2010-2011 POCC Lecture Series

March 24, 2011, 8:00 PM

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Pfizer

The Development of Scalable Processes for the Synthesis of Heterocyclic Pharmaceutical Intermediates using Batch and Flow Chemistry

Carolyn Hoff Lynch Lecture Hall
Chemistry Building, University of Pennsylvania

The Philadelphia Organic Chemist's Club

POCClub.org

Joel Hawkins received his B.S. in chemistry from the University of Illinois in 1981 and his Ph.D. in organic chemistry from MIT with Professor Barry Sharpless in 1986. He was an NIH Postdoctoral Fellow with Professor Robert Grubbs at Caltech from 1986 to 1987. As an Assistant Professor at the University of California at Berkeley from 1987 to 1993, he studied asymmetric Diels-Alder catalysts and fullerene chemistry. In 1993, he moved to Pfizer where he is a Senior Research Fellow in Chemical Research and Development and is particularly interested in the application of new technologies to drug development. In 2004 he received the Siegfried Medal from the University of Zurich and Siegfried Chemical for fundamental research in improving chemical processes.

Abstract: Case studies are presented for the development of scalable processes for heterocycles including varenicline, a CCK1 receptor agonist, a nicotinic alkaloid, tasocitinib, and celecoxib. Both batch and flow chemistry are represented, including the diastereoselective trickle bed flow hydrogenation of substituted pyridines. In one case, a very simple PAT, pH monitoring combined with HPLC profiling, revealed the source of an elevated and variable impurity and an easily implemented solution to control the process. The development and scale up of an asymmetric hydrogenation is described where focused screening is followed by DOE's with respect to continuous reaction parameters and the careful relay of tank purging and loading parameters from lab to scale. The affect of oxygen on catalyst screening is exemplified, and screening under anaerobic flow conditions is presented as an alternative. Lastly, the affect of stressing flow parameters is described for a continuous process on the pilot plant scale.