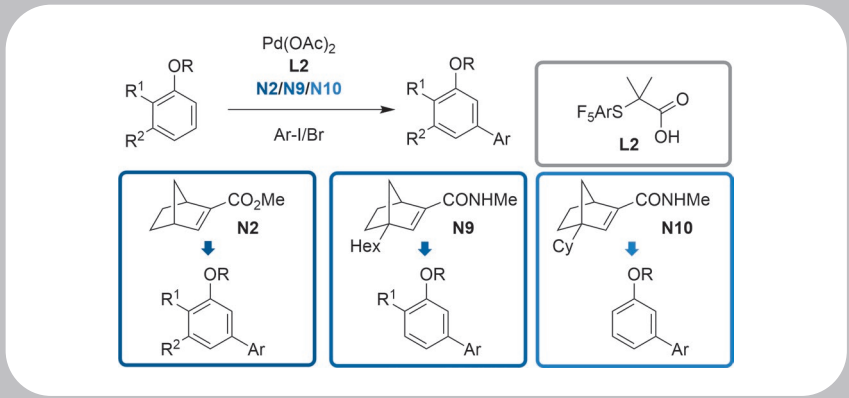
Synform

People, Trends and Views in Chemical Synthesis

2022/12

S,O-Ligand Promoted *meta*-C–H Arylation of Anisole Derivatives via Palladium/Norbornene Catalysis

Highlighted article by V. Sukowski, M. van Borselen, S. Mathew, M. Á. Fernández-Ibáñez



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Thieme

Dear Readers,

This December issue of SYNFORM wraps up another exciting year of organic synthesis, and it does so with a very special event: a *SynOpen Special* section to celebrate the new key milestone achieved by the Thieme Chemistry Open Access journal, which is already indexed in Web of Science as well as in Scopus: the assignment of an impact factor in 2023!! One of the most distinctive editorial features of *SynOpen* is the Graphical Review, which provides a concise overview of a topic from a unique format perspective, namely emphasizing graphical content with text kept to a minimum. In this *SynOpen Special* we present an interview with both Prof. Laurence M. Harwood (UK), who has been the *SynOpen* Editor-in-Chief since 2017, and Prof. Daniel Seidel (USA), who has been involved with the journal since 2019. On top of that, we have three brief *SynOpen* Highlight articles focusing on the three Graphical Reviews published so far, featuring some of the authors who share their thoughts about the reviews' topics and their authors' experience.

Further to the *SynOpen Special*, this December issue of SYNFORM continues with a Literature Coverage article on a conceptually new palladium-catalyzed *trans*-hydroalkoxylation leading to protected stereodefined β-amino alcohols, developed by the group of J. Waser (Switzerland). The next article is a Young Career Focus interview with Prof. Markus Kärkäs (Sweden), who spoke with us about his research interests and achievements in electrosynthesis, photocatalysis and transition-metal catalysis. The following Literature Coverage article focuses on an original way to promote *meta*-C–H arylation of anisole derivatives using *S*,*O*-ligands, which was conceived and realized by the group of M. A. Fernández-Ibáñez at the University of Amsterdam (The Netherlands). This very chunky SYNFORM issue is closed by the last literature highlight of the year, a key duty carried out very effectively and with great elegance by a SYNTHESIS paper published by the group of T. Sato (Japan), with their brilliant total synthesis of anti-inflammatory stemoamide-type alkaloids.

Enjoy your reading!

In this issue

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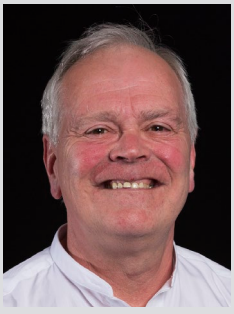
Editorial Board Focus: Professors Laurence Harwood and Daniel Seidel on the Open Access Journal SynOpen

Background and Purpose. *SynOpen* was launched in 2017 and, like its sister journals SYNTHESIS and SYNLETT, is geared towards publishing high-quality work that deserves to be considered for publication in an open-access format. *SynOpen* is an international peer-reviewed journal reporting current research results in the chemical sciences mainly but not exclusively, in the areas of synthesis, catalysis, organometallic chemistry, medicinal chemistry, photochemistry, polymers and materials synthesis. *SynOpen* offers the opportunity to publish both experimental and theoretical studies as well as to publish primary scientific data. It also publishes insightful review articles intended for new researchers as well as specialists in these fields. *SynOpen* is indexed in Web of Science as well as in Scopus and will receive an impact factor in 2023.

SYNFORM spoke with Laurence M. Harwood, Editor-in-Chief of *SynOpen*, and Daniel Seidel, Executive Editor of *SynOpen*, who were happy to share some background information regarding the journal and its unique features.

Biographical Sketches



Prof. L. M. Harwood

Laurence M. Harwood is Professor of Organic Chemistry at the University of Reading and Visiting Professor in Organic Chemistry at the University of Lincoln. He studied chemistry at Manchester University where he obtained his Ph.D. in 1978 in the group of Prof. J. K. (Hamish) Sutherland. After two years working for Prof. Marc Julia at the École Normale Supérieure in Paris as a Royal Society Postdoctoral Fellow, he returned to Manchester for his first academic position before moving to Oxford University and Merton College in 1983. He moved to his current position in 1995 and has been the *SynOpen* Editor-in-Chief since 2017. His research interests lie in applications of synthetic methodology to a wide range of natural and unnatural targets.

Prof. D. Seidel

Daniel Seidel studied chemistry at the Friedrich-Schiller-Universität Jena (Germany) and at the University of Texas at Austin (USA) (Diplom 1998). He performed his graduate studies in the laboratories of Prof. Jonathan L. Sessler, obtaining his Ph.D. in 2002. From 2002–2005, he was an Ernst Schering Postdoctoral Fellow in the group of Prof. David A. Evans at Harvard University (USA). He started his independent career at Rutgers University (USA) in 2005 and was promoted to Associate Professor in 2011 and Full Professor in 2014. In the summer of 2017, his research group moved to the University of Florida (USA). He has been on the Editorial Board of *SynOpen* since 2019.

INTERVIEW

SYNFORM *Describe SynOpen with 3 words.*

Prof. L. M. Harwood *SynOpen* has the strap line of "**fast, fair and flexible**", that so neatly sums up this innovative open-access adjunct journal to SYNTHESIS, SYNLETT and *Organic Materials*.

We are **fast** because we use Select Crowd Review[1] as the default option for assessing submitted manuscripts and this means that we expect to give authors a decision within five working days.

Select Crowd Review has transformed the standard peer-review process as it is not only "**fast**", but also "**fair**".[2] Why? Every time a manuscript is sent to the "Crowd" a "Select" number of those participating will have an interest in the sub-

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ject matter and so will comment from an informed viewpoint directly onto the manuscript. After sufficient comments have been received, Dr. Eduarda Silva, the Executive Editor tasked with running the review process, summarizes the comments and then passes them on to the Executive Editor overseeing the manuscript who can then make an informed decision. In this way, maverick recommendations are ironed out and a more holistic view of the manuscript can be communicated back to the authors – be that positive or negative – or, more likely, suggesting modifications before acceptance. On several occasions where a manuscript has eventually ended up being rejected, I have received a positive response from the authors, who have appreciated the speed of the decision and the reviewers' suggestions for improving the manuscript.

Of course, *SynOpen* is a wholly online journal and that allows it to be "**flexible**" in the type, format and content of articles we can publish – Letters, Papers, Reviews, Short Reviews, Graphical Reviews, Practical Synthetic Procedures, and Spotlights.

SYNFORM *Could you please tell us more about the board?*

Prof. L. M. Harwood I am the Editor-in-Chief and I am very ably supported by a great Executive Board composed of Professors Françoise Colobert, Daniel Seidel, Raji Reddy, Tian-Sheng Mei, and Eduarda Silva. Françoise is specifically tasked with Reviews and Short Reviews, Daniel looks after Graphical Reviews, Raji oversees outreach activities in India and the Middle East, Tiang-Sheng, who joined the board in October, oversees outreach activities in East Asia, Eddie looks after Select Crowd Review and I handle Spotlights. As a team we are diverse in our areas of expertise as well as geography, ethnicity and gender. Furthermore, whilst highly qualified, professional and committed, we have a relaxed and open working relationship, which means that communication is clear and rapid among us.

In addition to the Executive Board, we are establishing an Associate Board that brings an even wider range of expertise and diversity to the team. Finally, we have a very active group of Advisory Board Members who provide further back-up and who help to disseminate the *SynOpen* and Thieme messages world-wide.

The Associate Editors and Advisory Board do not merely represent a list of names of eminent organic chemists. These people are actively engaged in promoting and supporting *SynOpen*. I am so fortunate and proud to have the backing of so many esteemed colleagues – and friends – from around the world.

SYNFORM *What is unique about SynOpen?*

Prof. L. M. Harwood What isn't unique about *SynOpen*? From the very outset, we decided that we could not be just "another open access journal" but had to be bold and imaginative in the way the journal was constructed and operated and in its vision.

I believe that *SynOpen* was the first scientific journal to use Select Crowd Review as the default option, revolutionizing the peer review system and making it fit for purpose in the 21st century.

SynOpen has two unique article types, the Spotlight and the Graphical Review.

The Spotlight is a review-type article up to 3 template-based pages, including tables and graphics, which highlight the preparation and uses of selected reagents and methodologies in current research, so the bulk of references should be from the recent literature (2015 onward).

Daniel Seidel can tell you more about Graphical Reviews – his brainchild – but these are published in landscape format – exactly that used in PowerPoint presentations, making it simpler for authors to translate a research presentation into a publishable manuscript.

The "hands-on" approach of the Executive Editors is also very specific to *SynOpen*. We try to establish a personal bond with our authors, without ever compromising on scientific quality. Many successful authors had received personalized acceptance letters from me that start with "*Dear Professor X, it is with great regret that I must inform you that, despite my inner belief, on the basis of the reviewers' reports I am forced to accept your concoction of lies and filth……*" I understand that many of these acceptance emails are pinned up on laboratory noticeboards as a mark of a rite of passage for the team.

Something that is not only a part of *SynOpen* but also integral to SYNTHESIS, SYNLETT, *Organic Materials* and the many other Thieme journals is the spirit of the "Thieme Team". There is a real family feel to everybody who works for Thieme and this all comes down from the top. Dr. Albrecht Hauff, Chairman and CEO of Thieme Publishing Group, pays great personal attention to all the journals that Thieme publishes!

Finally – and I hope it comes through in what I have written – in all my experiences working with a wide range of chemistry journals for different publishing houses and chemical societies in various capacities, I have never experienced such pleasure to work with a team of eminent, committed, and enthusiastic people as those on the various Editorial and Advisory Boards of *SynOpen*, as well as the fantastic "Thieme Team". It is a great honor for me to have been associated with *SynOpen* since its inception in 2017.

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SYNFORM *What is a Graphical Review?*

Prof. D. Seidel A Graphical Review provides a concise overview of a topic in a series of full-page Figures, such as that shown in Figure 1 here, which heavily emphasize graphical content with text kept to a minimum. The layout of Graphical Reviews is horizontal, consistent with the way most of us use screens.

SYNFORM *How did you come up with the idea of this article type?*

Prof. D. Seidel We live in an era of ever-accelerating pace in research progress and continuously growing demands on our time. I felt that a new format is needed that would allow readers to rapidly gain an overview of a research topic that is new to them, or quickly catch up with recent developments in their areas of interest. While there will always be a place for traditional reviews, their accessibility can be limited in the sense that not every reader has the time or the interest for a time-consuming deep dive into a topic. Due to the highly graphical nature of chemistry, in particular synthetic chemistry, Schemes and Figures have long been the first items chemists examine when reading papers, including reviews. When done well, these graphics contain all key findings. So why not have an article format that is centered on graphical content? The idea to summarize material in graphical format is by no means new. In fact, research groups around the globe have provided lecture notes and group meeting slides online for at least two decades. While these materials have been embraced by the community, they are not necessarily streamlined, easily discoverable, or permanently available. In contrast, Graphical Reviews in *SynOpen* have a common layout, are peer-reviewed, well-referenced, and citable. Of course, like everything else in *SynOpen*, Graphical Reviews are fully open access.

REFERENCES

(1) See: https://www.thieme.de/en/thieme-chemistry/select-crowd-review-136859.htm.
(2) M. van Gemmeren, B. List *Synlett* **2021**, *32*, 885–891.
(3) S. Dutta, B. Li, D. R. L. Rickertsen, D. A. Valles, D. Seidel *SynOpen* **2021**, *5*, 173–228.

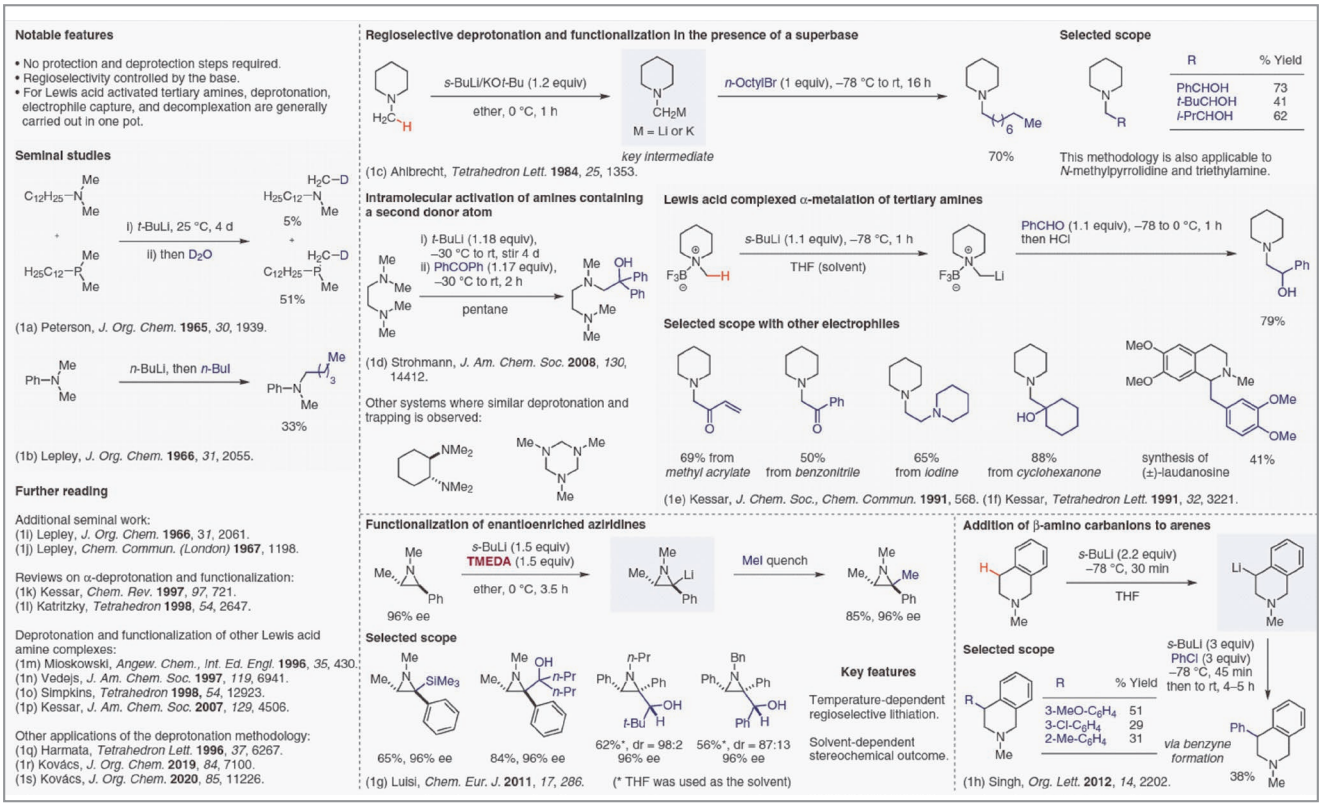


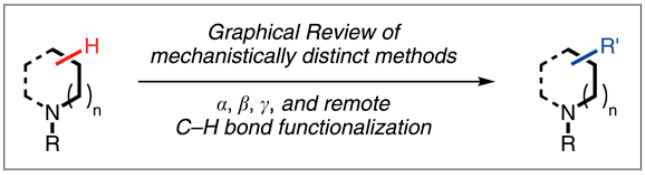
Figure 1 A full-page Figure from the first *SynOpen* Graphical Review[3]

C–H Bond Functionalization of Amines: A Graphical Overview of Diverse Methods

SynOpen **2021**, 5, 173–228

Functionalization of sp^3 C–H bonds in amines and their protected derivatives – such as amides, carbamates, *N*-aryl amines, etc., which have great relevance as pharmaceuticals as well as structural scaffolds in natural products, besides finding crucial applications in materials science – can be accomplished through a number of synthetic methodologies.

This vibrant area of research was reviewed in 2021 by the first Graphical Review in *SynOpen*, authored by the group of Professor Daniel Seidel (University of Florida, Gainesville, USA), which covered the most important methods in this field, together with the related underlying mechanisms, while tracing the origin of each approach back to the original seminal report or literature precedent.

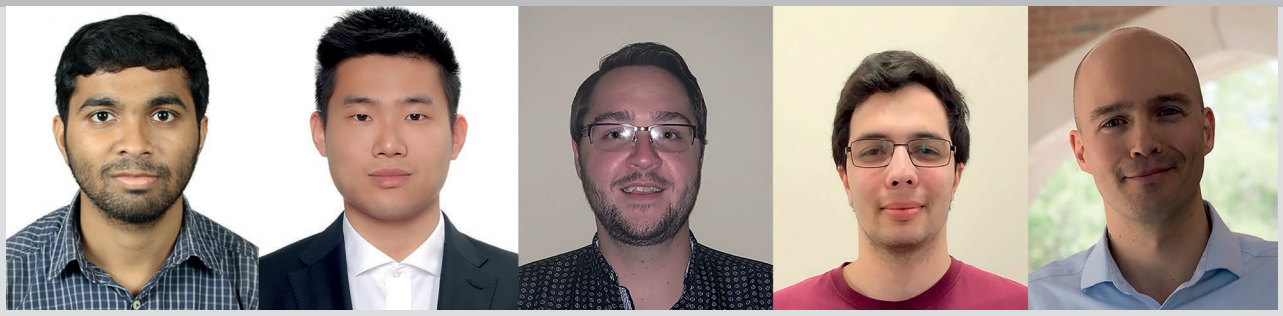


Scheme 1 Graphical abstract of the first *SynOpen* Graphical Review

Co-author Dillon Rickertsen, graduate student in the Seidel group, said: "Writing a Graphical Review presented itself with some initial challenges. One of these challenges was how we would depict the information. The images in the Graphical Review literally needed to be worth a thousand words. Having the artistic freedom to develop a format allowed us to explore several different layouts for each page. This was a great learning opportunity on how to present information in a very concise organized manner. It also presented challenges in deciding what papers in the review got drawn as reaction schemes and what papers were included in further reading. There were three big things that we wanted to make sure were captured in each Figure: seminal work, reaction mechanism, and impactful contributions to the field. I feel the finalized format that was used for the Graphical Review highlights these three factors well. Overall, I thought this was a good experience and feel that Graphical Reviews are a quick and efficient way to access information regarding a topic. I hope to see more Graphical Reviews on various topics soon."

First author Subhradeep Dutta, also a graduate student in the Seidel group, said: "It was a unique learning experience while working on the Graphical Review which is the first of its kind (as introduced by *SynOpen*). What's interesting is it incorporates all the qualities of a typical scientific review article and encapsulates it in a way that is visually appealing, engrossing, and lucid. It would give the readers a good insight of what has been done in a particular field of research and what is yet to be accomplished. I appreciate the efforts made by the Graphical Review team who made sure to maintain a good quality and high standard for the document. I hope this Graphical Review will encourage the scientific community to contribute to more reviews of this kind in the future. Happy to be a part of this great opportunity."

About the authors



From left to right: S. Dutta, B. Li, D. R. L. Rickertsen, D. A. Valles, Prof. D. Seidel

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Aryl Methyl Ketones: Versatile Synthons in the Synthesis of Heterocyclic Compounds

SynOpen **2022**, *6*, 110–131

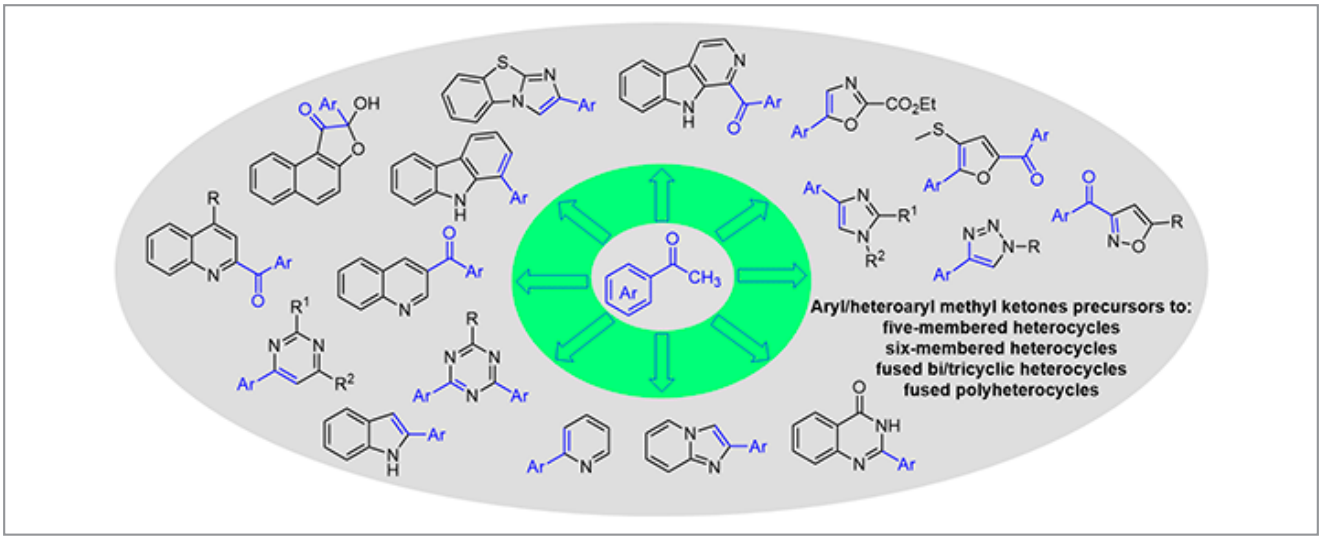
Aryl methyl ketones, including heteroaryl analogues, are useful, cost-effective and commercially abundant substrates for the synthesis of aromatic heterocycles. The latter are very frequently used as building blocks in drug discovery and development, as a broad range of heterocycles can be very commonly found as key structural features in biologically active compounds. Among the key features of heterocycles in medicinal chemistry are their capacity for modifying ADME (absorption, distribution, metabolism, excretion) and pharmacokinetic properties (lipophilicity/hydrophilicity, solubility, hydrogen bonding, etc.), while improving the toxicological profile of drug candidates.

Modern methods for accessing heterocyclic compounds from aryl methyl ketones have been recently reviewed by way of a Graphical Review in *SynOpen*, authored by Mark J. Mitton-Fry and co-workers (The Ohio State University, Columbus, USA).

Dr. Shabber Mohammed, co-corresponding author and a postdoc in the Mitton-Fry lab said: "I am pleased to share a few words about my experience in publishing my Graphical review in *SynOpen*. It was my first experience publishing in the scientific community as a corresponding author. In addition, the concept of Graphical Review was very new to me, although I easily accommodated it in the manuscript preparation. I am thankful to the editorial board for supporting each step in clarifying any doubt about the publishing process. Their timely responses were highly appreciated. I have been impressed with the excellent professionalism of constructive editorial work and the quick turnaround time for our manuscript as a publication. I am sure this wonderful knowledge-disseminating journal will reach millions of science readers in the future. I am thankful and grateful to *SynOpen* team members for accommodating my review in this journal."

About the authors

From left to right: S. Mohammed, J. S. West, M. J. Mitton-Fry



Scheme 1 Graphical abstract of the Mitton-Fry group's *SynOpen* Graphical Review

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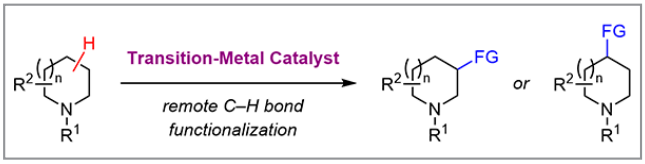
Transition-Metal-Catalyzed Remote C–H Bond Functionalization of Cyclic Amines

SynOpen **2022**, *6*, 286–305

The development of new synthetic methods to access differently substituted and functionalized cyclic amines is of great importance, because a large number of natural products and pharmaceuticals incorporate cyclic amines as key structural frameworks. Many of them contain single or multiple substituents on the ring at the α-position as well as at positions further away from the nitrogen atom. On the other hand, C–H bond functionalization of aza-heterocyclic substrates can be considered as one of the most direct and convenient strategies to access the title compounds, especially thanks to its effectiveness as a method for achieving the late-stage modification of parent cyclic amine structures in complex molecules.

This timely research topic has been recently covered by a Graphical Review in *SynOpen*, authored by the group of Dr. Weijie Chen (Tongji University, P. R. of China).



Scheme 1 Graphical abstract of the Chen group's *SynOpen* Graphical Review

Dr. Chen said: "In traditional review articles, it is not uncommon that explanatory texts are placed far away from the corresponding Schemes, readers thus easily get lost while searching for information between different pages. Moreover, review articles are usually quite long and plenty of readers only read Schemes carefully, since Schemes alone are often sufficient to provide the most important information about chemistry. Therefore, twenty or more pages of text are somewhat overwhelming and redundant. The new format of Graphical Review solves these problems well, demonstrating chemistry in a clearer and more efficient way without the distraction of text. The simplified format with dramatically reduced text and numbering also saves a lot of time for authors."

About the authors

From left to right: W. Chen, Z. Yang, X. Cao

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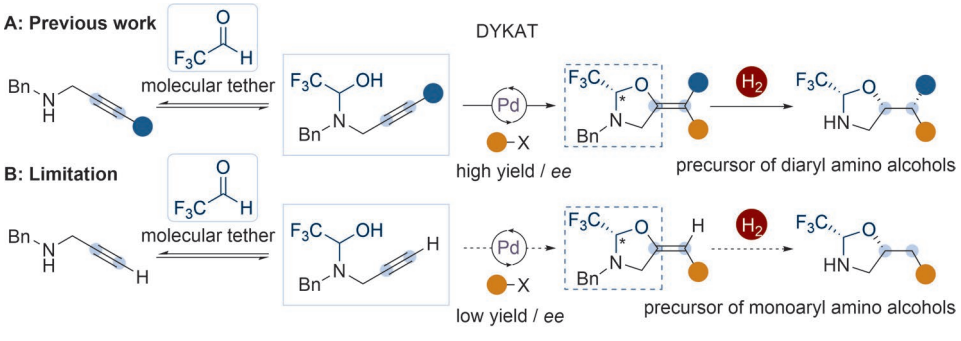
Palladium-Catalyzed *trans*-Hydroalkoxylation: Counterintuitive Use of an Aryl Iodide Additive to Promote C–H Bond Formation

ACS Catal. **2022**, *12*, 7565–7570

Stereodefined aryl-substituted β-amino alcohols are important compounds in organic chemistry, and find extensive use as ligands or building blocks in asymmetric synthesis, as well as in drug discovery. The development of stereocontrolled and efficient and catalytic synthetic methods to access these compounds remains a vibrant area of research in medicinal and bio-organic chemistry. The Waser group at Ecole Polytechnique Fédérale de Lausanne (Switzerland) has a long-standing interest in difunctionalisation reactions of unsaturated systems by exploiting molecular tethers to enhance reactivity and control selectivity. Recently, they reported a tethered asymmetric carboetherification of propargylic amines, aryl iodides and a trifluoroacetaldehyde-derived molecular tether to generate tetra-substituted olefins containing a rigid oxazolidine ring. Professor Jérôme Waser commented: "In further transformations, the installed trifluoromethyl group could shield one of the two diastereotopic faces of the olefin, acting as a *de facto* chiral auxiliary. For example, a hydrogenation reaction gave access to valuable enantioenriched diaryl amino alcohol scaffolds (Scheme 1A). Targeting chiral monoarylated amino alcohols, we wondered if we could extend the scope of the reaction to terminal propargylic amines (Scheme 1B). Unfortunately, after an extensive ligand screening, we concluded no high yield and enantioselectivity could be achieved. Another solution was needed."

Professor Waser recalls that, interestingly, during ligand screening in the previous carboetherification project, Dr. Luca Buzzetti (second author on the title paper) had observed the formation of the protodemetallation product as the by-product in presence of the DACH Phenyl Trost ligand (**L**) with very high asymmetric induction (Scheme 2). Therefore, the group decided to optimize this transformation. "To improve the yield of the protodemetallation product, the obvious solution was to omit the aryl iodide," explained Professor Waser. He continued: "However, using Ph-substituted internal propargylic amine as substrate did not deliver any protodemetallation product in the absence of aryl iodide. From the crude NMR of the reaction mixture, we could detect only the formation of tethered starting material. No cyclized product was observed when using Pd(II) salts as catalysts, with full recovery of the tethered starting material. This result clearly indicated the importance of an in situ formed ArPd(II) complex to promote the reaction." The authors of this study then decided to test a variety of aryl iodide derivatives with varying electronic and steric properties to see if they could switch the chemoselectivity towards the desired protodemetallation product, instead of the tetrasubstituted olefin product. Professor Waser remarked: "From the results, it was apparent that *ortho* substitution with a small potentially coordinating group (such as MeO, F) was beneficial for good yield and enantioselectivity."

With a major contribution from Dr. Ashis Das (first author on the title paper), the optimized conditions were applied to evaluate the scope of this transformation. "Both electron-rich and electron-poor substituents could be used on the *para*-



Scheme 1 Catalytically formed chiral auxiliary for the asymmetric synthesis of diaryl amino alcohols

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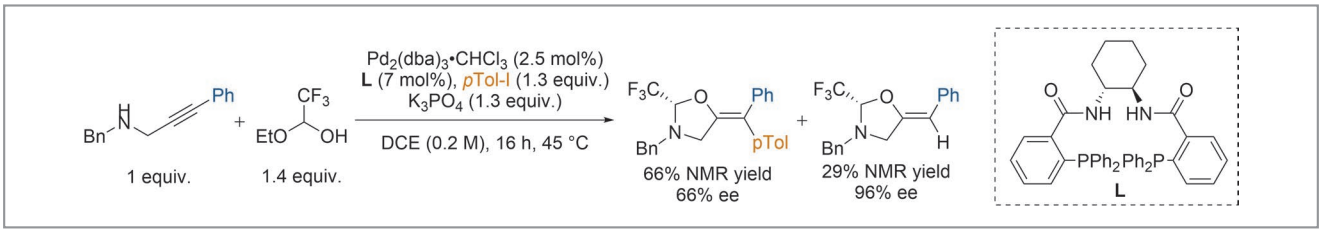
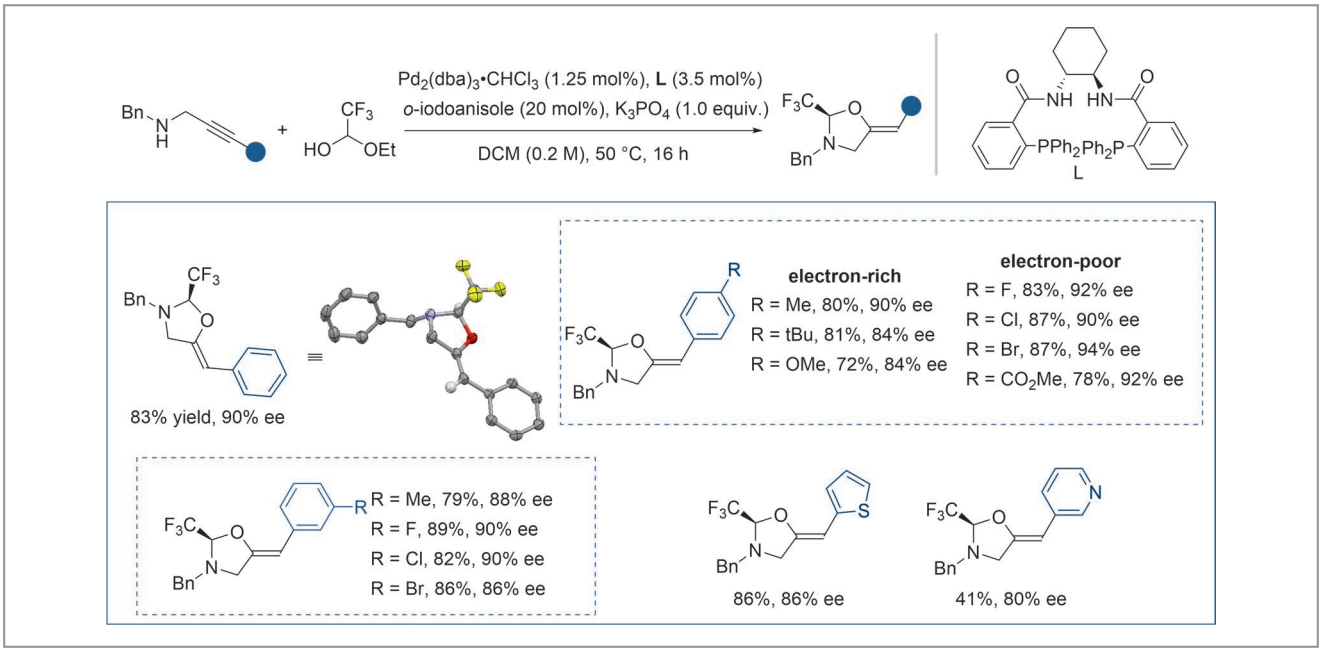


Scheme 2 Pd-catalyzed enantioselective oxyarylation of propargylic amines



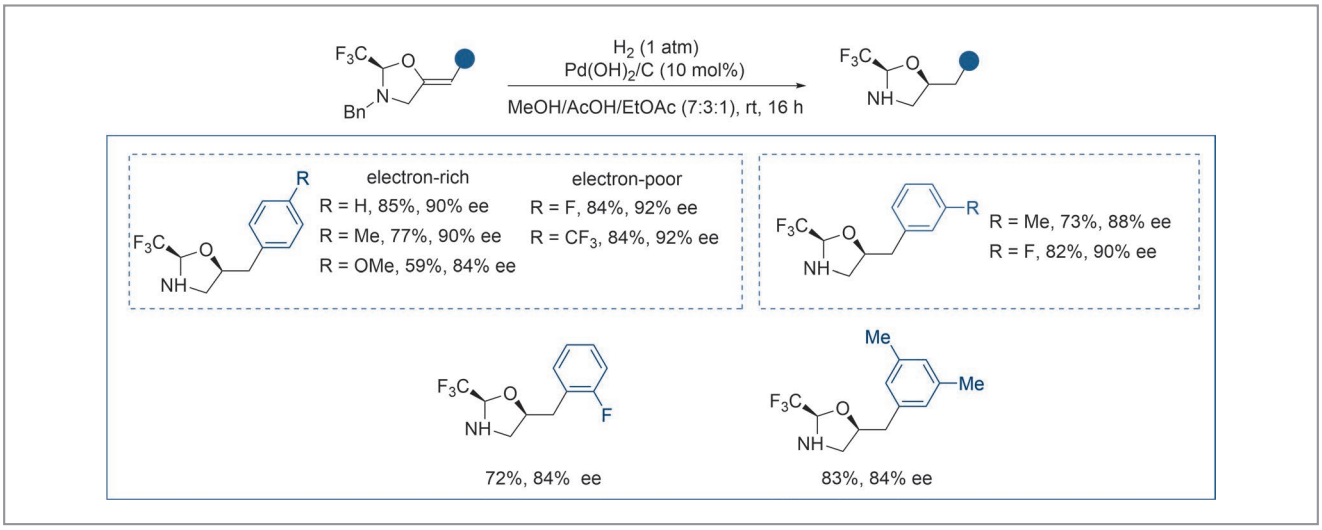
Scheme 3 Scope of the enantioselective cyclization – selected examples. Reactions performed on 0.4 mmol scale using 0.2 equiv. of aryl iodide and 1.4 equiv. of 1-ethoxy trifluoroethanol. Isolated yields and HPLC enantiomeric excess are given.

position of the aryl ring, and the products were obtained in 72–87% yield and 84–94% ee (Scheme 3)," explained Dr. Das. He added: "The reaction tolerated various functional groups such as halogens, ketones and esters at various positions on the aromatic ring. In addition, the reaction could be applied to substrates with heterocycles such as thiophene and pyridine on the alkyne."

The group then examined the stereoselective hydrogenation directed by the installed chiral oxazolidine and found that the hydrogenation worked well, without loss of enantiopurity, for a broad range of functional groups at different positions (Scheme 4).

"Concerning the promotion of the reaction by the aryl iodide additive, it would be difficult to understand why a more electrophilic palladium salt such as $PdCl_2$ or $Pd(OAc)_2$ would fail in the oxypalladation step," said Professor Waser. He continued: "Therefore, the aryl ligand may be important for accelerating the protodemetallation step by increasing the electron density on palladium. The potentially coordinating small *ortho* substituent may be important for promoting protodemetallation over reductive elimination. More in-depth mechanistic studies will be needed to elucidate the reaction mechanism and propose a model for stereo-induction and additive effects."

To conclude, Professor Waser remarked that his group have developed an effective palladium-catalyzed hydroalkoxylation of propargylic amines based on in situ tether formation, that is both economical and environmentally friendly. "Enantioenriched amino alcohol precursors were produced via diastereoselective hydrogenation driven by a chiral oxazolidine auxiliary that was catalytically generated," said Professor Waser. He concluded: "A key factor in the success of the



Scheme 4 Scope of the stereoselective hydrogenation – selected examples. Reactions performed on 0.2 mmol scale using $Pd(OH)_2/C$ (~20 wt%). Isolated yields and HPLC enantiomeric excess are given.

hydroalkoxylation reaction was the addition of an *ortho*-substituted aryl iodide to the reaction mixture, whose exact role in promoting the reaction is still unknown. The design and development of other enantioselective transformations based on the use of catalytically formed transient chiral auxiliaries are currently under investigation in our laboratory."

About the authors

Dr. L. Buzzetti

Luca Buzzetti was born in Morbegno, Italy, in 1990. He studied chemistry at the University of Pavia (Italy), where he obtained his Bachelor's (2012) and Master's (2014) degrees. From 2014 to 2018, he was a Ph.D. student under the supervision of Professor Paolo Melchiorre at the Institute of Chemical Research of Catalonia (ICIQ, Spain), where he worked on the development of enantioselective photochemical reactions. He then joined the group of Professor Jérôme Waser at EPFL (Lausanne, Switzerland) where he investigated asymmetric transition-metal-catalyzed reactions. Since 2020, he has worked as a R&D Lead Chemist at F.I.S. – Fabbrica Italiana Sintetici S.p.A.

Dr. A. Das

Ashis Das was born in West Bengal, India in 1994. He received his Bachelor's degree from Ramakrishna Mission Residential College Narendrapur, Kolkata (India) in 2015. He moved to the Indian Institute of Technology, Kanpur (India) for his Master's studies. In 2017, he received his Master's degree under the supervision of Prof. Basker Sundararaju. He joined the Waser group in 2017 to carry out his PhD. During his doctoral studies, he worked on the functionalization of alkenes and alkynes via tethering strategies. Graduating from EPFL (Switzerland) in 2022, he currently works at Sygnature Discovery, Nottingham, UK as a Scientist. He is currently working on medicinal chemistry projects in drug discovery.

M. Purinš

Mikus Purinš was born in Riga, Latvia, in 1994. He received his Bachelor's (2017) and Master's (2019) degrees in chemistry at Riga Technical University (Latvia) under the supervision of Professor Māris Turks. Currently, he is pursuing his doctoral degree under the supervision of Professor Jérôme Waser at the Swiss Federal Institute of Technology, Lausanne (EPFL), Switzerland. His current research interests include tethering strategies for selective functionalization of small molecules.

Prof. J. Waser

Jérôme Waser was born in Sierre, Valais, Switzerland, in 1977. He obtained his chemistry diploma at ETH Zurich (Switzerland) in 2001. From 2002 to 2006, he was a Ph.D. student at ETH Zurich with Professor Erick M. Carreira. He then joined Professor Barry M. Trost at Stanford University (USA) as an SNF postdoctoral fellow. From 2007 to 2014, he was an assistant professor at EPF Lausanne (EPFL). From 2014 to 2019, he was an associate professor at EPFL and since 2019 he is a Full Professor at EPFL. He is a recipient of the ERC Starting Grant (2013) and Consolidator Grant (2017), the Werner prize of the Swiss Chemical Society (2014), and the Springer Heterocyclic Chemistry Award (2016).

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Young Career Focus: Dr. Markus D. Kärkäs (KTH Royal Institute of Technology, Sweden)

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. Markus D. Kärkäs (KTH Royal Institute of Technology, Sweden).

Biographical Sketch

Dr. M. D. Kärkäs

Markus D. Kärkäs received his MSc degree from Stockholm University (Sweden) in 2008. In the same year he began his PhD studies under the direction of Professor Björn Åkermark at Stockholm University. His thesis concerned the development of artificial water oxidation catalysts. After receiving his PhD degree in 2013, he joined Professor Corey Stephenson's research group at the University of Michigan (USA) as a postdoctoral fellow. His postdoctoral work focused on the development of photochemical methods for valorization of lignin. In late 2016, he returned to the Department of Organic Chemistry at Stockholm University. In August 2018, he joined the Department of Chemistry at KTH Royal Institute of Technology (Sweden) as an Assistant Professor and was promoted to Associate Professor in March 2022. His research interests include photocatalysis, organic electrosynthesis, and transition-metal catalysis. He was awarded a Bürgenstock fellowship in 2018 and is a recipient of the 2022 Thieme Chemistry Journals Award.

INTERVIEW

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

Dr. M. D. Kärkäs Our research team focuses on developing novel and efficient synthetic methods for accessing valuable organic frameworks from relatively simple building blocks. The long-term goal is to contribute new advances to the strategies and tactics employed in organic synthesis. We are particularly interested in exploring sustainable technologies for accessing new chemical space within fundamental and applied research, in a more sustainable, safer, and cost-effective manner. Currently, research in our group focuses on addressing these challenges by leveraging the power of photocatalysis,[1] electrosynthesis[2,3] and transition-metal catalysis.[4–7] Especially, the former redox-modulating techniques provide the ability to selectively target functional groups in a molecule based on their different redox potentials. The use of low-energy visible light or electricity to mediate redox catalysis provides a platform for exploiting non-traditional bond constructions. This allows new bonds to be forged in a controlled and facile manner within the realm of green chemistry, affording a strategic paradigm for diversifying intermediates and final products.

SYNFORM *When did you get interested in synthesis?*

Dr. M. D. Kärkäs My interest in chemistry began in high school. During my undergraduate studies at Stockholm University, I was particularly lucky to have excellent lecturers who sparked my curiosity in the subject. Initially, I did not intend to pursue PhD studies (and particularly not in organic chemistry). However, like most practitioners of the art, during my master's studies, I was introduced to some of the most elegant and complex solutions in organic chemistry and was mesmerized. I became enthralled in the challenge of organic synthesis even though many (most?) of the experiments failed. Organic synthesis is an art where design and problem-solving are crucial components. Therefore, I decided to pursue PhD studies at Stockholm University (supervised by Prof. Björn Åkermark). Later, I expanded my chemistry horizons through postdoctoral research at the University of Michigan (supervised by Prof. Corey Stephenson). Collectively, all these experiences provided me with the skills for starting my independent career. Finally, I have been very fortunate throughout my graduate and postdoctoral studies to have had advisors

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who allowed me to carry out curiosity-driven research while also being incredibly supportive.

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

Dr. M. D. Kärkäs The modern world relies on organic synthesis in order to assemble the pharmaceuticals, agrochemicals and materials that are so pervasive in our modern society. Synthetic organic chemistry is a fascinating discipline that has been, and will continue to be, impactful across a range of research fields. Nevertheless, it will continue to draw inspiration from research advances in other disciplines, such as chemical biology, engineering, and physics. Organic synthesis is boundless and limited only by one's creativity, imagination, and persistence. The art of assembling and/or cleaving chemical bonds in a more controllable, effective, and sustainable manner continues to be an overarching objective. As a result, practitioners of organic synthesis have brought forward two of the most benign and versatile chemical reagents — electrons and photons. Albeit being broadly introduced recently, photocatalytic and electrosynthetic reaction manifolds have transformed the frontiers of forging bonds and expanded the repertoire of available activation modes. The development of more sustainable and cost-effective technologies for chemical processes could facilitate the transition from a fossil-based society to one that relies on renewable sources. Furthermore, automation and machine learning constitute additional areas that have the potential to fundamentally alter how synthetic chemists approach chemical challenges in the future. Ultimately, research advances in synthetic organic chemistry require synergy with other research disciplines, illuminating the essential role of collaborative, cross-disciplinary research endeavors.

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

Dr. M. D. Kärkäs As briefly mentioned above, our research team is pursuing three main topics: photocatalysis, electrosynthesis, and transition-metal catalysis (Scheme 1). Our research topics are constantly adapting with regard to the interests of our team members. Currently, free radical chemistry is a central theme as these intermediates can be leveraged to drive reactions that would otherwise be difficult to achieve through classical ionic/polar reaction manifolds. Traditionally, organic compounds have been assembled by reacting a pair of oppositely charged species — that is reacting a nucleophile, such as organomagnesium, with an electrophile, such as alkyl halide. However, the direct activation of native chemical bonds, such as carbon–hydrogen (C–H) and carbon–oxygen (C–O) bonds, represents a powerful strategy for improving the atom- and step-economy as well as streamlining chemical synthesis. The development of such controlled, modular functionalization platforms would significantly expedite non-traditional bond constructions and expand the synthetic repertoire.

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

Dr. M. D. Kärkäs Throughout the various stages of my research career, I am particularly pleased with some of the molecular single-site metal complexes, that were designed and developed during my PhD studies, which are capable of catalyzing water oxidation.[8,9] Furthermore, during my postdoctoral stay in the Stephenson group we were able to develop a redox-catalysis-based protocol for selective depolymerization of lignin, a recalcitrant and underexploited natural feedstock for aromatic commodity chemicals.[10] Recently, our research team initiated a project aiming at accessing unnatural α-amino acids.[11,12] We designed a redox-neutral photoredox-enabled approach for the stereoselective synthesis of α-amino acid derivatives (Scheme 1).[13] Here, unactivated carboxylic acids were employed as radical precursors and a metal-free acridinium catalyst was found to be the optimal photocatalyst. The developed protocol was applied to a variety of carboxylic acids and was shown to tolerate a diverse set of functionalities, including aliphatic and aromatic ethers and ketones; fluoro-, chloro-, and bromo-substituted aromatic substrates; aliphatic substrates containing CF_2, CF_3, and CCl_2 functionalities; and aryl cyanide- and alkyl aryl thioether-containing substrates. Gratifyingly, an array of pharmaceutically relevant compounds could also efficiently undergo decarboxylation, including cyhalofop, ciprofibrate, indomethacin, and diprogulic acid. Interestingly, intramolecular hydrogen bonding was not observed for the one-electron reduced species of the substrate (α-amino radical), thereby providing a rationale for the observed poor stereoselectivity when the reaction was conducted with a more reducing iridium-based photocatalyst. In collaboration with the Dinér group, our team recently exploited photoredox catalysis for synthesis of spiro-compounds. Here, a dearomative annulation approach was harnessed, involving C–O bond activation of aromatic carboxylic acids. Delightfully, the protocol could be extended to intermolecular tandem sequences involving C–O bond cleavage, radical addition to an alkene and 5-*exo*-trig cyclization, yielding complex spirocyclic lactam scaffolds.[14]

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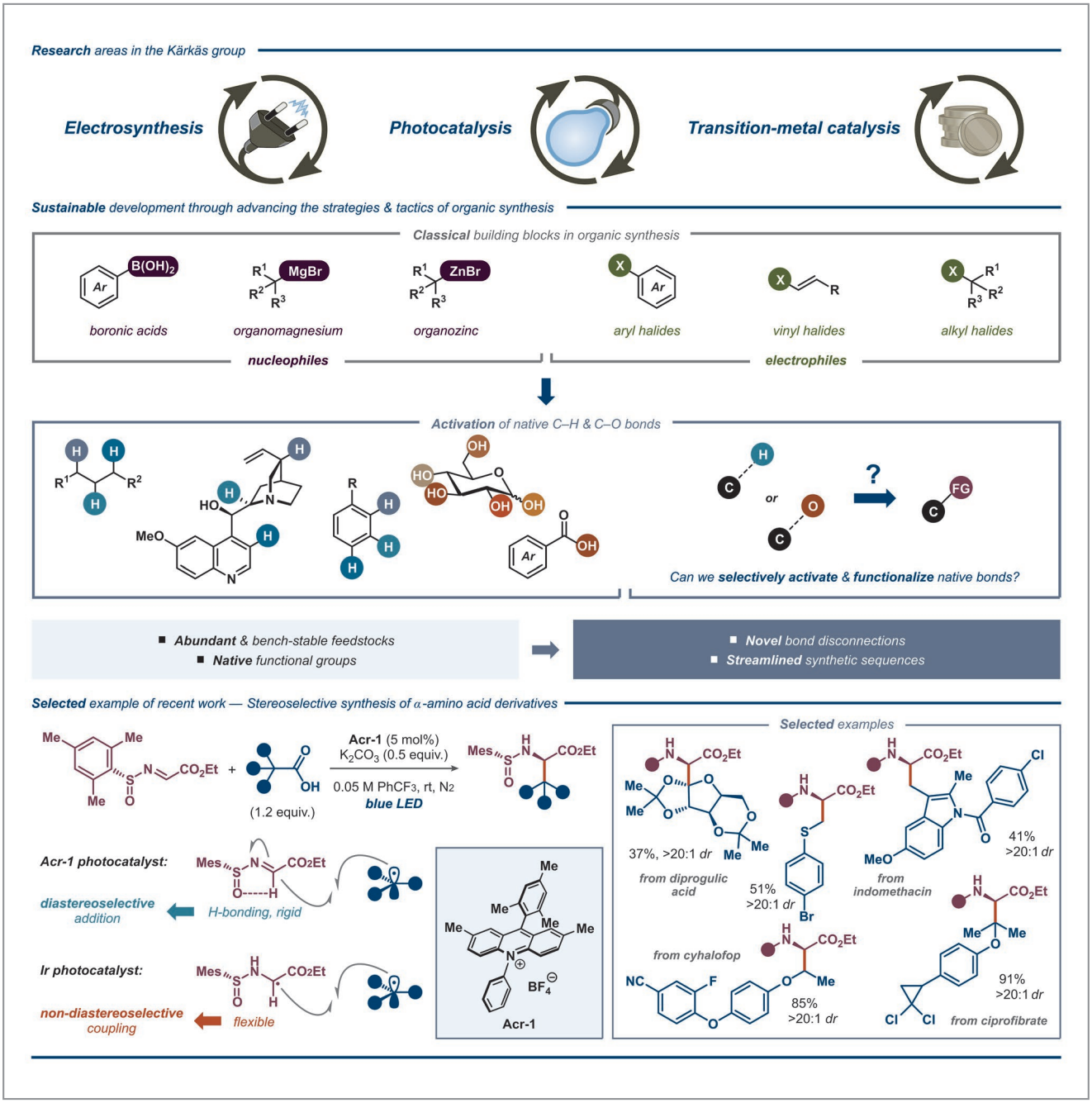
Personally, I am extremely proud of the ambitious and skilled young scientists that I have had the pleasure of working with throughout the years. Attracting a group of enthusiastic and talented scientists to establish a completely new lab and monitoring their scientific endeavors is a privilege. Mentoring is a privilege that one should take seriously. Thanks to the team members' curiosity and persistence, there are plenty of exciting projects in the pipeline.



Scheme 1 Research overview of the Kärkäs group

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S,O-Ligand Promoted *meta*-C–H Arylation of Anisole Derivatives via Palladium/Norbornene Catalysis

Angew. Chem. Int. Ed. **2022**, *61*, e202201750

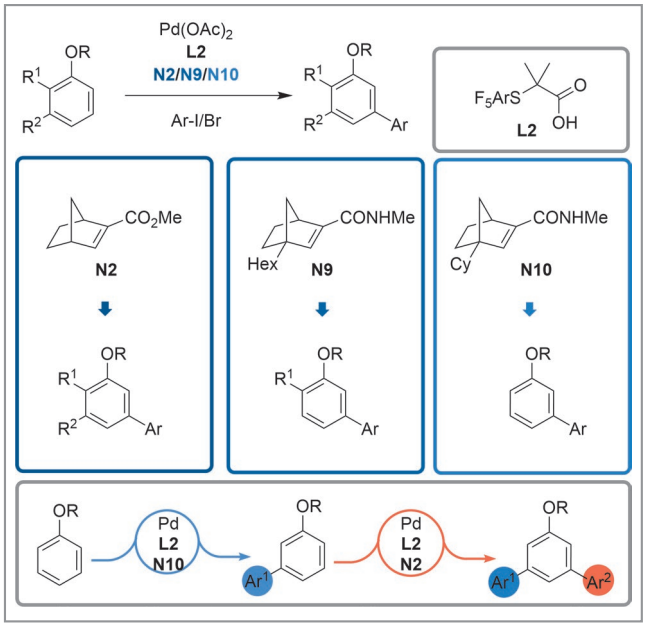
Palladium-catalyzed C–H functionalization reactions have become powerful synthetic tools in organic chemistry. However, most of the reported examples rely on the use of directing groups to increase the reactivity and selectivity of these processes. Only a few examples of efficient Pd-catalyzed C–H functionalization on non-directed arenes have been reported, and the presence of an external ligand is generally required.

The research group of Professor M. Ángeles (Tati) Fernández-Ibáñez at the University of Amsterdam (The Netherlands) has discovered a new type of *S,O*-ligand, namely thioether carboxylic acid, that can promote a variety of C–H functionalization reactions on non-directed arenes. "A unique feature of the Pd/*S,O*-ligand catalytic system is its high catalytic activity, enabling the functionalization of substrates that are unreactive using other catalysts," explained Professor Fernández-Ibáñez. She continued: "The site-selectivity of these processes is dictated by stereoelectronic effects, with the functionalization taking place at the most electron-rich position of the arene, similarly to electrophilic aromatic substitutions."

The functionalization of electron-rich arenes at the *meta*-position is challenging. Recently, the *meta*-arylation of anisole derivatives using palladium/norbornene (Pd/NBE) cooperative catalysis was reported for the first time (*J. Am. Chem. Soc.* **2019**, *141*, 14870–14877). Professor Fernández-Ibáñez commented: "However, in this manuscript several limitations were found, as for example the catalytic system did not work for anilines or for anisoles bearing electron-withdrawing substituents. As we experienced in our lab, these types of substrates are reactive in C–H functionalization processes using our Pd/*S,O*-ligand catalytic system (*J. Am. Chem. Soc.* **2019**, *141*, 6719–6725; *Eur. J. Org. Chem.* **2021**, *2021*, 4132–4135). Thus, we decided to investigate if we could overcome the limitations of the previously reported catalytic system by combining the Pd/*S,O*-ligand with an appropriate NBE."

Although the group's initial efforts on anilines were unsuccessful in obtaining the desired product, they were happy to see that under the conditions previously reported, anisole could be functionalized at the *meta*-position in high yields, demonstrating the compatibility of the Pd/*S,O*-ligand catalyst with NBE. "The high activity of the new catalytic systems allowed us to reduce the amount of Pd catalyst, and the NBE could be used in catalytic amounts, which is not very common in this type of transformation," said Professor Fernández-Ibáñez. She continued: "In addition, anisoles bearing electron-withdrawing substituents, which were previously unreactive, were also *meta*-functionalized. Furthermore, we found out that by using the appropriate NBE, we could perform the unsymmetrical meta-diarylation of anisole, which is in my opinion highly relevant, as it is difficult to achieve with an alternative synthesis using the simple anisole as starting material."

In addition to the methodology work, the group performed several experiments to obtain some insights about the mechanism of this transformation. "We were able to isolate the complex after the first C–H activation/NBE insertion, as well as the complex after the second C–H activation," revealed Prof. Fernández-Ibáñez, continuing: "We were surprised to see that the first C–H activation was not the rate-limiting step, which is generally the case, especially for non-directed C–H



Scheme 1 Direct synthesis of meta-arylated anisoles by reversing the conventional site-selectivity using the Pd/*S,O*-ligand catalytic system in conjunction with norbornene

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activation processes. We also observed that the presence of HFIP as solvent has a positive effect in the first C–H activation step. Although this behavior has been previously observed, the exact reason for this acceleration is still under debate and more research should be done in that direction."

"The field of C–H functionalization still has, after more than 20 years of research, a large number of challenges that need to be overcome," said Professor Fernández-Ibáñez. She concluded: "In the case of non-directed C–H functionalization reactions, the discovery of more active catalysts will be crucial for the development of new transformations such as those that involved electron-poor arenes. In addition, more active catalysts will also permit to reduce the catalyst loading, which is still too high in the majority of the reported methodologies for industrial applications. On the other hand, to achieve non-conventional selectivities, the use of NBEs as mediators is currently becoming a common approach. However, moving away from the NBE structure will open new possibilities for novel reactivities."

About the authors

V. Sukowski

Verena Sukowski started her academic career after working as a trained laboratory worker at Beiersdorf Ag (Hamburg, Germany) in the prototyping development of skin care products. She received her BSc degree in pharmaceutical chemistry from the TH Köln – University of Applied Sciences (Germany) in 2017, including one year research traineeship in the group of Prof. José R. Pedro (University of Valencia, Spain). She obtained her MSc in 2019 from the Vrije Universiteit Amsterdam, spending a year in the group of Prof. Eelco Ruiter (VU Amsterdam, The Netherlands). Currently, she is pursuing a Ph.D. with Prof. Fernández-Ibáñez (UvA Amsterdam, The Netherlands), investigating synthetic methodologies in the field of non-directed C–H functionalization.

M. van Borselen

Manuela van Borselen graduated from Leiden University of Applied Science (The Netherlands) with her Bachelor of Applied Science in Organic Chemistry (2017). After completing a chemistry premaster programme at the University of Amsterdam (Netherlands, 2018) she went on to become a technician in the Synthetic Organic Chemistry group at the University of Amsterdam in the group of Prof. Fernández-Ibáñez (2020).

Dr. S. Mathew

Simon Mathew received his Ph.D. in supramolecular photochemistry from Flinders University (Australia) with Assoc. Prof. M. R. Johnston in 2008. He has worked in Australia, Japan (JSPS fellow, Prof. Hiroshi Imahori), Switzerland (Profs. Michael Grätzel & Md. Khaja Nazeeruddin), USA (Visiting Fellow, Assoc. Prof. Jared Delcamp) and The Netherlands (Solardam Fellow, Prof. Joost Reek) developing research on topics including biofuels, dye-sensitized solar, phototherapeutics, metal-organic frameworks, gas separa-

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tion membranes, supramolecular chemistry, and light-driven catalysis. Currently, he is a laboratory manager within the van 't Hoff Institute for Molecular Sciences, managing the single-crystal X-ray diffraction facility and developing projects addressing bioinspired photoelectrocatalytic devices for sustainable chemical transformations, fuel production and self-assembled systems.

Prof. M. A. Fernández-Ibáñez

M. Ángeles (Tati) Fernández-Ibáñez is an Associate Professor in Organic Chemistry at the University of Amsterdam (The Netherlands). She received in 2006 her Ph.D. cum laude from Universidad Autónoma de Madrid (UAM), Spain, under the supervision of Prof. José L. García Ruano. During that period, she carried out a predoctoral stay in Boston College (USA), with Prof. Scott J. Miller. Subsequently, she joined as a postdoctoral researcher the group of Prof. Ben. L. Feringa at the University of Groningen (The Netherlands). After one year in the Medicinal Chemistry Institute at CSIC in Madrid (Spain), she moved to the UAM where she was appointed as Assistant Professor. In 2015 she took up a tenure-track position at the University of Amsterdam (The Netherlands) where she was promoted in 2017 to Associate Professor. Her research focuses on the development of new sustainable methodologies for the construction of complex organic molecules.

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Total Synthesis and Anti-inflammatory Activity of Stemoamide-Type Alkaloids Including Totally Substituted Butenolides and Pyrroles

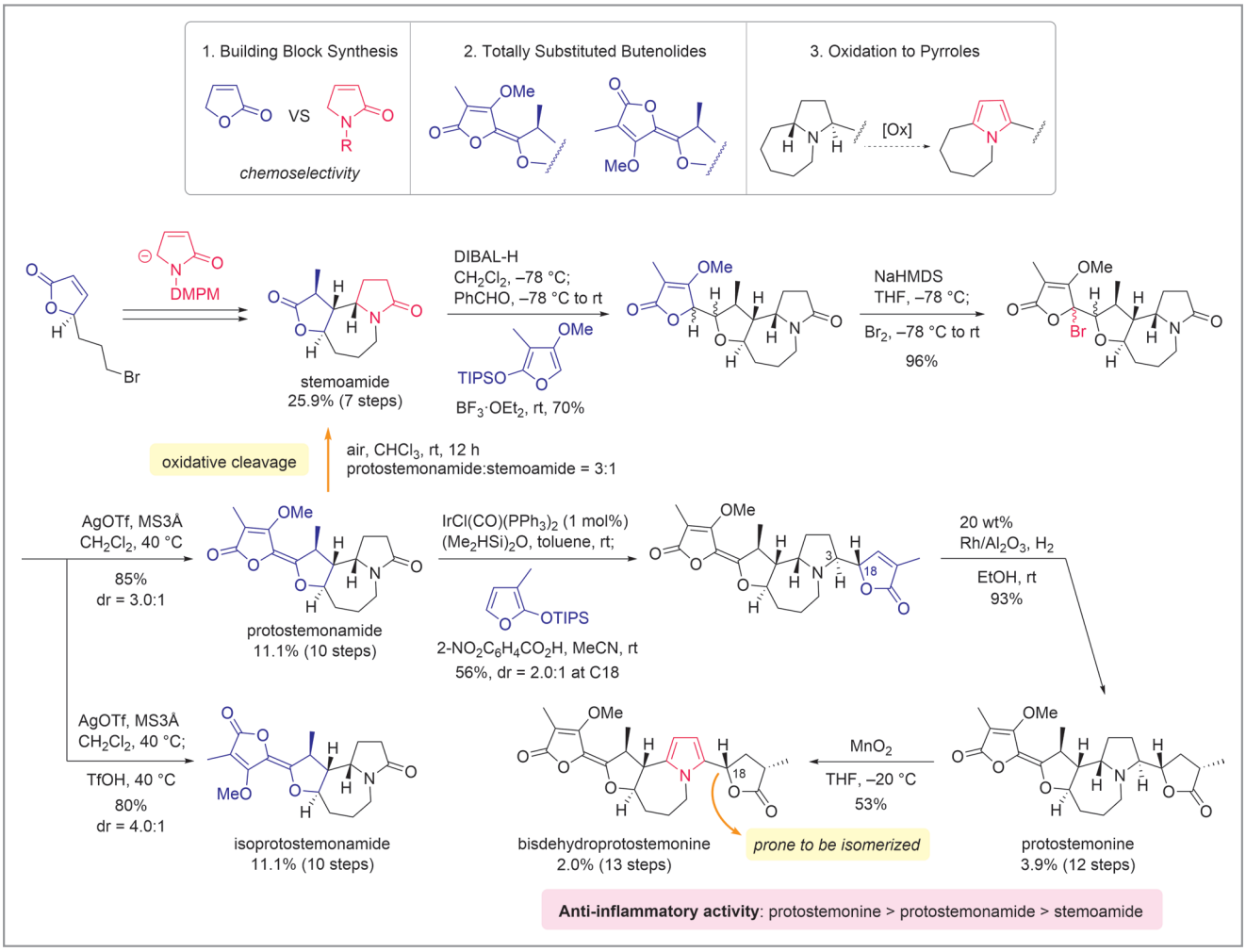
Synthesis **2022**, in press; DOI: 10.1055/a-1941-8680

Tricyclic stemoamide has been recognized as a very popular target for total synthesis. Indeed, many research groups have reported the total synthesis of this relatively simple natural product to demonstrate the utility of their own synthetic method. However, none had accomplished the total synthesis of the pentacyclic stemoamide-type natural products, despite the fact that pentacyclic protostemonine is known to show much better biological profiles, such as protective effects on acute liver failure and acute lung injury in mice. Some time ago, the group of Professor Takaaki Sato at Keio University (Yokohama, Japan) started a project that led to the publication of this SYNTHESIS paper. Professor Sato explained: "In this study, we developed three key methods: 1) the chemoselective assembly of five-membered building blocks by iridium-catalyzed reductive nucleophilic addition (examples: *J. Am. Chem. Soc.* **2017**, *139*, 18386–18391; *Org. Lett.* **2020**, *22*, 7502–7507), 2) the three-step stereodivergent synthesis of the totally substituted butenolides, and 3) the direct oxidation of the pyrrolidine groups to the corresponding pyrroles with MnO_2. These methods enabled us to achieve the unified total synthesis of stemoamide-type alkaloids and demonstrate the systematic structure–activity relationship involving the anti-inflammatory activities by inhibition of iNOS expression in macrophage cell line RAW264.7. We believe that our study opens up a whole new research chapter in the field of *Stemona* alkaloids, in terms of both synthesis and biological activity."

Professor Sato recalled that the original idea of this project arose in 2013. He commented: "My kid, two years old at that time, showed no interest in my research, but loved LEGO®-blocks. I thought: 'OK, my kid is playing with LEGO®-blocks, and his dad is playing with building blocks in chemistry. He would love me and my job!'" Professor Sato's motivation was simple, but as he commented, a project must contribute to solving issues in modern organic synthesis, in this case, the building block synthesis of stemoamide-type alkaloids by precise control of the chemoselectivity (amide vs ester). "I am very proud of my students, who have made accomplishments based on the initial rough sketch of my ideas," said Professor Sato. He continued: "I also appreciate the contribution of the groups of Prof. Urabe, Prof. Oishi and Prof. Simizu, who are wonderful collaborators. Unfortunately, total synthesis takes time. My kid grew up quickly, and is not playing with LEGO®-blocks anymore."

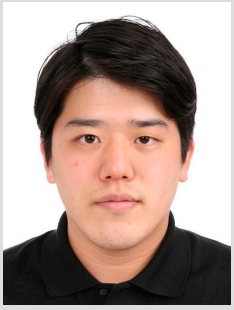
Mr. Soda, first author on the paper, said: "I felt very confident that our team would achieve this project when I found that the bromo group could be regioselectively installed into the tetracyclic intermediate, derived from tricyclic stemoamide. However, that was just the beginning." Mr. Soda explained that the most difficult part was the instability of each natural product. The following silver-mediated elimination provided tetracyclic protostemonamide, including the totally substituted butenolide. "I was so excited, and collected the NMR data overnight," remarked Mr. Soda. He went on: "I went to the NMR room to pick up the sample the next day and realized that the color of the sample had gained yellow. Reexamination of the TLC and NMR revealed that most of the sample had returned to the tricyclic stemoamide. It was a nightmare. Our sample spontaneously reverted back." Subsequently, Mr. Soda found that the oxidative cleavage of the tetrasubstituted olefin took place under aerobic atmosphere. The oxidation of the pyrrolidine group was also a tough step. "After oxidation of the pyrrolidine, the crude sample was pure, but various attempted purifications always led to the isomerization of the desired product," said Mr. Soda. He continued: "Finally, I obtained the pure spectroscopic data by super-quick filtration through a short pad of basified silica gel (1% Et_3N) within 20 seconds, and subsequent GPC (Gel Permeation Chromatography). Do not forget filtration of $CDCl_3$ through basic alumina before use upon measuring NMR. I learned a lot from these tough natural products."

Professor Sato said: "The key to success of this project was the development of nucleophilic addition to amide carbonyls. This reaction had received less attention than their construction due to their high stability. However, an amide group is one of the most abundant functional groups in organic synthesis, which means that it has a high potential for a broad range of applications such as total synthesis of complex natural products, late-stage modification of peptides and proteins, and supply of functional materials." Professor Sato concluded: "Currently, a number of research groups – including our group – have been engaged in this field, and further significant progress will be made in the near future."



Scheme 1 Unified total synthesis and anti-inflammatory activity of stemoamide-type alkaloids

About the authors



Y. Soda

Yasuki Soda received his B.Sc. degree in 2018 from Keio University (Japan) and his M.Sc. degree in 2020 from the same university under the direction of Professors Noritaka Chida and Takaaki Sato. He is currently pursuing his Ph.D studies in building block strategy for the synthesis of biologically active compounds in Professor Sato's group.

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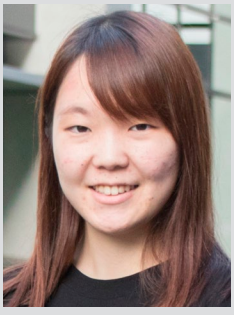

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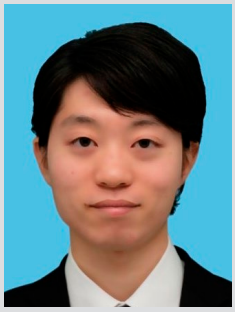

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Makoto Yoritate received his B.Sc. degree in 2013 and his Ph.D. degree in 2018 from Keio University (Japan); his PhD was under the direction of Professors Noritaka Chida and Takaaki Sato. He received a JSPS fellowship from 2015 to 2018. He spent two months in 2017 as a JSPS Research Fellow in Prof. Brian M. Stoltz's group (Caltech, USA). He was a postdoctoral researcher at the University of California, Berkeley (USA) with

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Professor John. F. Hartwig as a Naito Overseas research fellow (2018–2019). In 2019, he joined the faculty at Graduate School of Pharmaceutical Science, Kyushu University (Japan) as an assistant professor. He was awarded the Inoue Research Award for Young Scientists in 2020.

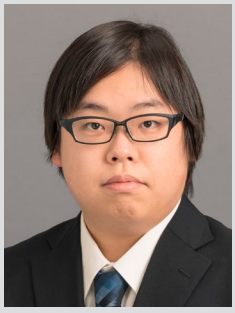
Dr. K. Fukaya

Keisuke Fukaya obtained his B.Sc. degree from Keio University (Japan) in 2012, where he conducted undergraduate research with Professor Noritaka Chida. He received his Ph.D. from the same university for work in natural product synthesis under the joint supervision of Professors Noritaka Chida and Takaaki Sato (2017). He then conducted post-doctoral research under Professor Michael J. Krische at the University of Texas at Austin (USA). In 2018, he joined the faculty at Toyama Prefectural University (Japan) as an Assistant Professor. His research focuses on computational approaches for the efficient synthesis of complex natural products.

Dr. D. Urabe

Daisuke Urabe received his Ph.D. degree in 2006 from Nagoya University (Japan) under the supervision of Professors Minoru Isobe and Toshio Nishikawa. He then carried out post-doctoral research with Professor Yoshito Kishi at Harvard University (USA) in 2006–2007. In 2008, he moved to the University of Tokyo (Japan) as an assistant professor in the research group of Professor Masayuki Inoue and was promoted to a lecturer in 2013. In 2017, he moved to Toyama Prefectural University (Japan) as a professor to start his independent career. He was awarded the Young Scientist's Research Award in Natural Product Chemistry in 2013, the Thieme Chemistry Journals Award in 2014, and The Pharmaceutical Society of Japan Award for Young Scientists in 2015. His research interests include the total synthesis of natural products, and theoretical chemistry of complex reaction systems.

Takeshi Oishi received his Ph.D. degree in 2002 from Keio University (Japan) under the supervision of Professor Noritaka Chida. Then he worked at the National Institute of Advanced Industrial Science and Technology (AIST, Japan) as a research fellow for two years. In 2005, he joined the School of Medicine, Keio University (Japan) as an assistant professor.



Dr. K. Mori

Kento Mori received his B.Sc. degree in 2017, and his Ph.D. degree in 2022 from Keio University (Japan) under the supervision of Professor Siro Simizu. He joined the Department of Applied Chemistry, Keio University as a research associate in 2021, and currently works with Professor Simizu.

Professor S. Simizu

Siro Simizu received his B.Sc. degree in 1993 from Keio University (Japan), and his Ph.D. degree in 1998 from the same university under the supervision of Professors Kazuo Umezawa and Masaya Imoto. He spent 12 years in Professor Hiroyuki Osada's group at RIKEN (Japan) as a researcher. He joined the Department of Applied Chemistry, Keio University as a lecturer in 2010. He was promoted to Professor in 2017. He was awarded the Young Investigator Awards of the Japanese Cancer Association in 2004, and the Young Investigator Awards of the Japanese Association for Metastasis Research in 2011.

Professor N. Chida

Noritaka Chida received his B.Sc. degree in 1979 from Keio University (Japan), and Ph.D. degree in 1984 from Tohoku University (Japan, under Professor Akira Yoshikoshi). From 1984 to 1987, he worked for Mercian Co. Ltd., as a researcher. In 1987, he joined the Department of Applied Chemistry, Keio University as a research assistant, and in 1988–1989, he spent one year as a postdoctoral researcher at the University of Pennsylvania (USA) with Professor A. B. Smith, III. He was promoted to Professor of Keio University in 2003. He retired in 2022, and is currently professor emeritus at Keio University. He was awarded the "BCSJ Award" from the Chemical Society of Japan in 2002, 2015 and 2017, and the Keio Gijuku award in 2021.

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Professor T. Sato

Takaaki Sato received his B.Sc. degree in 2001 from Tohoku University (Japan) and his Ph.D. degree in 2006, also from Tohoku University (supervisor: Professor Masahiro Hirama). He spent two years in Professor Larry E. Overman's group at the University of California, Irvine (USA) as a JSPS fellow. He joined the Department of Applied Chemistry, Keio University (Japan) as an assistant professor in 2008. He was promoted to Associate Professor in 2016. In 2022, he started his independent career at Keio University. He was awarded the Otsuka Pharmaceutical Co. Award in Synthetic Organic Chemistry, Japan in 2008, the Young Scientist's Research Award in Natural Product Chemistry in 2014, the Incentive Award in Synthetic Organic Chemistry, Japan in 2016, and the Thieme Chemistry Journals Award in 2019.

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