

Expedient Synthesis of Highly Functionalized Cyclic Imines

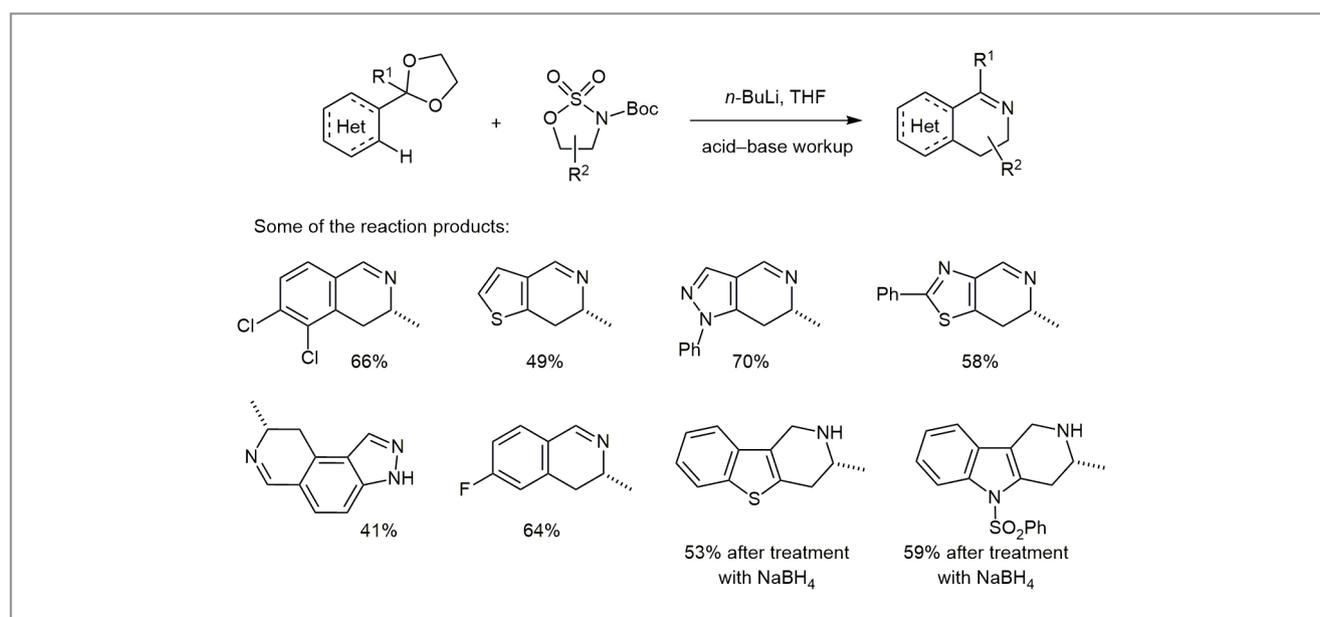
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Cyclic imines are very important building blocks in organic chemistry, and this is particularly true for cyclic imines fused with aromatic rings. Although a number of methods are available for accessing these scaffolds, most of them are affected by significant weaknesses including low regiochemical control, substrate limitations, and harsh reaction conditions. For these reasons, the development of straightforward and efficient methods for preparing cyclic imines incorporating aromatic rings remains an active area of research in organic synthesis. Recently, Dr. Thomas A. Moss from AstraZeneca Mereside (UK) reported a new efficient route for producing highly functionalized cyclic imines.

Dr. Moss said: “Since moving to AstraZeneca, the synthesis of novel, partially saturated fragments has been of particular interest to me. The pharmaceutical industry has really begun to consider the potential benefits of ring saturation, which is becoming increasingly important as we attempt to drug more and more challenging targets.” The main challenge – according to Dr. Moss – is to develop robust methodologies which can tolerate the wide array of heterocycles that commonly appear in drug molecules. “Fortunately, AstraZeneca encourages its chemists to find new and innovative solutions to synthetic problems, which then underpins our traditional drug development programs,” he explained.

Dr. Moss was interested in synthesizing a range of heteroaryl-fused cyclic imines, since these make convenient precursors to a range of products through their diverse reactivity profile. “Surprisingly, there were very few methods out there for the synthesis of these substrates, and most of those used harsh cyclization techniques,” explained Dr. Moss, adding: “Since a carbon–carbon bond-forming cyclization would be the limiting factor in electron-deficient substrates, we changed the approach to make the bond-forming stage an intramolecular condensation reaction.”

The main challenge was to build the saturated alkyl portion. Dr. Moss said: “We favored a directed *ortho*-metalation strategy as it generally gives predictable regioselectivity. Cyclic sulfamides turned out to be the best reagents for introducing this functionality.” He continued: “We have used these substrates in a number of previous methodologies and have found them to be generally superior to aziridines – the main advantage being that you don’t need strongly activating protecting groups to get acceptable reactivity in the ring opening.” Naturally the carbonyl group had to be protected during the metalation step. The AstraZeneca researcher found that cyclic acetals were not only stable, but could be deprotected simultaneously with the N-Boc under acid conditions, which allowed him to conduct the whole reaction to the



final cyclic imines in a one-pot sequential fashion. Normally it would take several steps to build such complexity, but Dr. Moss was able to access it in a single transformation from simple starting materials.

Dr. Moss concluded: "We were pleased to find that the reaction tolerated a range of common heterocycles. Although usually the carbon–carbon bond-forming reaction occurred through a directed *ortho*-metalation, it could also be performed by lithium–halogen exchange. This gives the methodology added flexibility as you are not restricted to metalation only at the most acidic carbon."

About the authors



Dr. T. A. Moss

Thomas Moss was born in Coventry (UK) in 1983. He received his Master's degree from the University of Oxford (UK), which included a final year project in Professor David Hodgson's group. He moved to Manchester (UK) in 2006 to study for a PhD in asymmetric organocatalysis under the supervision of Professor Darren Dixon. After a postdoctoral year at Imperial College London (UK), he joined AstraZeneca in 2011. His research interests are centered around developing new methods to partially saturated ring systems.