

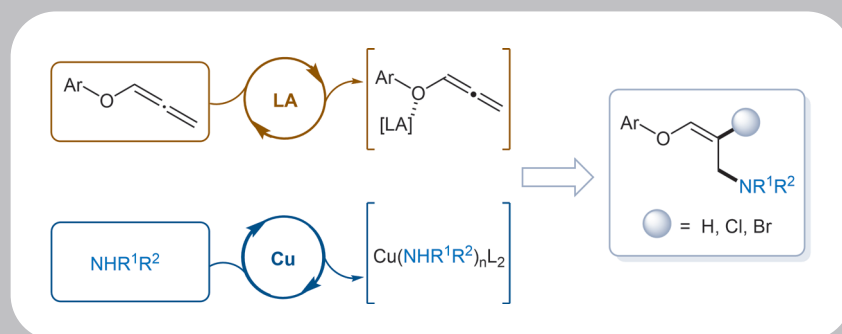
Synform

People, Trends and Views in Chemical Synthesis

2022/02

Synthesis of Medicinally Relevant Oxalylamines via Copper/Lewis Acid Synergistic Catalysis

Highlighted article by Z. Wu, M. Hu, Y. Jin, J. Li, W. Wu, H. Jiang



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Dear Readers,

Perhaps not surprisingly – given the winter season – Europe and the rest of the world are still grappling with the much-hated virus, which appears to like us very much and has no intention whatsoever to leave us alone. We are running out of Greek letters for the variants, and I am afraid we'll soon switch to words, followed by sentences... but the good news is that although the virus appears to be becoming increasingly infectious, it seems at least to be less harmful, although the mental health effect is not getting any better, is it, after two years of this struggle. After a glimpse at pseudo-normality with the return of some seminars and meetings in person – albeit with a constellation of anti-virus rules and precautions – online events are sadly returning as the preferred option, at least for the time being, which is definitely not very encouraging. I do feel that whoever came up with the motto “What doesn't kill you, mutates and tries again” was really spot on, besides having a very good sense of dark humour... Switching to the very reason for this brief editorial, I don't know how well our authors of this February 2022 issue of SYNFORM are coping with the persisting pandemic restrictions, but there is no doubt that the quality of their research is truly fantastic. The opening story comes from the labs of W. Wu and H. Jiang (P. R. of China) and their novel catalytic strategy for accessing medicinally relevant oxalylamines. The next article is a Young Career Focus interview with Y. Wang (USA) who reflects on his research – predominantly in the area of organometallic synthesis – and his past, present and future career prospects. The following Literature Coverage article focuses on the recent strategy using trisulfide-1,1-dioxides to achieve site-selective radical disulfuration of carboxylic acids, as published in an Angew. Chem. Int. Ed. article by D. A. Pratt (Canada). Last but certainly not least, we

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read about the carbonyl 1,2-transposition via triflate-mediated α -amination described in a Science article by G. Dong (USA).

Enjoy your reading!



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

Synthesis of Medicinally Relevant Oxallylamines via Copper/Lewis Acid Synergistic Catalysis

Sci. Adv. **2021**, *7*, eabh4088; DOI: 10.1126/sciadv.abh4088

Allylamines, especially those with easy-to-transform functional groups, are a critically important class of building blocks in the fields of organic synthesis and medicinal chemistry.¹ Typically, these compounds are also versatile synthetic intermediates in the atom-economical construction of alkaloids, amino acids, and complex natural products. “Transition-metal-catalyzed amination of olefins is an atom-economical pathway to construct ubiquitous C–N bonds,^{2,3}” said Professor Huanfeng Jiang, from the South China University of Technology (Guangzhou, P. R. China), whose research interests focus on the construction of C–C and C–X (X = O, N, S, etc.) bonds of unsaturated hydrocarbons catalyzed by transition metals with green oxidants. “Despite the simplicity and high efficiency of this reaction, amines with free N–H units often coordinate to transition metals more strongly than olefins, thus remarkably decreasing the reactivity of the catalyst.^{4,5} However, current strategies mostly build the *E*-type allylamines” added Professor Jiang, explaining that efficient and selective synthesis of *Z*-allylamines still remains a challenging task due to their thermodynamic instability.⁶ “Electron-rich alkoxyallenes, as a kind of olefin with multiple reaction sites and high activity, may solve the problem of the insufficient coordination ability with the catalyst in the traditional amination process,” said Professor Jiang. “Lewis acids are known to have an empty orbital, which can coordinate with a lone pair of electrons on the oxygen atom,” continued Professor Jiang, who added: “We envisioned that merging an oxygen atom in alkoxyallenes with a Lewis acid might effectively tune the selectivity of the accumulated double bonds. Meanwhile, the synergy effect of the copper atom and a Lewis acid would ensure the control of the configuration over the activated intermediate.” To verify the feasibility of this strategy, Master’s student Ziyang Wu tried to employ phenyl 1,2-propadienyl ether and *N*,2-dimethylaniline as the model substrates. As expected, when utilizing Cu(OAc)₂ as a catalyst and AgF as Lewis acid in CH₂Cl₂ at 50 °C for 6 hours, the hydroamination product (*Z*)-**3a** (Scheme 1) could be obtained, and the desired chloraminated product (*E*)-**4a** were afforded by using 60 mol% CuCl₂ under an oxygen (1 atm) atmosphere.

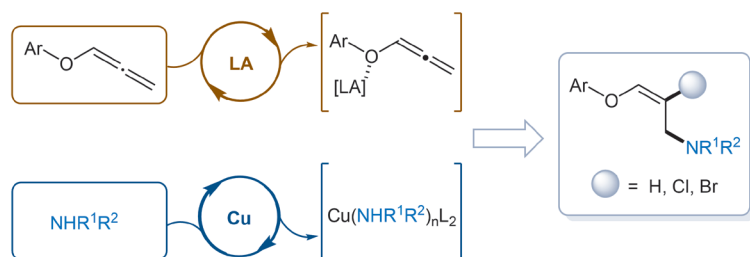
Ms. Wu then undertook a comprehensive screening of reaction conditions, demonstrating that Lewis acid and copper catalyst were essential for the success of this hydroamination

reaction and CuX₂ could work as both the catalyst and Lewis acid, playing the role of halogen source to realize the amination difunctionalization of allenes. To the group’s delight, this efficient amination of allenyl ethers showed broad substrate scope and high turnover number (TON > 1000). Moreover, the synthesis and late-stage functionalization of pharmaceutically relevant molecules and natural products, such as desipramine and pramoxine, were also feasible. “However, some products were obtained as *Z*- and *E*-type mixtures and the polarities of these isomers were very similar, which brought some troubles to the separation and purification work,” remarked Ms. Wu, continuing: “Eventually, we successfully separated several isomers through preparative chromatography.”

To gain more insight into the mechanism of the amination process, the group carried out a series of control experiments, including a deuterium labeling study, radical trapping experiments, and kinetic analysis experiments (Scheme 2). Professor Wanqing Wu, from the South China University of Technology (P. R. China), revealed that Ms. Wu made some interesting discoveries, specifically that the hydroamination and chloramination reactions might go through different pathways (Scheme 3) because of the different coordination by different Lewis acids. “A first-order dependence just on the concentration of Cu catalyst revealed that hydrolysis should be the rate-determining step, and the coordination and toxic effect of amines could be ignored,” said Professor Wu, who added: “Such a copper/Lewis acid synergistic catalysis may bring some enlightenment to other types of amination reactions.”

Professors Jiang and Wu concluded: “In short, the reaction exhibited broad substrate scope for amines as well as alkoxyallenes, which might provide a feasible way to synthesize valuable medicinally relevant oxallylamines. Our group will continue to explore efficient and green synthetic methods in the field of transition-metal catalysis to construct high-value-added chemical drugs and functional molecules.”

Reaction design and development

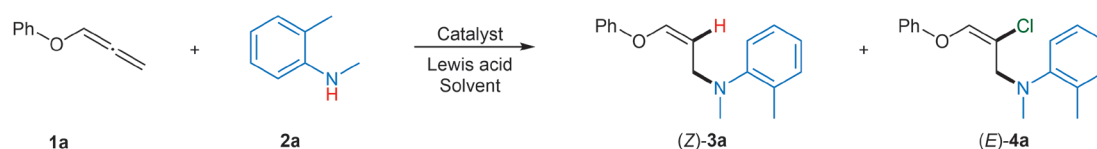


Challenges

- Control of regio- and stereoselectivity
- Competition between hydroamination and haloamination

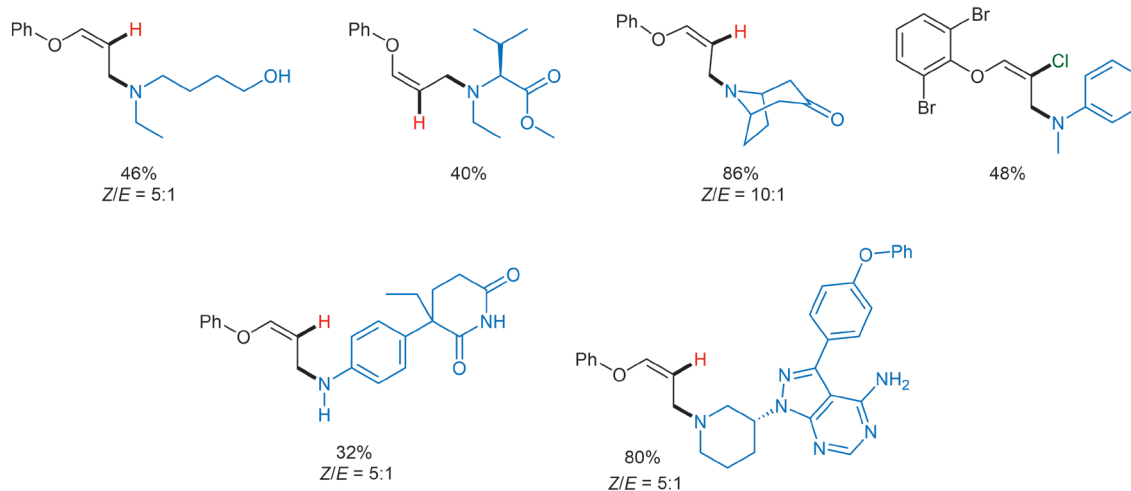
Advantages

- Highly chemo-, regio- and stereoselective
- Gram-scale synthesis with TON up to 1133
- 104 examples, up to 98% yield

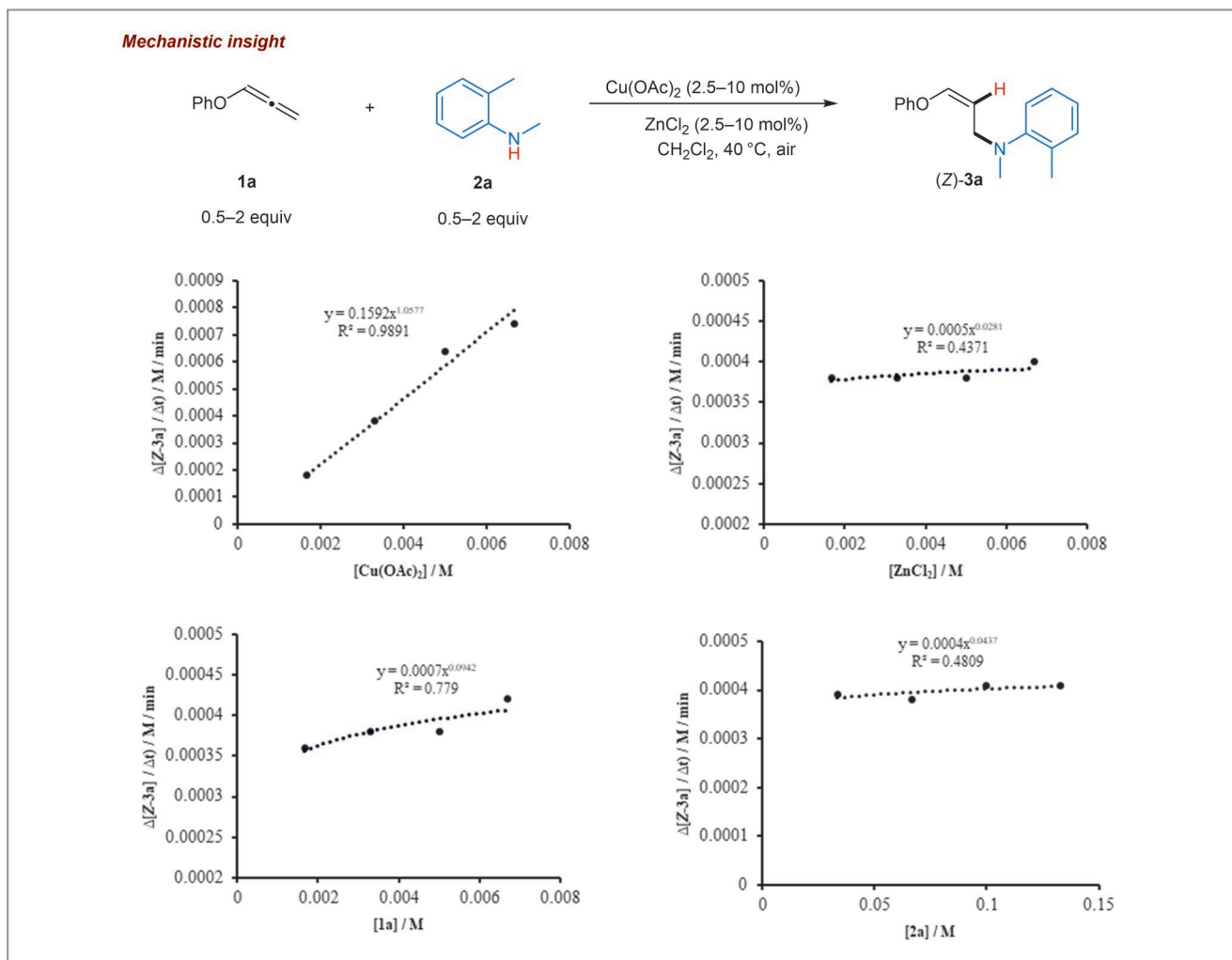


Catalyst	Lewis acid	Solvent	Yield of (Z)-3a (%)	Yield of (E)-4a (%)
Cu(OAc) ₂	ZnCl ₂	CH ₂ Cl ₂	98	ND
–	CuCl ₂	Dioxane	10	86

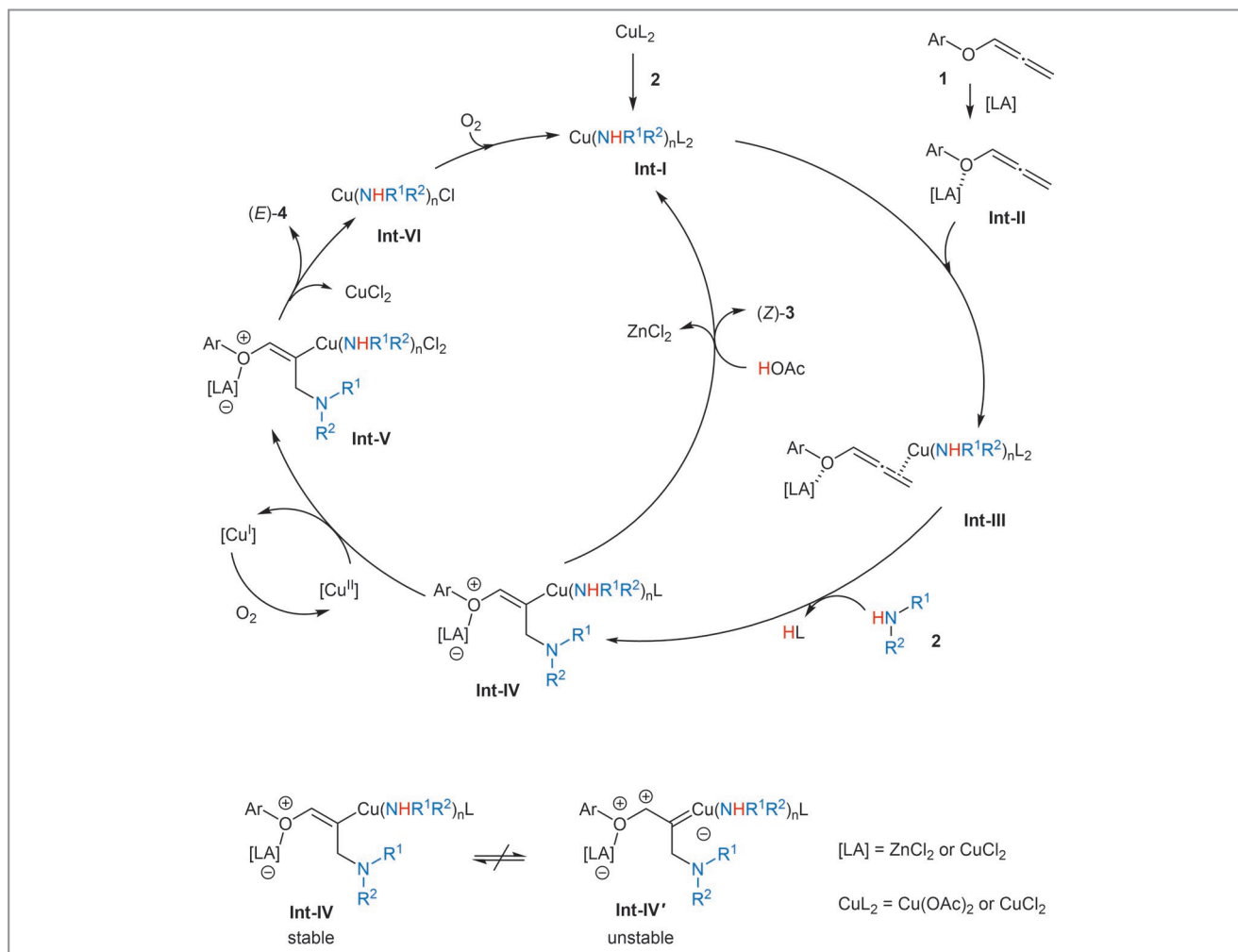
Selected examples



Scheme 1 Synthesis of medicinally relevant oxalylamines via copper/Lewis acid synergistic catalysis: Reaction design and development, and selected examples



Scheme 2 Synthesis of medicinally relevant oxalylamines via copper/Lewis acid synergistic catalysis: Mechanistic investigations



Scheme 3 Synthesis of medicinally relevant oxalylamines via copper/Lewis acid synergistic catalysis: Proposed mechanism

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Z.-Y. Wu

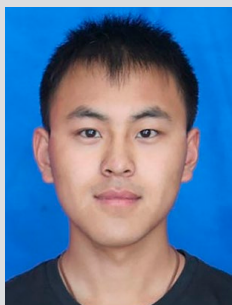
Ziying Wu was born in Zhejiang, P. R. China, in 1995. She graduated from Wenzhou University (P. R. China) in 2018 and is pursuing her Master's degree in Professor Huanfeng Jiang's group at the South China University of Technology (SCUT, P. R. China). Her current research interest focuses on the transition-metal-catalyzed amination functionalization of alkenes.

the School of Chemistry and Chemical Engineering at SCUT. His current research interests include transition-metal-catalyzed coupling reactions and green chemistry.



Prof. W.-Q. Wu

Wanqing Wu received her PhD from Peking University (P. R. China) with Professor Zhen Yang and Professor Chi-Sing Lee in 2010. Then she joined Professor Huanfeng Jiang's group as a postdoctoral researcher at the South China University of Technology (SCUT, P. R. China). In 2014, she was promoted to Professor and her research interests include the development and applications of carbon-heteroatom triple bond transformations.



M. Hu

Miao Hu was born in Inner Mongolia, P. R. China, in 1995. He received his B.S. degree from the South China University of Technology (SCUT, P. R. China) in 2017, and then joined Professor Huanfeng Jiang's group at the same university as a Ph.D. student. His current research interest focuses on transition-metal-catalyzed conversion of alkenes.



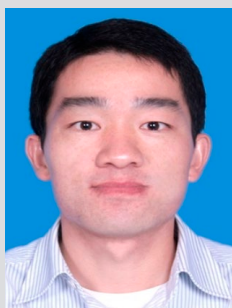
Prof. H.-F. Jiang

Huanfeng Jiang received his PhD from Shanghai Institute of Organic Chemistry (SIOC, P. R. China) with Professor Xiyan Lu in 1993. Then he joined Guangzhou Institute of Chemistry (P. R. China) as a research fellow. In 2003, he moved to the South China University of Technology (SCUT, P. R. China) as the Leading Professor of Chemistry. He received Chinese Chemical Society-BASF Young Investigator's Award in 2002 and National Natural Science Funds for Distinguished Young Scholar in 2006. His research interests focus on synthetic methodology, and green and sustainable chemistry.



Y.-B. Jin

Yangbin Jin was born in Anhui, P. R. China, in 1995. He received his B.S. degree from the South China Agricultural University (P. R. China) in 2018, and then joined Professor Huanfeng Jiang's group at the South China University of Technology (P. R. China) as a Ph.D. student. His current research focuses on transition-metal-catalyzed conversion of alkenes with green oxidants.



Prof. J.-X. Li

Jianxiao Li received his B.Sc. degree (2008) from Fuyang Normal University (P. R. China). He earned his M.S. degree under the supervision of Prof. Zhao-Yang Wang at South China Normal University (P. R. China) in 2011. He completed his Ph.D. studies in 2014 under the direction of Prof. Huanfeng Jiang at the South China University of Technology (SCUT). From 2014 to 2017, he worked as a postdoctoral fellow with Prof. Huanfeng Jiang. Now, he is an Associate Professor in

Young Career Focus: Professor Yiming Wang (University of Pittsburgh, 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 Professor Yiming Wang (University of Pittsburgh, USA).

Biographical Sketch



Professor Y. Wang

Yiming Wang was born in Shanghai, P. R. of China, and grew up in Boulder, Colorado (USA). He graduated with an AB/AM degree in Chemistry & Physics and Mathematics from Harvard University (USA) in 2008 after conducting research in the group of Professor Andrew Myers. After obtaining his Ph.D. under the supervision of Professor Dean Toste at the University of California, Berkeley (USA) in 2013, he conducted postdoctoral research in the laboratory of Professor Stephen Buchwald at the Massachusetts Institute of Technology (USA) as a National Institutes of Health Postdoctoral Fellow. He joined the Department of Chemistry at the University of Pittsburgh (USA) in Fall 2017.

INTERVIEW

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

Prof. Y. Wang My research group and I are currently interested in the applications of cationic iron catalysis in C–H functionalization chemistry. The functionalization of C–H bonds in hydrocarbons and other simple starting materials is an active area of research in modern organic synthesis that has the potential to lead to shorter and greener synthetic routes. Given the importance of building the framework of carbon–carbon bonds in organic synthesis and the ready availability of unsaturated starting materials, we are particularly interested in applying our approach to the construction of C–C bonds α to nonpolar π -bonds, such as those present in alkenes and alkynes. In general, α -C–H functionalization reactions leading to the installation of carbon-based fragments are not as well developed or as general as those leading to C–O or C–N bond formation, especially for propargylic C–H functionalization. Thus, we hope that our efforts in this area will expand the repertoire of available tools, including catalysts, reagents, and reaction conditions, for these underexplored areas of C–H functionalization chemistry. In addition to this major area of research, we are also interested in new applications of carbocationic intermediates, including vinyl cations.

SYNFORM *When did you get interested in synthesis?*

Prof. Y. Wang I became interested in organic synthesis as a purely intellectual activity when I took Professor David Evans's Advanced Organic Chemistry (Chemistry 206) course during the third year of my undergraduate studies. Although the course was too difficult for me at the time, and I did not do well in it, I came away with a deep impression of the intellectual depth and rigor of the field. More broadly, I gained an appreciation for the power and societal impact of organic syn-

thesis during my time working on the synthesis of tetracycline antibiotics in Professor Andrew Myers's group.

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

Prof. Y. Wang In my view, the role of organic synthesis has always been both that of a pure science and an applied science. Research in organic chemistry simultaneously satisfies basic human curiosity about the natural world while also playing an immensely impactful role in the development of new medicines and new materials that change society and everyday life. In recent years, developments in organofluorine chemistry, late-stage functionalization, and the synthesis of conjugated materials (to name a few areas) have been driven by demand of the end-users of organic synthesis and ultimately by societal need. At the same time, the proposal of exciting new activation modes for catalysis and the discovery of reactions with novel chemo-, regio-, and stereoselectivities continue to be driven by curiosity as much as applicability.

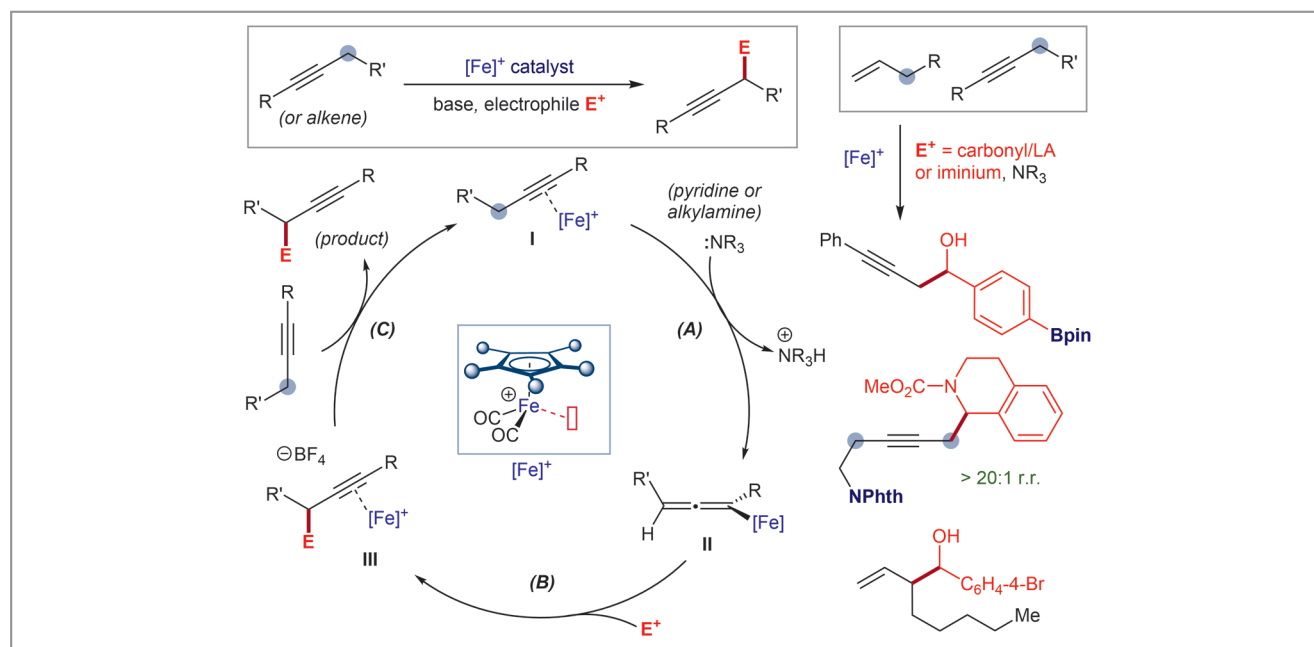
SYNFORM Could you tell us more about your group's areas of research and your aims?

Prof. Y. Wang My research group has worked extensively in the development of cyclopentadienyliron dicarbonyl com-

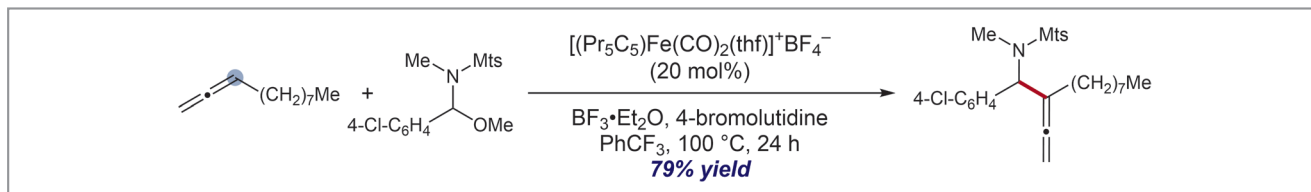
plexes for the functionalization of C–H bonds α to unsaturated C–C bonds. Much of the intellectual foundations of our work in this area were laid through stoichiometric studies by the group of Myron Rosenblum (Brandeis University) during the 1970s to the 1990s.^{1,2} In particular, the reported reactivity of cationic η^2 -alkene complexes and neutral σ -allyliron species based on the Fp ($\text{CpFe}(\text{CO})_2$) fragment led us to believe that catalytic C–H functionalization reactions could be developed using this chemistry.

We proposed a catalytic cycle, shown in Scheme 1, wherein (A) a cationic η^2 iron–alkyne complex (I) first undergoes deprotonation under mild, functional-group-tolerant conditions to afford neutral σ -allenyliron species II; (B) reaction of II with an electrophile takes place with $S_{\text{E}}2'$ regioselectivity to give a functionalized product still complexed to the cationic iron center (III); and (C) iron complex III then undergoes ligand exchange to deliver the organic product and regenerate iron complex I to complete the catalytic cycle. This was found to be a general strategy that could be applied to the functionalization of alkenes and alkynes with activated carbonyl (oxocarbenium) and iminium electrophiles.^{3,4} More recently, using a designer catalyst and well-optimized reaction conditions, this approach was also found to be applicable to the C(sp^2)–H functionalization of allene derivatives (Scheme 2).⁵

More recent work in our group has focused on improving catalyst efficiency, controlling stereoselectivity, and the devel-



Scheme 1 Catalytic cycle for Fe-catalyzed propargylic and allylic C–H functionalization and examples of products obtained under catalytic conditions



Scheme 2

opment of dual catalytic strategies. We hope to share these results with the synthetic community in the near future.

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

Prof. Y. Wang In terms of importance to my group's research program, and perhaps organometallic catalysis at large, I think my group's most important scientific achievement so far was the finding that the combination of an iron catalyst bearing a hindered, electron-rich ligand (e.g., $[\text{Cp}^*\text{Fe}(\text{CO})_2(\text{thf})]^+\text{BF}_4^-$, $\text{Cp}^* = \text{C}_5\text{Me}_5$) and a hindered pyridine or alkylamine base (e.g., 2,4,6-collidine or 2,2,6,6-tetramethylpiperidine) could enable catalytic turnover for the proposed catalytic cycle shown in Scheme 1. The perseverance, careful observation, and excellent intuition of the group's first postdoctoral scholar, Dr. Yidong Wang (Ph.D., East China Normal University), were crucial in making this finding.

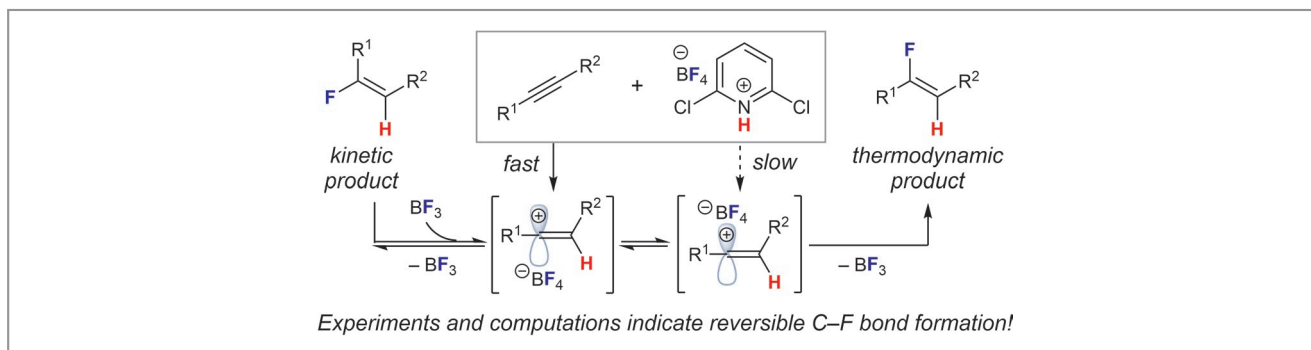
In terms of a fundamental insight discovered during the course of research, a particularly surprising finding was the discovery that an alkyne hydrofluorination reaction that our group developed likely proceeds via an Ad_2 mechanism with a reversible C–F bond-forming step (Scheme 3). Mechanistic experiments corroborated this proposal, which was initially suggested by our computational collaborators in the group of Professor Peng Liu (University of Pittsburgh).⁶ I found this

result (potentially relevant to the development of C–F bond activation reactions) to be highly unintuitive, given the well-known strength of the C–F bonds found in vinyl fluorides ($DH^\circ_{298} = 124 \text{ kcal/mol}$ in $\text{CH}_2=\text{CH}-\text{F}$).⁷

Matthew Farnok

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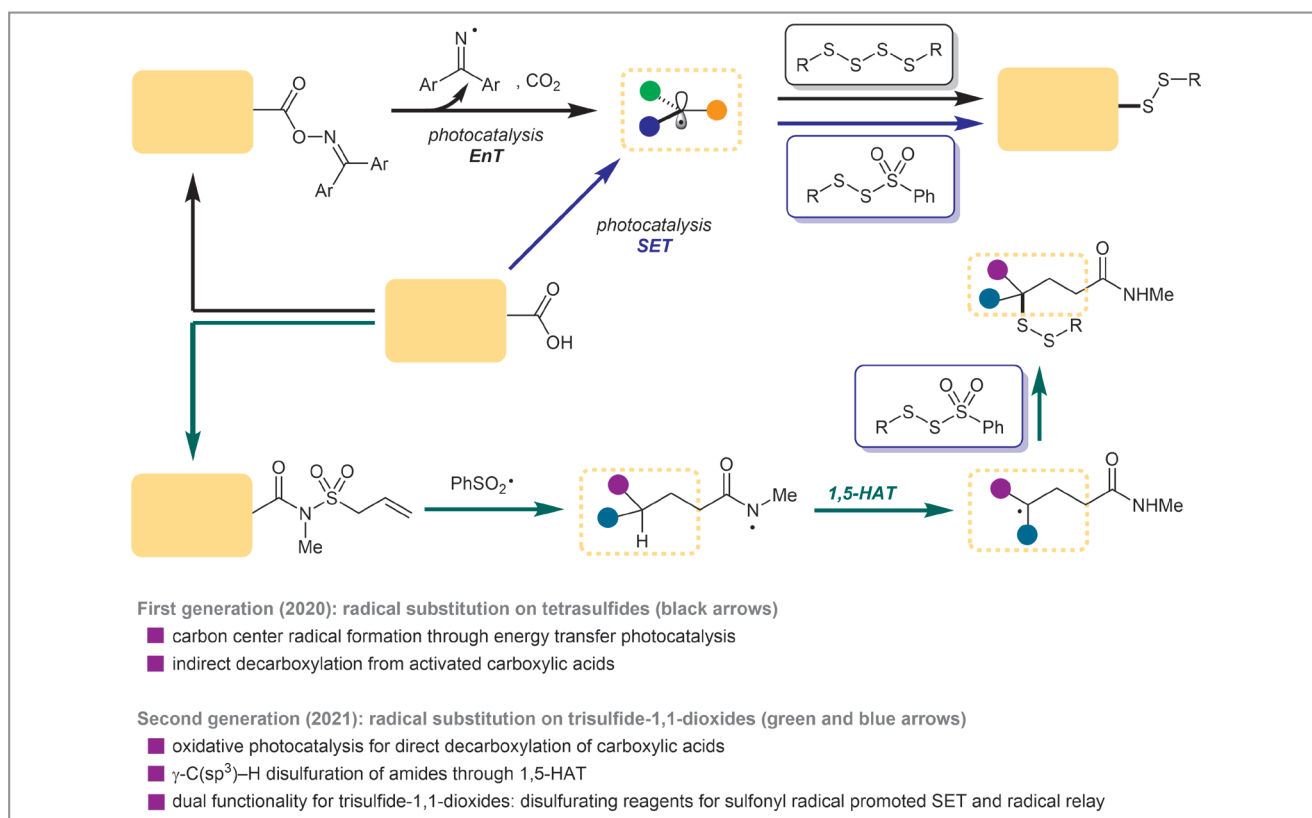
Scheme 3 Proposed mechanism for an alkyne hydrofluorination reaction

A Divergent Strategy for Site-Selective Radical Disulfuration of Carboxylic Acids with Trisulfide-1,1-dioxides

Angew. Chem. Int. Ed. **2021**, *60*, 15598–15605

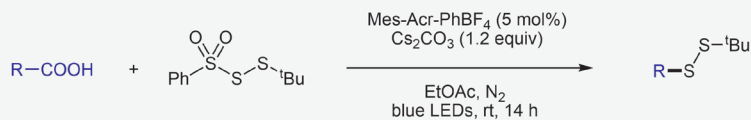
According to Professor Derek Pratt, from the University of Ottawa (Canada), making symmetric disulfides bonds is relatively easy: “Anyone that has worked with thiols knows that this often happens inadvertently, simply upon exposure to air,” he said, adding: “The preparation of unsymmetric disulfides is another matter. A thiol is generally first activated to reaction with another by converting it into an electrophile – the most common example being a symmetric disulfide. Thus, one thiol reacts with the symmetric disulfide derived from a second thiol to create an unsymmetric disulfide. This so-called ‘disulfide exchange’ reaction is ubiquitous in biology, but controlling these reactions in a synthetic context can be tricky since exchange reactions are generally equilibria and can require large excesses of thiol to push the reaction forward.”

The efforts of Professor Pratt’s group to develop a new approach to unsymmetric disulfides were derived from largely unrelated work to understand how allicin, the thiosulfinate responsible for the characteristic odour of garlic, reacted with radicals as an antioxidant.¹ “These studies eventually led us to study the reactivity of higher organosulfur compounds (which also occur in garlic), including trisulfide 1-oxides² and, eventually, tetrasulfides,³” explained Professor Pratt. He continued: “The polysulfides possess weak S–S bonds that make them highly amenable to radical substitution. In the context of antioxidant chemistry, the relevant radicals are peroxy radicals, which propagate the radical chain reaction known as autoxidation. However, we reasoned that in the absence of oxygen, reactions with alkyl radicals would take place instead, and this may be useful in the preparation of disulfides.”

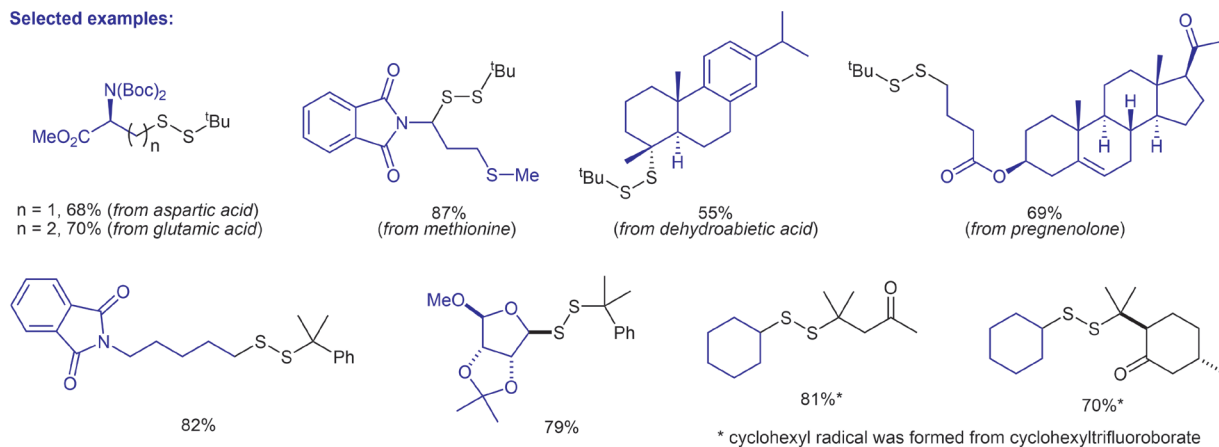
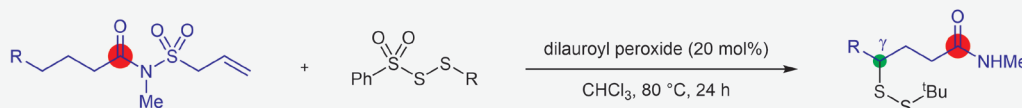


Scheme 1

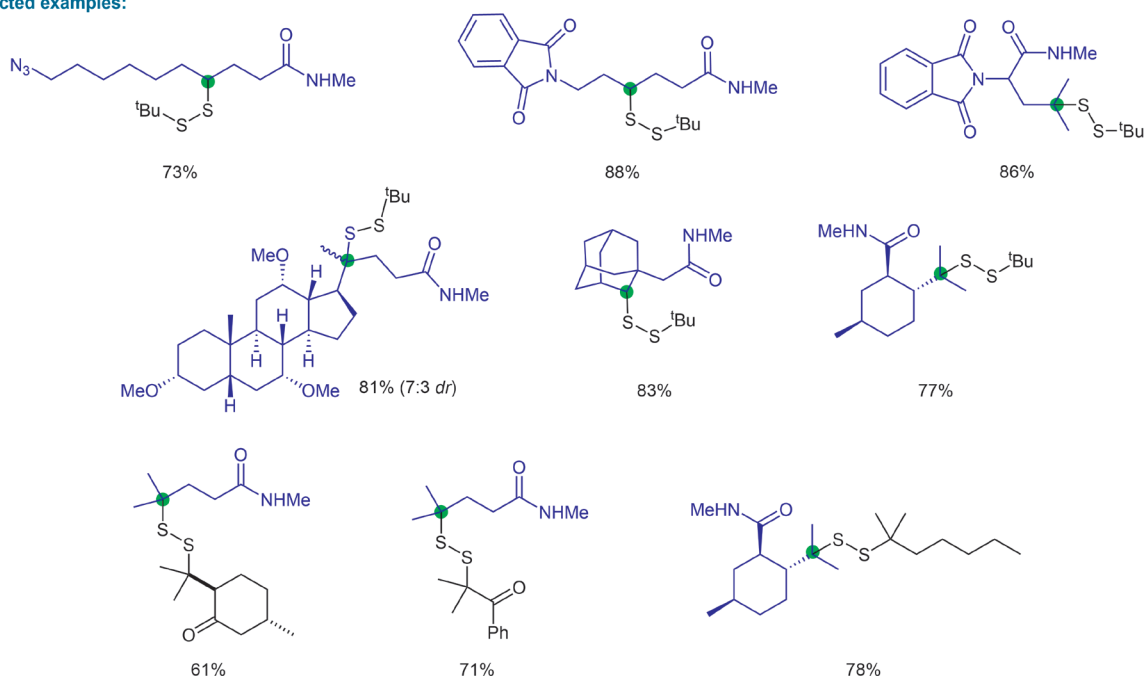
a) Photocatalytic decarboxylative disulfuration of carboxylic acids:



Selected examples:

b) γ -C(sp³)-H disulfuration:

Selected examples:



Scheme 2 Conditions and scope of the novel radical disulfurations using trisulfide 1,1-dioxides

The highlighted *Angew. Chem. Int. Ed.* article builds on the group's 2020 communication which first showed that radical substitution on tetrasulfides was an extremely efficient and versatile approach to unsymmetric disulfides (Scheme 1).⁴ Professor Pratt said: "In that work, we used activated carboxylic esters and energy-transfer photocatalysis to generate alkyl radicals. We had wanted to use carboxylic acids directly along with photoredox catalysis to generate the radicals, but couldn't make it work. The challenges are obvious, even if a feasible reagent could be identified, both it and the product must be reasonably compatible with the conditions of the oxidative decarboxylation to yield alkyl radicals, and polysulfides (including starting tetrasulfides and product disulfides) can react with not only oxidants, but also reductants, nucleophiles, and electrophiles!"

Professor Pratt explained that since some of the group's previous work had shown the possibility of doing radical substitution on oxides of trisulfides, they reasoned that these may be more stable to direct oxidation and also undergo homolytic substitution to make disulfides. "Trisulfide-1-oxides were found to be too labile to photolysis, leading to low yields," remarked Professor Pratt. He continued: "However, trisulfide-1,1-dioxides were more stable (given that the product sulfonyl radicals are less stable than sulfinyl radicals) and smoothly underwent substitution. Moreover, sulfonyl radicals are competent oxidants, which could turnover the photocatalyst in an overall redox-neutral process."

According to the authors, this radical disulfuration approach offers significant advantages over existing methods, given that it can be carried out without transition-metal catalysts, and under mild reaction conditions (Scheme 2, a). "Most importantly, it can be carried out on carboxylic acids directly, which is advantageous given their availability and because it can make late-stage disulfuration quite convenient. The substrate scopes are substantial, with a wide variety of amino acids, natural products and bioactive complex molecules being good or excellent substrates," Professor Pratt commented. The synthetic value of this strategy was further demonstrated by exploring the capacity of the trisulfide-1,1-dioxides to produce disulfuration products using alternative radical-generating systems, e.g., oxime esters and alkyltrifluoroborates. "However, one apparent limitation of this reaction is that monosulfides were formed when trisulfide dioxides featuring *n*-alkyl and phenyl substitution on the terminal sulfur atom were used," said Professor Pratt, who also noted that mechanistic investigations revealed that a combination of polar effects and steric effects impacted the selectivity of radical substitution.

"Following on from this, we felt it would be useful to be able to selectively introduce a disulfide via radical-mediated C–H functionalization," said Professor Pratt. Along these lines, the group has taken the first steps by demonstrating a C(sp³)–H bond disulfuration at the the γ -site of amides (Scheme 2, b). "The chemistry was achieved through a radical chain reaction using lauroyl peroxide as the initiator. Mechanistically, the sulfonyl radicals formed upon alkyl radical substitution on the trisulfide 1,1-dioxides add to the terminal carbon atom of an *N*-allylsulfonamide, thereby liberating an amidyl radical that could enable the radical to translocate to the γ -site of the amide through a 1,5-HAT," explained Professor Pratt.

The authors reckon that these synthetic approaches provide a divergent strategy for site-selective radical disulfuration of carboxylic acids. Professor Pratt concluded: "We expect this method to have broad application in late-stage disulfuration, in the field of asymmetric disulfide synthesis, and this will hopefully inspire more researchers to think about radical substitution at sulfur not just for disulfuration chemistry, but as a reliable means to introduce versatile sulfur-based functional groups."

Mattias Hansson

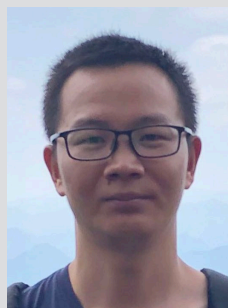
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*Prof. D. A. Pratt*

Derek A. Pratt received his B.Sc. from Carleton University (Canada) in 1999 where he had the privilege of working with Dr. Keith Ingold. Supported by the Natural Sciences and Engineering Research Council of Canada, he attended Vanderbilt University (USA) for his Ph.D. studies under the supervision of Professor Ned Porter. He then carried out postdoctoral research at the University of Illinois at Urbana-Champaign (USA) with Professor Wilfred van der Donk as a Jane Coffin Childs Fellow. Derek began his independent career in 2005 at Queen's University (Canada) as Canada Research Chair in Free Radical Chemistry, which he renewed following his recruitment to the University of Ottawa (Canada) in 2010. He was promoted to Full Professor in 2016 and was awarded a University Research Chair in 2021. Research in the Pratt group is focused on the reactivity of organic free radicals and applications in materials and medicine.

*Dr. Z. Wu*

Zijun Wu obtained his Ph.D. from Tsinghua University (P. R. of China) in July 2019 and focused on organic synthesis in the field of organocatalysis under the guidance of Prof. Jian Wang. He is currently performing postdoctoral research in Prof. Derek Pratt's group at the University of Ottawa (Canada). He has since switched into a different research area and is currently interested in understanding radical chemistry and chemical biology of sulfur-containing compounds.

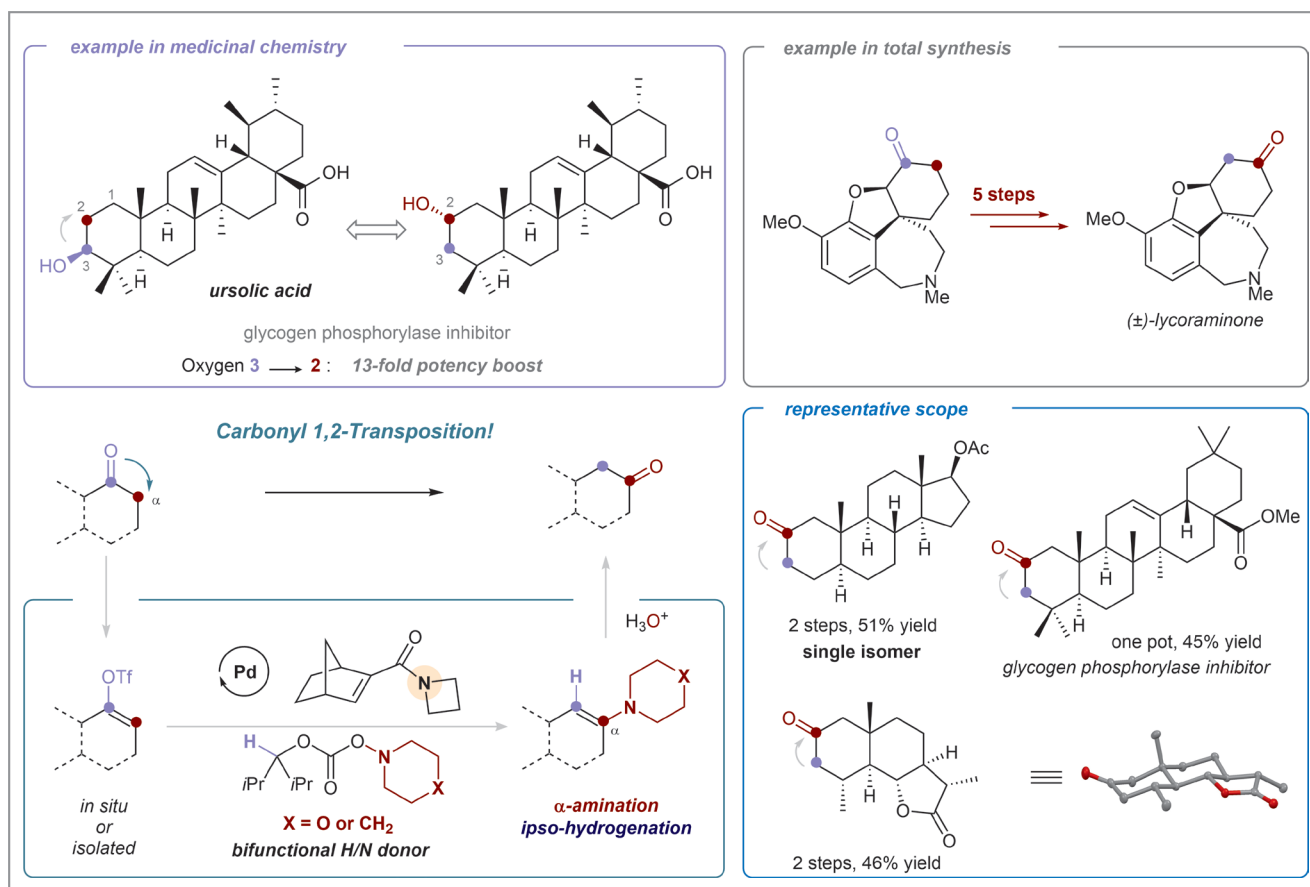
Carbonyl 1,2-Transposition through Triflate-Mediated α -Amination

Science 2021, 374, 734–740

Carbonyl groups – and their carbinol reduction products – are widespread in natural products, pharmaceutical agents, and other bio-related molecules. The location of the C–O functionality within a specific molecule is a key factor in determining its biological properties. For example, the C2-hydroxy analogue of ursolic acid displays 13-fold potency boost for inhibiting glycogen phosphorylase, relative to the parent compound. The group of Professor Guangbin Dong at the University of Chicago (USA) was interested in developing a synthetic method for selectively migrating a carbonyl oxygen within a given molecular structure, particularly to an adjacent carbon. “A facile carbonyl 1,2-transposition strategy would enable alternative synthetic designs starting from more accessible materials,” said Professor Dong. “Unfortunately, current

state-of-the-art carbonyl migration methods suffer from low efficiency, multiple-step functional group manipulation, and poor selectivity. For example, a five-step synthetic sequence was required to migrate the carbonyl to the adjacent carbon in the total synthesis of lycoraminone (see Scheme 1). Therefore, a general and efficient carbonyl 1,2-transposition method could be quite valuable.”

Professor Dong’s group has a long-term interest in the palladium/norbornene (Pd/NBE) cooperative catalysis, the original reactivity of which was first reported by Catellani in 1997 (*Angew. Chem. Int. Ed.* 1997, 36, 119–122). Professor Dong said: “This powerful strategy has allowed for a highly efficient and regioselective difunctionalization of arenes. Twenty-two years after its original report, the Catellani reaction



Scheme 1 The novel 1,2-transposition reaction and selected examples of its scope

was achieved in a non-aromatic system.” Indeed, Professor Dong’s group reported the first non-aromatic alkenyl Catellani reaction for simple alkenyl halides and triflates in 2019 (*Nat. Chem.* **2019**, *11*, 1106–1112), but at that time only C–C bond formation could be enabled at the *ortho* position with carbon-based electrophiles. “We envisioned that if an α -amination/*ipso*-hydrogenation of alkenyl triflates could be realized, i.e. using nitrogen-based electrophiles, the resulting ‘transposed’ enamine would give the carbonyl 1,2-shifted product upon hydrolysis,” explained Professor Dong.

After Dr. Jianchun Wang (first author of the group’s *Nat. Chem.* **2019** paper) finished the study on *ortho*-alkylation using alkenyl substrates, he had a discussion with Professor Dong on how to further extend this exciting reaction. Dr. Wang recalled: “*Ortho*-amination was at first thought as an unattractive transformation, because the enamine product would hydrolyze easily, but Professor Dong pointed out that this would be a special opportunity to migrate the carbonyl in ketone.” Realizing the value of this transformation, Dr. Wang screened various conditions for this reaction. While the initial attempts were unfruitful, he was lucky to identify 5–10% of the desired ketone as a product of one reaction, just before his graduation from the University of Chicago.

Shortly afterwards, Dr. Zhao Wu and Dr. Xiaolong Xu further explored this transformation using morpholine benzoate as the electrophilic amine source and isopropanol as the exogenous hydride source. “However, the reactions suffered from low conversion even after screening a number of different catalysts, ligands, NBE co-catalysts, and solvents,” remarked Professor Dong. He continued: “The design of difunctional H/N reagents was originally aimed at minimizing the premature hydrogenation side process. To our delight, however, this amino carbonate reagent not only reduced the side products, but substantially improved the reactivity. A hit with around 50% yield was obtained in a first try with isopropyl morpholino carbonate. Inspired by this exciting result, Dr. Wu synthesized a series of H/N reagents with various electronic and steric properties and eventually figured out the optimal one for this transformation.”

Professor Dong concluded: “This reaction offers a simple, yet straightforward, carbonyl 1,2-transposition method that is not trivial to realize otherwise. We hope it will be beneficial for medicinal chemists for the late-stage functionalization of carbonyl compounds, especially in the synthesis of complex and/or high-value products, thus providing synthetic chemists with an alternative retrosynthetic strategy.”

Mattie Fankle

About the authors



Dr. Z. Wu

Zhao Wu was born in Fuzhou, P. R. China. He obtained his B.S. degree in chemistry from University of Science and Technology of China in 2013. In the same year, he moved to the University of Illinois at Urbana-Champaign (USA) where he studied rhodium-catalyzed asymmetric reactions to access chiral nitrogen-containing molecules in Prof. Kami Hull’s research group. After earning his Ph.D. in 2018, he moved north to the University of Chicago (USA) where he joined Prof. Guangbin Dong’s lab as a postdoctoral researcher. Since then, he has been working on the Pd/NBE cooperative catalysis.



Dr. X. Xu

Xiaolong Xu was born in Huaibei, P. R. China. He received a B.S. in chemistry from Jiangsu University and a Ph.D. in organic chemistry from Shanghai Institute of Organic Chemistry (P. R. China) in 2020 under the direction of Prof. Zhi Li. He systematically studied organometallic catalysis as an exchange student at the University of Chicago (USA) under the direction of Prof. Guangbin Dong from 2019–2020. Then he joined Bioduro-Sundia as a senior research chemist where he explored new chemical processes to pharmaceutical synthesis.



Dr. J. Wang

Jianchun Wang received his B.S. degree in chemistry from Peking University (P. R. China) in 2014. In the same year, he joined Prof. Guangbin Dong’s research lab and he graduated from the University of Chicago (USA) in 2019. His research focused mainly on developing novel norbornene co-catalysts to solve long-standing limitations in Pd/NBE cooperative catalysis. He then began research with Prof. Robert H. Grubbs at California Institute of Technology (USA) as a postdoctoral researcher. In 2021, he joined the Shenzhen Grubbs Institute at the Southern University of Science and Technology (SUSTech, P. R. China) as an assistant professor.

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Prof. G. Dong

Guangbin Dong received his B.S. degree from Peking University (P. R. China) and completed his Ph.D. in chemistry from Stanford University (USA) with Prof. Barry M. Trost, where he was a Larry Yung Stanford Graduate fellow. In 2009, he began research with Prof. Robert H. Grubbs at California Institute of Technology (USA), as a Camille and Henry Dreyfus Environmental Chemistry Fellow. In 2011, he joined

the Department of Chemistry and Biochemistry at the University of Texas at Austin (USA) as an assistant professor and a CPRIT Scholar. Since 2016, he has been a professor of chemistry at the University of Chicago (USA). His research interests lie in the development of powerful chemical tools for addressing questions of biological importance.

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