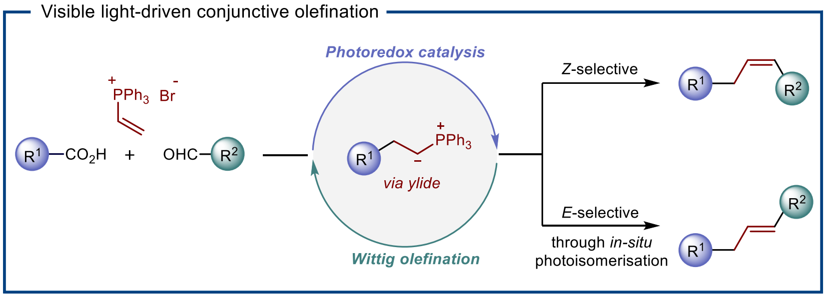
The Conceptual Development of a Conjunctive Olefination

D. Filippini,[a,b] M. Silvi*[a,b]

[a] GSK Carbon Neutral Laboratories for Sustainable Chemistry, University of Nottingham, Jubilee Campus, 6 Triumph Rd, Nottingham NG7 2GA, United Kingdom.

[b] School of Chemistry, University of Nottingham, University Park, Nottingham NG7 2RD, United Kingdom.

mattia.silvi@nottingham.ac.uk



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Abstract We recently discovered a functional group tolerant and transition metal-free *conjunctive olefination* reaction with applications in late-stage functionalization chemistry. In this Synpacts contribution, we analyze the conceptual background that has stimulated the discovery of this reactivity and reflect on the key aspects of its development.

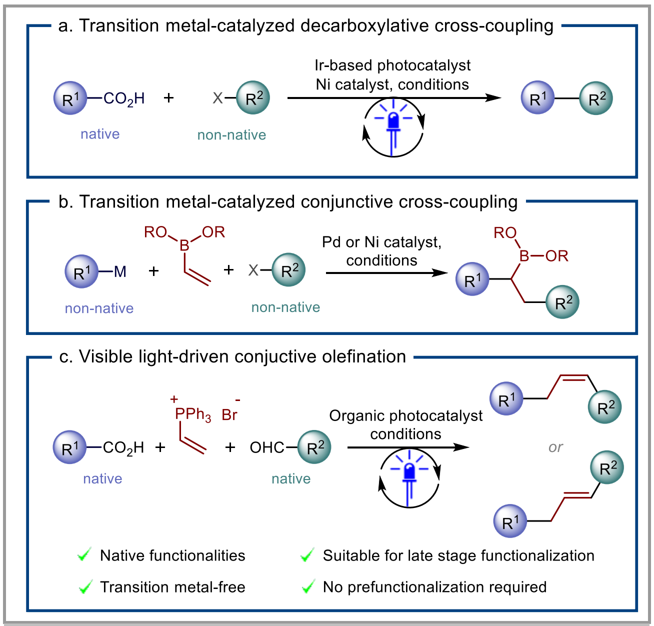
Key words Photoredox catalysis, Wittig reaction, Radical-polar crossover, Conjunctive olefination, Radical chemistry.

1. Introduction

Over the last two decades, radical chemistry has witnessed a renaissance,[1] mainly thanks to the discovery and the refinement of catalytic methods that allow the practical and selective generation of reactive radical species under remarkably mild conditions, e.g., photoredox catalysis[2] or electrochemical methods.[3] These recent advances have promoted the development of sophisticated dual catalytic manifolds,[4] enhancing the potential of established synthetic fields[5] such as organocatalysis and transition metal catalysis.[6]

In this vein, harnessing photoredox radical methods[2] and taming the often-unpredictable nature of nickel catalysis[7] has unlocked new pathways in cross-coupling chemistry. This has allowed the practical use of sp^3-hybridised partners – challenging substrates for this class of transformations – and the use of readily available functional groups (e.g., carboxylic acids, Scheme 1a)[8] in place of other traditional non-native functionalities (e.g., organometals or boron compounds),[9] thereby expanding the "toolbox" of the synthetic organic chemist.

While the methodologies mentioned above have promoted tremendous advances in organic synthesis, they all require the presence of non-native functional groups in at least one of the two coupling partners, e.g., (pseudo)halides. This reduces the chemical space accessible, especially in the context of late-stage functionalization,[10] as the installation of these functionalities may be challenging when complex fragments are involved in the process.



Scheme 1 a. Photoredox decarboxylative cross-couplings. b. Transition-metal catalyzed conjunctive cross-couplings. c. Transition metal-free conjunctive olefination. M: metal; X: (pseudo)halide.

We recently questioned whether we could develop a novel chemical strategy to structurally connect complex building blocks bearing only naturally recurrent functional groups, thereby unlocking access to new chemical space for the late-stage functionalization of bioactive molecules. To circumvent the drawbacks of traditional cross-coupling chemistry mentioned above, we conceived a distinct transition metal-free coupling strategy based on the use of a small structural carbon-based fragment to *conjoin* two complex partners. For resemblance to other elegant multicomponent couplings that use alkene reagents as “conjoining reagents” to connect coupling partners in *conjunctive cross-couplings*[11] (Scheme 1b) we defined our process *conjunctive olefination*[12] (Scheme 1c).

The reactivity connects pair of complex molecular partners through an unsaturated fragment acting as a “linchpin”, thereby providing chemists with a new practical and versatile technique for the late-stage functionalization of complex bioactive molecules.[12]

In the following sections, we will discuss the conceptual background that stimulated the invention and the development of our conjunctive olefination.

2. Conceptual Background

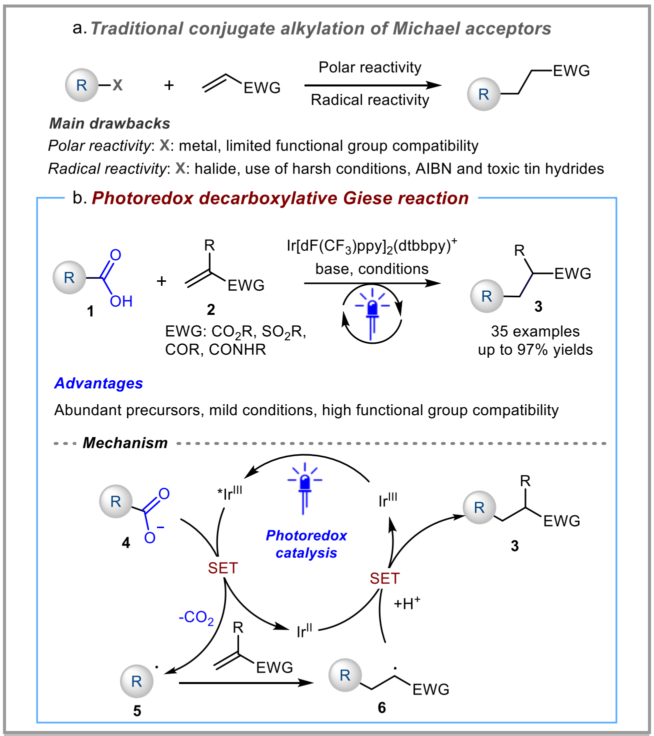
2.1 Photoredox-mediated Giese Reaction

Photoredox catalysis recently emerged as a popular area in organic chemistry, that tremendously impacted the way scientists plan chemical synthesis.[2] This strategy has provided myriad new opportunities for chemists, rejuvenating and enhancing the potential of radical chemistry, an established workhorse of synthetic chemistry. In this regard, photoredox catalysis allowed to perform radical reactions under remarkably mild reaction conditions,[13] in contrast to traditional methodologies which typically require high temperatures or ultraviolet irradiation, as well as the use of potentially explosive and toxic initiators (e.g., tin dimers, peroxides or azobisisobutyronitrile). The remarkable features of photoredox catalysis ensure significantly improved functional group tolerance in radical processes, and justify the popularity of the field.

An additional remarkable aspect of photoredox catalysis, that we found particularly meaningful for our target, is the ability to forge new C-C bonds exploiting starting materials which bear more abundant functional groups compared to other more traditional methods. For instance, while the conjugate alkylation of unsaturated Michael acceptors traditionally requires the use of organometallic carbon-nucleophiles,[14] or radical methods typically requiring organohalides and initiators (i.e., the Giese reaction),[15] Scheme 2a, photoredox catalysis allows the use of more abundant radical precursors such as carboxylic acids,[16] and even other functional groups such as alcohols[17] or amine derivatives[18] under very mild conditions.

In this regard, in 2014 the group of MacMillan has reported a remarkable modern revisitation of the classic Giese radical addition (Scheme 2b).[16] In the process, the addition of carbon-centered radicals to various acrylates **2** could be conveniently performed using carboxylic acids **1** as substrates and a visible-light-driven photoredox cycle based on an iridium photocatalyst. No toxic initiators or tin-derived compounds were necessary to run the reactions, which provided a variety of alkylated products **3** in synthetically useful yields.

In the process, depicted in Scheme 2b, single-electron transfer (SET) from carboxylates **4** to the photoexcited Ir^{*III} catalyst leads to the decarboxylative generation of radicals **5**, that undergo addition to the vinyl system of **2**. Reduction of the resulting electron-deficient radicals **6** by the reduced Ir^{II} photocatalyst leads to desired products **3** and regenerates catalytic species Ir^{III}.



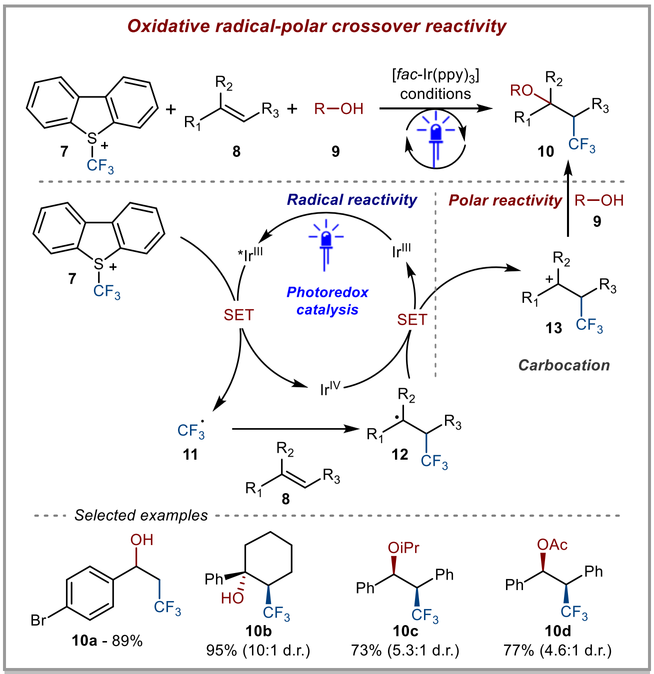
Scheme 2 a. Polar and radical traditional strategies for conjugate alkylation of Michael acceptors. b. Conjugate alkylation of Michael acceptors through photoredox decarboxylative Giese-type reaction. AIBN: azobisisobutyronitrile.

The chemistry discussed above was further refined by other research groups, which later demonstrated that more abundant organic photocatalysts could be used in place of rare transition metal-based structures,[19] further expanding the scope of radical acceptors and successfully applying the chemistry in the context of late-stage functionalization chemistry.[20]

2.2 Photoredox Radical-Polar Reactivity

While photoredox catalysis is generally considered a convenient method to promote radical reactivity, a remarkable additional aspect of this synthetic strategy is the ability to promote the mild formation of polar reactive intermediates (e.g., carbocations, carbanions) under remarkably mild conditions. Brönsted/Lewis acids or strong bases are traditionally required for the generation of such reactive species, but photoredox methods exploit single electron transfer reduction or oxidation of transient radical intermediates to promote the crossover from a radical to a polar process.[21] The polar reactive species produced can be exploited to develop further reactivity in the context of multicomponent couplings or intramolecular cyclization reactions.

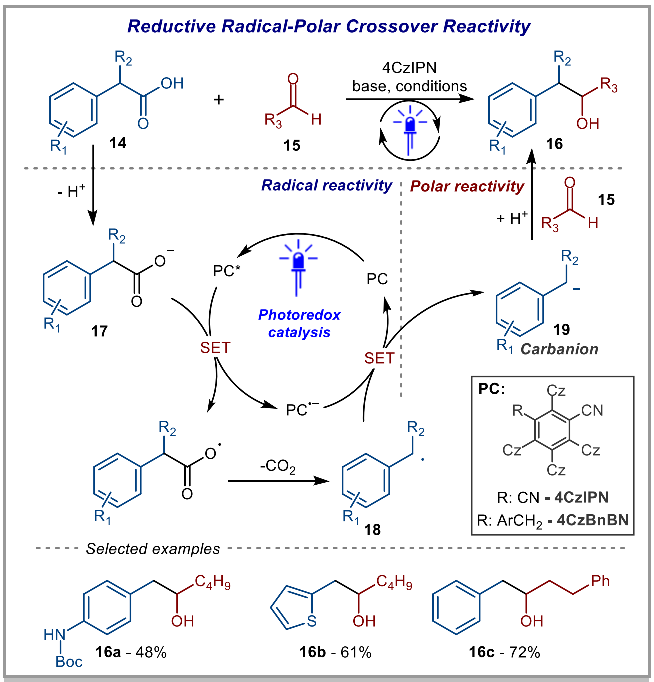
Recently, various research groups have demonstrated that carbocations can be generated under a photoredox radical-polar crossover regime and undergo a variety of chemical processes, including ring expansions,[22] 1,2-migration reactions[23] or multicomponent alkene carbo-functionalizations.[24] Remarkable examples of reactions were reported by Akita and others, who demonstrated that alkenes can undergo trifluoromethylative difunctionalizations under photoredox radical-polar conditions.[24]



Scheme 3 Photoredox oxy-trifluoromethylation of alkenes through an oxidative radical-polar crossover pathway.

In a typical process, shown in Scheme 3,[24b] facile single-electron reduction of the Umemoto reagent **7**[25] is mediated by an excited iridium photocatalyst (*fac*-Ir(ppy)$_3$) under visible light irradiation, leading to reactive trifluoromethyl radical **11**. Addition of **11** to alkenes **8** leads to the formation of carbon-centered radical intermediates **12**. Single-electron oxidation of these species by the oxidized Ir^{IV} complex regenerates the Ir^{III} catalyst, while mediating the crossover from a radical to a polar pathway to generate carbocations **13**. These highly reactive polar intermediates rapidly react with alcohols **9** to give fluorinated products **10**.

While the process described above is a remarkable example of the oxidation of radical centers to access carbocation reactivity, a complementary synthetic strategy in the context of photoredox radical-polar crossover chemistry is the reduction of radical centers to promote carbanion chemistry.[21] The carbanions generated in solution can undergo a number of sequential *in-situ* reactions, including cyclopropanations,[26] ring expansions[27] and alkene dicarbofunctionalizations.[28] A particularly representative example of reductive radical-polar reaction was reported by the group of König et al. which described a practical aldehyde benzylation protocol using arylacetic acids **14** under a photoredox regime (Scheme 4).[29] The reaction uses mild conditions and allows carbonyl alkylation, a process that would typically require highly nucleophilic organometallic reagents (e.g., Grignard reagents or organolithiums).



Scheme 4 Photoredox aldehyde benzylation through a reductive radical-polar crossover pathway. Cz: carbazolyl.

In the process, depicted in Scheme 4, visible light irradiation promotes the formation of excited organic photocatalyst PC*, which undergoes SET with carboxylates **17**, leading to the decarboxylative generation of radicals **18**. Single-electron transfer from the electron-rich photocatalyst radical anion PC$^{\bullet-}$ to radicals **18** closes the catalytic cycle and promotes the crossover from a radical to a polar pathway generating reactive carbanions **19** in solution. Finally, rapid addition to aldehydes **15** leads to the desired products **16**. Interestingly, although commercially available organic photocatalyst 4CzIPN[30] is used in this transformation, the authors observed the *in-situ* formation of the corresponding benzylated 4CzBnBN derivatives, proposed to be the active catalytic species in the process.

3. The Development of the Process

The transformations discussed above illustrate the ability of photoredox methods to drive hybrid catalytic manifolds where a variety of reactive intermediates (both radical and polar) are selectively generated in a specific sequence, and can be effectively leveraged to develop previously inaccessible reactivity.

In conceiving our conjunctive olefination chemistry, we surmised that upon carefully designing a novel radical-polar crossover strategy, we could combine two major pillars of organic synthesis – namely photoredox radical chemistry[2] and the Wittig reaction[31] – in a single multicomponent catalytic process. We speculated that such system would allow the development of a novel cross-coupling strategy, using commercially available vinyl-phosphonium **21** as “conjoining reagent” to combine the two coupling partners **20** and **22**, thus accessing conjunctive products **23** (Scheme 5).

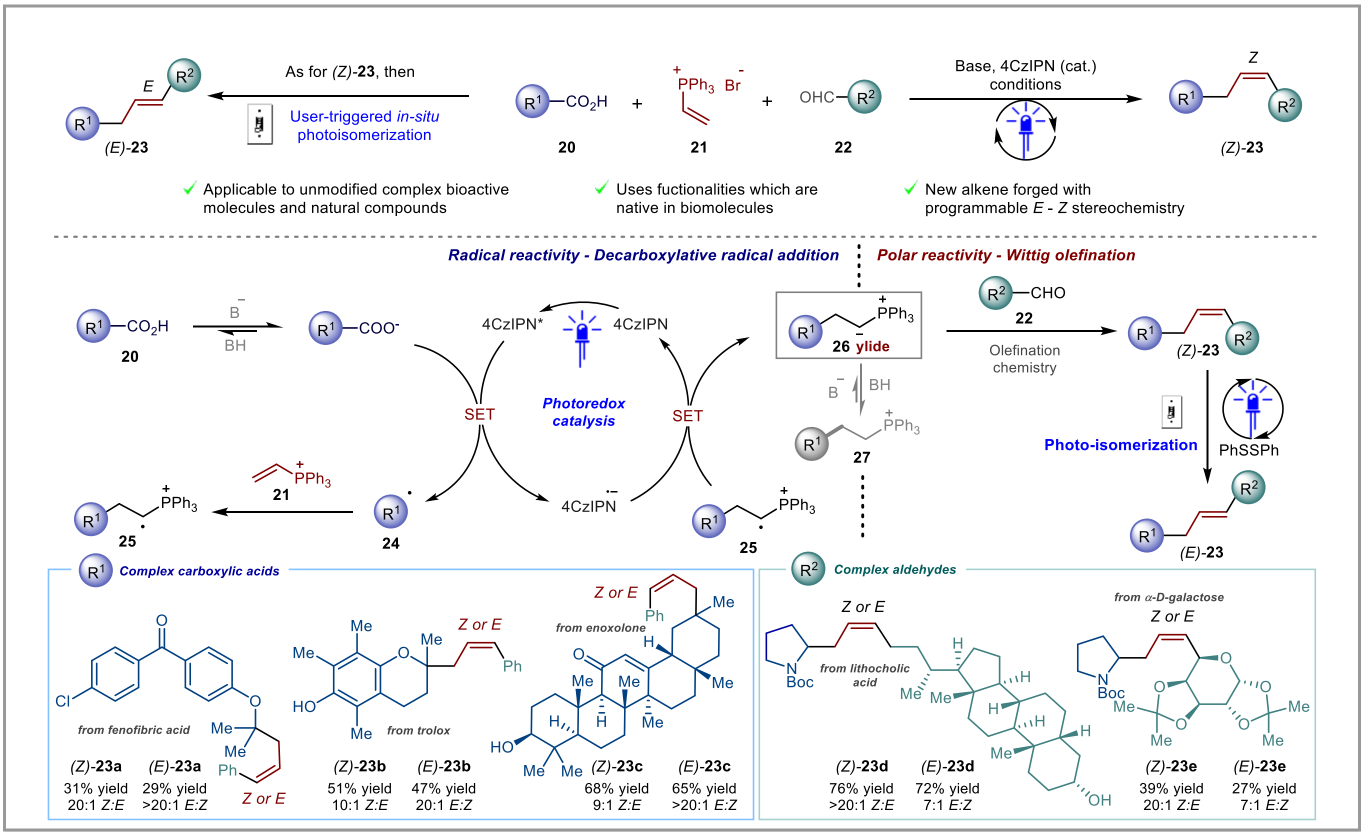
For our system, we hypothesized that photoexcited organic photocatalyst 4CzIPN would mediate the generation of carbon-centered radicals **24** upon oxidative decarboxylation of carboxylic acids **20**. We envisioned that under these conditions, the reactive radical species would readily add to the vinyl system of **21**,[32] leading to radical cations **25**. We then surmised that reduction these transient species would lead to the *in-situ* formation of ylides **26**, that would engage in sequential Wittig olefination with aldehyde partners **22**, giving access to conjunctive products **23**.

Our reactivity hypothesis presented significant challenges, as it implied advancing the field of photoredox catalysis in two key aspects. First, while a variety of acrylates were used as radical traps in photoredox-promoted radical processes,[20] the use of a vinyl phosphonium was never reported in this context, and the process would rely on the design of a catalytic manifold compatible with such a reactive reagent. Second, a radical-polar crossover process involving SET of a radical cation to generate an ylide was never described. In this regard, we predicted that finding the perfect match between the redox properties of radical cation **25** and the reduced photocatalyst 4CzIPN$^{\cdot-}$ was likely to be key for the success of our process.

Our experiments confirmed that, upon a thorough study of the photoredox cycle and a fine optimization of the process, our reaction could be successfully realized giving access to the desired conjunctive products **23**. The methodology was demonstrated to be highly functional group tolerant, including to protic functionalities (e.g., unprotected alcohols) and Lewis basic functionalities (e.g., heteroaromatics), thereby allowing the practical late-stage functionalization of complex molecules. As presented with selected examples in Scheme 5, the process allowed the selective functionalization of bioactive molecules and complex drugs in their native form, with no or minimal use of protecting groups, affording new derivatives **23a** – **23e**.

As expected from the classic Wittig olefination chemistry,[33] *(Z)*-alkenes were forged within our conjunctive products. Remarkably, we could demonstrate that *(E)*-products could also be accessed through a practical *in-situ* thermodynamic photoisomerization protocol obtained by the addition of $(PhS)_2$ to the reaction under visible-light irradiation.[34] In all case, both the desired *(E)* or *(Z)* isomers of the desired complex structures were selectively accessible upon user-defined simple modifications of the reaction procedure.

Interestingly, preliminary mechanistic studies suggested the presence of a parasitic acid-base equilibrium between the intermediate ylides **26** and the corresponding phosphonium salts **27** in solution. Under our reaction conditions, unstabilized ylides **26** react with aldehydes **22** to give products **23** shifting the parasitic equilibrium towards the products, a process that was observed to be facilitated by mild heating (Scheme 5).



Scheme 5 Visible-light driven conjunctive olefination, postulated reaction mechanism and selected examples of application in late-stage functionalization of complex bioactive molecules. Boc: *tert*-butoxycarbonyl.

In conclusion, by combining the features of photoredox radical reactivity with the Wittig reaction through a radical-polar crossover process, our research group has recently designed a novel synthetic strategy to cross-couple complex molecular fragments under remarkably mild conditions. Our transition metal-free process allows practical late-stage functionalization of native bioactive molecules and leverages an unsaturated linchpin with user-defined geometry to connect complex molecular fragments.

Our novel reactivity concept is expected to pave the way for the invention of novel powerful structures with various applications in pharmaceuticals, agrochemicals or for the invention of novel materials. We predict that the novel reactivity will inspire further advancement in the field of organic photoredox catalysis and radical-polar crossover reactions.

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Conflict of Interest

The authors declare no conflict of interest.

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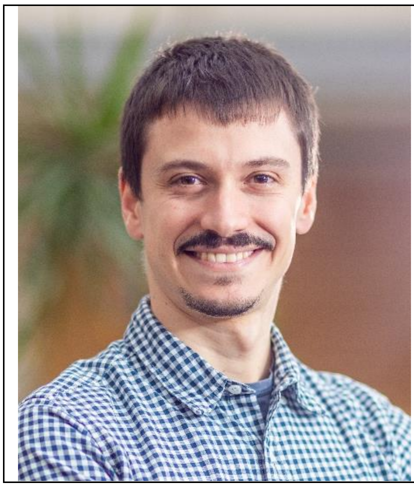
Biosketches

	**Mattia Silvi** studied chemistry as undergraduate student at the University Sapienza (Rome, Italy). He then carried out his doctoral studies at the Institute of Chemical Research of Catalonia, ICIQ (Tarragona, Spain) under the supervision of Prof. Paolo Melchiorre - working in the fields of organocatalysis and photochemistry - and at the University of Michigan (Ann Arbor, MI, United States) in the group of Prof. John P. Wolfe, working in the field of transition metal catalysis. He then moved to the University of Bristol (United Kingdom) in the group of Prof. Varinder K. Aggarwal, as a Marie Skłodowska-Curie Individual Fellow, where he carried out research in the fields of boron chemistry, prostanoids synthesis and photochemistry. In 2019 he started his independent career at the University of Nottingham (United Kingdom) as a Nottingham Research Fellow. His research group’s interests focus on organic chemistry, photochemistry and asymmetric catalysis.