International Research Training Group
“Selectivity in Chemo- and Biocatalysis”

Workshop on Artifical Metalloenzymes

and

Joint Symposium Aachen – Osaka

September 5th – 7th, 2016
Seminar Room 202, Institute of Inorganic Chemistry
RWTH Aachen, Germany

RWTH AACHEN UNIVERSITY OSAKA UNIVERSITY DFG JSPS

www.seleca.rwth-aachen.de
www.osaka-aachen.jp

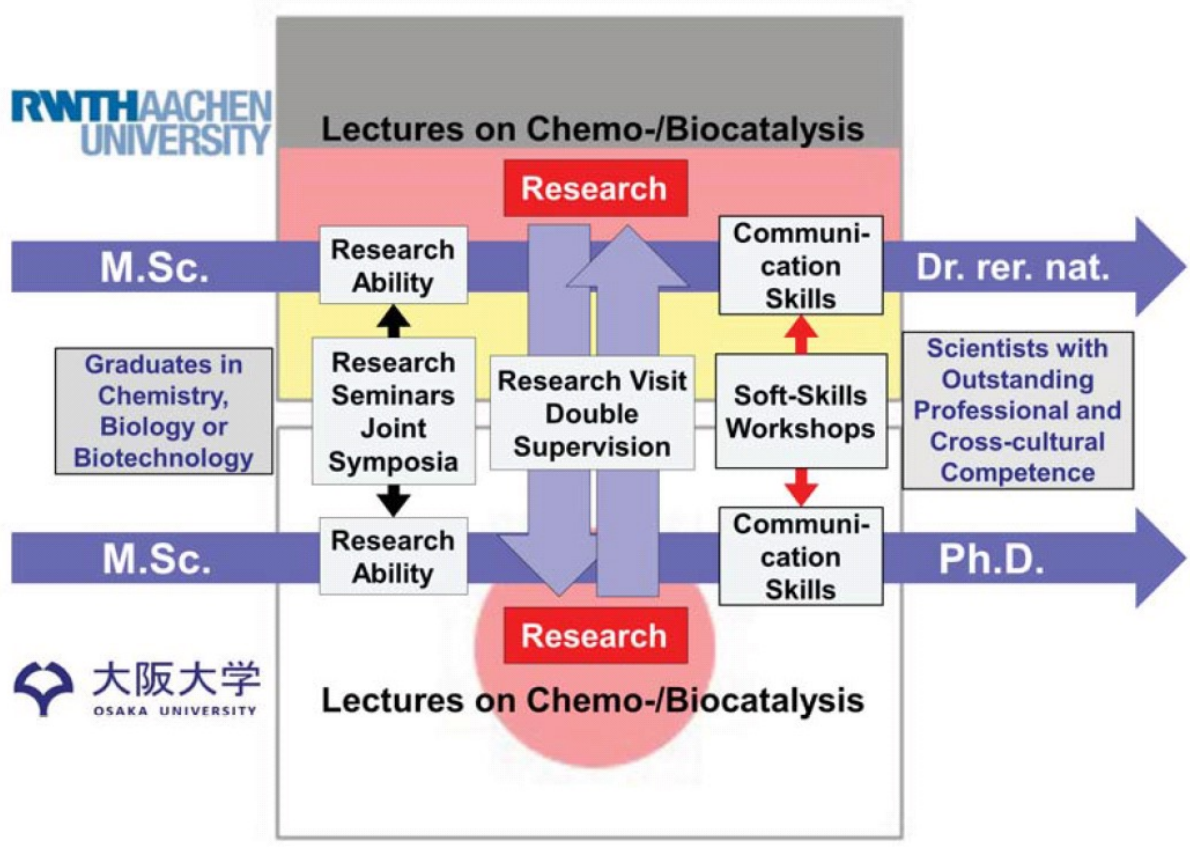
About SeleCa

Selectivity in catalyzed transformation of substrates provides the basis for sustainable ("green") production of chemicals in the future. The International Research Training Program "Selectivity in Chemo- and Biocatalysis (SeleCa)" aims at the understanding of efficient and selective catalytic reactions on the molecular level. Various aspects of both chemocatalysis and biocatalysis are used and combined in an unique interdisciplinary approach to selectively synthesize functionalized molecules and macromolecules.

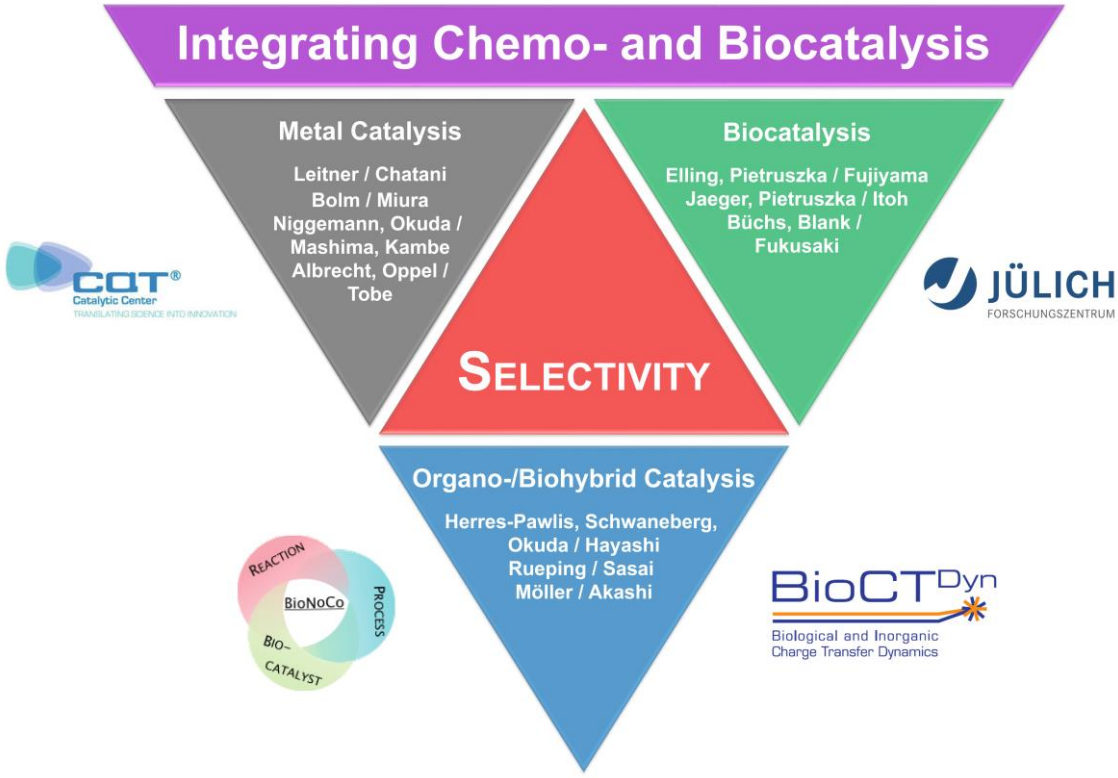
The cooperation involves
- twelve groups from RWTH Aachen University
- three associated groups each from Research Centre Jülich and RWTH Aachen
- eleven groups from Osaka University

An interdisciplinary research program towards new chemo- and biocatalytic transformations offers an educational platform for graduates.

Qualification Concept



Joint Projects



Metal Catalysis

- **Leitner / Chatani:** Selective Catalytic Functionalization of Aromatic Substrates from Petrochemical and Renewable Sources
- **Oppel, Albrecht / Tobe:** Selective Hydrogenation Catalysts Based on Molecular Recognition
- **Bolm / Miura:** Strategies for Efficient and Selective Formation of Carbon-Carbon and Carbon-Heteroatom Bonds
- **Rueping / Sasai:** Development and Applications of Novel Bifunctional Organocatalysts
- **Niggemann, Okuda / Mashima, Kambe:** Bimetallic Redox-Active Acidic Catalysts: Biomimetic Selective C-H Bond Functionalization and Switchable Polymerization

Biocatalysis

- **Jaeger, Pietruszka / Itoh:** Identification, Biochemical, and Functional Characterization of Novel Biocatalysts
- **Elling, Pietruszka / Fujiyama:** New Glycosynthases in Synthesis
- **Büchs, Blank / Fukusaki:** Selective Production and Analysis of Poly(*γ*-glutamic acid) (PGA) with Distinct Molecular Weight Distribution and Composition

Organo-/Biohybrid Catalysis

- **Möller / Akashi:** Multifunctional Polyethers through Chemical and Enzymatic Catalysis for Controlled Drug Release
- **Herres-Pawlis, Schwaneberg / Hayashi**: New Bis(pyrazolyl)bipyridinylmethane iron Complexes as Non-Heme Protein Models: Tailored Ligand Environment for Biomimetic Oxidation Reactions
- **Schwaneberg, Okuda / Hayashi:** Hybrid Biocatalysts for Selective Polymerizations

Workshop on
Artifical Metalloenzymes
Monday, September 5th, 2016

SeleCa Workshop on Artificial Metalloenzymes

PROGRAM
Monday, September 5th, 2016
Venue: Institute of Inorganic Chemistry, Landoltweg 1, Room 202, 52056 Aachen

	Welcome
9:00	Prof. Dr. Jun Okuda Spokesperson SeleCa, RWTH Aachen University
Chair:	Hassan Osseili, M. Sc.
9:10	Prof. Dr. Takashi Hayashi, Osaka University *"A Heme Pocket Is an Attractive Scaffold for Constructing a Hybrid Catalyst"*
9:40	Daniel F. Sauer, M. Sc., RWTH Aachen University *"Construction of Artificial Metatheases"*
9:55	Alexander Grimm, M. Sc., RWTH Aachen University *"Protein Engineering of Nitrobindin for Biohybrid Catalyst Development"*
10:10	Prof. Dr. Ulrich Schwaneberg, RWTH Aachen University *"Protein Engineering for Hybrid Catalysts"*
10:40 – 11:10	Coffee Break
Chair:	Andreas Thiel, M. Sc.
11:10	Assoc. Prof. Dr. Osami Shoji, Nagoya University *"Gaseous Alkane Hydroxylation by Cytochrome P450s Assisted by Decoy Molecules"*
11:55	Ass. Prof. Dr. Jared C. Lewis, University of Chicago *"Engineering Proteins for Selective Catalysis"*
12:40 – 14:00	Lunch Break
Chair:	Alexander Grimm, M. Sc.
14:00	Prof. Dr. Gerard Roelfes, University of Groningen *"Design and Application of Artificial Metalloenzymes Based on the Transcription Factor LmrR"*
14:45	Prof. Dr. Paul C. J. Kamer, University of St Andrews *"Artificial Late Transition Metalloenzymes for Catalytic Carbonylation and Cross-Coupling Reactions"*

15:30 – 16:00	Coffee Break
Chair:	Daniel F. Sauer, M. Sc.

16:00 Prof. Dr. Robertus J. M. Klein Gebbink, *Utrecht University*
"The Development of Semi-Synthetic Metallo-Enzymes Through Active-Site Directed Covalent Anchoring."

16:45 Prof. Dr. Romas J. Kazlauskas, *University of Minnesota*
"'Non-Catalytic' Residues Contribute to Hydrolysis and Lyase-Tpe Reactions in α/β-Hydrolase-Fold Enzymes"

17:30	End Workshop and Dinner

Prof. Dr. Takashi Hayashi

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Takashi Hayashi was born in Osaka, Japan, in 1962. He graduated from Kyoto University (Department of Synthetic Chemistry, Graduate School of Engineering) in 1985 and received his Doctor degree from Kyoto University (Department of Synthetic Chemistry, Graduate School of Engineering) in 1991 under the supervision of Professor Y. Itoh. He joined Kyoto University as an Assistant Professor in 1990. In addition, he worked as a Visiting Scientist with Prof. C.-H. Wong in the Scripps Research Institute at La Jolla, California in 1995-1996. Then, he moved to Department of Materials Chemistry, Kyushu University, as an Associate Professor in 1997, and concurrently became a PRESTO researcher supported by Japan Science and Technology Agency (JST) from 2000 to 2003. He was promoted to be a Full Professor at Department of Applied Chemistry, Graduate School of Engineering, Osaka University in 2005. At the same time, he became a Visiting Professor of Institute of Molecular Science for two years. Furthermore, he was an Invited Professor of University of Strasbourg in 2010. He received Progress Award in Synthetic Organic Chemistry, Japan, and 1st JPP Young Investigator Award in Porphyrin Chemistry in 2000. Furthermore, he received the Chemical Society of Japan Award for Creative Work in 2009. He served as an Associate Editor of Bulletin of Chemical Society of Japan in 2005-2011 and an Editorial Board Member of Journal of Bioinorganic Chemistry (Elsevier) and Journal of Porphyrins and Phthalocyanines (Society of Porphyrins and Phthalocyanines). In addition, he is selected as a council member of Society of Biological Inorganic Chemistry (SBIC) from 2015 to 2019. His current research interests lie in the area of bioinorganic chemistry, emphasizing directions to the modification of hemoproteins and nonheme proteins to obtain functionalized proteins and biomaterials. He has published more than 150 original papers.

Recent Publications:

1. Oohora, K. *et al*. *Angew. Chem. Int. Ed.* **2015**, *54*, 6277–6230.
2. Oohora, K. *et al*. *Chem. Commun.* **2015**, *51*, 1138–1140.
3. Hayashi, T. *et al*. *Chem. Commun.* **2014**, *50*, 12560–12563.
4. Fukumoto, K. *et al*. *ChemCatChem*. **2014**, *6*, 1229–1235.
5. Oohora, K. *et al*. *J. Am. Chem. Soc.* **2013**, *135*, 17282–17285.
6. Onoda, A. *et al*. *Chem. Commun.* **2012**, *48*, 9756–9758.
7. Oohora, K. *et al*. *Angew. Chem. Int. Ed.* **2012**, *51*, 3818–3821.
8. Onoda, A. *et al*. *Angew. Chem. Int. Ed.* **2012**, *51*, 2628–2631.

A Heme Pocket Is an Attractive Scaffold for Constructing a Hybrid Catalyst

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Hemoproteins are well-known and versatile metalloproteins. These proteins have one or plural heme cofactors located within the interior of the protein. One of the heme cofactors, protoheme IX (heme *b*), is non-covalently bound within the heme pocket. Thus, the heme *b*-containing hemoproteins can generally be converted into the apo-form under acidic conditions, and the addition of heme *b* or a related metal complex into a solution of the apoprotein triggers refolding to generate the corresponding reconstituted proteins. Our group has focused on this process and devoted our efforts to obtain a series of modified hemoproteins with artificially created cofactors, metal porphyrinoids, because it is found that a hemoprotein pocket after the removal of native heme is useful for an attractive scaffold as a metallocomplex-linked site to produce a new biocatalyst.[1] In this presentation, several examples of reconstituted hemoproteins will be reported:

(1) Replacement of heme *b* in myoglobin with manganese porphycene provides a hydroxylase model which promotes the C(sp^3)–H bond activation and the catalytic hydroxylation of substrates such as toluene, ethylbenzene and cyclohexane.[2]

(2) Conjugation of a diiron-carbonyl cluster with apocytochrome *c* is found to give a new [FeFe]-hydrogenase model which generates H_2 in the presence of a Ru complex as a photosensitizer.[3]

(3) Insertion of an organorhodium complex into a β-barrel of aponitrobindin via covalent linkage provides a polymerization catalyst for phenylacetylene in an aqueous media.[4]

References:

1. Hayashi, T. In *Handbook of Porphyrin Science*; Kadish, K. M.; Smith, K. M.; Guilar, R, Eds.; World Scientific, Singapore, 2010, Vol. 5, pp. 1–69.
2. Oohora, K.; Kihira, Y.; Mizohata, E.; Inoue, T.; Hayashi, T. *J. Am. Chem. Soc*. **2013**, *135*, 17282–17285.
3. Sano, Y.; Onoda, A.; Hayashi, T. *Chem. Commun*. **2011**, *47*, 8229–8231.
4. Fukumoto, K.; Onoda, A.; Mizohata, E.; Bocola, M.; Inoue, T.; Schwaneberg, U.; Hayashi, T. *ChemCatChem* **2014**, *6*, 1229–1235.

Construction of Artificial Metatheases

Daniel F. SAUER,[a] Tomoki HIMIYAMA,[b] Alexander GRIMM,[c] Ulrich SCHWANEBERG,[c,*] Akira ONODA,[b,*] Takashi HAYASHI,[b,*] Jun OKUDA[a,*]

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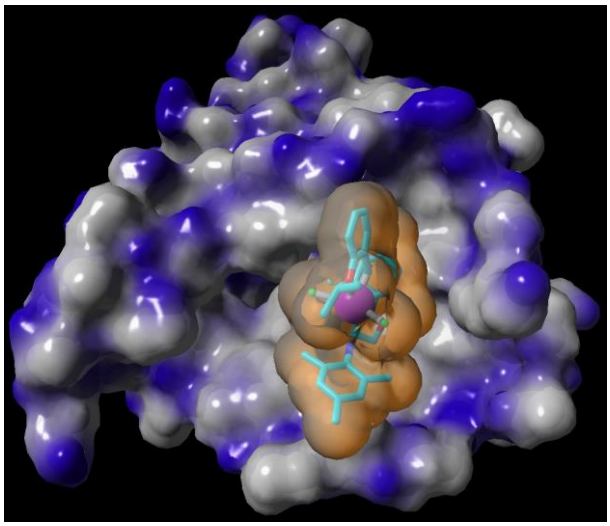

Figure 1: Grubbs-Hoveyda type catalyst incorporated into nitrobindin.

A precursor of a Grubbs-Hoveyda type catalyst for olefin metathesis was covalently incorporated in the cavity of β-barrel protein nitrobindin (Figure 1).[1] By analyzing the amino acid residues close to the active site and mutation of two positions to alanine, enough space was generated within the cavity to attach the catalyst properly. High activity could be achieved in the ring opening metathesis reaction of a 7-oxanorbornene derivative and in the ring closing metathesis reaction of water-soluble substrates. The explanation of the high activity is given by analysis of the cavity within the protein and the comparison to other artificial metatheases.[2] Additionally, first results for the improvement of the nitrobindin based system regarding coupling efficiency and catalytic activity will be given.

References:

1. Sauer, D. F.; Himiyama, T.; Tachikawa, K.; Fukumoto, K.; Onoda, A.; Mizohata, E.; Inoue, T.; Bocola, M.; Schwaneberg, U.; Hayashi, T.; Okuda, J. *ACS Catal.* **2015**, *5*, 7519−7522.
2. Sauer, D. F.; Gotzen, S.; Okuda, J. *Org. Biomol. Chem.* **2016**, *submitted*.

Protein Engineering of Nitrobindin for Biohybrid Catalyst Development

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Efforts to develop biocatalysts with new chemical reactivity and selectivity not found in nature have led to the construction of biohybrid catalysts (metalloenzymes).[1] Biohybrid catalysts have the potential to overcome limitations characteristic to both enzymes and synthetic catalysts. The use of artificial catalytic centers in biohybrid catalysts increases the range of applicable substrates that might not be catalyzed by enzymes due to their strict substrate-specificity. More importantly, the amino acid side chains in the protein scaffolds provide a second ligand sphere which enables selectivity towards substrates, e.g. enantioselectivity. These structural features are difficult to obtain in low-molecular synthetic catalysts.[2]

A number of hybrid catalysts have been developed capable of catalyzing non-natural C-C bond formation reactions, which belong to the most basic reactions in organic synthesis. These include a Hoveyda-Grubbs-type complex conjugated to the FhuA ΔCVF^{TEV} ß-barrel protein capable of performing ring-opening olefin metathesis (ROMP), and a Rh-nitrobindin (Rh-NB) hybrid that catalyzes the stereoselective polymerization of phenylacetylene.[3,4,5]

The objectives of the presented project focus on 1) developing a whole cell system for nitrobindin-based biohybrid catalysts, with the aim of simplifying and streamlining handling/processing, and lowering costs; 2) engineering the protein scaffold to enlarge the cavity for the incorporation of the metal catalyst (Figure 1).

Figure 1: Model of expanded nitrobindin

References:

1. Onoda, A. *et al. Chem. Commun.* **2012**, *48*, 9756–9758.
2. Matsuo, T. *et al. Bioorg. Med. Chem.* **2014**, *22*, 5638–5656.
3. Fukumoto, K. *et al. Chem. Cat. Chem.* **2014**, *6*, 1229–1235.
4. Philippart, F. *et al. Chem. Eur. J.* **2013**, *19*, 13865–13871.
5. Sauer, D. *et al. Chem. Asian J.* **2015**, *10*, 177–182.

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Ulrich Schwaneberg was born in Waiblingen, Germany, in 1969. He studied chemistry at the University of Stuttgart and received his diploma in 1996. His doctoral studies were also carried at the University of Stuttgart in the Institute of Technical Biochemistry under the supervision of Prof. R. D. Schmid. After his graduation in 07/1999, he moved as post-doctoral fellow to the lab of Prof. Frances H. Arnold at Caltech (USA) for two years. In January 2002, he was appointed as Assistant Professor at the Jacobs University Bremen and promoted 2006 ti the Associate Professor level. In January 2009, he moved to the RWTH Aachen University as Head of the Institute of Biotechnology and is furthermore co-appointed since 2010 in the Scientific Board of Director at the DWI Leibniz Institute for Interactive Materials. Furthermore, he has been appointed in the board of directors in the Bioeconomy Science Centre to advance and to focus NRW's (local government) research efforts in the area of bioeconomy. Developed mutagenesis technologies were commercialized in 2008 by establishing the SeSam-Biotech GmbH. He has a special interest in method development and tailoring of proteins for industrial applications and interactive materials and generated 13 patents and published > 160 original manuscripts.

Recent Publications:

1. Sauer, D. F., Himiyama, T., Tachikawa, K., Fukumoto, K., Onoda, A., Mizohata, E., Inoue, T., Bocola, M., Schwaneberg, U., Hayashi, T., Okuda, J. *ACS Catal*. **2015**, *5*, 7519–7522.
2. Cheng, F., Zhu, L., Schwaneberg, U. *Chem. Commun*. **2015**, *51*, 9760–9772.
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5. Dennig, A., Lülsdorf, N., Liu, H., Schwaneberg, U. *Angew. Chemie* **2013**, *53*, 8459–8462.

Protein Engineering for Hybrid Catalysts

Ulrich SCHWANEBERG[a,*]

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Protein engineering by directed evolution and semi-rational design have become widely applied strategies for tailoring enzyme properties to needs in biocatalysis.[1] Protein engineering concepts and highlights comprising reengineered monooxygenases for ortho-selective hydroxylation of halobenzenes[2], inversion of styrene epoxidation[3], double oxidation of cyclic alkanes und cofactor regeneration[4] and improvements in properties of hydrolases and oxidases (peracid formation, organic solvent[5]/salt resistance[6] and mediated electron transfer[7]) could already be realized. Recently, the construction of artificial enzymes at the border of biotechnology and chemistry attracted huge attention. To improve the catalytic activity and the selectivity, protein engineering is indispensable. The design of enzymes and improvement by biotechnological methods will be presented.

References:

1. (a) Shivange, A. V.; Marienhagen, J.; Mundhada, H.; Schenk, A.; Schwaneberg, U. *Curr. Opin. Chem. Biol.* **2009**, *13*, 19-25. (b) Ruff, A. J.; Dennig, A.; Schwaneberg, U. *FEBS J.* **2013**, *280*, 2961–2978.
2. Dennig, A.; Lülsdorf, N.; Liu, H.; Schwaneberg, U. *Angew. Chem.* **2013**, *53*, 8459–8462.
3. (a) Tee, K. L.; Schwaneberg, U. Angewandte Chemie **2006**, *45*, 5380–5383. (b) Shehzad, A.; Panneerselvam, S.; Linow, M.; Bocola, M.; Roccatano, D.; Mueller-Dieckmann, J.; Wilmanns, M.; Schwaneberg, U. *Chem. Commun.* **2013**, *49*, 4694–4696.
4. Staudt, S.; Burda, E.; Giese, C.; Müller, C. A.; Marienhagen, J.; Schwaneberg, U.; Hummel, W.; Drauz, K.; Groeger, H. *Angew. Chem.* **2012**, *52*, 2359–2363.
5. Kuper, J.; Wong, T. S.; Roccatano, D.; Wilmanns, M.; Schwaneberg, U. *JACS* **2007**, *129*, 5786–5787.
6. Lehmann, C.; Sibilla, F.; Maugeri, Z.; Streit, W. R.; de María, P. D.; Martinez, R.; Schwaneberg, U. *Green. Chem.* **2012**, *14*, 2719–2726.
7. Arango Gutierrez, E.; Meier, T.; Duefel, H.; Mundhada, H.; Bocola, M., Schwaneberg, U. *Biosensors and Bioelectronics* **2013**, *50*, 84–90.

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Professional Career

2002–2004	Postdoctoral fellow of the Core Research for Evolutional Science and Technology (CREST) project of Japan Science and Technology Agency (JST)
2004–2005	Postdoctoral fellow at Graduate School of Materials Science, Nara Institute of Science and Technology
2005–2006	Postdoctoral fellow at Graduate School of Science, Nagoya University
2006–2007	JSPS Postdoctoral fellow (SPD)
2007–2008	Assistant Professor at Research Center for Materials Science, Nagoya University
2008–2013	Assistant Professor at Graduate School of Science, Nagoya University
2013–present	Associate Professor at Graduate School of Science, Nagoya University

Education

1993–1997	Department of Applied Chemistry, Faculty of Engineering, Chiba University
1997–1999	Graduate School of Science and Technology, Chiba University
1999–2002	Graduate School of Science and Technology, Chiba University Received a PhD (Prof. Takayuki Nakahira)

Research Interests

1. Alteration of Substrate Specificity of Cytochrome P450s
2. Gaseous Alkane Hydroxylation by Cytochrome P450s
3. Engineering of Heme Acquisition Proteins

Recent Publications:

1. Shoji, O.; Fujishiro, T.; Nishio, K.; Kano, Y.; Kimoto, H.; Chien, S.-C.; Onoda, H.; Muramatsu, A.; Tanaka, S.; Hori, A.; Sugimoto, H.; Shiro, Y.; Watanabe, Y. *Catal. Sci. Technol.* **2016**.
2. Onoda, H.; Shoji, O.; Watanabe, Y. *Dalton Trans.* **2015**, *44*, 15316–15323.
3. Cong, Z.; Shoji, O.; Kasai, C.; Kawakami, N.; Sugimoto, H.; Shiro, Y.; Watanabe, Y. *ACS Catalysis* **2015**, *5*, 150–156.
4. Shirataki, C.; Shoji, O.; Terada, M.; Ozaki, S.-i.; Sugimoto, H.; Shiro, Y.; Watanabe, Y. *Angew. Chem. Int. Ed.* **2014**, *53*, 2862–2866.
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6. Kawakami, N.; Shoji, O.; Watanabe, Y. *Chem. Sci.* **2013**, *4*, 2344–2348.
7. Kawakami, N.; Shoji, O.; Watanabe, Y. *Angew. Chem. Int. Ed.* **2011**, *50*, 5315–5318.
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Gaseous Alkane Hydroxylation by Cytochrome P450s Assisted by Decoy Molecules

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Cytochrome P450BM3 (P450BM3) isolated from *Bacillus megaterium* is one of the most promising P450s for constraction of biocatalysts because of the highest monooxygenase activity among P450s reported so far. P450BM3 catalyzes hydroxylation of long-alkyl-chain fatty acids. As the substrate binding is crucial to initiate the catalytic cycle of P450BM3, substrates whose structures are largely different from that of fatty acid cannot be hydroxylated by P450BM3. We found that P450BM3 catalyzes the hydroxylation of inert alkanes by adding perfluorocarboxylic acids as a "decoy molecule" whose structure is similar to fatty acid.[1-5] The second-generation of decoy molecules prepared by modifying the carboxylate of perfluorocarboxylic acids with amino acids further activate P450BM3 for the hydroxylation of gaseous alkanes. Among the second-generation of decoy molecules examined, L-leucine modified perfluorinated carboxylic acid was the most effective for propane hydroxylation. The product formation rate reached more than 250/min.[6] Furthermore, we have succeeded in crystallizing the tryptophan modified perfluorinated nonanoic acid-bound form of P450BM3 and obtained its crystal structure at 1.8 Å resolution (Fig. 1).[6] We believe that the catalytic activity for gaseous alkane hydroxylation by wild-type P450BM3 would be improved further by optimizing the structure of the decoy molecule.

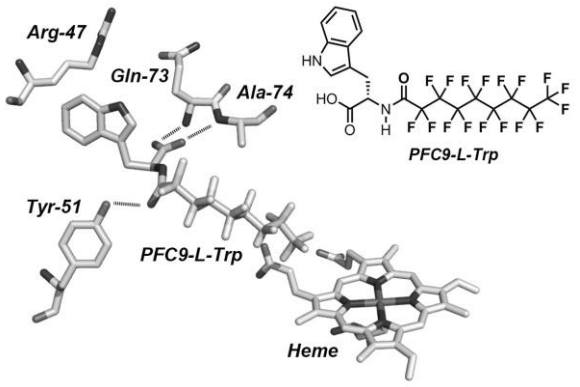

Figure 1: The active site structure of P450BM3 with *N*-perfluorononanoyl-L-tryptophan (PFC9-*L*-Trp).

References:

1. Kawakami, N.; Shoji, O.; Watanabe, Y. *Angew. Chem. Int. Ed.* **2011**, *50*, 5315–5318.
2. Shoji, O.; Kunimatsu, T.; Kawakami, N.; Watanabe, Y. *Angew. Chem. Int. Ed.* **2013**, *52*, 6606–6610.
3. Kawakami, N.; Shoji, O.; Watanabe, Y. *Chem. Sci.* **2013**, *4*, 2344–2348.
4. Kawakami, N.; Cong, Z.; Shoji, O.; Watanabe, Y. *J. Porphyrins Phthalocyanines* **2015**, *19*, 329–334.
5. Munday, S. D.; Shoji, O.; Watanabe, Y.; Wong, L.-L.; Bell, S. G. *Chem. Commun.* **2016**, *52*, 1036–1039.
6. Cong, Z.; Shoji, O.; Kasai, C.; Kawakami, N.; Sugimoto, H.; Shiro, Y.; Watanabe, Y. *ACS Catalysis* **2015**, *5*, 150–156.

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Education

2002-2007	Ph.D., Chemistry, University of California, Berkeley
1998-2002	B.S., Chemistry, University of Illinois at Urbana/Champaign

Research Positions

2011-Present	University of Chicago, Department of Chemistry (Assistant Professor)
2007-2010	California Institute of Technology, Department of Chemistry and Chemical Engineering (NIH NRSA Postdoctoral Fellow with Prof. Frances Arnold)
2002-2007	University of California, Berkeley, Department of Chemistry (Graduate student)
2001, 2002	Abbott Laboratories, Metabolic Disease Research (Research Intern, two summers)
1999-2002	University of Illinois at Urbana/Champaign, Department of Chemistry (Research Asst.)

Overview of Scientific Work

As long as organic molecules are needed by society, selective catalytic transformations of these compounds will be the raison d'être of synthetic organic chemistry. My group engineers enzymes to enable transformations that have proven difficult to control using conventional catalysts. For example, we evolved the stability, activity, and substrate scope of rebeccamycin halogenase (RebH) to enable halogenation of a range of biologically active compounds. We then developed a method to directly evolve RebH selectivity, resulting in the first examples in which any catalyst has been tuned to functionalize C-H bonds *ortho*, *meta*, and *para* to a substituent. To impart enzyme-like selectivity to transition metal catalysts and enable the use of these catalysts in living systems, we have developed methods to create and evolve artificial metalloenzymes (ArMs), hybrid catalysts comprised of synthetic metal complexes linked to protein scaffolds. We engineered dirhodium ArMs that catalyze enantioselective cyclopropanation and reduce byproducts resulting from reactions of catalytic intermediates with water. We then established that random mutagenesis and screening can improve ArM selectivity via non-active site mutations, providing a general means to evolve ArMs.

Recent Publications:

1. Andorfer, M. C.; Park, H. J.; Vergara-Coll, J.; Lewis, J. C. *Chem. Sci.* DOI: 10.1039/C5SC04680G.
2. Durak, L. J.; Payne, J. T.; Lewis, J. C. *ACS Catal*. **2016**, *6*, 1451–1454.
3. Srivastava, P.; Yang, H.; Ellis-Guardiola, K.; Lewis, J. C. *Nat. Commun.* **2015**, *6*, 7789.
4. Gu, Y.; Ellis-Guardiola, K.; Srivastava, P.; Lewis, J. C. *ChemBioChem*. **2015**, *16*, 1880–1883.
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Engineering Proteins for Selective Catalysis

Jared LEWIS[a,*]

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jaredlewis@uchicago.edu

Proteins have great potential as scaffolds to control the selectivity of catalysts and reactive intermediates contained within their structures. Techniques to improve the substrate scope and alter the selectivity of natural enzymes are now well established, and examples in which enzymes are used to catalyze synthetically useful, non-native reactions are appearing with increasing frequency. This trend of using proteins to control chemical reactivity has been further extended through the development of artificial metalloenzymes, hybrid catalysts comprised of synthetic cofactors linked to protein scaffolds. I will discuss efforts by my group aimed at engineering natural enzymes and artificial metalloenzymes for selective C-H bond functionalization and other challenging transformations. The examples presented will highlight the potential for molecular recognition and evolution to enable new methods and strategies for organic synthesis.

Prof. Dr. Gerard Roelfes

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https://www.roelfesgroup.nl
j.g.roelfes@rug.nl

Gerard Roelfes obtained his MSc and PhD (2000) from the University of Groningen, the Netherlands. His PhD research (supervisor Prof. Ben L. Feringa) was on synthetic models for non-heme iron oxygenases, which was a joint project with Unilever Research (Dr. R. Hage) and the group of Prof. Lawrence Que Jr. (Univ. Minnesota), in whose lab he carried out part of the work. After his PhD he went for a post-doc with Prof. Donald Hilvert at the ETH-Zürich (Switzerland), where he worked on synthetic strategies towards seleno-proteins, using a combination of chemical and biological methods. In 2003 he returned to the University of Groningen where he rose through the ranks and since 2015 is Full Professor of Biomolecular Chemistry & Catalysis.

PhD: University of Groningen (Prof. B.L Feringa)
Postdoc: ETH-Zürich (Prof. Donald Hilvert)
Assistant, Associate and full Professor: University of Groningen

The Roelfes groupsactive in the field of biomolecular chemistry, which is at the interface between organic, bio-inorganic and biochemistry. There are 2 main research themes in the group: bio-inspired catalysis and chemical biology. In the bio-inspired catalysis group we use nature as a source of inspiration to develop new concepts in catalysis, with a particular focus on sustainable catalysis in water. Important research topics are DNA-based asymmetric catalysis, artificial metalloenzymes and catalysis in water. In our chemical biology research we aim to develop novel tools for the study and manipulation of biological systems. The main research topics here are artificial allosteric biosystems and novel probes for the study of reactive oxygen species in living cells.

Recent Publications:

1. Bos, J.; Browne, W. R.; Driessen, A. J. M.; Roelfes, G. *J. Am. Chem. Soc.* **2015**, *137*, 9796–9799.
2. Drienovská, I.; Rioz-Martínez, A.; Draksharapu, A.; Roelfes, G. *Chem. Sci.* **2015**, *6*, 770–776.
3. Oelerich, J.; Roelfes, G. *Chem. Sci.* **2013**, *4*, 2013–2017.
4. Bos, J.; Fusetti, F.; Driessen, A. J. M.; Roelfes, G. *Angew. Chem. Int. Ed.* **2012**, *51*, 7472–7475.

Design and Application of Artificial Metalloenzymes Based on the Transcription Factor LmrR

Ivana DRIENOVSKÁ,[a] Lara VILLARINO,[a] Shreyans CHORDIA,[a] Gerard ROELFES[a,*]

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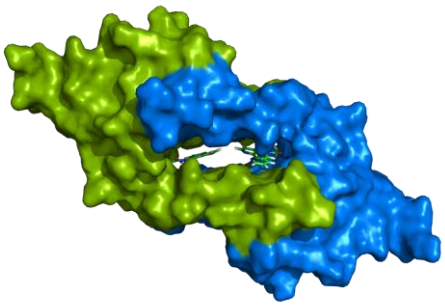
e-mail: j.g.roelfes@ru.gnl

The catalytic efficiency and high selectivities achieved by natural metalloenzymes are a source of inspiration for the design of novel bio inspired catalysts. A powerful approach for creating artificial metalloenzymes involves incorporating a synthetic transition metal catalysts into a biomolecular scaffold such as a protein or DNA. We have developed a new concept for the design of artificial metalloenzymes that involves creation of a novel active site at the dimer interface of the transcription factor LmrR (Lactococcal multidrug resistance Regulator).[1]



LmrR was selected as the protein scaffold because it contains an unusual large hydrophobic pocket on the dimer interface. Here, two novel classes of LmrR-based artificial metalloenzymes will be presented, involving either supramolecular anchoring of the metal complex[2] or biosynthetic incorporation of an unnatural metal binding amino acid using expanded genetic code methodology.[3] These artificial metalloenzymes have been applied successfully in catalytic asymmetric C-C bond forming and hydration reactions. Finally, our recent insights into how to design the second coordination sphere will be discussed.

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1. Bos, J.; Fusetti, F.; Driessen, A. J. M.; Roelfes, G. *Angew. Chem. Int. Ed.* **2012**, *51*, 7472–7475.
2. Bos, J.; Browne, W. R.; Driessen, A. J. M.; Roelfes, G. *J. Am. Chem. Soc.* **2015**, *137*, 9796–9799.
3. Drienovská, I.; Rioz-Martínez, A.; Draksharapu, A.; Roelfes, G. *Chem. Sci.* **2015**, *6*, 770–776.

Prof. Dr. Paul C. J. Kamer

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Paul C. J. Kamer did his Ph.D. in organic chemistry at the University of Utrecht. As a postdoctoral fellow of the Dutch Cancer Society (KWF) he spent 1 year at the California Institute of Technology and 1 year at the University of Leiden, where he worked on the development of phosphorothiate analogues of nucleotides. Then he moved to the University of Amsterdam to work in the field of homogeneous with Prof. Piet van Leeuwen, where he was appointed full professor of homogeneous catalysis in January 2005. In 2005 he also received a Marie Curie Excellence Grant to move his activities to the University of St Andrews where he is currently professor of Inorganic Chemistry. His current research interests are (asymmetric) homogeneous catalysis, organometallic chemistry, combinatorial synthesis, and artificial metalloenzymes.

Education/Positions:

1983 "Doctoraaldiploma" (comparable to MSc) Chemistry University of Amsterdam
1987 PhD. at the University of Utrecht: Enantioselective Polymerization of Isocyanides
1988 Post-doc fellowship of the Dutch Cancer Society with Peter Dervan, CalTech, CA, USA.
1989 Post-doc fellowship of the Dutch Cancer Society with J. van Boom, University of Leiden
1990 Assistant professor homogeneous catalysis, University of Amsterdam
1998 Associate professor homogeneous catalysis, University of Amsterdam
2005 Full professor homogeneous catalysis, University of Amsterdam
2005 Professor of Inorganic Chemistry, University of St Andrews

Short Overview about Scientific Work:

Paul Kamer has over 25 year experience in homogeneous catalysis and (bio)organic chemistry and published his work in >200 well-cited papers (h-index 61), patents and book chapters. His research has focused on the field of ligand synthesis based on phosphorus donor atoms by rational design assisted by molecular modelling. In addition to the study of well-known steric and electronic ligand effects, the influence of ligand geometries around the metal centre is a key issue in this research. By making use of the excellent molecular recognition properties of proteins and DNA, novel artificial transition metalloenzymes have been developed. He has been successfully active in the field of combinatorial development of phosphorus donor ligands and catalyst recycling. His research is focussing on the change to renewable feedstocks for the production of chemical and catalytic conversions of biomass**.**

Recent Publications:

1. Lahive, C. W.; Deuss, P. J.; Lancefield, C. S.; Sun, Z.; Cordes, D. B.; Young, C.; Tran, F.; Slawin, A. M. Z.; de Vries, J. G.; Kamer, P. C. J.; Westwood, N. J.; Barta, K. *J. Am. Chem. Soc.* **2016**, *138*, DOI: 10.1021/jacs.6b04144.
2. Heutz, F. J. L.; Erken, C.; Aguila, M. J. B.; Lefort, L.; Kamer P. C J. *ChemCatChem* **2016**, *8*, 1896.
3. Doble, M. V.; Ward, A. C. C.; Deuss, P. J.; Jarvis, A. G.; Kamer, P. C. J. *Bioorg. Med. Chem.* **2014**, *22*, 5657.
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Artificial Late Transition Metalloenzymes for Catalytic Carbonylation and Cross-Coupling Reactions

Paul C. J. KAMER[a,*]

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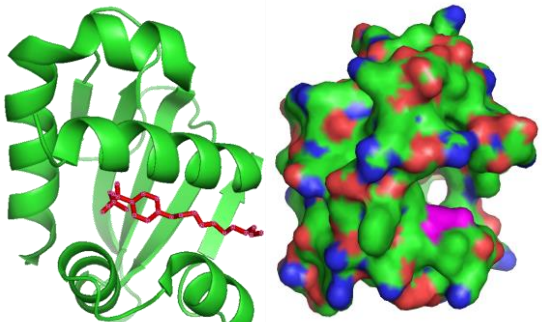
Rhodium catalyzed hydroformylation of alkenes is one of the most important industrial applications of homogeneous catalysis. A solution for the problem of catalyst separation and recovery is offered by aqueous phase catalysis as exploited Ruhrchemie/Rhone-Poulenc process. This process can only be applied to alkenes up to C4 chain length as a consequence of the low water solubility of higher alkenes.[1] Enzymes have proven to be very powerful catalysts for fast and selective conversions of organic substrates. Therefore we have set out to develop a hybrid transition metalloenzyme for rhodium catalyzed hydroformylation of higher alkenes in aqueous solvents.



a **b**

Figure 1: cartoon (a) and space filling structure (b) of SCP-2L

Artificial enzymes have been prepared by coupling of phosphine-ligands to a unique nucleophilic thiol of cysteine residue of Steroid Carrier Protein-2L (SCP-2L) of Human Peroxisomal Multifunctional Enzyme Type 2 (see Figure 1a,b) The protein has been efficiently and selectively modified with phosphines and phosphine-metal complexes.[2] These artificial metalloenzymes are efficient catalysts for the rhodium catalysed hydroformylation of higher alkenes such as dodecene and octadecene in water. Rate accelerations of 6-7 orders of magnitude have been obtained compared to the Rh-TPPTS catalyst

The concept of artificial metalloenzymes is also explored in other catalytic reactions such as copper-catalyzed Diels-Alder reaction and palladium catalyzed coupling reactions.

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1. Bahrmann, H; Boganovic, S.; van Leeuwen, P. W. N. M. In *Aqueous Phase Organometallic Catalysis*; Cornils, B; Herrmann, W., Eds.; Wiley VCH, Weinheim: **2004**; 2nd ed., pp 391–409.
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Prof. Dr. Robertus (Bert) J. M. Klein Gebbink

Organic Chemistry and Catalysis,
Debye Institute for Nanomaterials Science,
Utrecht University,
Universiteitsweg 99,
3584 CG, Utrecht,
The Netherlands

R.J.M. (Bert) Klein Gebbink (17.6.1969) received his academic education at Nijmegen University. Under the supervision of Prof. R.J.M. Nolte, he completed his Ph. study in 1998 with a thesis on supramolecular and bioinorganic chemistry. Following his graduation, he spent two postdoctoral years at Stanford University in the research group of Prof. T.D.P. Stack (TALENT stipend). In October 1999, an assistant professor track was accepted at Utrecht University (UU) in the Department of Metal-Mediated Synthesis. Within the framework of UU and the National Research School Combination: Catalysis (NRSC-C) he started a program with the title *Sustainable Homogeneous Catalysis*. For this program, he was awarded a *Jonge Chemici* scholarschip in 2001 and a *VIDI* award in 2004. In 2006 he was appointed to professor of *Homogeneous and Bio-inspired Catalysis* at Utrecht University, where he is head of the 'Organic Chemistry & Catalysis' group. He has authored about 200 peer-reviewed papers and 10 book chapters. As of January 2016, he acts as the coordinator of the EU Marie Sklodowska-Curie Initial Training Network (EU MSC-ITN) NoNoMeCat on non-noble metal catalysis.

Positions:

1999–2003	Utrecht University/ NRSC-C; senior post-doc
2003–2004	Utrecht University; assistant professor
2004–2006	Utrecht University; associate professor
2006–now	Utrecht University; full professor

General research interests: non-noble metal catalysis; catalytic biomass conversion; metals in synthesis; metals in biology.

Topical research interests: non-heme iron chemistry (biomimicry and oxidation catalysis); catalytic C–C and C-X formation; catalytic C–H activation; homogeneous catalyst immobilization; biomass to chemicals using homogeneous catalysis; construction of hybrid catalysts.

Recent Publications:

1. Basauri Molina, M.; Riemersma, C. F.; Würdeman, M.; Kleijn, H.; M. Klein Gebbink, R. J. M. *Chem. Commun.* **2015**, *51*, 6792–6795.
2. Raju, S.; Moret, M.-E.; Klein Gebbink, R. J. M. *ACS Cat.* **2015**, *5*, 281–300.
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The Development of Semi-Synthetic Metallo-Enzymes Through Active-Site Directed Covalent Anchoring

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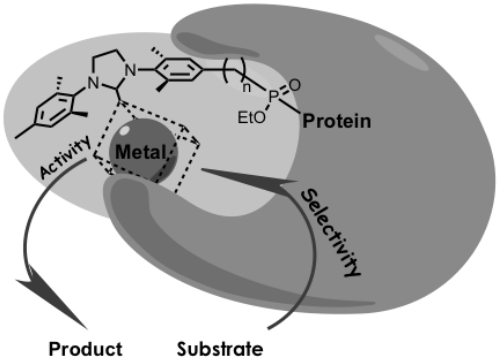
The incorporation of synthetic transition metal centers in large biomolecular scaffolds such as proteins, i.e. semi-synthetic enzymes, has gained considerable attention in the last decade as a strategy to enhance the selectivity of synthetic homogeneous catalysts, but also to span the reactivity of enzymes to non-biological transformations. In their design and construction, a robust and well-located incorporation of the metallic fragment in the proteinic host is preferred, particularly because the naturally occurring chiral environment of the peptidic backbone is responsible for the resulting (enantio)selectivity of these hybrids.

Recently, our group has reported a method to immobilize transition metal complexes in the active site of enzymes via covalent inhibition of lipases.[1] In the present work we have developed a series of hybrids using functionalized N-heterocyclic carbenes (NHCs) that coordinate to the metallic center, while also acting as the connector to the lipase host.[2] Protein-NHC metallocarbene hybrids with metals of the groups 8 to 11 have been prepared. Advances in the study of their activity in a range of transformations (e.g. hydrogenation, allylic alkylation, olefin metathesis) will be presented.



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1. (a) Kruithof C. A.; Casado, M. A.; Guillena, G.; Egmond, M. R.; van der Kerk-van Hoof, A.; Heck, A. J. R.; Klein Gebbink, R. J. M.; van Koten, G. *Chem. Eur. J*. **2005**, *11*, 6869. (b) Rutten, L.; Wieczorek, B.; Mannie, J.-P. B. A.; Kruithof, C. A.; Dijkstra, H. P.; Egmond, M. R.; Lutz, M.; Klein Gebbink, R. J. M.; Gros, P.; van Koten, G. *Chem. Eur. J.* **2009**, *15*, 4270; (c) Wieczorek, B.; Träff A.; Krumlinde P.; Dijkstra, H. P.; Egmond M. R.; van Koten, G.; Bäckvall, J.-E.; Klein Gebbink, R. J. M. *Tetrahedron Lett*. **2011**, *52*, 1601.
2. (a) Basauri-Molina, M.; Verhoeven, D. G. A.; van Schaik, A. J.; Kleijn, H.; Klein Gebbink, R. J. M. *Chem. Eur. J.* **2015**, *21*, 15676. (b) Basauri Molina, M.; Riemersma, C. F.; Würdeman, M.; Kleijn, H.; Klein Gebbink, R. J. M. *Chem. Commun.* **2015**, *51*, 6792.

Prof. Dr. Romas Kazlauskas

University of Minnesota
Dept. of Biochemistry, Molecular Biology & Biophysics
Saint Paul, MN 55108
USA

Massachusetts Institute of Technology (Ph.D. 1982)
Harvard University (postdoc with George Whitesides)
General Electric Company (1985-88)
McGill University, Montreal, Canada (1988-2003)
University of Minnesota (2003-
Visiting professor in Stuttgart (1995-6), Stockholm (2002-3), Seoul, South Korea (2009-14)

During his university studies, Kazlauskas worked at company that made catalysts for paint drying, then continued to study organometallic catalysts during Ph.D. He heard George Whitesides give an inspiring talk about biocatalysts and decided that biocatalysts were so much better than organometallic catalysts, that he switched research areas. He worked with George Whitesides as a postdoc and has studied biocatalysis ever since. He is an expert in protein engineering for biocatalysis & green chemistry

Recent Publications:

1. Devamani *et al*. *J. Am. Chem. Soc.* **2016**, *138*, 1046–56.
2. Rauwerdink & Kazlauskas *ACS Catal.* **2015**, *5*, 6153–6176.
3. Yin & Kazlauskas *Chem. Eur. J.* **2012**, *18*, 8130–8139.
4. Bornscheuer *et al*. *Nature* **2012**, *485*, 185–194.

‘Non-Catalytic’ Residues Contribute to Hydrolysis and Lyase-Type Reactions in α/β-Hydrolase-Fold Enzymes

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e-mail: rjk@umn.edu

α/β-Hydrolase-fold enzymes with the serine-histidine-aspartate catalytic triad have the same protein fold and the same catalytic machinery. Nevertheless, some catalyze hydrolyses, which follow the canonical esterase mechanism, while others catalyze lyase-type eliminations, which use a single step without an acyl enzyme intermediate.[1]

To identify which amino acids residues account for these differences, we first focused on residues that hydrogen bond to the substrate. Exchanging these residues between esterase SABP2 and hydroxynitrile lyase *Hb*HNL exchanged the catalytic abilities.[2] However, the engineered enzymes were less efficient than native enzymes indicating that non-catalytic residues also contribute to optimizing the active site.

Further evidence that non-catalytic residues contribute to catalysis comes from reconstruction of ancestral α/β-hydrolase-fold enzymes. These ancestral enzymes differed from modern enzymes only in non-catalytic residues, but, unlike modern enzymes, could catalyze both ester hydrolysis and lyase-type eliminations.[3]

Even when enzymes catalyze the same reaction type, they can follow different mechanisms. *Hb*HNL uses a lysine mechanism to promote cleavage of mandelonitrile. Esterase 5 from *Arabidopsis thaliana* (*At*EST5) also catalyzes cleavage of mandelonitrile, but lacks the key lysine and favors the opposite enantiomer. These differences arise from a different mechanism (oxyanion hole mechanism) in *At*EST5.[4] Further protein engineering of *At*EST5 and *Hb*HNL created mixed active sites that follow a third mechanism (asparagine mechanism) for the lyase reaction.

These studies show that enzymes with the same protein fold and catalytic triad can nevertheless catalyze different reactions and, even when they catalyze the same reaction, may use different mechanisms. ‘Non-catalytic’ residues both inside and outside the active site change substrate binding and can create new mechanisms. A better name for these residues is indirectly catalytic residues because they are essential to efficient catalysis.

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1. Rauwerdink, A. M.; Kazlauskas, R. J. *ACS Catal.* **2015**, *5*, 6153−76.
2. (a) Padhi *et al. Chem. Biol*, **2010**, *17*, 863-71; (b) Nedrud *et al. Chem. Sci.* **2014**, *5*, 4265−77.
3. Devamani *et al. J. Am. Chem. Soc.* **2016**, *138*, 1046−56.
4. Andexer *et al*. *ChemBioChem* **2012**, *13*, 1932−9.

Joint Symposium Aachen – Osaka
September 6th – 7th, 2016

Joint Symposium Aachen – Osaka

PROGRAM

Tuesday, September 6th, 2016

Venue: Institute of Inorganic Chemistry, Landoltweg 1, Room 202, 52074 Aachen

	Welcome
10:00	Prof. Dr. Jun Okuda, Spokesperson SeleCa, RWTH Aachen University
	Dr. Henriette Finsterbusch, Director, International Office, RWTH Aachen University
	Dr. Gerit Sonntag, Program Director, German Research Foundation (DFG)
Chair:	Mr. Alexander Grimm, M. Sc.
10:10	Prof. Dr. Kazuhito Fujiyama, Osaka University *"Production of Glucocerebrosidase by Glyco-Engineered Plant"*
10:40	Ass. Prof. Dr. Takao Ohashi, Osaka University *"Novel Membrane-Bound Type Plant Pectin-Degrading Enzyme"*
11:00	Ms. Roxanne Krug (née Tschersich), M. Sc., Jülich Research Center *"Laccases & Tyrosinases in Organic Synthesis"*
11:15	Ms. Patricia Liebhäuser, M. Sc., RWTH Aachen University *"Tyrosinase Model Complexes with Bis(pyrazolyl)methane Ligands"*
11:30 – 11:50	Coffee Break
Chair:	Mr. Andreas Thiel, M. Sc.
11:50	Prof. Dr. Jörg Pietruszka, Jülich Research Center *"Chemo-Enzymatic Production of Prodiginines"*
12:20	Ms. M. A. Stephanie Mertens, M. Sc., RWTH Aachen University *"Hybrid Catalysts for Selective Tandem Reactions"*
12:35	Mr. Marc Hayes, M. Sc., Jülich Research Center *"Glycosynthases: A New Approach to Screening and Characterisation"*
12:50	Mr. Hirofumi Harada, M. Sc., Osaka University *"In Situ Visualization of an Interdomain Motion in Cellobiose Dehydrogenase Anchored on a Heme-Modified Gold Surface Using High-Speed Atomic Force Microscopy"*
13:05 – 14:25	Lunch Break
Chair:	Mr. Steffen Mader, M. Sc.
14:25	Prof. Dr. Carsten Bolm, RWTH Aachen University *"Catalyses in Ball Mills"*
14:55	Mr. Kazutaka Takamatsu, M. Sc., Osaka University *"Copper-Mediated Decarboxylative Coupling of Benzamides with Benzoic Acids via Directed C-H Cleavage"*

15:10 Assoc. Prof. Dr. Koji Hirano, Osaka University
"Synthesis of α-Aminoboronic Acid and -silane Derivatives by Copper-Catalyzed Electrophilic Amination"

15:30 Ass. Prof. Dr. Takanori Iwasaki, Osaka University
"Nickel-Catalyzed Dimerization and Alkylarylation of 1,3-Dienes with Alkyl Fluorides and Aryl Grignard Reagents"

15:50 – 16:10 Coffee Break
Chair: Mr. Christian Göb, M. Sc.

16:10 Prof. Dr. Yoshihito Tobe, Osaka University
"Toward Periodical Modification of Graphite/Graphene Surfaces"

16:40 Mr. Kohei Iritani, M. Sc., Osaka University
"STM Observations of Complexation with Cyclic Array of Zinc Porphyrins at Liquid/Solid Interface"

15:55 Mr. Ayumu Ogawa, M. Sc., Osaka University
"Synthesis of a Cobalt Tetradehydrocorrin Complex Toward Catalytic CO_2 Reduction"

17:10 Mr. David van Craen, M. Sc., RWTH Aachen University
"Hierarchical Helicates – A Versatile Supramolecular Motif"

18:00 Dinner at "Elisenbrunnen"

Wednesday, September 7th, 2016

Venue: Institute of Inorganic Chemistry, Landoltweg 1, Room 202, 52074 Aachen

Chair: Ms. Ann-Kristin Wiegand, M. Sc.

9:30 Prof. Dr. Sonja Herres-Pawlis, RWTH Aachen University
"Fe^{II}, Zn^{II} and Cu^{II} Bis(pyrazolyl)methane Complexes for Lactide Polymerisation"

10:00 Ass. Prof. Dr. Haruki Nagae, Osaka University
"Reactivity of η^3-Allenyl- and Propargylyttrium Complexes Toward Insertion Reaction of C=N Double Bonds"

10:20 Mr. Tobias Schindler, M. Sc., RWTH Aachen University
"Group 6 Metal Complexes Featuring Tetradentate Bis(phenolate) Ligands"

10:35 Mr. Supriya Rej, M. Sc., Osaka University
"Mixed Ligated Tris(amidinate)dimolybdenum Complexes as Catalysts for Radical Addition of CCl_4 to 1-Hexene: Leaving Ligand Liability Controls Catalyst Activity"

10:50 Ms. Abhinanda Kundu, M. Sc., Osaka University
"Direct C-H Aminoalkylation of 2-Substituted Pyridine Derivatives Catalyzed by Yttrium Catalysts with N,N'-Diarylethylenediamido Ligands"

11:05 – 11:25 Coffee Break

Chair: Ms. Lu Lu, M. Sc.

11:25 Prof. Dr. Hiroaki Sasai, Osaka University
"Pd(II)-SPRIX Catalyzed Enantioselective Annulation of Alkenylindoles"

11:55 Mr. Kenta Kishi, M. Sc., Osaka University
"Enantioselective Synthesis of α-Methylidene-γ-Lactams via Amidation and Rauhut-Currier Reaction Sequence"

12:10 Mr. Hassan Osseili, M. Sc., RWTH Aachen University
"Alkali Metal Hydridotriphenylborates for Chemoselective Hydroboration Catalysis"

12:25 Mr. Kosuke Higashida, M. Sc., Osaka University
"Iridium(III)-Catalyzed (E)-Selective Semi-Hydrogenation of Alkynes Under Mild Conditions"

12:40 Mr. Masaya Hirano, M. Sc., Osaka University
"Iridium-Catalyzed Benzylic Carbon-Hydrogen Bond Silylation of 4-Alkyl–pyridine Derivatives"

12:55 – 14:15 Lunch Break

Chair: Ms. Anne-Katrin Bachon, Dipl.-Chem.

14:15 Dr. Masahiko Yamada, Kaneka Corporation
"Integrated Solutions to Non-Natural Amino Acids: Selection and Combination of Synthetic Technology and Biotechnology"

14:40 Mr. Koji Machida, M. Sc., Kaneka Corporation
"A Robust and Efficient Process of the HCV Protease Inhibitor Key Intermediate"

14:55 Prof. Dr. Lothar Elling, RWTH Aachen University
"Enzyme Cascades for the Synthesis of Glycan Oligomers and Their Presentation on Protein and Polymer Scaffolds"

15:25 – 15:45 Coffee Break
Chair: Mr. Marius Hoffmann, M. Sc.

15:45 Prof. Dr. Eiichiro Fukusaki, Osaka University
"Metabolomics-Based Semi-Rational Improvement of 1-Butanol Tolerance in Saccharomyces Cerevisiae"

16:15 Ms. Teruko Matsuo, M. Sc., Osaka University
"Development of Retention Index Prediction Model for Annotation of Unknown Compounds for GC/MS-Based Untargeted Metabolomics"

16:30 Ms. Birthe Halmschlag, M. Sc., RWTH Aachen University
"Metabolic Engineering of Bacillus Subtilis for Enhanced γ-Polyglutamic Acid Production"

16:45 Prof. Dr. Lars M. Blank, RWTH Aachen University
"Maximizing the Redox Cofactor Regeneration Rate for Redox Biocatalysis Using Whole-Cells"

Closing Remarks

17.15 Prof. Dr. Kazushi Mashima, Spokesperson SeleCa, Osaka University

18:00 Dinner

Program
On
Tuesday, September 6th, 2016

Prof. Dr. Kazuhito Fujiyama

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Short CV:

Education:

1980-1984	Department of Fermentation Technology, Faculty of Engineering, Osaka University
1984-1986	Master course, Department of Fermentation Technology, Graduate School of Engineering, Osaka University

Employment:

1988-2003	Assistant Professor International Center for Biotechnology, Osaka University
2003-2009	Associate Professor International Center for Biotechnology, Osaka University
2009-Now	Professor International Center for Biotechnology, Osaka University
2003-2004	Visiting scientist, Arizona State University (Dr. L. Joshi)
2004-Now	The Biodesign Institute at Arizona State University, Non-Resident Research Faculty (Adjunct Faculty)

Short Overview about Scientific Work:
Glyco-engineering of hetelogously-produced recombinant proteins, Plant glycobiology

Recent Publications:

1. Trempel, F.; Kajiura, H.; Ranf, S.; Grimmer. J.; Westphal, L.; Zipfel, C.; Scheel, D.; Fujiyama, K.; Lee, J. *BMC Plant Biol.* **2016***, 16,* 31.
2. Ohashi, T.; Hasegawa, Y.; Misaki, R.; Fujiyama, K. *Appl. Microbiol. Biotechnol.* **2016**, *100*, 687–696.
3. Hamorsky, K. T.; Kouokam, J. C.; Jurkiewicz, J. M.; Nelson, B.; Moore, L. J.; Husk, A. S.; Kajiura, H.; Fujiyama, K.; Matoba, N. *Sci. Rep.* **2015**, *5*, 8003.
4. Srichaisupakit, A.; Ohashi, T.; Misaki, R.; Fujiyama, K. *J Biosci Bioeng.* **2015**, *119*, 399–405.
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Production of Glucocerebrosidase by Glyco-Engineered Plant

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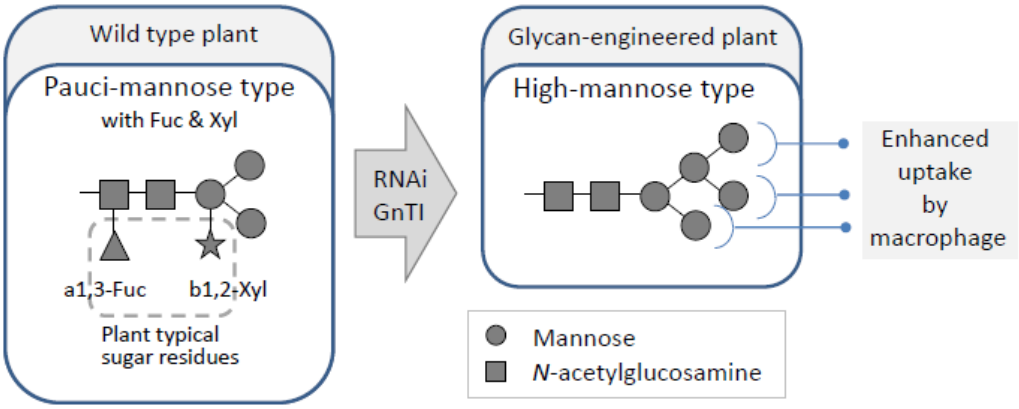
The production of therapeutic proteins in plants has gained attention, since human glucocerebrosidase (GC) produced by carrot suspension cultured cells has been approved for human use in US[1] and used for enzyme replacement therapy in patients with Gaucher's disease. Sometimes plant typical sugar residues on glycoproteins are debated for their antigenic activity. Hence, we engineered protein glycosylation pathway in *Nicotiana benthamiana*. RNA interference (RNAi) technology was applied to down-regulate the N-acetylglucosaminyl-transferase I (GNTI) expression in *N. benthamiana*, which would lead to high-mannose type structure with reduced plant sugars. This glyco-engineered plant (NbGNTI-RNAi) reduced content of N-glycans with plant typical sugars in endogenous glycoproteins. Then, this NbGNTI-RNAi was used as a promising host to produce human GC. The recombinant human GC was purified from the NbGNTI-RNAi plant expressing human GC was constructed and used for purification and characterization of recombinant human GC. N-Glycan structural analysis showed recombinant GC also carried high-mannose glycans, resulting in enhanced macrophage uptake.[2]

Finally, this study showed engineering of glycosylation pathway in plant improved properties of recombinant proteins.



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1. Bethencourt, V. *Nature Biotechnol*. **2009**, *27*, 681
2. Limkul, J,.; Iizuka, S.; Sato, Y.; Misaki, R.; Ohashi, T.; Ohashi, T.; Fujiyama, K. *Plant Biotechnol J.* **2016.** DOI: 10.1111/pbi.12529.

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Short CV:

Takao Ohashi graduated from Osaka University (Department of Chemistry, School of Science) in 2002. He received his Doctor degree (2007) from the Graduate School of Science, Osaka University under the supervision of Professor S. Hase. Afterwards he started his professional carrier as postdoc researcher of Asahi Glass Co., Ltd working with Professor K. Takegawa at Kagawa University. In 2008, he moved to Kyushu University accompanying Professor K. Takegawa's moving. In 2010 he became an Assistant Professor at International Center for Biotechnology, Osaka University working with Professor K. Fujiyama. His current special interest is on the elucidation of molecular mechanism of plant pectin biosynthesis/degradation toward plant cell wall engineering.

Recent Publications:

1. Ohashi, T.; Hasegawa, Y.; Misaki, R.; Fujiyama, K. *Appl. Microbiol. Biotechnol.* **2016**, *100*, 687–696.
2. Srichaisupakit, A.; Ohashi, T.; Misaki, R.; Fujiyama, K. *J. Biosci. Bioeng.* **2015**, *119*, 399–405.
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Novel Membrane-Bound Type Plant Pectin-Degrading Enzyme

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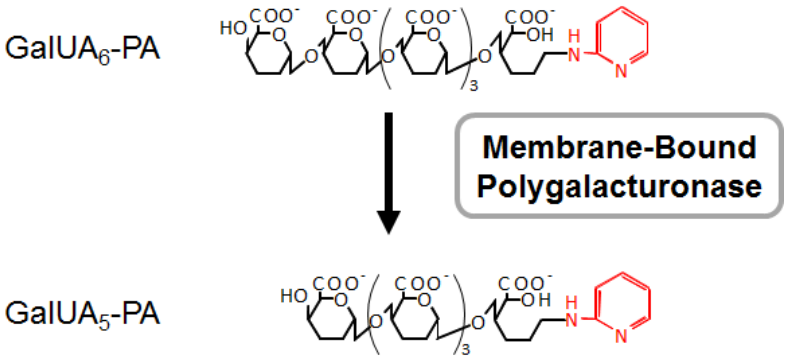
Pectin, one of the most abundant polysaccharides in plant cell wall, is highly branching acidic polysaccharides and consisted of high amounts of galacturonic acid (GalUA) residues. The backbone of pectin is composed of a linear chain of α1,4-linked GalUA, called polygalacturonic acid, and mainly degraded by polygalacturonase (PG). A number of PG activities and gene expressions have been detected in various plants. PGs are believed to be involved in numerous cell-separation processes in plant development, such as fruit ripening, pod and anther dehiscence, and organ abscission.[1] Although 69 PGs have been annotated in *Arabidopsis thaliana*, only 5 PGs were functionally characterized and reported to be secreted proteins.[2-4] While PG activity was detected in the microsomal fraction by our preliminary results, suggesting the presence of membrane-bound PG.[5] Then we speculated that some of the putative PGs carrying membrane-bound regions could be the membrane-bound PG polypeptides.



To identify the membrane-bound PGs, we cloned all putative membrane-bound PGs and expressed in tobacco BY-2 cells to determined their subcellular localization. In addition, the recombinant putative membrane-bound PGs were produced using yeast heterologous expression system for PG activity assay. Arabidopsis homozygous PG gene knockout mutants were obtained from the Arabidopsis Biological Resource Center. Some of the PG gene knockout mutants showed growth defects and altered stress responses. Here we will present the molecular characterization and the supposed functions of the membrane-bound PGs and discuss the possible future applications.

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Laccases & Tyrosinases in Organic Synthesis

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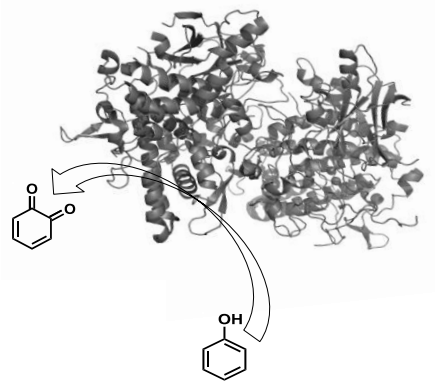
The interest in performing green/environmentally beneficial chemistry has increased within the last decade, moving enzyme mediated reactions increasingly also into the focus of organic chemistry. Laccases and tyrosinases, multi copper oxidoreductases, are widespread throughout the domains of plants, fungi, and microorganisms.[1] Their ability to not only oxidise, but also to hydroxylate (in the case of tyrosinases) low-molecular weight compounds, make the multicopper oxidases beneficial and versatile alternatives compared to toxic and expensive conventional oxidizing agents.[1,2] Our most recent results will be presented: The purification and application of the tyrosinase of *A. oryzae*[3] is investigated, comparing it with the laccase of *A.bisporus* with respect to oxidoreductase-mediated arylation reactions.[4]



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Tyrosinase Model Complexes with Bis(pyrazolyl)methane Ligands

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Tyrosinase is an important enzyme in the biosynthesis of the pigment melanin as it catalyses the oxidation of the phenolic substrate tyrosine to its *ortho*-catechol and subsequently to the corresponding *ortho*-quinone. The active site of the enzyme consists of two copper centres each coordinated by three histidine residues. With the absorption of dioxygen a μ-η^2:η^2-peroxodicopper(II) species is formed (Fig. 1). So far only a few catalytic models for tyrosinase have been developed.[1]

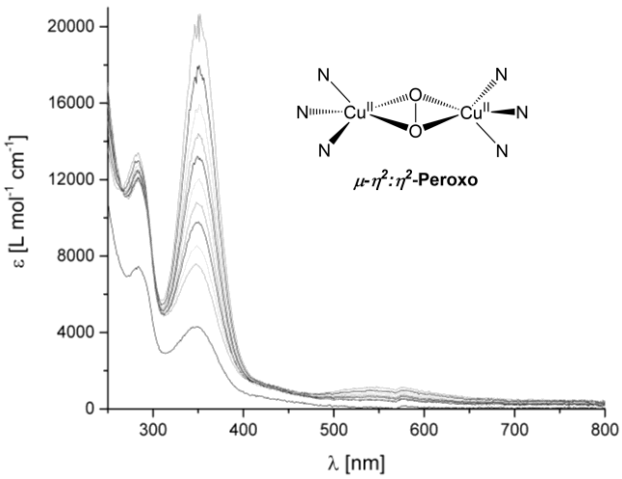

Fig. 1: UV/Vis spectra of the *side-on*-peroxo species.

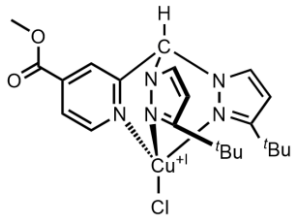

Fig. 2: Bis(pyrazolyl)-methane copper complex.

Bis(pyrazolyl)methane copper complexes (Fig. 2) can mimic the catalytic centre of tyrosinase not only structurally, they even oxidise phenolic substrates.[2] With the addition of dioxygen the formation of the *side-on*-peroxo complex can be monitored by UV/Vis spectroscopy due to its characteristic absorptions at 350 and 550 nm (Fig. 1). The use of bis(pyrazolyl)(pyridinyl)methane ligands resulted in enhanced stability towards thermal decomposition. Reacting the Cu_2O_2 species with electronically different phenolates showed that the hydroxylation of substrates is based on an electrophilic mechanism which is known from the natural enzyme. The model systems are able to catalytically convert phenolic substrates.

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Jörg Pietruszka was born in Hamburg in 1965. He studied chemistry at the University of Hamburg where he also obtained his doctorate (Dr. rer. nat.) in 1993 (Prof. W. A. König). After 2 postdoctoral years with Professor S. V. Ley (Cambridge, UK), he fulfilled the requirements for his 'Habilitation' – funded by a Liebig-Fellowship and a DFG grant – at the University of Stuttgart in 2001. In 2000/2001 he was a visiting lecturer at the University of Freiburg (Germany), 2001/2002 a guest professor at the University of Cardiff (Wales) and 2002/2003 he held a substitute-professorship at the University of Tübingen (Germany). In 2004 an offer for a professorship at the University in Gießen was declined; since 2004 he holds the position as full professor and chair of Bioorganic Chemistry at the Heinrich-Heine-University Düsseldorf. He is speaker of the graduate school on industrial biotechnology 'CliB2021-GC' as well as the interdisciplinary graduate school of protein science (iGRASP$_{seed}$) at the University of Düsseldorf with approx. 140 fellows.

His research interests include the development of new chemoenzymatic methods and their application in the synthesis of natural products.

Recent Publications:

1. Brauns, M.; Muller, F.; Gülden, D.; Böse, D.; Frey, W.; Breugst, M.; Pietruszka, J. *Angew. Chem. Int. Ed.* **2016**, *55*, 1548–1552.
2. Holec, C.; Neufeld, K.; Pietruszka, J. *Adv. Synth. Catal.* **2016**, *358*, 1810–1819.
3. Dick, M.; Hartmann, R.; Weiergräber, O.H.; Bisterfeld, C.; Classen, T.; Schwarten, M.; Neudecker, P.; Willbold, D.; Pietruszka, J. *Chem. Sci.* **2016**. DOI: 10.1039/C5SC04574F.
4. Dick, M.; Weiergräber, O.H.; Classen, T.; Bisterfeld, C.; Bramski, J.; Gohlke, H.; Pietruszka, J. *Sci. Rep.* **2016**, *6*, 17908.
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9. Classen, T.; Korpak, M.; Schölzel, M.; Pietruszka, J. *ACS Catalysis* **2014**, *4*, 1321–1331.
10. Bielitza, M.; Pietruszka, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 10960–10985.

Chemo-Enzymatic Production of Prodiginines

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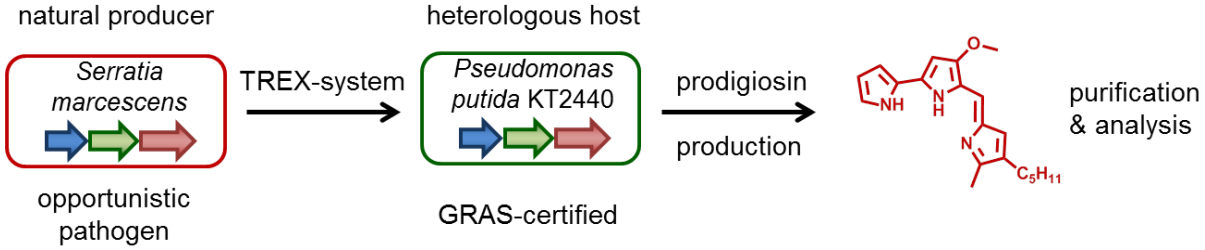
Prodiginines are a class of microbial secondary metabolites produced by different Gram-positive and –negative bacteria such as *Streptomyces coelicolor* and *Serratia marcescens.* Prodiginines exhibit various pharmacological relevant properties including antibiotic activities against various pathogens such as *Salmonella typhi*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*.[1] The red-pigmented tripyrrol prodigiosin is naturally synthesized from amino acid and acetate building blocks. Since *S. marcescens* is an opportunistic pathogen that accumulates prodigiosin in low amounts, the development of alternative strategies for an efficient synthesis independent of the original producer is of great interest.

Therefore, we developed the transfer and expression (TREX) system that facilitates the transfer, chromosomal integration and concerted expression of large gene clusters in bacteria.[2] The prodigiosin gene cluster from *S. marcescens* has been integrated into the chromosome of the GRAS-certified bacterium *Pseudomonas putida* accumulating prodigiosin at substantial levels. We will present our recent findings including a novel, fast and effective protocol for prodigiosin extraction and purification.[3]



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Hybrid Catalysts for Selective Tandem Reactions

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The use of biohybrid catalysts enables highly active and selective reactions like in ring-opening metathesis polymerization[1,2], demonstrating the effect of a protein scaffold surrounding a transition metal catalyst. The outer membrane protein FhuA of *Escherichia coli* is a suitable second ligand sphere for such catalysts, as it shows high stability due to its β-barrel structure and a wide inner channel diameter to host large catalysts and substrates[2]. The use of biohybrid catalysts in the outer membrane of whole cells allows chemical transformations in industrial scale, which is unattractive for isolated biohybrid catalysts due to high costs. Furthermore, the biohybrid catalysts could for the first time be subjected to Directed Evolution methods, which enable the generation of proteins with a tailor-made surrounding. The latter allows to improve e.g. the selectivity and activity of biohybrid catalysts to explore the synthetic potential of naturally not used metals. A combination of biohybrid catalysts and biocatalysts in tandem reactions allows selective biohybrid catalysis under mild reaction conditions from biocatalytic produced important natural building blocks such as fatty acids. An isolation of intermediates is redundant and feedback inhibition of products can be eliminated. The biohybrid catalysts constructed in previous works[1,2] resulted in the artificial metathease FhuA-Grubbs-Hoveyda active in various metathesis reactions. The corresponding alkene will be generated from fatty acids through P450 Ole_{TJE}, a newly investigated decarboxylase out of *Jeotgalicoccus* sp.

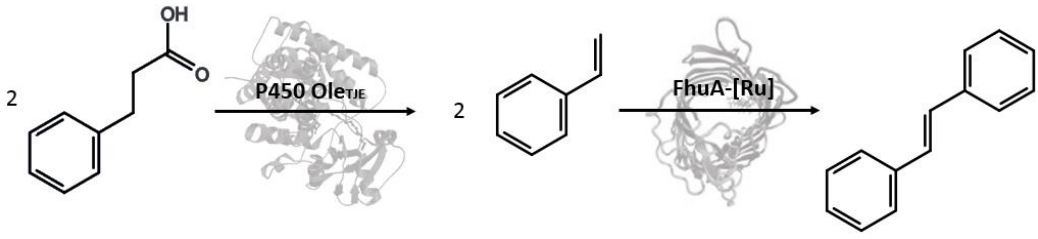

Figure 1: Hypothesized tandem reaction using P450 OleTJE and FhuA-[Ru] hybrid catalyst.

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Glycosynthases: A New Approach to Screening and Characterisation

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In the development of new bioactive compounds (anti-cancerogenous compounds, detergents, flavours etc.), naturally occurring glycosidic structures are gaining more and more attention throughout the pharmaceutical, food and detergent industry. The use of enzymes such as glycotransferases and especially glycosidases for the synthesis of glycosides has increased much in past years due to the laborious amount of steps required during chemical synthesis of complex glycosidic structures. In order to overcome the drawbacks of these natural enzymes during synthetic reactions, *Withers* and co-workers developed new genetically modified glycosidases. These 'glycosynthases' are void of hydrolytic activity and able to catalyse glycosidic bond synthesis using easily synthesised activated glycosyl donors (Figure 1).[1]

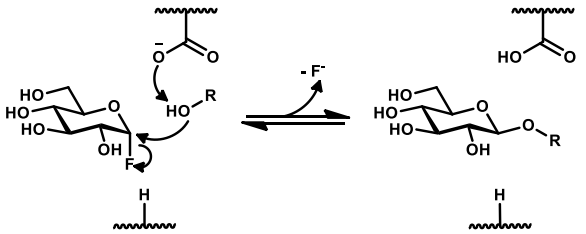

Figure 1: General reaction mechanism of a glycosynthase of which the nucleophilic amino acid residue has been mutated.

The identification and improvement of potential enzymes for synthetic use require screening methods allowing high-throughput, low cost and reproducible analysis of the enzymatic reaction.[2] Most commonly surrogate substrates containing chromo-/fluorogenic moieties are used for fast and parallel analysis in microtiter plates. The glycosidic compounds resulting from a glycosynthase reaction usually lack simple detectable moieties for a direct assay. In cooperation with the group of *Prof. Elling* and co-workers of the RWTH Aachen new glycosynthases with diverse properties were created. For a fast characterisation and screening of acceptor substrates, a new photometric indirect screening method was developed. In this presentation, we will present our current progress in this field of research.

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In Situ Visualization of an Interdomain Motion in Cellobiose Dehydrogenase Anchored on a Heme-Modified Gold Surface Using High-Speed Atomic Force Microscopy

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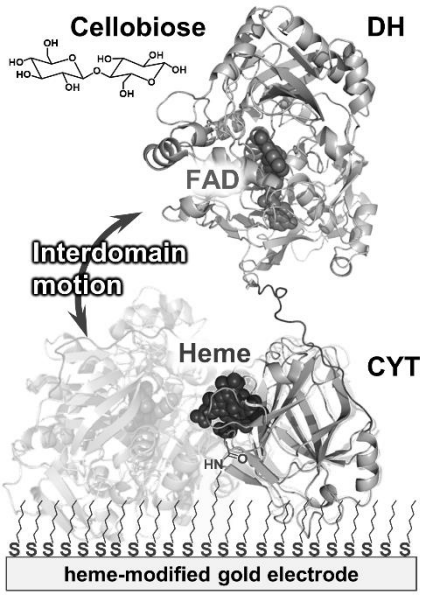
Cellobiose dehydrogenase (CDH) secreted by fungi is an enzyme that oxidizes plant disaccharides. CDH consists of catalytic dehydrogenase (DH) domain containing flavin adenine dinucleotide (FAD) and cytochrome (CYT) domain containing *b*-type heme. An interdomain electron transfer (ET) from DH to CYT has been proposed as a key step for catalysis.[1] However, the motional basis of the ET mechanism is still elusive. Here we demonstrate, for the first time, a direct visualization of the dynamic interdomain motion in CDH upon binding of the substrate by high-speed atomic force microscopy (HS-AFM).



Both cofactors, FAD and heme, were removed from recombinantly expressed CDH from basidiomycete *Phanerochaete chrysosporium* to obtain apoCDH. The reconstitution with FAD (FAD-apoCDH) is found to recover the original enzymatic activity, which was confirmed by colorimetric assay using 2,6-dichlorophenolindophenol.[2] The heme cofactor was covalently conjugated to SAM of 11-aminoundecathiol fabricated on a gold surface (Heme/Au). Quartz crystal microbalance measurement indicates that the FAD-apoCDH was reconstituted to Heme/Au via the specific heme–heme binding site interaction with a strong affinity (K_d = 0.55 μM). HS-AFM imaging of the CDH-immobilized electrode reveals that the dynamic motion of the DH_{CDH} domain becomes faster in a cellobiose-dose-dependent manner.

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Carsten Bolm was born in Braunschweig in 1960. He studied chemistry at the TU Braunschweig (Germany) and at the University of Wisconsin, Madison (USA). In 1987 he obtained his doctorate with Professor Reetz in Marburg (Germany). After postdoctoral training with Professor Sharpless at MIT, Cambridge (USA), Carsten Bolm worked in Basel (Switzerland) with Professor Giese to obtain his habilitation. In 1993 he became Professor of Organic Chemistry at the University of Marburg (Germany), and since 1996 he has a chair of Organic Chemistry at RWTH Aachen University (Germany). In 2012 he became an adjunct professor at WIT (Wuhan Institute of Technology), China, and in 2014 he was awarded a Distinguished Professorship RWTH Aachen University. He is Board Member of several journals and Associate Editor of the Journal of Organic Chemistry. His publication list has over 430 entries, and in 2014 and 2015 he was selected "Thomson Reuters Highly Cited Researcher". (Author profile: *Angew. Chem. Int. Ed.* **2014**, *53*, 6596–6597.)

Recent Publications:

1. Hermann, G. N.; Becker, P.; Bolm, C. *Angew. Chem. Int. Ed.* **2016**, *55*, 3781–3784.
2. Dong, S.; Frings, M.; Cheng, H.; Wen, J.; Zhang, D.; Raabe, G.; Bolm, C. *J. Am. Chem. Soc.* **2016**, *138*, 2166–2169.
3. Wang, H.; Cheng, Y.; Becker, P.; Raabe, G.; Bolm, C. *Angew. Chem. Int. Ed.* DOI: 10.1002/anie.201605743.

Catalyses in Ball Mills

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A significant number of catalyzed reactions can benefit from mechanochemical activation modes.[1] Illustrative examples are:

1. asymmetric Michael additions onto nitroolefins,[2]

2. diastereoselective alkylations of nickel complexes,[3]

3. solventless rhodium- and iridium-catalyzed C–H-bond functionalizations[4,5] including catalyst preparations,[6]

4. enzymatic kinetic resolutions,[7] and

5. lignin degradations.[8]

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Copper-Mediated Decarboxylative Coupling of Benzamides with Benzoic Acids via Directed C-H Cleavage

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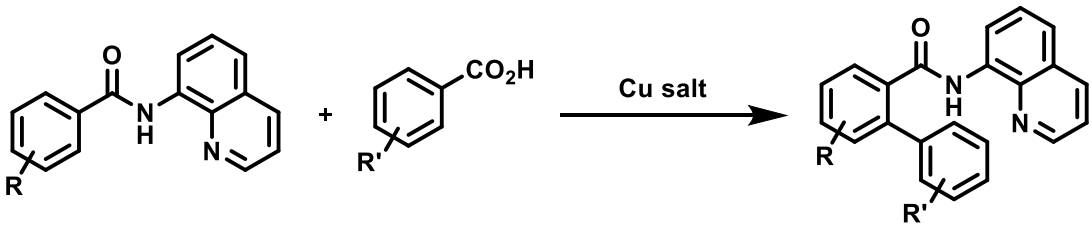
Metal-promoted decarboxylative couplings attract great interest as a useful tool for C–C and C–heteroatom bonds formation because stable and abundant carboxylic acids can be used as carbon nucleophiles. Since Gooβen et al. reported a Pd/Cu-cocatalyzed decarboxylative cross-coupling reaction of benzoic acids with aryl halides as pioneering work,[1] a variety of transition-metal-catalyzed decarboxylative couplings of carboxylic acids with various carbon electrophiles have been reported.[2]

Moreover, decarboxylative couplings combined with transition-metal-mediated C-H activation, namely decarboxylative C-H arylation are also developed. [2] These reactions have received significant attention due to their higher synthetic efficiency compared to the traditional cross-coupling technologies with organic halides and organometallic reagents. However, noble transition metals are essential in most cases.

On the other hand, our group has recently focused on inexpensive, less toxic, and abundant copper salts and developed copper-mediated C-H functionalization reactions.[3] Particularly, nitrogen-based directing groups enables such base metals to serve as good alternatives to precious transition metals and sometimes unique activators for otherwise challenging C-H transformations. Herein, we report a copper-mediated decarboxylative C-H arylation of benzamides with benzoic acids via 8-aminoquinoline-directed[4] C-H cleavage.



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4. Zaitsev, V. Z.; Shabashov, D.; Daugulis, O. J *J. Am. Chem. Soc.* **2005**, *127*, 13154.

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1999-2003:	Bachelor, Faculty of Engineering, Kyoto University
2003-2005:	Master, Department of Chemistry, Graduate School of Engineering, Kyoto University
2005-2008:	Ph. D., Department of Material Chemistry, Graduate School of Engineering, Kyoto University
2008.4 - 2008.9:	JSPS Postdoctoral Fellow, Department of Chemistry, Graduate School of Science, Kyoto University

Academic Career

2008.10-2015.3:	Assistant Professor at Department of Applied Chemistry, Graduate School of Engineering, Osaka University
2015.4 -:	Associate Professor at Department of Applied Chemistry, Graduate School of Engineering, Osaka University

Awards

Mitsubishi Gas Chemical Company Award in Synthetic Organic Chemistry, Japan (2011)
92nd Annual Spring Meeting of CSJ (Chemical Society of Japan), Best Presentation Award (Academic) (2012)
The Young Scholar's Lectures Award, 93rd Annual Spring Meeting of CSJ (2013)
13th GSC (Green Sustainable Chemistry) Award by Minister of Education, Culture, Sports, Science and Technology (2014)
The CSJ Award for Young Chemists (2016)

Research Interests

Organic synthesis and organometallic chemistry, especially, the development of new synthetic reactions catalyzed by transition metal catalysts

Recent Publications:

1. Tabuchi, S.; Hirano, K.; Miura, M. *Angew. Chem., Int. Ed.* **2016**, *55*, 6973.
2. Nishikawa, D.; Hirano, K.; Miura, M. *J. Am. Chem. Soc.* **2015**, *137*, 15620.
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Synthesis of α-Aminoboronic Acid and –silane Derivatives by Copper-Catalyzed Electrophilic Amination

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Organoboron and –silicon compounds are ubiquitous synthetic intermediates in modern organic synthesis because C–B and C–Si bonds can be readily transformed into versatile C–C and C–heteroatom bonds. Additionally, their unique biological activities have recently been uncovered. Among them, α-aminoboronic acid and –silane derivatives have now received significant attention since they are pharmacophores in several unique bioactive molecules. To date, many synthetic chemists have developed the efficient protocols for the preparation of the above target structures, however, there still remains a large demand for further development of catalysis directed toward versatile and highly functionalized α-aminoboronic acids and -silanes.

Our research group recently focused on an umpolung, electrophilic amination strategy with chloroamines and hydroxylamine derivatives and succeeded in the otherwise challenging catalytic hydroamination and aminoboration reactions of alkenes.[1] Here, we wish to present recent progress of this research project: copper-catalyzed hydroamination and aminoboration of boryl- and silyl-substituted alkenes for the synthesis of α-aminoboronic acids and -silanes.[2]

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1. (a) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2013**, *135*, 4934. (b) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 10830. (c) Sakae, R.; Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2014**, *16*, 1228. (d) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2014**, *16*, 1498. (e) Sakae, R.; Hirano, K.; Miura, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 613. (f) Sakae, R.; Hirano, K.; Miura, M. *J. Am. Chem. Soc.* **2015**, *137*, 6460.
2. Nishikawa, D.; Hirano, K.; Miura, M. *J. Am. Chem. Soc.* **2015**, *137*, 15620.

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Takanori Iwasaki was born in Osaka, Japan, in 1981, finished his BSc in 2004 and MSc in 2006 at Graduate School of Engineering Science, Osaka University and received his Ph.D. in 2009 from Osaka University under the supervision of Profs K. Mashima and T. Ohshima. During his Ph.D. course, he worked with Prof K. Kirchner, Vienna University Technology, Austria in 2005. He became an assistant professor at the Graduate School of Engineering, Osaka University in 2009, working with Prof N. Kambe. He received JSPC Award for Excellence 2008, Asahi Kasei Pharma Award in Synthetic Organic Chemistry, Japan in 2011, The Ube Foundation Young Researcher Award in 2014, and Special Lecture for Young Chemists in 96th CSJ in 2016. He was also selected as finalist of Reaxys PhD Prize 2010. His current research interests include understanding the chemical behavior of anionic transition metal complexes and the development of transition metal-catalyzed C–C and C–heteroatom bond formations applied to organic synthesis.

Recent Publications:

1. Iwasaki, T.; Min, X.; Fukuoka, A.; Kuniyasu, H.; Kambe, N. *Angew. Chem. Int. Ed.* **2016**, *55*, 5550–5554.
2. Iwasaki, T.; Shimizu, R.; Imanishi, R.; Kuniyasu, H.; Kambe; N. “Cu-Catalyzed Regioselective Hydroalkylation of 1,3-Dienes with Alkyl Fluorides and Grignard Reagents” *Angew. Chem. Int. Ed.* **2015**, *54*, 9347-9350.
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8. Ghaderi, A.; Iwasaki, T.; Fukuoka, A.; Terao, J.; Kambe, N. *Chem. Eur. J.* **2013**, *19*, 2951–2955.
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Nickel-Catalyzed Dimerization and Alkylarylation of 1,3-Dienes with Alkyl Fluorides and Aryl Grignard Reagents

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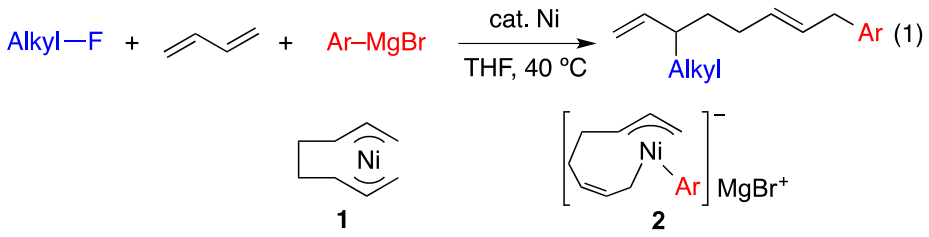
The oxidative dimerization of 1,3-butadiene on zero-valent nickel species is a useful process to construct higher unsaturated alkyl chains from easily accessible 1,3-butadiene, though the reaction of thus formed nickel(II) species **1** with carbon electrophiles is rarely discussed.[1] To expand the synthetic utility of the nickel complex, we assumed that the formation of the corresponding anionic complexes **2** by the reaction of the nickel complex **1** with an aryl Grignard reagent might enhance its nucleophilicity toward less reactive electrophiles. Herein, we report alkylarylation of the nickel(II) species by alkyl halides and aryl Grignard reagents to selectively give 1,6-octadienes having an alkyl and an aryl groups at 3- and 8-positions, respectively.[2]

When an alkyl fluoride was treated with *o*-tolyl Grignard reagent in the presence of 1,3-butadiene and catalytic amount of Ni in THF, the corresponding four-component coupling product was obtained in 86% yield as the sole regio- and stereoisomer (eq 1). In the present catalytic system, various alkyl fluorides and aryl Grignard reagents bearing substituent(s) at *ortho*-position smoothly and selectively underwent the reaction to the give desired four-component coupling products even though C–F bond is the strongest single bonds in organic compounds.

Mechanistic studies revealed that the present catalysis proceeds via oxidative dimerization of 1,3-butadiene, formation of anionic nickel species **2** by reacting with an aryl Grignard reagent, nucleophilic attack of the γ-position of the σ-allyl group on nickel complex **2**, and reductive elimination. The proposed key intermediate **2** was successfully isolated by the reaction of $Ni(cod)_2$ with 1,3-butadiene and an aryllithium reagent in a good yield.



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1979 (April): Assistant Professor, Faculty of Engineering, Osaka University
1984 (July): Senior Lecturer, Faculty of Engineering, Osaka University
1988 (May)-1989 (March): Visiting Professor, The University of Chicago (with Philip E. Eaton)
1992 (April): Associate Professor, Faculty of Engineering Science, Osaka University
1998 (October)-: Professor, Graduate School of Engineering Science, Osaka University
2003 (October)-2007 (August): Member of University Council, Osaka University
2007 (August)-2011 (August): Dean, Graduate School and School of Engineering Science, Osaka University
2012 (April)-2014 (March): Director, Center for Quantum Science and Technology under Extreme Conditions, Osaka University
2014 (April)-: Director, Research Center for Solar Energy Chemistry, Osaka University
2015 (April)-: Director, Institute for NanoScience Design, Osaka University

Awards:
The Chemical Society of Japan Award for Young Chemists (1986)
Synthetic Organic Chemistry Award, Japan (2012)
The Chemical Society of Japan Award (2015)
The 2017 Nozoe Lecturer (prospective: 2017 International Symposium on Novel Aromatic Compounds)

Short Overview about Scientific Work:
Physical organic chemistry with particular emphasis on supramolecular self-assembly of organic molecules at liquid-solid interfaces and synthesis and properties of exotic pi-conjugated molecules with diradical or multiradical character.

Recent Publications:
1. Fang, F.; Ghijsens, E.; Ivasenko, O.; Cao, H.; Noguchi, A.; Mali, K. S.; Tahara, K.; Tobe, Y.; De Feyter, S. *Nat*ure *Chem*. **2016**, 8, 711–717.
2. Tahara, K.; Nakatani, K.; Iritani, K.; De Feyter, S.; Tobe, Y. *ACS Nano*. **2016**, *10*, 2113–2120.
3. Ghijsens, E.; Cao, H.; Noguchi, A.; Ivasenko, O.; Fang, Y.; Tahara, K.; Tobe, Y.; De Feyter, S. *Chem. Commun.* **2015**, *51*, 4766–4769.
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Toward Periodical Modification of Graphite/Graphene Surfaces

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To take advantage of the properties of two-dimensional (2D) and layered carbon based materials, it is important to develop protocols for efficient chemical functionalization which can be done in a periodic manner in view of potential applications these materials to electronic devices, sensors, and catalysts. To this end, we selected covalent bond formation by radicals generated from diazonium reagents by electrochemical reduction to highly oriented pyrolytic graphite (HOPG) and graphene, which is a known common method of covalent modification of graphite (electrode), to clarify the effect of substituents on the grafting efficiency utilyzing local microscopy and spectroscopy techniques. For example, we found significant difference between the grafting densities resulting from *p*-nitrophenyl and 3,5-di-*t*-butyl radicals (Figure 1).[1] Our ultimate goal in this project is to modify the carbon based materials in a periodic manner with nanometer precision using templates or masks such as those we have developed during the last decade (Figure 2).[2]

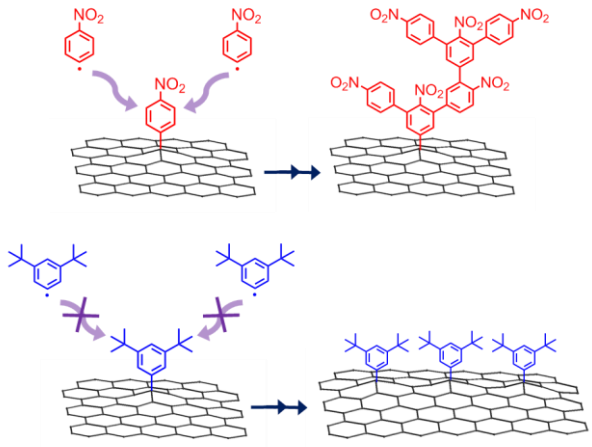

Figure 1. Schematic representation for diferent modes of grafting of graphene surface by aryl radicals.

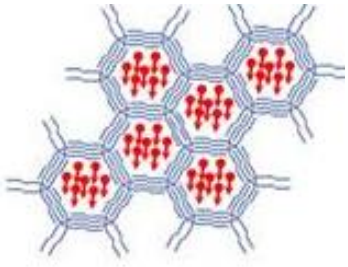

Figure 2. Schematic representation for grafting at masked space of graphene.

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2. Fang, F.; Ghijsens, E.; Ivasenko, O.; Cao, H.; Noguchi, A.; Mali, K. S.; Tahara, K.; Tobe, Y.; De Feyter, S. *Nature Chem*. **2016**, 8, 711–717.

STM Observations of Complexation with Cyclic Array of Zinc Porphyrins at Liquid/Solid Interface

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Construction of tailored two-dimensional (2D) porous molecular alignments has attracted intense interest in view of guest recognition at the nanoporous space. However, 2D networks with functional groups capable of binding specific guest molecules via non-covalent interactions other than van der Waals force have scarcely been achieved. Here we report the construction of 2D network with zinc porphyrin (ZnP) units which can bind guest molecules via charge transfer interaction or coordination bonding using a porous honeycomb network of dehydrobenzo[12]annulene derivative[1] as a template. For this purpose, we designed DBA **1** having three ZnP units at the end of alkyl chains alternately (Figure 1a). Moreover, we performed Scanning Tunneling Microscopy (STM) observations of complexation of the cyclically aligned ZnP units with guest molecules such as fullerenes C_{60} and C_{84}.

We already revealed that DBA **1** formed honeycomb type molecular alignment with six ZnP units placed cyclically in the pores at 1,2,4-trichrolobenzene (TCB)/HOPG interface (Figure 1b). Next, the co-adsorption of guest molecule on the monolayer of **1** was examined using C_{60} and C_{84}. When excess amount of C_{60} or C_{84} molecules was added, very bright features were observed cyclically in the honeycomb pores (Figure 1c, d). Because these bright features were not observed when fullerenes were absent, we considered that these very bright features correspond to C_{60} or C_{84} immobilized on the ZnP units.

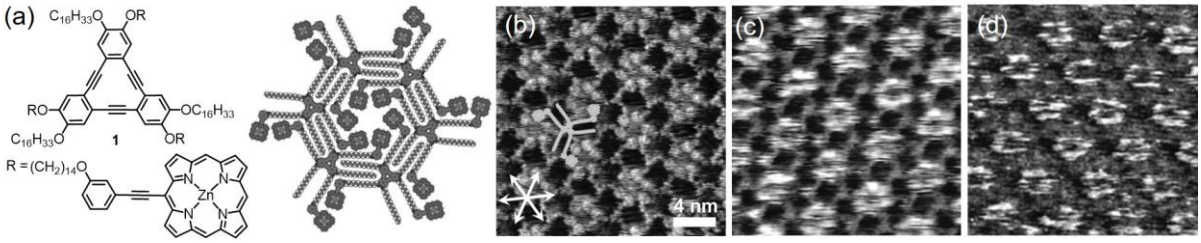

Figure 1. (a) Chemical structure of **1** and a model of honeycomb structure of **1**. (b) STM image of the self-assembled monolayer of **1** with its molecular model superimposed. (c, d) STM images of the molecular alignment formed by a mixture of **1** and C_{60} (c) or C_{84} (d).

References:

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Synthesis of a Cobalt Tetradehydrocorrin Complex Toward Catalytic CO_2 Reduction

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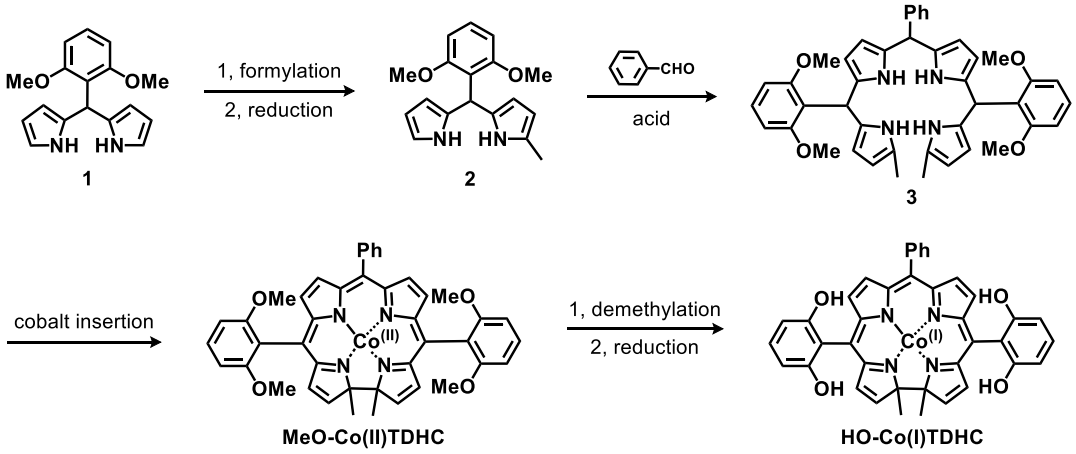
An effective conversion of carbon dioxide (CO_2) into energy-rich chemicals such as carbon monoxide, formic acid and hydrocarbons has attracted great attention because of its importance in a carbon-neutral energy cycle. To date, a variety of catalysts for CO_2 reduction reaction (CO_2RR) including homogeneous molecular catalysts, have been developed. However, the reports about non-precious metal-based molecular catalysts with high efficiency and/or product selectivity are limited. Recently, we started to synthesize a well-designed metal tetrapyrrole complex toward efficient CO_2RR as follows.

As a tetrapyrrole metal complex, we focused on cobalt tetradehydrocorrin (TDHC), a model complex of cobalamin. Due to its monoanionic structure, TDHC ligand effectively promotes the formation of the low valent cobalt species, which is known as the strong nucleophilic intermediate. In addition, four hydroxyl groups as proton donors are introduced on the phenyl groups at *meso*-positions toward the high efficiency and product selectivity for CO_2RR.[1)] The target catalyst, HO-Co(I)TDHC, was designed as shown in Scheme 1. In this presentation, we will report the details of synthesis, characterization and catalytic activity for CO_2RR.



Scheme 1. Synthesis of HO-Co(I)TDHC.

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Hierarchical Helicates – A Versatile Supramolecular Motif

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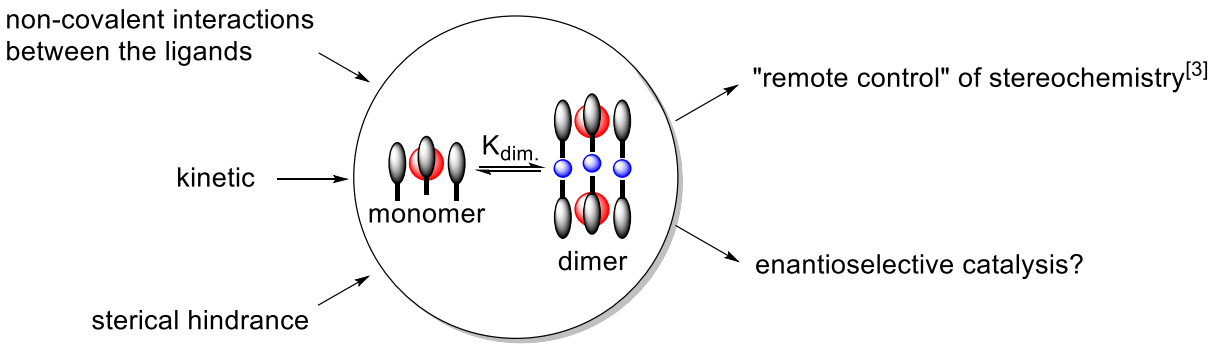
Since the beginning of life, helical structures such as DNA play a fundamental role in the chemistry of nature. On a macroscopic level this structural motif is found in springs, screws and even winding stairs to benefit from its unique properties. Roughly 2.5 billion years after cyanobacteria started producing oxygen and smoothed the way for higher developed life J.-M. Lehn defined the term “helicate” in 1987 and introduced this longstanding motif in chemistry.[1]

Hierarchically assembled lithium-bridged titanium helicates were developed by our group two decades later using catechols with keto or ester functionalities in the 3 position.[2] Since then a great variety of ligands were used to observe the equilibrium between a “Werner”-type triscatecholat complex (monomer) and the corresponding dimer bridged by lithium cations.

This work focuses on the deeper understanding of the equilibrium between monomer and dimer as well as on the usage of hierarchically assembled helicates.



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Program
On
Wednesday, September 7th, 2016

Prof. Dr. Sonja Herres-Pawlis

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Sonja Herres-Pawlis received her Doctor degree (2005) from the University of Paderborn under the supervision of Professor G. Henkel. The thesis topic was bioinorganic copper-dioxygen chemistry. She moved as Postdoc fellow to Stanford University, working with Prof. T.D.P. Stack. After moving back to Paderborn, she started her independent work. 2009 she moved to the Technical University of Dortmund to work at her habilitation on sustainable polymerization catalysts together with Prof. K. Jurkschat. In 2011, she received and accepted a call to an associate professor position for coordination chemistry at LMU Munich. 2012 she finished the Habilitation theses at TU Dortmund. At LMU Munich, she worked in bioinorganic chemistry and sustainable polymerization catalysis. In 2014, she received two calls for chairs of bioinorganic chemistry at TU Dortmund and RWTH Aachen. Since January 2015, she works in Aachen. She received several fellowships (for PhD period and Postdoc period) and several awards, most importantly in 2011, she won the Innovation Prize of the state of Northrhine-Westphalia and in 2014, the Arnold-Sommerfeld Prize of the Bavarian Academy of Arts and Sciences. She is speaker of the interdisciplinary DFG-research unit FOR1405 (“Charge transfer dynamics in bioinorganic copper complexes”).

Her current research interests lie in the area of bioinorganic and coordination chemistry, with strong emphasis on copper chemistry for oxygen and electron transfer, C-C coupling reactions but also atom transfer radical polymerization and lactide polymerization with zinc complexes. She has published over 100 original papers and 4 patents.

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Fe^{II}, Zn^{II} and Cu^{II} Bis(pyrazolyl)methane Complexes for Lactide Polymerisation

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One of the major requirements for catalytical activity is the presence of free coordination sites. Tridentate *N,N,N*-bis(pyrazolyl)methane ligands with pyrazolyls functionalized in 3-position tend to form bisfacial, coordinatively saturated complexes in combination with transition metals (Fe/Zn/Cu^{II}). The reasons herefore lie in the low sterical demand of the ligands, as well as in the partly occuring isomerisation of pyrazolyle substituents and the associated decrease of repulsive interactions.[1-3]

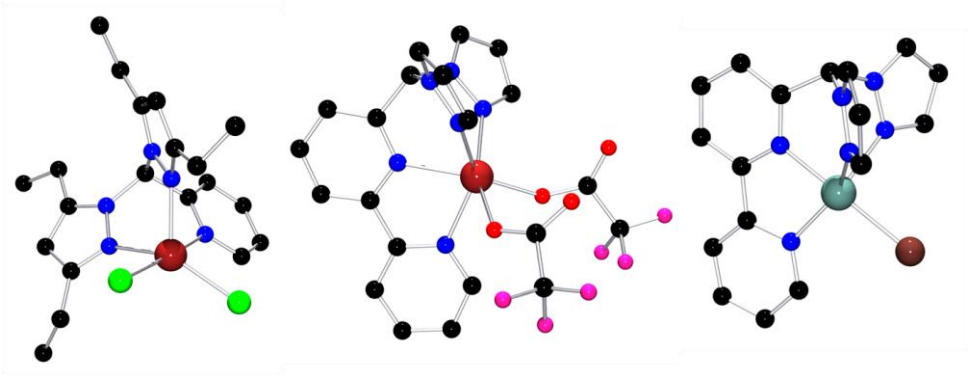

Figure 3. Molecular structure of [(L2)$FeCl_2$] (K1), [(L3)$Fe(CF_3CO_2)_2$] (K2) and $[(L1)CuBr]^+$ (K3).

To enforce the monofacial coordination mode two new ligands $HC(3,5\text{-}PhPz)_2(Py)$ **L1** and $HC(3,5\text{-}EtPz)_2(Py)$ **L2**, that are functionalised in 3- and in 5-position equally, were synthesised. The reaction of **L1** with several Fe/Zn/Cu^{II} salts leads to a wide variety of new, but bisfacial complexes. In contrast, the reaction of **L2** and $FeCl_2$ affords the monofacial complex [(**L2**)$FeCl_2$] **K1**. Another different approach to inhibit bisfacial coordination is the implementation of a fourth donor moiety. Hereby, the ligands $HC(Pz)_2(BiPy)$ **L3**, $HC(3,5\text{-}MePz)_2(BiPy)$ **L4** and HC(3-*t*BuPz)(BiPy) **L5** could be synthesised for the first time. The conversion with selected Fe/Zn/Cu^{II} salts results in complexes whose metal centers are coordinated by all four *N*-donors as shown in Figure 1 with [(**L3**)$Fe(CF_3CO_2)_2$] **K2** and [(**L1**)CuBr]Br **K3**. In a next step **K2** was tested as a single-site catalyst in ring opening polymerisation of *rac*-lactide. First studies have shown very promising results regarding molecular mass distribution and reaction control.

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Haruki Nagae was born in Tokushima, Japan, in 1987. He completed his B. Eng. in 2010, M. Eng. in 2012, and PhD in 2015 at the Graduate School of Engineering Science, Osaka University, under the supervision of Professor Kazushi Mashima. He joined Mitsui Chemicals, Inc. in 2015, and then began his academic career as a Specially Appointed Assistant Professor (full time) at the Graduate School of Engineering Science, Osaka University, in 2016. His doctoral research focused on carbon—carbon bond formation reactions through carbon—hydrogen bond activation mediated by early-transition metal complexes. He performed internships at the Department of Inorganic Chemistry at RWTH Aachen with Professor Jun Okuda for 3 months in 2010, and the Department of Chemistry at ETH Zürich with Professor Christophe Copéret for 4 months in 2012 and for 1 month in 2015.

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Reactivity of η^3-Allenyl- and Propargylyttrium Complexes Toward Insertion Reaction of C=N Double Bonds

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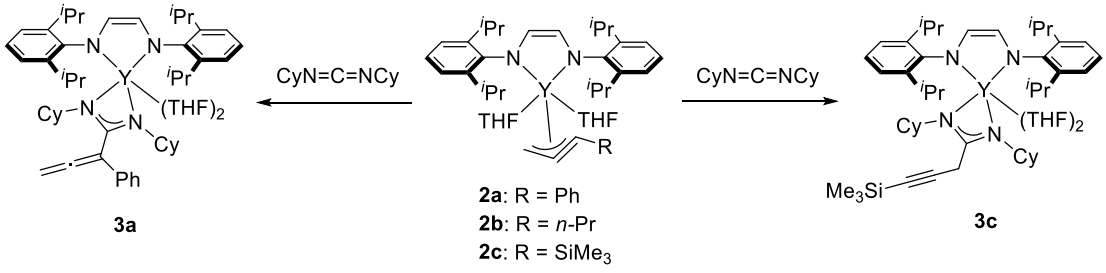
Allenyl and propargyl functionalities are important building units for pharmaceuticals and functional materials, and significant synthetic efforts have been made to construct such the organic skeletons. For introducing the allenyl and propargyl groups into the organic molecules, the corresponding organometallic reagents such as allenyl- and propargylmetal are used as key intermediates in the organic synthesis. Previously, we have successfully introduced allenyl and propargyl groups as an end-capping group of poly(2-vinylpyridine) through the initial C–H bond activation at propargyl position of internal alkynes by reacting with an alkylyttrium complex **1**.[1] Herein, we focused our effort to synthesize and characterize allenyl- and propargylyttrium complexes **2a**–**c**. In addition, insertion reactions of C=N double bond of imine and carbodiimide into metal–carbon bond of **2** were also described.

The complex **1** was reacted with internal alkynes to obtain η^3-allenyl/propargyl complexes **2a**–**c**. NMR measurements and single crystal X-ray analysis revealed that allenyl or propargyl character were depended on the substituent at the η^3- allenyl/propargyl moiety.

The different reactivity of η^3-allenyl/propargylyttrium moiety in complexes **2a** and **2c** was clearly demonstrated by the reaction with *N*,*N'*-dicyclohexylcarbodiimide (Scheme 1): treatment of **2a** with dicyclohexylcarbodiimide, CyN=C=NCy, yielded (η^2-amidinate)yttrium complex **3a** as a single product in 91% yield, in which the C=N bond was selectively inserted into the metal-allenyl bond to form allenylamidinato moiety. On the other hand, reaction of **2c** with CyN=C=NCy yielded complex **3c** in which the C=N bond was selectively inserted into the metal-propargyl bond to form propargyl amidinato moiety.



3a | **2a**: R = Ph; **2b**: R = *n*-Pr; **2c**: R = $SiMe_3$ | **3c**

Scheme 1: Reaction of **2a** and **2c** with *N*,*N'*-dicyclohexylcarbodiimide.

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Group 6 Metal Complexes Featuring Tetradentate Bis(phenolate) Ligands

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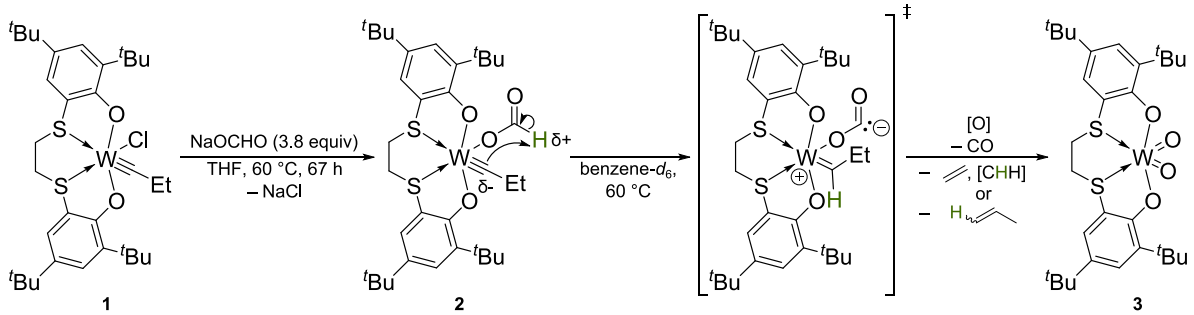
The acidity of the formate proton and the basicity of the alkylidyne carbyne are well documented, but little is known about any interaction between these two ligands.[1-3] Metalation and deprotonation of the formato ligand produces a dimetalloxycarbene which has been proposed as an intermediate in carbon-carbon-coupling reactions.[1] Interconversion reactions between alkylidyne, alkylidene and vinylidene complexes have been utilized to produce the targeted compounds, relying on reactions at the negatively polarized carbyne M(*δ*+)≡C(*δ*–).[4]

We report the synthesis and characterization of a tungsten propylidyne complex featuring a *cis*-coordinated formato ligand stabilized by an OSSO-type backbone. We prepared the (OSSO)W(CEt)(OCHO), **2**, complex through salt metathesis between (OSSO)W(CEt)Cl, **1**, and NaOCHO. Investigations on the basicity of the propylidyne ligand revealed an intramolecular deprotonation of the formate, producing the decomposition product (OSSO)WO_2, **3**. Studies with isotopic labelled formate complexes enabled the elaboration of a decomposition mechanism.



Scheme 1: Synthesis of complex **2** and intramolecular proton transfer to produce decomposition product **3**.

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Mixed Ligated Tris(amidinate)dimolybdenum Complexes as Catalysts for Radical Addition of CCl_4 to 1-Hexene: Leaving Ligand Liability Controls Catalyst Activity

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Radical addition of halogenated organic compounds to alkenes via homolysis of carbon-halogen bonds is a fundamental C-C bond forming reaction in organic chemistry. Our group has already reported that quadruply bonded paddlewheel Mo_2 complexes served as active catalysts for radical addition, radical polymerization, as well as hydrodehalogenation reactions.[1]

As a part of our continuous interest in such Mo_2-catalyzed radical addition reactions, we emphasized on the lability of L in mixed-ligated Mo_2 complexes, $\{Mo_2[CH(NAr)_2]_3(L)\}$, having predominant effect in the catalytic activity. In place of the acetate ligand, introduction of a labile trifluoromethane sulfonate ligand into the Mo_2 unit showed no induction period for the catalytic reaction (Figure 1), which indicating smooth formation of the catalytically active species. Based on these findings, we prepared catalytically active model complex **2**, which showed high catalytic activity in initial period (20 mins), though pyridine resulted decomposition of the Mo_2 catalyst. We also disclose the rate of the ligand substitution reaction of carboxylate ligand by Cl atom of CCl_4, overall reaction mechanism and UV spectral changes in the catalytic reaction.

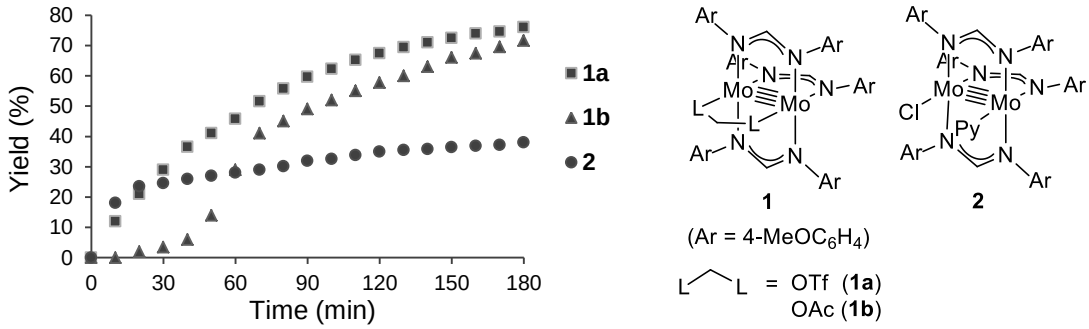

Figure 1. Reaction profile for radical addition reaction catalyzed by **1a**, **1b** and **2**.

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Direct C-H Aminoalkylation of 2-Substituted Pyridine Derivatives Catalyzed by Yttrium Catalysts with *N,N'*-Diarylethylenediamido Ligands

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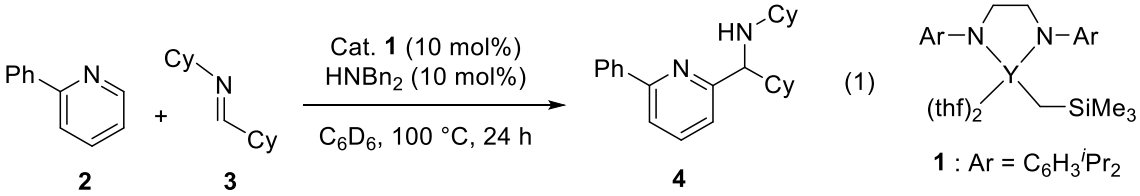
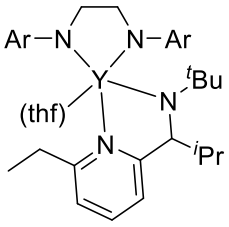
Pyridine derivatives are one of the important heterocyclic skeletons abundant in pharmaceutical drugs and agrochemicals. Direct functionalization of pyridine C-H bond has attracted recent interest in terms of atom economical and cost effective synthetic protocols. We recently reported the first catalytic *ortho*-C-H bond addition of pyridine derivatives to a polar C=N bond of imines using $Ln[N(SiMe_3)_2]_3$ as a catalyst, and, in addition, we found additive effects of $HNBn_2$ that improved the catalytic activity through the formation of heteroleptic Ln-amido species.[1] Aiming to develop more efficient catalysts tolerant to functional group, we screened various multidentate amines upon combined with $Ln[N(SiMe_3)_2]_3$ and $Y(CH_2SiMe_3)_3(thf)_2$, and we found that yttrium complexes with *N,N'*-diarylethylenediamines exhibited superior catalytic performance with a wide substrate applicability of imines (eq. 1).



2 **3** **4**

In a relevance to a reaction mechanism, we conducted a controlled experiment that a yttrium complex, $[ArNCH_2CH_2NAr]Y(CH_2SiMe_3)(thf)_2$ (**1**: Ar = $C_6H_3{}^iPr_2$) was treated with 2-ethylpyridine and *N*-(*t*-butyl)-2-methylpropan-1-imine to afford 5-membered metallacycle **5**, in which *ortho*-pyridyl position was aminoalkylated. Moreover, complex **5** was characterized by spectral data as well as X-ray crystallographic analysis and showed a catalytic activity under optimized reaction condition.



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Pd(II)-SPRIX Catalyzed Enantioselective Annulation of Alkenylindoles

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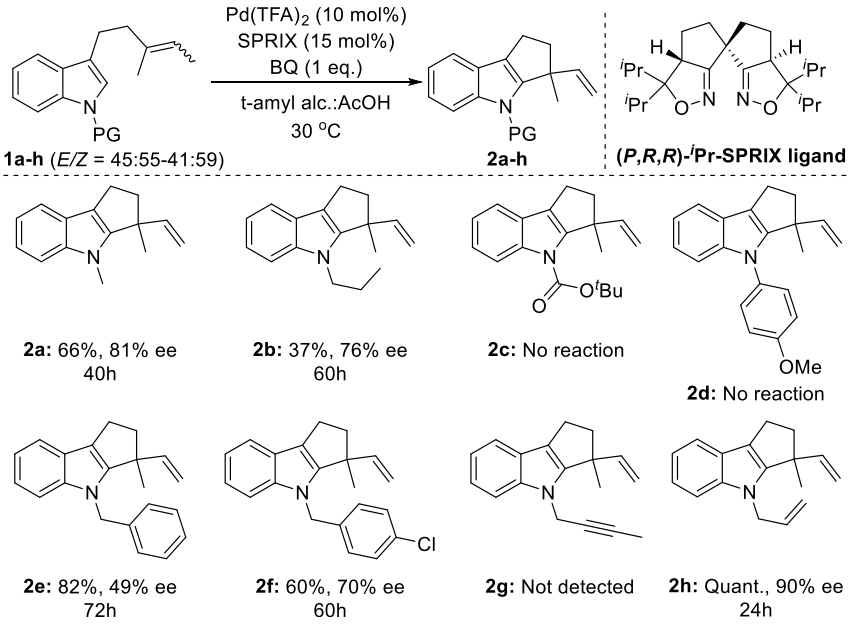
Fujiwara-Moritani reaction (oxidative Heck reaction) is a direct coupling of arenes with olefins via aryl C-H activation in the presence of palladium catalyst. Herein we report the first highly enantioselective palladium(II)-SPRIX catalyzed intramolecular Fujiwara-Moritani reaction of *E/Z*-alkenylindole **1** to give the annulated product **2** bearing a chiral quaternary carbon center. Although Ferreira and Stoltz developed this type of annulation for the first time with achiral Pd(II)-complex in 2003,[1,2] only an unsatisfactory enantioselectivity (up to 54% ee) has so far been reported.[3] We found SPRIX ligand[4] is effective to promote the enantioselective reaction. During our extensive screening of *N*-indole protecting groups, the annulation of allyl protected **1h** in the presence of $Pd(TFA)_2$-SPRIX at 30 °C gave the corresponding tricyclic indole **2h** in quantitative yield and 90% ee. As shown in the Figure, the replacement of allyl group with other electronically different protecting groups afforded inferior results.



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Enantioselective Synthesis of α-Methylidene-γ-Lactams *via* Amidation and Rauhut-Currier Reaction Sequence

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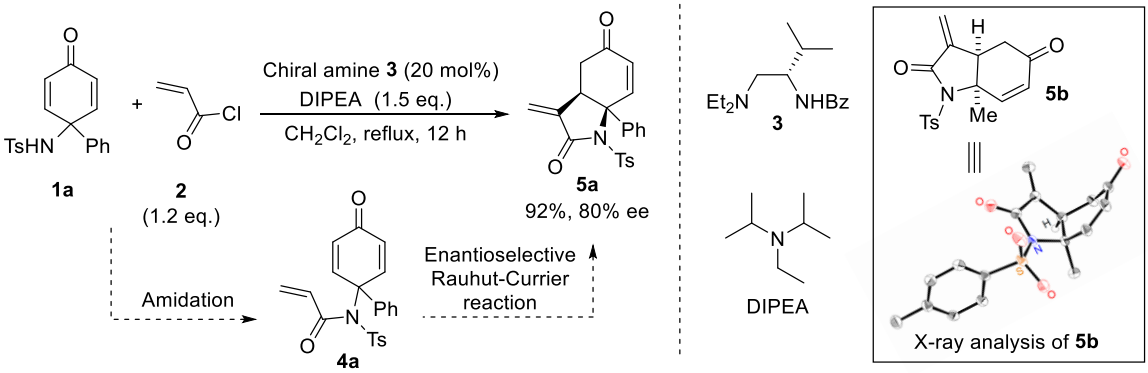
Since α-methylidene-γ-lactams showed a number of pharmaceutical benefits similar to those of lactone analogues with lower toxic side effect, attractive synthetic approaches for these lactams have been studied by a lot of researchers.[1] However, the synthesis of α-methylidene-γ-lactams often requires complex building blocks and encounters side reaction due to the highly reactive methylidene group. Therefore, the development of facile synthetic approach to these γ-lactams involving their asymmetric processes has been a great challenge for organic chemists.

Herein we report new enantioselective synthetic approach for α-methylidene-γ-lactams **5** through amidation and Rauhut-Currier[2,3] (RC) sequence. When dienone **1a** and acryloylchloride **2** were treated with 20 mol% of chiral amine **3** in the presence of *N,N*-diisopropylethylamine (DIPEA), bicyclic α-methylidene-γ-lactam **5a** was obtained in 92% yield and 80% ee without isolation of key intermediate **4a**. The absolute configuration of the product was unambiguously determined by X-ray crystallography. Substrate scope and reaction mechanism will be also discussed.



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Alkali Metal Hydridotriphenylborates for Chemoselective Hydroboration Catalysis

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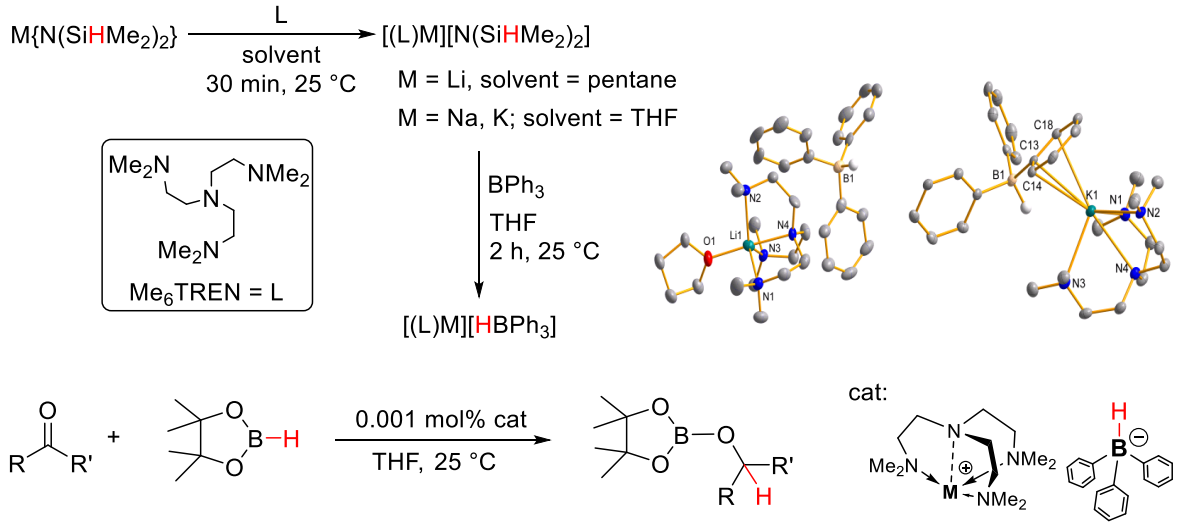
Hydridoborates $[HBR_3]^-$ are ubiquitous stoichiometric reducing agents in organic synthesis.[1] The nature of the metal and the boron substituents influence their selectivity.[2-5] We have synthesized a series of Me_6TREN-coordinated alkali metal hydridotriphenylborates $[(Me_6TREN)M][HBPh_3]$ (M = Li, Na, K) following *β*-SiH abstraction from the corresponding tetramethyldisilazides $[(Me_6TREN)M][N(SiHMe_2)_2]$. Among them, the lithium derivative shows remarkable efficiency in chemoselectivity toward catalytic hydroboration of carbonyls. All three metals activate CO_2 and also catalyze its hydroboration to selectively provide formylborane HCO_2Bpin without any over-reduction.



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Iridium(III)-Catalyzed (*E*)-Selective Semi-Hydrogenation of Alkynes Under Mild Conditions

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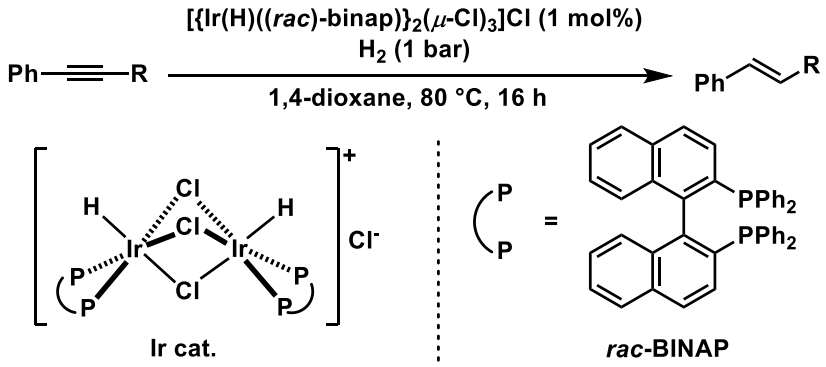
Semi-hydrogenation of alkynes is one of the most straightforward synthetic methodologies for synthesizing alkenes because of atom-economy. Most of semi-hydrogenation methods have been developed with the aid of heterogeneous catalytic systems such as Lindlar catalyst, which selectively produced (*Z*)-alkenes. Accordingly, (*E*)-selective semi-hydrogenation is in demand. Recently, homogeneous catalyst systems for (*E*)-selective semi-hydrogenations of alkynes have been reported under the high pressure or high temperature condition.[1,2] In this contribution, we report that dinuclear iridium(III) complexes bearing diphosphine ligands served as unique catalysts for hydrogenating alkynes to give the corresponding alkenes with high (*E*)-selectivity under atmospheric pressure of hydrogen gas at 80 °C. Based on mechanistic studies, we proposed a mechanism involving dual cycles of hydrogenation and isomerization with mononuclear iridium dihydride species which is the active species. Additionally, we revealed that dinuclear iridium(III) complexes worked as the dormant species to decrease the concentration of the active species according to the progress of alkyne hydrogenation; thereby, suppressing the over-reduction of alkenes.[3]



Scheme 1. Semi-hydrogenation of alkynes by iridium dinuclear complexes.

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Iridium-Catalyzed Benzylic Carbon-Hydrogen Bond Silylation of 4-Alkylpyridine Derivatives

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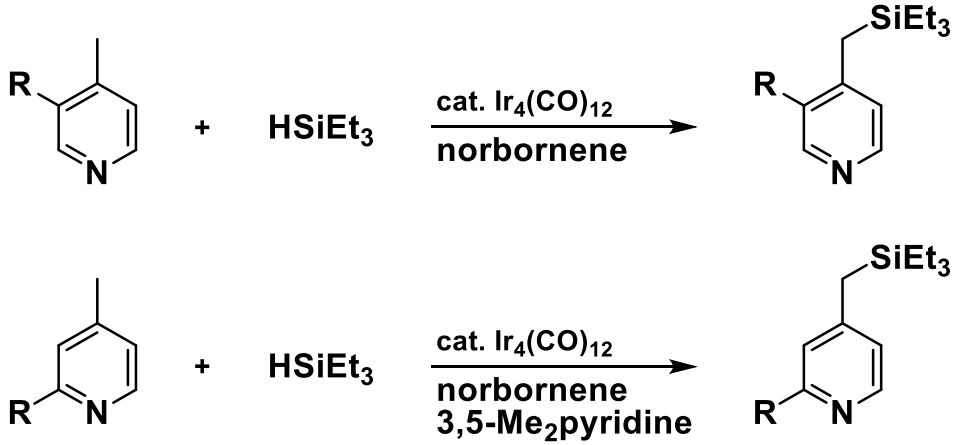
Organosilicon compounds are versatile synthetic intermediates in organic synthesis. Traditionally, these compounds are prepared by the reaction of silyl electrophiles with organolithium or magnesium reagents. Transition metal-catalyzed cross-coupling of aryl halides with hydrosilanes or disilanes is also useful method, especially, in case that base-sensitive functional groups are substituted on the aryl ring. Recent progress has been made in the direct C-H bond silylation with hydrosilanes or disilanes catalyzed by transition metal complexes,[1] with most of them being the silylation of C(sp^2)-H bonds. C(sp^3)-H bond silylation could also occur intramolecularly, or intermolecularly with the assistance of directing groups. Undirected intermolecular silylation of C(sp^3)-H bonds with late transition metals has been observed only as the minor side products during silylation of C(sp^2)-H bonds. Herein we report the iridium-catalyzed silylation of 4-alkylpyridines at the benzylic position with hydrosilanes leading to the production of 4-(2-silyl)alkylpyridines. The reaction of 4-alkylpyridines bearing a variety of functional groups at the 3-position proceeded in good yields. The low product yield in the reaction of 2-substituted 4-methylpyridine was improved markedly by the addition of some other pyridines, such as 3,5-dimetylpyridine.



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Integrated Solutions to Non-Natural Amino Acids: Selection and Combination of Synthetic Technology and Biotechnology

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Recent progress in medicinal chemistry has resulted in the frequent use of non-natural α-amino acids as pharmaceutical substances, typically in protease inhibitors.[1,2] These non-natural α-amino acids are derived from natural amino acids, thus showing structure similar but different from natural L-amino acids. While amino acids containing aromatic groups can be produced effectively and relatively easily by asymmetric catalysis,[3] such new and complex aliphatic amino acids often require specific methodologies.

Here we would like to articulate our technology to several non-natural aliphatic α-amino acids by selecting the optimum methodology covering both our noted biotechnology and synthetic technology with asymmetric induction, chiral pool, and dynamic resolution. The application of the combination of biotechnology and synthetic technology, our long time experience, will be also illustrated in protease inhibitor projects.

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A Robust and Efficient Process of HCV Protease Inhibitor Key Intermediate

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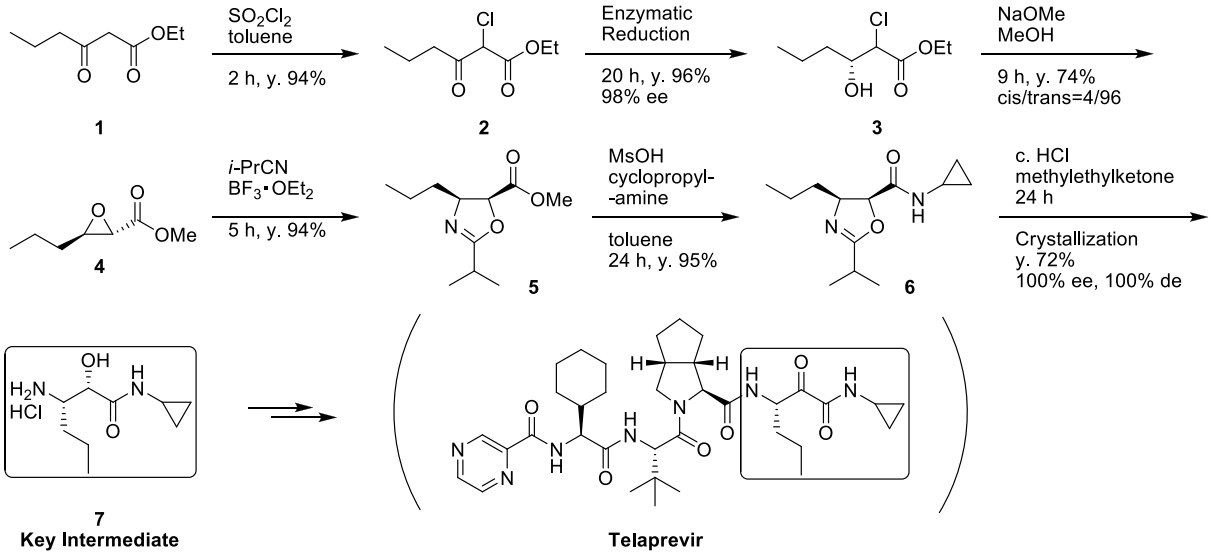
Hepatitis C, one of the worst widespread diseases in the world, causes both acute and chronic liver complications on the virus carriers. A hypodermic injection of pegylated INF-α used to be the standard treatment for hepatitis C infection. Recently orally administrable small molecular antivirals have been developed and used for hepatitis C chemotherapy instead of (or combined with) INF-α injection.

We started on a synthetic study of (2*S*,3*S*)-3-Amino-*N*-cyclopropyl-2-hydroxyhexanamide (compound 7) as a key intermediate of Telaprevir, one of the pioneer HCV protease inhibitors, to develop a robust and efficient process for large scale commercial production. We struggled with a chiral pool methodology at first, but the efficiency could not reach sufficient level. After intense investigation, we finally achieved an ideal process using asymmetric enzymatic reduction, our company has been developing for a long time (Scheme 1).



Scheme 1. Synthetic Route of the Key Intermediate of Telaprevir

Compound 1 was chlorinated to compound 2 followed by highly enantioselective enzymatic reduction (96% yield, 98% ee, compound 3). A base treatment of compound 3 with sodium methoxide promoted continuous epimerization, epoxidation and transesterification to afford compound 4 in a single step. In order to introduce an amino group at 3-position stereoselectively, Ritter type reaction was applied to compound 4. The reaction of compound 4 and isobutyronitrile proceeded to give an amino alcohol equivalent compound 5. We also discovered a direct amidation method from compound 5 to 6 with acid catalyst. Hydrolysis of compound 6 with hydrochloric acid followed by reactive crystallization afforded compound 7 in high quality.

In summary, we succeeded to develop a novel process of the Telaprevir key intermediate. In this process, high enantio- and diastereo-selectivities were achieved. The overall yield was high and only one purification was needed at the last step.

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Lothar Elling studied Biology and received his Doctor degree (1988) from RWTH Aachen University under the supervision of Professor Dr. H. Zahn. With a post-doctoral fellowship of the German Ministery for Education and Research he joined the Institute for Enzyme Technology of the Heinrich-Heine-University Düsseldorf in the Research Center Jülich, in 1988, working with Professor Dr. Dr. h.c. Maria-Regina Kula. In 1990 he became research associate heading the research group “Enzymes in Oligosaccharide Synthesis” at the same institute. In 1997 he finished his “Habilitation” and received the venia legendi for Enzyme Technology. Since October 2001 he is a full Professor at the Institute for Biotechnology, RWTH Aachen University. He is Head of the Laboratory for Biomaterials and member of the Directors Board in the Helmholtz-Institute for Biomedical Engineering. His research focus lies in the area of glycobiotechnology/biocatalysis regarding the topics – Biofunctionalization of biomaterial surfaces: Synthesis of glycoconjugates as biomolecular recognition structures for initiation of cell adhesion, cell differentiation, cell proliferation, and tissue formation. - Targeting of glycoproteins and cells: Development of diagnostic platform technologies for the detection of disease-related glycosylation defects; enzymatic synthesis of modified glycoconjugates. - Combinatorial biocatalysis: Cascade enzymatic reactions for the synthesis of glycoconjugates with in situ regeneration of nucleotide sugars. He has published over 120 original papers and book chapters, and filed several patents.

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Enzyme Cascades for the Synthesis of Glycan Oligomers and Their Presentation on Protein and Polymer Scaffolds

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Our on-going work focuses on the chemo-enzymatic synthesis of native and modified (neo)-poly-*N*-acetyllactosamine (poly-LacNAc) glycan oligomers by enzymatic cascade reactions[1], their binding characteristics to human galectins, and their use in a novel concept for the bio-functionalization of biomaterial surfaces building up a Glyco-BioInterface. Cascade reactions of Leloir-glycosyltransferases (GTs) in combination with nucleotide sugar synthesizing enzymes yielded poly-LacNAc oligomers[2] and *N*,*N*-diacetyllactosamine (LacDiNAc) oligomers[3]. Combination of GTs with a glycosynthase resulted in a series of type 1/type 2 poly-LacNAc oligomers[4]. In a chemo-enzymatic approach galactose oxidase was used for the synthesis of branched poly-LacNAc oligomers and sulfated poly-LacNAc oligomers[3b, 5]. Multivalent presentation of selected glycoconjugates on bovine serum albumin or as glycan ligands in glycopolymer brushes resulted in excellent binding characteristics of lectins (plant lectins and human galectins)[3a,6]. Further work is in progress to use specific glycoconjugates for the selective and efficient binding of lectins on sensor chips and as tools for molecular imaging and inhibition of tumor angiogenesis.

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Eiichiro Fukusaki entered a private company, Nitto Denko Co, after receiving master degree from Osaka University on 1985. He received PhD from Osaka University on 1993 through his company work. After ten years company experience, he returned back to Osaka University as an associate professor. On 2007 he has been assigned as a full professor in department of biotechnology, graduate school of engineering, Osaka University. He received several awards including; an Excellent Paper Award of the Society for Biotechnology, Japan [1993, 2003, 2007, 2009, 2012, 2015], the Japanese Society for Chemical Regulation of Plants Award for the Encouragement of Young Scientists. [2001]; the Society of Biotechnology, Japan 'Saito' Award [2004]; the Society of Biotechnology, Japan Achievement Award [2015]; Excellent Paper Award of Division of Chemical Information and Computer Science, The Chemical Society of Japan [2009]. He is a board member of the Society of Biotechnology, Japan. His current research interests are focusing on development and application of metabolomics technology. He has published over 200 original papers and 50 patents.

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1. Noguchi, S.; Putri, S. P.; Lan, E. I.; Laviña, W. A.; Dempo, Y.; Bamba, T.; Liao, J. C.; Fukusaki, E. *Metabolomics* **2016**,*12*, 26.
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Metabolomics-Based Semi-Rational Improvement of 1-Butanol Tolerance in *Saccharomyces Cerevisiae*

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Traditional approaches to phenotype improvement include rational selection of genes for modification, and probability-driven processes such as laboratory evolution or random mutagenesis. A promising middle-ground approach is semi-rational engineering, where genetic modification targets are inferred from systems-wide comparison of strains using omics technology. Since the metabolome is closely connected to the phenotype, comparison of metabolite profiles between strains may yield gene targets that are not detected on other omic levels. To demonstrate the power of metabolomics in strain engineering and phenotype improvement, a metabolomics-based, semi-rational strategy was applied to 1-butanol tolerance of *Saccharomyces cerevisiae*. In addition, a data-mining strategy that selects optimal data subsets for regression modeling using the Random Sample Consensus (RANSAC) algorithm was proposed to obtain additional information from metabolomics data.

Nineteen yeast single-deletion mutant strains with varying growth rates under 1-butanol stress were subjected to non-targeted metabolome analysis by GC/MS, and an OPLS regression model was constructed using metabolite peak intensities as predictors and stress growth rates as the response. From this model, metabolites positively and negatively correlated with growth rate were identified including threonine and citric acid. Based on the assumption that these metabolites were linked to 1-butanol tolerance, new deletion strains accumulating higher threonine or lower citric acid were selected and subjected to tolerance measurement and metabolome analysis. The RANSAC algorithm iteratively constructs submodels on small subsets of samples, tests remaining samples on the submodels, and retains submodels with a sufficient number of inliers (samples with error below a set threshold) as well as model robustness (Q^2). RANSAC-PLS was implemented using R scripting language with the basic installation extended with package ‘pls’.

The new strains exhibiting the predicted changes in metabolite levels also displayed significantly higher growth rate under stress over the control strain, thus validating the link between these metabolites and 1-butanol tolerance. These results successfully demonstrated the usefulness of metabolomics in semi-rational phenotype improvement.[1,2]

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Development of Retention Index Prediction Model for Annotation of Unknown Compounds for GC/MS-based Untargeted Metabolomics

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Identification of unknown compounds is a challenging task for gas chromatography/mass spectrometry (GC/MS) -based untargeted metabolomics. The popular ionization, Electron Ionization (EI), for trimethylsilyl (TMS)-compounds usually generates similar mass spectra among subclasses of small molecules such as sugars, amines, and fatty acids, where searching EI-spectra only should increase false positive identifications. Therefore, retention time (RT) or alkane-based retention indix (RI) is essential for narrowing-down candidate compounds. However, the reference of RT or RI is still limited (about 1,000) compared to the large amount of mass spectra database (more than 100,000). In this study, we have developed the RI prediction model for GC/MS-based metabolomics and applied it to identify unknown compounds in Chinese medicine *Senkyu*.

The AIoutput[1] database was used as the training set. The compounds (non-derivatized) structures were derivatized automatically by means of ChemAxon Jchem Reactor in addition to manual curations. The PaDEL-descriptors[2] and ChemAxon Jchem Calculator were utilized to calculate total 4563 chemical properties for each derivatized compound. Finally, the Partial Least Square Regression (PLS-R) was executed to obtain the relationship between RI and chemical properties.

The PLS-R model was constructed with high accuracy and robustness, R^2 = 0.965 and Q^2=0.915. In this research, we demonstrated the use of this prediction model to annotate novel compounds in *Senkyu*, Chinese medicine.

From 16 annotated metabolites which could be found by EI-spectra searching (>90%) followed by filtering false positive via retention time predictions. (±80.3 s) We could identify 5 novel compounds which were confirmed by authentic standards. The novel compounds will be contributed as a quality marker to separate their spices. (*Liguticum chuanxiong* Hort., and *Cnidium officinale* Makino.) Our strategy, EI-spectra searching plus RI-filtering, would be useful to the field of untargeted metabolomics.

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Metabolic Engineering of *Bacillus Subtilis* for Enhanced γ-Polyglutamic Acid Production

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Poly-γ-glutamic acid (PGA) is a polymer consisting of D- and L-glutamate monomers linked by amide bonds between the α-amino group and γ-carboxylic acid group. The polymer is mainly produced by *Bacillus* species.[1] Due to its various applications including the use as flocculant in wastewater treatment, cryoprotectant in food industry and hydrogel in pharma applications, the large-scale production of PGA is of high interest.[2] Especially for medical applications the need of a well-defined composition regarding the stereochemical and mass properties of the polymer arises. For this purpose we here propose to genetically engineer the Gram positive bacterium *Bacillus subtilis* to address the needs in PGA production.

The metabolic engineering of *B. subtilis* for enhanced PGA production is based on a markerless counter-selection system[3], which allows the reuse of antibiotic selection markers for multiple genetic alterations. The metabolic pathways for the production of PGA in *B. subtilis* are well known and will be analyzed using metabolomics data of PGA producing strains especially with regard to different media compositions.[4] Since both glutamate enantiomers are essential for cell growth, their synthesis cannot be completely prevented to alter the stereochemical composition of the PGA. The glutamate monomers are linked by the PGA synthetase, a membrane-associated enzyme complex encoded by the *pgsBCA* operon.[1] The synthesized polymer is secreted to the medium where it can be degraded by depolymerizing enzymes.[5] To enhance the PGA production and to decrease the molecular weight dispersity, the promoter region of the PGA synthetase gene is varied to enhance the production of PGA by *B. subtilis*. In addition, the genes encoding the depolymerizing enzymes are deleted to prevent PGA degradation. The stereochemical and size properties of the produced PGA will be investigated by chromatographic techniques. The here presented approach is discussed in the context of designer poly-γ-glutamic acid production.

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Short CV:

Blank studied Chemical Engineering from 1990 to 1997 at the University of Dortmund (Germany) and Biology from 1992 to 1997 at the Ruhr-University of Bochum (Germany). During his master theses he worked in the field of Metabolic Engineering in the group of Prof. E. T. Papoutsakis at Northwestern University, IL, USA and in yeast cell biology in the group of Prof. W.-H. Kunau at the Ruhr-University of Bochum. In his Ph.D. in the group of Prof. L. K. Nielsen at the University of Queensland, Australia (1998 to 2002), he developed a continuous process for hyaluronic acid production using lactic acid bacteria. During his Ph.D. he worked as a visiting scientist at the Technical University of Denmark (DtU), Lyngby, Denmark) from September until December 1999. From November 2004 until June 2011 Lars M. Blank lead the group Systems Biotechnology at the Laboratory of Chemical Biotechnology at the TU Dortmund and was a senior research fellow at the Leibniz-Institute ISAS in Dortmund. In January 2010 he finalized his Habilitation. On the 1st of July 2011 Blank became professor and head of the Institute of Applied Microbiology at the RWTH Aachen, Germany.

Blank focuses in his research on fundamental and applied aspects of microbial metabolism. Of specific interest is the interaction between the metabolic network and the introduced genetic and environmental perturbations. The research on in silico/in vivo metabolic network operation is aimed at a deeper understanding of cell function, with the ultimate goal of rational cell engineering. Blank is associate editor of Engineering in Life Sciences, Microbial Biotechnology, Fungal Biology and Biotechnology, and Metabolic Engineering Communication.

Recent Publications:

1. Zambanini, T.; Sarikaya, E.; Kleineberg, W.; Buescher, J. M.; Meurer, G.; Wierckx, N.; Blank, L. M.; *Biotechnology for Biofuels* **2016**, *9*, 67.
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Maximizing the Redox Cofactor Regeneration Rate for Redox Biocatalysis Using Whole-Cells

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A key limitation of whole-cell redox biocatalysis for the production of valuable, specifically functionalized products is substrate/product toxicity, which can potentially be overcome by using solvent-tolerant microorganisms.[1] Selected and adapted strains of *Pseudomonas putida* were reported to tolerate high concentrations of organic solvents and grew in the presence of a second octanol[2], toluene[2], and styrene phase. Using ^{13}C tracer based metabolic flux analysis, we investigated in solvent-tolerant *P. putida* strains the interrelationship of organic solvent tolerance and energy metabolism and quantified the NAD(P)H regeneration rate in the presence of these toxic solvents. The harsh growth conditions increased the energy demand of the microbes drastically. According to the driven by demand concept, the NAD(P)H regeneration rate was increased up to eightfold by two mechanisms: (a) an increase in glucose uptake rate without secretion of metabolic side products, and (b) reduced biomass formation. This points to a high energy and redox cofactor demand for cell maintenance, which limits the yield and hence the potential for redox biocatalysis. An estimated upper bound for the NAD(P)H regeneration rate available for redox biocatalysis suggests that cofactor availability does not limit however biocatalysis under optimized conditions, for example, in the absence of toxic solvent. We implemented such a high NAD(P)H regeneration rate by a co-substrate strategy taking advantage of an intrinsic NAD^+ dependent formate dehydrogenase. The results are discussed in the context of the applicability of these extremophiles as hosts for industrial biotechnology.

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Notes