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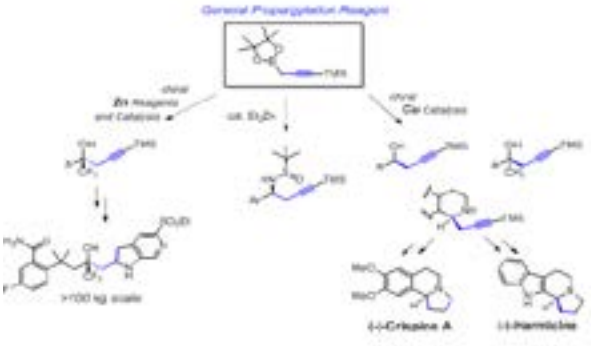
Challenges and opportunities in process research: The development of Cu and Zn catalyzed asymmetric propargylations

Daniel R Fandrick
Boehringer-Ingelheim Pharmaceuticals Inc., USA

The development of Zn and Cu catalyzed stereoselective propargylations is presented within the context to the challenges faced by process chemistry. The presentation is focused on a mechanistic perspective from the origin of the propargylation chemistry to addressing the scale up challenges and ultimate engineering towards a general asymmetric process. Access to the key propargyl borolane reagent on >200 kg scale was faithfully achieved through a flow chemistry process. Mechanistic elucidation, through kinetic analysis and DFT modeling, of the key and rate limiting B/Zn exchange revealed a Zimmerman-Traxler type transition state with inversion of the propargylic fragment. Utilization of this mechanism, allowed entry into the first example of a zinc catalyzed allenylation of alcohols and ketones. Application to sulfinimines provided high diastereoselectivity; however, significant challenges toward extension to cyclic aldimines were encountered due to the poor prior knowledge of the trimerization behavior. This trimerization was demonstrated as an equilibrium wherein previously undetermined equilibrium constants were elucidated and shown to be strongly substrate dependent. After rectification of this equilibrium, the asymmetric propargylation of cyclic aldimines was achieved allowing facile entry to the total synthesis of the indolizidines (-)-crispine A and (-)-harmicine.



Biography

Daniel R Fandrick received his BS degree from the University of California, San Diego under the guidance of Professor Joseph M O'Conner and PhD degree from Stanford University under the mentorship of Professor Barry M Trost. His graduate studies focused on the development of the dynamic kinetic asymmetric transformations of vinyl aziridines and allenes as well as their applications to total syntheses. After graduation, he joined the Chemical Development Group at Boehringer-Ingelheim Pharmaceuticals Inc., in Ridgefield, Connecticut, where he is currently a Senior Principal Scientist. At Boehringer-Ingelheim, he led the development of several novel asymmetric propargylation methodologies which provided general access to chiral homopropargylic alcohols and amines as well as application on pilot plant scale. He has published over 50 papers and numerous patents. His research interests are in the development of sustainable methodologies to provide efficient assess to pharmaceutically useful scaffolds.

daniel.fandrick@boehringer-ingelheim.com

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