Enantioselective α-Arylation of Ketones: Application to the Synthesis of (–)-Epibatidine

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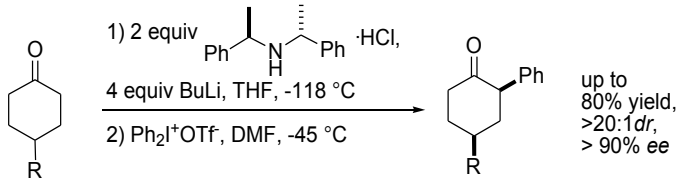
Epipedobates tricolor

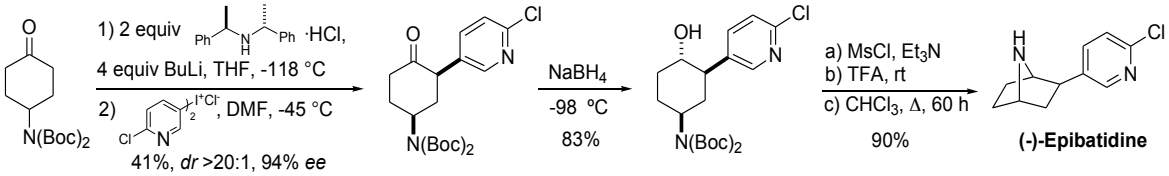
The enantioselective introduction of electrophiles α to carbonyl compounds occupies a central position in asymmetric synthesis. Although asymmetric α–alkylations have been well developed, high enantioselectivity in α-*arylation* of ketones has only been achieved in a limited number of cases.

We have developed a direct arylation reaction of cyclohexanones, employing diaryl iodonium(III) salts as electrophiles. The reaction was made enantioselective by the use of a chiral base, resulting in 2,4-substituted cyclohexaones in high yields and with high enantiomeric excesses and diastereoselectivities.



Scheme 1. Asymmetric coupling with Simpkins' base.

This methodology was applied in a short, enantioselective synthesis of (–)-Epibatidine, an alkaloid recently isolated from the Ecuadorian poison frog *Epipedobates tricolor*. The synthesis was accomplished in 6 steps and 31% overall yield, thus providing the shortest and most efficient asymmetric route to this important compound to date (Scheme 2).



Scheme 2. Synthesis (–)-Epibatidine.

V. K. Aggarwal and B. Olofsson, *Angew. Chem. Int. Ed.* **2005**, *44*, 5516-5519.