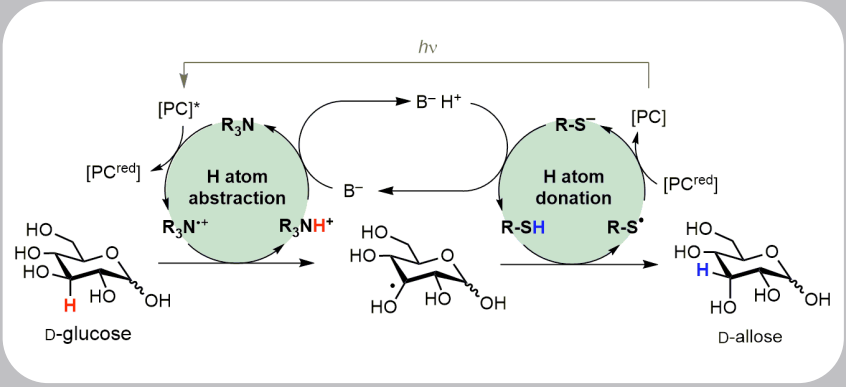
Synform

People, Trends and Views in Chemical Synthesis

2020/04

Synthesis of Rare Sugar Isomers through Site-Selective Epimerization

Highlighted article by Y. Wang, H. M. Carder, A. E. Wendlandt



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Thieme

Dear Readers,

This editorial space traditionally strives to cover light subjects or at least treat any subject with a light touch. However, while writing this editorial there is something ominous out there casting its shadow upon us: an almost unprecedented challenge to our health – and possibly even to our way of living – called COVID-19. This is not something that should be treated lightly, as it is not yet clear where this situation is going to take us all. No need to panic, but we need to be aware that – as stated by the World Health Organisation – we are in uncharted territory right now. If there is one thing that gives rational hope that this situation will eventually get better, much better, this is science and research. More specifically, it is the development of a vaccine, of a therapy to fight the virus. So often politicians, decision makers and even the general public tend to forget and play down the importance of science, of vaccines and pharmaceutical research, and the central role of basic science that is so important because it paves the way for the discovery of future therapies, 10 or 20 years down the line. If there is one positive aspect in this rather bleak situation, it is that the COVID-19 challenge will be a powerful reminder of the vital importance of having a strong and global research capacity, able to react quickly and synergistically to any sudden challenge to our health, economy and lifestyle. Building walls, cutting research funds and undermining the credibility of science and researchers is the most efficient way to help any coronavirus lurking out there. But let's try not to forget this lesson three days after a vaccine or a cure for COVID-19 has been found. We may not get another opportunity to regret it. And who knows whether the research presented in this new issue of SYNFORM – besides being scientifically top notch – will be useful for solving future challenges to our planet or to our health. The first article is an interview to welcome and introduce the new SYNTHESIS Editorial Board Member Professor Liu-Zhu Gong (P. R. of China). We also interview, in a Young Career Focus that closes the issue, T. Boddaert (France) who tells us about his interest in synthesis, foldamers and complex chemical architectures. The two Literature Coverage articles in this issue highlight the recent work of Y. Wang (USA) on the elegant use of iron complexes for performing the catalytic hydroxyalkylation of alkenes and alkynes, and the ground-breaking work published in Nature by A. Wendlandt (USA) on the site-selective epimerization of carbohydrates leading to rare sugars. And who knows whether this new exciting methodology will one day be instrumental for discovering and producing novel carbohydrate drugs and synthetic vaccines...

In this issue

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Editorial Board Focus: Professor Liu-Zhu Gong (University of Science and Technology of China, P. R. of China)

Background and Purpose. From time to time, SYNFORM portraits Thieme Chemistry Editorial Board or Editorial Advisory Board members who answer several questions regarding their research interests and revealing their impressions and views on the developments in organic chemistry as a general research field. This Editorial Board Focus presents Professor Liu-Zhu Gong (University of Science and Technology of China, P. R. of China) who joined the Editorial Board of SYNTHESIS with effect of January 1, 2020.

Biographical Sketch

Prof. L.-Z. Gong

Liu-Zhu Gong was born in October 1970 in Henan, China. He graduated from Henan Normal University (P. R. of China) in 1989. He received his M.S. degree from Chengdu Institute of Organic Chemistry (P. R. of China) in 1996 and Ph.D. from the Institute of Chemistry, Chinese Academy of Sciences (P. R. of China) in 2000. He was a visiting scholar (Joint PhD graduate student program) at the University of Virginia (USA) and an Alexander von Humboldt Research Fellow at the University of Munich (Germany). He became an associate professor of Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences in 2000 and was promoted to full professor in 2001. Since 2006, he has been a professor at the University of Science and Technology of China. He was appointed the Cheung Kong Scholar Professor of organic chemistry in 2008. He has been continuously working on asymmetric organocatalysis, organo/metal combined catalysis, and the total synthesis of natural products. The related achievements are reported in 162 peer-reviewed articles and 4 book chapters.

INTERVIEW

SYNFORM *Please comment on your role as a member of the Editorial Board of* SYNTHESIS*?*

Prof. L.-Z. Gong SYNTHESIS is one of the preeminent journals with over 50 years of history and holds a great reputation in the community. It has continuously been publishing inspiring contributions in synthetic chemistry. As a member of the editorial board, I am very happy and will try my best to serve for the journal, our authors, and our reviewers.

SYNFORM *How do you describe the value of a product such as* SYNTHESIS *to the chemistry community?*

Prof. L.-Z. Gong Synthetic chemistry is undoubtedly one of the most important fields among the physical sciences. A journal that focuses on publishing the latest scientific findings in synthesis is definitely greatly valuable to many communities, for example, materials science, life science, and even physics, far beyond the scope of the chemistry community.

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

Prof. L.-Z. Gong My research interest has long been focusing on asymmetric catalysis and organic synthesis, in particular on organocatalysis and organo-metal combined catalysis.

SYNFORM *You are a leading researcher with regard to synthetic organic chemistry and catalysis. Could you tell us more about how important you perceive this particular topic to be?*

Prof. L.-Z. Gong Molecules have ever changed the world and many of them are now still exerting great impact on the society by their functions. The goal of synthetic organic chemistry and catalysis is to create the most efficient methods to make highly valuable molecules from starting materials that cost almost nothing. It is not an overstatement that synthetic organic chemistry and catalysis have changed the world and will continue to do so.

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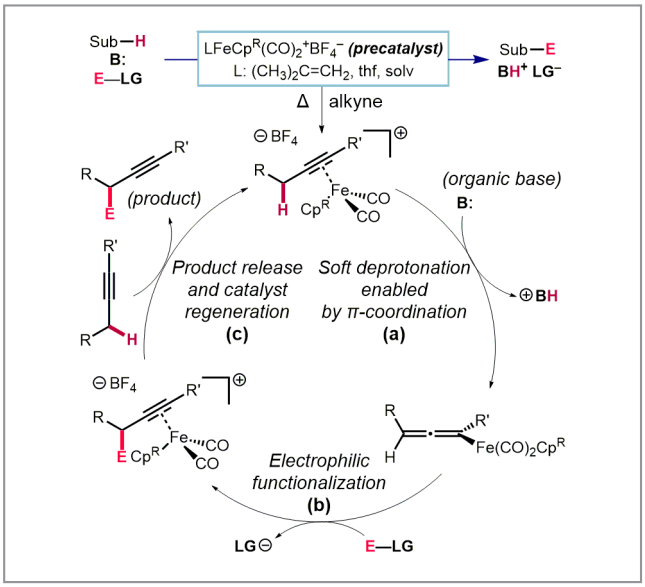
α-C–H Functionalization of π-Bonds Using Iron Complexes: Catalytic Hydroxyalkylation of Alkynes and Alkenes

J. Am. Chem. Soc. **2019**, *141*, 19594–19599

The α-functionalization of alkynes and alkenes with aldehydes reported in this study from the group of Professor Yiming Wang from the University of Pittsburgh (USA) is based on stoichiometric reactions of cationic alkene-iron π-complexes originally investigated by Myron Rosenblum and his research group in the 1970s. In particular, Rosenblum and co-workers observed that (i) cationic alkene complexes of cyclopentadienyliron dicarbonyl were strongly acidic, with α-protons undergoing quantitative deprotonation using triethylamine as the base; and (ii) the resulting δ-allyliron complexes were good nucleophiles.[1] Subsequent studies revealed that these allyliron complexes are transition-metal analogues of allylstannanes, having similar nucleophilicity[2] and reacting via an open-transition state S_E2' pathway.[3,4] However, the propargylic functionalization of alkynes was not investigated in detail in these, nor in subsequent, studies.

Nevertheless, given this reactivity, the Wang group posited that it would be possible to develop a catalytic functionalization of the α-position of nonpolarized C–C multiple bonds using the general catalytic cycle, shown in Scheme 1 for alkyne substrates. "We observed that this would be a redox-neutral process using electrophilic reagents for functionalization," explained Professor Wang. He continued: "We chose to investigate C–C bond formation using this process, since allylic (and propargylic) functionalization reactions that introduce carbon-based substituents (rather than heteroatoms) at the α-position are comparatively rare. Moreover, we wanted to focus our attention on alkynes rather than alkenes, since most known methods for allylic functionalization tend not to extend well to the corresponding propargylic functionalization reaction or result in other types of reactivity when applied to alkyne substrates,[5,6] while other reported transformations lead to the concomitant reduction or functionalization of the triple bond.[7,8]"



Scheme 1 Balanced equation and proposed catalytic cycle

Professor Wang pointed out: "Zhang and co-workers have designed gold catalysts for alkyne-to-diene isomerization[9] and propargylic C–H functionalization,[10] but there are some important differences between our system and the Zhang system. In our system, (i) the base is external rather than being built into the ligand; (ii) the reaction halts at the homopropargylic alcohol without subsequent metal-catalyzed cyclization of the initially formed product; and (iii) in some cases, alkenes can also be used as substrates."

The authors attribute the relative rarity of C–C bond-forming propargylic functionalization reactions to the incompatibility of many potential nucleophilic carbon sources with the oxidizing conditions typically employed for the installation of heteroatoms by C–H functionalization, but also to the more challenging energetics for the formal removal of H$^\bullet$ or H$^-$ from the propargylic position, as compared to the analogous allylic position, as evidenced by bond dissociation energy (BDE) and hydride ion affinity (HIA) data, shown for typical alkenes and alkynes in Figure 1.[11] "Given these considerations, we felt that a redox-neutral process that effects C–H functionalization through the removal of proton (H$^+$) may be able to overcome these challenges," said Professor Wang.

"Our initial attempts to implement the proposed catalytic cycle focused on the use of trityl cation (E–LG = CPh$_3$$^+BF_4$$^-$) as a model (or, perhaps 'toy') electrophile for the development of a proof-of-concept reaction and for initial exploration of reactivity," continued Professor Wang. After verifying that the reaction could be achieved stoichiometrically, the challenge, taken up by postdoctoral researcher Dr. Yidong Wang, was to

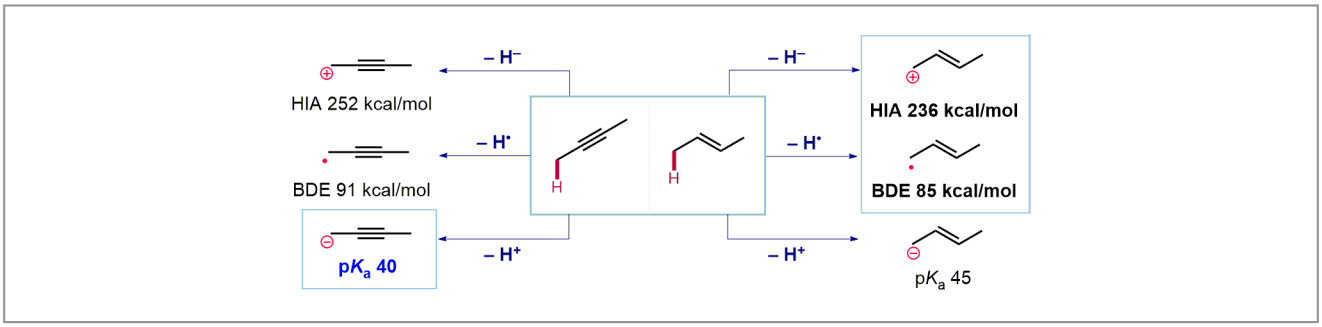
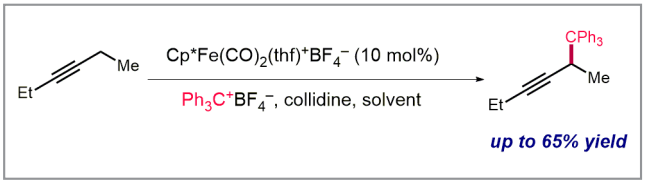


Figure 1 Comparative energetics of allylic and propargylic C–H activation

find a set of conditions wherein all three steps of the catalytic cycle are compatible (Scheme 2). Using 3-hexyne as the model alkyne and $[CpFe(CO)_2(3\text{-hexyne})]^+BF_4^-$ (Cp = C_5H_5) as the catalyst, a variety of bases were screened, including hindered secondary and tertiary alkylamines, tertiary anilines, hindered amidines (DBU) and guanidines (Barton's base), and Proton Sponge. However, Dr. Wang found that 2,6-dimethyl-substituted pyridines (collidine and lutidine) were uniquely successful, giving an initial hit of 14% yield (the rest gave < 2%). "Another crucial observation that Dr. Wang made was that the more hindered and electron-rich $[Cp^*Fe(CO)_2(3\text{-hexyne})]^+BF4^-$ (Cp^* = C_5Me_5) was particularly successful," said Professor Wang. In addition to disfavoring amine-deactivation of the cationic catalyst, subsequent kinetic experiments revealed that steps (b) and (c) of the catalytic cycle were also accelerated (results yet to be published).



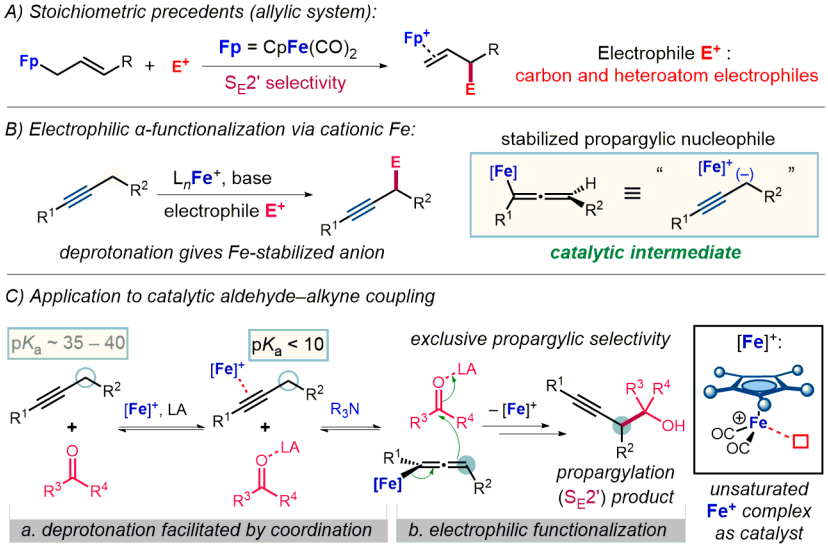
Scheme 2 Preliminary catalysis

"Using these findings, we sought to develop a more challenging but practically useful coupling of aldehydes and alkynes (Scheme 3)," said Professor Wang. He continued: "An additional parameter to consider was the nature of the Lewis acid used to activate the carbonyl group of the alkyne. It was found that $BF_3{\cdot}OEt_2$ was particularly effective in this regard, although certain silyl triflates also gave some coupling product. A re-optimization of the base revealed that tetramethylpiperidine (TMPH) was superior to the hindered pyridine bases. It was found that toluene was the optimal solvent for this process, although chlorinated solvents like dichloroethane or benzotrifluoride were also good choices. During the course of scope exploration (Scheme 4), it was found that the addition of catalytic zinc bistriflimide ($Zn(NTf_2)_2$) as an auxiliary Lewis acid, presumably for carbonyl activation, was beneficial for less reactive aldehyde substrates."

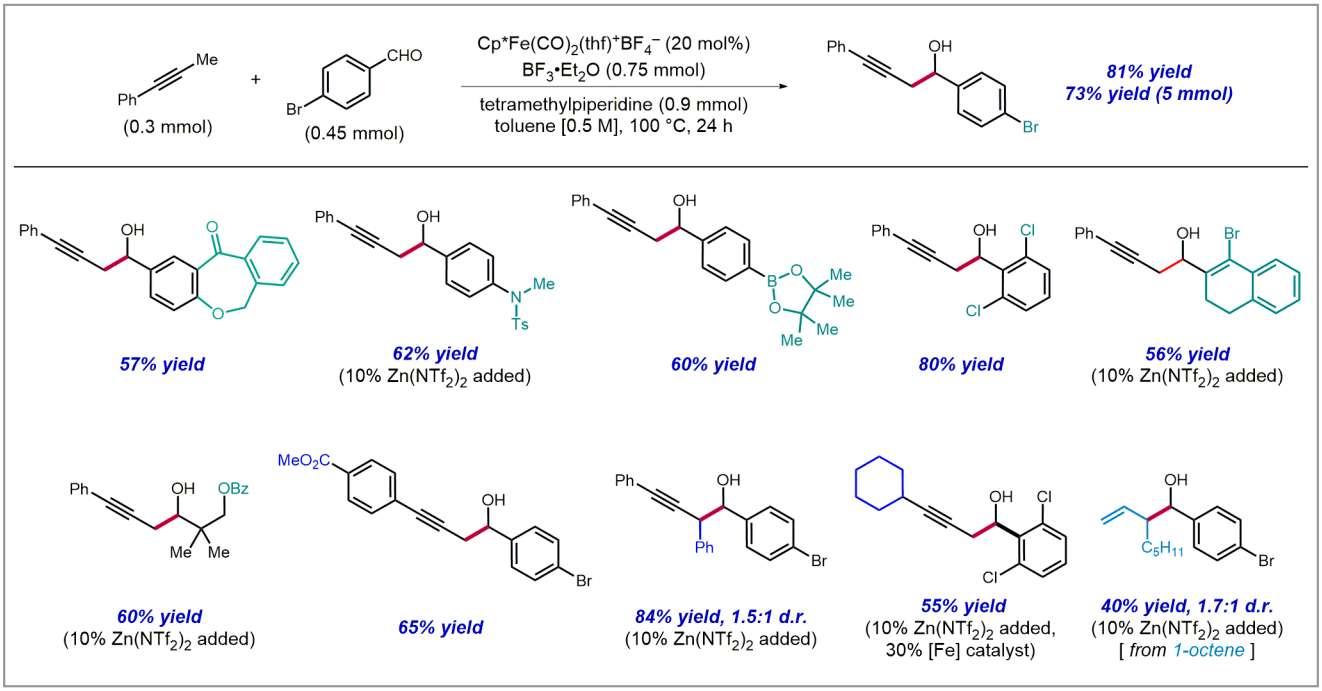
The scope of the process was then fully investigated by graduate students Jin Zhu, Austin Durham, and undergraduate Haley Lindberg. "A variety of electron-poor aryl aldehydes were competent substrates, as were some moderately electron-rich aryl aldehydes," explained Professor Wang. The group found that functional groups including a diaryl ketone, esters, pinacol esters, and tertiary sulfonamides, and aryl chlorides and bromides, including a 2,6-dichlorinated aldehyde, were tolerated. Similarly, α,β-unsaturated aldehydes, and other non-enolizable aldehydes, were also useful substrates. A somewhat narrower range of substituted aryl methyl alkynes were found to react efficiently, as did higher aryl alkyl alkynes. However, the latter class of substrates gave mixtures of diastereomers, generally with little diastereocontrol.

"Somewhat surprisingly, it was found that dialkyl alkynes were generally poor substrates, although previous α-tritylation of these substrates was successful, and the stoichiometric hydroxyalkylation with an aryl aldehyde in the presence of $BF_3{\cdot}OEt_2$ was also successful," remarked Professor Wang. He continued: "In certain cases, useful yields of the coupling product could still be obtained by using a higher loading of iron catalyst. Finally, we were pleased to find that these conditions were somewhat transferrable to terminal alkenes. For instance, 1-octene could be functionalized in 40% yield using the current conditions."

The group is currently conducting investigations into improved catalysts for faster reactions and higher turnover numbers. "Kinetic studies and *in situ* spectroscopic studies are being conducted to gain insight into the catalyst deactivation process and reasons behind the scope limitations," said



Scheme 3 Propargylic nucleophiles in catalytic alkyne-aldehyde coupling



Scheme 4 Reaction conditions and selected scope

Professor Wang, who concluded: "Improved catalysts will be applied to a variety of carbon and heteroatom electrophiles currently being explored. Ligands with bulky, chiral groups are also being investigated for the development of stereocontrolled C–H functionalization processes."

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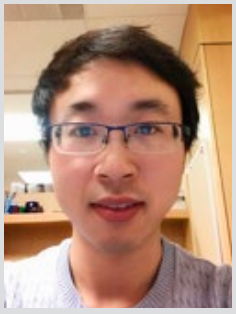
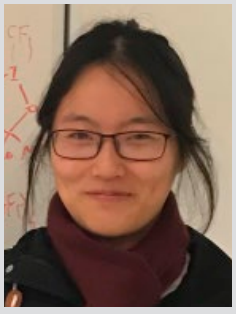
About the authors



Dr. Y. Wang

Yidong Wang was born in 1990 in Zhejiang Province (P. R. of China). He obtained his BSc degree at Northeast Normal University (P. R. of China) under the supervision of Prof. Xihe Bi in 2012. Then he moved to East China Normal University (P. R. of China) to begin his PhD studies. In 2017, he obtained his PhD under the supervision of Prof. Junliang Zhang. After that, he joined Prof. Yiming Wang's group as a postdoctoral researcher and focused on C–H bond activation of unsaturated bond catalyzed by iron(II).



J. Zhu

Jin Zhu was born and grew up in Jiangsu (P. R. of China). She graduated from Nanjing University (P. R. of China) with a BA degree in chemistry in 2018, where she studied in the group of Prof. Shaolin Zhu for her undergraduate thesis. Now, she is carrying out doctoral research in the Wang group at the University of Pittsburgh (USA).

A. Durham

Austin Durham was born and grew up in Harrisburg, Pennsylvania (USA). He received his Bachelor's degree at Hamilton College in New York (USA) where he worked under Professor Emeritus Robin Kinnel. He is currently conducting his PhD research on the use of iron catalysis for novel transformations under Dr. Yiming Wang at the University of Pittsburgh (USA).

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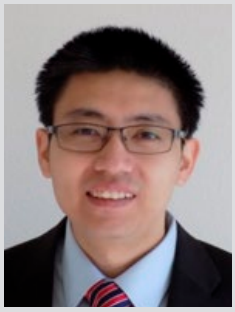
H. Lindberg

Haley Lindberg is working on her BS in chemistry from the University of Pittsburgh (USA) and is expected to graduate in April 2020. She joined Dr. Yiming Wang's lab in 2018 and her research currently focuses on new reactions catalyzed by iron.



Prof. Y. Wang

Yiming Wang was born in Shanghai (P. R. of China), and grew up in Boulder, CO (USA). He graduated with an AB/AM degree from Harvard University (USA) in 2008 after conducting research in the group of Prof. Andrew Myers. After obtaining his PhD under the supervision of Prof. Dean Toste at UC Berkeley (USA) in 2013, he was an NIH Postdoctoral Fellow in the laboratory of Prof. Stephen Buchwald at MIT (USA) before joining the Department of Chemistry at the University of Pittsburgh (USA) in the fall of 2017.

Synthesis of Rare Sugar Isomers through Site-Selective Epimerization

Nature **2020**, *578*, 403-408

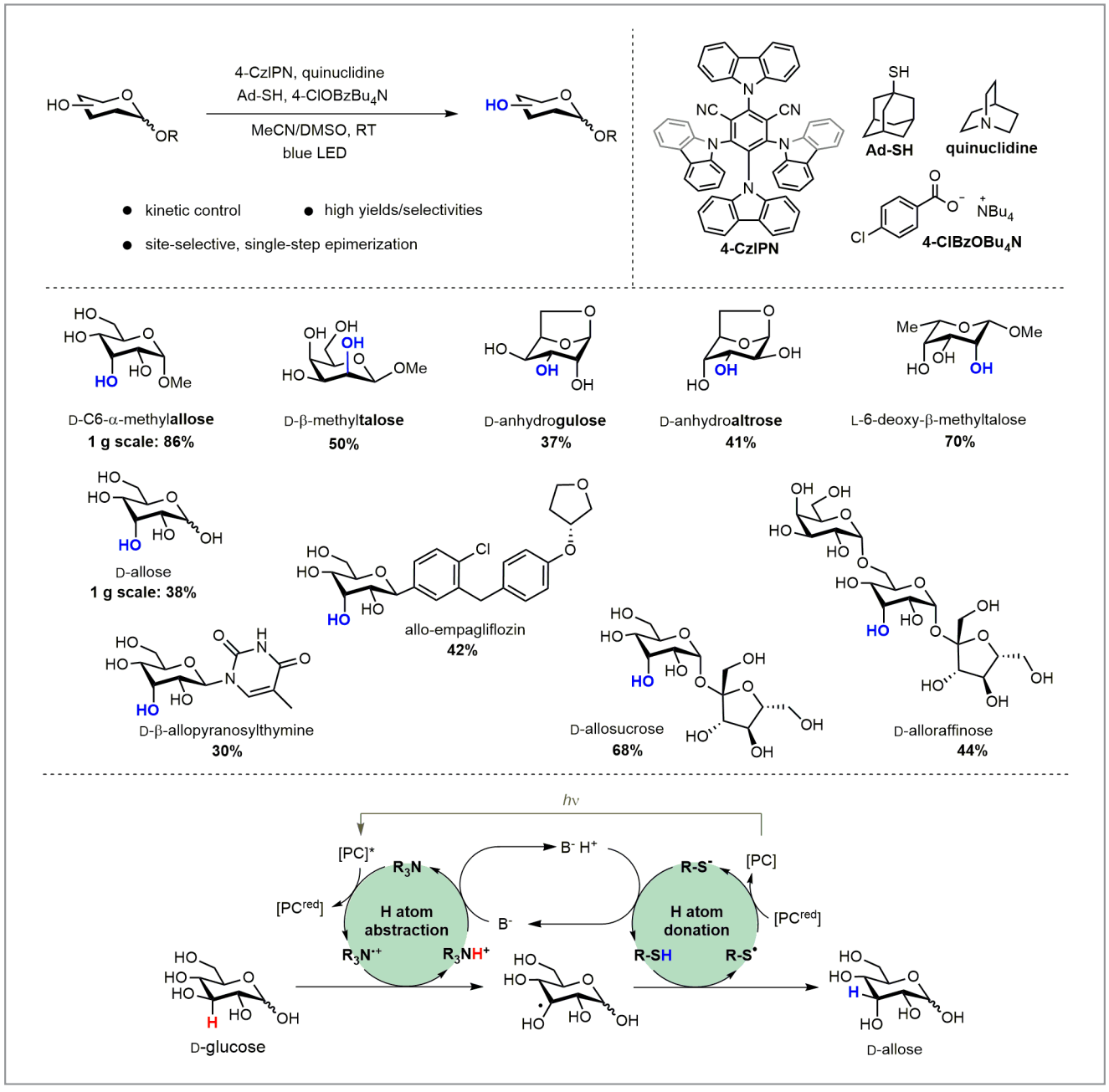
Rare sugars (e.g. D-allose, D-gulose, D-talose, L-glucose) feature prominently in glycosylated natural products and find important applications in the pharmaceutical, cosmetic, and food industries. Current strategies for the synthesis of rare sugars from biomass carbohydrates (e.g. D-glucose, D-galactose, D-xylose, L-arabinose, sucrose) remain very limited, and often involve chemical or enzymatic isomerizations resulting in intractable thermodynamic product mixtures. Recent groundbreaking work from the group of Professor Alison Wendlandt from the Massachusetts Institute of Technology (Cambridge, USA) developed and validated a dual catalyst system capable of promoting a highly site-selective epimerization of secondary alcohols in a kinetically controlled manner, and ultimately transforms naturally abundant sugars into their rare counterparts. "Synthetically, the product yields through this single-step epimerization reaction exceed almost all the other isomerization yields reported thus far," explained Professor Wendlandt, who continued: "Mechanistically, this transformation is realized through the sequential action of a hydrogen atom abstractor (quinuclidine radical cation) followed by a hydrogen atom donor (alkyl thiols), employing photochemical energy as the thermochemical driving force to reach this 'out-of-equilibrium' process. As a result, the consecutive C–H bond breaking and forming protocol represents a significant conceptual advancement."

The system is highly selective and works for a broad range of substrates, including completely unprotected monosaccharides (such as D-glucose, D-2-deoxyglucose, and L-fucose), polysaccharides, and other glycans. "In this work we also shed some light onto the underlying catalytic mechanism by carrying out a series of detailed mechanistic studies," said Professor Wendlandt. Nevertheless, the group is very keen to uncover the origin of the site-selectivity and diastereoselectivity, which remains elusive. "In parallel with the mechanistic elucidation aspect, we are equally interested in engineering different catalytic systems to epimerize other sites, so that we can streamline the synthesis of rare sugars not yet accessed by catalytic methods, including our newly developed protocol," remarked Professor Wendlandt, continuing: "For instance, the C5-epimerization of D-glucose would provide an access to D-idose, the only one of the five rare aldohexose isomers we have not achieved yet. In addition, we are trying to expand the current methodology beyond the synthesis of rare sugars and apply the selective C–H bond breaking and forming protocol to common organic molecules to selectively manipulate these stereogenic centers."

The direct, selective conversion of one completely unprotected sugar into another constitutes a 'dream reaction' according to Professor Wendlandt, who said: "Taking into account the simplicity of key factors such as reaction setup, ready accessibility of catalysts, as well as the high-yielding output of rare sugar products, this conceptually new method would circumvent the conventional lengthy synthetic route to rare sugars, simultaneously allowing to save time, energy, and resources. As both unprotected sugars and more complex glycans, such as a pyranose nucleotide, can serve as suitable reactants, this is a clear indication of the method's vast potential for biomass conversion and use in medicinal/pharmaceutical chemistry."

Professor Wendlandt pointed out that during the development of this project, several challenges in product identification and purification that are unique to carbohydrate chemistry had to be addressed. Firstly, the authors found that the paucity of full characterization data in the reported literature was a major hurdle for product identification. "Some rare sugars synthesized in our paper had not been reported before, while reports of other sugars were scattered in the literature, such as allo-sucrose which was synthesized and reported back in 1980," said Professor Wendlandt. Some data was key in helping the group confirm the identity of a sugar prior to full characterization, first and foremost ^{13}C NMR spectra. "Unsurprisingly many ^{1}H peaks of a starting material, sucrose, match closely to our observed product, allo-sucrose. Luckily, the ^{13}C NMR peaks were distinct enough for us to confirm an initial 'hit'," said Professor Wendlandt.

A second major challenge was product separation, which was quite difficult due to the high polarity and structural similarity to their parent reactants – especially in the cases of completely unprotected monosaccharides, oligosaccharides, and the pyranonucleoside. "In those cases where no separation could be achieved using classical silica gel chromatography, we had to turn to special amine-functionalized silica or ion-exchange chromatography with a self-prepared Ca^{2+} form of resin," explained Professor Wendlandt. She continued: "Un-

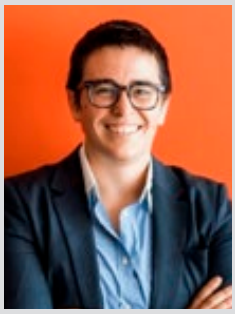


Scheme 1 Synthetic strategy, scope, and proposed mechanism

fortunately, these methods have no 'test scale', such as TLC to regular silica gel chromatography, leaving us blind in our initial purification attempts."

Glycans exhibit diverse physiological functions, ranging from energy storage and structure integrity to cell signaling and the regulation of intracellular processes. "In contrast to the biomass-derived monosaccharides, there are hundreds of distinct rare monosaccharides that are not readily accessible, thus limiting the scientific community's ability to explore the functions of the full glycan library," said Professor Wendlandt, who concluded: "We hope this effective and user-friendly synthetic protocol will change this situation."

About the authors



Prof. A. E. Wendlandt

Alison E. Wendlandt is currently the Cecil and Ida Green Career Development Assistant Professor in the Department of Chemistry at the Massachusetts Institute of Technology (USA). She was an undergraduate at the University of Chicago (USA) and carried out her PhD research at the University of Wisconsin – Madison (USA) under the supervision of Prof. Shannon S. Stahl. In 2015, Alison moved to Harvard University (USA), where she was an NIH Ruth Kirschstein Postdoctoral Fellow in the laboratory of Prof. Eric N. Jacobsen. She began her independent career at MIT in 2018.

Dr. Y. Wang

Yong Wang came from a beautiful city, Shaoxing, in Zhejiang province, China. He obtained both his B.S. (2009, advisor: Xiaonian Li) and M.S. (2012, advisors: Guofu Zhang and Chengrong Ding) degrees from Zhejiang University of Technology (P.R. of China). In 2013, he moved to the USA for his Ph.D. studies, working with Prof. X. Peter Zhang on the utilization of sulfonylhydrazones as aryl and alkyl diazo surrogates for asymmetric radical cyclopropanation and C–H alkylation via Co(II)-based metalloradical catalysis, and graduated from Boston College (USA) in 2018. He is currently working as a postdoctoral fellow in Prof. Alison Wendlandt's laboratory at Massachusetts Institute of Technology (USA), exploring novel organic transformations of carbohydrates.

H. Carder

Hayden Carder obtained his B.S. in chemistry from the University of Rochester (USA) in 2017. He worked as a research associate in the Benjamin Miller Lab at the University of Rochester Medical Center until starting his Ph.D. program at Massachusetts Institute of Technology (USA) in the fall of 2018.

Young Career Focus: Dr. Thomas Boddaert (Paris-Sud/Paris-Saclay University, France)

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. Thomas Boddaert (Paris-Sud/Paris-Saclay University, France).

Biographical Sketch

Dr. T. Boddaert

Thomas Boddaert studied chemistry at ESCOM-University of Cergy-Pontoise. He completed his PhD in 2009 at Aix-Marseille University under the supervision of Prof. Jean Rodriguez and Dr. Yoann Coquerel, working on the development of new domino/consecutive transformations in the field of organocatalysis. He then joined Prof. Jonathan Clayden at Manchester University (UK) as a one-year postdoctoral associate, working on the conformational control over the screw sense of achiral helical peptide foldamers. Late 2010, he returned to France for two additional postdoctoral years in the group of Dr. Jacques Maddaluno at the University of Rouen to study an intramolecular anionic rearrangement of organosilicate species in collaboration with Janssen-Cilag. In September 2012, he was appointed as an assistant professor at Paris-Sud/Paris-Saclay University (France). His current research interests focus mainly on cyclobutane derivatives, including their synthesis via photochemical approaches, studies of their chemical reactivity and their applications in the field of foldamer chemistry. In 2019, he received the Thieme Chemistry Journals Award.

INTERVIEW

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

Dr. T. Boddaert Cyclobutane derivatives are very versatile building blocks, thanks to the perfect balance between reactivity and stability. They can provide a source of chemical diversity due to their inherent ring strain as well as very interesting molecular scaffolds due to their specific behavior. Photochemical reactions can give an access to complex molecules that are difficult to obtain otherwise, such as our four-membered-ring compounds. Our research thus focuses on the development of new light-initiated reactions to prepare substituted cyclobutane and oxetane derivatives, but also to create molecular diversity through the combination of photochemical transformations in domino sequences. Our research is also centered on the reactivity of these four-membered-ring derivatives, which can be precursors of various functionalized compounds. Finally, the chemical behavior of cyclobutane moiety is being exploited to induce the robust global conformational organization of folded molecular architectures (Scheme 1).

SYNFORM *When did you get interested in synthesis?*

Dr. T. Boddaert While my interest in chemistry began during high school, my great passion for organic chemistry was born at the start of my further education thanks to my teachers. Indeed, two talented teachers (Dr. Jean Pierre Foulon and Dr. Gérard Cahiez) were able to share and pass on their love of organic synthesis. They delivered fascinating lecture courses in which they always included captivating practical details, anecdotes on the history of chemistry, personal chemical achievements… They taught me the crucial notions that I use daily as a researcher in organic chemistry, but at the same time they gave me valuable tools that I employ when I

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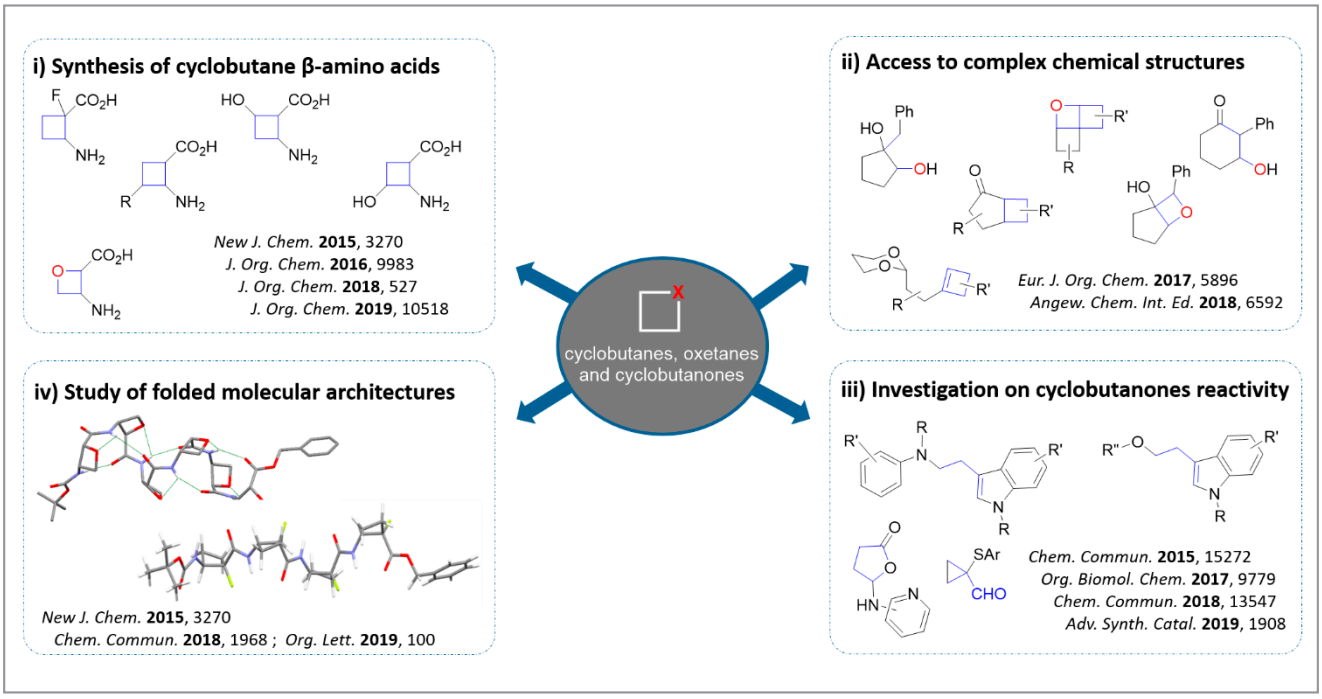

Scheme 1 Research overview

am in front of students as a teacher at the university. I will be always very grateful to these two chemistry teachers and the others I had in the following years.

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

Dr. T. Boddaert Today, society is unconsciously chemistry-dependent for drugs, materials, energy… and it will likely be the same in the future. Organic chemists will remain essential in these specific research fields but also in fundamental chemistry, to make new discoveries and to develop 'modern chemistry'. Indeed, while the pioneer organic chemists' aim was to establish new reactions and to increase the efficiency and selectivity of chemical transformations, the current and future job for chemists is to achieve similar results in an eco-compatible manner. Among environmentally friendly transformations, catalytic reactions using renewable catalysts, alternative activation modes and processes such as microwave irradiation, mechanochemistry, photochemistry and flow chemistry and multiple bond forming transformations (MBFT) via domino or consecutive sequences provide a promising response to the contemporary eco-compatible chemistry requirement.

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

Dr. T. Boddaert Our research interests are dedicated to the synthesis, the reactivity and the applications of four-membered-ring compounds. Functionalized cyclobutane scaffolds, prepared by photochemical approaches, are used as intermediates to prepare complex molecules and as building-blocks in well-organized molecular architectures. With these targeted applications, one of our current aims is to expand our library of functionalized cyclobutane β-amino acids, thanks to efficient, scalable and robust photochemical methodologies and to use them to construct the corresponding oligopeptides. With highly reactive intermediates, such as radical and/or excited species, light-initiated transformations are particularly compatible for MBFT processes. Our objective is to develop new domino, consecutive and/or multicomponent sequences which combine a photochemical step with thermal transformations or other photochemical reactions. Finally, the specific reactivity of cyclobutanones is still investigated to enlarge the potential of these derivatives as a source of chemical diversity (Scheme 1).

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

Dr. T. Boddaert One of our most important scientific results to date is an attractive synthesis of protected cyclobutane aldehydes and unprecedented tricyclic oxetanes from cyclopent-2-enones and alkenes in a selective manner via a domino process. While the cyclobutane aldehydes were obtained via a [2+2]-photocycloaddition then a Norrish-I cleavage followed by γ-hydrogen transfer, the tricyclic angular oxetanes were achieved by an additional intramolecular Paternò-Büchi reaction (*Angew. Chem. Int. Ed.* **2018**, *57*, 6592–6596). This achievement demonstrates the potential of photochemical transformations to access, both selectively and efficiently, original complex molecules from simple starting materials. It also highlights the possible combination of several photochemical transformations within a single domino sequence.

Coming soon

Literature Coverage

Reaction Scope and Mechanistic Insights of Nickel-Catalyzed Migratory Suzuki–Miyaura Cross-Coupling

Literature Coverage

Formyl-Selective Deuteration of Aldehydes with D_2O via Synergistic Organic and Photoredox Catalysis

Literature Coverage

Harnessing Applied Potential: Selective β-Hydrocarboxylation of Substituted Olefins

Further highlights

Synthesis **Review: Recent Advances in Synthetic Strategies to 2,3-Dihydrobenzofurans**
(by P. Lupattelli and co-workers)

Synlett **Account: Synthetic Studies Towards Spirocyclic Imine Marine Toxins Using *N*-Acyl Iminium Ions as Dienophiles in Diels–Alder Reactions**
(by D. P. Furkert, M. A. Brimble, and co-workers)

Synfacts **Synfact of the Month in category "Synthesis of Heterocycles": 2-Arylpiperidines by Palladium-Catalyzed Addition of Arylboronic Acids to Acylated 2-Hydroxypiperidines**

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