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Asymmetric Synthesis of Highly Functionalized Tetrahydropyran DPP-4 Inhibitor
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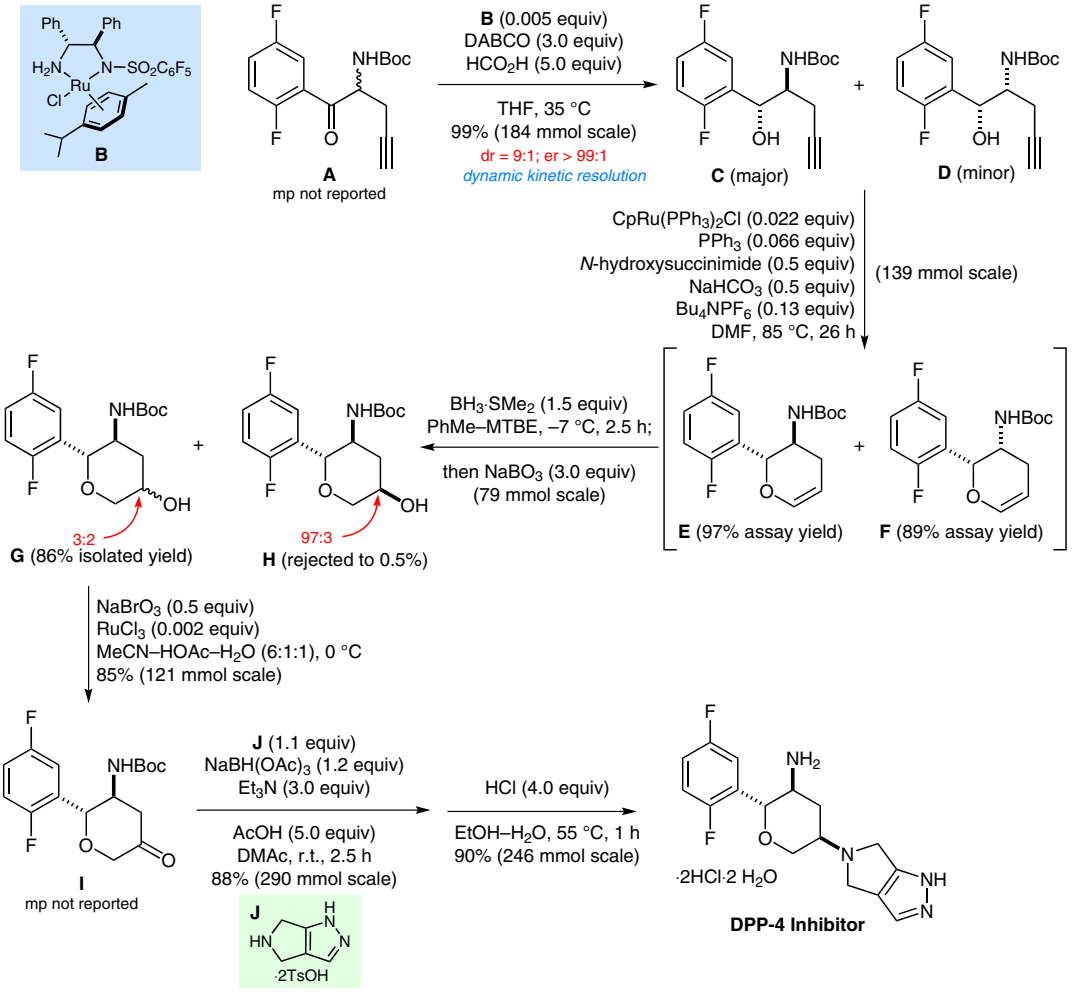
Asymmetric Synthesis of a DPP-4 Inhibitor



Significance: The target tetrahydropyran DPP-4 inhibitor was of interest for the treatment of type 2 diabetes. The synthesis depicted features three tandem ruthenium-catalyzed reactions: (1) an asymmetric transfer hydrogenation of ketone **A** with dynamic kinetic resolution (2) a cycloisomerization to form a dihydropyran ring and (3) an oxidation. The overall yield of the synthesis is 25%.

Comment: Extensive optimization of the asymmetric transfer hydrogenation established that significant contributors to the yield, dr and er included the use of the pentafluoro-substituted DAIPEN catalyst **B**, DABCO as the base and THF as the solvent. The reductive amination of ketone **I** with $NaBH(OAc)_3$ dramatically improved (dr = 19:1) using DMAc as solvent when the bis(tosylate) salt **J** was neutralized with Et_3N followed by pH buffering with HOAc.

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Category
Synthesis of Natural Products and Potential Drugs

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DPP-4 inhibitors
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dynamic kinetic resolution
cycloisomerization
reductive amination