

Asymmetric Synthesis of Esketamine

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The U.S. FDA has recently approved Spravato™ (esketamine) nasal spray as a rapidly acting antidepressant for adults with treatment-resistant depression (TRD), which represents one of the most significant milestones for depression treatment in decades. The drug substance has been produced for decades via a racemic synthesis of ketamine and its resolution. We herein wish to disclose an asymmetric synthesis of esketamine based on catalytic enantioselective transfer hydrogenation of enone and [3,3]-sigmatropic rearrangement of allylic cyanate. The catalytic asymmetric route to esketamine (99.9% ee, 50% overall yield) forms the base for the future development of the drug.