



**Silesian University
of Technology**

**FACULTY OF CHEMISTRY
DEPARTMENT OF CHEMICAL ORGANIC TECHNOLOGY
AND PETROCHEMISTRY**

mgr inż. Anna Wolny

Chemical Engineering

**EXTENDED ABSTRACT
DOCTORAL DISSERTATION**

**Projectable catalytic systems for the fine
chemicals synthesis sector**

Supervisor: prof. dr hab. inż. Anna Chrobok

Gliwice 2024

One of the main challenges associated with the ecological transformation of chemical technologies is the search for alternative, highly selective, active, and stable catalysts to replace the conventional acidic catalysts currently in use, as well as the elimination of volatile organic compounds and toxic reagents. Designing and implementing new catalytic systems with high activity and stability, which allow for their recovery and reuse, plays a key role in reducing the negative impact of the chemical industry on the environment. According to the concept of a circular economy, a catalyst should not only exhibit high activity and selectivity in a process but also demonstrate high stability, enabling reuse and minimal toxicity. Although homogeneous catalysts offer high activity due to the easy availability of active sites, their separation from the post-reaction mixture is challenging, which is why heterogeneous catalysts are more commonly used in industry. The distribution of active sites in heterogeneous catalysts, and thus their activity, can be enhanced by using materials with high surface area on which the catalytic phase is immobilized. An additional advantage of heterogeneous over homogeneous catalysts is their applicability in flow reactors.

The main aim of the studies conducted for this doctoral dissertation was to develop highly active and stable catalysts based on enzymes or acidic ionic liquids, dedicated to clean chemical technologies from the fine chemicals synthesis sector. An important aspect of the work was also the transformation of selected processes from batch to continuous-flow system.

Ionic liquids (ILs) are compounds composed of an organic cation and an organic or inorganic anion. Their main advantage is the ability to design their structure by selecting appropriate cations and anions, which allows for specific properties, making them widely applicable in the chemical industry. Ionic liquids are also characterized by low vapor pressure, high thermal stability, and a wide range of temperatures at which they remain liquid. A key group of ILs used as catalysts are acidic ionic liquids (AILs), which can be classified into Brønsted or Lewis types, depending on the nature of the acidic center. It is also possible to design AILs that combine both types of acidity, enhancing their catalytic potential. The main challenge in using AILs in industry is ensuring their stability and reusability. For this purpose, they are immobilized on solid supports, either physically (SILP) or chemically (SILLP) (Figure 1).

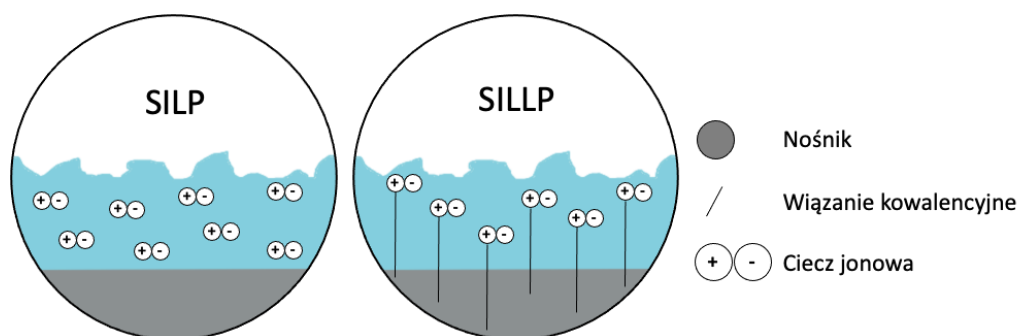


Figure 1. Graphical presentation of SILP and SILLP techniques.

Immobilization allows for easy catalyst separation from the reaction mixture and improves mass transfer to the catalytic centers, making them efficient in both batch and continuous processes. Silica-based materials are most commonly used for IL immobilization due to their well-developed surface area and controlled porosity. The stability and reusability of these catalysts give them significant potential for industrial applications. A key area of current research is the elimination of halogenated anions, which would improve process safety and efficiency while reducing costs related to corrosion and waste disposal. In the review article titled *"Silica-Based Supported Ionic Liquid-like Phases as Heterogeneous Catalysts"*, I presented an overview of the literature on the use of chemically immobilized acidic ionic liquids on silica materials as catalysts in organic synthesis.^{P1}

Enzymes are biocatalysts with an increasingly wide application in the chemical industry. Proteins are composed of amino acids, with only a few of these forming the active site, which gives them their unique selectivity and specificity in reactions. Lipases, a group of hydrolases, are the most commonly used enzymes in organic synthesis due to their broad substrate specificity and stability in organic environments. They can operate at high temperatures and over a wide pH range, making them suitable for industries such as pharmaceuticals, biofuels, and polymers. One challenge in using lipases in industry is their poor stability under changing reaction conditions. The most popular approach to increase enzyme's stability is its immobilization on solid supports, which not only enhances their stability but also their activity and selectivity. The most commonly used immobilization method is adsorption on a solid support, which must be carefully selected to ensure mechanical and thermal resistance as well as possibility of surface modification. Lipase activation occurs in a hydrophobic environment, a process known as "interfacial activation". Under these conditions, the lid covering the active site opens, allowing free access to the substrates. Hydrophobic supports such as carbon

nanotubes or hydrophobic polymers are often used for lipase immobilization. Due to its high porosity and cost-effectiveness, hydrophilic silica is also used, but surface modification with hydrophobic groups is necessary to improve lipase immobilization.

Ionic liquids play a crucial role in enzyme stabilization, creating supramolecular networks that stabilize enzymes active conformation and enhance their activity. Interactions between enzymes and ILs are key to maintaining the three-dimensional structure of proteins. Commonly used ILs for lipase stabilization include compounds based on imidazolium cations and anions such as chlorides or tetrafluoroborates. Combining immobilization and enzyme stabilization techniques in IL environments can significantly improve their efficiency. Various methods are available for combining ILs with supports, including enzyme immobilization on supports coated with ILs (SILP) or chemically modified with ILs (SILLP) (Figure 2). These techniques minimize the risk of enzyme leaching and allow for the reuse of catalysts, significantly improving the efficiency of industrial processes.

In the review article titled *“Ionic Liquids for Development of Heterogeneous Catalysts Based on Nanomaterials for Biocatalysis”*, I presented a literature review on the use of physically immobilized enzymes on SILP and SILLP-type supports as biocatalysts in organic synthesis.^{P2} Additionally, I provided a critical perspective on the application of SILP and SILLP-type biocatalysts in organic synthesis, along with future research prospects in the scientific commentary titled *“Supported Ionic Liquid Phase for Biocatalysis: The Current Applications, Synthesis, and Prospects”*.^{P3}

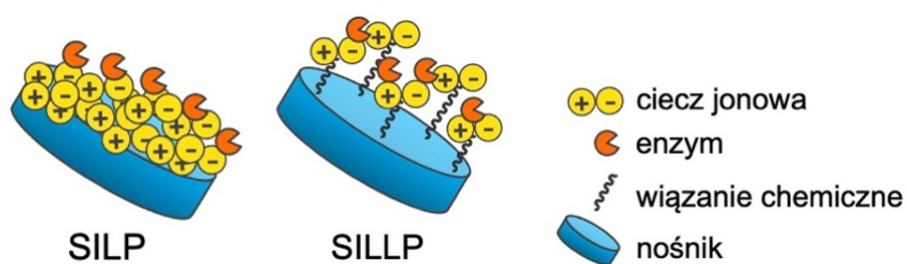


Figure 2. Stabilization techniques of enzymes by matrices modified with ionic liquids.

In line with the ongoing shift in the chemical industry towards sustainable technologies and the search for new, highly selective, active, and stable catalytic systems for processes in fine chemicals synthesis, my doctoral dissertation presents novel catalytic systems that were applied in model processes for synthesizing compounds from the fine chemicals sector.

The primary aim of the studies conducted in this work was to develop active and stable catalytic systems based on enzymes or acidic ionic liquids, specifically designed for the fine chemicals synthesis sector. I presented three new catalytic systems that were utilized in three model processes: Diels-Alder cycloaddition, kinetic resolution of ibuprofen racemate, and esterification of furfuryl alcohol with fatty acids. The new heterogeneous catalysts were based on Lewis-type acidic ionic liquids or lipase from *Aspergillus oryzae* and silica materials. A graphical representation of the developed catalysts and reaction schemes of the model processes is shown on Figure 3. All newly obtained catalysts were first subjected to detailed characterization using TGA, SEM-EDX, ^{29}Si MAS NMR, FT-IR, ICP, and adsorption-desorption analysis (BET/BJH), followed by catalytic activity tests in selected model reactions from the fine chemicals synthesis sector in a batch system.

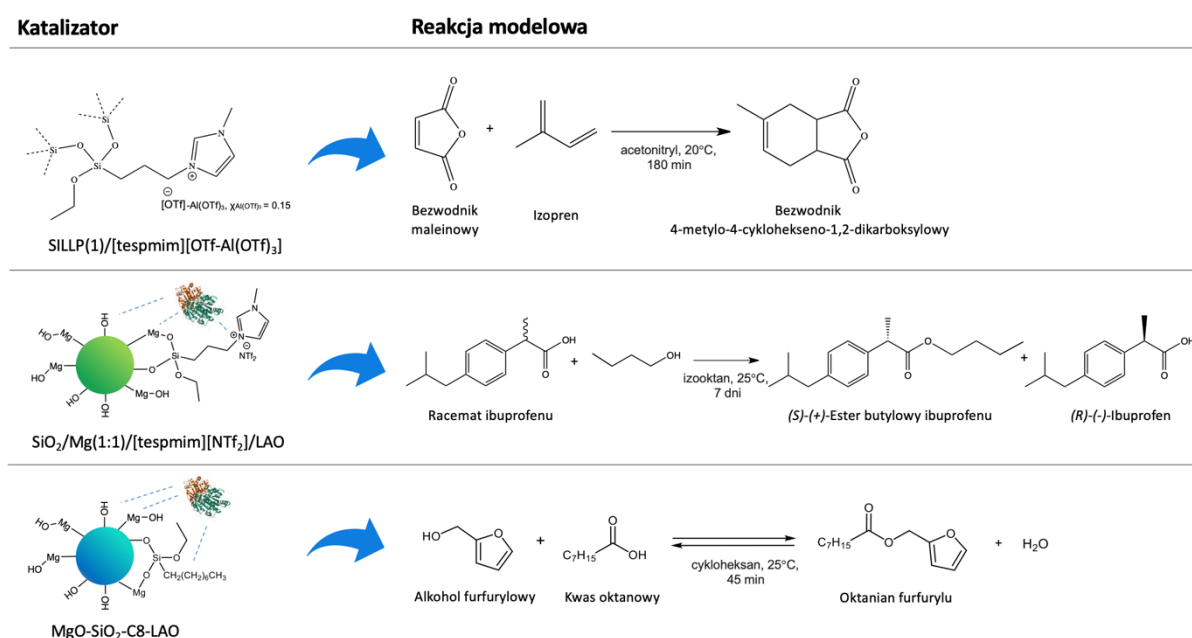


Figure 3. Structures of the catalysts and schemes of the model reactions used in this study.

In the studies on developing a heterogeneous catalyst based on the Lewis type acid ionic liquid [tespmim][OTf-Al(OTf)₃] and multimodal porous silica, I demonstrated that the order of introducing the active phase on the support's surface is crucial. The method involving the initial synthesis of the triflate ionic liquid followed by its attachment to the silica surface (with an IL content of 25.3 wt%) resulted in a catalyst that exhibited high conversion of maleic anhydride with isoprene in the Diels-Alder reaction (97%) over ten reaction cycles.^{P4}

In further research, I developed two biocatalytic systems for the kinetic resolution of ibuprofen racemate through enantiomeric esterification in the presence of lipase from *Aspergillus oryzae*. I designed a heterogeneous biocatalyst based on a SILLP carrier and hybrid silica materials, which contributed to enhanced protein activity and stability, enabling its reuse. Using native LAO, an enantioselectivity of 99.9% for (*S*)-(+)-ibuprofen ester was achieved with a racemate conversion of 34.8% after 24 hours, and 99.9% *ee* with 45.2% conversion after 48 hours, which is competitive with current literature data. The heterogeneous biocatalyst SiO₂/Mg(1:1)/[tespmim][NTf₂]/LAO (with 6.79 wt% IL and 3.96 wt% LAO) achieved a 35% conversion of ibuprofen racemate after 7 days, with 95% *ee* of the ester. Although dilution of the reaction system resulted in a decreased reaction rate, the high enantiomeric excess of (*S*)-(+)-ibuprofen ester was maintained in the subsequent reaction cycle.^{P5}

The subsequent studies I conducted as part of my doctoral work led to the development of a highly active and stable biocatalyst based on *Aspergillus oryzae* lipase and silica material doped with magnesium oxide and modified with octyl groups, MgO-SiO₂-C8-LAO. I tested the activity of the biocatalytic system in the esterification of furfuryl alcohol and octanoic acid. I demonstrated that the appropriate preparation of the matrix for lipase immobilization enables efficient immobilization on the carrier and active performance in the process. Doping silica with magnesium oxide further increased the catalytic activity of the protein. The biocatalyst I developed maintained its catalytic activity over 9 consecutive cycles of furfuryl alcohol esterification, after which I observed a slightly drop in substrate conversion from 90.2% to 84.6%. MgO-SiO₂-C8-LAO enabled the synthesis of furfuryl esters of octanoic, nonanoic, decanoic, lauric, and oleic acids with 100% selectivity.^{P6}

In cases where the stability of the catalyst in the reaction system was sufficient, I adapted the process to flow conditions (Figure 4). Flow technologies maximize production efficiency by improving mass transfer, due to the favourable surface-to-volume ratio of the introduced reagents. Additionally, continuous syntheses are easier to scale, more environmentally friendly, and easier to integrate with advanced monitoring and automation systems. All these advantages of flow-based processes contribute to increased safety and production efficiency.

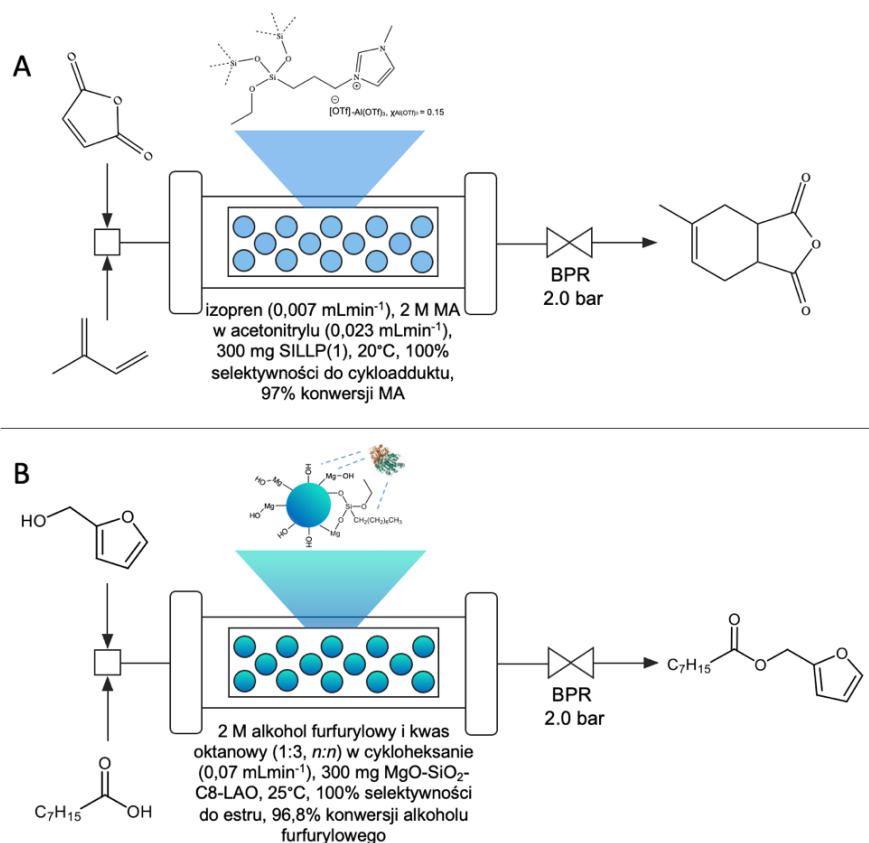


Figure 4. Graphical representation of developed processes under continuous-flow conditions.

The transformation of the model Diels-Alder reaction of maleic anhydride with isoprene to a continuous system, in the presence of the SILLP(1)/[tespmim][OTf-Al(OTf)₃] catalyst, after optimization of the conditions in the flow system, resulted in 97% of maleic anhydride conversion over 432 hours (TOF 104.3 h⁻¹) (Figure 4A). In this part of the research, the precise optimization of the synthesis pathway for SILLP triflate materials allowed for the development of a highly efficient and stable catalyst, which enabled the creation of Diels-Alder cycloadduct synthesis technology in both batch and continuous systems.^{P4}

The transformation of furfuryl octanoate synthesis in the presence of the MgO-SiO₂-C8-LAO biocatalyst enabled process intensification, achieving 96.8% conversion of furfuryl alcohol at a flow rate of 0.07 mLmin^{-1} ($\tau = 10.5 \text{ min}$) and a synthesis productivity of $6651 \text{ gh}^{-1}\text{L}^{-1}$ (Figure 4B). Under these conditions, the biocatalyst demonstrated excellent stability for 30 hours, maintaining a furfuryl alcohol conversion of 96.8%, with only a slight decrease to 85.7% observed after 48 hours of continuous performance. The productivity achieved in the continuous system was 21 times higher compared to the batch process ($6651 \text{ gh}^{-1}\text{L}^{-1}$ in the continuous system versus $320 \text{ gh}^{-1}\text{L}^{-1}$ in the batch system).

To highlight the sustainable nature of the developed method for producing furfuryl esters, I conducted a *Green Metrics* analysis of all available literature data on furfuryl ester synthesis, following the principles of Green Chemistry and utilizing the *Green Chemistry Metrics* toolkit by J. Clark. Additionally, I explored an alternative approach to evaluating the environmental impact of the developed method, analysing not only the ester synthesis process but also the earlier stages of the life cycle by preparing a synthetic tree. The summary of the green chemistry analysis concluded that the continuous synthesis technology for furfuryl esters developed in this work, using the MgO-SiO₂-C8-LAO biocatalyst, strikes a balance between a highly active, stable, reusable, and biodegradable catalyst, as well as an environmentally friendly and sustainable approach in chemical production.

List of publications:

- P1. **A. Wolny**, A. Chrobok, Silica-Based Supported Ionic Liquid-like Phases as Heterogeneous Catalysts, *Molecules* **2022**, 27, 5900. IF₂₀₂₂=4,600; MNiSW₂₀₂₂=140.
- P2. **A. Wolny**, A. Chrobok, Ionic Liquids for Development of Heterogeneous Catalysts Based on Nanomaterials for Biocatalysis, *Nanomaterials* **2021**, 11, 2030. IF₂₀₂₁=5,719; MNiSW₂₀₂₁=100.
- P3. **A. Wolny**, A. Chrobok, Supported Ionic Liquid Phase for Biocatalysis: The Current Applications, Synthesis and Prospects, *Curr. Org. Chem.* **2023**, 27, 1119–1122. IF₂₀₂₃=1,700; MNiSW₂₀₂₃=70.
- P4. **A. Wolny**, P. Latos, K. Szymańska, S. Jurczyk, A. Jakóbiak-Kolon, A. Chrobok, Construction of trifloaluminatate ionic liquid catalyst on the silica surface dedicated for continuous flow Diels-Alder synthesis, *Appl. Catal. A Gen.* **2024**, 676, 119676. IF₂₀₂₃=4,700; MNiSW₂₀₂₄=100.
- P5. **A. Wolny**, A. Siewniak, J. Zdarta, F. Ciesielczyk, P. Latos, S. Jurczyk, L.D. Nghiem, T. Jesionowski, A. Chrobok, Supported ionic liquid phase facilitated catalysis with lipase from *Aspergillus oryzae* for enhance enantiomeric resolution of racemic ibuprofen *Environ. Technol. Innov.* **2022**, 28, 102936. IF₂₀₂₂ = 7,100; MNiSW₂₀₂₂ = 70.
- P6. **A. Wolny**, D. Więclawik, J. Zdarta, S. Jurczyk, T. Jesionowski, A. Chrobok, Robust biocatalyst for the green continuous flow synthesis of esters from biomass-derived furfuryl alcohol and C8-C18 carboxylic acids *Green Chem.* **2024**, Advance article. doi.org/10.1039/D4GC03821E. IF₂₀₂₃ = 9,300; MNiSW₂₀₂₄ = 200.

Summary of Contributions:

Publication P1 (80%):

- Conceptualization of the research,
- Conducted literature review,
- Drafted the manuscript,
- Prepared all figures and tables,
- Contributed to manuscript revisions and prepared responses to reviewers.

Publication P2 (80%):

- Conceptualization of the research,
- Conducted literature review,
- Drafted the manuscript,
- Prepared all figures and tables,
- Contributed to manuscript revisions and prepared responses to reviewers.

Publication P3 (90%):

- Conceptualization of the research,
- Conducted literature review,
- Drafted the manuscript,
- Prepared all figures and tables,
- Contributed to manuscript revisions and prepared responses to reviewers.

Publication P4 (55%):

- Conceptualization of the research,
- Conducted literature review,
- Developed conditions for GC analysis and analyzed the resulting data,
- Synthesized SILLP materials and conducted experiments on catalytic activity in the Diels-Alder model reaction, optimized process conditions, conducted stability tests, and tested the catalyst's versatility with other dienes and dienophiles in batch systems,
- Analyzed SILLP silica materials using SEM-EDX,
- Isolated all obtained cycloadducts,
- Conducted activity and stability experiments on the selected SILLP material in the Diels-Alder model reaction in continuous flow, optimizing process conditions,
- Analyzed and interpreted all research results,
- Prepared all charts, figures, and tables,
- Drafted the manuscript,
- Contributed to manuscript revisions and prepared responses to reviewers.

Publication P5 (40%):

- Conceptualization of the research,
- Conducted literature review,
- Developed HPLC analysis conditions and analyzed the results,
- Conducted racemic ibuprofen separation experiments via esterification using native lipases, optimized process conditions,

- Analyzed silica supports and biocatalysts using SEM-EDX,
- Synthesized SILLP-type silica supports and biocatalysts and conducted activity tests of SILLP biocatalysts in the model ibuprofen racemic separation reaction through esterification, optimized process conditions, and conducted biocatalyst stability tests,
- Isolated the obtained ibuprofen ester,
- Analyzed and interpreted all research results,
- Prepared all charts, figures, and tables,
- Drafted the manuscript,
- Contributed to manuscript revisions and prepared responses to reviewers.

Publication P6 (50%):

- Conceptualization of the research,
- Conducted literature review,
- Developed GC analysis conditions and analyzed the results,
- Conducted esterification experiments of furfuryl alcohol and octanoic acid using native lipases,
- Modified silica supports with alkyltriethoxysilane groups, synthesized biocatalysts, and conducted activity experiments in the model esterification reaction of furfuryl alcohol and octanoic acid, optimized process conditions, conducted stability tests and examined biocatalyst versatility with other fatty acids in batch systems,
- Analyzes silica supports and biocatalysts using SEM-EDX,
- Conducted activity and stability experiments of the biocatalyst in the model esterification reaction of furfuryl alcohol and octanoic acid in continuous flow and optimized process conditions,
- Developed a method for isolating all obtained furfuryl esters,
- Analyzed and interpreted all research results,
- Conducted green process analysis of furfuryl alcohol and octanoic acid esterification using Green Metrics, compared it with other literature methods, and prepared a synthetic tree including all reagents used,
- Prepared all charts, figures, and tables,
- Drafted the manuscript,
- Contributed to manuscript revisions and prepared responses to reviewers.