

Metal-Free Photoredox-Catalysed Formal C–H/C–H Coupling of Arenes Enabled by Interrupted Pummerer Activation

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(Hetero)biaryl scaffolds are ubiquitous in the molecules that drive the main chemical industries. Such motifs are most commonly assembled using transition-metal-catalysed cross-couplings; however, the requirement to pre-functionalise both coupling partners and the use of precious-metal catalysts can result in costly procedures that produce substantial amounts of waste. According to Professor David Procter – an expert of cross-coupling chemistry and catalysis at the University of Manchester (UK) – a strong movement has recently formed within the synthetic community with the aim of developing (i) cross-couplings of non-prefunctionalised partners, that take place at the expense of C–H bonds, and (ii) cross-couplings that operate without using metals.

Professor Procter's group have long been drawn to the idea that sulfur can replace metals in cross-couplings by (i) activating substrates, and (ii) providing a center around which coupling partners can be assembled prior to coupling. In particular, the group have recently developed a range of C–H functionalisation processes that utilise the so-called interrupted Pummerer reaction of sulfoxides.

In their latest account, Professor Procter and his group have developed a highly effective strategy for the synthesis of (hetero)biaryls by combining the interrupted Pummerer activation of arenes with a subsequent visible-light-mediated reduction, using an organic photoredox catalyst. "The application of sulfonium salts in photoredox catalysis is underexplored. We had already shown that the interrupted Pummerer reaction of sulfoxides could be used to make *alkenyl*sulfonium salts that fed into a base-metal-catalysed process, and we were confident that similarly formed *aryl*sulfonium salts would be excellent substrates for photocatalysis," explained Professor Procter.

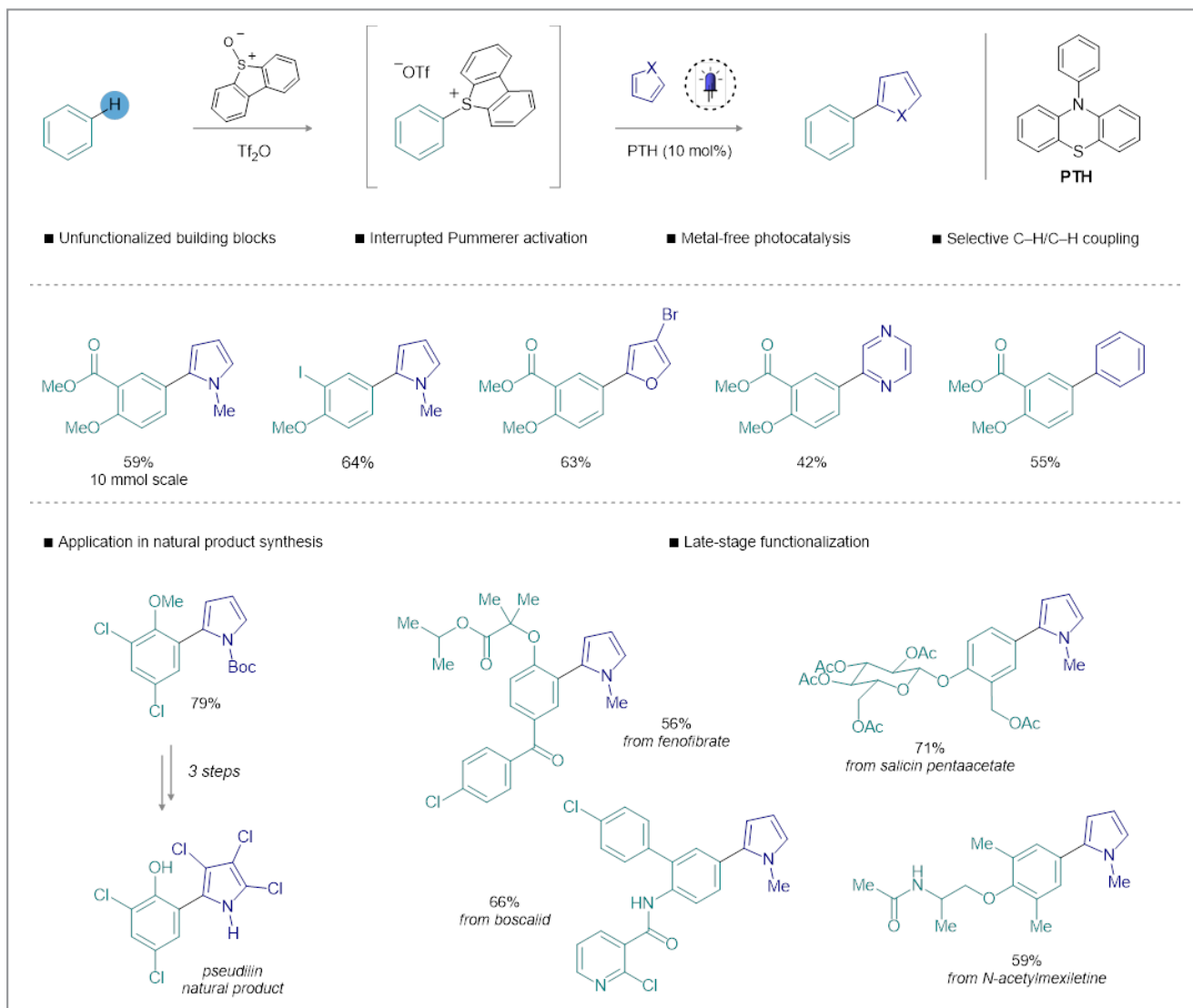
Indeed, by exploiting a commercial sulfoxide, dibenzothiophene S-oxide (DBTSO), as the process mediator, the authors achieved high selectivity and reactivity in C–H sulfenylation and sulfonium salt formation. EPSRC Doctoral Prize Fellow, Dr. Miles Aukland, continued: "We prepared a range of sulfonium salts and tested several photoredox catalysts, but identified the salt derived from dibenzothiophene and an organic photoredox catalyst, 10-phenylphenothiazine (PTH), as the most efficient combination." The photoredox catalyst is responsible for generating a reactive aryl radical from the sul-

fonium salt, which then engages in cross-coupling with the heteroarene partner. When compared to existing photoredox-catalysed approaches to make heterobiaryls, the group's approach avoids the practical issues of safety, stability and availability that are associated with aryl diazonium salts, and the highly negative reduction potentials of aryl halides. The authors also highlighted that the dibenzothiophene byproduct can be easily recovered and recycled, further improving the atom economy of the procedure. Lecturer Dr. Gregory Perry added: "By transforming simple arenes into sulfonium salts, we gained access to a class of bench-stable aryl radical precursors of complementary reactivity for use in formal C–H/C–H cross-couplings."

The authors showed how their strategy is suitable for the synthesis of a wide variety of (hetero)biaryl architectures (>50 examples). PhD student Mindaugas Šiaučiulis emphasised: "The process tolerates the presence of halide and triflate functional groups thus signalling its orthogonality to traditional cross-coupling." The team also showed that the process could be applied to the late-stage functionalisation of complex bioactive molecules and in the synthesis of natural products, such as the pseudilins.

When asked about the future of the field, Professor Procter responded, "The influence of light on the chemistry of sulfonium salts has long fascinated chemists. For example, a report by R. M. Kellogg in the 1970s described the light-mediated reduction of sulfonium salts and is viewed as one of the first examples of photoredox catalysis. The field of photoredox catalysis has exploded in the past ten to fifteen years; however, the photoredox chemistry of sulfonium salts has remained largely untouched. We hope that our report not only illustrates the accessibility and utility of sulfonium salts, but also showcases how the introduction of new substrates, prepared in innovative new ways, can lead to significant advancements in the burgeoning field of photoredox catalysis."

Mattes female



Scheme 1 Procter's strategy for metal-free, photoredox-catalysed, formal C–H/C–H coupling and selected examples

About the authors



Dr. M. H. Aukland

Dr. Miles H. Aukland obtained his MChem degree from the University of Manchester (UK) in 2014, working under the supervision of Prof. David J. Procter. He then continued in the Procter group to study towards his Ph.D., where he developed new sulfur-mediated C–H functionalization strategies using low-cost metals. In 2018, he was awarded a prestigious EPSRC Doctoral Prize Fellowship to work on the application of sulfonium salts in photoredox processes for C–C bond formation. In 2019, Miles moved to the Max-Planck-Institut für Kohlenforschung (Germany) to conduct postdoctoral research with Prof. Benjamin List.



M. Šiaučiulis

Mindaugas Šiaučiulis obtained his MSci Chemistry degree from the University of Nottingham (UK) in 2016, having completed a research project under the supervision of Dr. Elaine O'Reilly. He then moved to the University of Manchester (UK) for his doctoral studies in the group of Prof. David J. Procter, where he worked on the development of novel cross-coupling reactions mediated by sulfonium salts. Later in 2020, Mindaugas will move to a postdoctoral research position in the group of Prof. Lee Cronin at the University of Glasgow (UK).



A. West

Adam West received his MChem degree from the University of Manchester (UK) in 2019. During his degree he spent a year at Chromition Ltd., working on novel fluorescent polymer nanoparticles for bioimaging applications. His final-year research project was carried out under the supervision of Prof. David J. Procter and Dr. Miles Aukland, and focused on the use of photoredox catalysis for C–C bond formation. After graduation, Adam took up a position in the chemistry research department at Pfizer UK Ltd.



Dr. G. J. P. Perry

Dr. Gregory J. P. Perry received his MChem from the University of Liverpool (UK) in 2012 and his PhD in 2016 from the University of Manchester (UK). His doctoral studies were carried out in the group of Prof. Igor Larrosa and focused on decarboxylative and C–H transformations. In 2017, he moved to Nagoya University (Japan) to work with Prof. Kenichiro Itami on the application of C–H activation in chemical biology. Since 2018, Greg has been working as a Lecturer in Organic Chemistry within the group of Prof. David J. Procter at the University of Manchester (UK).



Prof. Dr. D.J. Procter

Prof. Dr. David J. Procter was awarded a BSc in chemistry from the University of Leeds in 1992 and his PhD in 1995 working with Prof. Christopher Rayner on organosulfur and organoselenium chemistry. He then spent two years as a Postdoctoral Research Associate with Prof. Robert Holton at Florida State University in Tallahassee (USA) working on the synthesis of Taxol. In late 1997 he took up a Lectureship at the University of Glasgow in Scotland and was promoted to Senior Lecturer in 2004. In 2004, he moved to a Readership at the University of Manchester (UK). David was promoted to Professor in 2008 and is currently Head of the Department of Chemistry.