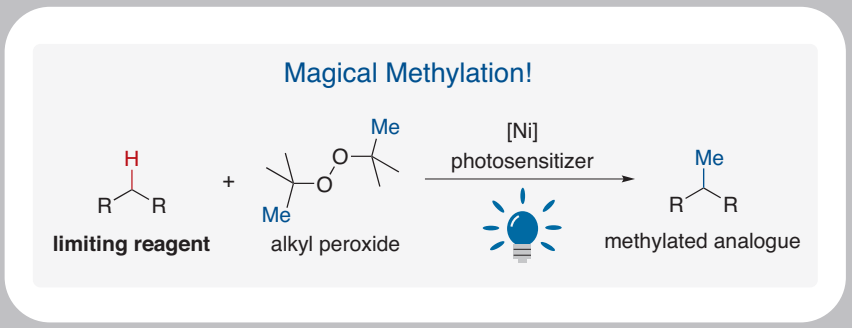
Synform

People, Trends and Views in Chemical Synthesis

2021/10

C(sp³)–H Methylation Enabled by Peroxide Photosensitization and Ni-Mediated Radical Coupling

Highlighted article by A. Vasilopoulos, S. W. Krska, S. S. Stahl



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Thieme

Dear Readers,

As the summer winds down and the days start to get shorter, there are strong hopes that the looming academic year will be as close as possible to normality, i.e. what it used to be before the pandemic. We will probably have to keep wearing face masks indoors, as well as continuing to behave a bit more cautiously than we used to do in our pre-Covid life, at least in terms of social gatherings, but – thanks to the vaccines – we are hopefully getting there now. So once again, we should be deeply grateful to science and research, which made possible an unprecedentedly fast development and distribution of a massive number of doses of effective vaccines. Meanwhile, anti-Covid drugs are being developed, and that will likely be the final nail in the coffin of this bloody virus, besides hopefully giving us some effective pharmacological weapon for coping with any other future wave of new coronaviruses. Sadly, not everybody is able to appreciate what science can do – and is already doing – for all of us, but I believe that, as researchers, we have a critically important duty to relentlessly inform and educate every single member of the public – and of our governing bodies too – about the merits and importance of science and research. In my opinion these are the only effective tools we have for facing the threats lurking in the future of humanity, be those medical or environmental or else. So let's make the voice of science heard, and try to be louder than the voice of anti-science!

This new issue of SYNFORM starts with a Young Career Focus interview with emerging researcher Guillaume Berionni (Belgium), who talks about his views on organic chemistry and his recent research achievements. The second article covers the ground-breaking radical Minisci-style approach to the selective C–H borylation of azines using boryl radicals developed by D. Leonori (United Kingdom). The next article presents an account of the recent *Science* paper by P. J. Walsh and E. J. Schelter (USA) on the role of chlorine radical complexation in photocatalytic C–H activation reactions. Finally, we have the opportunity to learn more about another recent *Science* paper, by S. S. Stahl (USA), on the C(sp^3)–H methylation via peroxide photosensitization/Ni-mediated radical coupling and its prospective applications in drug discovery and development.

Enjoy your reading!

In this issue

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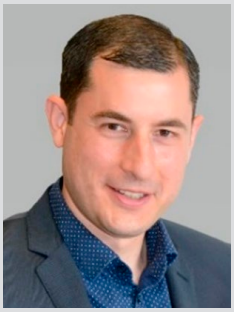
Young Career Focus: Prof. Guillaume Berionni (University of Namur, Belgium)

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 Prof. Guillaume Berionni (University of Namur, Belgium).

Biographical Sketch



Prof. G. Berionni

Guillaume Berionni received his PhD in 2010 from the University of Versailles, France. He then moved to the Ludwig Maximilian University of Munich (Germany) as a Humboldt postdoctoral fellow, and became independent PI researcher under the guidance of Prof. H. Mayr and Prof. P. Knochel. Since 2018, he has been professor of chemistry at the University of Namur, Belgium. His research interests are organoboron chemistry, main-group compounds, and organometallic reactivity. He is actively involved in teaching, especially at the Master's level.

INTERVIEW

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

Prof. G. Berionni My group's research interests range over a variety of topics within the fields of organometallic, main-group and physical organic chemistry (www.unamur.be/en/sci/chemistry/rco). Our current research focuses on the development of structurally unique nitrogen- and phosphorus-containing Lewis bases and new carbon- and boron-containing Lewis acids. We investigate their reactivity and properties, and then combine them in pairs with molecular linkers for creating new bifunctional acid–base catalysts. Creating new chemical entities based on main-group elements to mimic the rich and multifaceted chemistry of transition-metal complexes is an exciting challenge and requires a combination of state-of-the-art synthetic and computational chemistry.

SYNFORM *When did you get interested in synthesis?*

Prof. G. Berionni My interest in organic and organometallic synthesis began during my research activities throughout my chemistry studies in various universities in the area of Paris (France). I worked at the Universities of Paris-South-Saclay, Paris-Est (with Prof. Gosmini), Sorbonne – Pierre and Marie Curie University (Prof. Thorimbert and Prof. Malacria) and Paris-Cergy (Prof. Cahiez). All the researchers I met were fascinated by organometallic synthesis and reactions mechanisms. In the last year of my Master's studies, I published my first research communication (*Synlett* **2007**, *18*, 2829–2832), and it motivated me to start a PhD at the University of Versailles (Prof. Goumont and Prof. Terrier).

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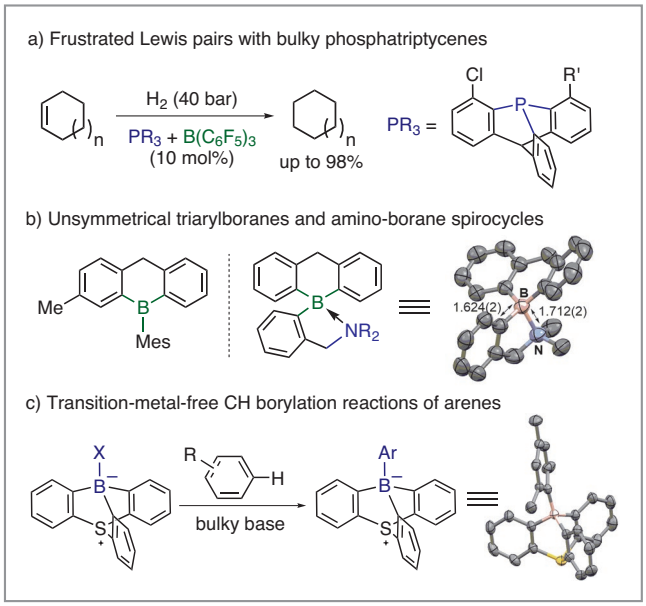
SYNFORM *What do you think about the modern role and prospects of organic synthesis?*

Prof. G. Berionni Organic synthesis, or the art of activating and selectively transforming chemical bonds and making new molecules is, and always will be, fundamental for the development of new chemical processes and materials. While reactions mediated by transition-metal catalysts have been known for more than a century, the last two decades witnessed spectacular developments in the emerging area of catalysis mediated by non-metallic species (organocatalysis, main-group catalysis, frustrated Lewis pairs catalysis, and photocatalysis).

Thus, I believe that in ten years from now, catalysts containing *s*- and *p*-block elements will transform the area of activation of strong covalent bonds (C–H, C–F, C–C) and will inspire chemists to develop more sustainable and cost-effective catalytic processes. Also, the quantification of the reactivity of organic and organometallic compounds will guide the efforts of synthetic chemists and allow them to explore uncharted catalysis space more quickly by building structure–reactivity models displaying predictive power.

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

Prof. G. Berionni Our group's research is principally focused on the synthesis and investigation of the reactivities of new carbon- and boron-containing acids, and of new sterically hindered bases (amines and phosphines). We subsequently combine these reactive entities to design transition-metal-free catalysts for hydrogenation reactions, C–H bond borylations, and other challenging reactions with small molecules. The main strategy for engineering new main-group catalysts, which we have been pursuing for a number of years, relies on the uses of polyaromatic linkers (anthracene, triptycene) to design unprecedented acid–base bifunctional catalysts with finely adjustable geometries and stereo-electronic properties (Scheme 1).



Scheme 1 Selected examples of ongoing research projects

We are combining advanced theoretical quantum chemical approaches, spectroscopic methods (NMR, stopped-flow spectrophotometers) and synthetic methods (pressure reactors, Schlenk lines, glove-boxes) throughout our work (Figure 1). Our long-term goal is the reprogramming of the reactivity of main-group compounds (from group XIII and XIV) by exploiting original concepts (pyramidal Lewis acids, low-reorganization-energy catalysts, curved linkers) towards new transition-metal-free catalyst development strategies.

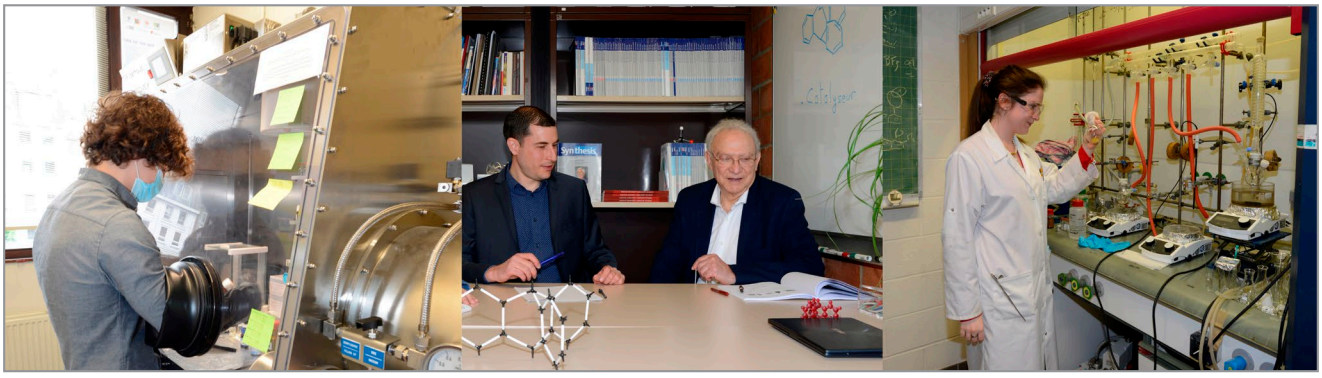


Figure 1 Researchers Arnaud Osi (left) and Jennifer Theissen (right) working at the organic chemistry labs and office meeting with Prof. Alain Krief (center). Photographs by Jean-Paul Dujeux.

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

Prof. G. Berionni My most important scientific achievement is the recent synthesis of the long-sought 9-boratriptycene Lewis acid (*Angew. Chem. Int. Ed.* **2020**, *59*, 12402). This nonplanar boron Lewis acid (Figure 2a) has puzzled several research groups for half a century and is one of the most pyramidal boron Lewis acids ever generated in solution (*Synlett* **2020**, *31*, 1639–1648). We also successfully developed a 9-bora-10-sulfonium-triptycene and a 9-bora-10-phospha-triptycene (Figure 2b) with a dual reactivity mode from Lewis acid to superacid via protonation/deprotonation of the phosphorus atom (*Angew. Chem. Int. Ed.* **2019**, *58*, 16889).

These achievements laid the foundation for one of our most productive research lines, and other unprecedented boron Lewis acids are currently being developed in our laboratories. I hope that we and other research groups will exploit the potential of these new classes of boron Lewis superacids in catalysis in the future.

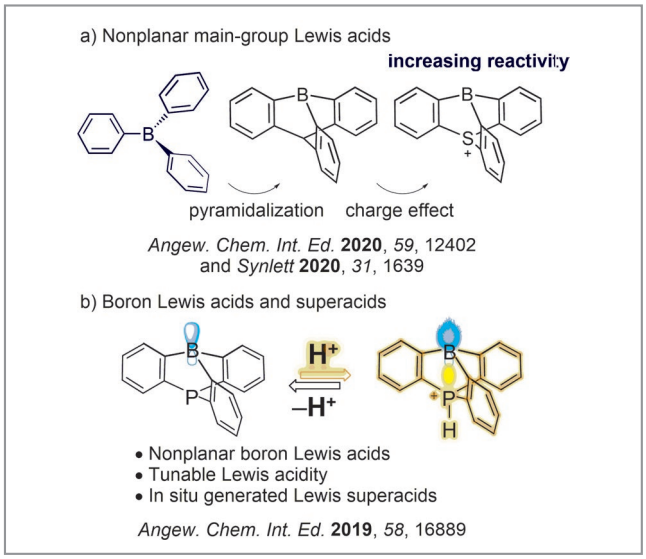

Figure 2 Pyramidal boron Lewis acids recently generated in solution

A Minisci Approach to C–H Borylation of Azines

Nature **2021**, *595*, 677–683

Borylated (hetero-)aromatics are fundamental building blocks in modern synthetic chemistry. They are used as coupling partners in Suzuki–Miyaura cross-coupling reactions, which account for ~30% of C–C bond formations in drug manufacture,[1] as well as many other processes, such as oxidation, Chan–Lam amination and fluorination.[2]

In general, C–B bonds in borylated (hetero-)aromatic compounds are constructed using the corresponding (hetero-) aryl halides via metalation–borylation or by transition-metal-catalysed borylations, among which the Miyaura borylation[3] is the archetypical example (Figure 1). Both approaches require pre-functionalisation of the aromatic core in a separate synthetic step, which sometimes can be problematic.

"Transforming an aromatic C–H bond into a C–B bond has so far been the 'playground' for transition-metal-catalysed C–H activation, mostly with Ir or Rh catalysts.[4] This approach has had a profound impact in synthetic chemistry and it is frequently adopted both in academia and industry," said Professor Daniele Leonori from the University of Manchester (UK).

"However, the generality and power of this approach are somewhat limited when azines are used as starting materials," explained Professor Leonori, who added: "This is because C–H activation responds mostly to steric factors (unless of course directing groups are present) and always leads to borylation far from the azine N-atom. Furthermore, borylated azines, where the boron is next to the N-atom, are unstable under the C–H activation conditions.[5]"

According to Professor Leonori, an additional challenge is that, while α-N borylated azines (e.g. C2-borylated pyridines) can be made by other approaches (e.g. azine halogenation followed by Miyaura borylation), they are difficult to handle due to a very fast protodeboronation reaction. This synthetic challenge has been recognised in the literature and it is frequently referred to as the '2-pyridyl problem'.[6]

Professor Leonori said: "I learned about the difficulties in making and handling 2-borylated pyridines and other azines while I was working with Prof. Varinder Aggarwal in Bristol (UK). Indeed, one of the projects I contributed to was aimed at the development of novel transition-metal-free cross-couplings between C2-lithiated pyridines and alkyl boronic esters.[7] This is also when I met Dr. Josep Llaveria, the industrial co-author in our *Nature* paper, who was the main researcher working on the topic and subsequently moved to Janssen."

Professor Leonori recalls that when he started his independent career at Manchester (UK), he focused on radical chemistry where one of the most important and applied reactivities is the addition of alkyl radicals to azines, which is now referred to as the 'Minisci reaction'.[8] "This process is a great way of forming C–C bonds at α-N positions on N-heteroaromatics and, crucially, it targets C–H bonds sometimes difficult to reach with C–H activation," explained Professor Leonori. He continued: "Furthermore, while our initial work was leading us towards the field of H-atom transfer (HAT),[9] I became very familiar with the great work of Professor Brian Roberts (University College London, UK), who – between the 1960s and the 1980s – reported many fundamental studies on the formation of boryl radicals from simple amine-boranes.[10] While these reactive intermediates have found limited application in synthesis, we were very interested by the underlying conclusions of Roberts' studies demonstrating how boryl radicals are very nucleophilic species, more than a standard carbon radical. This immediately led us to recognize that if were able to engage them in Minisci-style reactivity, then we would have developed a novel approach to access borylated azines with C–H selectivity orthogonal to the one observed in transition-metal catalysis (Scheme 1). We were also very interested by an additional aspect related to aromatic C–B bond formation under radical settings: while the addition of aryl

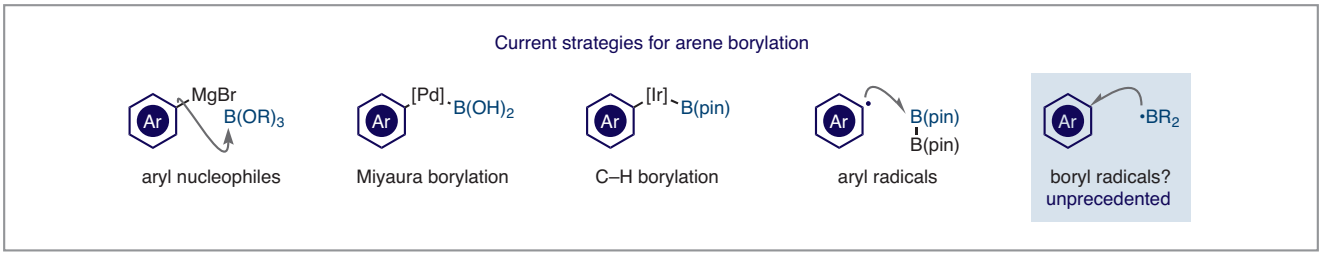

Figure 1 Approaches towards aromatic borylation

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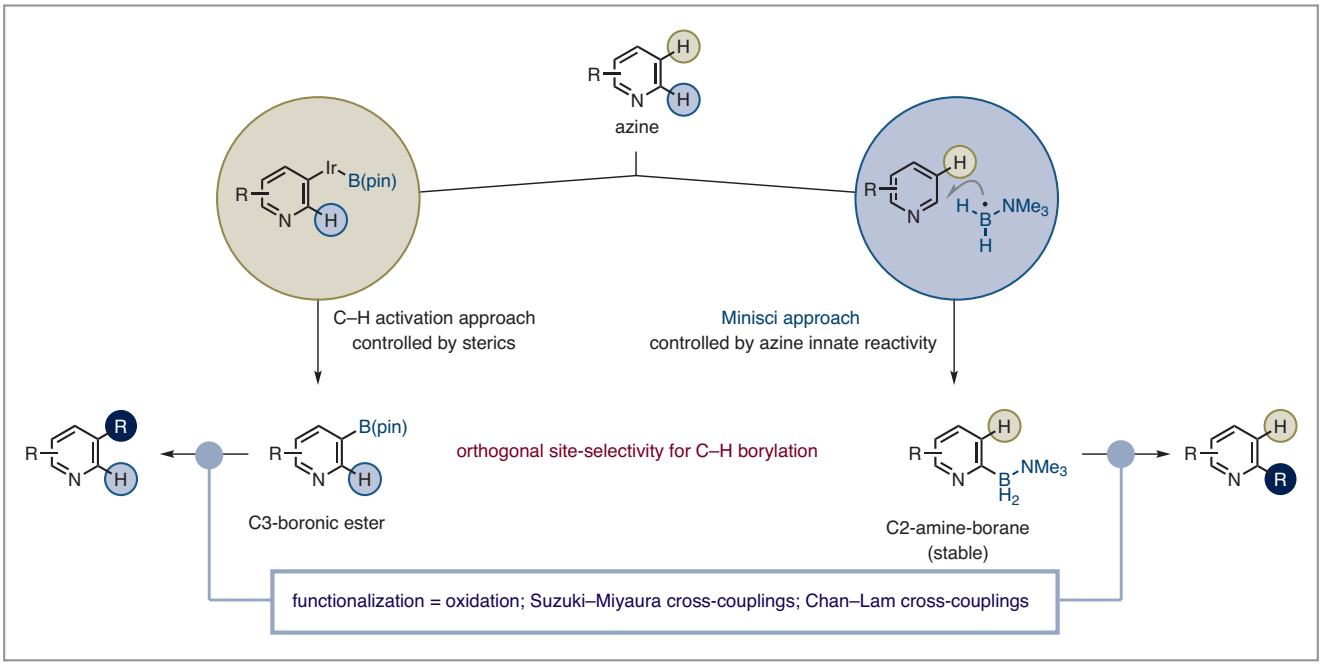

Scheme 1 An overview of the Minisci-style azine borylation using boryl radicals and its orthogonality with respect to C–H activation-based approaches

radicals to boron acceptors is well established, the other way around – the addition of boryl radicals to aromatics – is still very rare."

Professor Leonori acknowledged that he was very fortunate to discuss this novel approach for azine borylation with Dr. Ji Hye Kim, while she was a Marie Curie Fellow in his group. "Dr. Kim immediately decided to tackle this challenge and very quickly showed me that it was feasible and that the reaction products were remarkably stable crystalline solids (even suitable for X-ray analysis)," explained Professor Leonori. He continued: "These initial results made us believe this method could have the potential to address the two key problems discussed above: (1) it could provide a mechanistically distinct tactic for azine C–H borylation targeting currently elusive positions, while (2) giving stable materials for further application in cross-coupling technology. We also became very excited about this reactivity upon examining the computational results obtained by Prof. Nadeem S. Sheikh, demonstrating how Minisci borylation is actually more facile than standard Minisci alkylation."

To make sure that the group would address industrially relevant challenges, Professor Leonori reached out to Dr. Josep Llaveria at Janssen, informing him about the group's initial results and discussing the possibility of starting a collaboration on this topic. "This initial discussion led to a very fruitful collaboration; Dr. Llaveria was very involved in every aspect of the project and was also able to share with us many azine building blocks important to medicinal chemistry programs," remarked Professor Leonori. He continued: "This allowed us to benchmark our Minisci-style borylation across a broad range of systems for which limited (if any) applications in C–H borylation existed."

Upon evaluation of the synthetic versatility of the process, the group realised it was crucial to test the ability of these novel borylated materials in subsequent transformations. "This was a very exciting avenue for my group as the reactivity of azine–amine–boranes had never been evaluated before; in fact, these compounds had never even been made," said Professor Leonori. He remarked: "This part of the project proved a challenging task, but the combined efforts of Dr. Kim, together with final-year PhD student Timothée Constantin and postdoctoral researcher Dr. Marco Simonetti, who has a lot of experience wtih palladium catalysis, demonstrated how classical reactivity associated with aryl organoborons, like oxidation to phenol, Suzuki–Miyaura cross-coupling with aryl halides and Chan–Lam amination with amine and alcohol partners, could all be achieved. These proof-of-concept results provide support to the idea that these novel borylated materials might be considered viable coupling partners for future applications."

"The results described in our *Nature* paper have effectively opened a novel research line for my research group and we are now actively pushing the boundaries of boryl radical reactivity in different settings, as well as exploring the profile of the amine-borane products under transition-metal catalysis," said Professor Leonori, who concluded: "As a final comment, I would like to express all my gratitude to my co-workers for their passionate and hard work on this project, during such a challenging time."

REFERENCES

(1) (a) S. D. Roughley, A. M. Jordan *J. Med. Chem.* **2011**, *54*, 3451–3479. (b) D. G. Brown, J. Boström *J. Med. Chem.* **2016**, *59*, 4443–4458.
(2) D. G. Hall *Structure, Properties, and Preparation of Boronic Acid Derivatives. Overview of Their Reactions and Applications*, In *Boronic Acids*; D. G. Hall (Ed.); Wiley: New York, **2005**; Chap. 1, 1–99.
(3) W. K. Chow, O. Y. Yuen, P. Y. Choy, C. M. So, C. P. Lau, W. T. Wong, F. Y. Kwong *RSC Adv.* **2013**, *3*, 12518–12539.
(4) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig *Chem. Rev.* **2010**, *110*, 890–931.
(5) M. A. Larsen, J. F. Hartwig *J. Am. Chem. Soc.* **2014**, *136*, 4287–4299.
(6) X. A. F. Cook, A. de Gombert, J. McKnight, L. R. E. Pantaine, M. C. Willis *Angew. Chem. Int. Ed.* **2021**, *60*, 11068–11091.
(7) J. Llaveria, D. Leonori, V. K. Aggarwal *J. Am. Chem. Soc.* **2015**, *137*, 10958–10961.
(8) M. A. J. Duncton *Med. Chem. Commun.* **2011**, *2*, 1135–1161.
(9) S. P. Morcillo, E. M. Dauncey, J. H. Kim, J. J. Douglas, N. S. Sheikh, D. Leonori *Angew. Chem. Int. Ed.* **2018**, *57*, 12945–12959.
(10) B. P. Roberts *Chem. Soc. Rev.* **1999**, *28*, 25–35.

About the authors

Dr. J. H. Kim

Ji Hye Kim was born in Jinhae, South Korea and obtained her BSc and MSc degrees at Kyung Hee University (S. Korea). After short internship stays in the group of Prof. Sodeoka at RIKEN (Japan) and in the group of Prof. List at the Max-Planck-Institut für Kohlenforschung (Germany), which were sponsored by the National Research Foundation of Korea, she continued with her PhD studies under the supervision of Prof. List. Afterwards, Ji Hye conducted her postdoctoral research with Prof. Hyster at Princeton University (USA) and Prof. Leonori at the University of Manchester (UK).

T. Constantin

Timothée Constantin received his BSc (2016) and MSc (2018) in chemistry from Ecole Nationale Supérieure de Chimie de Montpellier (France). He then moved to the University of Manchester (UK) to pursue a PhD under the supervision of Prof. Daniele Leonori. His research focuses on the activation of carbon–halogen bonds and carbon–boron bond assembly.

Dr. M. Simonetti

Marco Simonetti received his MSc in 2010 from University of Insubria (Italy) under the supervision of Prof. Andrea Penoni. In 2011, he joined the group of Prof. Antonio Papagni at the University of Milano-Bicocca (Italy). Later, he joined Prof. Igor Larrosa's group at Queen Mary University of London (UK) where he obtained his PhD in 2015. He continued working with Prof. Larrosa at the University of Manchester (UK) on the development of Ru-catalyzed C–H functionalization reactions, until January 2018. In March 2018, he joined Prof. Daniele Leonori's group at the University of Manchester (UK) where is currently developing photocatalytic transformations.

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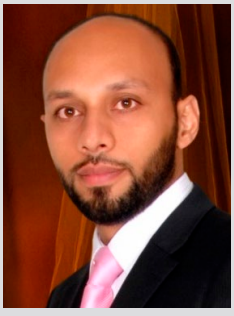
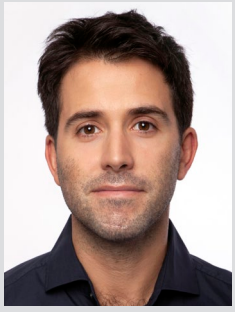
Dr. J. Llaveria

Josep Llaveria earned his PhD in 2011 from the Universitat Rovira i Virgili (Tarragona, Spain) under the supervision of Prof. Sergio Castillón. His work was focused on the synthesis of sphingoid bases by transition-metal-catalysed reactions. During his PhD, he enjoyed a short-term stay at Boston College (USA) under the supervision of Prof. A. H. Hoveyda, working on Z-selective cross-metathesis. After completing his PhD, Josep joined the Max-Planck-Institut für Kohlenforschung (Mülheim an der Ruhr, Germany) as a postdoctoral research associate to work on the synthesis of natural products under the supervision of Prof. A. Fürstner. He then moved to the University of Bristol (UK) in 2014 for a second postdoctoral stay, working in Prof. V. K. Aggarwal's group, to investigate new strategies towards stereospecific coupling of heterocycles with boronic esters. Josep started his industrial career at UCB (Slough, UK) in 2015 as a medicinal chemist before moving to Janssen (Toledo, Spain) in 2019.



Prof. N. S. Sheikh

Nadeem S. Sheikh was born in Lahore (Pakistan) and obtained his BSc and MSc from Government College University and Punjab University, respectively (both in Pakistan). He continued his doctoral studies with Prof. Richard Brown at Southampton, UK (2008) and then moved to Sheffield, UK (2008–2011) as a postdoctoral research assistant in the group of Prof. Iain Coldham. He has received several awards, including a gold medal and academic roll of honour during his BSc, merit and talent awards during his MSc and the ORSAS award for his PhD studies. In 2011, he joined King Faisal University, Saudi Arabia where he is currently serving as Associate Professor of Organic Chemistry. His research interests include computational catalysis for target-oriented organic synthesis and mechanistic investigations for synthetically significant organic transformations.



Prof. D. Leonori

Daniele Leonori obtained his PhD at the University of Sheffield (UK) under the supervision of Professor Iain Coldham (2010). After postdoctoral studies with Prof. Magnus Rueping (RWTH Aachen University, Germany) and with Prof. Peter H. Seeberger (Max Planck Institute, Germany) he joined the group of Prof. Varinder K. Aggarwal FRS as Research Officer (University of Bristol, UK). In 2014 he commenced his independent career at the University of Manchester (UK), where he is now Professor of Organic Chemistry. The group's main research interests are in the area of catalysis and synthetic chemistry, with a focus on the assembly of N-containing molecule.

Photocatalytic C–H Activation and the Subtle Role of Chlorine Radical Complexation in Reactivity

Science **2021**, *372*, 847–852

The transformation of small molecules, such as methane and ethane, into value-added chemicals is extremely attractive given their abundance in natural gas. The catalytic C–H functionalization of methane remains a major challenge in the chemical industry and an active area of research. The groups of Professors Patrick J. Walsh and Eric J. Schelter at the University of Pennsylvania (Philadelphia, USA) have been actively investigating this important topic over the last few years.

"While many common catalysts for C–H activation employ low-abundance transition metals, a recent thrust in the field of catalysis has been to develop catalysts based on earth-abundant elements, including certain lanthanides," explained Professors Walsh and Schelter. "Within lanthanides, cerium stands out for its accessible Ce(III)/Ce(IV) redox couple that, together with its characteristic electronic structure, make it attractive for photoredox applications." Prior efforts to develop cerium photoredox catalysts by the Costanzo labs and the Schelter labs demonstrated activation of benzylic C–H bonds of toluene. "In a recent breakthrough, Prof. Zhiwei Zuo (now at Shanghai Institute of Organic Chemistry, P. R. of China) reported a cerium photocatalyst capable of functionalizing methane, ethane, and higher alkanes (*Science* **2018**, *361*, 668–672). This discovery highlighted the broad utility of cerium photocatalysts and their potential applications to cleave unactivated C–H bonds," said Professor Schelter. He continued: "To rationalize the observed reactivity and explain a perceived beneficial impact of certain alcohols on the reactivity of the Ce-photoredox catalyst, Zuo's team proposed the intermediacy of a key cerium alkoxide, $[^{n}Bu_4N]_2[Ce^{IV}Cl_5(OR)]$, R = $-CH_2CCl_3$, $-CH_3$, $-CH_2CF_3$. This species was believed to generate Ce^{III} and alkoxy radicals (•OR) upon photolysis. Based on the proposed Ce^{IV}–OR photochemistry, Zuo has expanded Ce-photoredox catalysis to a wide range of alcohols and ketones, observing reactions attributed to alkoxy radicals, including beta-scission, intermolecular HAT to alkoxy radicals, and intramolecular 1,5-HAT to alkoxy radicals. From the perspective of inorganic chemistry, Zuo's proposed alkoxides raised questions in our minds about catalyst speciation and the spectroscopic similarity between the proposed 'cerium alkoxide' and $[NEt_4]_2[CeCl_6]$. Zuo's original paper was an impressive achievement in photocatalytic methane activation, but some of the details of the spectroscopy and mechanism piqued our interest, based on our work with a related catalyst. This observation, combined with our interests in lanthanide photochemistry, inspired us to investigate the proposed mechanism of the Ce-catalyzed functionalization of alkanes."

The hunt for the proposed cerium alkoxide was initiated with a three-pronged approach: independent synthesis, spectroscopic studies, and kinetics experiments. Professor Schelter explained: "Qiaomu Yang, the lead student author on the manuscript, first independently synthesized Zuo's proposed alkoxide intermediate. Metathesis of $NaOCH_2CCl_3$ with $CeCl_6^{2-}$ led to the isolation of $[CeCl_5(OCH_2CCl_3)]^{2-}$, which was characterized spectroscopically and by X-ray diffraction. The UV-vis spectrum of this compound was different than that of $CeCl_6^{2-}$ and different from the spectrum reported by Zuo, fueling our suspicions that cerium alkoxides were not involved in the chemistry." With an authentic sample of the proposed key intermediate as a reference, spectroscopic studies of stoichiometric and catalytic reactions were undertaken. Zuo's proposed catalyst, $[CeCl_5(OCH_2CCl_3)]^{2-}$, was found to be unstable to the reaction conditions, rapidly decomposing to $CeCl_6^{2-}$ upon irradiation. Moreover, the Philadelphia-based researchers found that addition of $HOCH_2CCl_3$ (up to 600 equiv) to $CeCl_6^{2-}$ in the absence of light or under irradiation under the conditions of the C–H functionalization induced no changes in the UV-vis spectrum from $CeCl_6^{2-}$, indicating that $[CeCl_5(OCH_2CCl_3)]^{2-}$ was not formed under these conditions.

"We next examined the kinetics of the C–H functionalization under catalytic conditions," said Professor Schelter. He remarked: "Comparison of rates with $CeCl_6^{2-}$ in the presence and absence of varying equivalents of $HOCH_2CCl_3$ indicated that alcohol had *no impact* on the rates of the photoredox C–H functionalization, supporting the hypothesis that it was not involved in the functionalization (Figure 1A, 1B). Kinetic isotope effect experiments using cyclohexane and cyclohexane-d_{12} with $CeCl_6^{2-}$ in the presence and absence of $HOCH_2CCl_3$ were identical (k_H/k_D = 2.0–2.1), suggesting that both reactions proceeded through a common intermediate. Furthermore, positional selectivity experiments with *n*-hexane with and without alcohol demonstrated that the catalyst in both reactions gave identical selectivity of C1:C2:C3 of 1.0:1.8:1.8, again pointing to the identity of the catalyst in these two reactions as being the same: $CeCl_6^{2-}$ (Figure 1C)."

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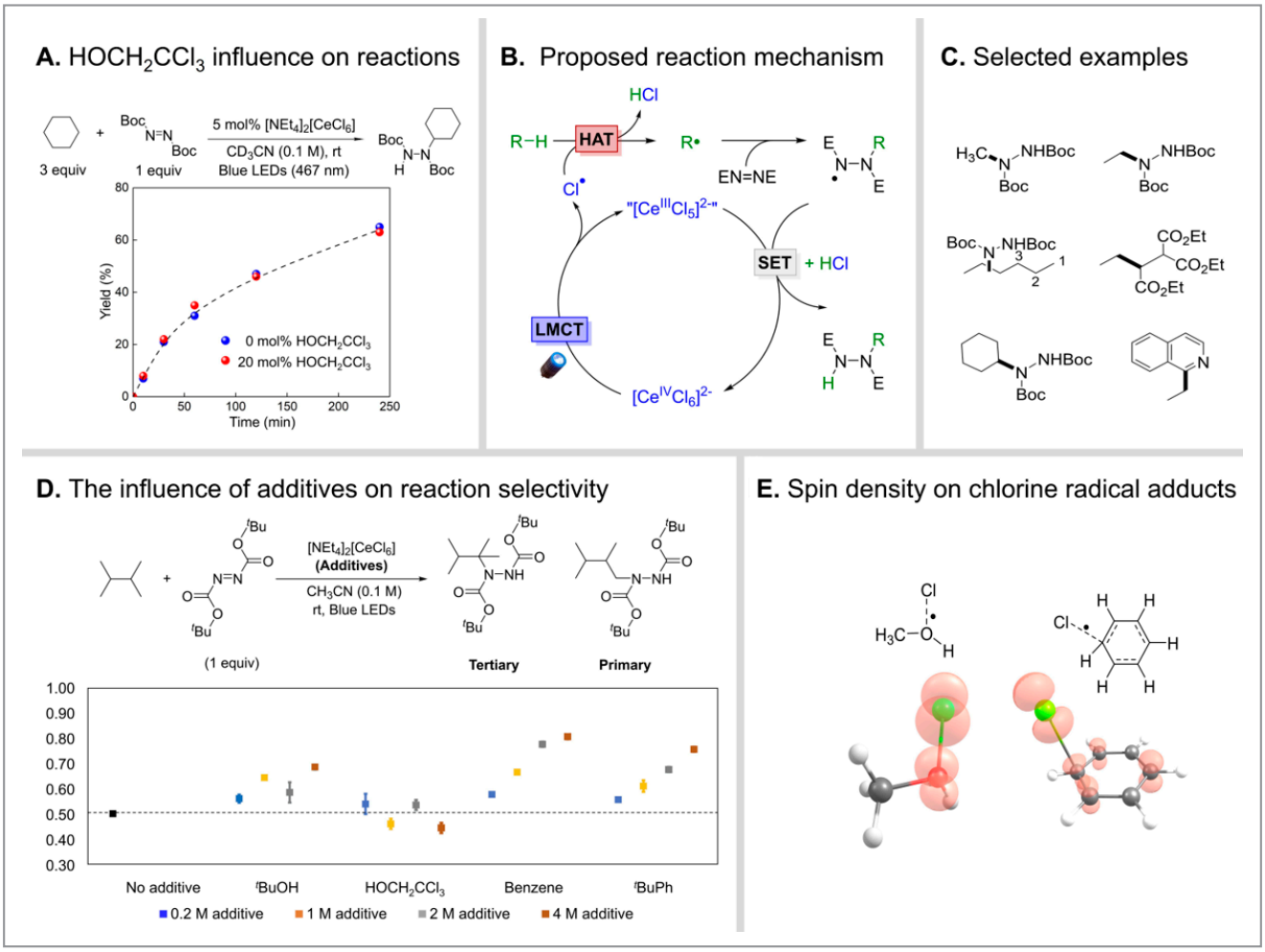


Figure 1 Highlights of the paper

Based on these studies, the authors of this *Science* paper proposed a revised mechanism (Figure 1B). "Photo-excitation of $CeCl_6^{2-}$ results in ligand-to-metal charge transfer (LMCT), leading to dissociation of •Cl and formation of the reduced Ce^{III} complex," said Professor Schelter, who continued: "The chlorine radical undergoes HAT with the alkane to generate the radical intermediate R• and HCl. R• is trapped by the diazo complex to give an *N*-centered radical. This intermediate undergoes reduction by Ce^{III} and protonation to generate the product hydrazine and close the catalytic cycle with formation of $CeCl_6^{2-}$."

Extensive studies in the presence and absence of alcohol revealed one instance where either methanol or $HOCH_2CCl_3$ had a beneficial impact on the C–H functionalization and that was with methane. "In this case, rather than the formation of alkoxy radicals, it is postulated that hydrogen-bonding of the alcohols to the methyl radical stabilizes this reactive intermediate," explained Professor Schelter.

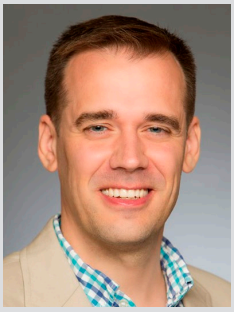
One of the pillars of Zuo's alkoxy radical mechanism was the 'alkoxy radical-like' chemistry that was observed, which included what appeared to be alkoxy radical trapping products. The team envisioned that understanding this behavior would have implications beyond applications of the Ce photoredox chemistry and be of value to the larger chemistry community. "The missing piece of the puzzle was if alkoxy radicals were not involved, what was responsible for the alkoxy radical-like reactivity?" said co-corresponding author Professor Patrick Walsh.

Based on prior observations in the literature, it was known that chlorine radicals can interact with Lewis basic sites on molecules, and that this interaction can delocalize the chlorine radical character to proximal atoms. Computational and

experimental studies were undertaken by Qiaomu Yang to measure the impact of alcohols and arenes on C–H cleavage selectivity. "Experimentally, 2,3-dimethylbutane, which has two types of C–H bonds, was used as a selectivity probe," said Professor Schelter. He continued: "With catalytic $CeCl_6^{2-}$, $HOCH_2CCl_3$ had no impact on the selectivity, whereas increasing concentrations of *t*-BuOH resulted in improved selectivity for the weaker methyne C–H bond. This change in selectivity toward the more reactive C–H bond could also be engendered by arenes, including benzene and *t*-BuPh (Figure 1D). As shown in Figure 1E, the chlorine radical interacts with the pi-cloud of the arenes, as established in the DFT study outlined in the manuscript. Taken together, these results indicate that adducts with the chlorine radical and methanol result in radical character delocalization on the oxygen of the alcohol. It is proposed that this behavior is responsible for the alkoxy radical-like reactivity observed by the Zuo team."

"The identification of species on the catalytic cycle and the mapping of reaction mechanisms is important for understanding the chemistry and to position the research community to design the next generation of catalysts," said Professor Schelter, who concluded: "We anticipate that the high reactivity of chlorine, and the ability to generate Cl• through LMCT of M–Cl bonds will continue to be important in the conversion of light hydrocarbons such as methane into value-added chemicals and fuels."

About the authors

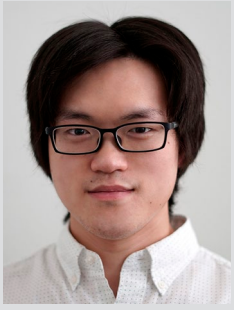


Prof. E. J. Schelter

Professor Eric J. Schelter was born in Pontiac, MI, USA. He earned a B.S. at Michigan Technological University (USA, 1999) where he worked with Rudy Luck. He earned a PhD at Texas A&M University (USA) where he worked with Kim R. Dunbar (2004) and was a postdoc at Los Alamos National Laboratory (USA, 2004–2009) with Drs. Jaqueline Kiplinger, Joe Thompson, and Kevin John. In 2009 he was appointed as an Assistant Professor at the University of Pennsylvania (USA). He was promoted to Associate Professor in 2015 and Professor in 2018. His research group studies separations chemistry, photochemistry, electronic structure, bio-inorganic modeling, and molecular materials chemistry especially of the lanthanide and actinide elements.

Prof. P. J. Walsh

Professor Patrick J. Walsh completed his B.A. at the University of California San Diego (USA) where he performed research with Prof. Charles Perrin. He obtained his Ph.D. at UC Berkeley (USA) with Prof. Robert G. Bergman (Ph.D., 1991) and was a postdoc with Prof. K. B. Sharpless at Scripps Research Institute (USA). From 1994–1999 he was an assistant professor at San Diego State University (USA) and professor at Centro de Graduados e Investigación, Instituto Tecnológico de Tijuana (Mexico, 1996–1999). In 1999 he moved to the University of Pennsylvania (USA).



Q. Yang

Qiaomu Yang was born and raised in Zhengzhou, Henan, China. He received his B.S. in chemistry from Tsinghua University (P. R. of China) in 2016 under the supervision of Prof. Zhongqiang Yang and Prof. Guifang Dong. He is currently a PhD candidate at the University of Pennsylvania (USA) under the supervision of Prof. Eric J. Schelter. His research interests include photochemical reactions, photophysical

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behavior and ligand design, as well as the understanding of the electronic and magnetic properties of chemical substances.

Dr. Y.-H. Wang

Yu-Heng (Larry) Wang was born and raised in Kaohsiung, Taiwan. He received his B.S. in chemistry from National Taiwan Normal University in 2007 and M.S. at the National Taiwan University in 2009. In 2012, he pursued his doctoral studies at the University of Wisconsin–Madison (USA) in Prof. Shannon S. Stahl's group. In 2018, he graduated and took a postdoctoral position supervised by Prof. Eric J. Schelter and Prof. Patrick J. Walsh at the University of Pennsylvania (USA). He returned to Taiwan and began his independent career as an assistant professor at National Tsing Hua University in 2020.

Dr. Y. Qiao

Yusen Qiao was born in Beijing, P. R. of China. He holds a B.S. in chemistry from Peking University (P. R. of China) and Ph.D. in inorganic chemistry from University of Pennsylvania (USA). Yusen was a postdoctoral researcher at Lawrence Berkeley National Laboratory (USA) from 2019 to 2020. In his Ph.D. and postdoc, he studied the synthesis, electronic structures, magnetism, photophysics and photocatalysis of lanthanide and actinide organometallics. He is currently a Senior Research Specialist at the Dow Chemical Company (USA) and develops new surfactant and alkoxylation technology.

C(sp^3)–H Methylation Enabled by Peroxide Photosensitization and Ni-Mediated Radical Coupling

Science **2021**, *372*, 398–403

Methylation of organic molecules is increasingly emerging as a very useful structural modification and biological profiling strategy in the rational design of bioactive compounds and drugs. In fact, a relatively subtle structural modification stemming from the introduction of a methyl group has the potential to strongly alter both pharmaco-dynamic and pharmaco-kinetic profiles of a drug candidate, as a consequence of changes in its stereo-electronic properties. According to Professor Shannon Stahl, from the University of Wisconsin-Madison (USA), methylated building blocks are a staple of medicinal chemistry library designs. "For example," explained Professor Stahl, "when an amine building-block is chosen to be included in a screening library, it is likely that various methylated analogues of that building-block will also be evaluated, if they are commercially available. The introduction of a methyl group can significantly affect the properties of the resulting drug lead. There are cases where the installation of a methyl group results in thousand-fold improvements in potency or results in defining drops in toxicity." Despite the importance of testing the outcome of introducing a methyl group at a C–H site, synthetic options are limited. Conventionally, 'magic methyl' effects are uncovered by screening methylated building blocks or by rerouting syntheses to incorporate a methyl group at an early stage. State-of-the-art protocols for C–H methylation are still encumbered by the use of directing groups or unsafe high-reactivity reagents. "My student Aris Vasilopoulos conceived a general C–H methylation strategy that features a 'radical relay' approach based on Kharasch–Sosnovsky C–H functionalization methods. These methods use a transition-metal catalyst and a peroxide-based oxidant," noted Professor Stahl.

Professor Stahl and Dr. Vasilopoulos, who led the experimental studies, began studying Kharasch–Sosnovsky-type reactions in the context of Cu-catalyzed benzylic C–H arylation using di-tert-butyl peroxide with aryl boronate esters. Aris explained, "These studies revealed a means to convert C–H into C–C bonds, but also highlighted a problem with C–H substrate conversion." He continued: "Under the 90 °C reaction temperature, low conversion of C–H substrate was observed, which led to solvent-level use of the C–H substrate, which would not be amenable to application on valuable drug-like compounds. We postulated that the tert-butoxyl radical formed from peroxide activation was competitively undergoing β-scission to form methyl radical and acetone, that was preventing efficient C–H substrate activation by hydrogen-atom transfer (HAT)." Literature studies from the 1960s by Wagner supported this hypothesis and revealed that HAT is more favorable at reduced temperatures. Other studies revealed that the peroxide could be activated at these reduced temperatures by using a photosensitizer with light. Professor Stahl noted that if the C–H substrate could be activated with limiting C–H substrate in the presence of a transition metal that can methylate the resulting intermediate, a new methylation reaction could be identified. This set of hypotheses set the stage for high-throughput experimentation efforts, led by Dr. Vasilopoulos at Merck's laboratories in Kenilworth, NJ (USA).

At Merck, Dr. Vasilopoulos screened a wide range of reaction parameters such as metal salts, ligands, photocatalysts, light sources, peroxides, acid and base additives, methyl sources, and solvents in 96-well arrays in search of an initial hit. In the first two-week Merck visit, nearly 1000 reactions were tested, but almost all of them showed no conversion of starting material. Dr. Vasilopoulos explained: "The reaction conditions that did show conversion either had 1–10% conversion to a possible methylated product or had conversion to a C–H oxygenation product (usually observed with tert-butyl hydroperoxide). One photocatalyst that showed 1–10% conversion of C–H substrate in these tests was $Ir[dF(CF_3)ppy]_2{}^{t\text{Bu}}bpyPF_6$ and, coincidentally, I found an unopened vial of 100 mg of this compound underneath my bench at UW-Madison." Testing this photocatalyst under relevant conditions with di-*tert*-butyl peroxide at UW-Madison led to a confirmed hit for 10% yield of methylation of ethylbenzene to cumene to be identified, with >50% conversion of the starting material. This reaction hit was then optimized for one substrate at Merck, using over ~2000 reactions, and then optimized in parallel for 8–12 other drug-like substrates, using over another 1000 reactions, to arrive near the final conditions published in the paper. Professor Stahl elaborated: "Mechanistic studies were then conducted to untangle the role of each reaction component as it relates to either HAT, β-scission, and/or C–C bond formation."

"The C–H activation reactivity allowed by photoactivation of di-*tert*-butyl peroxide is remarkably robust and tolerant of diverse functionality," said Professor Stahl, who continued:

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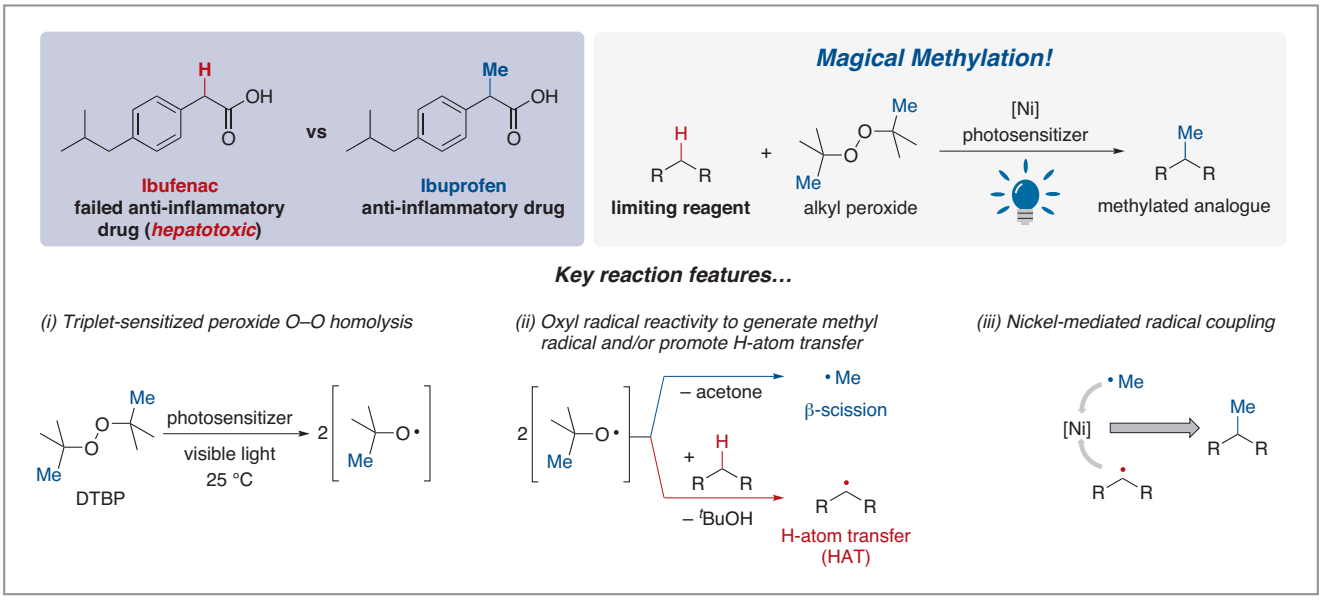

Scheme 1 The reported methylation and its key reaction features

"It is possible that this platform can be used to enable other 'radical relay' C–H functionalization reactions, such as other alkylation reactions." The identified methylation reaction conditions have been efficacious for methylation of several lead compounds. "Hopefully, it is only a matter of time before the reaction leads to identification of a 'magic methyl' effect in a bona fide drug lead," noted Professor Stahl.

Professor Stahl concluded: "Ultimately, this reaction offers a practical one-step non-directed late-stage C(sp^3)–H methylation reaction that uses all commercially available reagents. These features offer considerable advantages over other existing methods and should facilitate uptake by other researchers."

About the authors

Dr. A. Vasilopoulos

Aris Vasilopoulos was born in Nashua, NH (USA) and raised in the neighboring town of Amherst. He earned his B.S. degree in chemistry with a minor in computer science from Boston College (USA), where he also conducted three years of undergraduate research under the mentorship of Prof. Jeffery Byers. Aris then moved to the Midwest and specialized in organic chemistry at UW–Madison (USA) where he studied oxidative cross-coupling reactions in Prof. Shannon Stahl's research group. After obtaining his Ph.D. at UW–Madison, Aris joined the Advanced Chemistry Technology group at AbbVie in the greater Chicago area where he now explores and applies novel methods and techniques to medicinal chemistry programs.

Dr. S. W. Krska

Shane W. Krska was born in Deadwood, S.D. (USA). He received a B.S. in chemistry from the South Dakota School of Mines and Technology (USA) in 1992 and a Ph.D. in inorganic chemistry from the Massachusetts Institute of Technology (USA) in 1997 under the direction of Prof. Dietmar Seyferth. After conducting postdoctoral research with Professor Robert Bergman at the University of California, Berkeley (USA), he joined Merck & Co., Inc. as a senior research chemist in 1999. Dr. Krska has held positions in chemical engineering research and development, process research, and, most recently, discovery chemistry. He currently serves as distinguished scientist in the high-throughput experimentation and lead discovery capabilities group within discovery chemistry. His research interests include the development of high-throughput experimentation workflows and applications of catalysis to drug discovery and development.

Prof. S. S. Stahl

Shannon S. Stahl was born in Park Ridge, IL (USA). He obtained his B.S. degree from the University of Illinois at Urbana-Champaign (USA) in 1988 and a Ph.D. from Caltech (USA) in 1997 under the direction of Prof. John Bercaw. He was an NSF postdoctoral fellow at the Massachusetts Institute of Technology (USA) from 1997–1999, working with Prof. Stephen Lippard. He began his independent career at UW-Madison (USA) in 1999. His research group specializes in catalysis, with an emphasis on oxidation reactions, with applications to chemical synthesis, biomass conversion, and electrochemistry. Chemical synthesis efforts primarily target applications to pharmaceutical and fine chemical synthesis, and his industrial collaborations in this domain have been recognized by a US EPA Presidential Green Chemistry Challenge Award and the ACS Award in Affordable Green Chemistry.

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