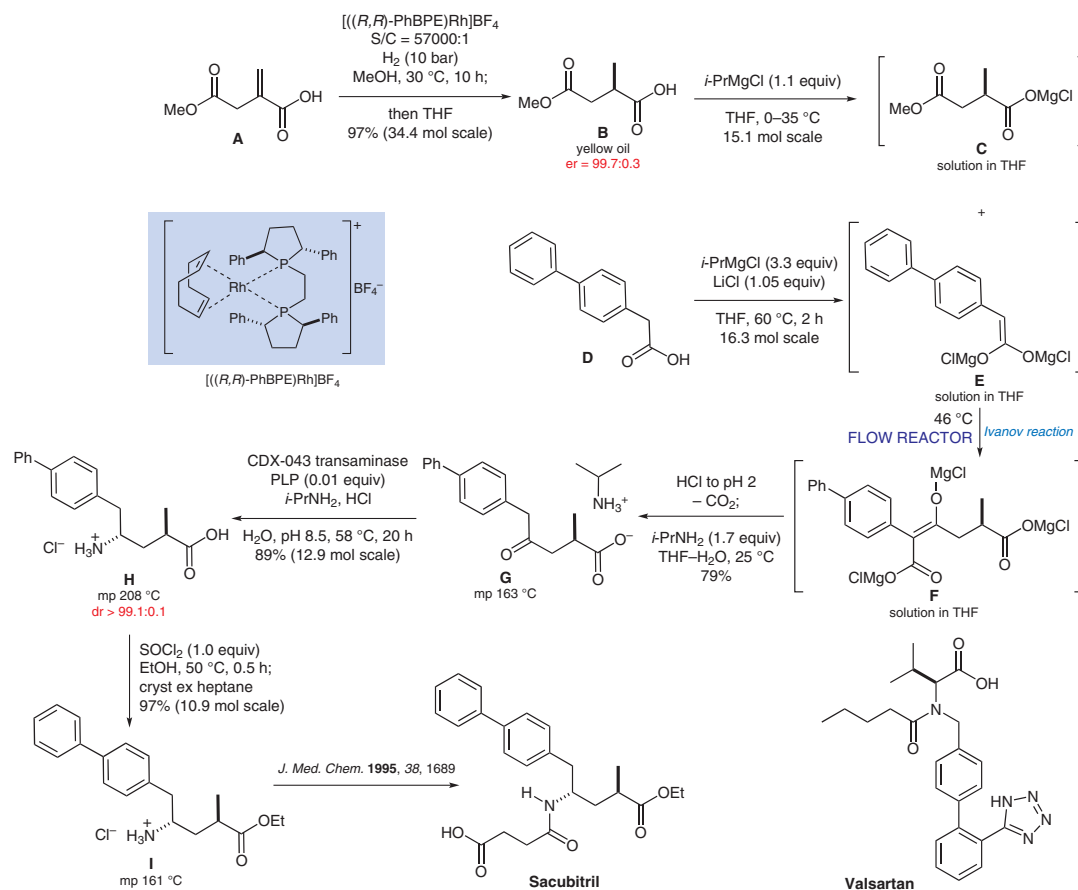


Synthesis of Sacubitril



Significance: Sacubitril is a nephriysin inhibitor used in combination with the angiotensin II inhibitor valsartan. The combination drug (LCZ696), marketed under the brand name Entresto®, was approved by the FDA in 2015 for the treatment of heart failure. A noteworthy step in the synthesis of sacubitril depicted features a flow reactor to perform the Ivanov reaction (*Synthesis* 1975, 83) by which the carboxylic acids **B** and **D** were condensed to give γ -ketoacid derivative **G** in 79% yield on a 15.1 mol scale.

Comment: The (R,R) -Ph-BPE-derived rhodium complex in methanol at 30 °C and a hydrogen pressure of 10 bar provided the best performance among the catalyst systems screened for the asymmetric hydrogenation of **A**. Complete conversion into **B** was observed in concentrations as high as 1.3 g/mL and catalyst loadings as low as S/C 74,000:1, providing the product in high purity and excellent enantioselectivity ($\text{er} = 99.7:0.3$).