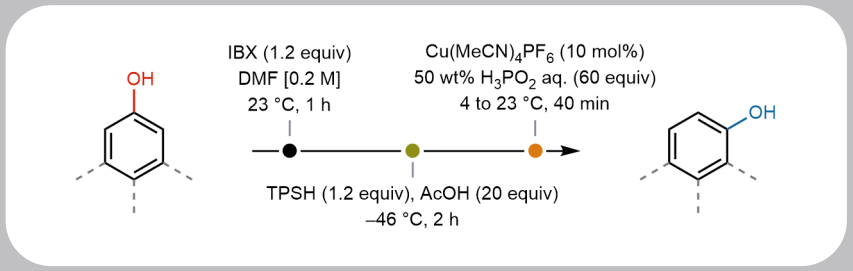
Synform

People, Trends and Views in Chemical Synthesis

2024/12

A *para*-to-*meta* Isomerization of Phenols

Highlighted article by S. Edelmann, J.-P. Lumb



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Dear Readers,

This December issue of SYNFORM starts with a Literature Coverage article featuring a fantastic work on the direct radical functionalization of native sugars recently published in *Nature* by B. G. Davis (UK) and M. J. Koh (Singapore). The next article covers a novel synthesis of acridines obtained by combining photo-excitation of *o*-alkyl nitroarenes with a copper-promoted cascade annulation reaction, that was developed by the group of Y.-M. Lin (P. R. of China), while the third article features a ground-breaking methodology for achieving *para*- to *meta*-isomerization of phenols, reported by J.-P. Lumb (Canada). The issue is closed by a Young Career Focus interview with the Thieme Chemistry Journals Awardee X. Hu (USA) who talks with us about his research and personal interests.

And this – dear Readers – is the final article of SYNFORM's history, because after nearly 20 years and over 230 issues – the first one published in 2005 – SYNFORM is about to be discontinued. It has been a great adventure and I will miss every bit of it. I should thank a long list of people here, first and foremost Prof. Peter Vollhardt – former Editor-in-Chief of SYNLETT – to whom I wrote, back in 2004, for introducing the idea of SYNFORM. Unfortunately, there is no room for thanking everyone who should be acknowledged, so I will limit the list to three key people:

My friend Alison Sage, based in Aberdeen (Scotland, UK), who shared all the editorial work with me over the last 15 years, always in an incredibly efficient and timely manner: THANK YOU Alison!!

Then the two key people at Thieme Chemistry: Susanne Haak (based in Stuttgart, Germany) and Selena Boothroyd (based in Whitehorse, Canada), who always supported Alison and me with great professionalism, patience and enthusiasm, making sure that all the draft documents sent by Alison and me could magically turn into the actual SYNFORM articles and issues: THANK YOU Susanne and Selena!!

Finally, I owe the biggest and most grateful THANK YOU to all of you, our AUTHORS and READERS, for making SYNFORM possible and successful throughout two decades.

THANK YOU & GOODBYE!

In this issue

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Direct Radical Functionalization of Native Sugars

Nature **2024**, *631*, 319–327

Carbohydrates exist ubiquitously in numerous living organisms, and their conjugates mediate various crucial biological processes. In these roles, carbohydrate-based compounds therefore gain and drive altered biological functions simply through the attachment of a substituent (small and large) at the anomeric C-1 carbon. However, the low abundance and extraction challenges associated with many bioactive sugar-based molecules found in natural sources, coupled with their enormous heterogeneity, consequentially hamper systematic biological studies. To 'plug this gap', synthetic carbohydrate chemistry has evolved as a branch of organic chemistry to be one of the most reliable technologies, albeit specialized, to attain notable quantities of carbohydrates and their derivatives, as well as useful analogues. Among various glycosides, *C*-glycosyl compounds, as counterparts to natural *O*-glycosides, are considered rarer yet prominent, due to their stability towards hydrolytic enzymes. These have, for example, been used as potential surrogates of *O*-glycosides in developing sugar-based therapeutics. However, unlike enzymatic *C*-glycosylation in which the glycosyl moiety of an unprotected nucleotide sugar donor is precisely transferred to an acceptor through anomeric functionalization with exceptional regio- and stereoselectivity, currently established non-enzymatic *C*-glycosylation mostly relies on a sequential protection, functionalization and deprotection strategy to transfer native sugars into tailored chemical glycosyl donors for subsequent C–C bond coupling delivering targeted *C*-glycosyl compounds. "The long reaction sequence of these approaches inevitably compromises the efficiency and essentially prevents further application in complicate biological milieu," said Prof. Ming Joo Koh from the National University of Singapore, whose research group has a strong interest in the synthesis of complex carbohydrates. He added: "Many research groups, including ours, have endeavoured tirelessly to conceive a protecting-group-free chemical glycosylation approach that can directly transform native sugars into the desired glycosides by selective functionalisation at the anomeric position. However, this has proven to be extremely challenging."

Inspired by biological *S*-glycosylation, a biomimetic 'cap and glycosylate' strategy to directly transfer native sugars into various classes of glycosides and glycoconjugates, thereby bypassing unnecessary protecting group manipulation, has been recently revealed by Prof. Benjamin G. Davis (the Rosalind Franklin Institute and University of Oxford, both in the UK) and Prof. Ming Joo Koh. This direct radical functionalization approach now provides a streamlined access to what the authors consider is essentially equivalent to a 'clean', unprotected glycosyl moiety that allows diverse and robust formation of *C*-, *S*-, *Se*-glycosides, as well as *O*-glycosides. Moreover, because of its aqueous- and bio-compatibility, this protocol can be readily and seamlessly applied even to biomacromolecules, realizing the direct post-translational chemical glycosylation of proteins from sugars that come directly from nature.

Prof. Davis said: "Our group has spent a number of years exploring the idea of inserting information into biological molecules, such as proteins and sugars, to alter their function. One of the things that we have found is that carbon-centred radicals are wonderfully useful yet benign reactive intermediates for achieving new chemistries in biological systems. In this research, by generating free glycosyl radicals as intermediates directly from native sugars, we are trying to mimic what is happening in biology to make the synthesis of these glycosides and glycoproteins far more efficient. This efficient 'harvesting' of native sugars that can be plugged directly into new glycoconjugates has the potential to open up a number of different avenues, including the development of diverse sugar-based therapeutics."

Considering the efficiency, benign reaction conditions and exceptional biocompatibility of this protocol, Prof. Koh concluded: "We believe that this biomimetic 'cap and glycosylate' technology would pave the way towards modernizing carbohydrate and glycoconjugate synthesis without the need for protecting groups. This would bring enormous benefits in saving costs, time and manpower, empowering researchers to rapidly access saccharides and offering a practical platform to introduce fully unprotected glycosyl groups into biological systems."

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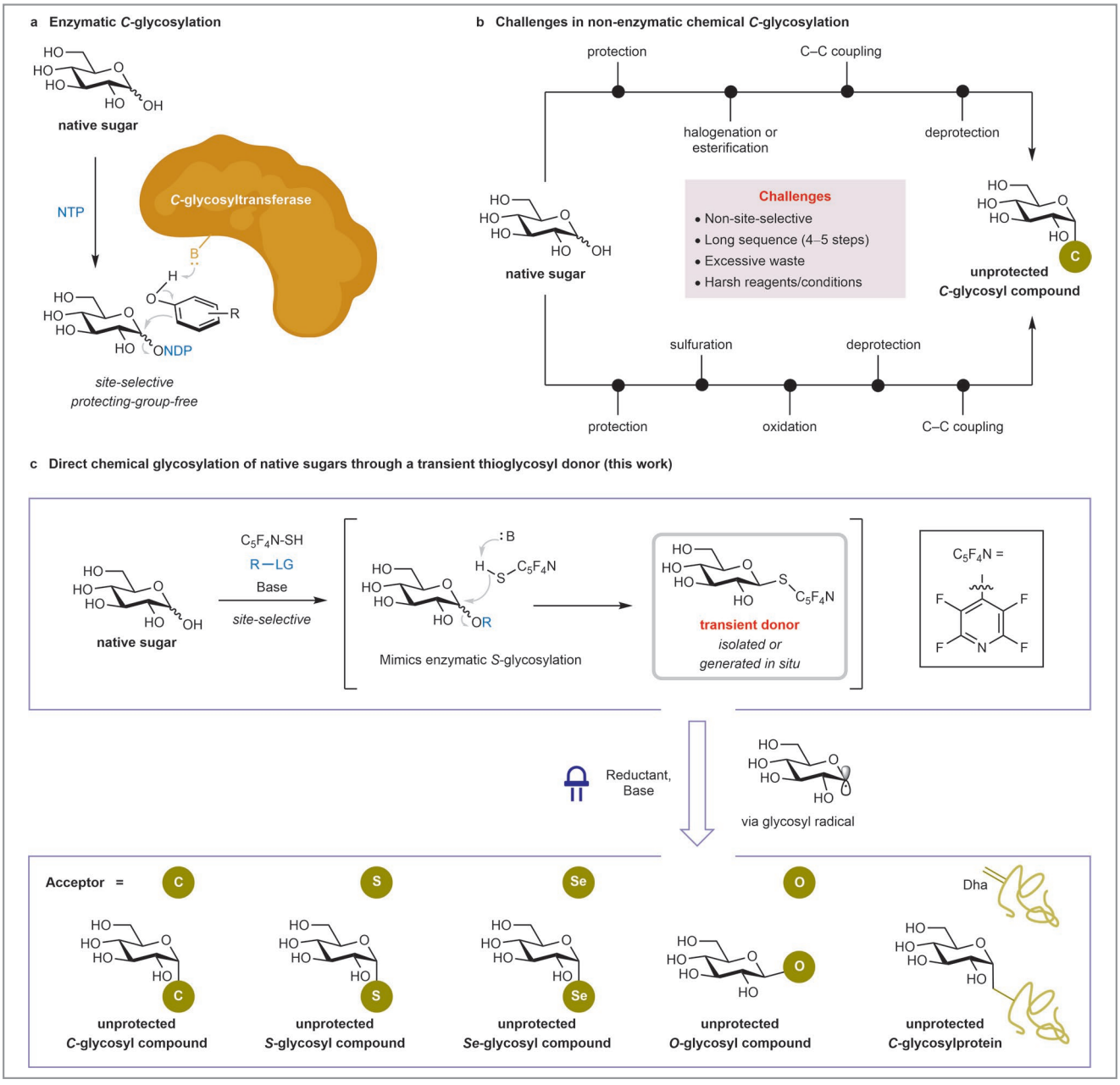


Figure 1 Design of a 'cap and glycosylate' strategy for functionalization of native sugars [credit: Jiang et al., *Nature* **2024**, *631*, 319–327]

About the authors

Dr. Y. Jiang

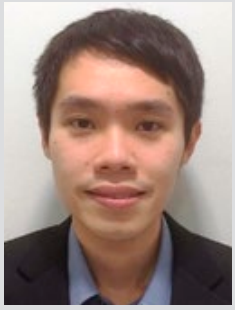
Yi Jiang obtained his B.S. and M.S. degrees from Lanzhou University, P. R. of China. After that, he pursued his Ph.D. studies at the National University of Singapore (Singapore) under the supervision of Prof. Ming Joo Koh and secured his Ph.D. in 2023. In the same year, he joined Prof. Benjamin G. Davis's group at University of Oxford (UK) and the Rosalind Franklin Institute (UK) for postdoctoral studies. His research interests revolve around post-translational mutagenesis of proteins by chemical methods.

Dr. Y. Wei

Yi Wei obtained her Ph.D. in 2019 at Central China Normal University (P. R. of China) under the supervision of Prof. Liang-Qiu Lu and Prof. Wen-Jing Xiao. Starting in 2020, she carried out postdoctoral research at the National University of Singapore (Singapore) with Prof. Ming Joo Koh for three years. Since then, she has begun her independent career at South-Central Minzu University (P. R. of China). Her research interests are mainly focused on light-driven radical-mediated glycosylation.

Prof. B. G. Davis

Benjamin G. Davis received his B.A. (1993) and D.Phil. (1996) at University of Oxford (UK) where he studied carbohydrates with George Fleet. After influential periods at the University of Toronto (Canada) and the University of Durham (UK), he moved to Oxford in 2001 and was promoted to Professor in 2005. In 2019 he became the Science Director for Chemistry at the Rosalind Franklin Institute (UK). The Davis group's research centers on the chemical understanding and exploitation of biomolecular function with an emphasis on carbohydrates and proteins. In 2015, he was elected to the Royal Society.



Prof. M. J. Koh

Ming Joo Koh obtained his Ph.D. with Prof. Amir H. Hoveyda at Boston College (USA) in 2017 and carried out postdoctoral studies in the same group. He joined the Department of Chemistry at the National University of Singapore as an Assistant Professor in 2018 and was promoted to Associate Professor in 2023. Research in the Koh group focuses on developing sustainable and practical transformations that address critical challenges in chemical synthesis through base-metal catalysis, radical chemistry and cross-coupling.

Modular Assembly of Acridines by Integrating Photo-Excitation of *o*-Alkyl Nitroarenes with Copper-Promoted Cascade Annulation

Angew. Chem. Int. Ed. **2024**, e202409653

Acridines play pivotal roles in natural products, pharmaceuticals, molecular probes, and optoelectronic devices.[1] However, conventional synthetic methodologies often require the use of specialized starting materials, anaerobic and moisture-free procedures, as well as multiple sequential steps for disparate functional group installations.[2]

Recently, a research team led by Professor Yu-Mei Lin at Xiamen University (P. R. of China) has developed an innovative and modular approach to the synthesis of acridine derivatives, leveraging the synergistic combination of photo-excitation of *o*-alkyl nitroarenes with copper-mediated cascade annulation (Scheme 1). "This method significantly simplifies the synthesis of a diverse array of acridine compounds and expands the range of possible structures, including unsymmetric and multi-substituted derivatives (Scheme 2)," explained Professor Lin. She continued: "The method starts with the photo-excitation of *o*-alkyl nitroarenes, progressing through intramolecular hydrogen atom transfer and oxygen relocation steps to generate crucial amine intermediates. A subsequent copper-induced cascade – encompassing Chan–Lam amination, Friedel–Crafts acylation, and aromatization – completes the one-pot formation of diverse acridine derivatives. The *o*-alkyl nitroarene precursors are easily obtained through the coupling of alkyl halides with *o*-nitroaryl boronic acids."

Through further assembly, a structurally diverse library of acridinium salts (more than 30 types) can be synthesized through a streamlined, single-step methylation process using the derived acridine precursors (Scheme 3). "Significantly, several of these acridinium salts, including compounds **94**–**100**, have not been previously synthesized nor documented in the previous literature," said Professor Lin, who told SYNFORM that the synthesized acridinium salts have shown extraordinary oxidative strength in their excited states, with reduction potentials spanning from 2.08 to 3.15 V, outperforming many known photocatalysts[3] (Scheme 3). "This unique characteristic designates them particularly suitable for catalyzing oxidative transformations, making them promising candidates for photochemical reactions," remarked Professor Lin. She concluded: "This research represents a significant advance in the field of acridine chemistry, providing a versatile and efficient method for synthesizing structurally diverse acridine compounds. The ease of incorporating substitutions in precursors and the exceptional properties of the resulting acridinium salts open up new possibilities for the development of advanced photocatalysts and pharmaceuticals."

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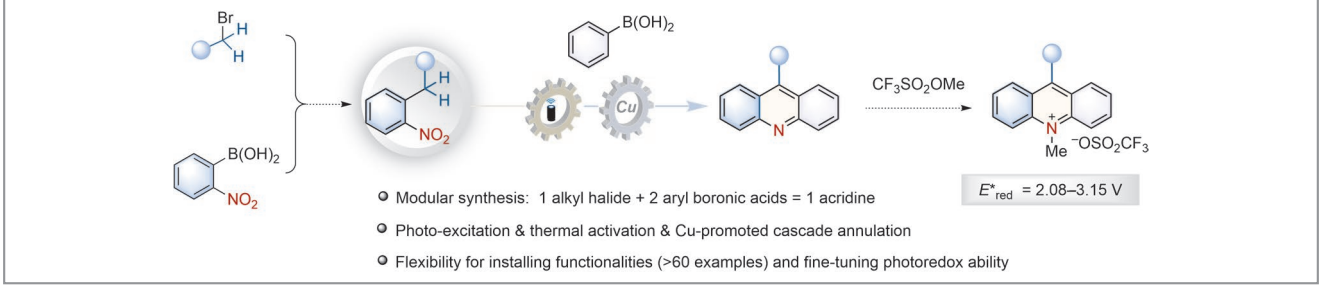
(2) Y. Lian, J. R. Hummel, R. G. Bergman, J. A. Ellman *J. Am. Chem. Soc.* **2013**, *135*, 12548–12551.
(3) (a) Y.-X. Cao, G. Zhu, Y. Li, N. Le Breton, C. Gourlaouen, S. Choua, J. Boixel, H.-P. Jacquot de Rouville, J.-F. Soulé *J. Am. Chem. Soc.* **2022**, *144*, 5902–5909. (b) S. C. Sau, M. Schmitz, C. Burdenski, M. Baumert, P. W. Antoni, C. Kerzig, M. M. Hansmann *J. Am. Chem. Soc.* **2024**, *146*, 3416–3426.



Scheme 1 Modular assembly of acridines and their N-methylation

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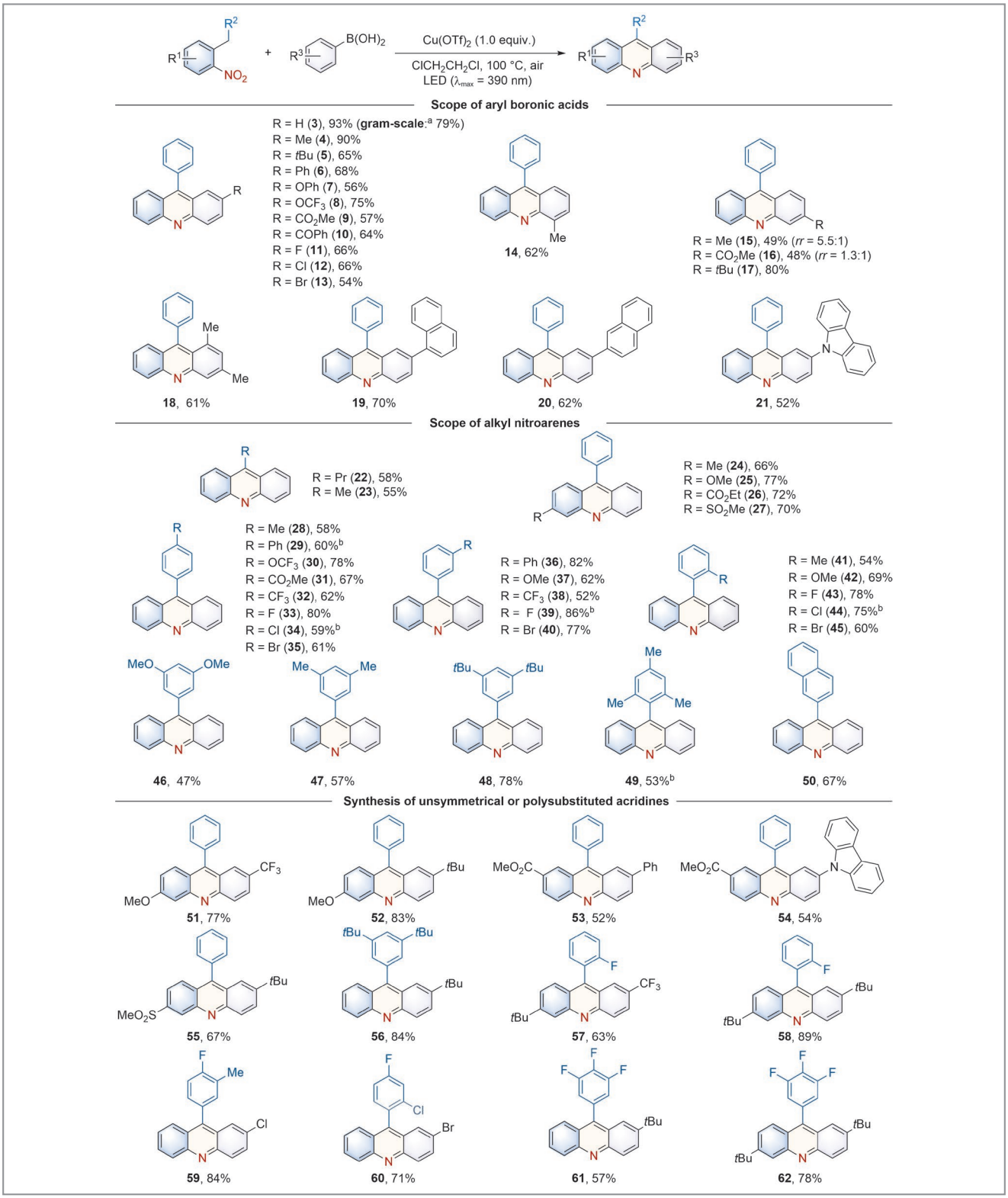

Scheme 2 Substrate scope. [a] Reaction performed with two 50 W LED lamps (λ_{max} = 390 nm). [b] Reaction performed using $Cu(OTf)_2$ (0.12 mmol).

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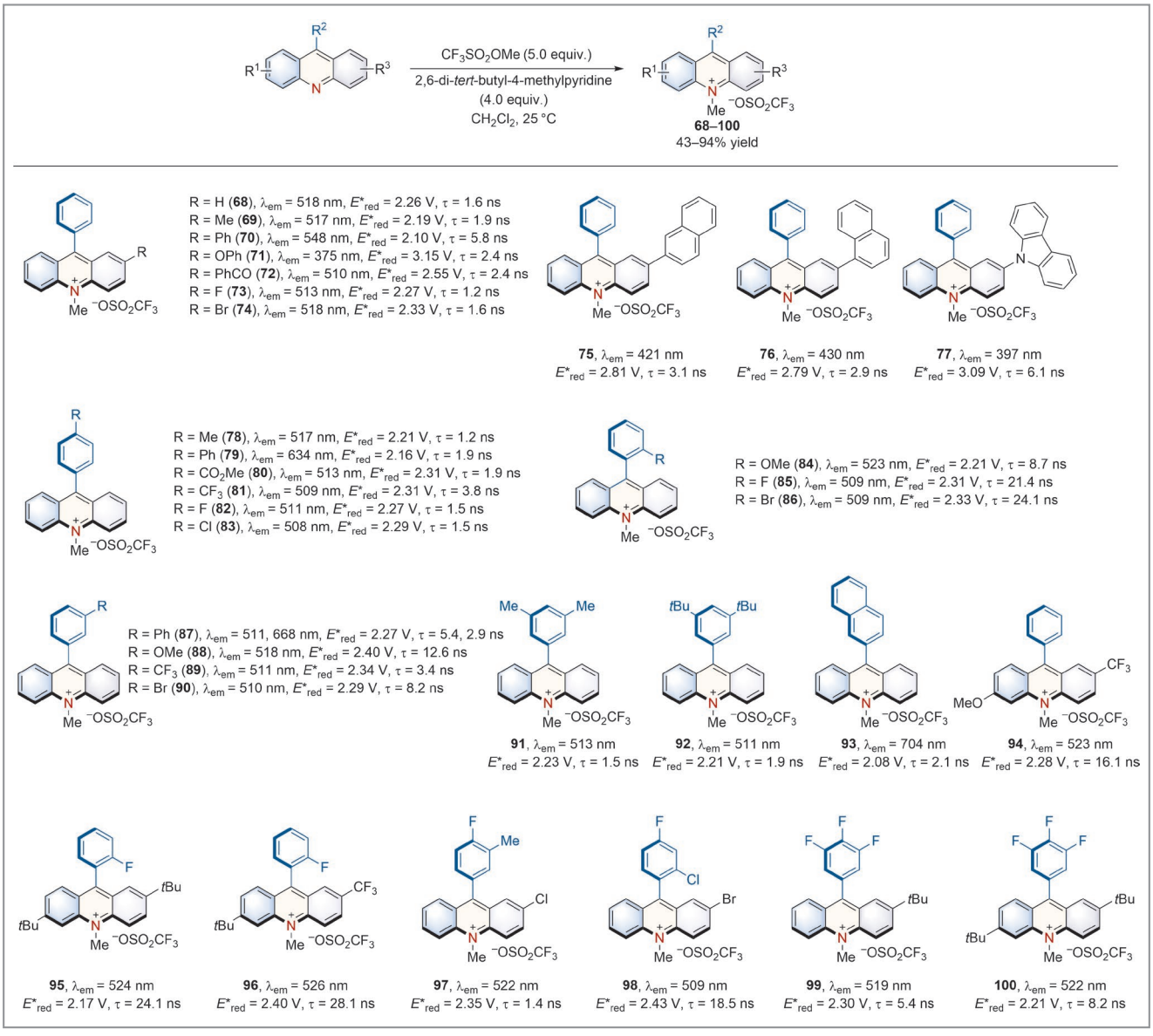
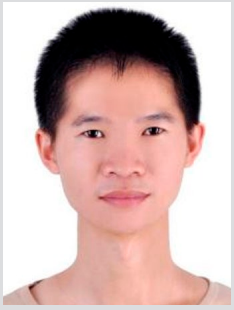


Scheme 3 Synthesis of acridinium-based photocatalysts and their photophysical properties

About the authors



H. Huang

Haichao Huang received his B.Sc. degree from Fujian Medical University (P. R. of China) in 2019 and his M.Sc. degree from Huaqiao University (P. R. of China) in 2022. He is currently a Ph.D. candidate at Xiamen University (P. R. of China). His research focuses on the development of visible-light photocatalysis and light-induced C–H functionalization.

Y. Jiang

Yifan Jiang earned his bachelor's degree from Heilongjiang University (P. R. of China) in 2023 and is currently pursuing a master's degree at Xiamen University (P. R. of China). His research interest lies in the excited state chemistry of nitroaromatics.

Dr. W. Yuan

Wei Yuan obtained his Ph.D. in organic chemistry from Xiamen University (P. R. of China) under the supervision of Prof. Eric Meggers and Prof. Lei Gong. In 2018, he joined Prof. Chuan He's group as a postdoctoral researcher at Southern University of Science and Technology (P. R. of China). In 2023, he joined Xiamen Medical College (P. R. of China) to start his independent research career. His current research interests include asymmetric catalysis, biocatalysis, and medicinal chemistry.

Prof. Y.-M. Lin

Yu-Mei Lin received her Ph.D. from Xiamen University (P. R. of China) in 2010, directed by Prof. Haiping Xia. Then, she worked with Prof. Stefanie Dehnen at Philipps-University Marburg (Germany), as a Humboldt Alexander fellow. She joined Xiamen University as an Associate Professor in 2013 and was promoted to Professor in 2023. Her research focuses on transition-metal carbene chemistry and the design of new photocatalysts.

A *para*-to-*meta* Isomerization of Phenols

Nat. Chem. **2024**, *16*, 1193–1199

Phenols are a common functional group of many important molecules, including the amino acid tyrosine and its many derivatives, secondary metabolites from across the tree of life, and a plethora of industrial chemicals, including many that are essential to pharmaceutical, agrochemical and materials industries. Phenols are defined by an aromatic ring with a hydroxy substituent (-OH group), whose properties are intimately linked to neighbouring substituents. Phenol isomers localize electron density differently, have different dipoles, acidities, redox potentials and abilities to engage in hydrogen bonding or π-interactions. The resulting substituent effect could be strategic to explore as a 'late-stage' or 'peripheral' (*J. Med. Chem.* **2024**, *67*, 11459–11466) modification, but a phenol isomerization faces a number of formidable challenges (Figure 1a). These include the need to both break and reform strong bonds with high chemo- and regioselectivity, often without a clear thermodynamic bias for a given isomer. "There are only two related examples in which the substituents of a phenol, namely substituents other than the -OH group, were isomerized, but both methods required forcing conditions and exhibited limited scope (*J. Org. Chem.* **1968**, *33*, 3415–3418; *Tetrahedron Lett.* **1982**, *23*, 1673–1676)," explained Professor Jean-Philip Lumb, from McGill University (Canada).

To bring about a chemo- and regioselective isomerization of phenols, Professor Lumb, together with PhD student Simon Edelmann, capitalized on the intermediacy of an *ortho*-quinone. Professor Lumb told SYNFORM: "An electrophilic and redox-active oxidation product of phenols has been a topic of study in our group for a number of years (*Angew. Chem. Int. Ed.* **2014**, *53*, 5877–5881; *J. Am. Chem. Soc.* **2014**, *136*, 7662–7668). *ortho*-Quinones can be accessed from phenols by *ortho*-oxygenation under a variety of conditions, including those of Pettus and co-workers (*Org. Lett.* **2002**, *4*, 285–288) using 2-iodoxybenzoic acid (IBX) (Scheme 1a). For the purposes of a 1,2-isomerization, oxygenation introduces the requisite oxygen atom at C2 with complete regiocontrol, and also differentiates the oxygen atoms at C1 and C2 of the quinone by virtue of substituent effects. What remains is a method for the selective reductive deoxygenation of an *ortho*-quinone **2** that would provide *meta*-phenol **3** to complete the isomerization form *para*-phenol **1** (Scheme 1a)."

According to Professor Lumb, while *ortho*-quinones are relatively uncommon intermediates in synthetic methodologies, they can be versatile coupling partners with a variety of nucleophiles, including with amines (*ACS Catal.* **2017**, *7*, 3477–3482; *Chem. Eur. J.* **2017**, *23*, 8596–8600; *Chem* **2017**, *2*, 533–549). "This precedent led us to investigate hydrazine-based reagents for the reductive deoxygenation of **2**, following a Wolff–Kischner like mechanism," explained Professor Lumb. He continued: "Here, a note regarding reagent selection is merited. Whereas typical hydrazine-based reductants are relatively electron rich, a suitably deactivated reagent was required for condensation with *ortho*-quinone **2** to avoid undesired reduction to either semi-quinone or catechol oxidation states. Promiscuous redox is a perennial challenge when working with *ortho*-quinones, and a likely reason they are not more widely utilized. Nevertheless, we found that commercially available sulfonyl hydrazide **8** (TPSH), possessing a 2,4,6-triisopropyl arene, was ideally suited to react with *ortho*-quinone **2**, affording diazoquinone **6** following a cascade of condensation and α-elimination (see **4** in Scheme 1b). The selection of TPSH reflects the numerous elements of reactivity

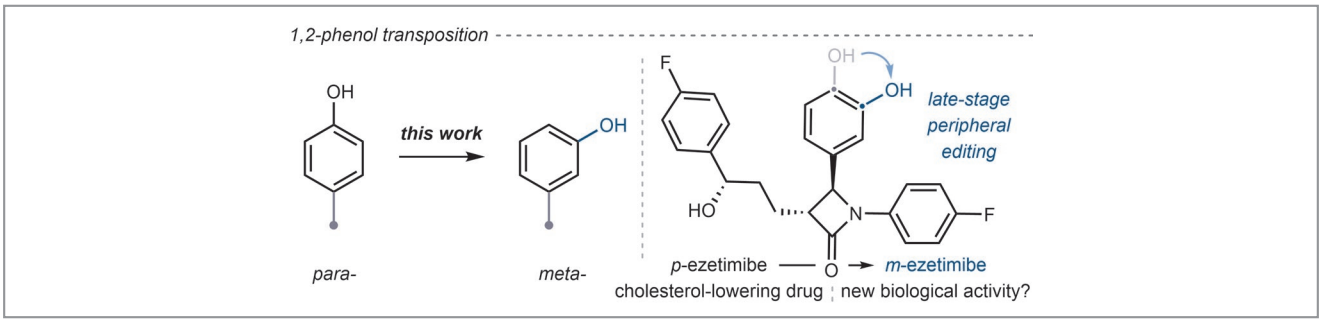


Figure 1 Transposition of *para*-phenols into *meta*-phenols for late-stage peripheral editing of bio-active molecules

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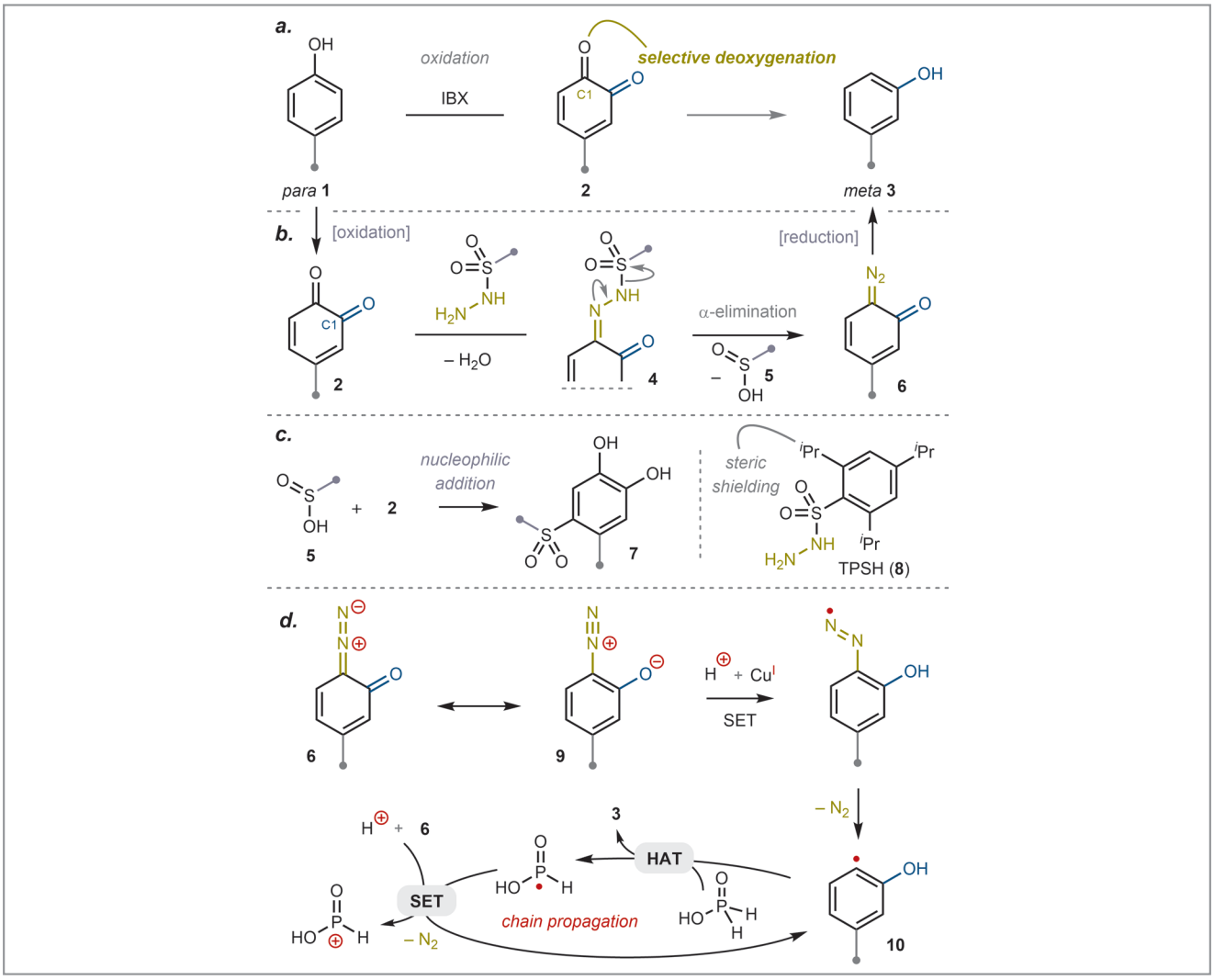


Scheme 1 (a) and (b) Overall strategy for the isomerization. (c) Problematic addition of the sulfinic acid byproduct. (d) Proposed mechanism for reduction of the diazoquinone.

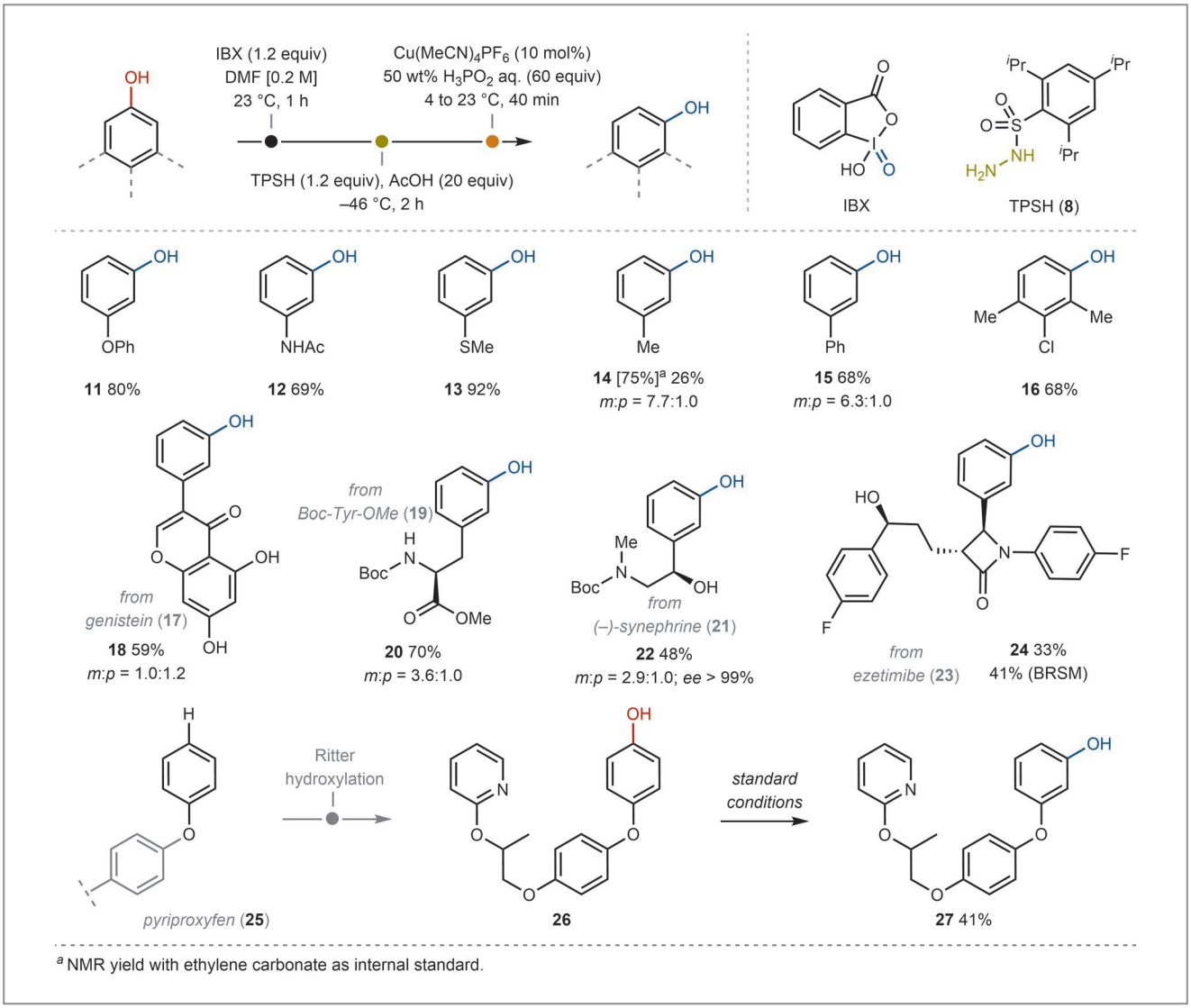
that needed to be balanced, including selectivity for condensation over electron transfer, regioselectivity for condensation at C1 over C2, the rate of α-elimination to ensure a one-pot protocol, and finally, the reactivity of sulfinic acid **5** that is formed as a byproduct. For less sterically demanding derivatives of TPSH, we observed competitive conjugate addition to *ortho*-quinone **2**, leading to catechol **7** as an undesirable addition product (Scheme 1c)."

Finally, to convert diazoquinone **6** into *meta*-phenol **3**, the authors explored classical conditions for the reduction of diazonium salts, recognizing their similarities to the zwitterionic resonance structure of **9**. "We found that a combination of hypophosphorous acid (H_3PO_2) and a Cu(I) salt effected chemoselective reduction, drawing inspiration from Kornblum (*J. Am. Chem. Soc.* **1950**, *72*, 3013–3021)," remarked Professor Lumb, adding: "We suspect that this process involves a radical-chain mechanism that is initiated by Cu(I) and that leads to the liberation of N_2 and an aryl radical **10**. Hydrogen atom transfer (HAT) with H_3PO_2 would then propagate the radical chain, while providing product **3** (Scheme 1d)."

As a one-pot, sequential process, in which the reaction mixture is progressively transferred to reagents by cannula additions, the isomerization exhibits good functional group tolerance and generally affords high yields. Heteroatom substituents, including oxygen, nitrogen and sulfur (**11**–**13**) are particularly effective at directing the isomerization to afford

single regioisomers, but even relatively simple aliphatic substituents, such as methyl (**14**), are tolerated and provide synthetically useful ratios of products (Scheme 2). "We illustrated the versatility of the reaction on natural products, including genistein (**17**) and tyrosine derivative **19**, to provide *meta*-isomers **18** and **20** in short order from commercially available starting materials," said Professor Lumb. He went on: "Finally, we showed the utility of our method in the late-stage diversification of (–)-synephrine (**21**) and ezetimibe (**23**), along with the agrochemical pyriproxyfen (**25**), to provide isomers that would otherwise be difficult to prepare from commercial sources (Scheme 2)."

In summary, the authors have developed a method to isomerize phenols that should facilitate the synthesis of isomers which could otherwise be difficult or costly to prepare. "Generally speaking, *meta*-substituted phenols are more difficult to make and less abundant than their *para*-isomers because of the well-known directing effects of phenols in most bond-forming reactions," said Professor Lumb, who concluded: "This new tool could benefit synthetic, medicinal and materials scientists by facilitating the diversification of readily available feedstocks, to explore a substituent effect that should have a dramatic impact on properties and thus performance. Related methods of scaffold editing have gained



Scheme 2 Selected examples of reaction scope

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recent attention (*Nat. Synth.* **2022**, *1*, 352–364), particularly from medicinal chemists, as they create new opportunities to diversify chemical space. We see many opportunities to apply a phenol isomerization to this objective."

About the authors

S. Edelmann

Simon Edelmann obtained his B.Sc. at the University of British Columbia Okanagan, Canada (2019) where he worked on the synthesis of fluorescent dyes and kainic acid analogues for the study of neuroreceptors under the guidance of Prof. Frederic Menard. Simon joined the Lumb group as a PhD student in 2019 and is working on developing methods to better utilize *ortho*-quinones in organic synthesis.

Prof. J-P Lumb

Jean-Philip Lumb is an Associate Professor of Chemistry at McGill University (Canada). He obtained his Ph.D. from the University of California, Berkeley (USA) in 2008 working with Dirk Trauner before completing a postdoctoral fellowship at Stanford University (USA) with Barry Trost. His group is interested in oxidation chemistry, and often applies the tactics of biomimicry and catalysis to facilitate the synthesis of complex organic molecules. In 2019, Professor Lumb was awarded the Keith Fagnou Award from the Canadian Chemical Society, and in 2023, he received the X–Chem Research Excellence Award, also from the Canadian Chemical Society.

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Young Career Focus: Dr. Xiaoran Hu (Syracuse 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 Dr. Xiaoran Hu (Syracuse University, USA).

Biographical Sketch

Dr. X. Hu

Xiaoran Hu grew up in Henan province (P. R. of China) and received a B.S. in chemistry from Nanjing University in 2010. During his doctoral studies with Prof. Samuel Thomas at Tufts University (USA, 2012–2017), Xiaoran developed strategies to photo-control polymer self-assembly and cargo release. Xiaoran then conducted postdoctoral research in polymer mechanochemistry in the Division of Chemistry and Chemical Engineering at Caltech (USA, 2017–2021), mentored by Prof. Maxwell Robb. After that, Xiaoran furthered his postdoctoral training in biomaterials and drug delivery with Profs. Shaoyi Jiang in the Meinig School of Biomedical Engineering and Geoffrey Coates in the Department of Chemistry and Chemical Biology at Cornell University (USA, 2021–2022). Dr. Xiaoran Hu joined the faculty at Syracuse University (USA) in 2022, where his group's research has been dedicated to the development of stimuli-responsive chemistry for sensing and controlled-release applications.

INTERVIEW

SYNFORM *Which field of organic chemistry are you interested in the most and why?*

Dr. X. Hu I am mostly interested in stimuli-responsive organic materials. In this branch of organic chemistry, we focus on designing new molecules and building bonds in such a way that these molecules, once prepared, can be deconstructed or manipulated in predictable ways by applying external stimuli such as ultrasound[1–3] and light.[4–6]

Even before majoring in chemistry, I've always been intrigued by the wide variety of materials that are part of our daily lives, the reason behind their differing properties, and how these properties may be controlled. It is a satisfaction to understand the structure–property relationships at the molecular level and use this understanding to rationally design materials with specific properties that can solve real-world problems.

SYNFORM *Following that, what is the focus of your current research activity?*

Dr. X. Hu 'Gated reactivity' involves systems where a reactive species is kept inactive or 'gated' until a particular trigger activates or 'unmasks' the reactivity. Based on this concept, we have developed smart materials and systems for various applications, including sensing and controlled release (Figure 1).

The Hu group at Syracuse University (USA) recently introduced a new method to manipulate the atropisomer stereochemistry of configurational diarylethene mechanophores, thereby regulating diarylethene's photochemical properties.[1,2] Coupling force with stereochemistry and molecular configuration represents a general method, and our group is actively investigating novel configurational mechanophores following this overarching design principle.

Employing the 'gating' concept, our team is also actively working on materials systems for controlled release and drug

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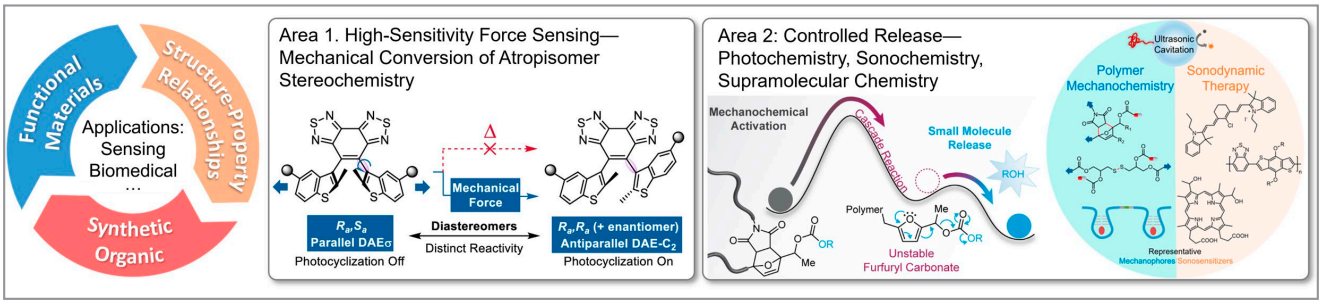

Figure 1 Overview of research in the Xiaoran Hu group at Syracuse University. Reproduced with permission from references 1, 3, and 7. Copyright 2023, American Chemical Society. Copyright 2024, American Chemical Society. Copyright 2019, American Chemical Society.

delivery applications, that are responsive to light, ultrasound, or supramolecular interactions. A couple of manuscripts are under preparation in this direction.

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

Dr. X. Hu Organic chemistry serves as the foundation across various disciplines. For materials chemists, organic chemistry offers valuable insights for designing new materials, fueling hypothesis-driven materials research that extends the limits of current material properties and functionalities. On the other hand, synthetic organic chemistry provides a rich toolbox that enables the construction of new molecules and macromolecules. This capability unlocks remarkable opportunities within the broader fields of science and engineering, offering chemical solutions to global challenges and advancing human well-being.

SYNFORM *Which difficulties are there for young upcoming chemists in your field? Do you have any tips?*

Dr. X. Hu It is important to stay updated with the latest developments in the field, while focusing on identifying and establishing one's research niche that has the potential for sustainable external funding. Moreover, new assistant professors will face responsibilities beyond what is typically covered in graduate and postdoctoral training. This includes building and managing a research group, overseeing research projects while crafting strategic grant proposals, and managing non-research obligations such as teaching and curriculum development.

One tip I have learned from my postdoc mentors on launching a research program is to begin acting on an idea once it is conceived instead of waiting for the perfect idea, while remembering to keep open-minded and flexible during the project and constantly explore new avenues and opportunities as the project progresses.

SYNFORM *Could you tell us something about yourself outside the lab, such as your hobbies or extra-work interests?*

Dr. X. Hu During the COVID pandemic, I discovered a passion for indoor bouldering and now spend a few hours each week climbing at the gym. Additionally, snowboarding is a sport I've enjoyed since early in my graduate school days.

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

Dr. X. Hu The most important of my independent research accomplishments so far is the development of a new type of configurational mechanophore. This work, detailed in our 2023 publication in the *Journal of the American Chemical Society*,[1] introduces an innovative mechanism for converting a mechanophore into its configurational diastereomers. Besides the novelty and generality of the mechanism, our approach features a unique combination of advantages that position it as an enabling technology in high-sensitivity stress sensing: (1) This type of configurational mechanophore features remarkably high mechanosensitivity, evidenced by experimental and computational discoveries reported in our 2023 *J. Am. Chem. Soc.* paper. We will soon submit a new manuscript that focuses on understanding and enhancing the mechanical sensitivity of configurational mechanophores. (2) The conversion of configurational stereochemistry is irreversible and permanent, providing a stable readout that signals the mechanical activation event even after lifting the force. Previous high-sensitivity conformational mechanophores only provide a transient signal under applied force.

Additionally, during my postdoctoral training in Professor Maxwell Robb's lab at Caltech, we developed a furan-maleimide mechanophore system that introduced the concept of controlled release of covalently bound functional molecules through the mechanical effect of ultrasound.[7–10] This mechanistically innovative technology harnesses ultrasound waves to mechanically trigger the release of covalently bound cargo molecules from polymer chains in solution, marking a significant advancement in ultrasound- and force-controlled release systems.

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Coming soon

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