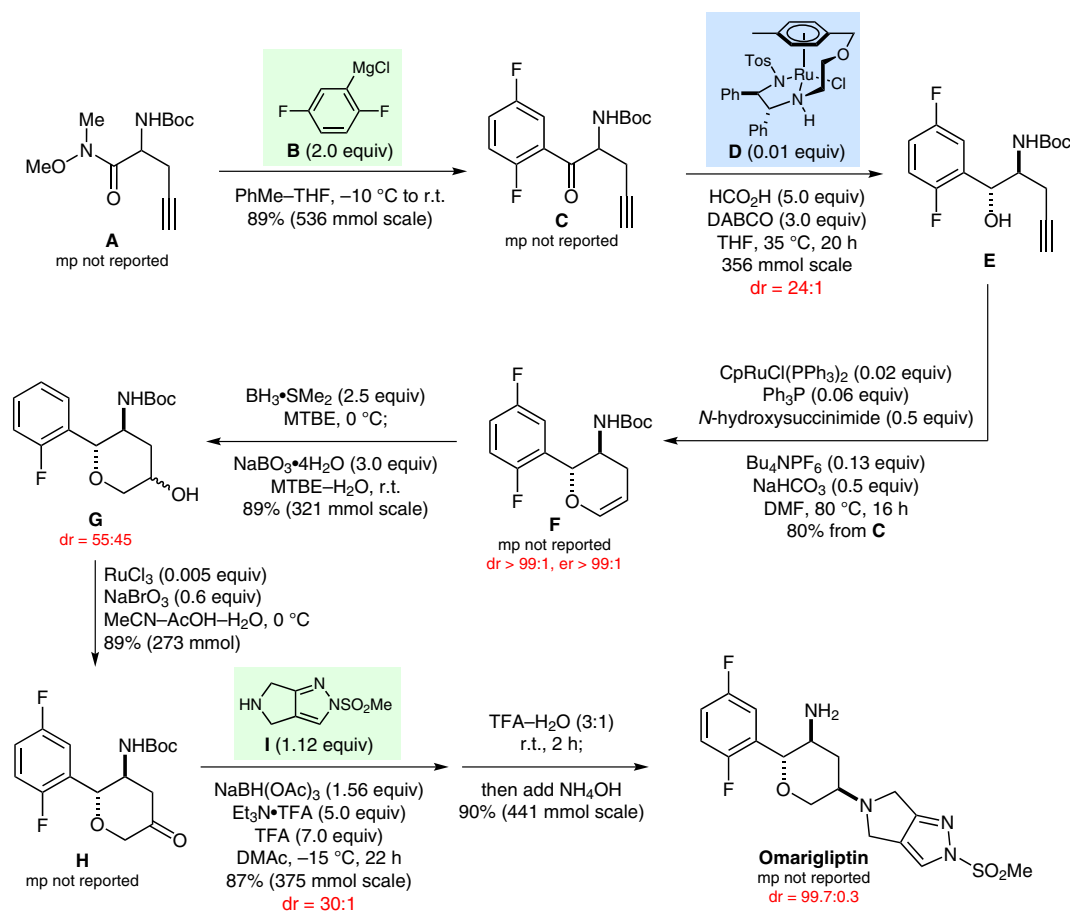


## Synthesis of Omarigliptin



**Significance:** Omarigliptin (MK-3102) is a dipeptidyl peptidase-4 (DPP-4) inhibitor that has received marketing authorization in Japan for the once-weekly treatment of type 2 diabetes. The synthesis of pyranone **H** depicted features three ruthenium-catalyzed reactions: (1) a DKR reduction of *rac*- $\alpha$ -aminoketone **C** to set the two contiguous stereogenic centers, (2) a cycloisomerization of alkyne **E** to dihydropyran **F**, and (3) a ruthenium-catalyzed oxidation of pyranol **G** to the desired pyranone **H**.

**Comment:** The Takasago tethered ruthenium(II) catalyst **D** is a highly efficient asymmetric transfer hydrogenation catalyst. The catalyst loading was reduced to 0.1 mol% without sacrificing selectivity and reaction kinetics. It was critical to apply efficient N<sub>2</sub> sparging during the reaction to remove CO<sub>2</sub>; otherwise, the reaction could stall if this was allowed to accumulate. For the discovery synthesis of omarigliptin, see: T. Biftu et al. *J. Med. Chem.* 2014, 57, 3205.