Autonomous discovery, development and optimisation of organocatalytic reactions through intelligent chemical robots

Chirality plays an important role in nature, as molecules of different chirality can exhibit vastly different properties. Organic compounds that have nonsuperimposable mirror images are called enantiomers. For example, *R*(+)-limonene exhibits the smell of oranges while its mirror image, *S*(-)-limonene, smells of lemons. This inherent molecular property is also very important in drug molecules because while one enantiomer might exhibit the desired pharmaceutical activity, the other one might be inactive or, even worse, toxic. Therefore it is important to selectively synthesize molecules with the desired chirality. A large part of the field of chemical catalysis, and in particular of organocatalysis, is devoted to the selective synthesis of chiral molecules. In organocatalysis, a small organic molecule, the catalyst, is used to imprint the right chirality during the chemical reaction it catalyses. Recently, the Nobel prize has been awarded for the development of methods that allow the synthesis of chiral molecules using such chiral organocatalysts. However, despite the huge progress made in recent decades, we are still far from being able to efficiently design the synthesis of any chiral molecule. Usually, the development of new (organo)catalytic methods requires extensive and time-consuming optimisation, which is usually performed manually. Therefore new enabling technologies are needed to speed up this process. Automation and robotic approaches have started to play an important role in the chemical sciences. The use of automated approaches can speed up the research process, make the experiments more repeatable and free researchers from repetitive tasks, so they can focus on the design of new transformations. In this project, we propose to investigate the field of organocatalysis with chemical automation and robotics that will ultimately be guided by artificial intelligence. We will construct a high-throughput platform with unique specifications capable of performing chemical experiments, automated purification of the products and determination of optical purity with an experimental throughput of about 36 experiments per day (which is equivalent to about one month of work of an advanced organic chemist). The platform will work as follows: The robotic arm will be responsible for the preparation of reaction mixtures and liquid handling, a preparative HPLC for purification and characterization of reaction mixtures, and HPLC with chiral stationary phase for enantiomeric excess determination. The experiments to be performed by the platform will be scheduled and arranged to maximize the experimental throughput. First, we will investigate the usefulness of the constructed platform as a part of the reaction self-optimizing system, for which the goal will be to maximize the enantiomeric excess and yield of a given catalytic reaction. Then we will examine the autonomous discovery of the new organocatalytic reactions, by a robotic screening of the new combinations of electrophiles and nucleophiles. The robotic platform will be working in a so-called closed-loop, where the outcome of previous experiments will be feed to an artificial intelligence, that will use this information to decide what steps to take next, thus continuously learning and improving its performance. We will also use the platform as a robotic assistant to investigate subtle effects in organocatalysis such as solvents and non-linear effects that are hard to investigate manually due to their time-consuming nature. The project will generate significant new knowledge and data how intelligent chemical robots can be applied to assymetric synthesis and show organic chemist community how human experimenter can be assisted by automation.