Category

Synthesis of Heterocycles

Key words

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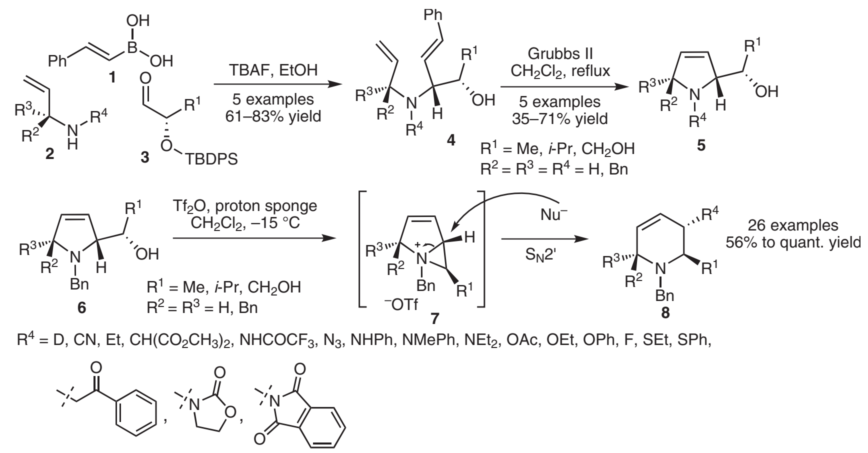
Synthesis of Enantiopure Piperidines via an Aziridinium Ring Expansion Reaction



Significance: Reported is an efficient and versatile synthesis of enantiopure 3-substituted piperidines **8** from the easily accessible chiral pyrrolinols **5** and **6**, involving an irreversible regioselective nucleophilic ring opening–ring expansion of an aziridinium salt **7** (see Review). This transformation was achieved via the irreversible formation of the aziridinium salt and subsequent ring expansion to form the piperidine under kinetic control, opening the aziridinium salt at the most hindered position. These aziridinium salts were formed by treating a hydroxymethylpyrroline with triflic anhydride in the presence of proton sponge at –15 °C. Then, a large variety of carbon, nitrogen, oxygen, sulfur and fluoride nucleophiles were introduced into the resulting tetrahydropyridine products. 5-Substituted pyrrolines are also compatible with this ring expansion. The diastereomeric purity and enantiomeric excess of the pyrroline is preserved. In all cases, only one isomer has been observed, except when organocuprates are used (–78 °C, *anti*-S_N2/*syn*-S_N2 = 18:1 when R^1 = Me). A very interesting synthesis of substituted pyrrolinols **5** via a Petasis–Mannich and ring-closing-metathesis sequence (**4** → **5**) in >99% ee and de was also reported.

Comment: The piperidine ring constitutes an important scaffold in many natural products and pharmaceuticals; for example, '32 of the Top 200 Brand-Name drugs by Retail Dollar in 2009' contain piperidine fragments. Although a number of methods are available for the synthesis of enantiopure 3-substituted piperidines, many suffer from drawbacks of substrate scope, the required separation of diastereomeric mixtures, limited substitution and lack of general synthetic procedures (J. Cossy *J. Chem. Rec.* **2005**, *5*, 70). Therefore, the present methodology allows the general synthesis of 3-functionalized, C-2 and C-6 mono-, di- or trisubstituted piperidines with high diastereocontrol. The Petasis–Mannich synthesis of substituted pyrrolinols requires the presence of α-hydroxy aldehydes **3**, which are challenging to prepare in enantiopure form even at moderate scale.

Review: T. X. Métro, B. Duthion, D. Gomez Pardo, J. Cossy *Chem. Soc. Rev.* **2010**, *39*, 89-102.

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