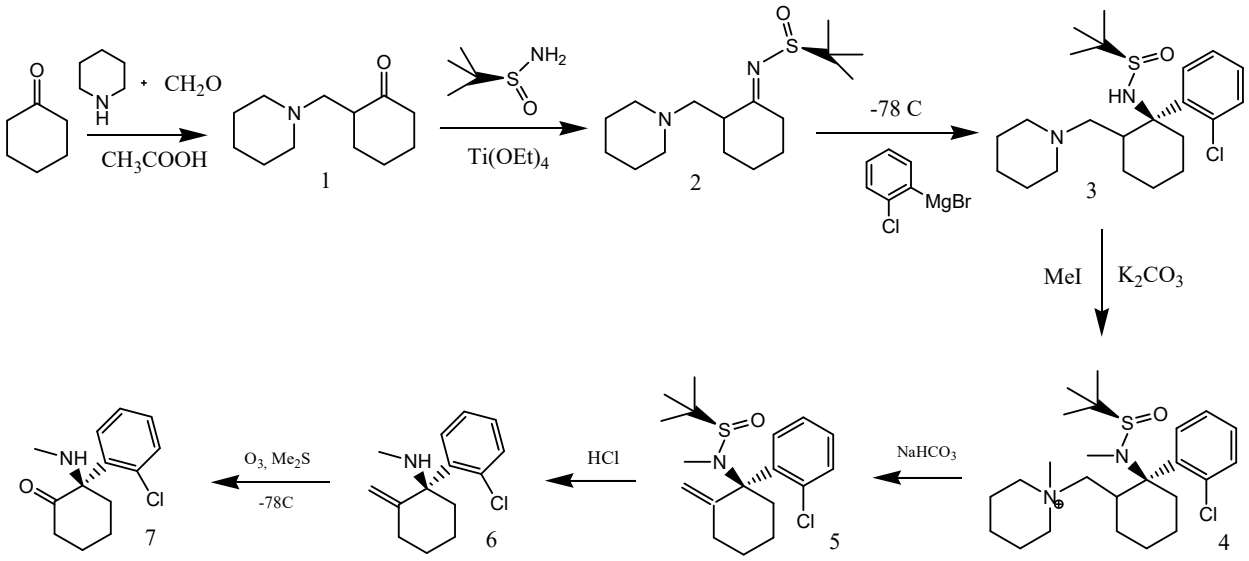
A New asymmetric synthesis of S-Ketamine anesthetic using chiral auxiliary and Mannich Base precursor

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Abstract

2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone (Ketamine), has been widely used as an anesthetic and analgesic drug. For the asymmetric synthesis of (S)- ketamine, can be use to chiral auxiliaries such as tert-butanesulfinamide (tBS). Direct condensation of tBS with aldehydes and ketones provides tert-butanesulfinylimines in uniformly high yields. The tert-butanesulfinyl group activates the imines for the addition of many different classes of nucleophiles, serves as a powerful chiral directing group, and after nucleophilic addition is readily cleaved by treatment with acid. In this work, for reach to the 2- (N-piperidino methyl)-1- phenyl cyclohexyl amine (1), we started with the cyclohexanone and using manich reaction achived to an aminoketone (Scheme 1). Then, we made the sulfinylimin (2) by the condensation of tBS with aminoketone. In addition, $Ti(OEt)_4$ is effective for reach to N-tert-butanesulfinyl ketimine in 85% yield. At next, we provided a new chiral center (3) using Grignard reagent as nucleophile at -78 ◦C (75% yield). At after multi step, finally, the (S)-ketamine synthesized under ozonolize condition and gave the good yield and enantioselectivity (85% yield and %85 ee).



Scheme 1. Asymmetric synthesis of S-Ketamine