Valorisation at HIMS

Chemistry research that matters

Van ’t Hoff Institute for Molecular Sciences
The Sustainable Chemistry theme is focused on the development of new technologies that enable efficient and sustainable chemical transformations. Efficient production of chemicals is crucial to ensure a sustainable society with a growing world population increasingly facing problems associated with scarcity of materials, energy and feedstock. Catalysis is the key enabling technique to ensure atom & energy efficient synthesis and to store and release chemical energy.

The theme works on the development of new (cheap and sustainable) catalysts to improve the efficiency of chemical transformations and to efficiently convert solar/electrical energy to fuels (electocatalysis, photocatalysis) and vice versa (fuel cells), thus contributing to solving energy and sustainability problems.

The strengths of the Sustainable Chemistry team are in catalyst design, synthesis, kinetics, (spectroscopic) characterization, modeling and testing catalysts under applied conditions. The team consists of a group of highly interdisciplinary and world-renowned top-researchers. The theme is strong in both fundamental research and applied catalysis, and was recently appointed as a university Research Priority Area.

On the fundamental side, the Sustainable Chemistry team collaborates with several top-scientists and renowned scientific institutes all over the world. Applied research is performed in close collaboration with several industrial partners and in spin-off companies.

Transition(base) metal catalysis
Kinetic DFT studies & spectroscopy
Fuel cell technology & electrochemistry
Homo-, hetero-, organo- and bio-catalysis
Biomass conversion to fuels and chemicals
Bio-inspired (supramolecular & metalloradical) catalysis
Short-cuts & new methods in (enantio)selective synthesis
Homogeneous and supramolecular catalysis

Supramolecular approaches

Rational Ligand design

Bio-inspired Catalysis

Key expertise:
Hydroformylation
Asymmetric hydrogenation
C-C and C_X bond formation
Water oxidation/proton reduction
Ligand synthesis
Combinatorial approaches
Lead optimization
Kinetics/mechanism

Valorization goals
Industrial application of newly developed catalysts
Solar to fuel devices (not on the poster)
One-pot Metallo-Radical Approach to 2H-Chromenes

2H-Chromenes are important structural motifs that exist in numerous natural products (e.g., tannins and polyphenols found in teas, fruits, and vegetables) and medicines possessing interesting biological activities (Figure 1).

2H-chromenes are crucial substructure of a wide variety of known pharmaceutical agents and drug candidates, and find applications as photochromic materials and dyes. However, all previously developed synthetic methods involve waste-generating multistep reactions, use complicated pre-functionalized starting materials, have a limited degree of functional group tolerance and/or lead to formation of regioisomeric product mixtures. Therefore, the development of shorter, more efficient and broadly applicable synthetic routes towards 2H-chromenes is in demand. Building on our ‘carbene-radical’ chemistry (Figure 2), we recently developed a novel metallo-radical route to 2H-chromones.

Cobalt(III)–carbene radicals, generated by metalloradical activation of salicyl N-tosylhydrazones by cobalt(II) complexes of porphyrins readily undergo radical addition to terminal alkynes to produce salicyl-vinyl radical intermediates (Figure 3). Subsequent hydrogen atom transfer leads to the formation of 2H-chromenes in a one-pot reaction. The process tolerates various substitution patterns and produces the corresponding 2H-chromene products in good isolated yields.

The successful development of this new catalytic reaction is expected to trigger further developments in catalytic radical-induced cyclization processes for selective syntheses of heterocycles that are difficult to prepare otherwise.
Non-functionalised polyolefins (e.g. polyethene) have found their way in many commodity applications due to their outstanding properties, such as solvent resistance and thermal stability. Nowadays, these materials can easily be obtained in large scales and at low cost with very high precision of the polymer microstructures. However, due to their lack of functional groups they generally have poor surface chemistry properties.

Synthetic methods that allow controlled incorporation of polar functionalities into a polymeric carbon-chain are rather scarce. The most widely-applied commercial approach to obtain functionalised polyolefins is post-functionalization reactions of existing polyolefin chains, requiring harsh reaction conditions with limited control.

Over the past few years we developed a novel synthetic method to prepare functionalized carbon-chain polymers; Rhodium-mediated ‘stereoregular polymerization of functionalized carbenes’ proved a versatile new polymerization methodology (Figure 1).

The method involves an unusual carbene migratory insertion chain-growth process which elongates the polymeric carbon-chain with one ‘carbene carbon’ unit in each insertion step. This allows formation of highly substituted and highly stereoregular (syndiotactic) carbon-chain polymers with unusual properties.

**Figure 1. 'Rhodium-mediated 'carbene-polymerization'.**

**Figure 2. Liquid-crystalline behavior of 'poly-carbenes'**

**Variation of monomers & (co)polymers**

Besides a variety of different diazo compounds, also sulfur yildes can be used as ‘carbene-monomer’ precursors. Copolymerization of different ‘carbene monomers’ as well as copolymerization of functionalized ‘carbenes’ with ethene proved possible.

**Figure 2. Co-polymerization of carbenes and ethene.**

**Valorization goals**

Developing new synthetic methodologies for functional, stereoregular polymer synthesis based on the rhodium-mediated ‘carbene polymerization’. 
Smart Systems for Small Molecule Activation

Many challenges exist in (homogeneous) catalysis
- direct conversion of C-H and C-C bonds, formation of C-N and C-O bonds
- selective functionalization of small molecules (N₂, NH₃, H₂O, CO₂, P₄ ...)
- energy-related chemistry & biomass conversion

New concepts are required to induce paradigm shift in establishing such transformations
- cooperative catalysis with smart (‘reactive’) and adaptive ligands to activate substrates
- bioinspired bimetallic catalysis
- first row transition metal catalysis

Reactive ligand concepts are rapidly emerging as relevant alternatives to ‘classical’ catalytic approaches. We are actively pursuing these strategies, with the aim to unravel new low-energy pathways for known reactions and to uncover totally new reactivity and catalytic applications.

We have initiated a research program on first row & late transition metal chemistry with cooperative and redox-active ligands.

Expertise & Interests
(Reactive) Ligand Design
Synthesis (Inorganic and Organometallic)
Coordination Chemistry
X-ray Crystallography
Small Molecule Utilization
Cooperative Catalysis
Hydrosulffination Reactions
Photocatalysis & Energy

Valorization goals
The group is highly interested in collaborative applied research [e.g., bilateral, TKI, STW, EU] on inorganic synthesis, ligand/catalyst screening, route scouting or analysis. Proven experience with industrial projects (CatchBio, Aspect, Evonik, DSM).
Understanding Catalysts and their Performance

The rational design of catalysts and materials is often hampered by the lack of detailed understanding of their performance, i.e. their changing structural and electronic properties during reaction to understand their reaction mechanism. We apply a breath of spectroscopy techniques, using different wavelengths and energies, to provide complementary information on the system under investigation. A special focus is towards X-ray spectroscopy methods.

We do not only “just” apply available spectroscopy techniques, but also develop new techniques, including the required operando instrumentation and cells, as well as data analysis and theoretical methods.

Application of the techniques to industrially interesting catalytic processes and materials has been pursued, providing unprecedented insights in catalysts properties, reaction intermediates and mechanisms in the field of homogeneous and heterogeneous catalysis, photochemistry and photocatalysis, electrochemistry and materials science.

Example: Three Way Car Exhaust Catalysts

• Probing polysulfides and S-radical intermediates during LiS battery cycling
• Type of species and their rate of formation depending on electrolyte solvent
• Insights in battery deactivation mechanisms

Example: Industrial Ethene Trimerisation Catalyst

• Activation: [CrCl₃(decyl-SNS)] (5 mM) + 10 eq. AlMe₃
  – End state (~3 hrs): loss halide (methylation) and disproportionation
  – Catalytic Intermediate after 1 s: 4-coordinate Cr(II) with deprotonated NH

Example: LiS Battery

• Probing polysulfides and S-radical intermediates during LiS battery cycling
• Type of species and their rate of formation depending on electrolyte solvent
• Insights in battery deactivation mechanisms

Example: Pigments BiMoVOₓ

• Doping oxidic materials - analyse structural and coloutistic properties
• Screening materials incl. UHV surface science and catalysis

Valorization goals

Detailed understanding of reaction mechanisms and catalyst/material performance allow the rational design of new, better and more sustainable catalysts and materials and associated processes.
Conversion of Biomass into High-value Chemicals

90% of chemicals are derived from crude oil now. Fluctuating prices and concerns over the environmental impact of petrochemical processes require developing sustainable and more environmentally-friendly alternatives. We research on converting lignocellulosic biomass into high value chemicals using heterogeneous catalysts. Examples are conversion of glycerol/lactic acid to acrylic acid, levulinic acid to γ-valerolactone and xylose to xylitol. The interaction of the catalysts with biomass derived substrates and reaction environment are also studied by advanced spectroscopic and microscopic techniques.

Levulinic acid to γ-valerolactone

Ru/ZrO$_2$ catalyst selectively converts levulinic acid to γ-valerolactone. The catalyst is not deactivated after several recycling tests.

Ru/ZrO$_2$ catalyst

Levulinic acid $\rightarrow$ γ-valerolactone

Ru nanoparticles are uniformly deposited on zirconia support and are resistant to agglomeration.

H$_2$

100% yield

Xylose to xylitol

Ru/TiO$_2$ rutile catalyst selectively converts xylose to xylitol. The catalyst is stable and does not deactivate.

Xylose

H$_2$

Xylitol (>90% yield)

Ru/TiO$_2$ rutile catalyst

Activity of TiO$_2$ supported Ru catalyst is structure sensitive. Ru/TiO$_2$-rutile catalyst is more efficient than Ru/TiO$_2$-anatase for converting xylose to xylitol. TEM studies show that Ru nanoparticles are better dispersed with small, uniform sizes on rutile TiO$_2$. This may be due to the better interaction of RuO$_2$ (rutile structure) with rutile TiO$_2$.

Ru/anatase-TiO$_2$ catalyst. Ru is non-homogeneously distributed and particle size is bigger. Also, a mismatch between RuO$_2$ and TiO$_2$ structures is evident from the model. This indicates the importance of knowing the structural details when developing catalysts.

References

2. Carlos Hernandez Mejia, Heather Greer, Wuzong Zhou, Gad Rothenberg, N. Raveendran Shiju, manuscript under preparation.

Valorization goals

Developing efficient heterogeneous catalytic routes to chemicals from biomass.

Correlating structural properties of catalysts with activity.
Metal-organic frameworks as selective adsorbers

In the chemical, petrochemical and pharmaceutical industries separation technology is a key element in the production of pure compounds. A large portion of the production costs are associated with purification steps, for instance using solvent extraction, adsorption, crystallization and distillation processes. Metal-organic frameworks (MOFs) are a new class of porous materials whose surface area, pore structure and thermal stability depend strongly on their individual components. This makes them interesting for selective molecular separations. MOFs can separate molecules through either physical sieving or on the basis of chemical affinity and even chemical bonding.

We designed a new MOF built from lanthanum ions and pyrazine-based linkers. This MOF is microporous, with 1D channels that easily accommodate water molecules. Its framework is highly robust to dehydration/hydration cycles. Unusually for a MOF, it also features a high hydrothermal stability. This makes it an ideal candidate for air drying as well as for separating water/alcohol mixtures.

The robustness of the frameworks is confirmed by XRD and the water adsorption. The isotherms are practically identical after three consecutive activation-uptake cycles. Transient uptake measurement experiments indicate that the intra-crystalline diffusivities in LaMOF are of the order of $10^{-14} \text{m}^2\text{s}^{-1}$. Transient breakthrough simulations for water/alcohol mixture confirm that water/alcohol mixtures can be separated cleanly using our MOF.

**Figure 1.** 3D structure of [La(pydc)$_2$(H$_2$O)$_2$]·2H$_2$O. Non-coordinated water molecules were removed for clarity.

**Figure 2.** TGA curves of the MOF as synthesized (black), activated at 200 °C (red), after 24 h air exposure (black) and after 72 h air exposure (green).

**Figure 3.** Water (circles) and methanol (square) adsorption isotherms of the MOF activated at 200 °C.

**Figure 4.** Kinetic water adsorption measured at 25 °C. The continuous red line represents the model fit of the experimental data for transient uptake.

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**Valorization goals**

Developing new adsorbers for highly efficient molecular separations.
Advanced Electrochemical Devices for Efficient Power Generation, Energy Storage and Chemicals Production

**Fundamental Principles**

- **Configurations**
  An advanced electrochemical device usually has a sandwich structure, which is consisted of an anode, an electrolyte and a cathode. (right, a schematic of proton exchange membrane fuel cells)

- **Active sites in electrodes**
  Triple-phase boundary (TPB), where the electronic conductor, ionic conductor and open pores meet, is the active site of electro-catalytic processes, all the individual phase must be physically contiguous.

- **Operation modes**
  Advanced electrochemical devices can work in either fuel cell mode to generate electricity and capture CO₂ or electrolysis cells mode to store energy. Both modes can be used to produce chemicals.

**Novel Materials**

- **To Design**
  Catalysts used in the device should be affordable, active and stable. Herein, mixed ionic and electronic conductor (MIEC, e.g., La₉Sr₂TiO₉) was used to maximize TPB and promote stability while active phases provide sufficient electro-catalytic activity.

- **To Use**
  Novel materials developed are simple but not simplistic, and are readily available for industrial applications (right, coking resistant coatings on 3D complex structures).

- **To Understand**
  Fundamental studies provide us insights into materials behaviors under different conditions. The example reveal BaZrₓCe₀.₅₋ₓYₓOₓ electrolyte degrade in ambient air through a micromechanical mechanism.

**Power Generation**

When the electrochemical device is working under fuel cell mode, it can generate electricity:

- with high efficiency (up to 80 %)
- using diverse fuels including hydrocarbons and sour gas (H₂S containing natural gas)
- with combined heat and power supply
- co-producing value-added chemicals

**Energy Storage**

When the electrochemical device is working under electrolysis cell mode, it can convert excess power from the grid into chemical fuels while consuming H₂O and CO₂ only.

- Catalysts play vital roles in products selectivity, e.g., H₂ prefers to form on Ni while CO prefers to form on Ti.
- System efficiency is the key and challenging factor of CO₂ reduction, e.g., the current density is usually several mA cm⁻².

**Chemicals Production**

Electrochemical device can produce value-added chemicals through:

- (de)hydrogenation, e.g., ethylene production;
- (de)oxidation, e.g., oxygen purification;
- Electrocatalytic selective oxidation, e.g., CO concentration from syngas.

**State-of-the-art**

To minimize the ohmic loss, electrodes and electrolyte membranes should be adequately thin. We use spin-coating or screen printing to fabricate these thin dense/porous films.

**Versatile**

To adapt the properties of different electrode catalysts, infiltration methods was developed.

**Scalable**

High performance electrocatalysts are synthesized via a variety of methods, some of which, e.g., combustion and spray pyrolysis are compatible with industrial processes.

**Advanced Materials Processing**

- Porous structures with controllable pore sizes and surface functionalities
- Impregnation of catalyst nanoparticles and fluid substrates

**Sustainable Chemistry**

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**References**

- N. Yan, et al., J. Power Sources, 789(2012), 164-169

**ValORIZATION GOALS**

- Diversify the application of electrocatalysts, particularly in industrial reaction processes.
- Utilize electrochemical device as an alternative method for various purposes at a larger scale.

**Table**

<table>
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<tr>
<th>Chemicals Production</th>
<th>Electrically producing</th>
<th>Ethylene production through electro-dehydrogenation of ethane while superposing electricity using CuCrO₂ catalysts (in collaboration with NREL chemists).</th>
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Multistep synthesis of valuable complex compounds

**Mission:** The development of efficient and selective, diversity-oriented synthetic methodologies, in particular organocatalytic and biocatalytic procedures, and the target-oriented preparation of molecules of relevance in chemistry, biology and medicine.

**Bronsted acid organocatalysis**

Efficient catalytic asymmetric Pictet-Spengler reactions of N₂ substiuted tryptamines have been developed. Important biologically active indole alkaloids have been synthesized. Currently, the chemistry is expanded to the isoquinoline natural compound class series.

**Chan–Lam peptide activation**

C-terminal peptide elongation by traditional coupling reagents (DCC, HATU...) is mostly accompanied by partial epimerization due to the formation of oxazolone intermediates. We currently develop an epimerization-free approach to peptide aryl esters via the so called Chan–Lam reaction. This is a Cu(II)-mediated esterification of carboxylic acids with aryl boroxines.

**Peptide Rotaxanes**

Microcin J25 is an example of a naturally occurring rotaxane (a so-called 'lasso peptide') that cannot be prepared using the current methods. A new strategy is required to synthesize these natural rotaxanes. The steps to bind the building blocks on the scaffold are based on robust reactions: oxime-igation and 'click'-reactions.

**Cinchona alkaloid-based organocatalysis**

Cinchona alkaloids are well known for their antimalaria properties. In our lab these privileged molecules are elaborated further for organocatalytic purposes.

**Solanoeclepin A**

A biologically active compound isolated from the roots of the potato plant. It is a potent hatching agent of the potato cyst nematode. Its unique structural features makes it a challenging synthetic target. The retrosynthetic analysis of solanoeclepin A reveals two synthetic fragments, the right- and left-hand side.

**ValORIZATION GOALS**

Research is directed at improvement of the efficiency, selectivity, and sustainability of synthetic protocols through the development of novel methodologies, in particular catalytic procedures.
Synthetic applications of C-H bond activation strategies

The direct and selective functionalization at C-H bonds provides a myriad of benefits from the economical and environmental point of view compared with the traditional approach since no preactivation of the starting materials is required. However, this strategy is still in its infancy and many challenges need to be overcome before this approach can become a routine synthetic tool for organic chemists. The low reactivity of the C-H bond and the poor selectivity observed are the main challenges in the field.

To overcome the current challenges, we focus on the development of new ligands capable of increasing the selectivity and reactivity of the C-H functionalization. We are currently working on the following research topics:

- Ligand-promoted oxidative cross-dehydrogenative coupling towards the synthesis of biaryls.
- Ligand-promoted C-H oxidation of simple arenes.
- Design and synthesis of traceless directing groups.
- Direct C(sp³)-H functionalization of amino acids

**Metal-Catalyzed C(sp³)-H Functionalization Using Traceless Directing Groups**

**Biaryl Synthesis via Oxidative Cross-Dehydrogenative Coupling**

**Metal-Catalyzed C(sp³)-H Functionalization of Amino Acids**

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**ValORIZATION GOALS**

Developing new efficient methodologies for the synthesis of value chemicals and materials using the C-H functionalization strategy.
Biocatalytic routes for the sustainable manufacture of valuable chemical products

Biocatalytic cascades
Multiple biocatalytic reactions can be carried out sequentially in a single flask (in vitro) or microbial host cell without the need for isolation of intermediates and purification steps. This approach leads to economic and environmental benefits since time-consuming intermediate work-ups are not required; furthermore, the use of organic solvents for extraction and purification as well as energy for evaporation and mass transfer is minimised.

In this context, our group has recently developed a dual-enzyme hydrogen borrowing process that enables the asymmetric amination of a broad range of secondary alcohols to afford the corresponding \((R)\)-configured amines in elevated optically pure form. Furthermore, amination of primary alcohols proceeded up to quantitative conversion. The biocatalytic system utilizes ammonia as the simplest amine donor and generates water as the sole innocuous by-product.

![Diagram of hydrogen-borrowing amination of alcohols.](image)

**Fig. 1.** Hydrogen-borrowing amination of alcohols. The method relies on a combination of two enzymes: an alcohol dehydrogenase operating in tandem with an amine dehydrogenase

Non-aqueous biocatalysis
Biotransformations have been mainly studied in aqueous or biphasic aqueous-organic systems. We are currently working on the development of novel biocatalytic and chemo-biocatalytic processes in non-aqueous systems (also using immobilised enzymes). Biocatalysis in organic solvents shows various advantages, for instance: ease of enzyme recovery and recycling, increased substrate solubility, ease of product recovery, influence on thermodynamics and kinetics of enzymatic reactions, etc.

Enzyme engineering
An important aspect of our research is the generation of new enzyme variants through semi-rational protein engineering. These novel enzymes will be capable of catalysing chemical reactions that are unknown in nature. Consequently, they can be integrated into biocatalytic as well as chemo-enzymatic pathways to solve challenging synthetic problems, shorten synthetic routes and improve efficiency. In particular, we are now focusing on the engineering of stereocomplementary amine dehydrogenases \((i.e.\) for the synthesis of \((S)\) and \((R)\) configured amines\) that can perform the reductive amination of carbonyl compounds at the expense of ammonia and generating water as the sole by-product. Another goal is to extend the activity of the enzymes towards the synthesis of secondary and tertiary amines.

![Diagram of amine dehydrogenase with bound NADH cofactor.](image)

**Fig. 2.** Amine dehydrogenase with bound NADH cofactor.

The HIMS-Biocat lab
Our lab is equipped with state-of-the-art facilities for molecular biology and enzyme engineering (gene cloning in bacteria, mutagenesis, generation and high-throughput screening of enzyme libraries), microbiology (microbial cultivation and expression of enzymes), biochemistry (enzyme purification, characterisation and kinetics via UV-vis spectroscopy), analytics (GC and HPLC analysis), bio-organic chemistry (organic synthesis using enzymes and chemo-enzymatic synthesis) and special techniques (enzymes immobilisation, cultivation of strains under anaerobic conditions and biocatalysis / enzymology with oxygen-sensitive enzymes).

Valorization goals
The generation of new enzyme variants and the implementation of these enzymes into artificial biosynthetic pathways for the sustainable conversion of inexpensive renewable resources into structurally diverse and valuable chemical products.