An Alternative Scalable Process for the 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.