Public summary of PhD-thesis of Cecilia Bottecchia
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Visible light-induced organic chemistry at the microscale enables modification of bioactive molecules

The use of visible-light to drive chemical transformations has attracted a lot of attention in the field of organic synthesis as a sustainable alternative to the thermal activation of organic substrates. Researcher Cecilia Bottecchia demonstrated how the use of a photocatalyst - a molecule that can harvest visible light - combined with the implementation of miniaturized continuous-flow reactors can open new horizons for the modification of amino acids and peptides under mild reaction conditions.

Sunlight strikes our planet every hour with more energy than we consume in a whole year. Therefore, throughout the years many researchers have worked on the idea to employ solar light to activate organic molecules and to use photochemistry as a suitable alternative to thermally-induced chemical transformations.

The mild reaction conditions given by light activation are also of particular interest for the modification of biomolecules, as they tend to degrade at high temperatures. Moreover, as a consequence of the growing interest in peptides as drug candidates, the need for selective chemical transformations aimed at the modification of amino acids, as well as robust techniques to incorporate exogenous entities in peptides and/or proteins, are of fundamental importance in chemical biology.

This research focused on the development of methods for amino acid modifications in peptides, relying on the use of visible light. To achieve this goal, the main research problems to be addressed were the choice of appropriate catalytic systems to harvest visible light and the design of suitable reactors necessary to carry out these transformations.

Up to date the use of sunlight to drive chemical reactions is still far from reality. Photochemical transformations are mostly performed under irradiation from artificial UV-light sources, as the vast majority of organic molecules only absorbs light in the UV-range, which is only a a minor percentage of the solar irradiance. Moreover, the high costs, poor efficiency and health risks associated with the use of UV lamps render the implementation of UV-photochemical reactions impractical and expensive on the large scale. Safe, inexpensive and tunable new visible light sources such as LEDs, led to the recent popularity of photoredox catalysis. By employing light-harvesting molecules, known as photocatalysts, reactions otherwise unattainable under thermal or UV activation became possible, and resulted in milder and more sustainable reaction conditions.

Despite these advances in the use of visible light to activate organic substrates, the main practical issue preventing the widespread use of photochemical transformations in the chemical industry is that efficient irradiation of the reaction vessel is difficult on a large scale.

To overcome this hurdle, we tested the use of continuous-flow microreactors. The narrow channels of typical microreactors - internal diameter below 1 mm - ensures a uniform irradiation of the entire reaction mixture and these type of reactors proved to be highly suitable for photochemical applications. As an example, we successfully developed three different reactions for the modification of the amino acid cysteine - chosen as ideal target to be modified, owing to its relatively high reactivity and to its low abundance in peptides and proteins. The implementation of continuous-flow reactors

specifically designed to carry out these transformations afforded increased yields and reduced reaction time compared to batch methods.

Thus, this research illustrates how the powerful combination of photoredox catalysis and continuous-flow microreactors can result in novel approaches for amino acid modification. Possible future applications of these methods could involve the late stage modification of therapeutic peptides, such as their decoration with cytotoxic drugs, tracers or tools for immobilization.

Title of PhD-thesis: Photocatalytic modification of bioactive molecules in continuous-flow microreactors. Promotor: Dr. Timothy Noël, TU/e.