

# Chemical synthesis – half-time achievements and outlook

Summary of research activities in WP4: Design and management of chemicals, materials and processes

Aji Mathew, Joseph Samec, Belén Martín-Matute, Jan-Erling Bäckvall, Per-Olof Syrén and Adam Slabon

## **A report from the Mistra SafeChem Programme**

**Title:** Chemical synthesis – half-time achievements and outlook  
Summary of research activities in WP4:  
Design and management of chemicals, materials and processes

**Date:** 2022-11-30

**Deliverable number:** D4.4

**Contact person and email:** Belén Martín-Matute, [belen.martin.matute@su.se](mailto:belen.martin.matute@su.se)

## **About the authors**

**Aji Mathew** Professor, Materials chemistry, biobased nanoparticles and functional materials, Stockholm University, Department of materials and environmental Chemistry, Sweden

**Joseph Samec** Professor, Sustainable chemistry and biomass valorization, Stockholm University, Department of organic chemistry, Sweden

**Belén Martín-Matute** Professor, Sustainable organic synthesis and catalysis, Stockholm University, Department of organic chemistry, Stockholm, Sweden

**Jan-Erling Bäckvall** Professor, Catalytic organic chemistry, Stockholm University, Department of organic chemistry, Sweden

**Per-Olof Syrén** Associate Professor, Chemistry for life science, KTH Royal Institute of Technology, Sweden

**Adam Slabon** Professor, Sustainable inorganic chemistry, Chair of inorganic chemistry, University of Wuppertal, Germany

Mistra SafeChem is funded by Mistra (project number 2018/11).

Views and opinions expressed in this report are those of the authors only and do not necessarily reflect those of the entire Mistra SafeChem Programme or Mistra.

# Progress report on textile recycling to functional additives

Professor Aji Mathew

In the first part of Mistra SafeChem, Mathew and co-workers focused on upcycling of postconsumer textile into nanocellulose using acid hydrolysis using sulphuric acid (conventional route) and further developed a new milder processing route where citric acid was used for acid hydrolysis. It was found that this process route resulted in upcycling the cotton fraction in the textiles to cellulose nanocrystals while the polymer fraction (polyester or acrylics) was recovered without any decrease in molecular weight of cellulose. Interestingly the separated cellulose nanocrystals showed residual dyes from the textiles and non-cellulosic organic impurities was estimated using NMR to be in the range of 0.2-2.2 wt%.

A deeper evaluation of the non-cellulosic organic components in the textiles was performed using non-targeted screening (in collaboration with WP3 in Mistra SafeChem) which showed several compounds and the organic compounds in the nanocrystals was lower compared to the starting textile materials. Furthermore, the organic compounds in acrylic cotton materials and its nanocrystals were relatively fewer compared to than in polycotton and its nanocrystals. The result from this work is published in *Ruiz Caldas et al, ACS Sust Chem Eng. 2022, 10: 3787*.

Figure 1 shows the sulphuric acid (conventional) process and the citric acid (milder) process.

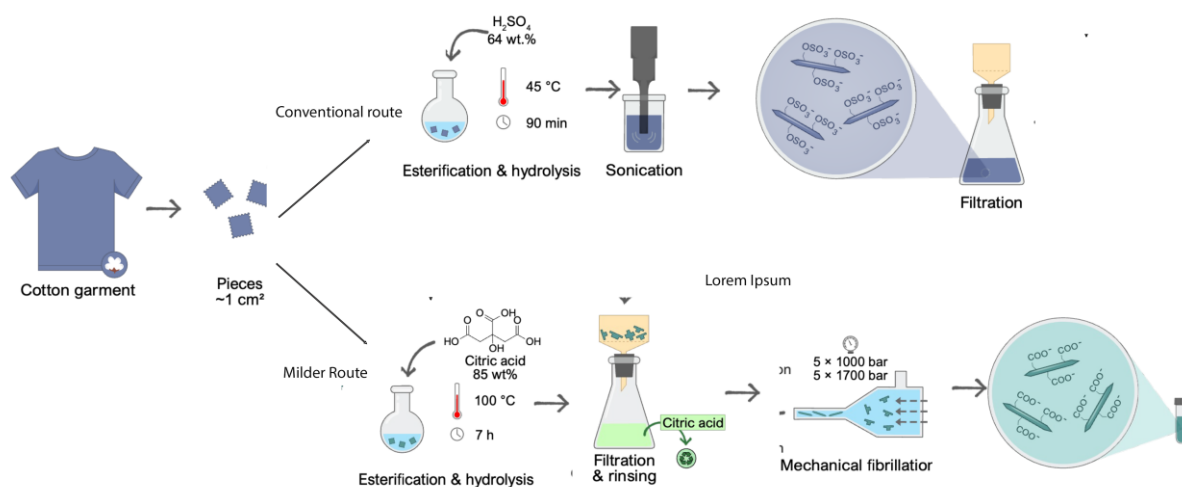


Figure 1. The sulphuric acid (conventional) process and the citric acid (milder) process.

We developed a new method to isolate cellulose nanocrystals from cotton and cotton blend textiles using citric acid. Cotton was esterified using an 85 wt.% solution of citric acid at 100°C and further disintegrate using a high-pressure homogenizer. The final product, citrated cellulose nanocrystals (CitCNCs), was a dispersion of needle-like nanoparticles with high crystallinity.

We also performed a screening LCA in collaboration with Mistra SafeChem WP5 to compare the environmental impact of the processes for producing cellulose nanocrystals from textiles following the traditional process and citric acid process. The production of cellulose nanocrystals using the traditional process from wood derived microcrystalline cellulose was used as a benchmark system. It was noted that producing the CNC from textile has a significant environmental benefit compared

to wood as the source. However, the case of citric acid hydrolysis, the environmental burden was higher. This was assigned to the citric acid production. Figure 2 shows the prepared cellulose nanocrystals and the screening LCA.

Therefore, we identified a simple way to recover around 60% of the citric acid with a purity above 90%, which paves the way to minimize the use of virgin citric acid and thereby the environmental impact of the process. This work is under preparation for publication in *Nature Sustainability*.

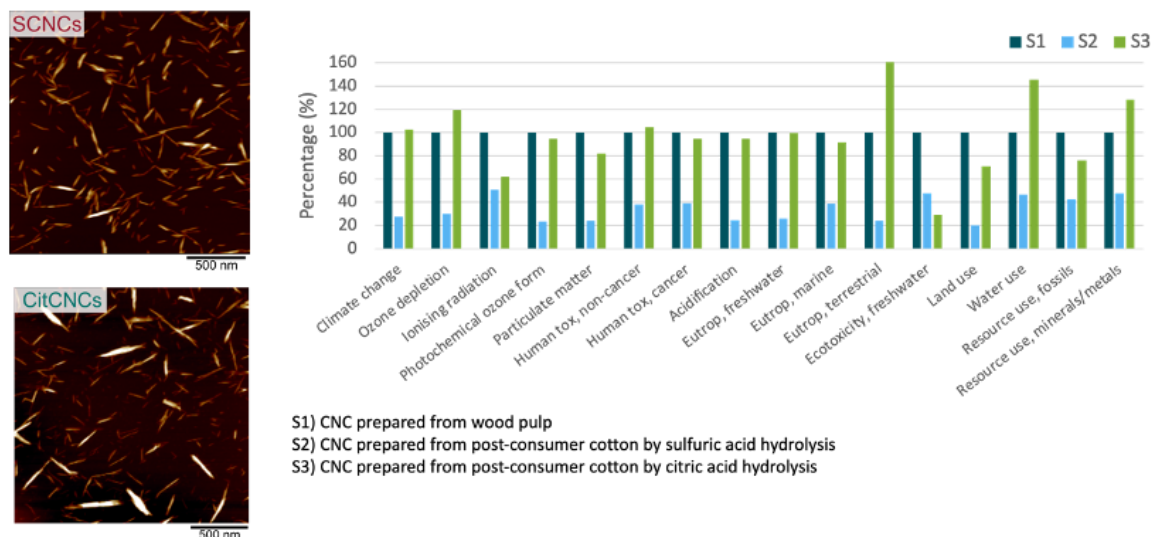


Figure 2. The prepared cellulose nanocrystals and the screening LCA.

Samec group also developed an alternate catalytic methanolysis process to recycle polycotton. The process resulted in high yield of dimethyl terephthalate (95%) and ethylene glycol (89%) while cotton fraction was recovered without any degradation. The cellulose fraction is fibrillated into nanocellulose or converted into textile fibres following the viscose process. A manuscript is under preparation.

## Valorization of forestry residues to textile fibers and biofuels

Professor Joseph Samec

Tops and branches are a low value side-stream from forestry. One third of the trees end up as tops and branches and is either left in the forests to decay or transported away to be incinerated. We have experience developing pulping methods for the woody part of this raw material that converts it to a dissolving grade pulp.

Within Mistra SafeChem, and in collaboration with Professor A Mathew and Karlstad University, we have been able to regenerate and spun viscose fibers. We have also performed an LCA that gives beneficial results on the footprint categories. We are now developing a catalytic approach in the bark part of the tops and branches.

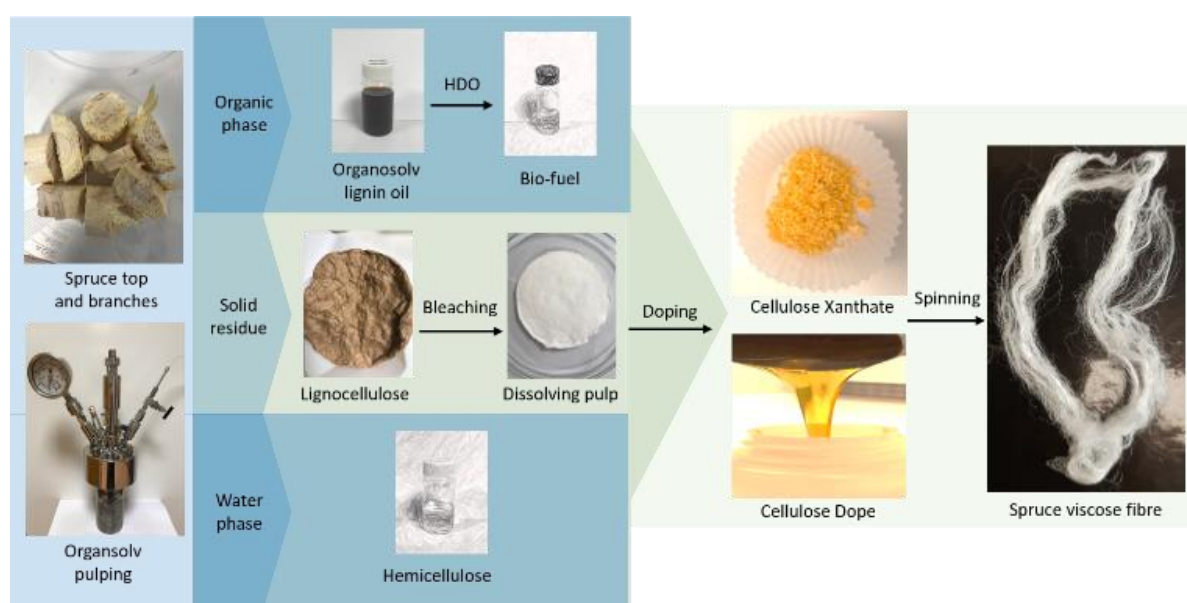


Figure 3. Outline of the viscose fiber production from spruce of top and branches.

Bark beetles infest forestry all around Europe and has, in the last five years, ago also become a problem in Sweden due to climate change. Only in 2019, ten million cubic meters of spruce was infested by the bark beetle. The wood that stems from the infection should be removed from the forests to mitigate further contamination. The wood unevenly dries and cannot be used in current pulp mills and is usually incinerated to a low value.

We have developed a fractionation to convert beetle infested spruce to a dissolving grade pulp that could be further converted to Lyocell, a man-made natural fiber. We have scaled up the process and together with Aditya Birla Group produced 200 grams in a small pilot facility. The quality of this pulp is now evaluated together with Borås Textile University. In addition to the textile fiber, the lignin has been upgraded to a biofuel. An LCA has been performed showing advantages in the footprint categories. The first part of this work has been submitted.

## Progress on catalysis for sustainable and safe synthesis of organic molecules

Professor Belén Martín-Matute

During the first two years of SafeChem, Professor B. Martín-Matute and her team have worked on new approaches to access organic compounds in a sustainable and safe manner. These studies have been done in collaboration with Mistra SafeChem WP3, WP4, WP5 and AstraZeneca. In particular, the work has been done in two main areas of research:

### Electrochemical methods that enable the use of water and of CO<sub>2</sub> as feedstock to the synthesis of organic compounds

Hydrogenation reactions are broadly used in the industry, including food, pharmaceutical and petrochemicals industries. Traditionally, hydrogen gas, which is derived from fossil resources, is used as the reductant. The hydrogenation is catalyzed by a transition metal, typically palladium, which is a scarce metal.

Within Mistra SafeChem we have worked on a method for the reduction of alkynes using water as the reductant. In this method, we have used a recyclable nickel foam as a catalyst, instead of the traditionally used palladium catalyst. Further, the Ni foam also reduces water to hydrogen electrochemically, and thus this method also substitutes hydrogen gas by tap water and electricity (*ChemSusChem* 2021). This project is being continued by applying the protocol for the reduction of alkenes (figure 4), which are more challenging substrates than alkynes.

In collaboration with WP3 and WP5, we are now focused on assessing the sustainability of the new processes, by performing life-cycle-based assessments and hazard assessments. We also perform non-target screenings for more complete chemical footprints in the life cycle assessment (manuscript in preparation). With AstraZeneca we are applying the new method to the synthesis of organic molecules of interest to the industry.

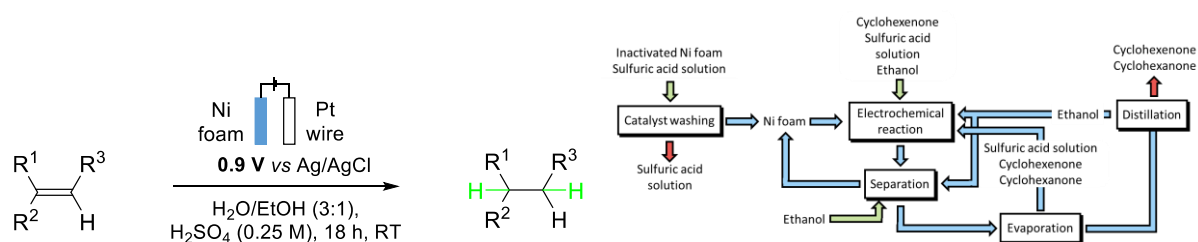


Figure 4. Olefin reduction using a Ni-foam and water as the hydrogen source, and LCA analysis.

Together with the group of Professor Adam Slabon, we have developed a protocol that enables to use carbon dioxide (CO<sub>2</sub>) as a carbon source for the production of chemicals. CO<sub>2</sub> is reduced electrochemically to CO using an electrocatalyst, and the CO thus produced is used to construct organic molecules, giving access to carboxylic acids and amides (figure 5). The electrocatalyst is fully recyclable.

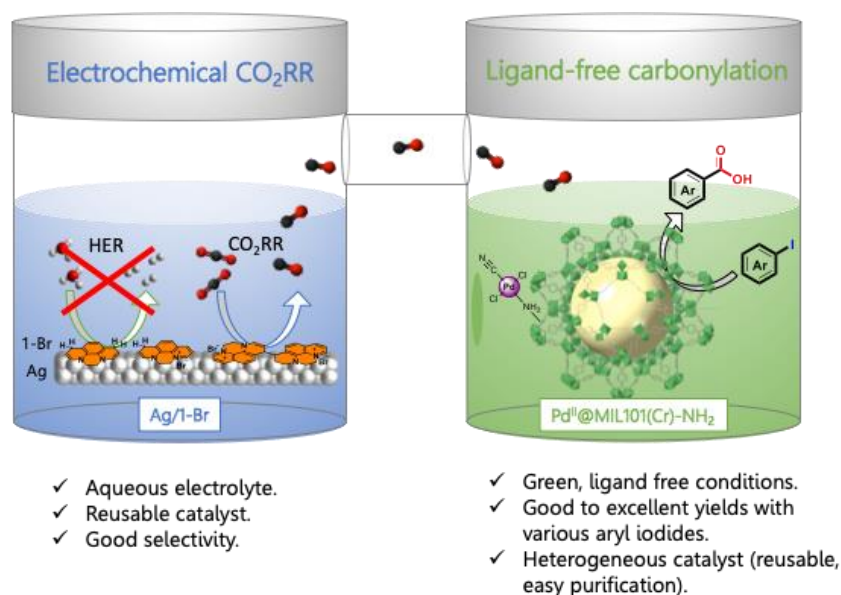


Figure 5. (Figure by Robin Gueret)

## Late-stage functionalization of complex organic compounds

Late-stage functionalization (LSF) is a desired chemoselective transformation on a complex organic molecule, such as a drug or a pharmaceutical, to provide at least one analogue in sufficient quantity and purity for a given purpose. It enables to obtain matched molecular pairs or drug-like analogues. It therefore provides fast access to new potential drugs in a single chemical transformation. LSF enables the straightforward creation of chemical libraries to access new potential pharmaceutical in a single synthetic step, saving chemical resources, particularly organic solvents, and in a fast manner. Here we have worked on two different projects:

### Late-stage functionalization via C–H activation

The direct functionalization of carbon-hydrogen (C–H) bonds is a straightforward and atom-economical approach for introducing diverse functional groups into a molecule. The method gives significant benefits in terms of time and costs, since it diminishes the number of chemical transformations needed to synthesize the target compound. This is of great importance for late-stage transformations of target molecules, which positively impacts the environmental output of the chemical industry.

Two challenges must be taken into account for functionalizing C–H bonds: the first one is the relatively inert nature of aromatic C–H bonds (bond dissociation energy at 25 °C = 113 kcal/mol), and the second one relates to selectivity, since numerous C–H bonds with similar activation energies are usually present within a molecule. WP4 have worked in close collaboration with AstraZeneca and has developed methods for the late-stage C–H methylation and C–H amination of different drugs (figure 6). The team achieved high selectivity using an iridium catalyst.

In the continuation of this research, the team will focus on replacing the catalyst in a way that it can be recycled and reused as well. The results were published in *Chem. Eur. J.* 2021, *iScience* 2021 and *JACS Au* 2022.

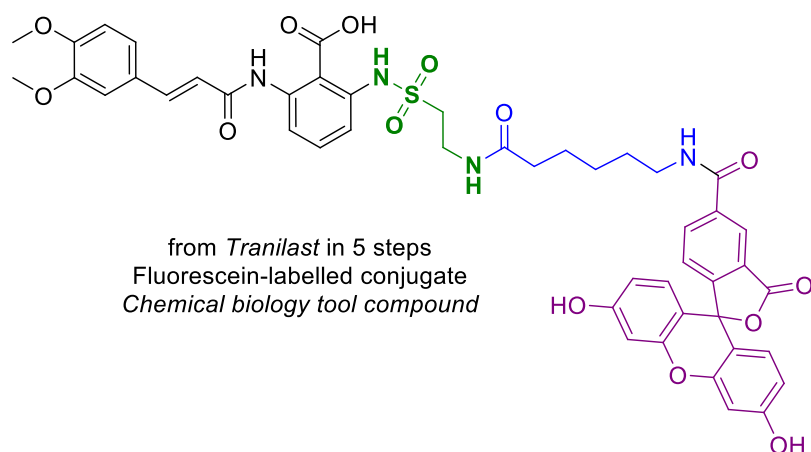


Figure 6. *Tranilast* is an antiallergic drug.

### Late-stage functionalization of amino acids

Nonnatural  $\alpha$ -amino acids are important organic molecules with outstanding applications in drug discovery, as small-molecule drugs or as components in peptide therapeutics. A simple, atom-economical, and versatile method to prepare a wide range of these compounds would also enable to construct new proteins with modified biochemical properties. Yet, the synthesis of nonnatural  $\alpha$ -amino acids by modifying available precursors is cumbersome due to their zwitterionic nature and involves a great number of additional protection/deprotection steps.

Our studies in this area have disclosed a method in which an iridium catalyst is employed to achieve the selective mono-N-alkylation of unprotected  $\alpha$ -amino acids in a single step, by using alcohols, available from bioresources, as alkylating agents. The targeted modified  $\alpha$ -amino acids are obtained in quantitative yields after a simple filtration, and do not require further purification. By using alcohols having a long aliphatic chain, we have applied the method to the synthesis of biodegradable surfactants. Further, the new NHC-Ir catalyst developed for this method is recyclable.

This work has been recently published in *Chem* 2022. In the future work we will apply this method to the synthesis of peptide-based polymers (figure 7).

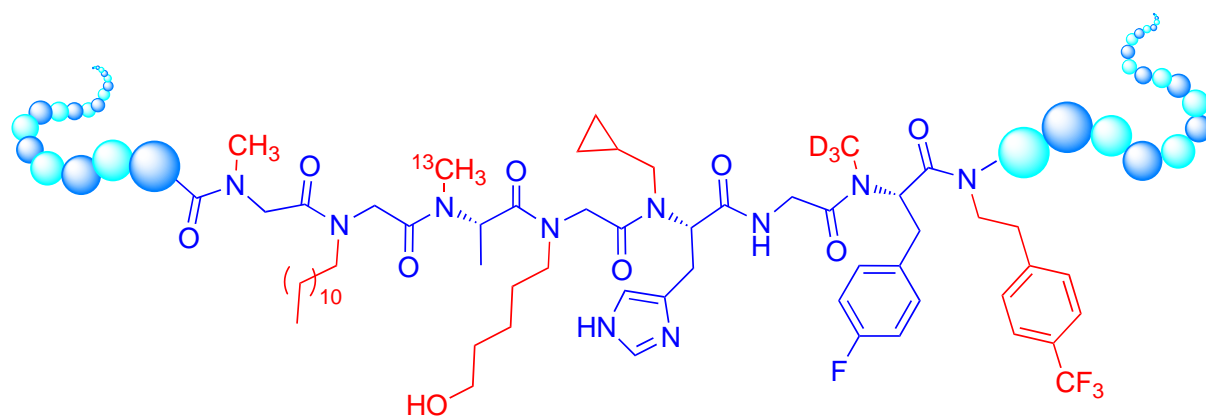


Figure 7.



## Progress report within the area of metal catalysis

Professor Jan-Erling Bäckvall

During the first two years of Mistra SafeChem, Professor Jan-E. Bäckvall and his team have worked on new approaches to access organic compounds in a sustainable and safe manner. In particular, the work has been done in the area of catalysis, in collaboration with different WP within SafeChem, as well as AstraZeneca and Perstorp.

The team has focused on the use transition metals immobilized on various materials such as mesocellular foam or nano- and microcrystalline cellulose. In some cases, co-immobilization of metals and enzymes on carriers have also been studied. In one of the early studies a heterogeneous palladium catalyst immobilized on crystalline nanocellulose for selective oxidative carbonylation was developed (*Angew. Chem. Int. Ed.* 2020, 59, 10391–10395). This heterogeneous catalyst showed a very good recyclability and could be recycled up to 9 times without any significant change in yield. There is a remarkable triggering of the Pd catalyst by silver. This heterogeneous process can be applied for a one-pot-two-step construction of polycyclic systems with multiple chiral centers (figure 8).

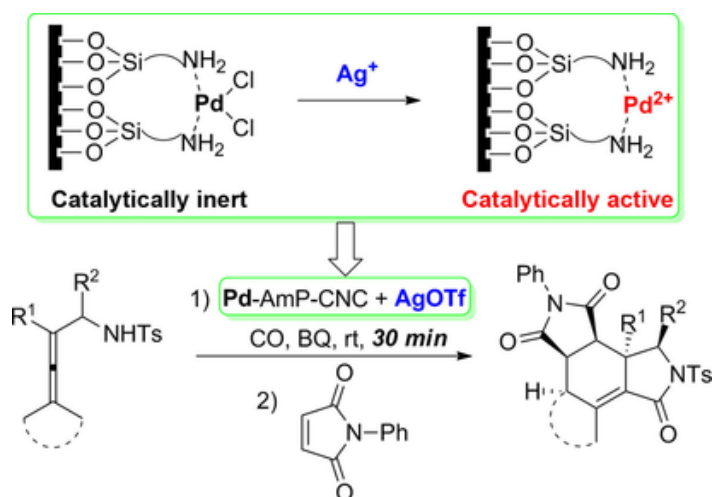
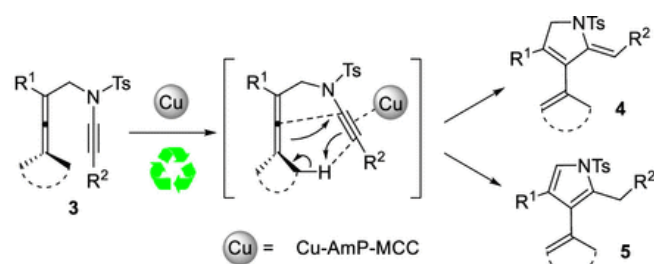


Figure 8. A recyclable heterogeneous palladium catalyst for the synthesis of complex organic compounds. *Angew. Chem. Int. Ed.* 2020, 59, 10391).

In a subsequent study an amino-supported Pd catalyst was used for the stereoselective synthesis of cyclopentenols via an oxidative domino reaction (*Angew. Chem. Int. Ed.* 2021, 60, 670–674). These compounds are key substructures and synthons of many bioactive compounds. Palladium was immobilized either on mesocellular foam or on crystalline nanocellulose and the two catalyst preparations gave very similar results. There was a remarkable recyclability of the heterogeneous Pd catalyst, where the kinetics of the reaction was almost identical in the 1st and 7th run. More recently the use of a first-row transition metal in a carbocyclization of an allenyne was reported (*ACS Catalysis* 2022, 12, 1791-1796). In the latter carbocyclization, which was a cooperation with Magnus Johansson at AstraZeneca, nanocopper immobilized on microcrystalline cellulose was employed as catalyst. Interestingly, it was demonstrated that the nanocopper catalyst could be recycled many times without any measurable loss of activity.



Cellulose based Cu nanocatalysis: high regioselectivity, good stability and recyclability

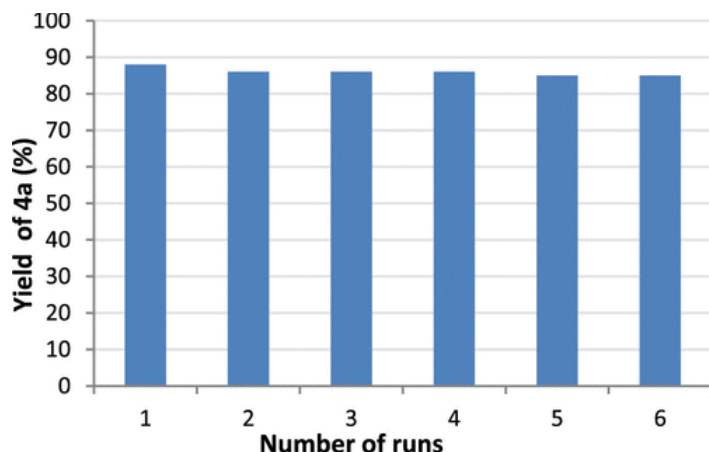


Figure 9. Top: Synthesis of indoles using a first-row transition metal catalyst. Bottom: Recyclability of the Cu-catalyst.

A review on efficient immobilized palladium in oxidative cascade reactions was reported by the Bäckvall group (*Acc. Chem. Res.* 2021, 54, 2275–2286). Another review on aerobic oxidations in metal-catalyzed reactions was also reported by the same group (*Angew. Chem. Int. Ed.* 2021, 60, 15686–15704). Iron-catalyzed cross-couplings of propargylic substrates, relevant for obtaining immobilized first-row metal-catalyzed reactions, was developed by the Bäckvall group (*Angew. Chem. Int. Ed.* 2021, 60, 22178–22183). The reaction was found to be highly stereospecific allowing the preparation of chiral allenes with high enantioselectivity. A review on the topic was written by the same group (*J. Organometal. Chem.* 2022, 964, 122304). Co-immobilization of nanometal particles (Pd) and an enzyme on microcrystalline cellulose (Avicel) led to an artificial plant cell wall for dynamic kinetic resolution of amines (*Chem. Commun.* 2021, 57, 8814–8817). In the latter reaction the immobilized metal works in tandem with the immobilized enzyme. The metal racemizes the amine and then the enzyme transforms one of the enantiomers to enantiomerically pure product.

Recently, the nanocopper catalyst mentioned above was found to efficiently catalyze the coupling of propargylic substrates with Grignard reagents to give allenes (H. Wu, Z. Zheng, J. Kajanus, M. J. Johansson, J.-E. Bäckvall: "Heterogeneous Copper-Catalyzed Cross-Coupling for Sustainable Synthesis of Diverse Allenes", manuscript to be submitted). This study is the first example on the use of a heterogeneous catalyst for stereoselective couplings of propargylic substrates. The study was done together with Magnus Johansson at AstraZeneca.

The study on heterogeneous hydrogenation of  $\alpha,\beta$ -unsaturated bio-aldehydes (together with Perstorp AB) has progressed successfully and for the first time we have been able to obtain good enantioselectivity in the heterogenous hydrogenation (unpublished results to be reported in November 2022). A patent on this work is planned.

## Progress report on enzyme catalysis

Associate Professor Per-Olof Syrén

In the first part of Mistra SafeChem, focus was on upcycling of biomass into biomaterials by green chemistries founded on engineered enzymes. An inherent bottleneck preventing the full potential of biocatalysis for upcycling of wood-derived metabolites is low activity and stability displayed by natural enzymes, preventing high yields and conversions at industry-relevant rates. We thus set out to generate biocatalysts with enhanced robustness and developed a sequence-based protein engineering pipeline for that purpose, resulting in the following project-related publications: *J. Phys. Chem. B. 2022, 126, 3809–3821*; *J. Am. Chem. Soc. 2021, 143, 3794–3807*.

Benefitting from enzymes with high stability, we generated a chemoenzymatic approach to upcycle inert wood-based building blocks of relevance to Swedish forest industry (represented by Holmen), into monomers and further onto biopolymers. Our approach enabled generation of a novel family of bio-based polyesters from biomass and coatings thereof, presented in the following project-related publication: *JACS Au 2021, 11, 1949–1960*.

In the second phase of the program, we are developing a safe-by-design approach for fragment-based synthesis, adhering to the 12 principles of green chemistry, and utilizing amide bond synthesis as a case-study. This work is performed in close collaboration with industry (represented by AstraZeneca), WP3 and WP5. Benefitting from the *in-silico* toolbox generated in Mistra SafeChem, our approach considers safety and toxicity even before onset of coupling reaction (figure 10).

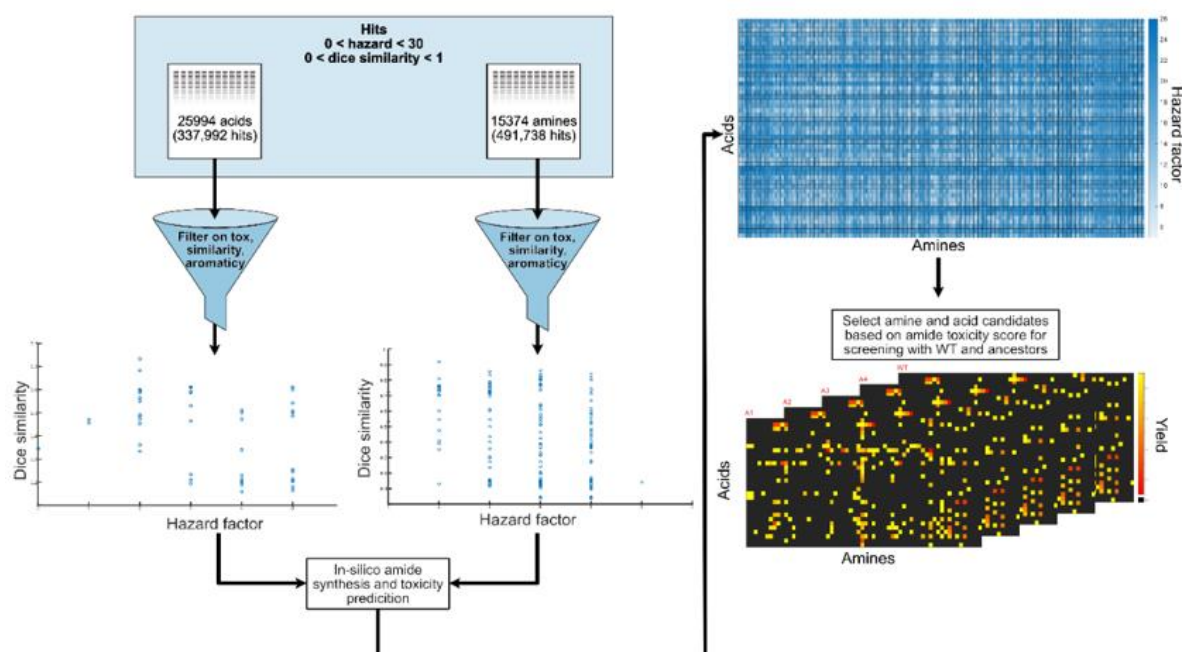


Figure 10.

As biocatalytic system, McbA was selected as amide bond-synthesizing enzyme. We performed ancestral sequence reconstruction with the aim to create improved enzyme variants with higher catalytical efficiency and stability. Computational work on McbA has produced four sequences encoding enzymes with potential ancestral folds. These sequences have been synthesized, cloned

into plasmids, and transformed into commercial *E. coli* strains, and all the strains successfully produced the ancestral enzymes. Protocols for producing and purifying the ancestral enzymes have been constructed and optimized. Initial tests for the activity of the enzymes have been made with four amine and acid combinations, and the reactions have been analysed by HPLC. Two of the ancestral enzymes, A1 and A2, showed activity, with A2 exceeding McbA in product yield for two substrate combinations. Work to perform coupling reactions from the safe-by-design approach is ongoing, most promising reactions will be benchmarked by LCA.

## Progress on tailoring of designed green chemical processes for fine particle recovery and reuse

Professor Adam Slabon

During the first two years of SafeChem, Professor Adam Slabon and his team have worked on new approaches to unravel the potential of biobased lubricants and coatings for prevention of nanoparticle hazard, which can originate from current solution.

In the first part, the focus was on identifying nanoparticle-based hazard using transmission electron microscopy in connection to combination of nanoscale spectroscopy. In brief, lubrication of an internal combustion engine is critical for energy and material losses (figure 11). Engine lubricants contain a number of functional additives including zinc dialkyldithiophosphate, which is a commonly used antiwear additive that forms by in situ decomposition a protective interface at the metal surface.

We have presented a detailed nanoscale investigation of carbonaceous soot nanoparticles generated from real engine conditions. By combining macroscale XPS with high-resolution STEM-EELS-EDX, we revealed that such a soot nanoparticle matrix contains also 3–5 nm ZnO-based nanoparticles with additions of phosphorus and sulphur, originating from the organometallic antiwear additive. Under the consideration of the obtained chemical information on the carbonaceous matrix and (ZnO:P,S) nanoparticles and the generally known suggestion of potential toxicity for soot nanoparticles, our method allows us to predict nanoparticle-based hazards from mechanochemical applications and also their formation mechanism. These are critical information and also the basis of toxicity assessment, both for theoretical predictions and experimental testing for the estimation of overall life-cycle analysis, including the environmental impact.

Our results disclose the tribofilm decomposition under real field conditions and hint toward potentially unidentified toxicological nanoparticle hazards with respect to organophosphate-containing lubricants (*Ultramicroscopy* 2020, 219, 113116, *ACS Appl. Nano Mater.* 2021, 4, 220–228). We have also developed green nitrogen-doped carbon catalyst systems that are not prone to potential nanoparticle hazards, due to their environment-neutral design (*Chem. Mater.* 2020, 32, 7273-7273).

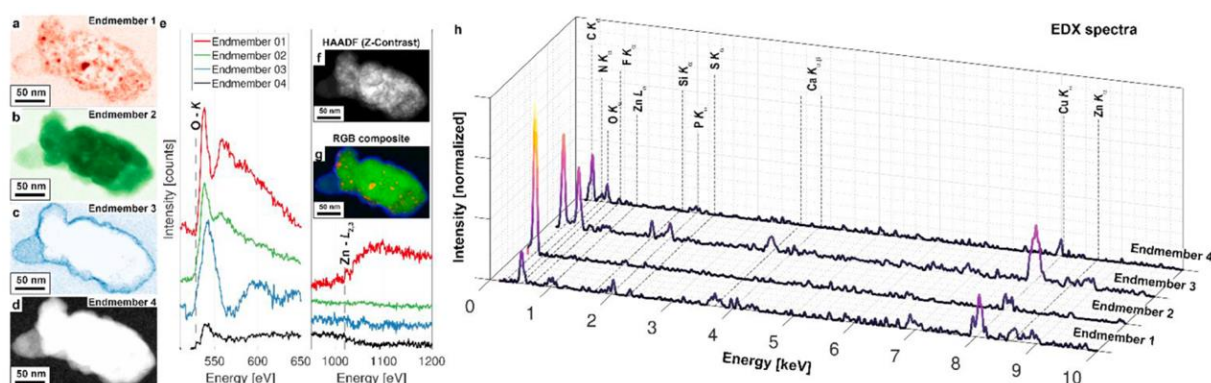
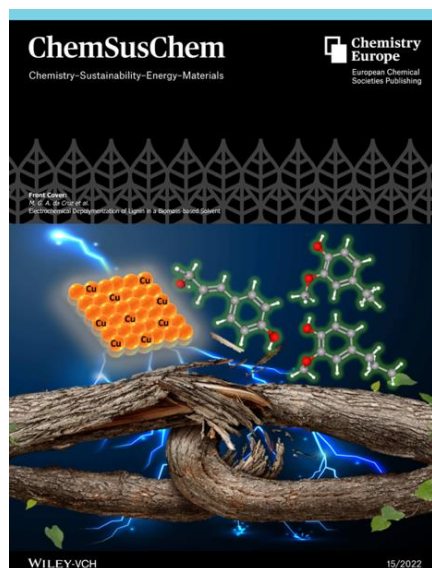


Figure 11. STEM EELS&EDX based on multimodal data fusion for analysing complex nanoparticles.



In the second part of the project, we have addressed the design principles of green chemistry to unravel the chemical structure of lignin by depolymerization for sustainable bio-coatings (*ChemSusChem* 2022, 15, e202200718).

Breaking down lignin into smaller units is the key to generate high value-added products. Nevertheless, dissolving this complex plant polyphenol in an environment-friendly way is often a challenge. Levulinic acid, which is formed during the hydrothermal processing of lignocellulosic biomass, has been shown to efficiently dissolve lignin. Herein, levulinic acid was evaluated as a medium for the reductive electrochemical depolymerization of the lignin macromolecule. Copper was chosen as the electrocatalyst due to the economic feasibility and low activity towards the hydrogen evolution reaction. After depolymerization, high-resolution mass spectrometry and nuclear magnetic resonance spectroscopy revealed lignin-derived monomers and dimers. A predominance of aryl ether and phenolic groups was observed. Depolymerized lignin was further evaluated as an anti-corrosion coating, revealing enhancements on the electro-chemical stability of the metal. Via a simple depolymerization process of biomass waste in a biomass-based solvent, a straightforward approach to produce high value-added compounds or tailored biobased materials was demonstrated.

At present, we are developing new extraction methods, because we discovered that this is the critical aspect that needs to be overcome for reductive electrochemical depolymerization. This approach is evaluated in connection to LCA and potential biodegradation as a collaboration with WP5.

We foresee that our developed methodology will allow us in the next year to elaborate on sustainable coatings based on depolymerized lignin for several applications, i.e. biolubrication and anti-wear coatings to prevent nanoparticle formation. We target for the next project year to increase the number of published articles, because we have now our own “chemical feedstock” in the form of depolymerized lignin, which gives us an advantage to conventional lignin chemistry.

## **About Mistra SafeChem**

Mistra SafeChem is a research programme with the vision to enable and promote the expansion of a safe, sustainable, and green chemical industry.

The programme is developed with the twelve principles of green chemistry as a fundament.

The research combines the potential of innovative manufacturing processes, tools for hazard and risk screening, and life cycle assessment with ambitions and opportunities for the development and growth of a safe and sustainable chemical industry.

### **More information:**

News from the programme, publications, and persons to contact you find at the website

**[mistrasafechem.se](http://mistrasafechem.se)**

### **Programme host:**

IVL Swedish Environmental Research Institute



[www.mistrasafechem.se](http://www.mistrasafechem.se)

FUNDED BY



The Swedish Foundation for  
Strategic Environmental Research