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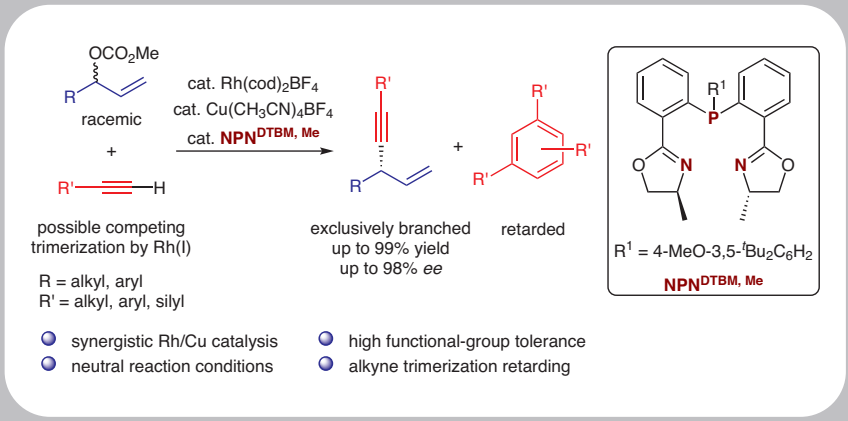
Regio- and Enantioselective Allylic Alkylation of Terminal Alkynes by Synergistic Rh/Cu Catalysis

Highlighted article by W.-Y. Huang, C.-H. Lu, S. Ghorai, B. Li, C. Li



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Dear Readers,

A new year almost inevitably brings novelties and changes, which should be particularly welcome this year, as 2021 will hopefully be very different from its troubled predecessor. But for me the new year is definitely going to be very different, and if I can – for once – add a personal note to this first editorial of 2021, I would like to announce that after nearly 12 fantastic and rewarding years in the United Kingdom, I have decided to return to Milan, Italy. There will always be a special place in my heart for Scotland, a truly wonderful country, but the UK has changed a lot during the past decade and a convinced and enthusiastic pro-European like me could not continue to pretend that everything was alright after Brexit. So, here I am, back in the mainland Old Continent and ready for an exciting new challenge. Amidst all these changes, one thing that will remain constant is my commitment to SYNFORM.
I hope this will be very clear from the start, namely from this first 2021 issue: the thoroughly deserved honour of the first article is all for R. Gilmour and J. J. Molloy (Germany) with their ground-breaking *Science* article on the boron-enabled geometric isomerization of alkenes. The following Literature Coverage article is another outstanding Science paper – by M. Sawamura (Japan) – and again involves the use of boron, in this case for the iridium-catalyzed asymmetric remote C–H borylation of aliphatic amides and esters. The third article comes from the labs of C. Li (P. R. of China) and covers the regio- and enantioselective Rh/Cu-catalyzed allylic alkylation of terminal alkynes. The issue is wrapped up by a very interesting Young Career Focus interview with our first up-and-coming researcher, M. Pawlicki (Poland).

Enjoy your reading!

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Boron-Enabled Geometric Isomerization of Alkenes via Selective Energy-Transfer Catalysis

Science **2020**, *369*, 302–306

Simple alkene fragments are important constituent building blocks in many biological processes where geometry often underpins function. Retinal (vitamin A) is an excellent example where the geometric isomerization is the basis of the one–zero switch in human vision. Achieving spatiotemporal control over alkene geometry in a laboratory paradigm represents a fundamental yet significant challenge for the group of Professor Ryan Gilmour at the Westfälische Wilhelms-Universität Münster (Germany). "There are numerous methods to generate stereo-defined alkene fragments for complex polyene synthesis, but these reactions often suffer from poor selectivity, and typically require independent synthesis of both isomers. An isomerization strategy (Figure 1) would be advantageous," said Professor Gilmour.

Professor Gilmour's group has been exploring energy transfer catalysis, which provides a potentially expansive solution to this fundamental problem in enabling readily accessible *E*-alkenes to be isomerised to their more challenging *Z*-forms (for references see the original article). However, Professor Gilmour noted: "These approaches come with some notable limitations, including the need for a bulky styrenyl chromophore to achieve efficient, selective energy transfer from an excited state photosensitizer to the substrate."

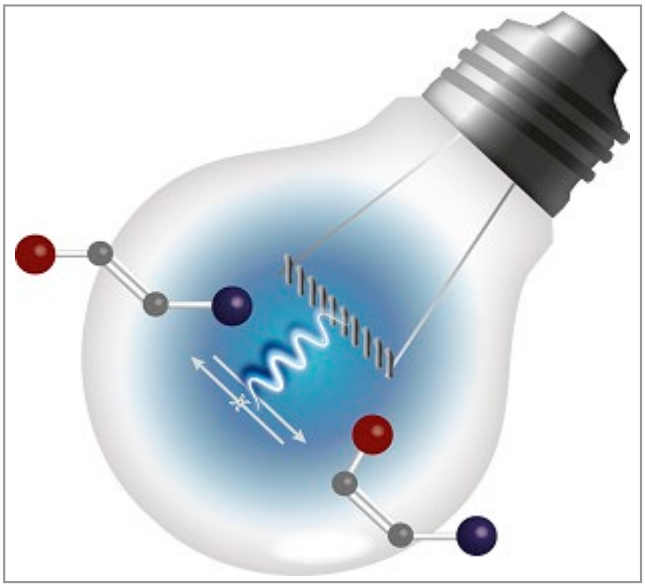

Figure 1 *E* → *Z* photoisomerization of simple alkenes

Similarly, the group found that substituents were required to achieve high levels of stereoselectivity due to the generation of 1,3-allylic strain. "Stereo-defined polyenes are common in bio-active small molecules and serve as potent therapeutics such as alitretinoin and isotretinoin, which are themselves attractive synthetic targets," explained Professor Gilmour. He continued: "However, polyenes typically lack styrenyl chromophores and bulky α-substituents. As site-selective geometric isomerisation of polyenes by energy-transfer catalysis is underdeveloped, developing simple alkene fragments that readily undergo photocatalytic isomerization would provide a solution. A key consideration was identifying ambiphilic systems to enable iterative coupling for the programmable synthesis of geometrically defined polyenes."

Addressing this challenge, the operationally simple isomerization of small ambiphilic β-boryl acrylates was realized by the Gilmour group with excellent selectivity using thioxanthone as an inexpensive organic photocatalyst (Scheme 1). "We believed introduction of the boronic ester motif would enable a boron-gating mechanism in which the boron p-orbital plays a pivotal role in modulating energy transfer," explained Dr John Molloy, who is the first author of the study. He told SYNFORM: "In conjugation, energy transfer is efficient; however, after a 90° rotation the p-orbital is perpendicular, and this enables directionality. Due to the popularity of organoborons and carbonyl compounds in synthetic chemistry, these geometrically defined fragments are versatile."

Concerning the applications and future perspectives of this groundbreaking methodology, Professor Gilmour noted that it lends itself to programmable polyene synthesis. "We demonstrated that with expedient access to both isomers, a modular synthesis of stereodefined polyene therapeutics such as alitretinoin and isotretinoin could be realized. By extension, this chemistry could be further incorporated into the synthesis of various natural and unnatural polyenes," said Professor Gilmour. He continued: "In addition, the traceless boron motif provides a synthetic handle for downstream stereospecific manipulations and so I believe that these densely functionalized, geometrically defined alkene fragments will

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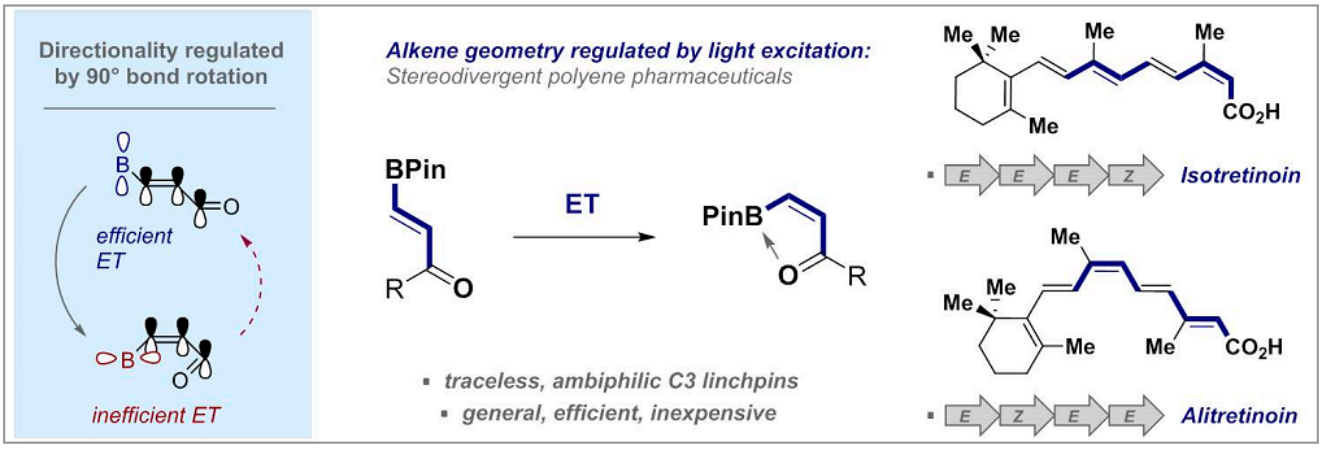

Scheme 1 An overview of the photocatalytic isomerisation of ambiphilic β-borylacrylates for the programmed construction of complex polyenes

serve as useful synthons in organic synthesis. Similarly, isomerization-enabled stereodivergence serves as a platform to branch into new 3D chemical space as demonstrated in the Diels–Alder reaction." The Gilmour group believes that expedient, operationally simple access to both fragments will lead to more stereodivergent transformations with application in synthetic sequences.

Professor Gilmour concluded: "From the perspective of stereospecific alkene functionalization, this platform is attractive in enabling stereo-divergence from common building blocks, thereby circumventing the current need to prepare both alkene isomers independently."

About the authors

Dr. J. J. Molloy

John J. Molloy was born in Glasgow where he obtained his Master's degree under the supervision of Dr. Allan Watson at the University of Strathclyde (UK, 2014). This included a research stay at the Beatson Institute for Cancer Research (UK). He continued his doctoral studies with Dr. Watson at Strathclyde (2018), which included a short secondment with Prof. Ryan Gilmour at the Westfälische Wilhelms-Universität Münster (Germany). After a short research stay at the University of St Andrews (UK), John returned to WWU as an Alexander von Humboldt Post-doctoral research fellow in the group of Prof. Gilmour (2018).

M. Schäfer

Michael Schäfer was born in Stadtlohn, Germany. He obtained a B.Sc. degree from the Westfälische Wilhelms-Universität Münster (Germany) under the supervision of Prof. Andrea Rentmeister (2016). After a short research stay at the University of California Irvine (USA) under the supervision of Prof. Chris Vanderwal, he obtained his M.Sc. degree at the WWU in the group of Prof. Ryan Gilmour (2018) where he is currently a second year doctoral student.

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M. Wienhold

Max Wienhold was born in Lohne (Germany) and obtained his B.Sc. degree at the WWU Münster (Germany), supervised by Prof. Ulrich Hennecke (2017). After a short research stay at the University of St Andrews (UK), working with Prof. Andrew D. Smith he obtained his Master's degree under the supervision of Prof. Ryan Gilmour (2019). He continued his doctoral studies in the group of Prof. Gilmour and is currently a first year doctoral student.

T. Morack

Tobias Morack was born in Berlin (Germany) and attended Humboldt-Universität zu Berlin (Germany). He received his B.Sc. degree in 2015 after completing his thesis work under the supervision of Prof. Stefan Hecht. He then moved to the Westfälische Wilhelms-Universität Münster (Germany) to complete his Master's degree (2017) including a research stay at the University of Cambridge (UK) working with Prof. Steven V. Ley FRS and an industrial stay at Bayer AG in Wuppertal (Germany). Tobias is currently a third-year doctoral student at the WWU Münster working with Prof. Gilmour.

Dr. C. G. Daniliuc

Constantin G. Daniliuc was born in Romania and received his Diploma in 2002 at the University 'Al. I. Cuza'Iasi (Romania). He moved to the Technical University of Braunschweig/ Institute of Inorganic and Analytical Chemistry (Germany) for his Master's studies as a beneficiary of an Erasmus/Socrates Scholarship and received his Ph.D. from the same university in 2008 under the supervision of Professor W.-W. du Mont. Since 2012, he has been Head of the Crystallographic Laboratory of Organic Chemistry Institute at WWU University of Münster (Germany), where is associated with several projects in Prof. Gilmour's research group.

Prof. R. Gilmour

Ryan Gilmour was born in Ayrshire, Scotland (UK, 1980) and was educated at the universities of St Andrews and Cambridge (both in the UK). He held research fellowships at the Max-Planck-Institut für Kohlenforschung (Germany, with A. Fürstner) and the ETH Zürich (Switzerland, with P. H. Seeberger) before being appointed as Alfred-Werner-Assistant-Professor of synthetic organic chemistry at the ETH Zürich (2008-2012). In 2013 he moved to the WWU Münster (Germany) where he is Chair of Organic Chemistry and CiMIC Professor of Chemical Biology. He is the recipient of several awards including the Ruzicka Prize, ERC Starter (2013) and Consolidator Grants (2019), and the current holder of the Prof. David Ginsburg Lecturership at the Technion (2020-2021).

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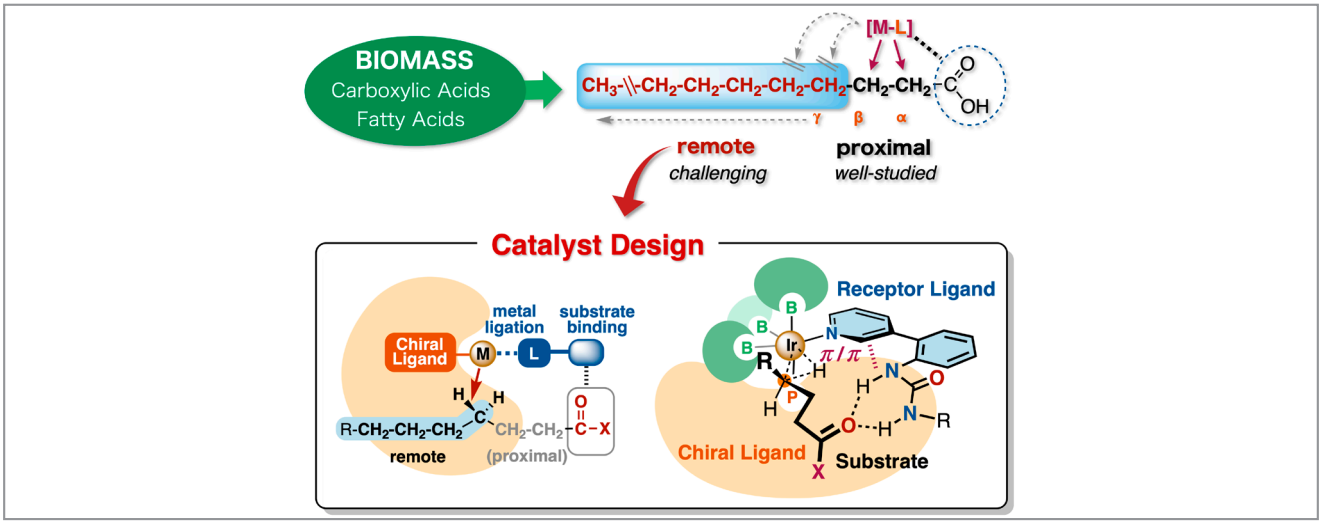
Asymmetric Remote C–H Borylation of Aliphatic Amides and Esters with a Modular Iridium Catalyst

Science **2020**, *369*, 970–974

Aliphatic carboxylic acids and their derivatives such as amides, esters and the longer-chain fatty acids are widely distributed and abundant in nature, with their paramount importance prominently reflected in a variety of natural products, bioactive molecules and pharmacologically relevant compounds. "These renewable biomass resources are attractive precursors for the production of industrially significant materials, including plastics, as well as for the synthesis of drugs and other therapeutically important compounds," said Professor Masaya Sawamura from Hokkaido University (Sapporo, Japan). He continued: "In this context, the direct modification within the hydrocarbon framework of these readily available feedstock chemicals via C–H activation is an appealing strategy in accessing structurally diverse derivatives, compared to presently used methodologies which rely on tedious elaborations through traditional and costly transformations." According to Professor Sawamura, while the direct and selective activation of C–H bonds in these raw materials represents a more environmentally friendly and step-economic process, current strategies are limited to the functionalization of proximal C–H bonds located one or two carbons away (α or β) from the carbonyl group (Scheme 1). "Chemical modification of remote C–H bonds is far less developed and presently available techniques target terminal γ-methyl C–H only. An ultimate goal is the development of a catalytic enantioselective approach that will enable the functionalization of C–H bonds at a single methylene site beyond the β-position, providing structurally diverse chiral compounds, a type of reactivity that natural enzymes can facilitate efficiently," he added.

Professor Sawamura and co-workers from his organometallic chemistry research group recently reported a modular iridium catalyst that allows the activation – and subsequent borylation – of γ-methylene C–H bonds located three carbons away from the carbonyl group of aliphatic esters and amides, giving chiral alkyl organoboronates.

Professor Sawamura's group has been working tirelessly on the development of novel synthetic organic reactions using carefully designed, high-performing catalysts to enable the realization of efficient molecular transformations. As part of their C–H functionalization program, they have previously developed a catalytic borylation protocol using heterogeneous silica-supported monophosphines as ligands (*J. Am. Chem. Soc.* **2013**, *135*, 2947–2950; *J. Am. Chem. Soc.* **2012**, *134*, 12924–12927; *J. Am. Chem. Soc.* **2011**, *133*, 19310–19313; *J. Am. Chem. Soc.* **2009**, *131*, 5058–5059). In 2017, the Sawamura group reported that this catalytic borylation can



Scheme 1 Catalyst design concept for the activation of remote γ-methylene C–H bonds in carboxylic acid derivatives

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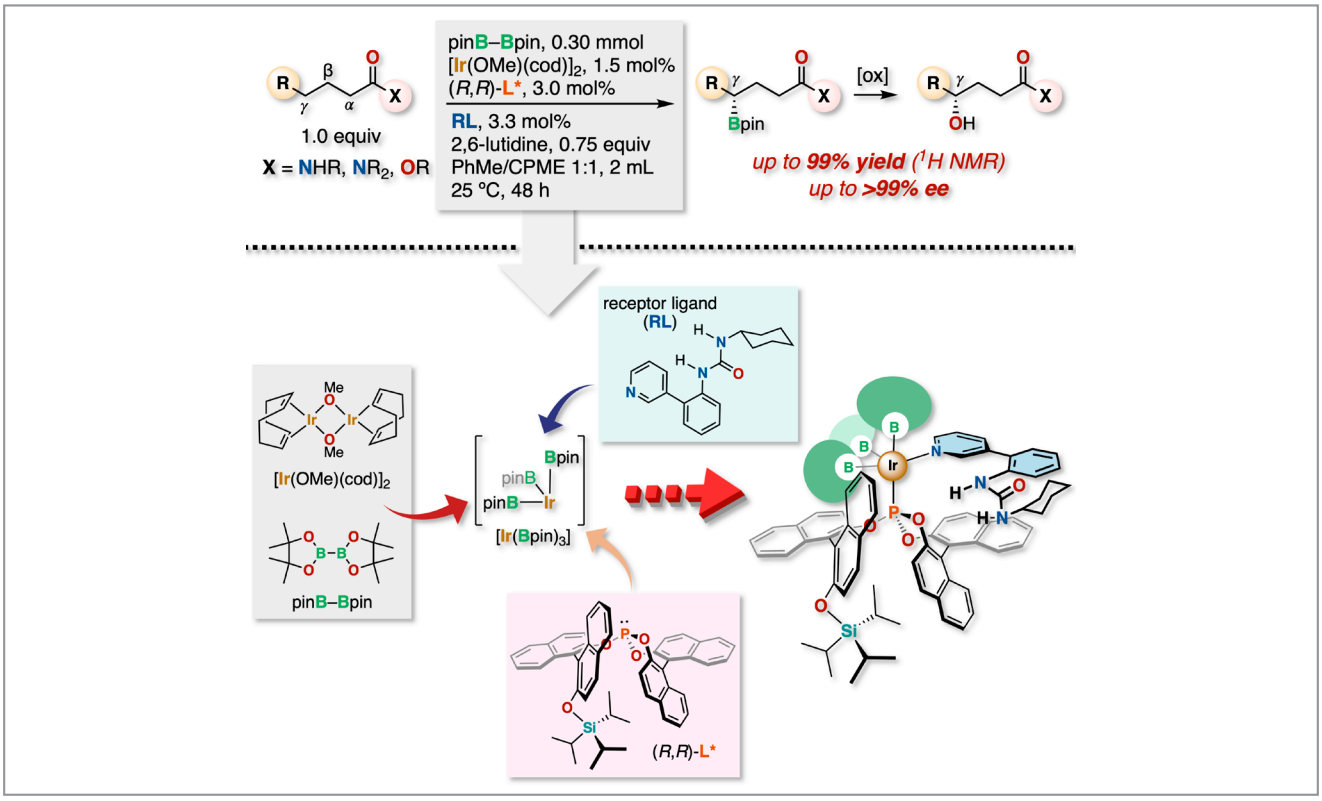
also be achieved under homogeneous catalysis using chiral phosphoramidite ligands, albeit with moderate enantioselection (*Chem. Lett.* **2017**, *46*, 1747–1750). Professor Sawamura remarked: "This preliminary result inspired us to look into a different catalyst architecture to realize a completely enantioselective reaction. Following extensive experimental and computational collaborative works, we disclosed the discovery of an innovative iridium-catalyst system based on a sterically demanding monophosphite ligand bearing an atropisomeric silyloxy-modified binaphthyl backbone. Remarkably, this type of catalyst exerts excellent enantioselectivities (up to 99% ee) in the highly challenging differentiation of enantiotopic unactivated methylene C(sp^3)–H bonds in acyclic alkyl groups (*J. Am. Chem. Soc.* **2019**, *141*, 6817–6821). It also allows for the direct site- and enantio-selective borylation of *N*-adjacent methylene C(sp^3)–H bonds in a wide range of substrate classes, including pharmaceutical agents, even enabling the straightforward synthesis of the clinically important anticancer drug *bortezomib* (*J. Am. Chem. Soc.* **2020**, *142*, 589–597)." Professor Sawamura noted that crucial to the reactivity of this catalytic system is the creation of a chiral reaction pocket for substrate accommodation, along with the generation of weak attractive interactions contributing to the overall stabilization of the transition state, a feature analogous to catalytic pockets of enzymes. "These successes have been instrumental in proposing an entirely different approach in the design of a catalytic system that is suitable for the remote C–H activation in aliphatic carboxylic acid derivatives. Through molecular modelling, my group envisaged that the metal-coordinating pyridine and the metal-activated C–H bond site – which in our previous studies were linked intramolecularly in the chiral catalytic pocket – might be replaced with a heterodimer composed of a pyridine derivative (receptor ligand) covalently connected to a noncovalent interaction donor moiety through an appropriate spacer and a C(sp^3)–H borylation substrate having a complementary functional group (Scheme 1). Thus, the modular catalyst is assembled in situ, using 1:1 toluene (PhMe)/cyclopentyl methyl ether (CPME) as the solvent system, from [Ir(OMe)(cod)]$_2$, bis(pinacolato)diboron, a chiral monophosphite ligand, and a pyridine receptor ligand endowed with a urea function for substrate binding in the second coordination sphere via hydrogen-bonding interaction (Scheme 2)."



Scheme 2 Modular assembly of the chiral catalyst for the remote γ-methylene C–H bond borylation of aliphatic carboxylic acid derivatives

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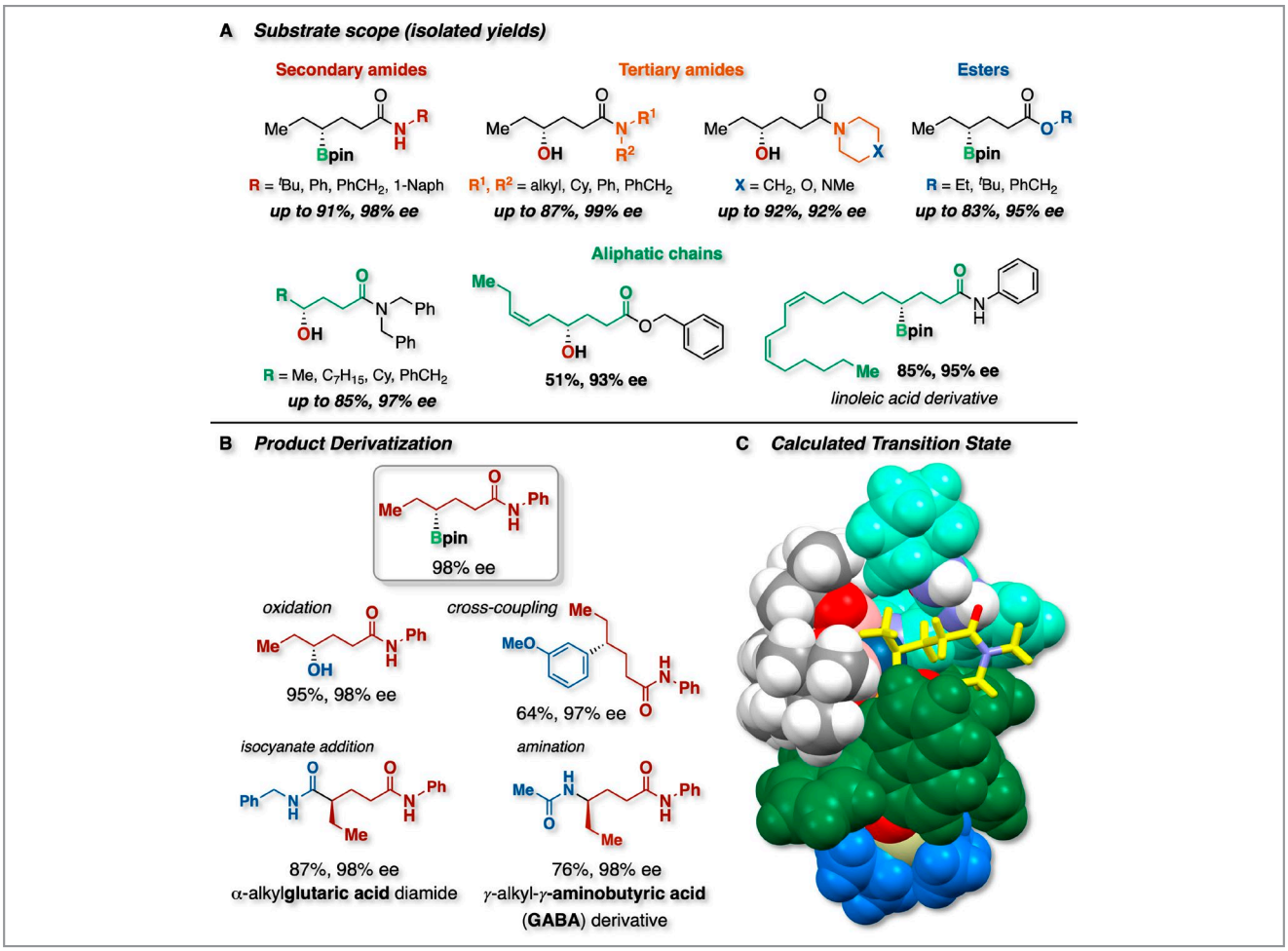
explained Professor Sawamura. He continued: “During the course of reaction development, the structure of the urea-pyridine ligands proved to be critical in determining site selectivity and driving reactivity. Alterations to the linker or spacer or utilization of isomeric pyridyl ligands led to diminished reactivity (up to 17% γ-borylation was observed) and shifting of the site selectivity towards β-C–H bonds, indicating that the remote directing efficiency heavily relies on the design of the receptor ligand. The reactions were performed at 25 °C (up to 99% yield and >99% ee), optimization experiments showed a negative temperature–reactivity correlation, which is in accord with the postulated hydrogen-bonding interaction between the receptor ligand and the substrate, which should be less favorable at elevated temperatures. The observed reactivity is truly surprising in terms of how small individual components are pieced together to form one functional catalytic system that brings about unprecedented reactivity and selectivity.”

The group found that their asymmetric borylation tolerated a wide range of substrates, as shown in Scheme 3A. Aliphatic secondary and tertiary carboxamides underwent the enantioselective borylation exclusively at the γ-methylene C–H bond. Esters were also amenable to react, exhibiting complete site selectivity in the asymmetric borylation of the aliphatic acyl group.

Longer-chain carboxylic acid derivatives were likewise shown to be suitable substrates. “The protocol allowed variation in the aliphatic chains, both in terms of chain length



Scheme 3 Scope of the asymmetric remote C–H borylation (A), and the derivatization of the enantioenriched alkylboronate (B). The space-filling model of the calculated transition state (C) showed a chiral reaction pocket for substrate (yellow) binding formed by the [Ir(Bpin)$_3$], binaphthyl frameworks of the chiral monophosphite ligand (green), the isopropyl (iPr) groups in the triisopropylsilyl (TIPS) moiety of the ligand (blue) and the urea-pyridine receptor ligand (cyan).

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and functionalities present," said Professor Sawamura, who noted that an impressive tolerance towards unsaturation on the chain makes fatty acid derived substrates (including the amide derivative of linoleic acid, the doubly unsaturated essential omega-6 fatty acid) amenable to the asymmetric borylation (Scheme 3A). "These results are expected to find important applications in creating novel methodologies for introducing molecular complexity and chemical modification in fatty acids that are both renewable and readily available resources," explained Professor Sawamura, who continued: "This whole process is truly remarkable, with the catalyst being able to distinguish between two enantiotopic C–H bonds at the γ position of the aliphatic chain in all cases. Another key feature of the reaction is the utilization of limiting amount of substrate (stoichiometric amount with pinB–Bpin), as typical C–H borylation systems normally require neat conditions or excess amount of the substrate."

The synthetic utility of the asymmetric borylation was demonstrated by the transformations of γ-alkylboronates (Scheme 3B). For example, transformations of the γ-borylhexanoic acid anilide gave the corresponding alcohol, the γ-arylated derivative, the α-alkylglutaric acid diamide, and a γ-alkyl-γ-aminobutyric acid (GABA) derivative via oxidation, cross-coupling, isocyanate addition, and amination reactions, respectively.

Professor Sawamura pointed out that quantum chemical calculations, focusing on C–H bond cleavage by the catalyst, revealed the generation of an accessible surface as a deep cavity created by the modular catalyst, that presents the urea hydrogen-bonding site at the outer rim with the Ir atom at the bottom of the groove. The three-dimensional representation (Scheme 3C) of the calculated transition state also showed the presence of stabilizing noncovalent interactions. Professor Sawamura said: "One of the naphthalene rings of the monophosphite ligand displays π/π interactions not only with the pyridine moiety but also with the *ortho*-phenylene linker of the receptor ligand, while the substrate is bound in the cavity not only through hydrogen bonding with the urea moiety, but also through C(sp^3)–H···O interactions and London dispersion interactions that seem to contribute to the substrate binding in the catalytic cavity. Overall, these features mimic those of natural enzymes that have intricate active sites for substrate binding. The interactions within this groove position the substrate, bringing the targeted site in close proximity to the catalytic center and enabling the desired reactivity." The authors believe that the work presented here provides an example of exceptional remote directing and orienting effect, displaying optimal reactivity for small-molecule catalysis, similar to that usually featured by natural enzymes. Professor Sawamura said: "My team and I believe that this strategy can be generalized towards enantiocontrolled production of stereogenic centers at even more distal positions, relative to various functional groups, by proper design of receptor ligands. In this way, the utilization of readily available and renewable feedstock chemicals for the production of functional materials and pharmaceutical compounds will be realized. This should help in alleviating the problems of increasing energy demand, as the synthesis of these significant molecules often requires huge amounts of fossil fuels, as well as laborious and costly methodologies." He concluded: "On a final note, our group, composed of experimental, theoretical and information scientists, are confident that this work will change the way chemists think about catalyst design. Bridging the gap between enzymatic, supramolecular, and small-molecule catalysis, we are encouraged that innovation from this work will enable the creation of simple, efficient, and readily accessible catalysts inspired by nature, hoping that this will stimulate future research efforts along these lines."

About the authors

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Ronald L. Reyes finished his BSc in chemistry from the University of the Philippines-Diliman in 2007 and his MSc in chemistry from the Ateneo de Manila University, Philippines in 2012. Thereafter, in 2015, he joined the Organometallic Chemistry Group at the Faculty of Science, Hokkaido University under the supervision of Prof. Masaya Sawamura where he obtained his PhD in 2018. He was appointed as a postdoctoral researcher at the Institute for Chemical Reaction Design and Discovery (WPI-ICReDD) at Hokkaido University (Japan), 2018 to 2020. Presently, he is an assistant professor at ICReDD. He works mainly on the strategic functionalization of C–H bonds allowing the preparation of molecules with three-dimensional structural diversity.

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M. Sato

Miyu Sato was born in 1997 in Niigata (Japan) and lived there before moving to Hokkaido (Japan). She received her BSc in chemistry from Hokkaido University (Japan) in 2020. Currently, she is a member of the Organometallic Chemistry Group under the supervision of Prof. Masaya Sawamura, studying to earn her MSc.

Dr. T. Iwai

Tomohiro Iwai received his Bachelor (2006) and Master (2008) of Science degrees from Hokkaido University (Japan). He received his Ph.D. from Kyoto University (Japan) in 2011 under the supervision of Professor Yasushi Tsuji. He has been an assistant professor at Hokkaido University since 2011. He received The Encouragement Award from Hokkaido Branch of the Chemical Society of Japan (2018). His research interest is on the development of highly efficient metal catalysis based on ligand design.

Dr. K. Suzuki

Kimichi Suzuki received his PhD from Yokohama City University (Japan) in 2010 under the direction of Prof. Masanori Tachikawa. After joining the NEDO project as a postdoctoral fellow at AIST, he worked at SUMITOMO Chemical. Co., Ltd. Afterwards, he worked with Prof. Morokuma at Kyoto University (Japan) and Prof. Maeda at Hokkaido University (Japan). Since 2019, he is an associate professor at the Institute for Chemical Reaction Design and Discovery at Hokkaido University. His research interest is on the development of an efficient reaction path search algorithm for large molecular systems and its applications.

Prof. S. Maeda

Satoshi Maeda received his PhD from Tohoku University (Japan) in 2007 under the direction of Prof. Koichi Ohno. Soon after, in 2007–2010, he worked under the supervision of Prof. Ohno and Prof. Keiji Morokuma as a JSPS research fellow. In 2010–2012, he was appointed as an assistant professor of the Hakubi project at Kyoto University (Japan) under the guidance of Prof. Morokuma. In the years from 2012–2017, he joined the group of Prof. Tetsuya Taketsugu at Hokkaido University (Japan) as an assistant professor and later appointed as an associate professor. At present, he is now a full professor at Hokkaido University and the director of the newly established Institute of Chemical Reaction Design and Discovery, a part of the World Premier International Research Center Initiative (WPI-ICReDD). He has been working on the development of automated reaction path search methods.

Prof. M. Sawamura

Masaya Sawamura is a Distinguished Professor of Hokkaido University (Japan). In 1989, shortly after obtaining his PhD from Kyoto University (Japan), under the supervision of Professor Yoshihiko Ito, he was appointed as an Assistant Professor at the same faculty. Thereafter, he spent one year at Harvard University (USA) under the guidance of Professor Stuart L. Schreiber (1993–1994) as a researcher. In 1995, he transferred to the Tokyo Institute of Technology and to the University of Tokyo (both in Japan), joining the group of Professor Eiichi Nakamura as an Assistant Professor. He was then promoted to lecturer in 1996 and to associate professor in 1997. Since 2001, he has been affiliated as a full professor at Hokkaido University. Moreover, he is a principal investigator at the Institute of Chemical Reaction Design and Discovery, a part of the World Premier International Research Center Initiative (WPI-ICReDD).

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Regio- and Enantioselective Allylic Alkylation of Terminal Alkynes by Synergistic Rh/Cu Catalysis

J. Am. Chem. Soc. **2020**, *142*, 15276–15281

1,4-Enynes are important building blocks in organic synthesis, as they are endowed with a versatile combination of reactive double and triple bonds. Transition-metal-catalyzed asymmetric allylic substitutions represent the main method for accessing chiral 1,4-enynes in an enantioselective manner. "Alkynyl-aluminum/boron compounds and alkynyl carboxylic acids (Scheme 1a) were successfully utilized in 1,4-enynes synthesis (see the original paper for references). However, from the viewpoint of atom- and step-economy, direct asymmetric allylation of easily available terminal alkynes is attractive but challenging," explained Professor Changkun Li at Shanghai Jiao Tong University (Shanghai, P. R. of China), who continued: "Sawamura and Ohmiya's Cu-catalyzed asymmetric allylic alkylation of triisopropylsilylacetylene with (*Z*)-allylic phosphates (Scheme 1a) provides a nice solution to this challenge (*J. Am. Chem. Soc.* **2014**, *136*, 13932–13939). Tan and Lee previously developed a Cu/guanidine catalyst for enantioselective allylic alkynylation of cyclic allylic bromide, in which the regioselectivity aspect is not addressed (*J. Am. Chem. Soc.* **2018**, *140*, 8448–8455). Therefore, a new catalyst system that can control both the regioselectivity and the enantioselectivity in the coupling of general terminal alkynes and unsymmetrical allylic precursors is still in high demand."

Previously, Professor Li's group developed a new catalyst system based on rhodium and chiral bisoxazolinephosphine (NPN*) ligands (*ACS. Catal.* **2020**, *10*, 4491–4496) by following their reported cobalt/NPN*-catalyzed regioselective and enantioselective allylic amination (*J. Am. Chem. Soc.* **2019**, *141*, 11430–11434). "Rh and Co behave similarly in terms of regioselectivity and enantioselectivity, but rhodium catalysis is more generally applicable in terms of substrate scope, compared to cobalt," said Professor Li. Under the catalysis of Rh/NPN*, both branched racemic and linear (*Z* and *E*) mono-substituted allylic carbonates could be converted into branched allylic products with branched/linear ratios over 20:1 and excellent enantioselectivities. Different nitrogen, carbon, oxygen and sulfur pro-nucleophiles could be used under neutral conditions, and – as explained by Professor Li – the problem of low regioselectivity for challenging alkyl-group-bearing allylic precursors could be solved.

"The Sonogashira coupling of aryl halides with terminal alkynes by synergistic Pd and Cu catalysis is one of the most powerful methods to prepare internal alkynes. Some recent reports have extended the scope of aryl halides to aliphatic halides in the asymmetric Sonogashira coupling (*Nat. Chem.* **2019**, *11*, 1158–1166)," said Professor Li. "However, the Sonogashira-type reaction using allylic precursors is rarely reported. The main obstacle to extending the reaction to alkynes is that terminal alkynes exhibit various reactivities in the presence of transition metals such as Pd, Ir and Rh, which are normally used in asymmetric allylic substitutions." In Professor Li's latest work, a highly branch-selective and enantioselective allylic alkylation of a variety of functionalized aryl, aliphatic and silyl alkynes with challenging racemic allylic carbonates has been developed under neutral conditions by synergistic Rh and Cu catalysis (Scheme 1b).

Professor Li explained that terminal alkynes with different functional groups can successfully react under the optimized conditions: "Aldehyde, hydroxyl, pyridyl, trimethylsilyl, cyano, amide and chloride groups were tolerated. Dienynes could be prepared efficiently when enynes were used. The highly diastereoselective allylic alkylation of ethisterone indicates this method can be used in late-stage functionalization of complex molecules too. Sterically bulky allylic carbonates bearing isopropyl, cyclohexyl and phenyl groups were readily converted into the products in high yields. The formation of a quaternary carbon center was also realized under the same conditions, although the enantioselectivity was only moderate." Professor Li revealed that an investigation on ligand development for highly enantioselective quaternary carbon construction is ongoing: "*N*-Benzyl-2-ethynylaniline reacts selectively at the sp C–H bond instead of the nitrogen atom, which allows the chiral 2-allyl indole preparation after gold-catalyzed cyclization."

Single-crystal X-ray diffraction analysis and comparison with literature data confirmed that the absolute configuration of the allylic alkylation products of terminal alkynes is opposite to the configuration generated in reactions of nitrogen and other nucleophiles. "We believe that a mechanism involving the transmetalation of Cu-acetylide to rhodium complex and subsequent reductive elimination is the most likely scenario. Stoichiometric reaction of NPN/Rh-allyl complex with Cu-acetylide further supports the notion that the ligand for Cu is mandatory, probably because it breaks down the oligomers to

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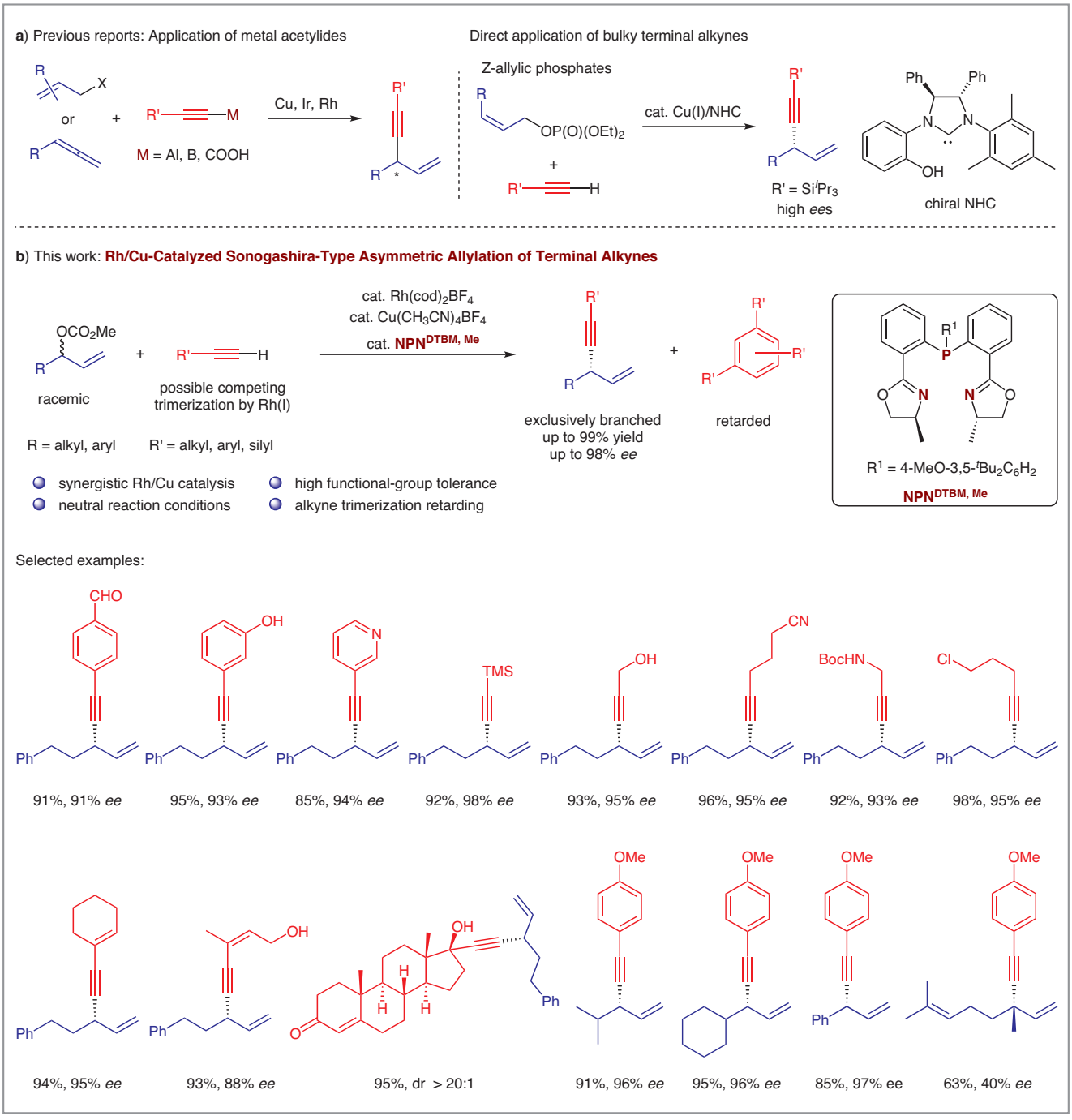

Scheme 1 (a) Previous examples of allylic alkynylations reported in the literature; (b) experimental conditions and scope of this work.

monomeric Cu-acetylide. The crystal structure of the tetrahedral CuI/NPN complex further supports this conclusion," said Professor Li, who added: "Actually, this complex has been prepared and characterized by Mr. Bing Li over a very long time. However, we did not find any good application of it until this reaction had been optimized."

Professor Li thinks that the Rh-catalyzed trimerization of terminal alkynes to form trisubstituted benzenes could be

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retarded by the fast reaction of rhodium complex with allylic carbonates. "The use of acetonitrile as the solvent is essential for the success of this reaction and other solvents lead to the fast consumption of terminal alkynes. The ligand with smaller methyl groups on the oxazoline ring is also important for achieving high yields." He then revealed: "Following a request by one of the reviewers, this ligand effect was identified to accelerate the transmetalation of Cu-acetylide to Rh complex. It is worth mentioning that a fast interconversion of diastereomeric π-allylrhodium/NPN complexes through rhodium(I)-catalyzed allyl exchange – other than the π-σ-π isomerization – was proposed when D-labeled allylic carbonates were tested for the reaction, which was requested by another reviewer."

Professor Li concluded: "A highly branch-selective and enantioselective allylic alkylation of terminal alkynes through synergistic Rh and Cu catalysis has been reported in our paper. Rh was used to control the regioselectivity and the enantioselectivity, while Cu was the key to activating the alkynes. The competing alkyne trimerization by the Rh(I) complex could be retarded using acetonitrile as solvent. Mechanistic studies support the inner-sphere reductive elimination C(sp)–C(sp^3) bond formation process."

About the authors

Dr. W.-Y. Huang

Wen-Yu Huang was born and raised in Jilin Province, P. R. of China. He received his B.Sc. in organic chemistry from Nanchang University (P. R. of China) in 2010 and Ph.D. in organic chemistry from Nagoya University (Japan) in 2017 under the supervision of Professor Toshio Nishikawa and Associate Professor Atsuo Nakazaki. He is now working as a postdoctoral fellow with Professor Changkun Li at Shanghai Jiao Tong University (P. R. of China). His research focuses on transition-metal-catalyzed enantioselective allylic alkylation reactions.

C.-H. Lu

Chun-Hua Lu was born in Jiangxi Province, P. R. of China. She received her B.Sc. in applied chemistry in JiangSu University (P. R. of China). She then joined the research group of Prof. Changkun Li in Shanghai Jiao Tong University (P. R. of China) and received her M.Sc. in 2020. Her work focuses on Pd- and Rh-catalyzed asymmetric synthesis.

Dr. S. Ghorai

Samir Ghorai was born and raised in India. He graduated with a B.Sc. in chemistry (H) (2009) and M.Sc. in inorganic chemistry (2011) from Vidyasagar University, India. Then he pursued his Ph.D. (2015) at the Indian Institute of Technology Guwahati (IITG; India). There, he worked under the supervision of Prof. Chandan Mukherjee in the inorganic and bioinorganic field of metal-radical complexes. In 2016, he moved to Daegu Gyeongbuk Institute of Science and Technology (DGIST; South Korea) for postdoctoral studies with Prof. Jaeheung Cho. Since 2017, he has been working as a postdoctoral fellow at Shanghai Jiao Tong University (SJTU; P. R. of China) with Prof. Changkun Li. His research focuses on cobalt-catalyzed asymmetric allylic substitution reactions.

B. Li

Bing Li graduated from Qingdao Agricultural University (Qingdao, P. R. of China) with a B.Sc. (2011) in medicinal chemistry and from Nankai University (Tianjin, P. R. of China) with an M.Sc. (2014) in organic chemistry. In 2017, after a few years in pharmaceutical industry, he joined the research group of Changkun Li at Shanghai Jiao Tong University as a Ph.D. candidate. His work focuses on Rh-catalyzed regio- and enantioselective allylic substitution reactions with chiral NPN ligands.

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Prof. C. Li

Changkun Li was born in Beijing, P. R. of China, in 1982. He received his B.Sc. (2004) and Ph.D. (2010) from Peking University (P. R. of China) with Professor Jianbo Wang and Yan Zhang. In 2010–2012, he worked as a postdoctoral fellow at Kyoto University (Japan) with Professor Masahiro Murakami. Then he moved to Freiburg (Germany) to work with Professor Bernhard Breit as a Humboldt Fellow. In 2016, he joined Shanghai Jiao Tong University (P. R. of China) as a tenure-track associate professor. His research now focuses on asymmetric catalysis using cobalt and rhodium with chiral tridentate ligands.

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Young Career Focus: Prof. Miłosz Pawlicki (Jagiellonian University, Kraków, Poland)

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 Prof. Miłosz Pawlicki (Jagiellonian University, Kraków, Poland).

Biographical Sketch

Prof. M. Pawlicki

Miłosz Pawlicki studied chemistry at the University of Wrocław (Poland), eventually completing his M.Sc. degree in amino acid and peptide chemistry. At the same university, he completed his Ph.D. studies in 2004 with the mentorship of Prof. Lechoslaw Latos-Grażyński focusing on the synthesis of oxygen-containing porphyrinoids. Between 2007 and 2009 he was a Marie-Curie Fellow working as a post-doctoral researcher with Prof. Harry L. Anderson in Oxford, UK. In 2009 he returned to Poland and started his independent research path at the Department of Chemistry, University of Wrocław as an assistant professor and associate professor after gaining a D.Sc. degree in 2016. Now he is an associate professor at the Jagiellonian University (Poland, Kraków) where he focuses on the potential that is available in organic chromophores where the switching between aromatic and antiaromatic delocalisation is possible.

INTERVIEW

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

Prof. M. Pawlicki Along with my collaborators I focus my research activity on several aspects of conjugation and delocalisation within unsaturated hydrocarbons. The delocalisation in strongly conjugated systems leads to aromatic or antiaromatic paths and that is what we are mostly interested in when designing and synthesising new structural motifs. We are mostly interested in deep changing of observed behaviour by introducing several modulators that can lead to control of the spectroscopic activity. Thus the modulation and control of delocalisation by switching between available options within one skeleton and based on fundamental modifications (redox, protonation–deprotonation) and covalent involvement of electron-deficient (boron) or electron-rich (nitrogen) elements remain central points of our work.

SYNFORM *When did you get interested in synthesis?*

Prof. M. Pawlicki I think it was during the second year of my undergraduate studies. I was flipping through an old textbook, Morrison & Boyd's Organic Chemistry (the first textbook translated to Polish), and I found the intriguing Kiliani–Fisher reaction that modifies carbohydrates. The elegance of elongation of a carbohydrate chain had a significant influence on my fascination with synthesis. And even though currently we do not work on carbohydrates, I really appreciate the reactivity of carbonyl functionality and the potential that this small functional group has. Actually, we are using the mentioned functionality in our current designs of skeletons for making further processes involving a C=O unit, like the McMurry coupling or Wittig reaction. It has a significant influence on our synthetic strategy for accessing the cyclic and strongly conjugated molecules we are looking for.

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

Prof. M. Pawlicki In the current world we can actually define two major fields of applicability where the modern role of organic synthesis is easily noticeable. The first one is an industrial part where the knowledge of organic synthesis is important for day-to-day life as the newly synthesized molecules have shown an enormous influence on the progress made by the world in the last several decades. Without question, the industrial usage of organic synthesis would not be possible without the fundamental studies focused on establishing new methodologies that are creating additional roles for organic synthesis. The huge potential of new molecules that find their place in many fields would not be possible without organic synthesis that creates a solid basis for being very optimistic about the prospects of this field.

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

Prof. M. Pawlicki The work we are conducting focuses on understanding the observed properties and correlating them with the structure, eventually deriving the expected behaviour from a carefully planned and designed skeleton. The important aspect of our research involves controlling the final outcome of our target molecule. We are focusing on several fundamental initiators (protonation/deprotonation and also redox modification) that modify the observed delocalisation paths and substantially change the final outcome. In our current research, an important role has been attached to triphyrin(2.1.1) (Figure 1) – a strongly conjugated structure that in addition creates a perfect environment for boron(III) (another crucial player in our projects). By merging together those elements we can modulate two fundamental aspects strongly linked with conjugated systems – the optical and magnetic responses. Both of those aspects actually have significant applicability potential with respect to modulation of absorbance/emission (*Chem. Commun.* **2015**, *51*, 11362–11365) or switching from aromatic to anatiaromatic paths (Figure 1, Part A; *Angew. Chem. Int. Ed.* **2014**, *53*, 2992–2996; *Angew. Chem. Int. Ed.* **2015**, *54*, 1906–1909) eventually stabilising diatropic and paratropic currents in one system at the same time (Figure 1, Part B; *Chem. Eur. J.* **2019**, *25*, 15477–15482). Following those general ideas, we have introduced several switchable structural motifs where the final behaviour can be modulated, thereby substantially changing the observed outcome. Importantly, those processes show reversibility which creates further possibilities for applications.

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

Prof. M. Pawlicki I won't be extremely original if I say that I hope the biggest achievement is still to come. Nevertheless, I have several results on the list that bring a story to my mind.

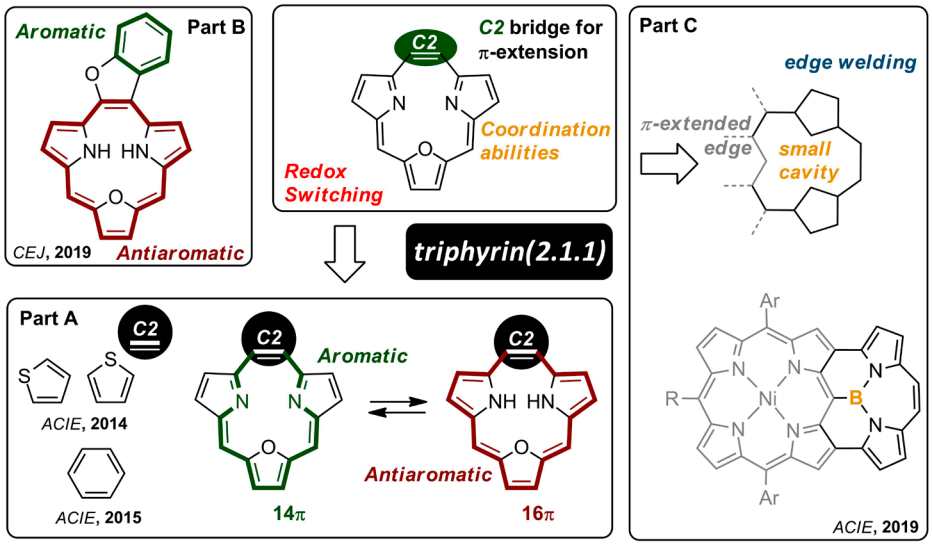

Figure 1 Classical way of reductive amination

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It is typical that the newest work is the most important one but while looking on our hitherto designed systems I can see the evolution of the general idea of controlling the behaviour of designed skeletons. But the most important so far is a modulation of strongly conjugated skeleton with specific edge-welding with triphyrin(2.1.1) (Figure 1, Part C) that created a system with a changeable delocalization path (*Angew. Chem. Int. Ed.* **2019**, *58*, 10946–10950). The presented approach opens the potential for modulation of well-defined structures by a controlled 'defecting' and introduction of an electron-deficient element that in addition can be further changed via an axial coordination, thereby influencing overall behaviour.

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Coming soon

Literature Coverage

Diversity-Oriented Synthesis of Peptide-Boronic Acids by a Versatile Building-Block Approach

Literature Coverage

Ozonolysis of Alkynes – A Flexible Route to α-Diketones: Synthesis of AI-2

Literature Coverage

Migratory Functionalization of Unactivated Alkyl Bromides for Construction of All-Carbon Quaternary Centers via Transposed tert-C-Radicals

Further highlights

Synthesis **Review: Recent Developments in Transition-Metal-Catalyzed Asymmetric Hydrogenation of Enamides**
(by P. Phansavath, V. Ratovelomanana-Vidal and co-workers)

Synlett **Account: [(bpy)CuSCF$_3$]: A Practical and Efficient Reagent for the Construction of C–SCF$_3$ Bonds**
(by Z. Weng and co-workers)

Synfacts **Synfact of the Month in category "Flow Chemistry": Continuous Cryogenic Lithium–Halogen Exchange**

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