A Chemoselective Strategy for Late-Stage Functionalization of Complex Small Molecules with Polypeptides and Proteins


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Dear Readers,

June marks the beginning of summer, which is synonymous with holidays, but SYNFORM has no intention whatsoever of going on holiday and if there was any doubt it is worth having a look at this new very thick issue, featuring four vibrant Literature Coverage articles. The first is an impressive study authored by a consortium of world-leading authors, led by B. L. Pentelute (USA), showing that complex and bioactive small molecules can be readily and late-stage functionalized with polypeptides and proteins via selenium-containing linkages, providing a variety of bioconjugates, including antibody–drug conjugates. In the second article, P. Melchiorre (Spain) goes through his group’s recent work on the photochemical generation of a wide range of alkyl radicals, mediated by an N-indole-dithiocarbamate anion, and their manifold reactivity with heteroaromatics and Michael acceptors. The third contribution covers the development of a method for chiroptical screening and monitoring of asymmetric reactions based on a halocoumarin chromophoric sensor, as a useful alternative to the mainstream NMR and HPLC methods for discriminating between enantiomers, as described by C. Wolf (USA), the leading author of this study. Finally, in the last article of this issue, J. Scaiano (Canada) introduces the concept of ‘catalytic farming’ as a novel concept for improving the overall performance of homogeneous catalysts.

I might just get on with booking my holidays now...

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A Chemoselective Strategy for Late-Stage Functionalization of Complex Small Molecules with Polypeptides and Proteins

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The conjugation of small molecules to biopolymers has gained tremendous interest over the last several decades. These hybrid molecules can potentially harness the strengths of the small molecules and proteins to deliver new classes of therapeutics that were previously inaccessible with each component independently. Antibody drug conjugates (ADCs) for targeted cancer treatment highlight the promise of conjugate therapies in modern medicine.\(^1\) Methods to construct these classes of molecules typically rely on the reaction of the nucleophilic residue within the biopolymer (i.e. cysteine or lysine) in combination with a preinstalled electrophilic handle (i.e. maleimide or activated ester) on the small molecule of interest. Professor Bradley Pentelute, from the Massachusetts Institute of Technology (MIT, USA), explained that due to the abundant nature of nucleophilic residues in these biopolymers, the corresponding conjugates are typically heterogeneous and the site of modification is often challenging to predict. “Additionally, multistep syntheses are often required to introduce the electrophilic handles on the small molecules to enable the conjugation step to proceed,” he said.

Selenocysteine (Sec, U), the 21\(^{st}\) proteinogenic amino acid, is a structural analogue of cysteine, but with a selenol in place of the thiol. “Due to its inherent redox profile, Sec favors the oxidized form rather than the corresponding selenol,” said co-author Dr. Daniel Cohen of biopharmaceutical company AbbVie North Chicago, USA, who continued: “Amidst our investigation into the utilization of Sec as a bioconjugation handle for the preparation of small-molecule–biopolymer conjugates, we determined that the Se–S bond could behave as a latent electrophile such that a new Se–C bond can be formed in the presence of a copper reagent and a nucleophilic (hetero)aryl boronic acid (Figure 1, A, eq. 1).\(^2\)” Further exploration by the authors into this innate electrophilicity revealed that (hetero)aryl with electron-rich functional groups can react directly even in the absence of copper reagent to form new Se–C bonds. “The significance of this work is that this strategy uses inborn native nucleophilicity of small molecules with different biological function in combination with oxidized Sec to provide conjugation to biopolymers (Figure 1, A, eq. 2),” explained Dr. Cohen, continuing: “The approach is selective in regards to both the biopolymer and the small molecule, but more importantly no pre-functionalization of the small molecule is necessary.”

Professor Pentelute said: “We have been able to demonstrate this approach with numerous classes of small molecules to conjugate therapies (Figure 1, B), in particular, vancomycin.” Utilizing the native nucleophilicity of vancomycin, the authors were able to prepare new peptide–vancomycin conjugates with excellent site-selectivity, with regard to both the biopolymer and the small molecule. Professor Pentelute also noted that, importantly, the aforementioned conjugates showed improved \textit{in vitro} potency against Gram-positive and Gram-negative pathogens than either the peptide or vancomycin alone. “Expansion of this work into the protein area was demonstrated by conjugating vancomycin to a 6 kDa affibody protein, and genistein to a 150 kDa immunoglobulin-G antibody, in a two-step sequence (Figure 1, C),” said Professor Pentelute, who concluded: “Notably, labeling these proteins using our method did not result in diminished binding of the proteins to their corresponding targets.”

REFERENCES

Scheme 1 (A) The Se–S bond behaves as a latent electrophile. (B) Small molecules conjugated to a selenocysteine peptide (indicated with a red dot). (C) Vancomycin and genistein conjugates.
Stephen L. Buchwald has been a faculty member at Massachusetts Institute of Technology (MIT; USA) since 1984 and is currently the Camille Dreyfus Professor and an Associate Head of the Department of Chemistry. During his time at MIT he has been the coauthor of over 495 published or accepted papers and 52 issued patents. He has received a number of honors and awards, most recently the 2018 Tetrahedron Prize for Creativity in Organic Chemistry, the 2018 Dr. Karl Wamser Innovation Award (from the Technische Universität München) and the 2019 Roger Adams Award from the American Chemical Society.

Daniel Cohen graduated salutatorian from State University of New York New Paltz (USA) with a B.A. in chemistry in 2007. As an undergraduate in the Dhar lab, he studied the antimicrobial and antifungal activity of α-pinene derivatives. Daniel received his Ph.D. in 2013 from Northwestern University (USA). Under the tutelage of his graduate advisor Karl A. Scheidt, Daniel developed new annulation strategies in N-heterocyclic carbene catalysis. From there Daniel moved on to complete his postdoctoral studies at MIT (USA) with Stephen L. Buchwald and Bradley L. Pentelute. His research involved metal catalysis to construct new bonds in small molecules and biomolecules. Currently, Daniel is a Senior Scientist at AbbVie where he works as a Medicinal Chemist in the Oncology Discovery Department.

Colin Fadzen obtained his B.A. in physics and biochemistry and M.S. in chemistry from the University of Pennsylvania (USA) in 2013, where he worked in the laboratory of Prof. E. James Peterson on minimalist chromophores to monitor conformational changes in proteins using unnatural amino acid mutagenesis and native chemical ligation. He then moved to Boston (USA) to join the Harvard/MIT M.D.-Ph.D. program. He completed his graduate work in the laboratory of Prof. Bradley Pentelute in the MIT Department of Chemistry, graduating in 2018. His dissertation focused on the design of perfluoroaryl-based macrocyclic peptides for the improved delivery of chemotherapeutics across the blood–brain barrier and for the improved delivery of phosphorodiadiminate morpholino oligonucleotides into muscle cells for the treatment of Duchenne muscular dystrophy. He is currently completing his M.D. at Harvard Medical School (USA) and will graduate in 2020. Notable awards include the Roy and Diana Vagelos Science Challenge Award (2012) and Dean’s Scholar, Penn College of Arts & Sciences (2013).

Liana Hie earned her BSc at University of California Davis (USA), working with Prof. Xi Chen on chemoenzymatic synthesis of oligosaccharides. She then moved to University of California Los Angeles (USA) to study nickel catalysis under the guidance of Prof. Neil K. Garg. Following her doctoral work, she joined the laboratory of Prof. Scott Miller at Yale University (USA) as an NIH Postdoctoral Fellow studying site-selective modification of natural products via glycosylation reactions. Liana is currently employed by the FMC Corporation as a Discovery Research Investigator.

Scott J. Miller was born in Buffalo, NY (USA). He received his B.A. (1989), M.A. (1989) and Ph.D. (1994) degrees from Harvard University (USA), where he worked with David Evans as a National Science Foundation Predoctoral Fellow. Subsequently, he traveled to the California Institute of Technology (USA) where he was a National Science Foundation Postdoctoral Fellow with Robert Grubbs until 1996. For the following decade, he was a member of the faculty at Boston College (USA), until joining the faculty at Yale University (USA) in 2006. In 2008, he was appointed as the Irénée duPont Professor of Chemistry.
Bradley L. Pentelute is currently a tenured Associate Professor at MIT Department of Chemistry (USA), an Associate Member of the Broad Institute of Harvard and MIT (USA), an Extramural Member of the MIT Koch Cancer Institute (USA), and Member of the Center for Environmental Health Sciences MIT. He received his undergraduate degree in psychology and chemistry from the University of Southern California (USA), and his M.S. and Ph.D. in organic chemistry from the University of Chicago (USA) with Prof. Steve Kent. He was a postdoctoral fellow in the laboratory of Dr. R. John Collier at Harvard Medical School (USA).

Chi Zhang received his Ph.D. from MIT (USA) in 2017 under the supervision of Prof. Brad Pentelute. He is currently a postdoctoral associate with Prof. Ed Boyden at MIT Media Lab. His research focuses on developing tools for highly multiplexed protein analysis in complex biological systems. Chi is a recipient of several awards: 2015 Bristol–Myers Squibb Fellowship in Synthetic Organic Chemistry, 2016 Regeneron Prize for Creative Innovation, 2016 Genentech Chemical Research Award, 2016 Alfred R. Bader Award for Student Innovation, and 2018 IUPAC-Solvay International Award for Young Chemists.
Photochemical Generation of Radicals from Alkyl Electrophiles Using a Nucleophilic Organic Catalyst

*Nat. Chem. 2019, 11, 129–135*

Photocatalysis continues to represent a vibrant area of research in modern organic synthesis. Recently, a new photochemical strategy for generating radicals has been developed by Professor Paolo Melchiorre and co-workers Dr. Bertrand Schweitzer-Chaput and Dr. Matthew Horwitz (two postdoctoral fellows), and PhD student Eduardo de Pedro Beato, from the Institut Català d’Investigació Química (ICIQ, Tarragona, Spain). Professor Melchiorre explained: “The motivation at the basis of this research project was the following: Radical chemistry offers powerful and unique ways of making molecules, that are often complementary to classical methods proceeding via ionic pathways. Advances within the field have been spurred by the identification of powerful strategies that allow access to radicals under mild conditions. Ultimately, all modern radical generation strategies rely on the bond dissociation energy (BDE) or the redox properties of the precursors to form the target open-shell intermediate. The synthetic potential of radical chemistry would therefore be greatly expanded by methods that go beyond these established activation manifolds to provide complementary ways of generating open-shell intermediates.”

This group’s latest study documents a photochemical catalytic strategy that harnesses different physical properties of the substrate to form carbon radicals (Figure 1). “We designed the readily available, air- and moisture-stable dithiocarbamate anion catalyst 1, which is adorned with an indole chromophoric unit. This organic catalyst is nucleophilic enough (*Org. Biomol. Chem. 2011, 9, 8046–8050*) to activate alkyl electrophiles by displacing a variety of leaving groups via an \( \text{S}_2 \) pathway. The resulting photon-absorbing intermediate affords radicals upon homolytic cleavage induced by visible light,” said Professor Melchiorre, who went on to explain that the method operates readily under visible-light irradiation (commercial blue LEDs) and grants access to open-shell intermediates from a variety of substrates (including difficult-to-reduce alkyl chlorides and mesylates) that would be incompatible with, or inert to, traditional radical generating strategies, including photoredox catalysis.

“This strategy possesses a variety of unique features,” continued Professor Melchiorre. “Mechanistically, the reaction is noteworthy as it exploits an \( \text{S}_2 \) process (a fundamental ionic path) to generate radicals. This unique activation mode allowed the predictable and chemoselective activation of \( \text{S}_2 \)-prone substrates in the presence of otherwise reactive functional groups, which would be incompatible with traditional radical generation methods. From a synthetic perspective, substrate scope investigations (Scheme 1) indicate that unprotected polar functional groups (acids, alcohols, aldehydes) and nitrogen-containing heterocycles (including thiazole, isoxazole, pyrazole, and triazole scaffolds) are all well-tolerated. These common motifs are often found in drug molecules, but generally represent a significant tolerability challenge for synthetic methods.”

Professor Melchiorre handed over to Dr. Schweitzer-Chaput, explaining: “Bertrand contributed very much to the realization of the chemistry, since he was involved in the discovery and initial development of the radical generation strategy.”

Dr. Schweitzer-Chaput remarked: “We demonstrated that this new radical generation strategy has a potentially wide scope of application (Scheme 1). For example, we have applied it for developing a Giese-type radical conjugate addition, a Minisci-type functionalization of electron-rich aromatic substrates, and a tandem radical conjugate addition/cyclisation forming oxindole compounds.” The authors also described how the method’s mild reaction conditions and high functional group tolerance could be advantageous for streamlining the preparation of a marketed drug, for the late-stage elaboration of biorelevant compounds and for enantioselective radical catalysis. In addition, the experimental simplicity and the low cost of the catalyst allowed the group to implement a multigram-scale application using commonly available glassware and light irradiation equipment.

“Making such reactive radical intermediates is not new, as radical chemistry has been around for more than a century,” acknowledged Professor Melchiorre. However, the classic way to conduct radical reactions involves precursors with weak bonds and a high-energy radical initiator, such as a peroxide, along with elevated temperatures, or the transfer of electrons to a general radical ion intermediate, which can then fragment into the desired reactive radical. “Our system is fundamentally different since it relies on the formation of a covalent C–S bond between the dithiocarbamate anion catalyst and a suitable electrophile, through an \( \text{S}_2 \) substitution reaction,
which can then undergo photolysis with blue light to form the reactive radical,” explained Dr. Schweitzer-Chaput. He continued: “Catalyst turnover is then provided by a one-electron reduction back to the active dithiocarbamate anion. Because of the peculiar mechanism of radical generation, the reactions do not use strong bases, or oxidative or reductive conditions and they can therefore tolerate a wide variety of functional groups. Acidic protons, Lewis basic sites, unprotected alcohols or amides, easily oxidised heterocycles or reduced aryl iodides, and even an unprotected aldehyde, did not interfere with this activation mode and delivered the products in good to excellent yields with minimal side reactions.”

Optimisation of the catalyst started from the commercially available potassium ethyl xanthogenate, a commodity chemical, which performed reasonably well as a catalyst, but required the use of specialised 405 nm LEDs. “We wanted to use more widely available and energy-efficient blue LEDs that emit at around 450 to 460 nm. After several months of structural optimisation, we found that the indole-containing catalyst matched all of our requirements: it performs extremely well as a catalyst under blue light irradiation, it is easy to handle under open air, it doesn’t require particular storage conditions, and finally it is made in one step from commercially available materials on tens of grams scales in an afternoon for a very low cost,” said Dr. Schweitzer-Chaput, adding: “This provides an additional advantage over photo-redox catalysis, a field which has become popular in the last few years.” Most of the photoredox catalysts commonly used nowadays are based on more expensive ruthenium or iridium complexes, or organic dyes. “With this in mind, we have shown that our model reactions could be scaled up, in batch as well as in flow, to synthetically useful multigram scales,” remarked Dr. Schweitzer-Chaput. He continued: “We also demonstrated the use of complex molecular scaffolds with other reactive functionalities, such as cortisone, as radical precursor, suggesting that this system could be applied to a variety of contexts, notably in medicinal chemistry programs to functionalize advanced intermediates of complex synthetic plans.”

The group is now looking to expand this catalytic strategy to different classes of radical precursors and radical acceptors as well as looking for other turnover events to regenerate the active dithiocarbamate anion catalyst 1. All of this stays with the general idea to provide solutions to synthetic challenges that are not currently met using conventional ionic or radical strategies.

Dr. Horwitz elaborated further: “The S₄-N₂ mode of activation is a feature that allows substrates, such as alkyl chlorides, that are ‘out of range’ of traditional photoredox catalysts to be used as radical precursors.” He continued: “The homolytic bond cleavage makes this feature possible and is enabled by the indole chromophore, while the flexibility of the catalyst turnover step is what allows multiple reaction subtypes...
to emerge from a single mechanistic paradigm. The most exciting part of this chemistry for me is that we could generate radicals from very complex molecular frameworks (most notably cortisone) and use those radicals to perform different types of late-stage transformations. The fact that, in that synthetic scheme, alcohols can be rapidly converted into radical precursors (through the formation of a mesyl group) can open up new synthetic pathways.”

**Scheme 1** Reaction scope: radical precursors suitable for the Giese addition to dimethyl fumarate; tandem radical addition/cyclization of *N*-arylacylamides affording 3,3-disubstituted oxindoles; and radical functionalization of electron-rich (hetero)arenes. Ms: mesylate.
Because there is such a broad selection of commercial alkyl halides and pseudohalides available, the group is finding that it is very easy to try out new ideas for radical transformations with this system. “This aspect expedites the discovery process and opens up a lot of new conceptual territory to study,” said Dr. Horwitz. He continued: “At times, it was difficult to decide on what systems to study for this first report because there are many possibilities for new reaction development and late-stage functionalization. We were happy that we could find a collection of examples that proved the points we wanted to make about this chemistry.”

Professor Melchiorre wrapped up by concluding: “We believe that this photochemical strategy, by providing a fundamentally new activation mechanism to generate open-shell intermediates, can offer fresh opportunities for enhancing the potential of radical chemistry, expanding the way chemists think about making molecules.”

About the authors

**Paolo Melchiorre** studied chemistry at the University of Bologna (Italy), where he received his PhD in 2003, working in the area of asymmetric catalysis. In 2002, Paolo spent a research period at the Center for Catalysis at Århus University (Denmark), where his studies centered on enantioselective organocatalysis. From 2003, Paolo worked as a postdoctoral associate at the Industrial Chemistry Faculty of the University of Bologna. In October 2007, he started his independent career as an Assistant Professor at the University of Bologna. In September 2009, Paolo joined the Institute of Chemical Research of Catalonia (ICIQ) in Tarragona (Spain) as an ICREA Professor and ICIQ Group Leader. Paolo has also been a Tenured Senior Group Leader at Istituto Italiano di Tecnologia (IIT), Genoa (Italy) since October 2018. His current scientific interests lie in the discovery and mechanistic elucidation of catalytic enantioselective strategies for chemical synthesis, mainly using photochemical and radical reactivity patterns. The final aim is to develop sustainable and innovative catalytic methods to streamline the preparation of complex chiral molecules.

**Matthew A. Horwitz** grew up in Flat Rock, North Carolina (USA) and obtained a Bachelor’s degree in biochemistry from Columbia University (USA). He subsequently obtained a Ph.D. under the supervision of Jeffrey S. Johnson at the University of North Carolina at Chapel Hill (USA), where he studied organocatalysis and total synthesis. He then worked in the laboratory of Paolo Melchiorre at the ICIQ (Spain) as a postdoctoral researcher. He now works as a postdoctoral researcher at the University of Oxford (UK) in the group of Véronique Gouverneur.

**Bertrand Schweitzer-Chaput** was born in Sèvres, France. He received his Bachelor’s degree from Versailles-Saint-Quentin University and his Master’s degree from Paris XI University, both in France. He then moved to Germany for doctoral studies at the Max-Planck-Institut für Kohlenforschung under the supervision of Martin Klussmann. His thesis dealt with mechanistic studies and development of organocatalytic oxidative coupling transformations. He finally joined the group of Paolo Melchiorre to work on novel photocatalytic systems for radical generation.

**Eduardo de Pedro Beato** was born in Madrid (Spain). He obtained his B.Sc. and M.Sc. in organic chemistry from Universidad Autónoma de Madrid (Spain), where he carried out his Master’s studies under the supervision of Carmen Carreño. He then spent two years in industry working at Eli Lilly & Co. He started his graduate studies at ICIQ (Spain) in 2017, joining the group of Paolo Melchiorre. His research focuses on the development of new organic transformations through photoexcitation of organic intermediates.

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The pace of scientific discoveries and developments in academic and industrial laboratories has reached staggering dimensions with the introduction and widespread use of generally available automated high-throughput experimentation equipment. “The full utilization of high-throughput screening (HTS) methodologies in asymmetric reaction development efforts, however, has been lagging behind for some time,” noted Professor Christian Wolf from Georgetown University (USA). “While hundreds of reactions can easily be conducted on the microscale using microwell plate technology, it is still quite a challenge to determine both yield and enantiomeric excess \((ee)\) without product isolation or at least partial work-up”.

He added: “Recent advances with optical techniques that are compatible with parallel data generation from minute sample amounts are about to expand the toolbox of synthetic chemists. In the last few years, the chiroptical sensing field has left its ‘Mauerblümchen’ (‘wallflower’) image behind by shifting the focus to real-world applications. As a result, increasingly practical molecular sensors that allow HTS of crude asymmetric reaction mixtures via UV, fluorescence or circular dichroism analysis have been developed and put to the test.”

Direct yield and \(ee\) determination of asymmetric reactions requires a rugged assay that generates accurate data in the presence of possibly interfering chemicals, including starting materials, catalysts, reagents and by-products. To accomplish this challenging task, the group of Professor Wolf has now introduced an optical method with broadly applicable coumarin sensors exhibiting attractive click chemistry features.

Professor Wolf said: “In our search for a chromophoric sensor that is capable of direct asymmetric reaction screening, several 4-halocoumarins that can covalently bind a variety of nucleophilic target compounds were investigated. Proton NMR and UV studies performed with 4-chloro-3-nitrocoumarin and 1-phenylethylamine as analyte showed that this can be accomplished quantitatively in less than 15 minutes at millimolar concentrations and without by-product formation.” The group studied the performance of the sensor under various conditions to confirm broad solvent compatibility and tolerance of air and moisture. “Importantly, the substrate binding does not generate an additional stereogenic center,” explained Professor Wolf. He continued: “This facilitates the chiroptical analysis because it avoids complications that could arise from the formation of diastereomeric mixtures. The sensing event coincides with a colorimetric change and the formation of characteristic UV and CD signals allows concentration and \(ee\) analysis of the target compound. The optical click sensing assay is applicable to a wide variety of substrates including amines, amino alcohols, amino acids and alcohols (Scheme 2). We can use chloroform, dichloromethane, methanol or toluene as solvents and the sensing of amino acids can be performed in aqueous acetonitrile, which is attractive with regard to biological applications.”

With a rugged sensing assay in hand, the group attempted simultaneous \(ee\) and concentration analysis of nine scalemic samples of 1-(2-naphthyl)ethylamine by comparing the induced CD and UV spectra with calibration curves (Scheme 3). Professor Wolf said: “The absolute configuration of the major
enantiomer was assigned by comparison of the sign of the induced Cotton effect to a reference sample. Our click sensing gave accurate results in all cases. For example, the sensing of a sample containing (R)-1-(2-naphthyl)ethylamine in 4.00 µM and 25.0% ee gave 4.34 µM and 24.0% ee (Scheme 3, entry 1).

Professor Wolf continued: “To determine the usefulness of our optical sensor in asymmetric reaction analysis, we selected the iridium-catalyzed asymmetric hydrogenation of N-methyl-1-phenylethan-1-imine using several ligands with various catalyst loadings. The sensing was carried out with 200 µL aliquots of crude reaction mixtures and the calculated conversion and ee obtained by chiroptical sensing were compared to traditional NMR and chiral HPLC analysis. The results were within a 5% error margin, which is generally considered...
acceptable for HTS applications. “Our optical assay is significantly faster and produces less waste than the traditional reaction analysis,” remarked Professor Wolf, continuing: “The sensing assay generated approximately 6 mL of solvent waste per analyte and was complete within 1 hour while the traditional approach produced 540 mL and required more than 7 hours (Scheme 4).”

Professor Wolf concluded: “We have developed an efficient, robust optical method for quantitative chirality sensing of a wide range of substrates. Our coumarin sensor possesses attractive click chemistry features and was successfully applied to asymmetric reaction analysis utilizing only milligram quantities of the crude material. We have demonstrated that optical reaction analysis can be fast, and that it eliminates cumbersome purification steps and reduces chemical waste,
time and labor. Altogether, optical chirality sensing with click chemistry coumarin probes offers new means to accelerate asymmetric reaction development efforts at reduced cost.”

**REFERENCES**

F. Yushra Thanzeel obtained her B.Sc in chemistry from the University of Peradeniya (Sri Lanka) in 2015. During her undergraduate studies, she worked with Prof. Ratnayake Bandara on alkaloid intercalation of C. grandis alkaloids into Montmorillonite (MMT) clay. She joined Prof. Christian Wolf’s laboratory at George-town University (USA) in 2015 to pursue a Ph.D. During her first year of graduate school, she developed a substrate-specific sensing assay to quantify the concentration and enantiomeric composition of cysteine in biologically relevant media. In addition, her research comprises the design and synthesis of chiroptical sensors, chiral recognition studies, high-throughput screening, bio-conjugation and medicinal chemistry.

Kaluvu Balaraman graduated from Madurai Kamaraj University (India), with an M.Sc. in chemistry in 2007. He earned his Ph.D. in chemistry from IIT-Madras (India) in 2012 under the supervision of Prof. V. Kesavan, where he developed a novel class of tartaric acid derived bis( oxazoline) ligands for various asymmetric transformations. In 2013, he joined the group of Prof. Philippe M. Loiseau at the University of Paris Sud (France) for two years as a postdoctoral researcher in a CEFIPRA (Indo-French) project to investigate nanotechnology-based treatments of leishmaniasis. He continued working as a postdoctoral fellow (2015–2018) with Prof. Christian Wolf at Georgetown University (USA) where he developed new catalytic methodologies for the synthesis of fluorinated organic compounds. Currently, he is working as Assistant Research Professor at Georgetown University where he is playing a leading role in anticancer, Parkinson and Alzheimer drug development projects.

Christian Wolf obtained his Ph.D. in 1995 from the University of Hamburg (Germany), working with the late Wilfried König on chiral biphenyls and cyclodextrin modifications. After postdoctoral work with the late William Pirkle at the University of Illinois (USA), he took an R&D position at SmithKline Beecham Pharmaceuticals (USA), in 1997. In 2000, he started as Assistant Professor at Georgetown University, Washington, DC (USA). He was appointed Associate Professor with tenure in 2006 and Full Professor in 2011. He has served as Director of the GU Medicinal Chemistry Shared Resource Center since 2017 and is cofounder of Enantiosense LLC. Current research interests include synthetic methodology, asymmetric catalysis, optical sensing methods, high-throughput screening, molecular recognition, stereodynamics of chiral compounds, cross-coupling reactions and medicinal chemistry aimed at the development of new treatments for cancer and brain diseases.
Catalytic Farming: Reaction Rotation Extends Catalyst Performance

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The use of heterogeneous catalysis has improved the separation and reusability of catalyst materials considerably compared to their homogeneous counterparts. Nevertheless, the turnover of these catalysts can still suffer from different deactivation pathways. “Current techniques to overcome this issue involve the use of heat and/or high oxygen or hydrogen pressures, a process that is usually expensive and wasteful,” said Professor Juan Scaiano from the University of Ottawa (Canada), whose group has been researching this area for several years. “As green chemistry practices have inspired many changes in the industrial synthesis of traditional chemicals, alternative strategies based on the reduction of waste production while regenerating the catalysts activity are welcomed.”

Dr. Anabel Lanterna, one of the co-authors, added: “Since we started our venture towards the use of heterogeneous catalysis, we have been looking for processes that can reactivate the catalytic activity in a more environmentally friendly manner. Inspired by practices in agriculture, we decided to explore a new strategy named ‘catalytic farming’ due to its resemblance to the crop rotation approach that farmers have been using for centuries.” Dr. Lanterna continued: “As farmers know, a crop can deplete the soil of nutrients that other crops can restore in the following growing season, therefore rotation of the crops can improve the yields and extend the durability of the field productivity. Likewise, we can use reactions that can ‘reactivate’ the catalyst for another type of reaction in the

**Scheme 1** (A) Three different reactions photocatalyzed by Pd-decorated TiO$_2$. (B) Yields of the reactions after different catalytic cycles, demonstrating that reaction rotation extends the catalytic activity of the material; the colors represent the different reactions shown in part A.
subsequent catalytic cycle (Scheme 1). At this point it is important to highlight that none of the strategies tested could be done without properly knowing the catalytic mechanism and the changes the catalyst might undergo during catalysis.”

This strategy is not limited to the systems the group has studied; indeed, it can be extended to different catalytic systems as long as the catalysts can be employed for more than one catalytic reaction. “This implies thorough knowledge of the catalytic mechanisms taking place in each case, or at least knowledge regarding the changes in the catalyst chemical structure. The strategy also shows potential for flow chemistry, as we envision that different consecutive reactions can be catalyzed simply by changing reagents at the flow system input,” said Professor Scaiano.

“It is important to highlight that farmers have taken years to develop the best crop rotation practices, and yet there is no preferred choice among them,” remarked Professor Scaiano. He continued: “Thus, the perfect rotation sequence also considers other external parameters such as usefulness of the crop, economic competence and environmental liability. Likewise, in chemistry, there is no perfect reaction rotation order and the strategy can vary from one chemist to the other.”

In this particular case, the group faced cases where, despite appearing suitable for reaction rotation, the system evolved in a different way on the bench. Professor Scaiano concluded: “Noticeably, the work summarized in this contribution is the result of many trials, both fruitful and ineffective ones, and great perseverance as we always believed this strategy would find its way to a successful story.”
About the authors

Ayda Ali Elhage, originally from Lebanon, is currently a PhD candidate in chemistry at the University of Ottawa (Canada). She earned her undergraduate degree in chemistry from the Lebanese University in Beirut (Lebanon). She completed a high school teaching certificate at the Faculty of Education, Beirut, Lebanon then started to share her passion for molecules to high school students in public and private schools for many years. After moving to Ottawa, Canada in 2011, she worked at Lycée Claudel, a private French school, for three years. In September 2014, Ayda quit her job to pursue graduate studies under the supervision of Prof. Juan Scaiano at the University of Ottawa. Her research is focused on the development of supported metal nanomaterials (plasmonic and/or non-plasmonic metals) for heterogeneous photocatalytic systems. She is also working on developing a new type of heterogeneous catalyst for potential uses in continuous-flow photochemistry, by functionalizing glass fiber surfaces prior to metal nanoparticle decoration for organic transformation applications.

Anabel E. Lanterna obtained her PhD in chemistry from the National University of Córdoba (Argentina) in 2013. During her PhD studies, she spent some time at the University of Johannesburg (South Africa) and at the University of Valencia (Spain) working on plasmonic metal nanoparticles. After she graduated, she joined the Scaiano group at the University of Ottawa (Canada), where she began her work in heterogeneous photoredox catalysis. Since then she has published more than 20 contributions in peer-reviewed journals, with more than 10 of these in the field of heterogeneous photocatalysis. She is the recipient of the 2018 Canadian Society for Chemistry (CSC) Award for Young Materials Chemists and the 2018 Inter-American Photochemical Society (IAPS) Gerhard Closs Postdoctoral Award. Currently, she is interested in the design and study of new nanomaterials for use in catalysis and health applications.

Juan C. (Tito) Scaiano holds the Canada Research Chair in Applied Photochemistry at the University of Ottawa (Canada). Professor Scaiano’s scientific career includes the publication of over 700 scientific papers, two books and several book chapters. He is recognized for his work in photochemistry and nanotechnology and his h-index is 77. His research interests include organic photochemistry, nanomaterials, catalysis, sunscreens, and single-molecule spectroscopy. He is the founder of Luzchem Research, an Ottawa-based instrument manufacturer. His research group of about 15 co-workers currently concentrates on the study of nanomaterials and catalysis.