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

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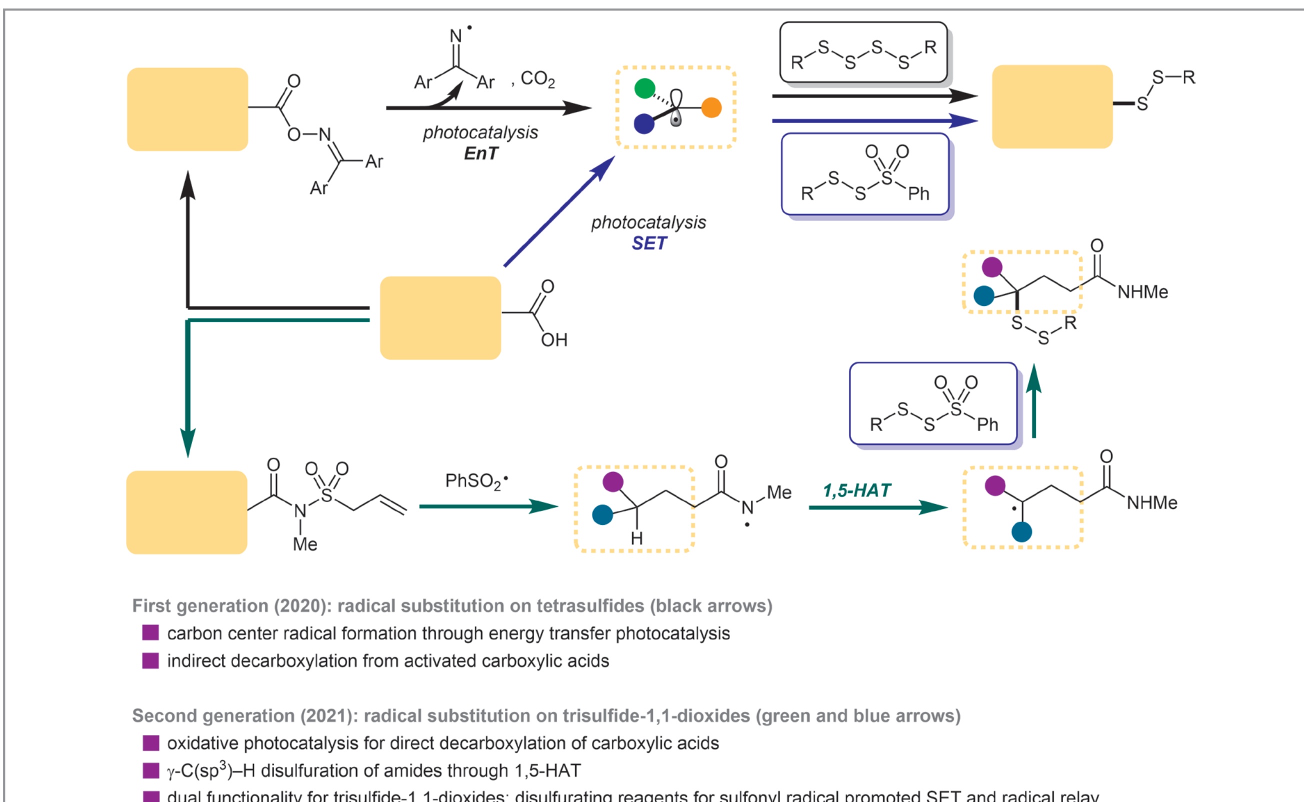
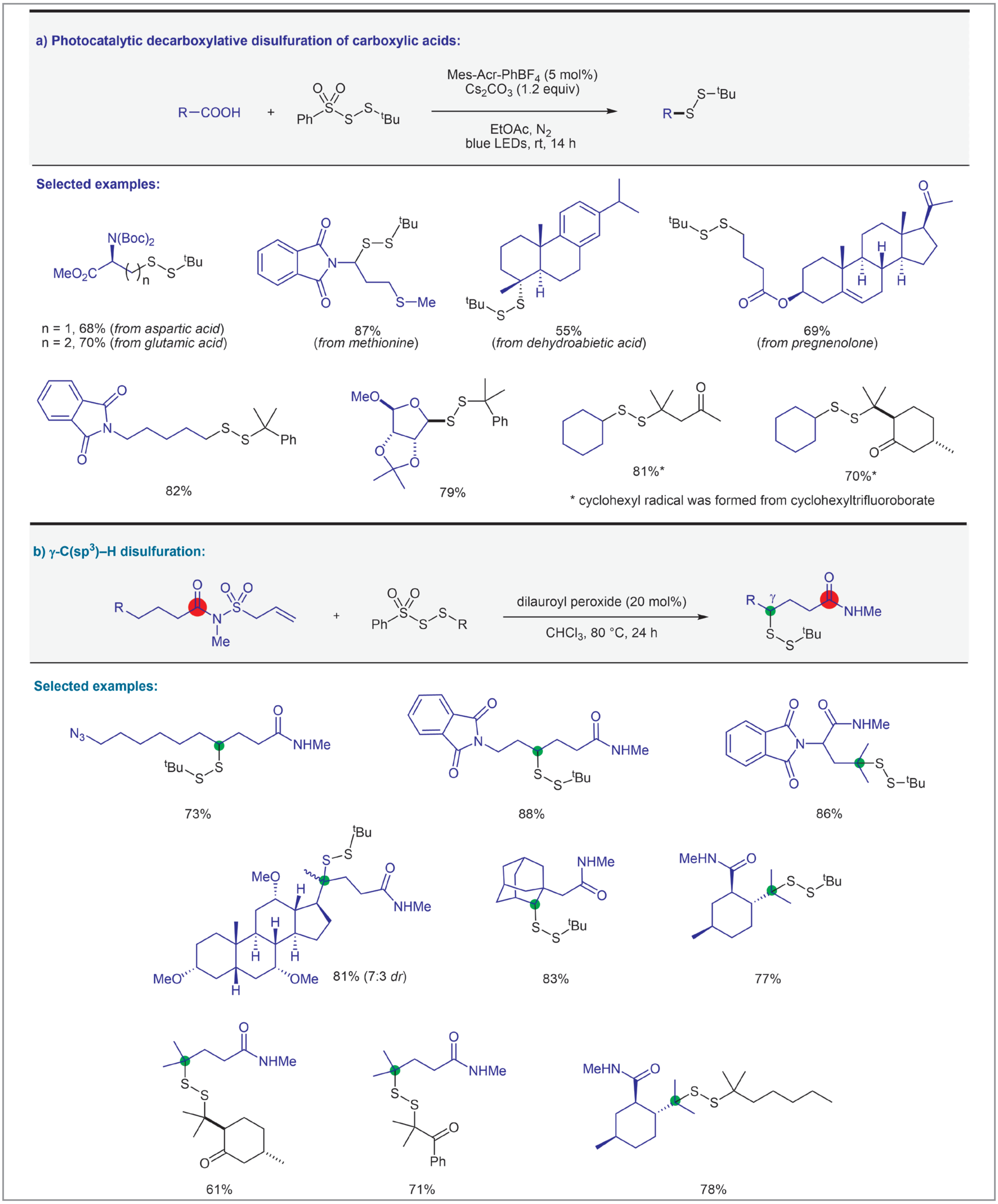
According to Professor Derek Pratt, from the University of Ottawa (Canada), making symmetric disulfides bonds is relatively easy: “Anyone that has worked with thiols knows that this often happens inadvertently, simply upon exposure to air,” he said, adding: “The preparation of unsymmetric disulfides 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-oxides[2] 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 peroxyl 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



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

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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 $C(sp^3)$–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."

Matteo Zanda

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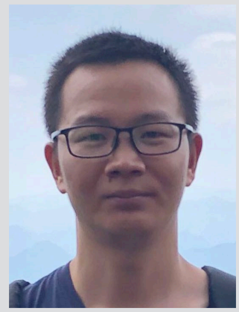
About the authors

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.

