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Integrated continuous-flow photooxygenation processes with solid-supported sensitizers for the safe and sustainable production of fine chemicals and pharmaceuticals (PICPOSS)

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What is PICPOSS? – PICPOSS is a multidisciplinary and multi-institutional research project on "integrated continuous-flow photo-oxygenation processes with solid-supported sensitizers for the safe and sustainable production of fine chemicals and pharmaceuticals" (**P**rocédé **I**ntensifié **C**ontinu de **P**hoto-**O**xygénation avec **S**ensiblisateur **S**upporté pour une production durable et sure de molécules d'intérêt pour la chimie fine et l'industrie pharmaceutique) funded by the French Research Agency ANR (ANR-15-CE07-0008-

01) under its Collaborative Research Project (projet de recherche collaborative, PRC) program. The project has a total value of 503k€, started in March 2016 and will run for 42 months. It involves funded positions for one PhD student (36 months) and two post-doctoral researchers (18 and 24 months).

The PICPOSS consortium – PICPOSS consists of five partner organizations, four from France and one from Australia.

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This multidisciplinary team brings together different fields of expertise, in particular on photochemical reactor engineering & process intensification, mechanistic & preparative photochemistry, solid-supported sensitizer development, organic chemistry and continuous-flow photochemistry & reactor development. The broad and complementary expertise of the PICPOSS team will help to identify photochemical reaction and process limitations as soon as they arise, and to develop strategies to overcome these.

Research context and background – To face the growing challenges of industrial sustainability, new production technologies must be urgently developed. As part of the more general concept of "green engineering", process intensification combines a set of tools and methods that implement Green Chemistry principles into manufacturing processes.[1] Due to their resource- and energy-intensive natures, Fine Chemical and Pharmaceutical industries are especially concerned of these engineering and research needs.[2]

Organic photochemistry has the potential to emerge as a key synthesis pathway and technology for sustainable chemical production.[3] Selective transformations with high chemical and quantum yields can be typically accomplished, in many cases without any chemical activation. The ability to achieve molecular complexity and diversity with a "flick of a switch" makes photochemistry essential for the synthesis of biologically active compounds in medicine or agriculture. It also plays a crucial role in many other chemical fields including material and environmental sciences.

Among the large portfolio of photochemical transformations, **sensitized photooxygenations** involving singlet oxygen ($^1O_2$) are particularly attractive and have been applied to the oxygenation of terpenes such as alpha-pinene, citronellol or furfural, and more recently to the industrial synthesis of the antimalarial drug artemisinin. These transformations enable the incorporation of molecular oxygen under mild conditions.[4] Despite this advantage, photooxygenations have not found widespread implementations in the chemical industry. This reluctance is mainly due to the currently available technologies and procedures, which (i) require outdated batch reactors (often operating in a circulating loop and with high dilutions, requiring intensive cooling) equipped with energy-demanding mercury lamps (having limited lifetimes and high replacement costs), (ii) implement soluble sensitizers (that need to be removed by resource-intensive purifications) and (iii) commonly utilize non eco-friendly solvents (that are transparent and chemical inert but hazardous).

Continuous micro-structured technologies play a key part in the process intensification strategy. Their advantages for preparative photochemistry have been recently highlighted on lab-scales, however, flow photochemical studies in industry are still rare.[5] The combination of continuous microstructured technologies with energy- and cost-efficient **LEDs light sources** represents a promising alternative for industrial implementation of photooxy-genations under greener, safer and atom- and energy-efficient conditions.

Figure 1. Continuous-flow spiral-shaped microphotoreactor for gas-liquid photooxygenations (LGC, Toulouse).

Objectives and research goals – Ultimately, PICPOSS seeks to develop a continuous flow process for the sustainable production of fine chemicals and pharmaceuticals through sensitized photo-oxygenations. The specific research aims are:

- to **use LED-driven continuous-flow microreactors** as an energy-efficient and safe technology that increases yields and selectivity of industrially relevant sensitized photooxygenations due to the control of key operating parameters,[6]

- to **implement solid-supported photosensitizers** as a strategy to reduce or circumvent downstream separation processes, and also as an advanced photochemical synthesis concept,[7] and
- to establish a **methodology for smart scale-up** and to realize an **proof-of-concept on large demonstration-scales**.[8]

The breakthroughs developed will overcome safety and cost concerns of currently available technologies (batch reactors, energy-demanding mercury lamps, toxic solvents) and will thus open new opportunities for the industrial synthesis of valuable fine chemicals via sensitized photooxygenation. PICPOSS will focus on two benchmark reactions of industrial relevance: the photooxygenation of alpha-terpinene, a common essential oil component, and of furfural obtained from hemicelluloses contacting waste from agriculture. The anthelmintic drug ascaridole and the valuable synthesis intermediate 5-hydroxyfuran-2[5H]-one are obtained from these transformations. It is envisaged that the protocols developed by PICPOSS can be transferred to other photooxygenation reactions.

<u>Scientific program</u> – PICPOSS involves four scientific tasks, supported by an additional coordination and management stream.

Task 1 aims to study benchmark photooxygenations in batch reactors. Eco-friendly solvents will be studied and various sensitizers investigated (commercially available, advanced sensitizers synthesized in **Task 3**). Side reactions (including sensitizer decomposition) will be determined, and analytical conditions for an easy reaction monitoring in continuous-flow microreactors will be established.

Task 2 is devoted to the transfer of the benchmark photooxygenations to continuous-flow reactors using solubilized photosensitizers. It also includes the characterization of gas-liquid mass transfer in these microstructured reactors and the determination of the incident photon flux by actinometry.[9]

Task 3 concerns the preparation and characterization of various new sensitizing materials. Commercial and advanced lab-made sensitizers will be firstly immobilized on commercial silica/polymer beads. Subsequently, sensitizing colloids systems (polymer particles, microgels) will be synthetized as they offer higher surface areas and/or enable core-functionalization. These materials will be fully characterized and their stability, photobleaching, turnover frequency and quantum yields for singlet oxygen production evaluated. The most efficient and stable sensitizing materials will be tested in batch reactors (**Task 1**) for their subsequent implementation in micro-reactors.

In **Task 4**, photooxygenations will be carried out in continuous-flow microreactors using solid sensitizing materials. For each reaction, a screening of operating conditions will be performed to define an operating domain and to maximize the reactions' outputs. Experiments will also be conducted in meso-scale flow-equipment to demonstrate the proof-of-concept for scale-up. Finally, the performances of the different batch and microreactors will be compared for each of the chosen sensitizing material. Likewise, the effectiveness of the advanced solid-supported sensitizers will be demonstrated by comparison with their solubilized counterparts. Combining experiments and modelling tools, guidelines will be established to assess the feasibility of flow photochemistry with sensitizing materials, and to address smart scale-up issues.

<u>Conclusion</u> – PICPOSS is a multidisciplinary research project that will develop novel processes, technologies and protocols for industrially relevant photooxygenation reactions under continuous-flow conditions using advanced, photosensitizing materials. The results obtained by PICPOSS will be of significant relevance to the fine-chemical (e.g. fragrance & flavour) and pharmaceutical industries.

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