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VIRTUAL CHEMIST or computer-aided design in asymmetric catalysis

The field of asymmetric catalysis has revolutionized organic synthesis over the past fifty years, not only by making new reactions possible or faster, but also by promoting the synthesis of a single stereoisomer as the main product.[1] However, the development of new chiral catalysts remains a real challenge that often results in a long and laborious process, requiring the synthesis and evaluation of several ligands and catalysts in an iterative manner. To address these challenges, the Moitessier group developed VIRTUAL CHEMIST (VC), a computational platform integrating physics-based methods to predict stereoselectivity.[2] While VC has successfully reproduced over 350 stereoselectivities across multiple reaction classes, its accuracy remains insufficient for ranking catalysts.

This talk presents a new approach to enhance VC by integrating machine learning and transition state optimization to improve both accuracy and efficiency. A refined transition state search algorithm will be discussed to selectively optimize promising catalysts. This machine learning model trained on VC-generated data will predict catalytic performance, even for reactions with limited experimental data. Finally, generative models will be employed to design novel catalysts, with experimental validation of computationally predicted candidates. This will be demonstrated on an asymmetric organocatalyzed Diels-Alder reaction where the reaction mechanism was studied more thoroughly. In particular, our group was able to show that the pKa of various catalysts could be linked to the catalytic activity and hence build a pKa predictor based on Graph Neural Network to include this information within our platform.[3] By merging computational and experimental chemistry, this research aims to accelerate catalyst discovery, making computational tools more accessible for organic chemists and advancing the integration of Machine Learning in reaction design.

[1] S. Pinus, J. Genzling, M. Burai-Patrascu, N. Moitessier, Nature Catalysis 2024, 7, 1272-1287. [2] M. Burai Patrascu, J. Pottel, S. Pinus, M. Bezanson, P.-O. Norrby, N. Moitessier, Nature Catalysis 2020, 3, 574-584. [3] J. Genzling, Z. Luo, B. Weiser, N. Moitessier, ChemRXiv 2024.

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