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Synthesis of (*S*)-Ketamine via [1,3]-Chirality Transfer of a Stereocenter Created by Enantioselective Aldol Reaction
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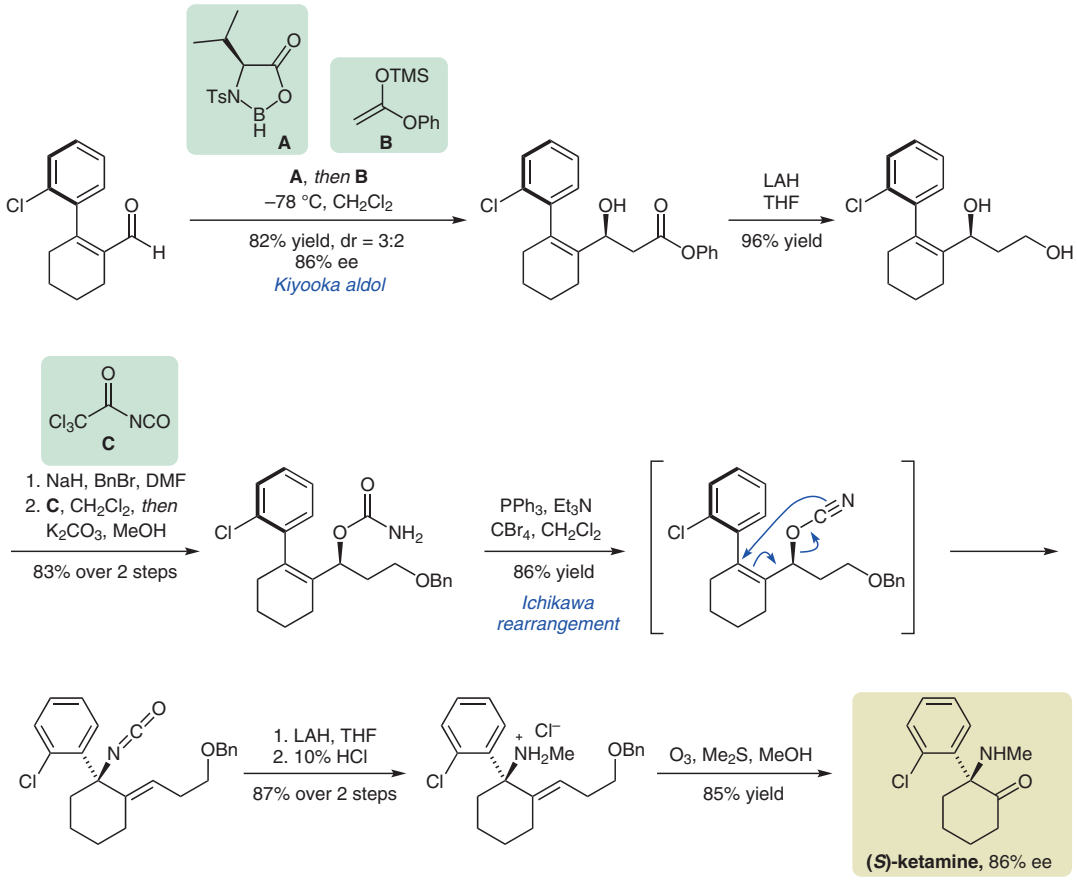
An Enantioenriched Synthesis of (*S*)-Ketamine



Significance: Ketamine is an anesthetic and analgesic that has been used in both human and veterinary medicine since 1963. While commercially available as a racemic mixture, the *S*-enantiomer has more potent anesthetic effects while also avoiding the side effects of the *R*-enantiomer such as restlessness, agitation, and hallucinations. In order to access enantioenriched (*S*)-ketamine, the Kiyooka group developed a short synthesis that provides the desired product in 36% yield.

Comment: The synthesis begins with a highly selective Kiyooka aldol reaction which affords the desired enantiomer in 86% ee as a 3:2 mixture of atropisomers. After reduction and benzyl protection of the primary alcohol, the secondary alcohol reacts with trichloroacetyl isocyanate and hydrolyzes to give a carbamate. Exposure to dehydrating conditions affords an allyl cyanate which undergoes an Ichikawa rearrangement with stereochemical retention. Reduction and HCl salt formation sets the stage for the final ozonolysis which provides (*S*)-ketamine.

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