

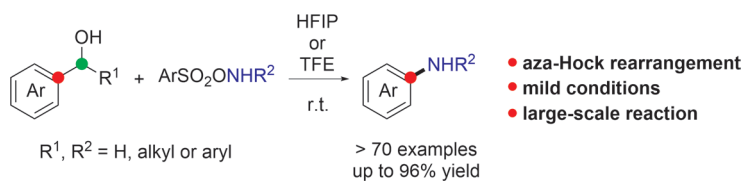
# Synform

People, Trends and Views in Chemical Synthesis

2022/04

## Hydroxylamine-Mediated C–C Amination via an Aza-Hock Rearrangement

Highlighted article by T. Wang, P. M. Stein, H. Shi, C. Hu, M. Rudolph, A. S. K. Hashmi



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## Dear Readers,

For many years, these editorials used to cover either scientific or professional or everyday life topics with a light touch, hopefully without being silly, because I thought that life was already sufficiently complicated and nobody needed an extra load of pressure before browsing the research content of SYNFORM. Well, I was wrong. And naïve. Because whatever we were going through as a community in those happy days, it was nothing compared to what was about to happen. First, two years of pandemic that disrupted our lives, our work and our economies, and now the Russian invasion of Ukraine, with its tragic toll of death and destruction, and the terrifying possibility of a global nuclear war just around the corner. Three years ago, we were still living in a magic bubble where the worst thing that could happen to us as scientists would probably be the rejection of a grant application or a paper. Then our labs had to shut down for many months because of the virus, with our students and postdocs suffering the most in this situation. And now the entire world is being turned inside out and upside down by this horrible war. The first effects on research are already visible. It is yesterday's news that the European Commission has suspended cooperation with Russian and Belarusian institutions in research, science and innovation, blocking all contracts, agreements and related funding. I am seeing widespread calls on social media for boycotting Russian science, with some journals – such as the Journal of Molecular Structure – already banning manuscripts submitted from Russian institutions. Whether or not this is the right thing to do, it won't stop here; actually, this is probably just the beginning. I won't hide that I am scared to know where all this will eventually lead us. This paralyzing feeling of impotence is probably the worst thing for us who are lucky enough not to be directly involved with this absurd war, so I would like to endorse and praise the Thieme initiative #StandWithUkraine to donate €50,000 to Doctors Without Borders for helping people in Ukraine. We are all with you dear Ukrainian friends, and I really hope we'll see each other again soon at some conference, enjoying discussions about chemistry, research and collaborations, as we used to do in those happy days before all this started... An emotional hug to all of you from us at Thieme Chemistry. This April issue is opened by the total synthesis of the

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polycyclic natural anticancer compound Hamigeran M by M. Dai (USA), which relies heavily on a series of innovative C–H bond functionalizations. The next literature coverage article comes from the group of A. S. K. Hashmi (Germany) and describes a novel approach to anilines from the corresponding benzylic alcohols through a hydroxylamine-mediated aza-Hock rearrangement. An interesting Young Career Focus interview with the 2022 Thieme Chemistry Journals Awardee J. G. West (USA) is the third article of this issue, which is closed by another literature coverage article, this time from France, and specifically from the labs of J. Moran and D. Leboeuf and their hexafluoroisopropanol-driven Friedel–Crafts arylation of aliphatic alcohols and epoxides to give 1,2-diarylethanes, aryl-alkanes and related compounds.

Enjoy your reading, without forgetting what is going on in Ukraine...

*Matteo Zanda*

### Contact

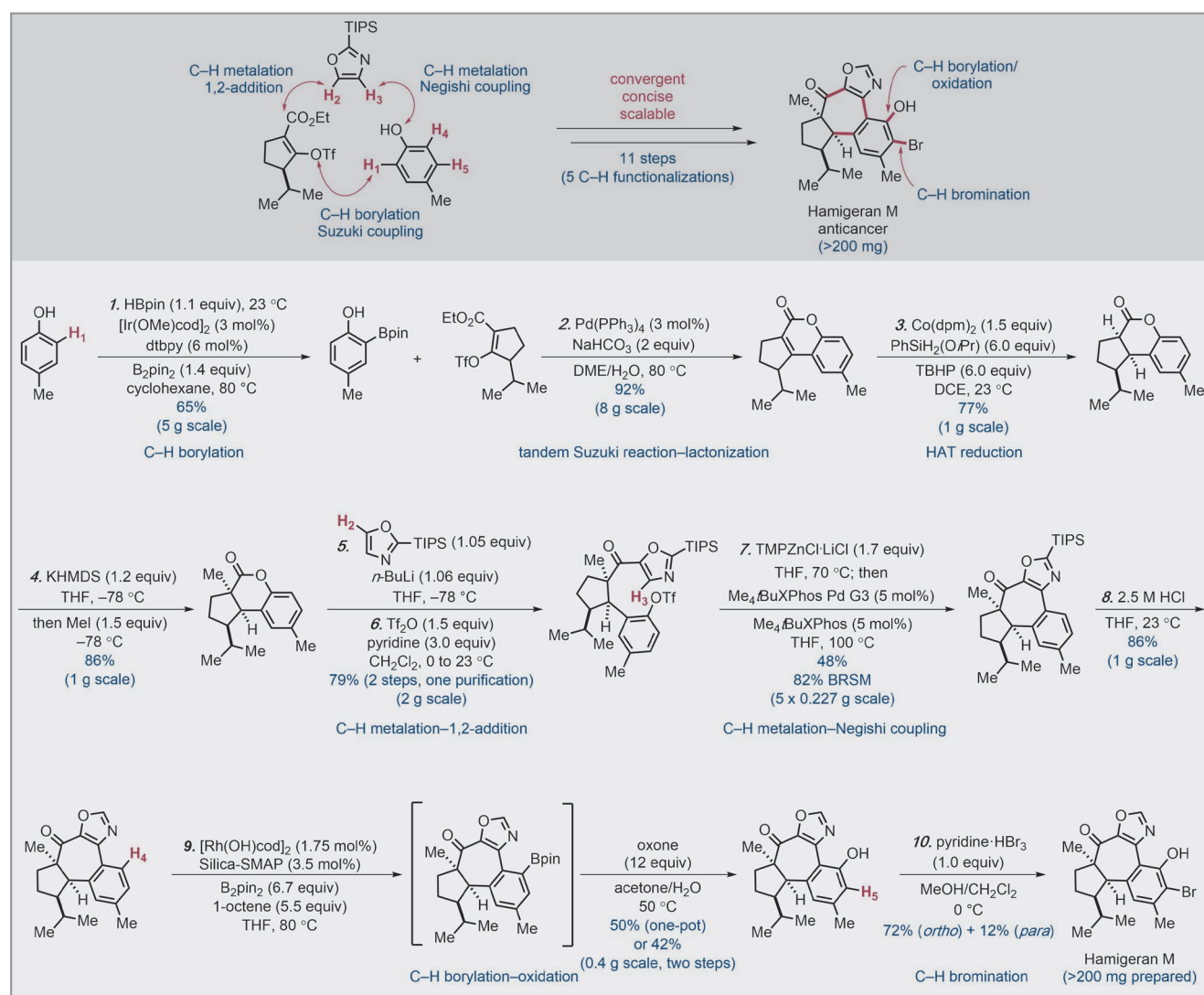
If you have any questions or wish to send feedback, please write to Matteo Zanda at: [synform@outlook.com](mailto:synform@outlook.com)

# 11-Step and Scalable Total Synthesis of Hamigeran M Enabled by Five C–H Functionalizations

*J. Am. Chem. Soc.* **2021**, *143*, 20084–20089

Advances in the field of C–H functionalization have brought revolutionary changes in the total synthesis of natural products. Direct functionalizations of C–H bonds in complex structural settings can significantly enhance synthetic efficiency and economy by avoiding preliminary functional group installations and subsequent manipulations. The group of Professor

Mingji Dai, from Purdue University (West Lafayette, Indiana, USA), has been developing innovative strategies and methodologies to facilitate the total synthesis and biological profiling of complex bioactive natural products (for recent examples of contributions from the Dai group: *Angew. Chem. Int. Ed.* **2021**, *61*, e202115633); *J. Am. Chem. Soc.* **2021**, *143*, 16383–16387;



**Scheme 1** Total synthesis of hamigeran M

*J. Am. Chem. Soc.* **2021**, *143*, 4379–4386; *Angew. Chem. Int. Ed.* **2021**, *60*, 24828–24832; *J. Am. Chem. Soc.* **2020**, *142*, 13677–13682). They recently reported the first total synthesis of the anticancer natural product hamigeran M. “Our synthetic strategy centers on several enabling C–H functionalizations. The hamigeran molecules are challenging synthetic targets, but with promising therapeutic potential,” said Professor Dai. His group and several other groups around the world are particularly interested in the hamigerans with a 6-7-5 tricyclic carbon skeleton. Among them, hamigeran M showed potent activity against leukemia cancer cell proliferation and features a unique oxazole moiety, which is rare in terpene natural products of marine origin. “While the oxazole moiety was formed toward the end of hamigeran M’s biosynthesis, we decided to use an oxazole as a key building block and take advantage of its reactivity for two key C–H functionalizations to forge two C–C bonds in the seven-membered ring,” said Professor Dai.

Their synthesis is summarized in Scheme 1. Five C–H functionalizations enabled Professor Dai and co-author Baiyang Jiang to complete a concise and modular total synthesis of hamigeran M in 11 steps. “These C–H functionalizations include a C–H borylation to the arylboronate building block for the next tandem Suzuki coupling–lactonization, a C–H metalation–1,2-addition to introduce the oxazole moiety, another oxazole C–H metalation–Negishi coupling to close the seven-membered ring, a late-stage oxazole-directed C–H

borylation–oxidation to install the hydroxyl group, and the last electrophilic C–H bromination. In addition to these C–H functionalizations, the HAT reduction of the tetrasubstituted double bond is highly challenging, but essential for the synthesis,” said Professor Dai. “Except for the electrophilic C–H bromination, which is a given, we had to treat each of the other four C–H functionalization reactions and the HAT reduction as individual methodology development projects and my co-author Baiyang Jiang deserves all the credit in realizing these transformations and completing the total synthesis,” commented Professor Dai. Their synthesis was also scalable and already provided over 200 mg of hamigeran M for them to profile and understand its biological activity, especially anticancer activity. Meanwhile, the concise and modular nature of the synthetic route also opened the gate for the synthesis of more natural and synthetic analogues, in order to improve the corresponding biological function. “We are excited to continue the hamigeran adventure, both synthetically and biologically,” concluded Professor Dai.

*Mattis Fank*

### About the authors



Prof. M. Dai

**Mingji Dai** was born in Pengzhou, Sichuan (P. R. of China). He received his B.S. degree from Peking University (P. R. of China) in 2002. After two years’ research with Professors Zhen Yang and Jiahua Chen in the same university, he went to New York City (USA) in 2004 and pursued graduate studies under the guidance of Professor Samuel J. Danishefsky at Columbia University. After earning his Ph.D. in 2009, he took a postdoctoral position

in the laboratory of Professor Stuart L. Schreiber at Harvard University (USA) and the Broad Institute (USA). In August 2012, he began his independent career as an assistant professor in the Chemistry Department and Center for Cancer Research of Purdue University (USA). He was promoted to associate professor with tenure in 2018 and full professor in 2020. He is currently a Showalter Faculty Scholar of Purdue University.



B. Jiang

**Baiyang Jiang** was born in Chengdu, Sichuan (P. R. of China). He received his B.S. and M.S. degrees from Peking University (P. R. of China), where he conducted research in the laboratory of Professor Suwei Dong. He joined Professor Mingji Dai’s group at Purdue University (USA) in 2017 and is currently pursuing his graduate studies in complex natural product total synthesis.

# Hydroxylamine-Mediated C–C Amination via an Aza-Hock Rearrangement

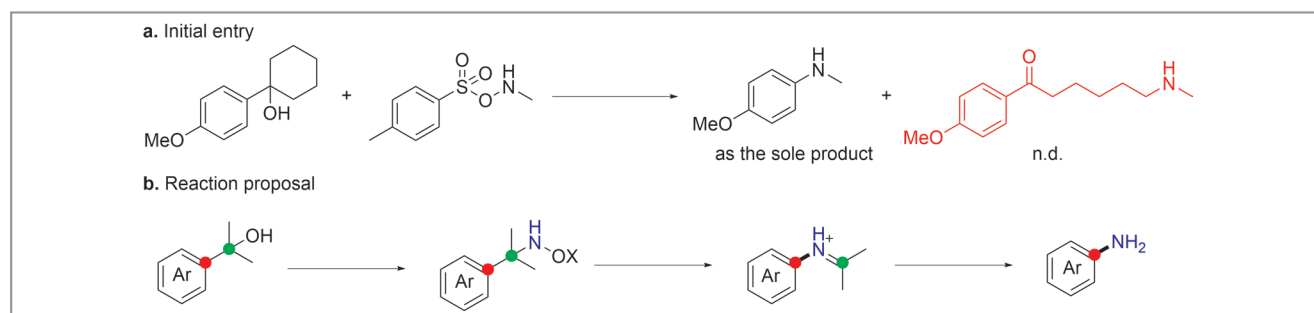
*Nat. Commun.* **2021**, *12*, 7029; DOI: 10.1038/s41467-021-27271-y

Anilines are precursors to many industrial chemicals, including dyes, resins, perfumes, pigments, herbicides, fungicides, agrochemicals, pharmaceuticals, explosives, various polymers such as polyurethanes and rubber chemicals. “For this reason, aniline synthesis is a common task for many chemists, but is always accompanied by chemoselectivity issues using both traditional nitration–reduction or modern arene C–H amination,” said Professor A. Stephen K. Hashmi, from Heidelberg University (Germany), who added: “However, C–C amination is an alternative way to address such site-selectivity issues. A few methods have been reported for harnessing this strategy to afford the desired anilines, albeit with hazardous reagents or harsh conditions: decarboxylative amination,<sup>1</sup> Beckmann rearrangement,<sup>2</sup> and Schmidt-like rearrangement<sup>3</sup> are among these methods. Therefore, new strategies for aniline synthesis via C–C amination in mild conditions are needed urgently.”

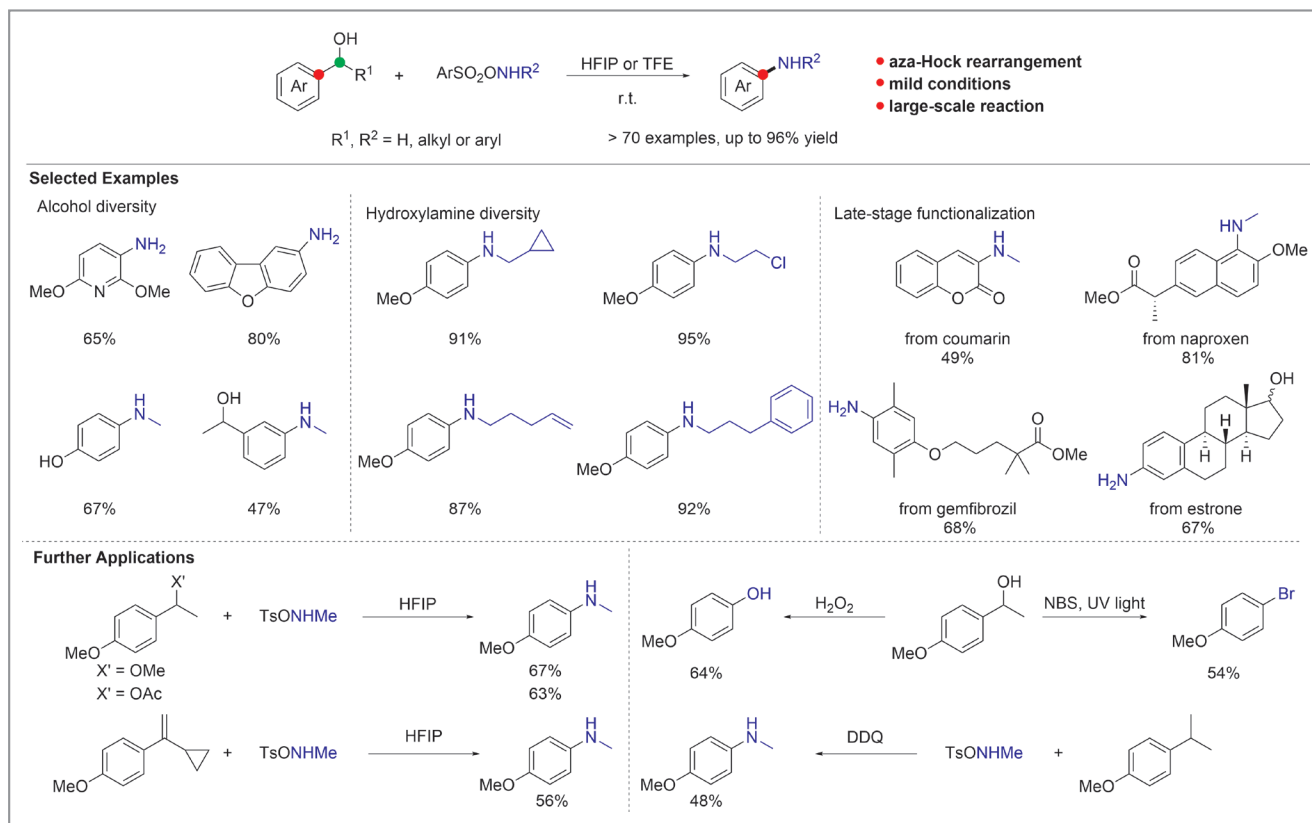
The group of Professor Hashmi is focused on gold chemistry and photochemistry research. “This aza-Hock amination – which plays a key role in our recent effort published in the title *Nat. Commun.* article – is based on our first work, ‘A metal-free direct arene C–H amination’,<sup>4</sup> which was developed following a serendipitous discovery in 2019,” said Professor Hashmi, who revealed that following this research, first author Tao Wang wondered: “Can we afford the sole product of aniline isomers via the more challenging C–C amination pathway?” Professor Hashmi explained: “The initial entry point for such a conversion started from tertiary benzyl alcohol with the aminating reagent (TsONHMe) in HFIP, which presented an unexpected result: the aniline, rather than the aliphatic amine, was isolated as the sole product (Scheme 1a).” Subse-

quent experiments with different benzylic alcohols exhibited similar outcomes: anilines as the products. Then an aza-Hock rearrangement for the transformation was proposed by Tao Wang in the 2021 paper.<sup>4</sup> “Cumene hydroxylamine derivatives, owing to the weak N–O bond (similar to the O–O bond in cumene hydroperoxide), are susceptible to a Hock-type rearrangement in an acidic solvent, yielding anilines as products,” explained Professor Hashmi (Scheme 1b).

“This aza-Hock amination shows quite a broad substrate scope (Scheme 2): a variety of anilines are accessible from normal benzylic alcohols/hydroxylamine derivatives,” said Professor Hashmi, who went on by explaining that late-stage functionalizations and large-scale reactions are also viable under the standard conditions; further application showed all benzylic cation precursors – like benzylic ether/ester, styrene and even alkylarenes – are accessible with the aza-Hock rearrangement, which serves as a valuable tool for aniline synthesis. “Besides, phenol and aryl bromide are also accessible with a similar strategy. For the substrate with two benzylic alcohol groups, only one alcohol group is cleaved,” said Prof. Hashmi, adding: “The hydrolysis of protonated imines in the reaction mixture, occurring only during the workup with sodium hydrogen carbonate (and not in situ with the one equivalent of neutral water formed in the reaction), explains the selective cleavage of one C–C bond instead of two C–C bonds in substrates with two reactive benzylic alcohol groups; the iminium group in the intermediate iminium tosylate electronically de-activates the arene ring, so the second benzylic alcohol does not react anymore.”



**Scheme 1** Initial entry and reaction proposal



Scheme 2 Aza-Hock rearrangement: reaction scope and further applications

Prof. Hashmi concluded: “Despite some early evidence for such a reactivity pattern, its synthetic utility would be limited until it was confirmed for certain by our studies. Thus, our report might pave the way for further protocols based on this reactivity pattern in the future.”

Matthew Fanale

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## About the authors



Dr. T. Wang

**Tao Wang** is from Xiangcheng, Henan, P. R. of China. He received his B.S. in pharmacy from Henan University (P. R. of China) in 2013 and obtained his M.S. in pharmaceutical chemistry from Chengdu Institute of Biology, Chinese Academy of Sciences (P. R. of China) in 2016. Then he worked in Bioduro (Shanghai, P. R. of China) as a scientist. He pursued his Ph.D. in organic chemistry from Heidelberg University (Germany) under Prof. A. Stephen K. Hashmi's supervision since 2018. He completed his Ph.D. in 2021 and now is researching chemical biology.



P. M. Stein

**Philipp M. Stein** received both his B.Sc. (2017) and M.Sc. (2019) degrees in chemistry from Heidelberg University (Germany). In recognition of his outstanding study achievements, he was awarded a scholarship from the Dr. Sophie-Berntsen Fund. For his Ph.D. studies he joined the research group of Prof. A. Stephen K. Hashmi in 2019. He works in the field of homogeneous gold catalysis and the investigation of reaction kinetics. Since 2020 he is a full scholarship holder funded by the Hector Fellow Academy.



H. Shi

**Hongwei Shi** is from Anhui, P. R. of China. He earned his B.S. in pharmaceutical engineering from Ningxia University (P. R. of China) in 2014. He earned his M.A. at Shaanxi Normal University (P. R. of China) in 2017, where he performed research with Prof. Jun Yang, mainly focusing on the total synthesis of natural products. He began his Ph.D. studies at Heidelberg University (Germany) in 2018, where he is developing gold-catalyzed cross-coupling reactions under the mentorship of Prof. A. Stephen K. Hashmi.



Dr. C. Hu

**Chao Hu** was born in Jingzhou, P. R. of China. He received his Ph.D. in 2020 under the supervision of Prof. A. Stephen K. Hashmi at Heidelberg University (Germany), where his doctoral work investigated mainly gold-catalyzed cycloisomerization reactions. In 2021, he joined Prof. Tian Qin's group at the University of Texas Southwestern Medical Center (USA) for post-doctoral research on boron chemistry in drug discovery.



Dr. M. Rudolph

**Matthias Rudolph** studied chemistry at the University of Stuttgart (Germany). He received his diploma grade in 2004. After that he pursued Ph.D. studies in the field of gold catalysis under the supervision of A. Stephen K. Hashmi until 2008. Since 2008 he is permanently employed at the Ruprecht-Karls University, Heidelberg (Germany) as a scientific co-worker. His research interest is mainly focused on methodology development in the field of homogeneous gold catalysis.



Prof. A. S. K. Hashmi

**A. Stephen K. Hashmi** studied chemistry at Ludwig-Maximilians-Universität München (Germany). He obtained his diploma and PhD with Prof. G. Szeimies in the field of nickel- and iron-catalyzed cross coupling of highly strained organic compounds. As a postdoc with Prof. B. M. Trost at Stanford University (USA) he investigated palladium-catalyzed enyne metathesis. During his habilitation with Prof. J. Mulzer at Freie Universität Berlin (Germany), Frankfurt University (Germany) and the University of Vienna (Austria), he developed enantiomerically pure organopalladium compounds and new palladium-catalyzed conversions of allenes. In 1998, a Heisenberg fellowship of the Deutsche Forschungsgemeinschaft (German Research Foundation) for a proposal on gold-catalyzed reactions for organic synthesis – still a major focus of the group – was awarded to him. His next stations were the University of Tasmania (Australia) and Marburg University (Germany). He was appointed to associate professor for organic chemistry at Stuttgart University (Germany) in 2001 and since 2007 he is full professor for organic chemistry at Heidelberg University (Germany).

## Young Career Focus: Prof. Julian G. West (Rice University, USA)

**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. Julian G. West (Rice University, USA).

### Biographical Sketch



Prof. J. G. West

**Julian G. West** is a Canadian-American chemist who firmly believes the greatest advances in science are only possible through supporting and empowering a diverse team of scholars.

Julian spent his mentored career collecting different chemistry experiences in the US and Canada. He received his B.Sc.H. in chemistry from the University of British Columbia Vancouver (Canada), studying photodecarboxylations with Dr. Glenn Sammis. Next, he pursued his Ph.D. as an NSF Graduate Research Fellow at Princeton (USA) with Dr. Erik Sorensen, investigating photocatalytic reactions using earth-abundant elements. Finally, he was an NIH and Resnick Postdoctoral Fellow at Caltech (USA), where he investigated inorganic chemistry and electrocatalysis with Drs. Harry Gray and Brian Stoltz.

Julian joined Rice University (USA) in July 2019 as an assistant professor of chemistry, where he and his group have been captivated by the possibilities of free radicals in catalysis. His group seeks to develop a broad collection of useful reactions, and many projects come from exciting student ideas.

Julian recognizes the importance of work–life balance to creativity in science and self-actualization as a person, and group members pursue a wide range of interests outside of lab. Personally, he likes to play music, run, and sometimes write magazine articles.

Julian and his group have been recognized by awards including the NIH Maximizing Investigator's Research Award, the ACS PRF Doctoral New Investigator Award, a CPRIT Scholar in Cancer Research Award and being named on the 2021 Forbes 30 Under 30 – Science list. He is particularly proud of receiving the 2021 Rice Graduate Student Association Faculty Teaching and Mentoring Award.

### INTERVIEW

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

**Prof. J. G. West** Our current research has several intersecting themes: free-radical chemistry, earth-abundant element catalysis, and photochemistry. These main topics are mixed-and-matched by our group members in their pursuit of interesting new chemical reactions, from radical hydrogenation to C–F bond formation. We are not too tied to specific applications as long as they could be useful to someone and/or teach us something new about reactivity.

**SYNFORM** *When did you get interested in synthesis?*

**Prof. J. G. West** I found organic chemistry fairly interesting the first time I encountered it in college and always enjoyed the coursework. However, the first time I became seriously interested in pursuing synthesis research as a career was during my undergraduate research with Prof. Glenn Sammis at UBC. Glenn's kindness, enthusiasm, and sincere belief in the potential of his group members really made the difference in my decision to apply to graduate school in synthesis, and his excellent advice helped me to pick outstanding mentors (especially Profs. Erik Sorensen, Harry Gray, and Brian Stoltz) who similarly prioritize mentoring and supporting their trainees. This thoughtful support really grew my interest in the field and paying it forward is my primary motivation as a professor!

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

**Prof. J. G. West** Organic synthesis is a beautiful field that will always have a role in modern life (so long as we need to make covalent molecules of carbon and hydrogen!). In my view, the next great frontier in organic synthesis is not in a flask, but in how we interact with one another. The historic culture of organic synthesis has not been an inclusive one, and I think that truly changing this will be transformative for



the field, not just in the wealth of new ideas and perspectives brought by recruiting and engaging researchers from historically excluded groups, but also in taking the time to seriously reevaluate how to teach, mentor, and research effectively.

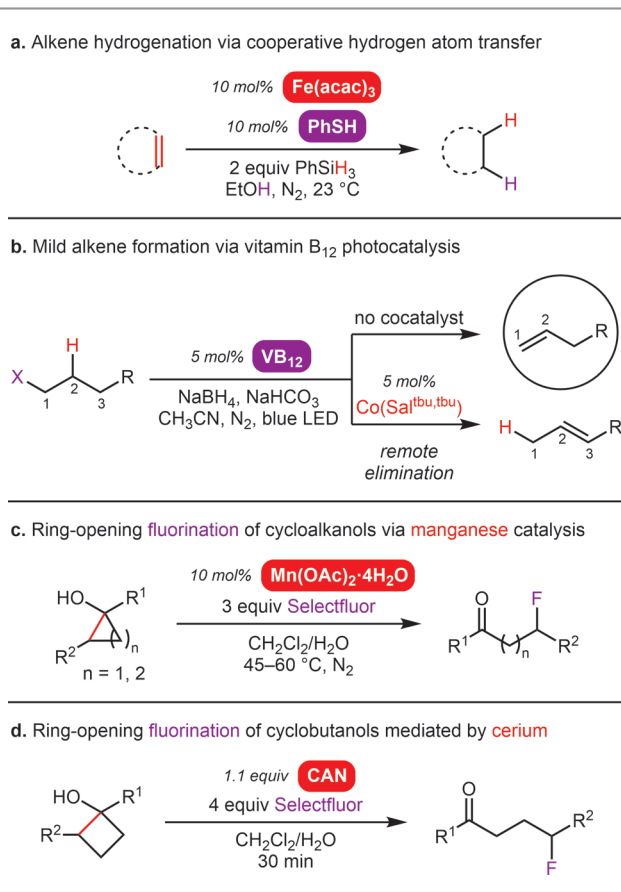
One example of how we are trying to build an inclusive culture in our group is to emphasize the importance of work-life balance and respecting everyone's time outside the lab. Expecting significant efforts outside of normal business hours (e.g. evening or weekend group meetings) can be very challenging for people with caregiving obligations or other commitments, so we do not schedule meetings and events outside normal business hours (9–5) in our lab. Similarly, flexibility can be important to work around other commitments, so we do not have “set hours,” though this freedom does not mean working all the time (I encourage ~40 h/week). I also try to normalize and model this approach by following it myself: I never come in after dinner or on the weekend!

I've been really lucky to recruit a diverse team of co-workers interested in this environment, and I think that we have succeeded (so far) because of it, not in spite of it!

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

**Prof. J. G. West** Our area of research is constantly evolving in response to the interests of our group members; however, I would say that all our current projects fit broadly into the chemistry of free radicals. These intermediates have such rich and diverse reactivity that they can't help but catch the imagination of aspiring synthetic chemists! Thus far, we've found some intriguing cooperative hydrogen atom transfer (cHAT) reactivity of iron and thiol cocatalysts for hydrogenation, some fascinating vitamin B12 photocatalysis for making olefins, and a really direct approach for C–C bond fluorination using cerium or manganese (Scheme 1). In addition to expanding on these areas, we also have some new, student-driven projects in photocatalysis that are just starting to develop and we hope to be able to share soon!

In terms of aims, I would say that I take a “bottom-up” approach to research and training. I think that great science is not something dreamed up by a charismatic “genius” leader, but rather the natural result of curious people being empowered and supported in their explorations. Thus, my greatest aim is to help my group members figure out the questions that get them excited and give them the tools and support to answer them! Some of this support is to encourage everyone to foster their development outside of lab as well, both for the benefits to creativity and because life isn't just about work.



**Scheme 1** New reactions developed by the West group thus far

To sum it up, my primary goal is to help my group members to develop as scientists and people; great chemistry will naturally follow!

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

**Prof. J. G. West** I am incredibly proud of every project we have pursued in our lab, especially given the extreme impacts of the COVID-19 pandemic on our research. Every paper we've published has been during the pandemic, and my group has had to overcome some fearsome challenges both in the lab (including occupancy limits, supply chain strain, ever-changing research policies) and outside (including health challenges for friends and family, social distancing, and the ongoing stress of a global pandemic) to finish them. It's absolutely remarkable what these scientists have been able to do under such adversity and I am so grateful to work with them.

I hope that the chemists of the future will come to view some of our research as important; however, I think that helping my group members past, present, and future become curious and balanced scientists will be my most significant achievement.

A handwritten signature in orange ink that reads "Matthew Farah".

# Unlocking the Friedel–Crafts Arylation of Primary Aliphatic Alcohols and Epoxides Driven by Hexafluoroisopropanol

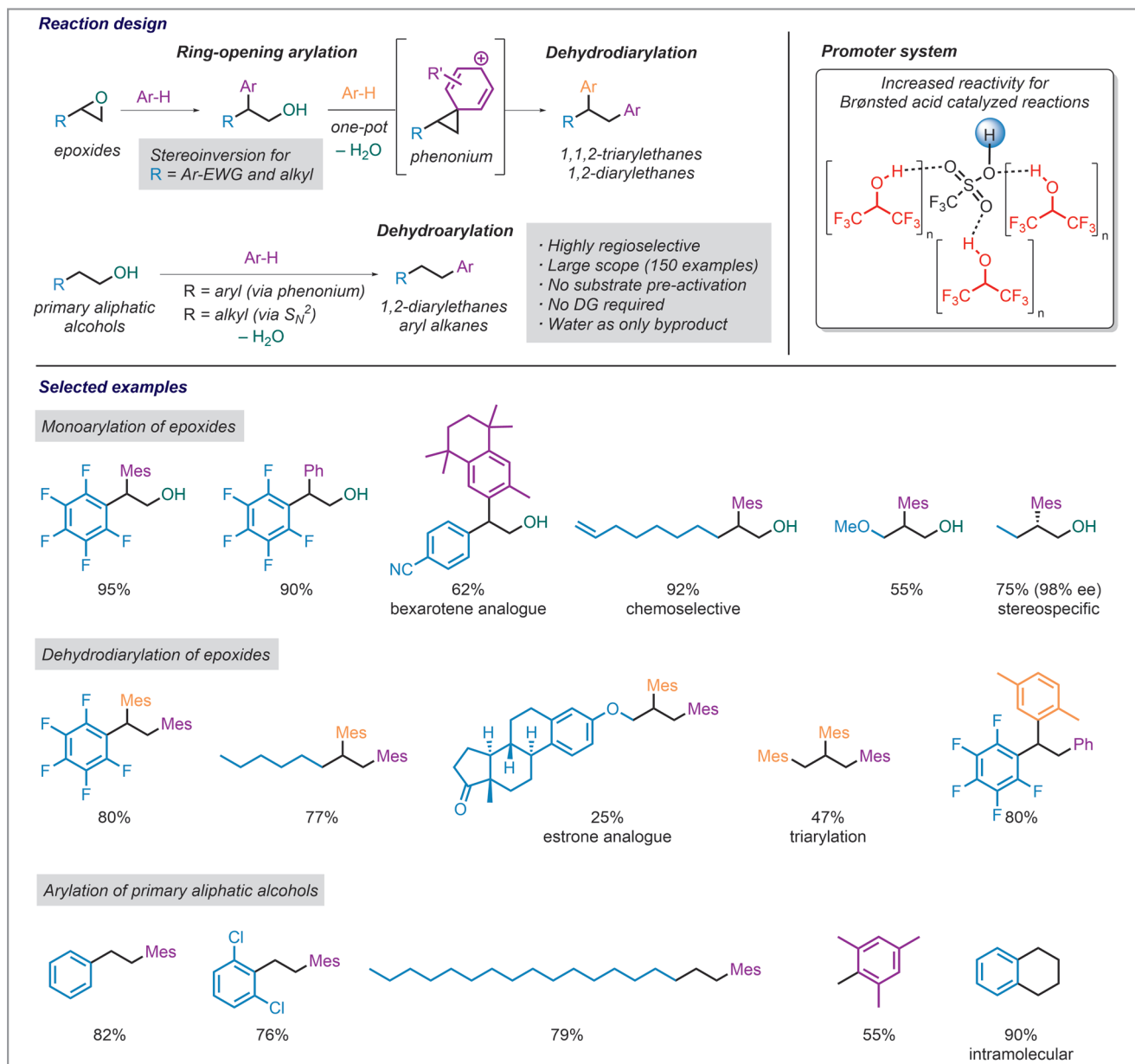
*Chem* 2021, 7, 3425–3441

The Friedel–Crafts alkylation is an important way to form  $C_{sp^2}$ – $C_{sp^3}$  bonds. Traditionally, the reaction starts from alkyl halides and uses a stoichiometric quantity of a Lewis acid such as aluminium trichloride. However, alkyl halides are usually prepared from alcohols. Using alcohols directly in the Friedel–Crafts reaction removes the steps and reagents needed for the pre-activation of the alcohol and eliminates the associated waste. Direct Friedel–Crafts reactions starting from alcohols date back to the 1940s, but they were initially limited to tertiary aliphatic alcohols and were carried out with large excesses of Brønsted acids as the promoters, which were often used directly as solvent. Over the subsequent 70 years, the Friedel–Crafts reaction with alcohols was eventually extended to other substitution patterns, such as benzylic, allylic, and propargylic alcohols, otherwise known as  $\pi$ -activated alcohols. Chemists also started to realize that the reaction could be achieved with catalytic quantities of a Lewis or Brønsted acid promoter. However, highly electronically deactivated  $\pi$ -activated alcohols and primary aliphatic alcohols have always remained challenging due to the difficulty (or impossibility) of forming a carbocation intermediate from such substrates. In 2017, the group of Prof. Joseph Moran at the University of Strasbourg (France) found that the combination of catalytic quantities of the strong Brønsted acid TfOH and the solvent hexafluoroisopropanol (HFIP) was an excellent promoter system for direct Friedel–Crafts reactions of electronically deactivated benzylic<sup>1</sup> and propargylic alcohols.<sup>2</sup> “What is important to understand is that HFIP is not innocent here. Its capacity to generate H-bond networks is a key factor to significantly harness the acidity of the promoter system and activate rather challenging substrates,” said Professor Moran. He added: “We then became excited about the prospects of using this catalytic system to enable direct Friedel–Crafts reactions of primary aliphatic alcohols longer than two carbons, which had been a longstanding challenge in the field. Primary aliphatic carbocations are too unstable, so the reaction needs to operate through an  $S_N^2$ -type mechanism, which is not so easy, because competing carbocation rearrangements lead to undesired branched products,” he explained.

At the same time, Dr. David Leboeuf, who was then working at the University Paris-Saclay (France), had been exploring how Lewis and Brønsted acid catalysts in HFIP could push the

boundaries of classic synthetic transformations such as the hydroarylation of highly deactivated styrenes<sup>3</sup> and halofunctionalization of unactivated alkenes,<sup>4</sup> making similar observations as Prof. Moran regarding the role of HFIP. “I started to think about whether the TfOH/HFIP system might enable Friedel–Crafts reactions of electronically deactivated epoxides and aliphatic epoxides, which were classically excluded from Friedel–Crafts methodologies. Rather than compete against each other on these closely related problems within the same country, we decided to align our forces,” said Dr. Leboeuf, who moved to Strasbourg in 2019. He continued: “The interesting thing about merging these two projects is that the product of a Friedel–Crafts reaction of an epoxide is a primary alcohol, so solving both problems at the same time allowed us to develop sequential Friedel–Crafts reactions starting from epoxides, where two different arenes can be introduced into the molecule in a single experiment.”

In the end, the team was able to show that primary aliphatic alcohols and electronically deactivated epoxides could undergo Friedel–Crafts reactions with a variety of arenes under very similar conditions (5–10 mol% TfOH in HFIP) – only the temperature varied. The researchers found that electronically deactivated epoxides, such as pentafluorophenylstyrene oxide, react at 0–40 °C, and undergo stereochemical inversion upon opening for most substrates. Primary phenylethanol reacts at 60 °C because of their ability to react through a phenonium ion intermediate. Simple primary aliphatic alcohols that must react through a direct  $S_N^2$  reaction require higher temperatures of 140 °C in a sealed tube. “As anticipated, we could combine the epoxide and alcohol reactions in one pot to directly access complex arylated scaffolds from epoxides,” remarked Prof. Moran. The overall reaction schemes and selected examples are shown in Scheme 1. However, epoxides and primary aliphatic alcohols weren't the only substrates that ended up undergoing Friedel–Crafts reactions under these conditions. “The conditions turned out to be compatible with secondary and tertiary aliphatic alcohols, oxetanes, isochromans, and aziridines as electrophiles,” explained Dr. Leboeuf. “This is as close as you can get right now to general conditions for the Friedel–Crafts reaction without stoichiometric pre-activation,” he added, continuing: “Yet Joseph and I both often get the criticism that HFIP is expensive



**Scheme 1** Friedel–Crafts reactions of electronically deactivated epoxides and primary aliphatic alcohols without stoichiometric activating agents

and corrosive. However, based on the simplicity of our system and the fact that those reactions cannot be accomplished in traditional solvents with existing catalysts, the reward is greater.”

Of course, great research does not happen without a great team. “The lion’s share of the credit must go to the co-workers who did the experiments, especially to PhD student Shaofei Zhang, who did the bulk of the work, and to postdoctoral fel-

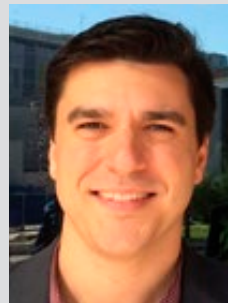
low Dr. Marie Vayer, who helped push it over the line,” said Dr. Leboeuf. Professor Moran added: “The work also relied on preliminary results generated by two previous PhD students and an MSc intern, all of whom are co-authors on the paper. We’re also grateful to Prof. Chris Rowley at Carleton University (Canada) and his PhD student Nazanin Rezajooei for their help with DFT calculations.”

*Matthew Farnik*

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**Joseph Moran** is a professor and group leader at ISIS, a joint institute of the University of Strasbourg (France) and the CNRS. After completing his PhD in organic chemistry (André Beauchemin, University of Ottawa, Canada), he took postdoctoral positions in chemical biology (John Pezacki, NRC Canada) and transition-metal catalysis (Michael Krische, University of Texas at Austin, USA). He moved to France as an assistant professor in 2012 and was promoted to full professor in 2018. His research interests include prebiotic systems chemistry, supramolecular catalysis, and the use of vibrational strong coupling in organic chemistry.



Dr. D. Leboeuf

**David Leboeuf** is an associate professor at the University of Strasbourg (ISIS) in France. He earned a PhD in 2009 at the Université Pierre et Marie Curie (France), where he explored new transition-metal-catalyzed cyclizations with Max Malacria. He then moved to the University of Rochester (USA) with Alison J. Frontier to investigate abnormal Nazarov electrocyclizations (2010–2012). After a second postdoctoral stay at the Institut Català d'Investigació Química (ICIQ, Spain) with Antonio M. Echavarren, developing new gold catalysts (2012–2013), he was appointed by the CNRS as assistant professor in 2013 at the Université Paris-Saclay (France). In 2019, he joined ISIS (UNISTRA), where he is currently developing new simple synthetic methods featuring supramolecular chemistry, cultivating the use of HFIP in synthesis.

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### — Literature Coverage

#### Insertion of Ammonia into Alkenes To Build Aromatic N-Heterocycles

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