

Discovery and Development of a Novel Asymmetric Hydrogenation of an Unprotected Enamine in the Synthesis of Januvia: Process Improvements via Mechanistic Insight

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Despite the elegance and atom economy of asymmetric catalysis, its application to industrial production of pharmaceutical active ingredients has lagged the scientific progress made in academia. The Merck catalysis laboratory has undertaken a systematic analysis of the barriers to implementation of asymmetric hydrogenation at scale and has formulated a successful strategy to bring this technology in house and maximize its value to Merck. As a result, an increasing number of asymmetric hydrogenations are currently being incorporated into processes at Merck.

This presentation will provide an overview of the technology employed and catalytic processes developed, highlighting the development of an asymmetric hydrogenation process for the synthesis of Januvia®, a once-daily medicine with novel mechanism for the treatment of type-II diabetes. For this process, the initial development of an unprecedented asymmetric hydrogenation of unprotected enamines was followed by a thorough mechanistic study employing kinetic studies, spectroscopic studies of catalyst binding and theoretical calculations. In the course of the study a novel procedure for overcoming product inhibition was developed leading to a more efficient catalytic reaction.