

# Anti-Markovnikov Hydroamination of Homoallylic Amines

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Hydroamination, or the addition of an amine across an unsaturated C–C bond, is an attractive disconnection for C–N bond formation. Not only is this reaction completely atom-economical, but this transformation readily couples two easily accessed functional groups. Hydroamination can form either the Markovnikov product or the anti-Markovnikov product, where the C–N bond is formed at either the internal or terminal position of the olefin, respectively. Metal catalysts are often used for promoting hydroamination reactions, which are generally hampered by high activation energy and unfavorable entropy. While the Markovnikov selective addition of an N–H bond across an alkene is relatively well known, direct anti-Markovnikov hydroamination has remained a significant challenge to synthetic chemists. This transformation is considered to be particularly challenging, as it requires the nucleophilic amine to attack the less electrophilic terminal carbon and results in the formation of the more sterically encumbered internal [M]–C bond. However, elegant approaches using nucleophilic hydrides and electrophilic amines have recently been developed, allowing for reversal of the regioselectivity at the expense of the atom- and step-economy.

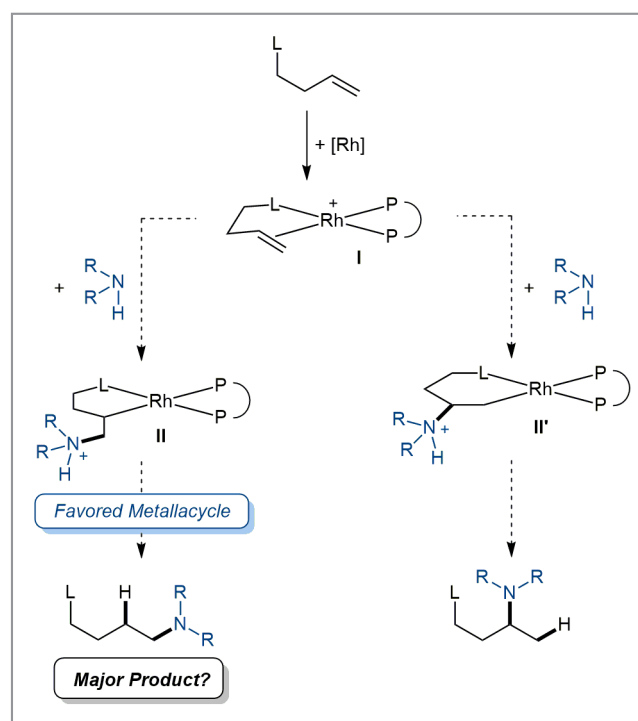
The group of Professor Kami Hull at the University of Illinois at Urbana–Champaign (USA) is interested in studying alternative strategies for controlling the selectivity of olefin functionalization reactions. Professor Hull said: “Previously, we reported that a cationic rhodium complex can catalyze the hydroamination of *N*-allylimines for the synthesis of 1,2-diamines. In this transformation, coordination by the Lewis basic imine promotes reactivity, assists in enforcing chemo- and diastereoselectivity, and slows the formation of undesired side products.” The key intermediate in this transformation is a proposed five-membered metallacycle intermediate that is formed between the rhodium catalyst and substrate. The group hypothesized that this intermediate localizes the metal center at the terminal position of the olefin and not at the internal position (which would form a far more strained four-membered metallacycle).

“With this in mind, we considered that substrates with a Lewis basic group and homoallylic olefin may also be able to undergo this transformation,” explained Professor Hull, who continued: “In this case, the Rh–C bond could be formed at either the terminal or internal position of the olefin to give rise to either a six- or five-membered metallacycle, respectively. As a five-membered metallacycle should be less strain-

ed than the six-membered alternative, we reasoned that the strain developing in the regioisomer-determining transition state may favor the formation of the anti-Markovnikov product.”

The group began their investigations with 1,1-diphenyl homoallyl amine on the assumption that this should promote bidentate substrate binding through the Thorpe–Ingold effect. To their gratification, this substrate formed the desired anti-Markovnikov product (and 1,4-diamine) when morpholine was employed as a nucleophile. “With some optimization, it was determined that 5 mol% [Rh(cod)<sub>2</sub>]<sub>2</sub>BF<sub>4</sub> and 5 mol% DPEphos in DME at 100 °C for 48 hours were the optimal conditions,” said Professor Hull. These conditions were shown to be general for a variety of relatively electron-rich secondary cyclic amines as well as *N,N*-dimethylamine, to afford the desired products in good to excellent yield and as a single regioisomer (>20:1).

Professor Hull commented: “Interestingly, the reaction conditions were less selective for anti-Markovnikov hydroamination when substrates with smaller groups adjacent to the amine directing group are employed. This suggested to

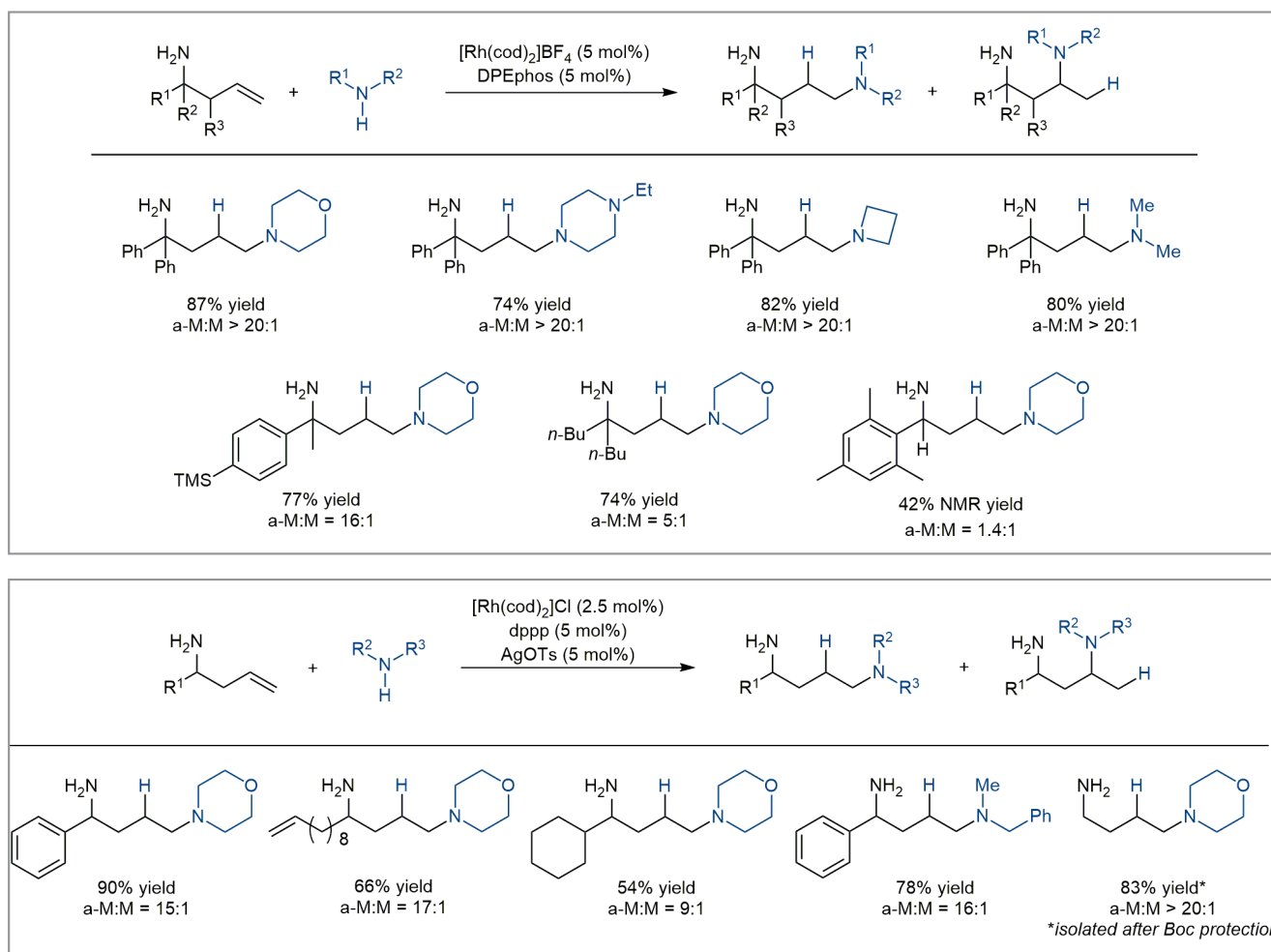


us that with DPEphos the strain difference between the five- and six-membered metallacycle was no longer sufficient to dictate the regioselectivity. Although frustrating at the time, fortunately we found that utilization of dppp restored the regioselectivity with less-hindered substrates, such that even homoallyl amine affords the desired anti-Markovnikov product.”

The Hull group is interested in investigating the mechanistic principles behind the catalysis they develop, towards a greater understanding of organometallic chemistry as a whole. Professor Hull and co-workers have previously demonstrated that proximal Lewis basic groups can direct the Rh-catalyzed anti-Markovnikov hydroamination of homo-

allylic amines. “Currently, we are investigating the mechanism of the transformation and seeking to better understand the profound ligand effect we observe, with the ultimate goal of developing a more general catalyst. We are also interested in determining if cobalt, rhodium’s smaller, cheaper, and more reactive sibling, can catalyze a similar reaction,” said Professor Hull. She concluded: “Finally, we are excited about the potential of this reaction being applied in the synthesis of biologically active compounds, as 1,4-diamines are a common functionality and prevalent in a variety of pharmaceuticals that treat neurological disorders.”

*Matthew Fenske*



## About the authors



Prof. K. L. Hull

**Kami L. Hull** received her B.A. degree in chemistry from Macalester College (USA) in 2003. She obtained her Ph.D. from the University of Michigan (USA) in 2009 under the mentorship of Professor Melanie S. Sanford. She went on to be an NIH postdoctoral fellow at Stanford University (USA) from 2009–2012 in the laboratory of Professor Barry M. Trost. Professor Hull joined the faculty at the University of Illinois at Urbana–Champaign (USA) in fall 2012.



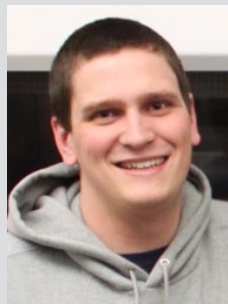
S. C. Ensign

**Seth Ensign** received his B.S. in chemistry from James Madison University in Harrisonburg, VA (USA), where he worked in the research group of Professor Debra L. Mohler. He is currently a fourth-year Ph.D. student at the University of Illinois at Urbana–Champaign (USA) under the mentorship of Professor Kami L. Hull. His research focuses on developing new, regioselective rhodium-mediated hydroamination reactions.



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His interests include the in-depth study of organometallic reaction mechanisms, obscure and interesting simple organic molecules, and reading science fiction.



K. D. Kortman

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**Lee J. Weir** received his B.S. degree in specialized chemistry from the University of Illinois at Urbana–Champaign (USA) in 2015. While studying there he was a member of the Hull Research Group from 2013–2015.