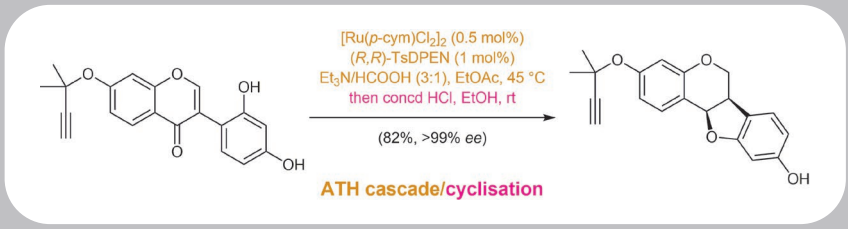
Synform

People, Trends and Views in Chemical Synthesis

2020/10

Asymmetric One-Pot Transformation of Isoflavones to Pterocarpans and Its Application in Phytoalexin Synthesis

Highlighted article by P. Ciesielski, P. Metz



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Dear Readers,

In these incredibly challenging and uncertain times it is becoming increasingly difficult for me to strike a light note in these editorials, especially after reading the morning newspapers which are a litany of bad and incredibly worrying news, such as “the virus might be growing again, out of control”, “thousands of job losses due to the economic crisis” and, worst of all, “wildlife in catastrophic decline”. Shall I continue? Of course not. And not because I intend to bury my head in the sand, pretending things are all right after all, but because all these unsettling events and grim perspectives are not doing any good to my mental sanity. I think we all need a fresh perspective and we need to make the most of this gloomy situation, the creation of which we contributed to heavily through our reckless behaviour, all of it: the virus, the looming environmental catastrophe and the politicians we elected. I am not sure scientists – including myself of course – have done and are doing enough to steer the world away from this worrying direction, and even though a lot of people – including politicians and decision makers – will continue to turn a deaf ear to what scientists have to say, the advice of science has never been more important and necessary to help dig the world out of this mess. Some of us are already very good at communicating and making ourselves heard by the general public but many others are not, and we all need to learn – urgently – how to talk effectively to the people out there in the street, contributing to every citizen’s life-long education and information. If we do not, others – with a different and more sinister agenda - will continue to fill this empty information space. As naïve as it may sound, I am convinced that this is a very important role scientists can play, if we want to start reading better news in the newspapers. Now, talking of research communication – let’s have a look at our October SYNFORM issue. M. Kojima and S. Matsunaga (Japan) kick off with a brilliant piece of work published in SYNTHESIS on the sequential α-alkylation/allylic substitution using allyl 4-chlorophenyl sulfone. A new, clever method for monitoring solid-phase peptide synthesis in a very simple, user-friendly manner – developed by H. Konno (Japan) – is the subject of the second article. C. Wang (P. R. of China) is the protagonist of the Young Career Focus interview, then the issue is closed by P. Metz (Germany) and co-workers with their one-pot transformation isoflavones to pterocarpans, recently published in *Nat. Commun.*

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In this issue

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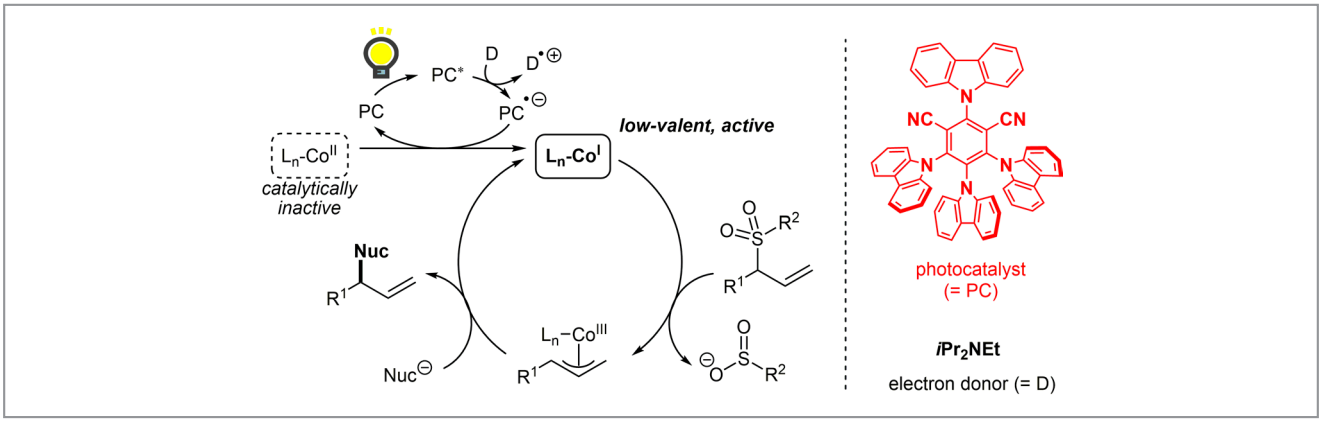
Allyl 4-Chlorophenyl Sulfone as a Versatile 1,1-Synthon for Sequential α-Alkylation/Cobalt-Catalyzed Allylic Substitution

Synthesis **2020**, *52*, 1934–1946

Sulfones are well-known chemical chameleons, namely building blocks that can behave as either nucleophiles or electrophiles depending on how they are activated and reacted. For example, a sulfone can stabilize an adjacent carbanion or alternatively can be displaced by a carbon nucleophile, upon suitable activation. For this reason, some sulfones can be considered as 1,1-dipole synthons. This peculiar reactivity of sulfones continues to attract the interest of organic chemists and represents an invaluable source of new reactions. The story of this SYNTHESIS paper started with a discovery by Professor Kojima's and Professor Matsunaga's group at Hokkaido University (Japan) in 2018: at that time, they were studying the dual cobalt-photoredox catalysis for allylic alkylation. "The system can be considered as a new type of metallaphotoredox catalysis[1] and worked very well for branch-selective substitutions of allyl carbonates and allyl carboxylates," said Professor Kojima. He continued: "However, we were motivated to identify a unique feature of cobalt catalysis compared to the established rhodium or iridium catalysis." Gratifyingly, Professor Kojima discovered that the cobalt-photoredox system was uniquely effective for substitution of allyl sulfones, which proceeded via challenging C–S bond cleavage and was not feasible using the known noble-metal-based catalysis (Scheme 1).[2] Professor Kojima said: "Koji Takizawa and I also discovered that the 4-chlorophenylsulfonyl leaving group facilitated the allylic substitution, presumably due to greater leaving-group ability of 4-chlorophenylsulfinate compared to phenyl sulfinate."

In 1990, Trost and Merlic proposed the potential of allyl sulfone as an ambiphilic 1,1-synthon.[3] "Its application in multistep synthesis remained a challenge, however, partly because the regioselectivity in the molybdenum-catalyzed substitution of allyl sulfones remained modest," remarked Professor Kojima. He continued: "We envisioned that sequential base-mediated α-alkylation and cobalt-photoredox-catalyzed allylic substitution might provide a solution to this problem."

Graduate student Tomoyuki Sekino took over the study and explored the potential of allyl 4-chlorophenyl sulfone as a 1,1-synthon (Scheme 2). Professor Kojima said: "An unexpected problem came up in base-mediated α-alkylation. Initial trials using butyllithium and an alkyl iodide, followed by acidic workup using aqueous NH_4Cl, afforded an inseparable mixture of allyl sulfone and vinyl sulfone." This "isomerization problem" was solved by Professor Tatsuhiko Yoshino's and Professor Shigeki Matsunaga's suggestion that quenching the reaction under milder protonation conditions might circumvent the undesired isomerization. Professor Kojima said: "Following their advice, Tomoyuki identified the optimal workup method (addition of 1 M AcOH in THF at –78 °C) which finally enabled the practical use of the allyl 4-chlorophenylsulfone as a 1,1-synthon."



Scheme 1 Design of photoredox-enabled cobalt catalysis for substitution of allyl sulfones

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With support from undergraduate students Shunta Sato and Kazuki Kuwabara, Tomoyuki Sekino revealed the broad scope of the sequential α-alkylation/cobalt-catalyzed allylic substitution of allyl sulfones (Scheme 2). "In general, group 9 metal catalysis (rhodium[4] or iridium[5]) affords branched products in high regioselectivity in allylic substitution," explained Professor Kojima. He continued: "Cobalt catalysis was no exception, and the photoredox-enabled cobalt catalysis allowed access to synthetically valuable branched products in >20:1 regioselectivity in most cases. Notably, functional groups including ester and Weinreb amide were tolerated under the two-step transformations. We anticipate that such functional group compatibility will be beneficial for future applications in the synthesis of complex molecules."

"Compared to rhodium- or iridium-catalyzed methods, the study of cobalt-catalyzed allylic substitution has just begun[6]," said Professor Kojima. He concluded: "Furthermore, the merger of photoredox and cobalt catalysis[7] is also a new and untapped research area compared to nickel-photoredox[8] or copper-photoredox[9] systems. With these two promising directions in sight, we would like to unlock more potential and demonstrate the unique utility of photoredox-enabled cobalt catalysis for organic synthesis."

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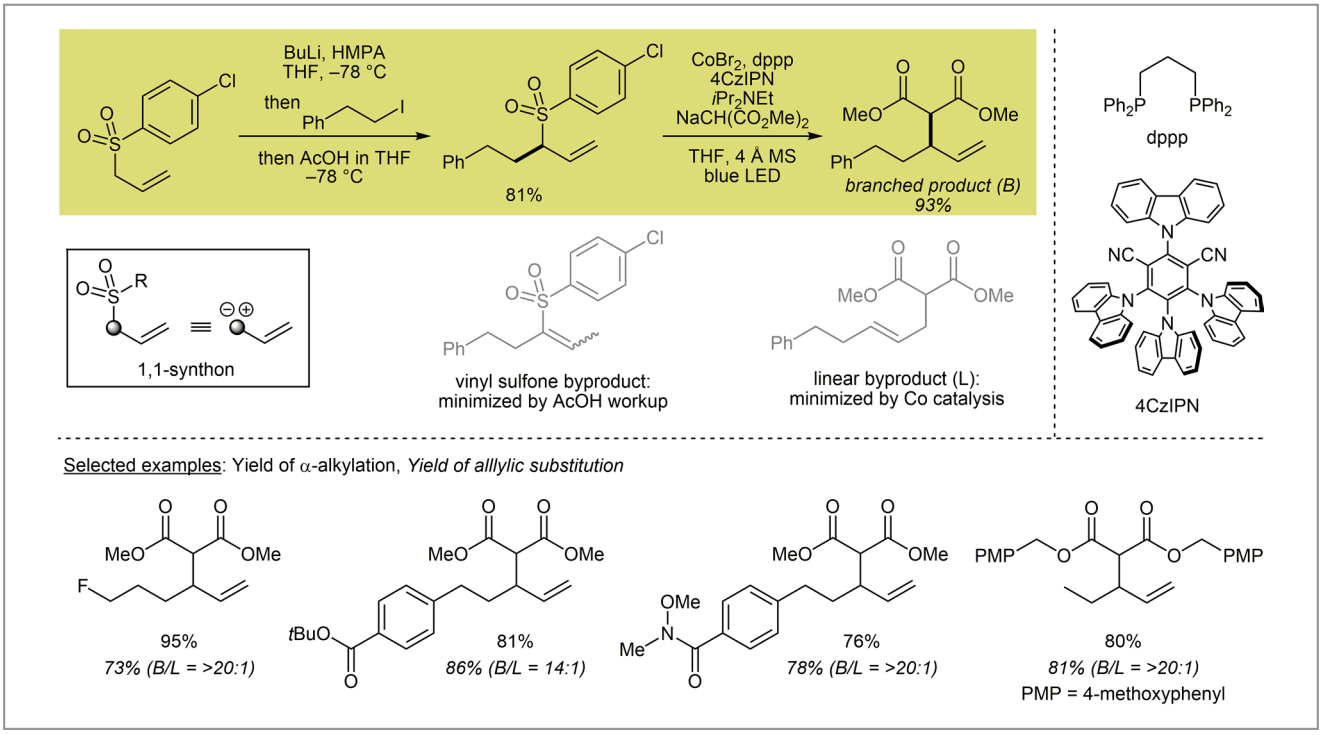
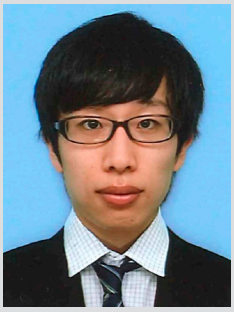


Scheme 2 Sequential transformations of allyl 4-chlorophenylsulfone as a 1,1-synthon

About the authors



T. Sekino

Tomoyuki Sekino was born in Shizuoka (Japan) in 1993. He studied at the Department of Pharmaceutical Sciences, University of Shizuoka (Japan), where he received his B.Sc. in 2018 under the guidance of Prof. Kei Manabe. Since 2018 he has been carrying out his Ph.D. studies under the supervision of Prof. Shigeki Matsunaga in the Graduate School of Pharmaceutical Sciences, Hokkaido University (Japan). His research interest is the development of novel reactions employing cobalt metallaphotoredox catalysis.

S. Sato

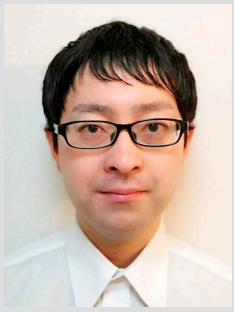
Shunta Sato was born in Sapporo (Japan) in 1997. He studied at the Faculty of Pharmaceutical Sciences, Hokkaido University (Japan). In 2020, he received his B.Sc. degree and became a graduate student under the supervision of Prof. Shigeki Matsunaga. His main research interest is dual photoredox and transition-metal-catalyzed methodologies.

K. Kuwabara

Kazuki Kuwabara was born in Kanagawa (Japan) in 1997. Since 2017, he has been an undergraduate at Hokkaido University (Japan) and joined Prof. Shigeki Matsunaga's group in 2019. His research interests lie in visible-light photoredox catalysis.

K. Takizawa

Koji Takizawa studied chemistry at Hokkaido University (Japan) and obtained his B.Sc. in 2017 under the supervision of Prof. Shigeki Matsunaga. He earned his M.Sc. in the same group in 2019. Then he joined Sekisui Chemical Co., Ltd., Advanced Technology Institute Corporate R&D Center (Japan) in 2019. He is experienced in total synthesis, transition-metal catalysis and photoredox catalysis.



Prof. T. Yoshino

Tatsuhiko Yoshino received his Ph.D. in 2014 from the University of Tokyo (Japan) for his studies of homogeneous metal catalysis and organic synthesis under the guidance of Prof. Masakatsu Shibasaki and Prof. Motomu Kanai. He then joined the laboratory of Prof. Matthew W. Kanan at Stanford University (USA) as a postdoctoral fellow, where he worked on CO_2 utilization reactions. He was appointed as an assistant professor at Hokkaido University (Japan) in 2015, and promoted to a senior lecturer in 2018. He received the 4th Thomson Reuters Research Front Award in 2016 for the studies on cobalt-catalyzed C–H functionalization reactions. His current research interests are focused on the metal-catalyzed C–H functionalization reactions, asymmetric catalysis, and the development of novel molecules and reactions for organic synthesis.

Prof. M. Kojima

Masahiro Kojima studied chemistry at the University of Tokyo (Japan) and obtained his B.Sc. (2012) and Ph.D. (2017) for his studies of photoredox catalysis and related reactions under the guidance of Prof. Motomu Kanai. In 2014, he spent two months as a visiting student in Prof. Dirk Trauner's group at LMU Munich (Germany), working on total synthesis of natural products. After a postdoctoral study of metal-catalyzed C–H functionalization with Prof. John F. Hartwig at UC Berkeley (USA), he joined Prof. Shigeki Matsunaga's group at Hokkaido University as an assistant professor in 2018. He is interested in photochemistry, transition-metal catalysis and novel methodologies for organic synthesis.

Prof. S. Matsunaga

Shigeki Matsunaga earned his Bachelor's degree in 1998 from the University of Tokyo (Japan), where he continued his PhD work under the supervision of Professor Masakatsu Shibasaki and completed the work in 2003. He took up an assistant professor position in Prof. Shibasaki's group at the University of Tokyo in 2001 and was promoted there to a senior

lecturer in 2008. He joined Prof. Motomu Kanai's group at the University of Tokyo in 2010 and was promoted to an associate professor in 2011. In 2015, he moved to Hokkaido University (Japan) as a full professor. He is the recipient of the Chemical Society of Japan Award for Young Chemists (2006), Mitsui Chemicals Catalysis Science Award of Encouragement (2009), Merck–Banyu Lectureship Award 2010, Asian-Core-Program Lectureship Awards 2015 and 2018 (Korea, Thailand, China, Singapore), 4th Thomson Reuters Research Front Award (2016), Negishi Award (2018), Mukaiyama Award (2020), and others. His research interests are in the development of cooperative asymmetric catalysts, C–H activation catalysts, and their application to the synthesis of biologically active compounds.

Stain Protocol for the Detection of N-Terminal Amino Groups during Solid-Phase Peptide Synthesis

Org. Lett. **2020**, *22*, 3309–3312

Solid-phase peptide synthesis (SPPS) – pioneered by the 1984 Nobel Prize winner Robert Bruce Merrifield – is the method of choice for the preparation of polypeptides. This highly versatile technology is used worldwide for the manual as well as automated synthesis of a wide range of peptides. Despite its success, direct monitoring of reactions on resin is not as straightforward as for reactions in solution where samples can be easily collected and directly analysed through a variety of analytical and spectroscopic methods, such TLC, HPLC and NMR. The Kaiser test – based on the reaction between primary amino groups and ninhydrin which develops an intense blue color – is destructive and can easily lead to false positives (for example when Fmoc protecting groups are labile to the pyridine contained in the test cocktail) or negatives (secondary amines such as proline give rise to a rather ambiguous red-brownish color). Besides, the Kaiser test is time-consuming and the test cocktail contains highly toxic reagents such as KCN.

The group of Professor Hiroyuki Konno at Yamagata University (Japan) recently reported a new test protocol to detect *N*-terminal amino groups during Fmoc-SPPS using a reversible and non-destructive reaction. Professor Konno explained: "This is a novel approach attempted for the first time by our research group, since for a hundred years ninhydrin has been used as a detecting reagent for primary amino groups. The Kaiser test with ninhydrin results in blue staining and is definitely useful, but it sacrifices the small amount of resin used for the test and cannot detect most secondary and tertiary amino groups." He continued: "Interestingly, our methodology can detect most primary, secondary and tertiary amino groups, using a reversible process and coloration. Therefore, we do not need to lose any resin."

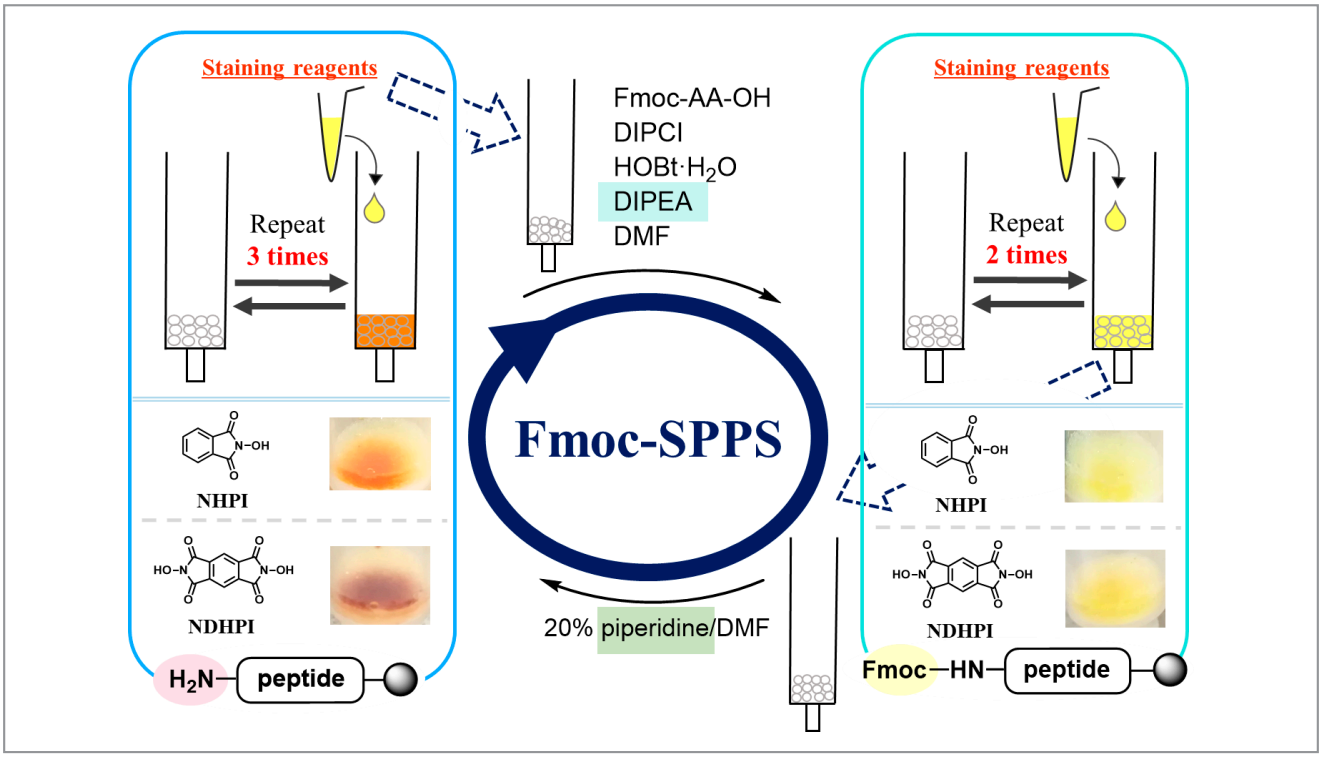


Figure 1 The protocol of staining of free amino groups and protected amino groups.

The group tested all 20 proteogenic amino acids, some *N*-methyl amino acids, and Aib to ensure that all of them could be detected by their new approach. Professor Konno remarked: "Fortunately, no byproducts have ever been shown in HPLC analysis."

The new protocol for staining free amino groups and protected amino groups is shown in Figure 1. "This is a unique method that makes it very easy to check the presence of amino groups," explained Professor Konno. He continued: "In addition, only cheap reagents and no expensive analytical equipment are required. As I saw the red crystal of the complex with *N*-hydroxyphthalimide and dimethylamine, I had a "Eureka moment" concerning this amino group staining. Since the red color disappears as the complex is dissociated, I immediately felt that this phenomenon was valuable."

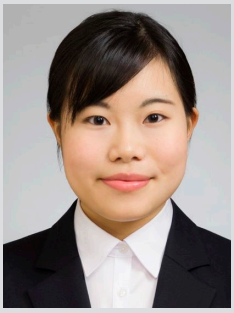
Professor Konno then paid tribute to Rio Suzuki, the sole co-worker, who performed all the experiments and analyzed the data. Professor Konno remarked: "She is an outstanding student and the success of this research is due to her deep insight and sharp observant eye."

Professor Konno concluded by speaking about potential or actual applications for their work, saying: "In the future, one of our most important aims is to reduce the stoichiometric proportions of reagents used by this system in peptide synthesis, not only to reduce costs but also the environmental impact of the protocol."

About the authors

Prof. H. Konno

Hiroyuki Konno is currently a professor at Graduate School of Science and Engineering, Yamagata University (Japan). He received his Ph.D. from the Pharmaceutical Institute, Tohoku University (Japan) in 1999 under the supervision of Prof. Kunio Ogasawara. He conducted postdoctoral research at University of Pennsylvania (USA) with Prof. Amos B. Smith, III as a JSPS fellow. He was an Assistant Professor of Tokushima University (Japan), Kyoto University (Japan) and Kyoto Prefectural University of Medicine (Japan) for eight years. In 2009, he began his independent career at Yamagata University. His research interests mainly focus on enzyme inhibitors, solid-phase synthesis and total synthesis of peptidyl natural products.



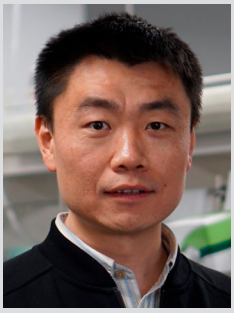
R. Suzuki

Rio Suzuki obtained her B.Eng. degree from Yamagata University (Japan) in 2018. She then obtained a Master's degree in 2020 under the supervision of Prof. Hiroyuki Konno. She is currently a researcher at DENKA Co. Ltd. in Japan. Her research focuses on bioorganic chemistry (especially solid-phase peptide synthesis).

Young Career Focus: Dr. Chao Wang (The University of Tokyo, Japan)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Dr. Chao Wang (The University of Tokyo, Japan).

Biographical Sketch



Dr. C. Wang

Chao Wang (王　超) was born in Shaanxi Province (陕西省), P. R. of China. He obtained his BS degree in 2002 from Peking University (北京大学), P. R. of China. He continued his doctoral research under the supervision of Professor Zhenfeng Xi (席 振峰 教授) at the same university and obtained his PhD in 2007. After that, he carried out postdoctoral research at Purdue University, USA, with Professor Ei-ichi Negishi (根岸　英一　教授). In 2009, he joined Professor Masanobu Uchiyama's lab (内山　真伸　教授) at RIKEN, Japan as a JSPS postdoctoral fellow, and later as a RIKEN-SPDR fellow. He is now an assistant professor at the Graduate School of Pharmaceutical Sciences (Professor Uchiyama's lab), the University of Tokyo, Japan. In this current position, he has received the Pharmaceutical Society of Japan Award for Young Scientists (2018), the Chemist BCA Award 2019 (MSD Life Science Foundation), and the Thieme Chemistry Journals Award 2020. His research involves synthetic organic chemistry, organometallic chemistry, and computational chemistry.

INTERVIEW

SYNFORM *What is the focus of your current research activity?*

Dr. C. Wang One of our ongoing research projects is to establish conceptually new and practically useful protocols that enable cleavage of inert C–O/C–N bonds in a selective and mild manner by means of transition-metal catalysis, photocatalysis, and/or other reaction patterns. We are also focusing on exploring novel and efficient reactions and reagents for synthetic transformations of group 14 elements that are of versatile applicability in organic synthesis and functional materials, as well as medicinal chemistry.

SYNFORM *When did you get interested in synthesis?*

Dr. C. Wang In the second semester of my first year at Peking University, we began to be taught organic chemistry. The textbook we used was named *Basic Organic Chemistry* (基礎有機化学), *2nd Edition*, edited by a group of professors led by Prof. Qi-Yi Xing (邢 其毅 教授: 1911–2002), a great Chinese chemist and educator. This textbook deeply impressed many generations of chemists in China, who give it a hearty nickname in Chinese: 邢大本 (Xing's Great Book). It is not only a friendly, accessible, and engaging primer to organic chemistry, but also a comprehensive and in-depth account that provides a panoramic view of organic chemistry. This book is fantastic to me. It is fertile soil where my interest in organic chemistry sprouted. It was also fortunate that I met several fantastic lecturers in the organic chemistry courses, Prof. Weiwei Pei and Prof. Jiaxi Xu (my BS thesis advisor) who were in charge of the organic chemistry course, Prof. Jianbo Wang who guided me in the organic chemistry lab and physical organic chemistry courses, Prof. Jian Pei who taught me in the course on stereochemistry, and Prof. Zhenfeng Xi (my PhD thesis supervisor and my life-long mentor) who taught me organometallic

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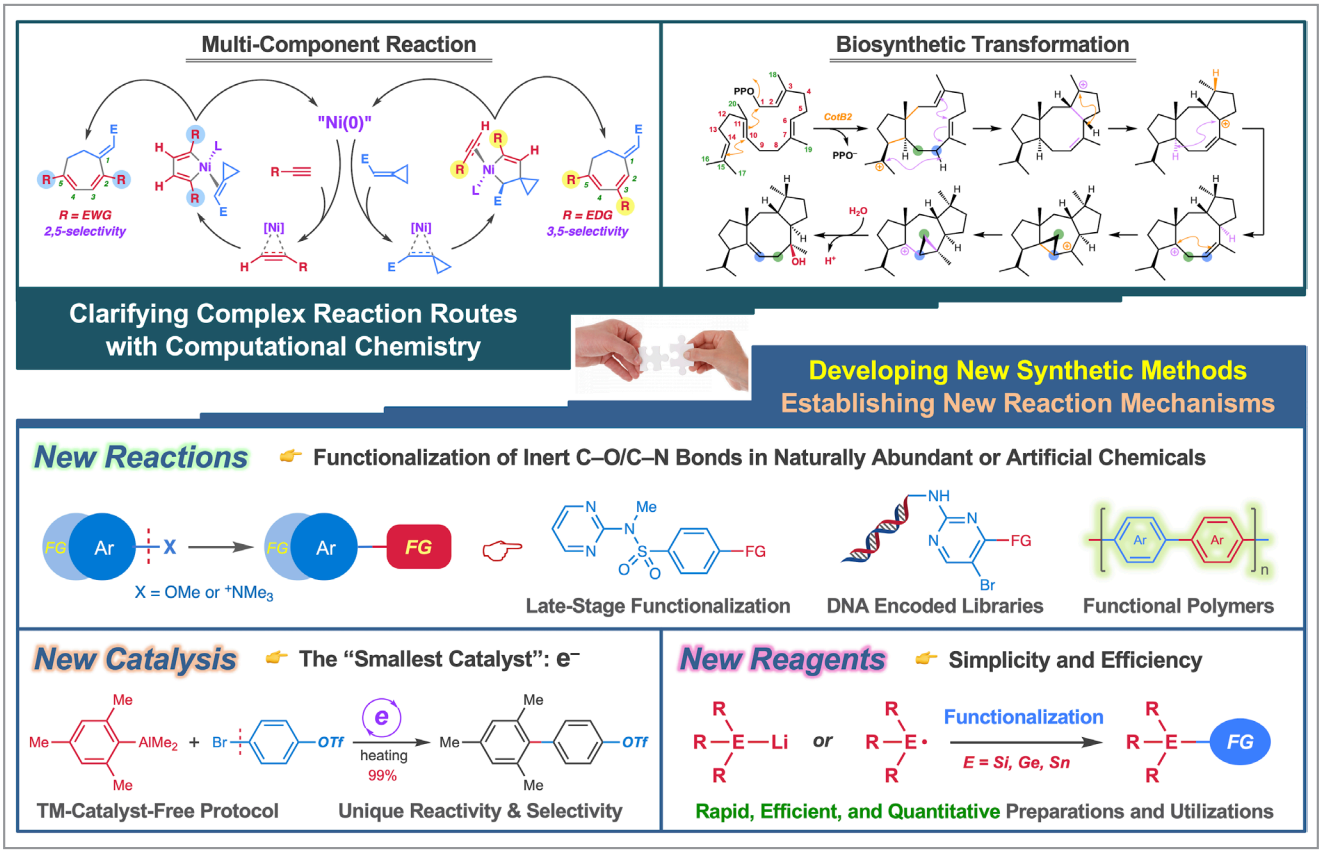
chemistry. With their guidance and encouragement, I became fascinated with organic chemistry and decided to pursue my career in it.

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

Dr. C. Wang This is a big question. Just in view of my research areas, I think that synthetic chemistry has demonstrated great ability to create products of high value to provide an impressive range of useful and necessary substances and materials for human use. However, current chemical synthesis is highly dependent on the utilization of non-renewable fossil fuels and noble metals. Fossil fuels contain highly reduced molecules (with many C–H bonds), which must be oxidized during most chemical processes, leading to large emissions of CO_2. In the future, we need to replace fossil-fuel-based traditional synthetic protocols with novel strategies based on biomass feedstocks, renewable resources and clean energy. We also need to utilize non-precious elements more efficiently, to break the dependence on expensive, rare noble metals. I believe that future innovations of synthetic chemistry will make great contributions to the transformation of our lifestyle to one with reduced natural and social costs and for achieving a sustainable society.

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

Dr. C. Wang I joined Prof. Masanobu Uchiyama's group in 2009 after I finished my postdoctoral research with Prof. Ei-ichi Negishi. From Prof. Uchiyama, I have learned a great deal, including computational chemistry, elements chemistry and physical chemistry. The integration of computations and experiments provides an efficient approach for our research that is focused on establishing breakthrough methodology for molecular transformations, including: 1) efficient protocols for inert bond cleavage enabling facile syntheses and/or late-stage transformations of functional molecules/polymers; 2) direct C–C bond formation method involving one electron as



Scheme 1

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the 'smallest catalyst'; 3) mild, rapid, and quantitative procedures for introducing functional elements such as Si, Ge, or Sn; and 4) clarification of complex reaction mechanisms as well as biosynthetic routes by means of computational chemistry (Scheme 1).

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

Dr. C. Wang In 2015, we described our computational study on the mechanism of Ni-catalysed inert C–O bond cleavage reaction (*Chem. Eur. J.* **2015**, *21*, 13904–13908). As early as in 1979, Wenkert reported the first Ni-catalysed cross-coupling through etheric Ar–OR bond cleavage. This was very 'abnormal', because the OR group 'normally' acted as an electron-donating 'stand-by' in most reactions of arenes. This breakthrough was overlooked for decades, but now substantial experimental efforts have been made toward the development of improved conditions since 2004. Even so, the mechanism of this type of reaction remained unclear. By DFT calculations, we successfully established a reasonable reaction pathway involving the anionic Ni(0)-ate complex. This study not only explained the experimental facts well, but also provided a new type of reaction mechanism for cross-coupling, distinct from the conventional catalytic cycle of oxidative addition, transmetalation, and reductive elimination.

In the same year, we also reported a facile, rapid and quantitative protocol for the preparation of stannyl or germyl lithiums that facilitated diverse transformations (*J. Am. Chem. Soc.* **2015**, *137*, 10488–10491; Patent JP6452500; highlighted in *Synform* **2016**, A38–A39). Most synthetic methods for stannyl or germyl lithium species (E–Li, E = Sn or Ge) have suffered from poor yield, low atom-efficiency, less stability, and generation of toxic by-products. By catalytic use of polycyclic aromatic hydrocarbons (e.g. naphthalene, DBB) as simple and efficient accelerators of electron transfer, we have, for the first time, established a fast and quantitative preparative method of E–Li since the discovery of such reagents in the 1950s. This straightforward protocol can be achieved with 100% Sn-atom economy without formation of any (toxic) by-products, and E–Li obtained by this method is highly stable and can be stored for months at ambient temperature. Further, the E–Li reagent prepared by our method shows excellent reactivity in a variety of transformations with high tolerance of diverse functional groups, indicating a great potential for efficient preparation of Sn- or Ge-contained functional molecules.

More recently, we demonstrated a new method to generate silyl radicals ($R_3Si•$) through visible-light-induced decarboxylation reaction of silyl carboxylic acids ($R_3SiCOOH$) (*Angew. Chem. Int. Ed.* **2020**, *59*, 10639–10644). $R_3SiCOOH$ can be prepared in high yield by reaction of CO_2 with the corresponding $R_3Si–Li$ or $R_3Si–Na$ reagents. It was first synthesized in the 1950s, as a 'heavy' analogue of carboxylic acid. However, despite the easy accessibility and high stability, the reactivity and synthetic utility of $R_3SiCOOH$ have been largely ignored until now. We found that irradiation of $R_3SiCOOH$ with blue LEDs in the presence of a commercially available photocatalyst could release silyl radicals, which can further react with various alkenes to give the corresponding hydrosilylation products in good to high yields with broad functional group compatibility. Meanwhile, germyl radicals ($R_3Ge•$) were similarly obtained from germyl carboxylic acids ($R_3GeCOOH$).

While I believe that my most important achievements lie ahead of me, I am indeed delighted with the progress that we have made in these fields, overlooked so long.

Asymmetric One-Pot Transformation of Isoflavones to Pterocarpans and Its Application in Phytoalexin Synthesis

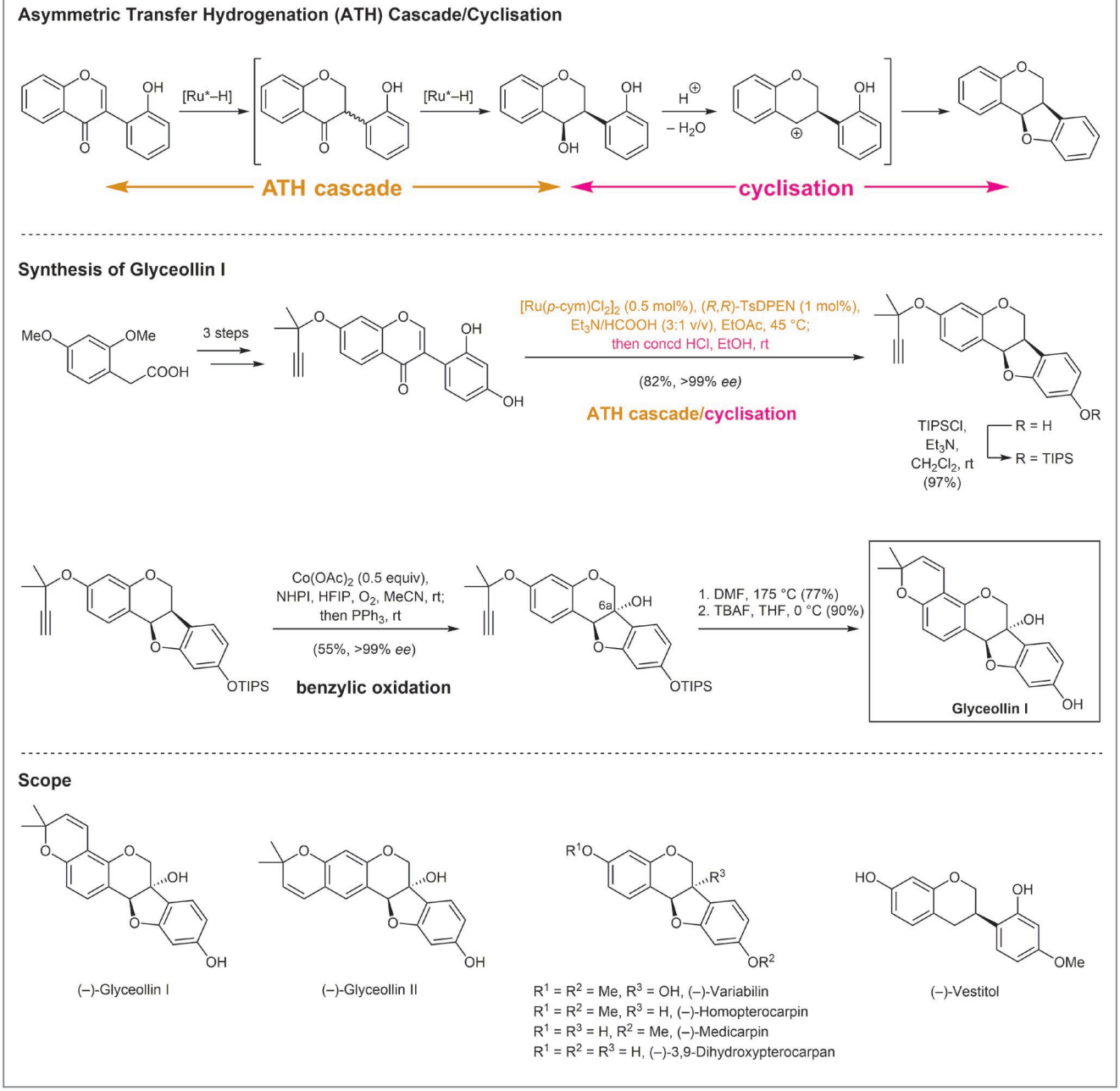
Nat. Commun. **2020**, DOI: 10.1038/s41467-020-16933-y

Phytoalexins are structurally diverse, low-molecular-weight secondary metabolites that are produced *ex novo* in appreciable amounts by plants following a pathogenic attack. These antimicrobials may be isolated from stressed soy plants and, owing to their interesting biological properties, have attracted the attention of many research groups in recent years. Some phytoalexins have shown capacity for selectively modulating the activity of the oestrogen receptor, which plays an important role in the growth of oestrogen-related cancers, e.g. mammary carcinoma or ovarian cancer. Furthermore, their anti-inflammatory and anti-cholesterolemic activity, as well as further health-promoting effects, are under investigation all over the world.

However, the isolation of the pure phytoalexins from natural sources is generally challenging. The development of a concise catalytic access to structurally defined phytoalexins, such as the enantiopure pterocarpans glyceollin I and glyceollin II, is an important entry to these compounds and was the driving force of the research described in a paper recently published by Professor Peter Metz and Dr. Philipp Ciesielski (Technische Universität Dresden, Germany). Professor Metz commented: "With our work we wanted to make these phytoalexins and further isoflavonoids more readily available, especially for detailed studies on their bioactivity."

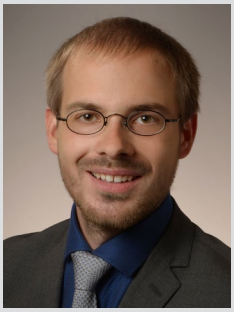
Professor Metz noted that a common pathway for the enantioselective construction of the 6a-hydroxypterocarpan skeleton of several phytoalexins is the Sharpless asymmetric dihydroxylation (SAD) of a suitable isoflav-3-ene. But as the SAD of isoflav-3-enes requires stoichiometric amounts of the toxic and expensive osmium tetroxide and of chiral ligand as well – as demonstrated in the first asymmetric synthesis of glyceollin I by the Erhardt group (University of Toledo, USA) – a novel catalytic access was desirable (for references, see the original paper).

"Some years ago, we found that a ruthenium-catalysed asymmetric transfer hydrogenation (ATH) of racemic isoflavanones succeeds with a highly selective dynamic kinetic resolution to give the corresponding enantiomerically pure isoflavan-4-ols in yields exceeding 90%," said Professor Metz. He continued: "Now, for the first time, we were also able to use an isoflavone as a substrate for ruthenium-catalysed ATH. In this process a conjugate reduction to a racemic isoflavanone is carried out first, which is then reduced with dynamic kinetic resolution. Aiming for the pterocarpan skeleton, the ATH can be quenched with hydrochloric acid after dilution with ethanol to achieve a smooth cyclisation." Searching for suitable conditions for the regioselective installation of the benzylic hydroxyl group at C-6a, the authors found an adapted protocol from the group of Ishii (Kansai University, Japan), which was superior to the other methods tested. "Indeed, we believe we are the first to apply this aerobic oxidation to a complex molecule," explained Professor Metz. He concluded: "Using this biomimetic strategy, only eight steps were necessary to secure glyceollin I in good overall yield from the commercially available (2,4-dimethoxyphenyl)acetic acid. Furthermore, our approach – illustrated in Scheme 1 – gave access to several other naturally occurring phytoalexins in an efficient manner and high enantiomeric purity."



Scheme 1 Asymmetric transfer hydrogenation cascade/cyclisation in the synthesis of glyceollin I and scope of the phytoalexins synthesised

About the authors



Dr. P. Ciesielski

Philipp Ciesielski studied chemistry at the Technische Universität Dresden (Germany) and obtained his MSc degree in 2014. During his PhD studies under the supervision of P. Metz he focused his research on the development of asymmetric total syntheses of bioactive isoflavonoids. He received his PhD in 2019.

Prof. P. Metz

Peter Metz studied chemistry at the University of Münster (Germany), where he received his Diploma (1979) and PhD (1983) under the guidance of H. J. Schäfer. After a postdoctoral research stay with B. M. Trost (1983–1984; University of Wisconsin-Madison, USA), he returned to Münster and completed his Habilitation in 1991. Following temporary full professorships at the University of Hamburg (Germany, 1992–1993), the University of Kiel (Germany, 1994) and the Technische Universität Dresden (Germany, 1996), he became a full professor at the TU Dresden (1997). His research interest covers the total synthesis of biologically active natural products and their analogues, as well as the development of novel methods and strategies for stereoselective synthesis.

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