Design, Synthesis and Visible-Light-Induced Non-Radical Reactions of Dual-Functional Rh Catalysts

Highlighted article by S. Ouchi, T. Inoue, J. Nogami, Y. Nagashima, K. Tanaka

C–H borylation

[2+2+2] cycloaddition
Dear Readers,

This very rich November issue of SYNFORM continues with the introduction of Editorial Board members who recently joined the Thieme Chemistry family of journals. I am very glad to welcome here Professor Akimitsu Narita (Okinawa Institute of Science and Technology Graduate University, Japan) who joined the Editorial Board of Organic Materials with effect of January 2023, who is the protagonist of a brief interview about his new role and research interests.

The issue is effectively kicked off by a Literature Coverage article on the stereospecific synthesis of complex chiral sulfoxides via nickel-catalysed enantioselective hydrosulfenation of alkynes, developed by G. Lu and Q.-W. Zhang (P. R. of China). The second Literature Coverage article covers a detailed and intriguing study of the visible-light-induced non-radical reactions promoted by dual-functional rhodium catalysts, recently published by the group of K. Tanaka (Japan). The follow-up article is a Young Career Focus interview with the 2023 Thieme Chemistry Journals Awardee Christoph Nitsche (Australian National University, Australia) who tells SYNFORM about his research and personal interests. The next Literature Coverage article covers an exciting work recently published in SYNTHESIS by the group of Philipp Kohler (Switzerland) – from the private sector – on a very effective method to achieve the Suzuki–Miyaura coupling utilizing aryl nosylates and diethanolamine boronates.

Enjoy your reading!

Matteo Zanda

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Contact
If you have any questions or wish to send feedback, please write to Matteo Zanda at: synform@outlook.com
Nickel-Catalysed Enantioselective Hydrosulfenation of Alkynes

Nat. Catal. 2023, 6, 487–494

Chiral sulfur compounds – such as sulfoxides and sulfoximines – have broad applications in various areas of chemistry, especially at the interfaces with biology, drug discovery and materials science. Often, molecules with different stereochemistry at the sulfur atom exhibit dramatically different chemical and biological properties, which renders critically important the capacity of synthesizing these molecules in a stereocontrolled and stereospecific manner. “As a continuation of our research on the catalytic asymmetric synthesis of P-stereogenic compounds, we have expanded our synthetic strategy to include the synthesis of other coordinating elements, in collaboration with the Gang Lu group from Shandong University,” explained Professor Qing-Wei Zhang from the University of Science and Technology of China (Hefei, P. R. of China). He continued: “Given the significant applications of sulfur-containing chiral compounds in pharmaceuticals and materials sciences, we aimed to develop a more efficient and convenient approach for synthesizing S-stereogenic compounds.” Among the various strategies available, transition-metal-catalyzed asymmetric hydrofunctionalization emerges as the most promising method in terms of atom-economy and efficiency. Building upon our previous research, we have established that the asymmetric hydrophosphinylation reaction of conjugated enynes, under the catalysis of a nickel complex, proceeds through a protonation mechanism. Inspired by this mechanistic pathway, we postulated that sulfoxides, which can be considered analogous to phosphine oxides, can also be constructed using similar methodologies.

It has been reported that alkynes or alkenes can undergo a concerted reaction with in situ generated sulfenic acid, resulting in the formation of the corresponding racemic sulfoxides. However, for over half a century, the chiral version of this method has not been achieved. Professor Zhang said: “Our research focuses on addressing several key challenges associated with this approach: 1) identifying a suitable catalytic system to prevent the occurrence of concerted background reaction; 2) mitigating the poisoning effect of sulfenic acid on the transition-metal catalyst; and 3) attaining high enantioselectivity and regioselectivity of the reaction. Leveraging our extensive investigations in nickel catalysis, we have successfully achieved the regio- and enantioselective hydrosulfenation of alkynes under mild reaction conditions, providing a reliable method for the preparation of structurally diverse chiral alkenyl sulfoxides (Figure 1).”

Professor Zhang revealed that during their initial explorations, it was found that the ligand was critical to the success of the reaction, both in terms of reactivity and enantioselectivity. “Among the ligands investigated, the electron-rich Ph-BPE [1,2-bis((2R,5R)-2,5-diphenylphospholano)ethane] demonstrated superior performance, likely due to its ability to effectively stabilize the nickel catalyst through strong coordination, thereby minimizing its susceptibility to poisoning effects,” explained Professor Zhang, who continued: “Remarkably, the reaction exhibited a broad functional group tolerance, enabling the late-stage modification of several specific drugs. The resulting alkenyl sulfoxide product also exhibited utility as a versatile Michael acceptor, displaying high reactivity towards a diverse range of nucleophiles.”

The reaction mechanism was investigated using a combination of experimental and computational methods in collaboration with Prof. Gang Lu, which confirmed the group’s initial expectations, aligning with their previous discoveries. Specifically, it was observed that the nickel catalyst coordinated with the alkyne following the Dewar–Chatt–Duncanson model. “Through π-back donation, this coordination led to an enhancement in both the electron density and basicity of the alkyne, resulting in a greater negative charge on the terminal carbon,” said Professor Zhang. He went on: “Simultaneously, the sulfenic acid coordinated with the nickel catalyst via its sulfur atom, further augmenting the basicity of the alkyne. Additionally, the electron transfer to the Ni-alkyne moiety increased the acidity of the sulfenic acid. This enhanced acidity of the sulfenic acid – in addition to the enhanced basicity of the alkyne – collectively facilitated the subsequent protonation step. Importantly, due to the electron-rich nature of the terminal carbon, the proton transfer occurred selectively from the sulfenic acid to the terminal carbon, thereby dictating the regioselectivity of the reaction. The investigation of these mechanisms holds significant implications for the design of additional nickel-catalyzed asymmetric hydrofunctionalization reactions aimed at synthesizing chiral compounds with heteroatom-stereogenic centers.” Professor Zhang concluded: “By understanding the intricate details of these reaction mechanisms, researchers can make informed choices when designing catalytic systems and ligands, ultimately leading to the efficient and selective synthesis of a wide range of chiral compounds with heteroatom-stereogenic centers.”
REFERENCES

About the authors

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Design, Synthesis and Visible-Light-Induced Non-Radical Reactions of Dual-Functional Rh Catalysts

*Nat. Synth. 2023, 2, 535–547*

In visible photocatalysis, a catalyst absorbs photons from a visible-light source and undergoes an electronic excitation to a higher energy state. This excited-state photocatalyst can then interact with organic substrates to initiate a wide range of reactions, which are otherwise much more challenging under conventional thermal conditions. In recent years, photocatalysis has emerged as a powerful tool in organic synthesis, revolutionizing the way chemists design and execute a large number of transformations.

A single transition-metal complex that performs both visible-light absorption and chemical transformation is an ideal photocatalyst. Currently, such transition-metal catalysts are mainly limited to radical mechanisms. This *Nature Synthesis* paper by Professor Ken Tanaka and co-workers at the Tokyo Institute of Technology (Japan) explores the topic and finds a powerful solution, which could open the way to new avenues in organic photocatalysis. Dr. Yuki Nagashima, co-corresponding author on the paper, told SYNFORM: “The paper describes our development of rhodium-based unprecedented photocatalysts – spiro-fluorene-indenoindenyl (SFI)-Rh(I) complexes – that can act as a single photocatalyst with high light-harvesting abilities and facilitate non-radical mechanisms. This catalyst successfully extends the scope of typical rhodium-catalyzed reactions to challenging substrates under visible-light irradiation.”

Dr. Nagashima went on to reveal how the paper resulted from an unexpected development of an earlier project: “We were originally investigating Pt or Au-catalyzed spirocycliza-
tion reactions (Org. Lett. 2021, 23, 1934–1939). During the course of this study, we isolated an unanticipated product, spiro-fluorene-phenylene vinylenes, which can be one of the most suitable ligands to rhodium-based photocatalysts. The synthesis of the rhodium complex by using this ligand is successful, which also surprised us.”

Dr. Nagashima concluded: “Our next goal is to extend the potential to be a versatile light-driven catalyst that can break through the ground-state limitations in various photoreactions.”

Yuki Nagashima

received his BSc (2012), MSc (2014), and PhD (2019) from The University of Tokyo (Japan) under the supervision of Professor Masanobu Uchiyama. After working at Mitsubishi Tanabe Pharma Corporation (Japan) as a medicinal chemist (2014–2020), he moved to Tokyo Institute of Technology (Japan) as an Assistant Professor in the research group of Professor Ken Tanaka from 2020. His research interests are focused on the development of photoinduced reactions and catalytic reactions combined with computational chemistry.

Ken Tanaka

received his BSc (1990) and MSc (1993, Professor Koichi Narasaka) from The University of Tokyo (Japan). He joined Mitsubishi Chemical Corporation (Japan) in 1993. He obtained his PhD (1998, Professor Takeshi Kitahara) from The University of Tokyo and then worked as a post-doctoral fellow at MIT, USA (Professor Gregory C. Fu, 1999–2001). In 2002, he moved to Tokyo University of Agriculture and Technology (Japan) as an associate professor and was promoted to full professor in 2009. In 2014, he moved to Tokyo Institute of Technology (Japan) as a full professor. His research is focused on organic and organometallic chemistry.

About the authors
Interview

SYNFORM What is the focus of your current research activity?

Assoc. Prof. C. Nitsche My present research revolves around the biocompatible modification of peptides and proteins. Our particular focus lies in selective chemical modifications that can be carried out under conditions applicable to bioconjugation, imaging, and peptide display technologies, where the need for selective and robust chemical modifications is crucial. The simpler and more reliable these chemical transformations are, the higher the chances that they will find broad applications.

SYNFORM When did you get interested in synthesis?

Assoc. Prof. C. Nitsche I studied the classical chemistry curriculum in Germany, which was heavy on synthetic chemistry. I became fascinated by how synthetic compounds can manipulate biological systems, igniting my interest in medicinal chemistry and chemical biology. During my undergraduate studies, I synthesised several molecules that were tested in cellular apoptosis assays. This direct link between synthesis and biological activity has intrigued me ever since. I moved on to pursue a PhD in medicinal chemistry and a postdoc in structural biology to learn more about the biological aspects, while synthesis has remained an essential part of my research.

SYNFORM What do you think about the modern role and prospects of organic synthesis?

Assoc. Prof. C. Nitsche A central aspect of organic chemistry has always been studying and manipulating compounds of natural origin, which, in the broadest sense, is still what my current research is focused on. The continuing importance of organic chemistry for biomedical sciences has recently been
demonstrated by the Nobel Prize awarded to Bertozzi, Meldal and Sharpless for the development of click chemistry and bioorthogonal chemistry.

**SYNFORM** Could you tell us more about your group’s areas of research and your aims?

Assoc. Prof. C. Nitsche We have developed biocompatible reactions that are valuable in peptide-based drug discovery and protein bioconjugation. One of our primary goals is to create simple methods that can restrict the flexibility of peptides, thereby enhancing their potential as drug candidates. Through our biocompatible modifications, we have demonstrated the ability to simultaneously improve the biological activity, proteolytic stability, and cell membrane permeability of peptides.

**SYNFORM** What is your most important scientific achievement to date and why?

Assoc. Prof. C. Nitsche The modification of peptides and proteins using bismuth(III) has gathered some attention. In 2017, I discovered that bismuth can be utilised to selectively attach probes to proteins. Since then, we have further expanded this work, for example, to constrain peptides. The use of bismuth in peptides and proteins is intriguing due to its simplicity and its potential for therapeutic applications.

**SYNFORM** Could you tell us something about yourself outside the lab, such as your hobbies or extra-work interests?

Assoc. Prof. C. Nitsche I have three children who keep me both busy and entertained. In my free time, I enjoy gardening, reading, and going on bush walks. I am also working on improving my surfing skills, taking it step by step.

**SYNFORM** What is the most exciting aspect of your job, the one you like the most?

Assoc. Prof. C. Nitsche What I find most enjoyable about my job is the daily interactions with my research group. Working with highly motivated and innovative students at all levels is incredibly rewarding. The best moments undoubtedly occur when the students find that an idea, once just sketched on a piece of paper, actually works, or when they make an unexpected discovery.
Suzuki–Miyaura Coupling of Aryl Nosylates with Diethanolamine Boronates

Synthesis 2023, 55, 3159–3171

This SYNTHESIS paper was authored by a research team led by Dr Philipp Kohler, from the Chemistry Process R&D group, Idorsia Pharmaceuticals Ltd. (Allschwil, Switzerland). Dr Kohler told SYNFORM: “Our work was inspired by a recent development project, in which we had to implement a Suzuki coupling of two heterocyclic entities: one with a phenolic functionality, the other featuring a boronate. In the discovery route, the building blocks were activated in the standard fashion: the phenol (Ar1) as the triflate, the other building block (Ar2) as the pinacol boronate, which was prepared through lithiation of the corresponding bromide and quenching with a suitable borylation reagent.”

Dr Kohler explained that both Ar1–OTf and Ar2–B(pin) were oils and used as crude material or purified by chromatography. Additionally, the conditions for their preparation were not considered favorable due to cryogenic conditions. “We accepted the challenging goal to find derivatives that were prepared under ‘process-like’ conditions and purified by crystallization,” he said, continuing: “This led us to the identification of the nosylate and the diethanolamine (DABO) boronate as suitable, crystalline substrates. The ensuing Suzuki coupling required some screening of conditions because of the lowered reactivity compared to the triflate/pinacol boronate combination.”

Eventually, the authors ended up preparing the nosylate using NsCl and DIPEA in 2-methyltetrahydrofuran (MeTHF) – a green reaction solvent. “The boronate was prepared by C–H borylation using an iridium catalyst and B2(pin),” said Dr Kohler. He went on: “The intermediate, non-crystalline, pinacol boronate was converted into the DABO boronate by reaction with diethanolamine, resulting in crystallization from the reaction mixture. For the Suzuki coupling, reaction optimization resulted in a system of Pd(OAc)2 and SPPhos. These conditions were successfully scaled up to 600 g scale.”

Based on this success story, the authors were motivated to generalize the Suzuki coupling conditions to make them available for a wide range of relevant substrates. At this point, they were less interested in optimizing the formation of the substrates themselves, since the synthesis of nosylates as well as DABO boronates is well described in the literature. Hence, they recommenced their work by identifying more general reaction conditions for the coupling on model substrates, which were identified using the authors’ Pd(OAc)2/XPhos/K2CO3 system. Dr Kohler explained: “Water was required for conversion; therefore, one can assume the free boronic acid to be the reactive species. We went on to prepare a variety of nosylates and DABO boronates to investigate the substrate scope. To our delight, all of the prepared starting materials turned out to be highly crystalline, thereby validating our rationale. Most of the substrates were successfully tested in the Suzuki coupling, although certain heterocyclic DABO boronates and sterically hindered nosylates were not tolerated. In a competition experiment, a reactivity order of Cl > Ons > OTs was determined.”

Dr Kohler ended by saying: “We believe that this piece of work has relevance for process chemists, as it offers the benefit of crystalline substrates in combination with a common catalytic system. Furthermore, we hope that it raises awareness in discovery chemistry for the various possibilities of modern cross-coupling reactions, which are not necessarily limited.
to optimization of the catalytic system itself.” He concluded: “A potential extension of the work might be the generalization of the previously mentioned sequence of C–H borylation and conversion into the DABO boronate, followed by Suzuki coupling.”

**About the authors**

**Philipp Kohler** received his Ph.D. in 2010 from ETH Zürich (Switzerland) with Prof. F. Diederich. He then moved to the University of California, Irvine (USA), for postdoctoral studies with Prof. L. E. Overman. In 2012, he accepted a position as R&D chemist at Dottikon ES (Switzerland), before moving on to Idorsia (then Actelion), Switzerland, in 2014. He has been active as a process chemist at Idorsia since then, working on >10 small-molecule APIs spanning preclinical to late-stage development.

**Gabriel Schäfer** obtained his PhD in 2014 from ETH Zürich (Switzerland) under the supervision of Prof. J. Bode. After completing a postdoctoral research stay with Prof. F. D. Toste in Berkeley (USA), he started his industrial career in 2015 as a Process Chemist at Actelion Pharmaceuticals (Switzerland). After the acquisition of Actelion by J&J and the subsequent demerger of Idorsia Pharmaceuticals in 2017, he worked as a Senior Scientist in Idorsia’s Chemistry Process R&D group (Switzerland). In this function, he developed robust and scalable chemical routes for Idorsia’s preclinical candidates and clinical assets. In 2020, he was promoted to Group Leader of the Chemistry Process R&D group, leading a fantastic team of 20 highly motivated people. His work has been published in over 20 publications and patents. He also serves as a member of the “Early Career International Advisory Board” of Helvetica Chimica Acta.

**Timothé Perrin** obtained his Master’s degree in molecular and macromolecular chemistry from the National College of Chemical Engineering in Mulhouse (France) in collaboration with Idorsia (Switzerland), where he worked in the medicinal chemistry department with Dr. S. Diethelm, in 2023. He then worked for 4 months as a research associate in process chemistry under the supervision of P. Kohler, Idorsia. He is currently employed as a process development chemist at PolyPeptide (Belgium).
Editorial Board Focus: Dr. rer. nat. Akimitsu Narita  
(Okinawa Institute of Science and Technology Graduate University, Japan)

Background and Purpose. From time to time, SYNFORM portraits Thieme Chemistry Editorial Board or Editorial Advisory Board members who answer several questions regarding their research interests and revealing their impressions and views on the developments in organic chemistry as a general research field. This Editorial Board Focus presents Dr. rer. nat. Akimitsu Narita (Okinawa Institute of Science and Technology Graduate University, Japan) who joined the Editorial Board of Organic Materials with effect of January 2023.

Biographical Sketch

Akimitsu Narita was born and raised in Yokohama, Japan. He received his Bachelor’s and Master’s degrees in chemistry at the University of Tokyo (Japan) under the supervision of Professor Eiichi Nakamura. He then joined Professor Klaus Müllen’s group at the Max Planck Institute for Polymer Research (MPIP) in Mainz, Germany and obtained his doctorate in chemistry from Johannes Gutenberg University of Mainz in 2014. In the same year, he became a project leader in the Synthetic Chemistry Department at MPIP. In 2018, he joined OIST as an Assistant Professor (Adjunct) to lead the Organic and Carbon Nanomaterials Unit. He is now working full-time as an Assistant Professor at OIST since 2020.

Interview

SYNFORM You are a leading researcher in the field of organic materials science. Could you tell us more about the importance of that field and your current research activities?

Dr. rer. nat. A. Narita Organic materials can be the basis for the development of new technologies as well as for the advancement of various fields of sciences. My group is currently focused on the synthesis and characterizations of large polycyclic aromatic hydrocarbons and other related nanocarbon molecules with unique structures and properties. Through the elucidation of the structure-property relationship, we aim at developing materials with optimal optoelectronic and photophysical properties for potential applications, including organic lasers, bioimaging, and solar energy conversion.

SYNFORM Please comment on your role as a member of the Editorial Board of Organic Materials?

Dr. rer. nat. A. Narita I am excited to serve as an Associate Editor of this young journal and contribute to its further development, especially strengthening its coverage of carbon-rich organic materials and synthetic methods beyond the conventional organic synthesis.

SYNFORM Could you tell us something about yourself outside the lab, such as your hobbies or extra-work interests?

Dr. rer. nat. A. Narita I played the trumpet in a university orchestra during my studies and still like to listen to classical music.
Coming soon

- Literature Coverage
  Multi-site Programmable Functionalization of Alkenes via Controllable Alkene Isomerization

- Literature Coverage
  Mechanistic Snapshots of Rhodium-Catalyzed Acylnitrene Transfer Reactions

SYNTHESIS Highlight
Synthesis and Immunological Evaluation of *Escherichia Coli* O1-Derived Oligosaccharide–Protein Conjugates toward Avian Pathogenic *Escherichia Coli* O1 Vaccine Development

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**Synthesis**  
Review: Synthesis of Heterocycles from Donor-Acceptor Cyclopropanes: A Five-Year Recap  
(by A. Deepthi and co-workers)

**Synlett**  
Account: Bioinspired Total Syntheses of Secologanin-Related Natural Products: A Demonstration of the Power of Secologanin in the Flask  
(by H. Ishikawa, J. Sakamoto)

**Synfacts**  
Synfact of the Month in category “Metals in Synthesis”: Fluorocarbonylation Via Palladium/Phosphine Synergistic Catalysis

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