Presentation Title: **Mechanistic Investigations into Rhodium-Catalyzed Asymmetric Allylic Amination toward α-Trisubstituted α-Tertiary Amines**

Corresponding Author: Madhawee Ketipe-Arachchi
Affiliation: Wayne State University, USA
Phone: (+1)313-802-9403
Email: gp8332@wayne.edu
WhatsApp: (+1)313-802-9403
Other Authors: Hien Nguyen, Bernhard Schlegel

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Abstract:

Forging quaternary stereocenters has long been sought after in the realm of modern synthetic chemistry. Among the fundamental structural motifs in organic chemistry, the synthesis of α-tertiary amines poses a surprisingly formidable challenge. Nonetheless, α-tertiary amines are privileged structures present myriad of bioactive molecules. A highly efficient asymmetric synthesis of α-trisubstituted α-tertiary amines from racemic allylic trichloroacetimidates has been developed using chiral bicyclo[2.2.2]octadiene-ligated rhodium catalyst. This protocol achieves highly sterically demanding bond assembly leading to a fully substituted carbon and fully substituted nitrogen, in a single step offering precise control over regioselectivity and enantioselectivity to furnish α-trisubstituted α-tertiary amines. The synthetic utility is showcased by efficient preparation of α-tertiary amines featuring pharmaceutically relevant secondary amine cores with good yields and excellent selectivities (branched:linear >99:1, up to 99% enantiomeric excess). Mechanistic investigations were conducted using synergistic experimental and computational studies. DFT calculations and kinetic experiments showed that the rate of conversion of the less reactive π-allyl intermediate to the more reactive isomer via π-σ-π interconversion was faster than the rate of nucleophilic attack onto the more reactive intermediate. Altogether, these data imply that the *Curtin-Hammett* conditions are met in the amination reaction, thereby leading to dynamic kinetic asymmetric transformation. The thermodynamically more stable π-allyl intermediate was found to be kinetically more reactive, leading to the major (*S*)-enantiomer of the product. Isotopic labeling experiments established that the nucleophilic addition occurs *via* an *outersphere* nucleophilic addition with an inversion of π-allyl stereochemistry. The observation of complete branched selectivity is noteworthy and as corroborated by computations might be attributed to the hydrogen bonding interactions between β-oxygen of allylic substrate and amine-NH that greatly assist the delivery of amine nucleophile onto more hindered internal carbon of the π-allyl intermediate.

Biography:

Madhawee Ketipe-Arachchi embarked her academic journey earning BSc degree from University of Sri Jayewardenepura, Sri Lanka, in 2017. She earned her PhD (Organic Chemistry) from Wayne State University, USA, in 2023. Currently she works as a R&D scientist at AAPharmaSyn, and her research interests focus on the development of new asymmetric methods for the synthesis of bioactive molecules, mechanistic studies and medicinal chemistry.