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An Alternative Scalable Process for the Synthesis of a Key Intermediate of Omarigliptin
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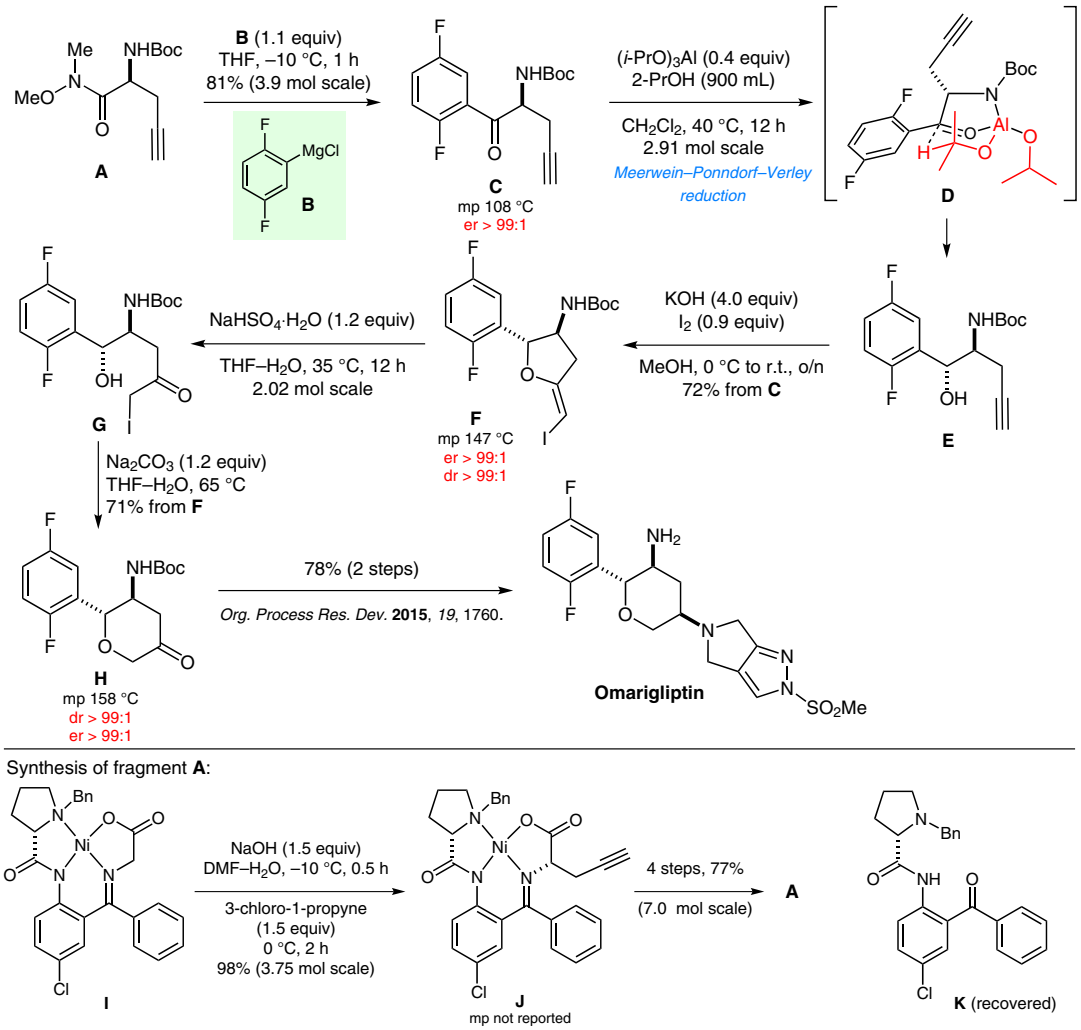
Synthesis of a Key Intermediate of Omarigliptin



Significance: Wang and co-workers describe a kilogram-scale asymmetric synthesis of intermediate **H** en route to omarigliptin, a DPP-4 inhibitor that is of interest for the treatment of diabetes. The key steps in the synthesis depicted are (1) the diastereoselective substrate-controlled Meerwein–Ponndorf–Verley reduction of α-aminoketone **C** and (2) the stereoselective intramolecular 5-*exo*-dig iodoetherification of alkynol **E**.

Comment: Synthesis of **A** began with the asymmetric α-alkylation of nickel(II) complex **I** with 3-chloro-1-propyne. The choice of solvent and temperature was critical to achieve a reproducible conversion and high stereoselectivity for this alkylation. Best results were obtained using sodium hydroxide in DMF at –10 °C. At the end of the reaction, water was added to the reaction mixture, and product **J** crystallized out from the aqueous media.

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Category
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Key words
omarigliptin
DPP-4 inhibitor
Meerwein–Ponndorf–Verley reduction
asymmetric enolate alkylation
iodoetherification

Synfact of the month

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