G. LEMONNIER, A. CHARETTE* (UNIVERSITÉ DE MONTRÉAL, CANADA)

Stereoselective Synthesis of 2,3,6-Trisubstituted Tetrahydropyridines via Tf_2O-Mediated Grob Fragmentation: Access to Indolizidines (–)-209I and (–)-223J
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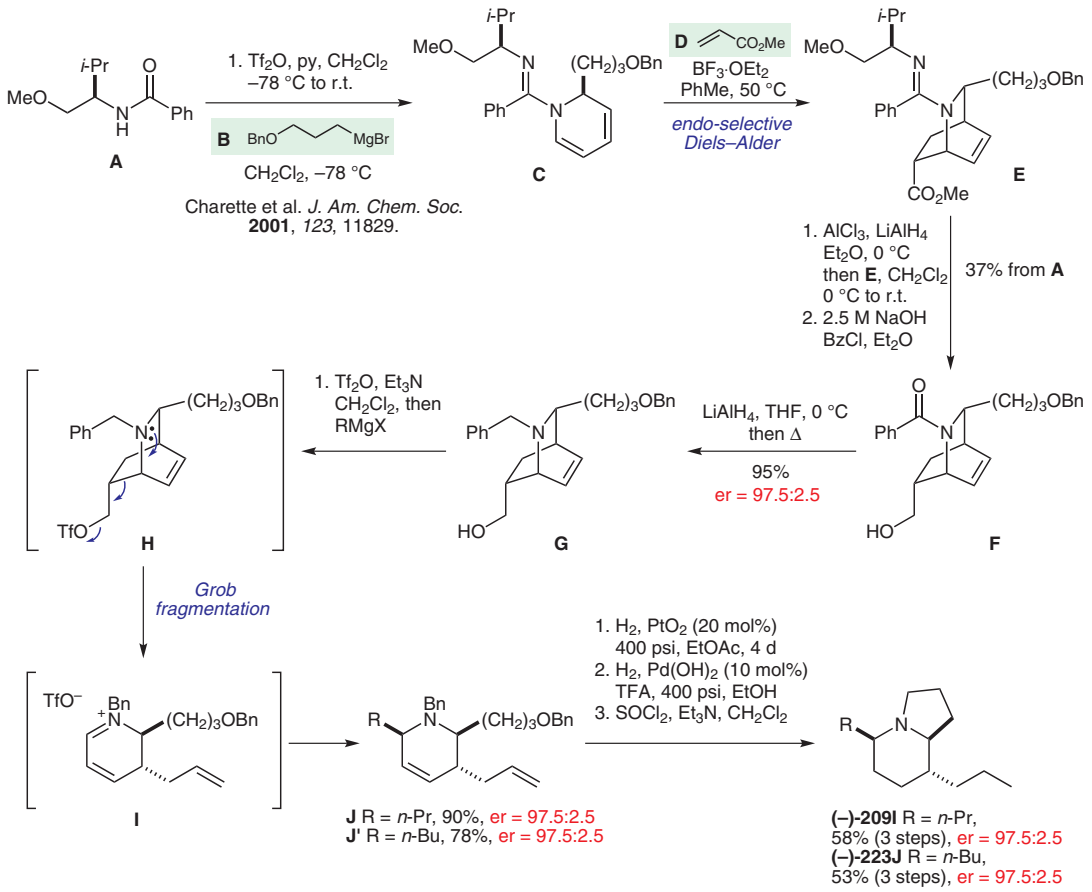
Synthesis of (–)-209I and (–)-223J



Significance: Piperidines and indolizidines provide the core of many biologically active natural products and pharmaceutical drugs. Previous methodology by Charette has involved the formation of dihydropyridinium salts from a Grob fragmentation using a stoichiometric amount of an expensive silver salt. The above work demonstrates a silver-free process via the use of an *O*-triflyl intermediate (**H**) to generate such species, with the synthesis of natural products (–)-209I and (–)-223J showcasing this methodology.

Comment: The desired scaffold for the key Grob fragmentation was constructed from valinol derivative **A**, with an *endo*-selective Diels–Alder reaction to give **E**. This core was elaborated in further two steps, with the Grob fragmentation initiated by formation of triflate **H**. Interception of the resulting dihydropyridinium salt (**I**) with the appropriate Grignard reagent resulted in high regio- (C2 position) and stereoselectivity. A further three-step synthesis gave (–)-209I and (–)-223J.

SYNFACTS Contributors: Steven V. Ley, James R. Frost
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Category

Synthesis of Natural Products and Potential Drugs

Key words

Diels–Alder reaction

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pyridinium ions