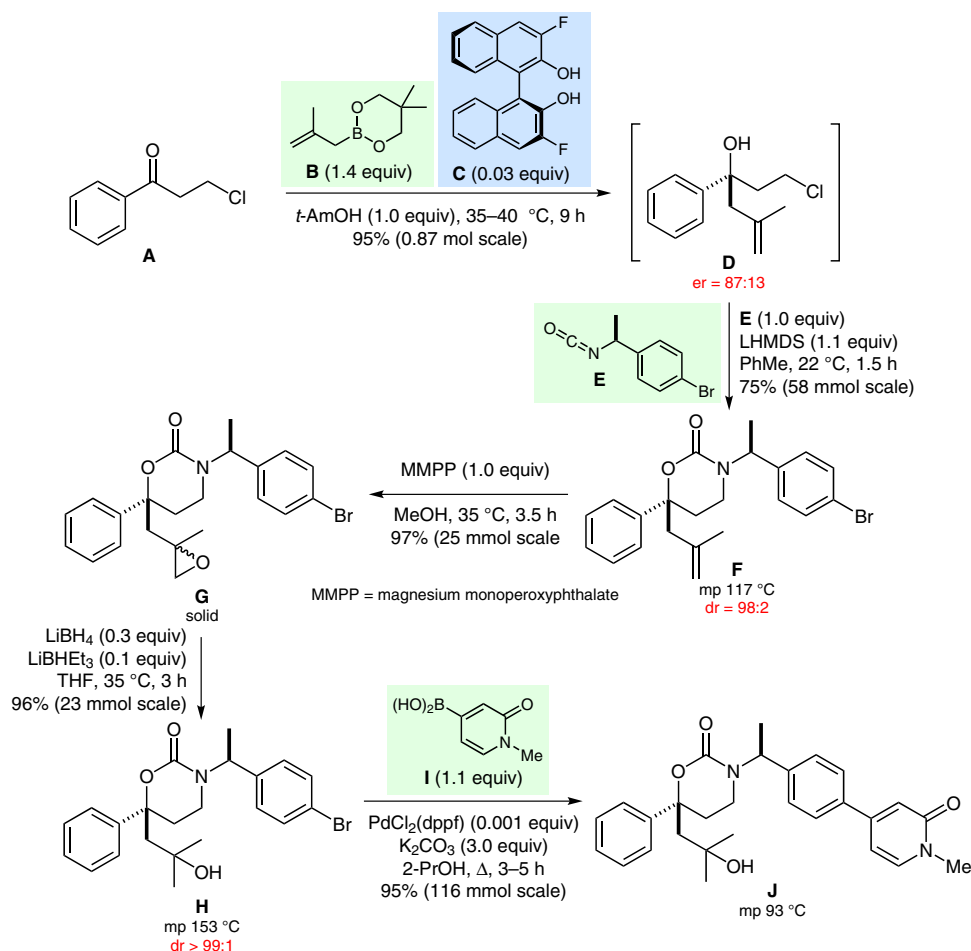


Synthesis of an 11- β -HSD-1 Inhibitor via Asymmetric Methallylation



Significance: The target molecule **J** inhibits 11- β -hydroxysteroid dehydrogenase-1 (11- β -HSD-1), an enzyme that catalyzes the reduction of inactive cortisone to the active glucocorticoid cortisol. An elevated glucocorticoid level correlates to metabolic comorbidities such as obesity, diabetes, dyslipidemia, and atherosclerosis. The key feature of the synthesis depicted is an asymmetric methallylation of 3-chloro-1-phenylpropan-1-one (**A**) catalyzed by (*S*)-3,3'-F₂-BINOL (**C**) under solvent-free and metal-free conditions.

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Comment: The five-step process delivered the target API **J** in 53% overall yield on a multikilogram scale. Direct hydration of **F** to **H** using oxygen and Co(acac)₂ as the catalyst in 2-propanol stalled at 62% conversion after 4 h at 75 °C, even in the presence of 40 mol% Co(acac)₂. Reductive cleavage of the epoxide **G** by the use of a catalytic amount of LiBHET₃ (0.1 equiv) in the presence of stoichiometric LiBH₄ (0.3 equiv) proceeded in 96% yield after 3 h at 35 °C.