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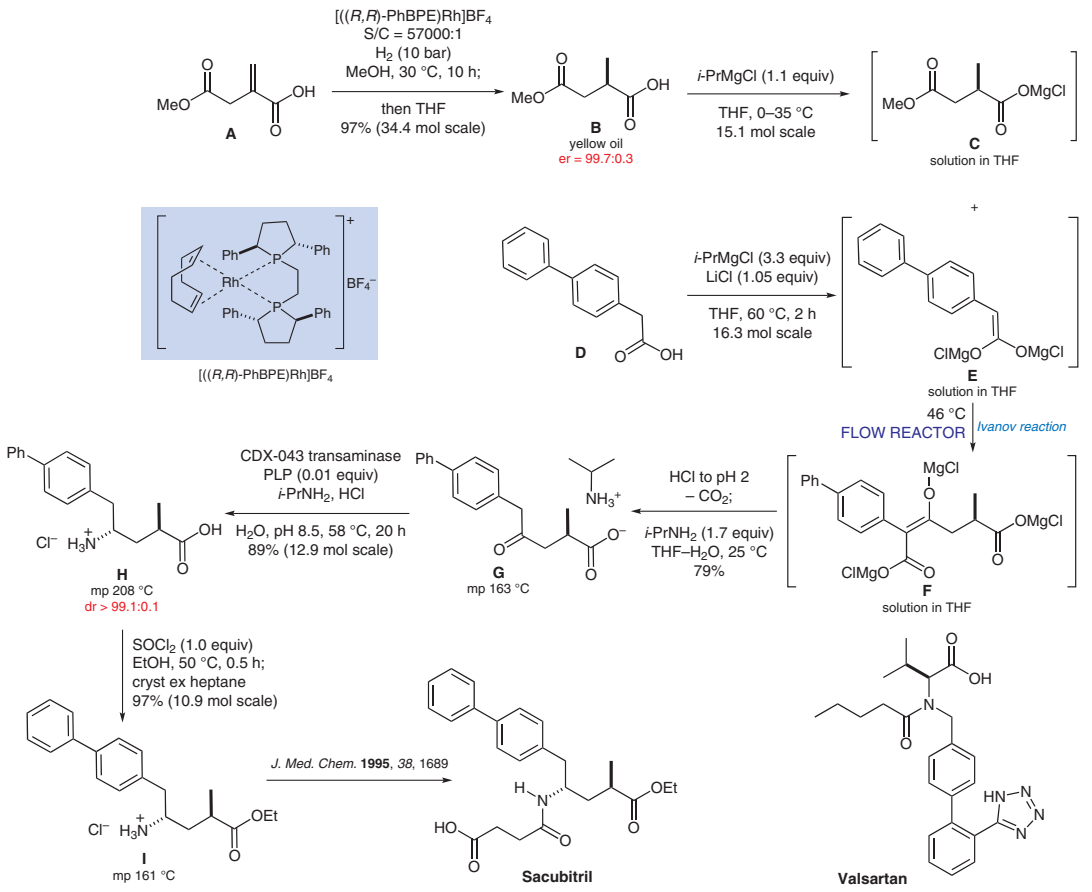
Application of Transition-Metal Catalysis, Biocatalysis, and Flow Chemistry as State-of-the-Art Technologies in the Synthesis of LCZ696

J. Org. Chem. **2020**, *85*, 6844–6853.

Synthesis of Sacubitril



Significance: Sacubitril is a nephrilysin 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 (er = 99.7:0.3).

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Synfacts 2020, 16(08), 0877 Published online: 21.07.2020
DOI: 10.1055/s-0040-1707096; **Reg-No.:** K04920SF

Category

Synthesis of Natural Products and Potential Drugs

Key words

sacubitril

LCZ696

asymmetric hydrogenation

rhodium catalysis

flow reactor

Ivanov reaction

transaminase