

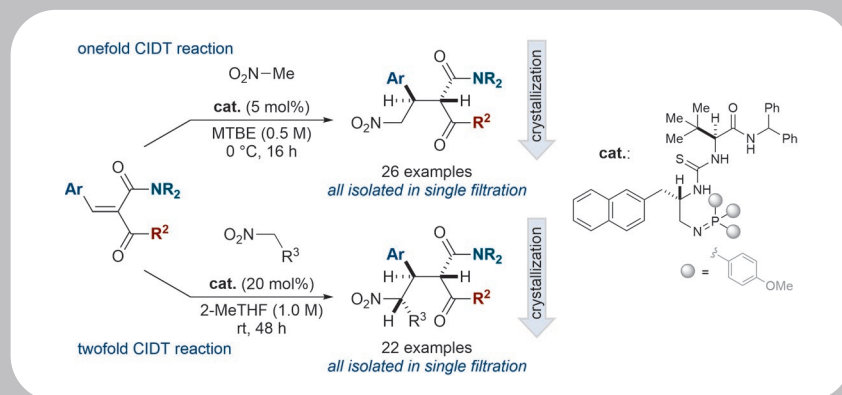
Synform

People, Trends and Views in Chemical Synthesis

2022/11

Doubly Stereoconvergent Crystallization Enabled by Asymmetric Catalysis

Highlighted article by P. De Jesús Cruz, W. R. Cassels, C.-H. Chen, J. S. Johnson



Contact

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Dear Readers,

It's October 5th 2022, 11.30 AM: one year ago, the amazing and fantastic news that our SYNLETT Editor-in-Chief – Ben List – had been awarded the Nobel Prize in Chemistry was shaking the ground, just like an earthquake. One year later, the 2022 Nobel Awardees have just been announced, and it's once again extremely exciting for organic synthesis: they include Morten Meldal (Denmark) and Barry Sharpless (USA, this is the 2nd Nobel Prize in Chemistry for him!!), for their pioneering work on metal-catalyzed “click chemistry”, especially the copper-catalyzed azide–alkyne cycloaddition (CuAAC), and Carolyn Bertozzi (USA) for her pioneering work on metal-free “click chemistry” targeted to living systems and biomedicine applications, where metals like copper are generally toxic in the concentrations required for promoting click chemistry. Professor Bertozzi and Professor Sharpless were both featured in SYNFORM (see for example, SYNFORM **2008**, page A118 and SYNFORM **2019**, page A13), and the organic chemistry community will be delighted with the Nobel Prize awarded to these three trailblazers of bioorthogonal chemistry. Warmest congratulations to these three giants of chemistry from the Thieme Chemistry family!!

This November issue of SYNFORM is opened by a Literature Coverage article on the synthesis of *N*-aryl aziridines using *N*-aminopyridinium reagents as traceless activating groups, as recently reported in *Nat. Commun.* by David Powers (USA). The next article covers a *Science* paper by Jeffrey Johnson (USA) who developed an innovative approach to asymmetric synthesis, centered on a crystallization-induced diastereomer transformation that – following a Michael reaction – allows the convergence of all of the resulting equilibrating species

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to a single solid stereoisomer. The third article focuses on the powerful catalytic reductive ring opening of epoxides described in a *Chem* paper by Eisuke Ota and Junichiro Yamaguchi (Japan). Closing the issue is a Young Career Focus interview with Sandip Murarka (India) about his research interests, current activity and future plans.

Enjoy your reading!



Contact

If you have any questions or wish to send feedback, please write to Matteo Zanda at: synform@outlook.com

N-Aminopyridinium Reagents as Traceless Activating Groups in the Synthesis of *N*-Aryl Aziridines

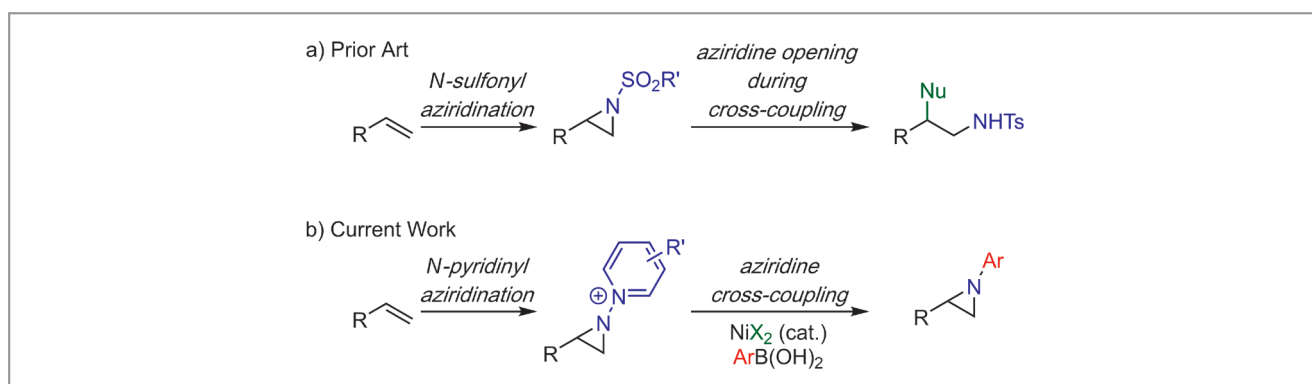
Nat. Commun. **2022**, *13*, 3341

Nitrene transfer catalysis has been broadly investigated, because it provides the opportunity to efficiently install nitrogen-containing functional groups via C–H amination or olefin aziridination. Professor David Powers' group at Texas A&M University (USA) became involved in this area of science while studying the inorganic chemistry of metal nitrenes. Professor Powers told SYNFORM: "Over the past 5 years, our group has been developing new tools to study the chemical structures of transient nitrenes by *in crystallo* photochemistry (e.g., *J. Am. Chem. Soc.* **2020**, *142*, 19862–19867 and *J. Am. Chem. Soc.* **2019**, *141*, 16232–16236). During these studies we came to realize that while enormous progress has been made in nitrene transfer chemistry, significant limitations plagued most modern methods. Namely, reactions were either limited to intramolecular reactions or required the presence of strongly electron-withdrawing *N*-substituents, which resulted in *N*-protected products (Scheme 1a)." Professor Powers explained that the most common *N*-protecting groups are sulfonamides, phthalimides, and carbamates, but these nitrogen derivatives can be difficult to deprotect and derivatize in the downstream chemistry, which limits the utility of nitrene transfer catalysis in the synthesis of diverse *N*-functionalized products. The Powers group envisioned that *N*-aminopyridinium salts could expand the utility of formal nitrene transfer chemistry because these reagents are inherently bifunctional (Scheme

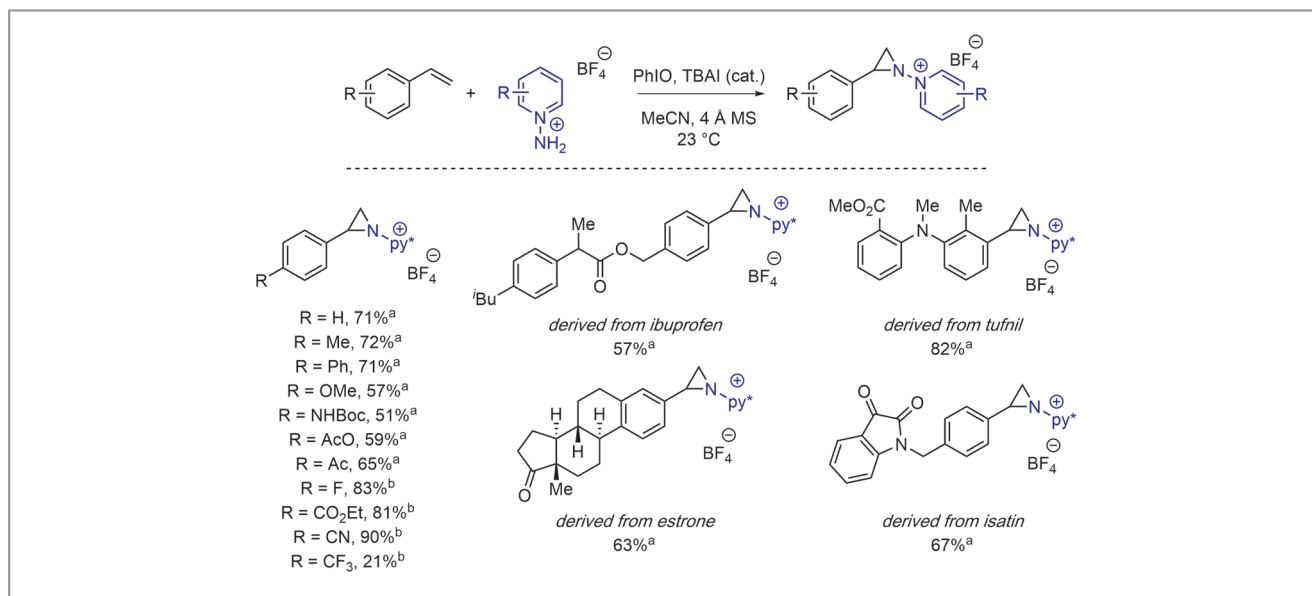
1b). Professor Powers said: "The *N*-amino group can engage as a nucleophilic moiety in an amination reaction and the N–N bond in the resulting aminopyridinium compound could be engaged as an electrophilic moiety."

Initially, the group's efforts to achieve olefin aziridination were predicated on synthesis of the iminoiodinane derived from *N*-aminopyridinium salts and iodosylbenzene, which they envisioned could be used in Rh- or Cu-catalyzed nitrene transfer reactions. "Despite many experiments, we were never able to isolate an *N*-aminopyridinium analogue of PhI=NTs," remarked Professor Powers. He continued: "We next sought to generate this intermediate *in situ* by combining iodosylbenzene and *N*-aminopyridinium salts in the presence of olefinic substrates and various transition-metal catalysts. Ultimately, these experiments revealed that efficient aziridination of styrenyl olefins could be achieved without metal catalysts but with the addition of a catalytic amount of iodide (Scheme 2)."

With access to *N*-pyridinium aziridines, the group was attracted to the potential to use these unique compounds as substrates in metal-catalyzed cross coupling to forge new C–N bonds. "This idea was based on 1) Prof. Mary Watson's beautiful C–C cross coupling using *N*-alkylpyridinium electrophiles (e.g., *J. Am. Chem. Soc.* **2017**, *139*, 5313–5316), and 2) the potential that the low-lying LUMO of our substrates would enable cross coupling without aziridine ring opening, which



Scheme 1 Olefin aziridination often requires strongly electron withdrawing *N*-substituents that can be challenging to remove and are not present in many synthetic targets of interest. We reasoned that development of aziridination using *N*-aminopyridinium reagents would provide the opportunity for facile *N*-derivatization by metal-catalyzed activation of the N–N bond.



Scheme 2 Optimized conditions for, and selected examples of, olefin aziridination using *N*-aminopyridinium reagents. ^a Conditions: styrene (1.0 equiv), 2,4,6-triphenyl-*N*-aminopyridinium tetrafluoroborate (1.0 equiv), iodosyl benzene (PhIO, 1.0 equiv), tetrabutylammonium iodide (TBAI, 5 mol%). ^b Conditions: styrene (1.0 equiv), 2,4,6-triphenyl-*N*-aminopyridinium tetrafluoroborate (1.6 equiv), PhIO (1.6 equiv), TBAI (20 mol%).

would contrast the cross-coupling reactions of other *N*-functionalized aziridines,” said Professor Powers, who continued: “While we had initially developed the olefin aziridination chemistry using both *N*-aminopyridinium and the 2,4,6-triphenyl analogue, during our studies of Ni-catalyzed cross coupling, we found the triphenyl version was required for efficient cross coupling with arylboronic acid nucleophiles (Scheme 3, top; py* = 2,4,6-triphenylpyridinyl). While Pd catalysts were tried in the optimization, they turned out inactive in our cross-coupling. We rationalized that Ni is more compatible with single-electron processes than Pd, and cleavage of *N*-substituted pyridinium salts begins with a single-electron transfer to the pyridinium π*. This observation is in contrast to related Ni-catalyzed coupling that we developed in the context of C–H aminopyridylation, in which the unsubstituted pyridinium was a good substrate for coupling (*Angew. Chem. Int. Ed.* **2022**, *61*, e202200665).”

Professor Powers went on to list a few observations that were made during optimization of the aziridine cross-coupling chemistry:

1) The reaction proceeds in more reproducible yield when one equivalent of 2,4,6-collidine is added. The specific role of this additive is not known at this time.

2) Separation of triphenylpyridine, which is a byproduct of C–N cross-coupling, from the *N*-aryl aziridine was challenging

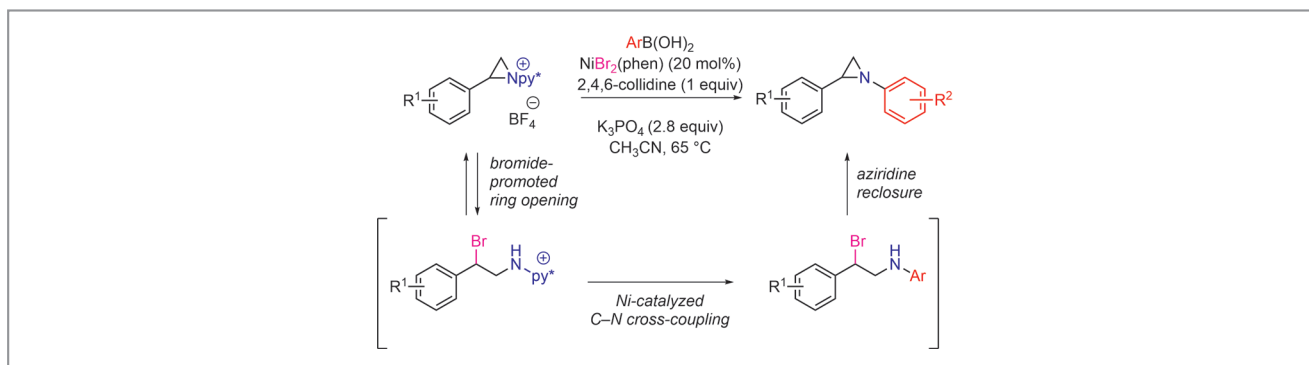
for some substrates and required purification by preparative HPLC.

3) The counter anions of the Ni catalyst were important for efficient catalysis, with bromide being particularly effective.

Professor Powers remarked: “Spectroscopic studies indicated that the bromide ion was opening the aziridines to generate 1,2-bromoamines. Further, exposure of these bromoamines to our cross-coupling conditions resulted in *N*-aryl aziridines. These observations led us to propose the reaction pathway illustrated in Scheme 3 in which reversible aziridine opening is promoted by the bromide counterion and cross-coupling is accomplished by the Ni ion. Further investigations are still needed in order to understand this unusual cross-coupling reaction.”

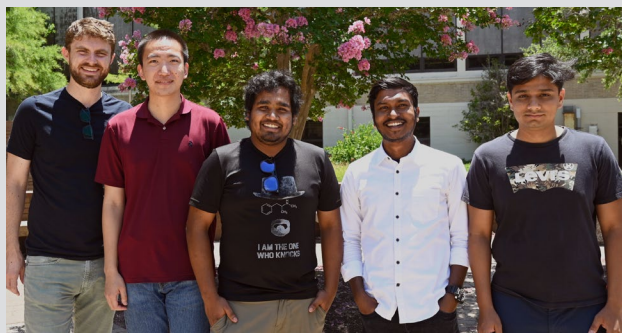
Professor Powers concluded: “Access to *N*-pyridinium aziridines provides a number of exciting new directions to explore. Particular current interest is focused on using these species as precursors to *N*-centered aziridinyl radicals for use in synthesis. In addition, significant mechanistic work is underway to better understand the selective *N*-functionalization that we observe under Ni-catalyzed cross coupling, which contrasts ring opening chemistry that has been observed under similar conditions with *N*-tosylaziridines.”

Mattias Fank



Scheme 3 Top: Ni-catalyzed *N*-pyridinium aziridine cross coupling. Bottom: Proposed cross-coupling mechanism that proceeds through reversible aziridine opening and reclosure. The proposed mechanism suggests a bifunctional role for the NiBr_2 catalyst: the bromide ion is responsible for aziridine opening and the Ni ion is responsible for the C–N cross-coupling chemistry.

About the authors



From left: David Powers, Hao Tan, Samya Samanta, Asim Maity, Pritam Roychowdhury

Hao Tan was born in Shandong Province (P. R. of China). He completed his B.Sc. from Nankai University, Tianjin (P. R. of China). He joined the group of Dr. Powers at Texas A&M University (USA) in 2019. Currently he is working as a graduate student pursuing a Ph.D. in organic synthesis. His research interest focuses on the development of new amination chemistry based on installation of derivatization of *N*-aminopyridiniums.

Samya Samanta was born in West Bengal, India and completed his B.Sc. and M.Sc. degrees at the Indian Institute of Technology, Kharagpur (India) under the supervision of Prof. N. D. Pradeep Singh. In his Master's project, he worked on organophotoredox-mediated amide and benzothiazole synthesis. During his undergraduate studies, he also worked as an intern under Prof. David Berg at University of Victoria (Canada) on palladium- and platinum-based catalyst design for polymerization, and under Prof. Leong Weng Kee at Nanyang Technological University (Sin-

gapore) on osmium cluster complexes. Currently his research is on C–H amination chemistry under Prof. David C. Powers at Texas A&M University (USA).

Asim Maity was born and raised in West Bengal (India), and completed his B.Sc. from Jadavpur University, Kolkata (India), and M.Sc. from the Indian Institute of Technology Kharagpur (India). He then moved to the USA for his graduate studies and received his PhD in chemistry from Texas A&M University (USA). His doctoral research was focused on the sustainable synthesis and application of hypervalent iodine compounds. Asim is currently a Senior Research Specialist in the Dow Chemical Company.

Pritam Roychowdhury was born in Kolkata (India) and received his BS in 2016 from West Bengal State University (India). He then moved to Indian Institute of Technology, Kharagpur (India) for his M.Sc. studies and completed his thesis under the supervision of Prof. Amit Basak. Soon after, he travelled to Texas A&M University (USA) for his PhD studies under the guidance of Prof. David C. Powers. In the Powers laboratory, he is working on utilizing bifunctional reagents for amination chemistry.

David Powers received a B.A. from Franklin and Marshall College (USA) and a Ph.D. from Harvard University (USA). He pursued postdoctoral training at the Massachusetts Institute of Technology (USA) and Harvard University. He joined the faculty at Texas A&M University (USA) in 2015 and was promoted to Associate Professor in 2021. His research group is interested in the chemistry of reactive intermediates, catalysis in confined environments, and novel methods in group-transfer catalysis.

Doubly Stereoconvergent Crystallization Enabled by Asymmetric Catalysis

Science **2022**, *376*, 1224–1230

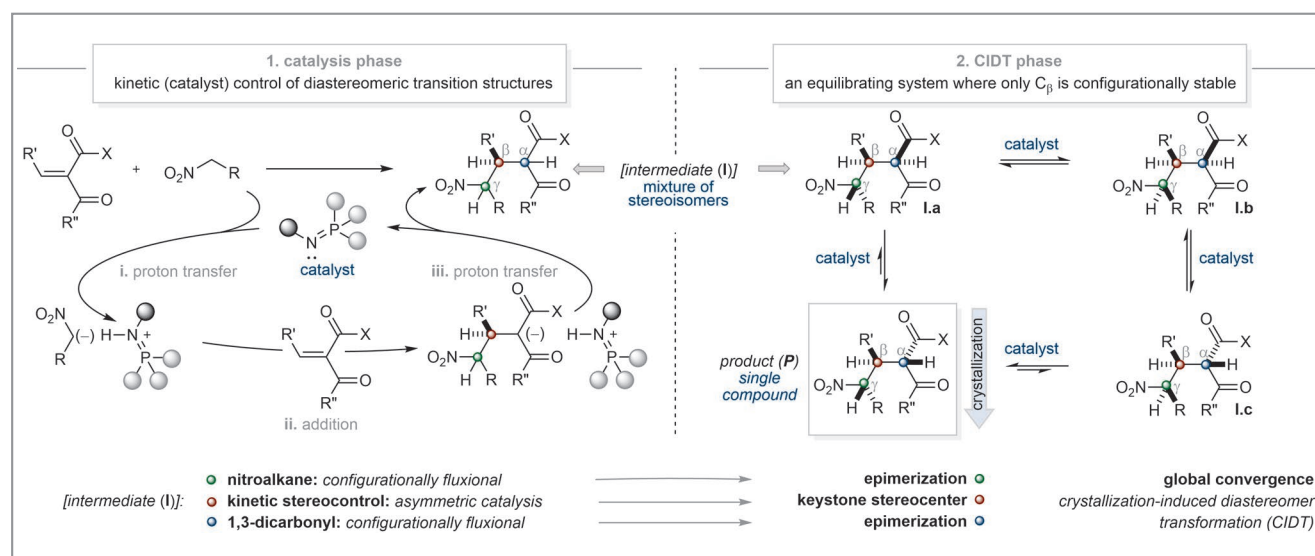
Tremendous progress continues to be made in the field of asymmetric catalysis, such as the development of new and better catalysts for the efficient construction of carbon–carbon (C–C) and carbon–heteroatom (C–X) bonds. Professor Jeffrey Johnson at the University of North Carolina at Chapel Hill (USA) pointed out to SYNFORM that reaction design tends to focus on how to maximize kinetic selectivity in the bond-forming step, while considerations around post-reaction processing (e.g. purifications) tend to receive less attention. “The result of this prioritization is that even for highly efficient reactions, significant time and resources must be spent on isolation of the desired product, which limits the potential application on large scale or in other laboratories without the appropriate equipment,” he remarked.

According to Professor Johnson, an ideal purification method is the direct crystallization or purification of the desired product from the crude reaction mixture. “When there are one or multiple stereochemically fluxional stereocenters, one can design a crystallization-induced diastereomer transformation (CIDT) in order to converge all of the equilibrating species to a single solid stereoisomer. CIDTs are highly desirable in process chemistry because they provide a means to generate dia-

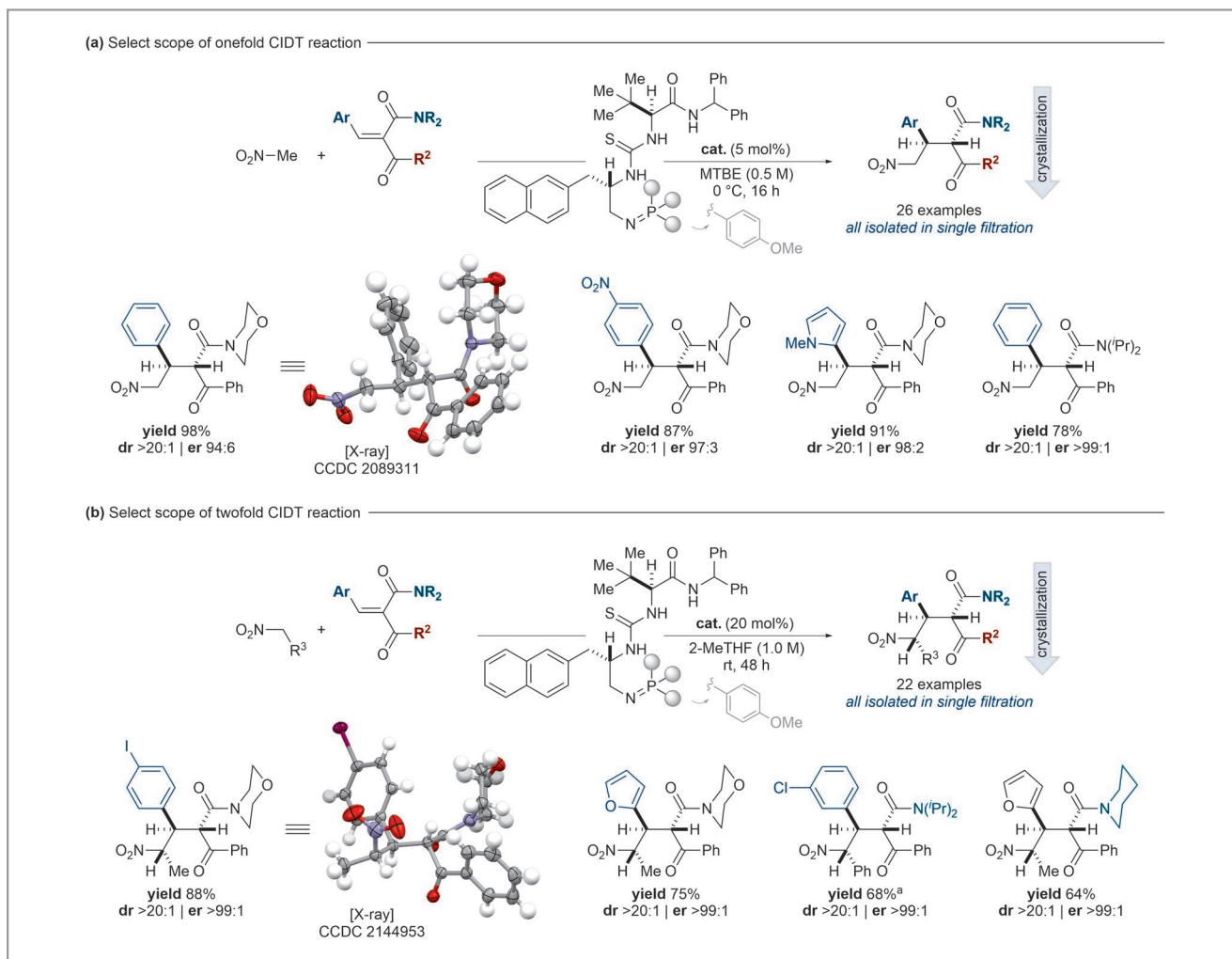
stereoenriched material without additional elaborate purification methods. There are a number of examples of discrete CIDTs populating the literature, but usually limited to a single example or an auxiliary-controlled crystallization,” said Professor Johnson.

The Johnson group was interested in developing an asymmetric Michael reaction between nitroalkanes and alkylidene β -keto amides to generate three asymmetric centers, but could not improve the diastereoselection beyond ~1:1:2:2 when the reactions were under homogeneous conditions. Professor Johnson said: “Pedro de Jesús Cruz (first author on the paper) noted that upon changing to certain ethereal solvents, the reactions become increasingly heterogeneous over time, and this change correlated to a large bump in diastereoselectivity. Perhaps most exciting was the finding that when the heterogeneous mixtures were filtered, the solid was diastereoisomerically pure product in most cases.”

The group established that these reactions were undergoing a two-phase phenomenon (Scheme 1): “The Dixon iminophosphorane catalyst initially controls the absolute kinetic enantioselectivity at C_β , but the product of this initial “catalysis phase” is then a mixture of diastereomers at C_α and C_γ ,



Scheme 1 Merger of asymmetric catalysis and crystallization-induced diastereomer transformations



Scheme 2 Select scope of CIDT reactions. ^a Reaction run in MTBE (1.0 M) as solvent.

explained Professor Johnson, continuing: “The catalyst then interconverts the four resulting diastereomers. One diastereomer selectively precipitates to provide the solid single stereoisomeric product (“CIDT phase”). The catalyst functions in two roles where it initially catalyzes the C–C bond forming step with high enantioselectivity, and subsequently mediates the equilibration of the resulting four diastereomers of product.”

The dearth of examples of this sort of two-phase, one-pot catalysis approach provides impetus for the Johnson group and others to push this paradigm going forward. Professor Johnson said: “The one-pot approach is more efficient and greener compared to previous asymmetric catalytic methods: significant savings in time and solvent use are accrued by obviating further purification steps. Because the desired pro-

ducts crash out of the crude reaction mixture, they can all be accessed in high purity by a single filtration on a simple fritted funnel (no flash chromatography). The reactions proved to be remarkably general and user-friendly to run (Scheme 2).”

Professor Johnson concluded: “We hope that this developed merged asymmetric catalysis/CIDT strategy will be adopted and applied in future reaction design. The generality of the developed nitroalkane addition suggests the strategy holds tremendous untapped potential in future asymmetric catalytic platforms.”

Matthew Farnik

About the authors



From left: Prof. J. S. Johnson, W. R. Cassels, Dr. P. De Jesús Cruz, Dr. C. H. Chen

Pedro de Jesús Cruz received his B.S. in chemistry from the University of Puerto Rico (Puerto Rico) in 2016 with high distinction and honors in chemistry, where he conducted research under Prof. Edgardo Rivera. He completed his Ph.D. studies at the University of North Carolina at Chapel Hill (USA) in 2022, working in the laboratories of Prof. Jeffrey S. Johnson where he explored new catalytic stereoconvergent reactions. During his doctoral studies, he was also an NIH Ruth L. Kirschstein predoctoral fellow and was awarded the DOW BEST symposium and Corteva DELTA research awards. He is currently a Discovery Chemist at Merck.

William R. Cassels received his B.A. in chemistry from the College of the Holy Cross in Worcester, Massachusetts (USA), where he conducted research under Prof. Kevin J. Quinn. He began his Ph.D. studies at the University of North Carolina at Chapel Hill (USA) in 2018, working in the laboratory of Prof. Jeffrey S. Johnson. His research focuses on the development of new organocatalytic stereoconvergent reaction manifolds of β -dicarbonyls.

Chun-Hsing (Josh) Chen received his Ph.D. in physical chemistry from Brandeis University (USA) in 2010 under the supervision of Prof. Bruce Foxman. He was a postdoctoral fellow and later became a research crystallographer at the Indiana University Molecular Structure Center (USA). Josh joined the University of North Carolina at Chapel Hill Department of Chemistry (USA) as a director of the X-ray Crystallographic Core Laboratory (XCL) in September 2018.

Jeffrey S. Johnson has been a faculty member at the University of North Carolina at Chapel Hill (USA) since 2001 and has held the A. Ronald Gallant Distinguished Professorship since 2014. His research focuses on stereoselective synthesis and catalysis.

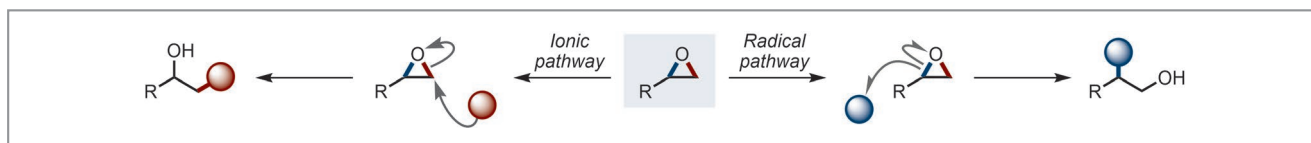
Catalytic Reductive Ring Opening of Epoxides Enabled by Zirconocene and Photoredox Catalysis

Chem **2022**, *8*, 1762–1774

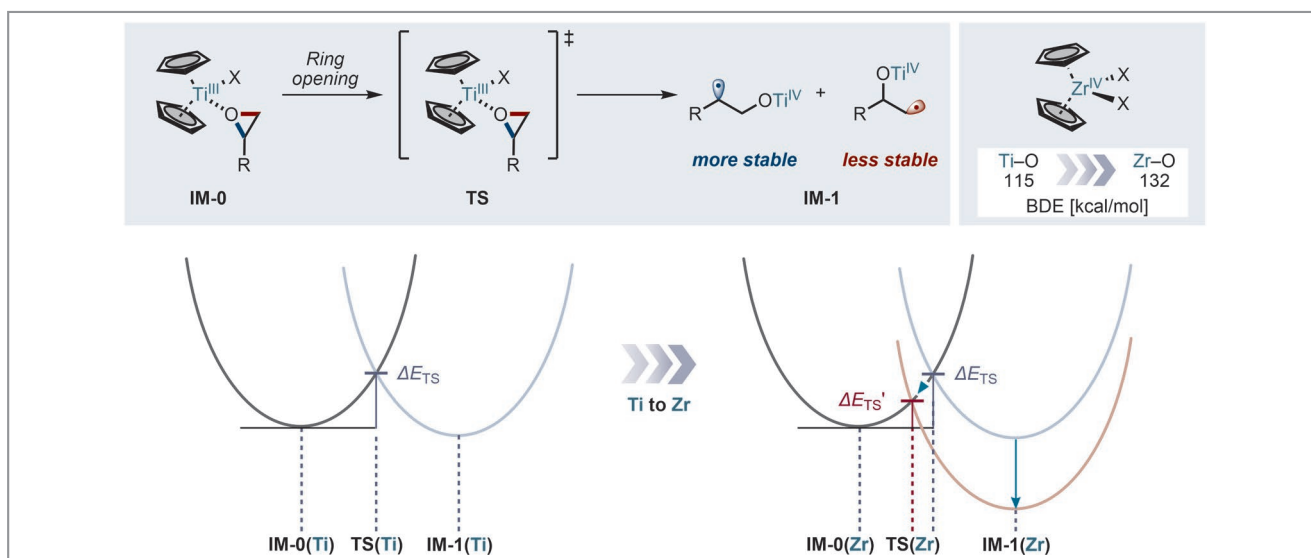
The epoxide ring is a key structural motif frequently found in biologically active compounds, natural feedstocks, and various synthetic intermediates. Generally, epoxides act as electrophiles, but C–O bond homolysis furnishes a nucleophilic carbon radical that can subsequently undergo a variety of functionalizations (Scheme 1).

“The most common catalyst for transformations related to epoxide C–O bond homolysis is titanocene(III) which has been exclusively exploited over the past 30 years by synthetic chemists,” said Professor Junichiro Yamaguchi, from Waseda University (Tokyo, Japan), who added: “The mildness of the reaction conditions has enabled this transformation to be involved in numerous natural product syntheses. With titanocene catalysis, homolysis preferably occurs at the C–O bond to give a more stable radical.” Considering the Bell–Evans–Polanyi

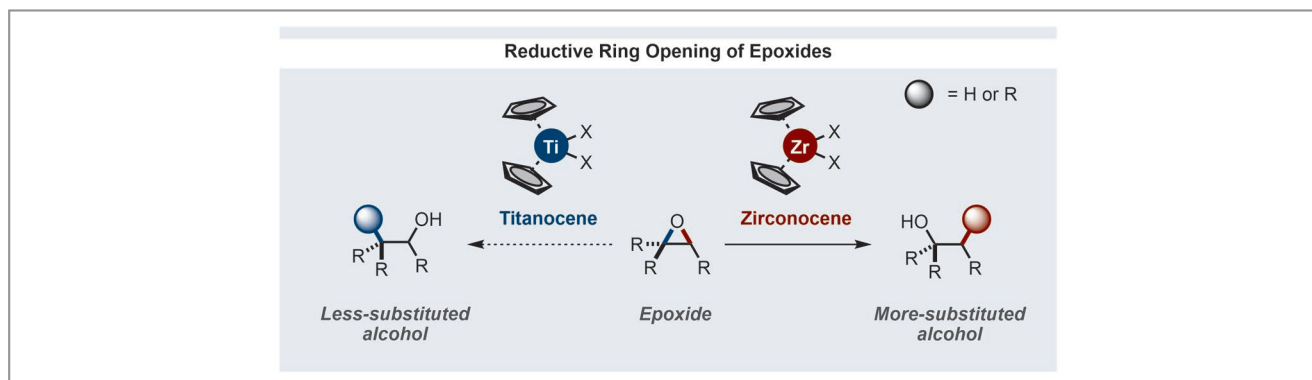
principle, activation energy decreases if the ring-opening step becomes more exothermic. Likewise, the transition state would shift earlier and become more similar to the starting material. According to the Hammond postulate, in an earlier transition state the contribution of the stability of the resulting radicals to regioselectivity would diminish. Intrigued by the higher oxophilicity of zirconium compared to titanium, Professor Yamaguchi’s group became interested in using zirconocene for the ring opening of epoxides (Scheme 2). Assistant Professor Eisuke Ota, a co-author on the paper, said: “We reasoned that the stronger oxophilicity of zirconium relative to titanium should render the ring opening exothermic. On this basis, we envisioned that the use of zirconocene would impact the conventional regioselectivity in the ring opening of epoxides.”



Scheme 1 Ring opening of epoxides



Scheme 2 Titanocene-catalyzed ring opening of epoxides and shifting transition state using zirconocene



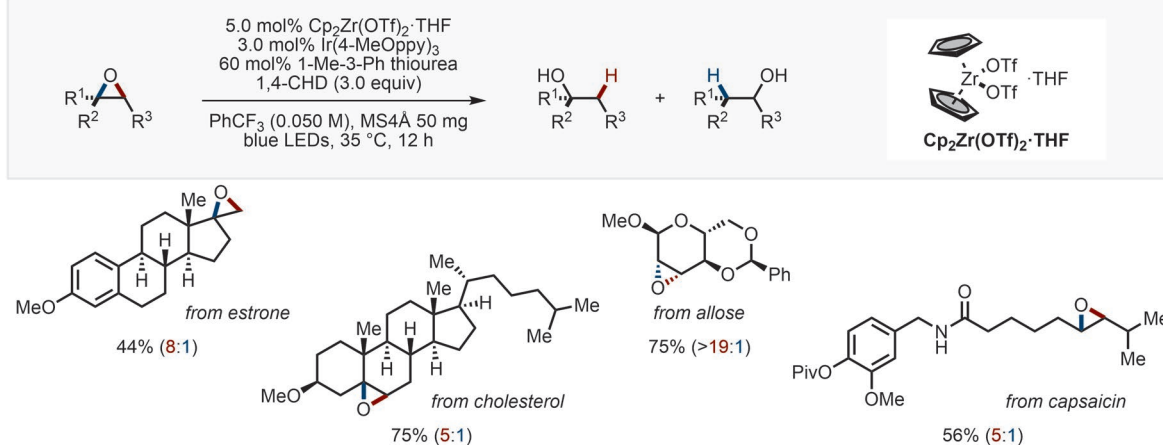
Scheme 3 Complementary regioselectivity in the reductive ring opening of epoxide between titanocene and zirconocene catalysis

Professor Ota remarked: “Fortunately, we succeeded in developing a catalytic protocol for the ring opening of epoxides using zirconocene and photocatalysis, even though zirconocene(III) has been scarcely utilized in organic synthesis. Compared to the well-established ring opening methods with titanocene, the present protocol exhibited reversed regioselectivity to afford the more-substituted alcohols (Scheme 3).” He continued: “This reaction is remarkably general, as it smoothly cleaves C–O bonds of epoxides in the presence of a variety of functional groups (Scheme 4). Natural-product-derived epoxides are also tolerated. Not only hydrogenation, but also radical cyclization was achieved with electron-deficient alkenes. Furthermore, the ring opening of benzyl ethers afforded a series of benzylidene acetals.”

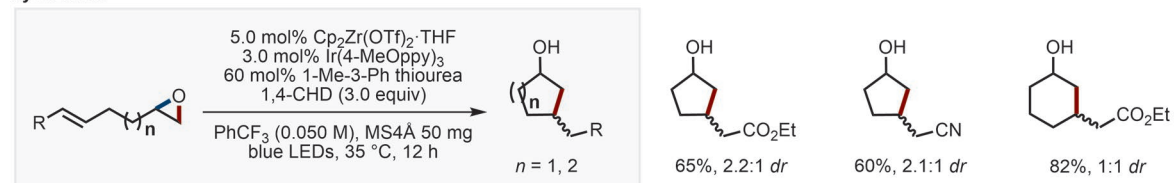
Professor Ota concluded: “The contrasting regioselectivity renders our catalytic protocol complementary to conventional methods using titanocene. We believe that this method for reductive opening will become a strategically important transformation of epoxides in synthetic chemistry, that may lead to revisiting the potential of zirconocene chemistry.”

Mattes Fank

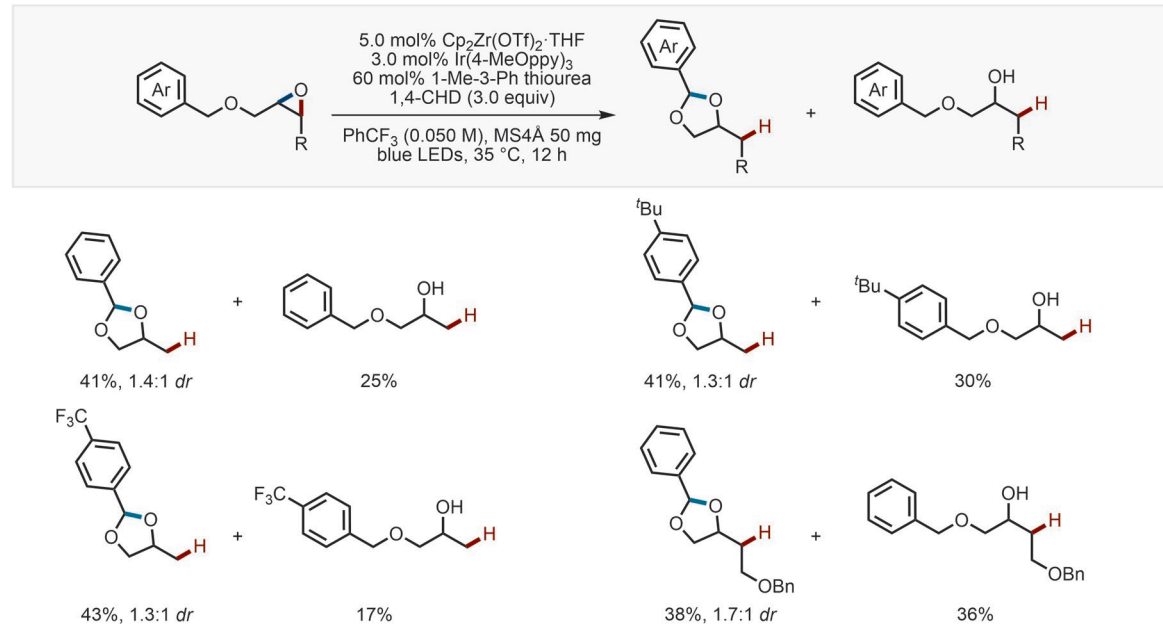
Hydrogenation



Cyclization



Acetal Formation



Scheme 4 Selected examples of reductive ring opening

About the authors



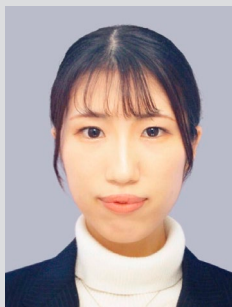
K. Aida

Kazuhiro Aida was born in Tokyo, Japan in 1997. He received his B.Sc. (2020) and M.Sc. (2022) degrees from Waseda University (Japan). Currently, he is a Ph.D. candidate in the group of Junichiro Yamaguchi at Waseda University. His research has focused on the development of inactive bond cleavage reactions using photoredox catalysis.



M. Hirao

Marina Hirao was raised in Tokyo, Japan. She received her B.Sc. degree (2021) from Waseda University, Japan. She is currently pursuing her M.Sc. degree at Waseda University in Prof. Junichiro Yamaguchi's group, where she has been carrying out research work focusing on the ring-opening functionalization of heterocyclic compounds using photoredox catalysis.



A. Funabashi

Aiko Funabashi was born in Tokyo, Japan, in 1997. She received her B.Sc. (2020) and M.Sc. (2022) degrees from Waseda University (Japan) under the guidance of Prof. Junichiro Yamaguchi. Since the spring of 2022, she has been an industrial researcher. Her research interests are the development of photoredox-catalyzed reactions.



Dr. N. Sugimura

Natsuhiko Sugimura received his B.Sc. degree from Shibaura Institute of Technology (Japan) in 1999 and his M.Sc. degree from Tokyo Institute of Technology (Japan) in 2001. After working as a researcher at the Olympus Corporation for nine years, he moved to Waseda University (Japan) as an analytical chemistry engineer in 2010. During his tenure, he obtained his Ph.D. from Tokyo University of

Technology (Japan) in 2017. His main research fields are NMR, MS, and computational chemistry.



Prof. E. Ota

Eisuke Ota was born in Chiba in 1987 and raised in Tokyo, Japan. He received his B.Sc. (2010) and M.Sc. (2012) degrees from Keio University (Japan) under the guidance of Prof. Shigeru Nishiyama. He then joined the group of Prof. Mikiko Sodeoka at RIKEN (Japan), where he completed his Ph.D. in 2016. After working as a postdoctoral researcher for one year at the same place, he became a JSPS Overseas Research Fellow in the lab of Robert

Knowles at Princeton University (USA). Since the fall of 2018, he has been an assistant professor at Waseda University (Japan) working with Prof. Junichiro Yamaguchi. His research interests are the development of photochemical bond cleavage methods for organic synthesis and chemical biology.



Prof. J. Yamaguchi

Junichiro Yamaguchi was born in Tokyo, Japan, in 1979. He received his Ph.D. in 2007 from the Tokyo University of Science (Japan) under the supervision of Prof. Yujiro Hayashi. From 2007 to 2008, he was a postdoctoral fellow in the group of Prof. Phil S. Baran at The Scripps Research Institute (USA; JSPS postdoctoral fellowship for research abroad). In 2008, he became an assistant professor at Nagoya University (Japan) working with Prof. Kenichiro Itami and was promoted to associate professor in 2012. He then moved to Waseda University (Japan) as an associate professor (principal investigator) in 2016 and was promoted to full professor in 2018. His research interests include the total synthesis of natural products and the innovation of synthetic methods.

Young Career Focus: Dr. Sandip Murarka (Indian Institute of Technology Jodhpur, India)

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 Dr. Sandip Murarka (Indian Institute of Technology Jodhpur, India).

Biographical Sketch



Dr. S. Murarka

Sandip Murarka completed his BSc in Chemistry (Hons.) at Midnapore College, Vidyasagar University (India) in 2005, and MSc at IIT Bombay (India) in 2007. After obtaining an M.S. from Rutgers University (USA) in 2009, he moved to Germany to pursue his PhD at the University of Münster under the supervision of Prof. Armido Studer. After completion of his Ph.D. (2013), he worked as a Max-Planck postdoctoral research fellow in the laboratory of Prof. Herbert Waldmann at Max Planck Institute of Molecular Physiology, Dortmund (Germany, 2013-2016). Following a year-long stay (2016-2017) as a Team Leader in a reputed pharmaceutical company, Syngene International Limited, he decided to move back to academia. In May 2017, he joined the Indian Institute of Technology Jodhpur (India) as an Assistant Professor and was promoted to the post of Associate Professor in June 2022. His current research activities include study of novel activation modes and development of chemoselective and sustainable transformations towards the synthesis of biologically relevant and interesting molecular architectures.

In 2022, he was awarded the Thieme Chemistry Journals Award by the editorial boards of the journals SYNTHESIS, SYNLETT, and SYNFACTS. In the same year, he was also inducted as an Early Career Advisory Board (ECAB) Member of the Wiley-VCH Journal *ChemistrySelect*. In 2020, he became a lifetime Fellow of Indian Chemical Society (FICS). He is also a recipient of the Early Career Research Award (ECRA) from Science and Engineering Research Board (SERB), India (2018), and an Innovation in Science Pursuit for Inspired Research (INSPIRE) Faculty Award from the Department of Science & Technology (DST), India (2016).

INTERVIEW

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

Dr. S. Murarka The motivation of our research in organic synthesis and catalysis comes from the tremendous societal impact it holds on today's global problems of health, food, energy, and the environment. We are primarily focused on unraveling new activation modes of unsaturated π -bonds and unreactive C-H bonds, enabling us to forge chemical bonds in an unprecedented fashion. We utilize a chemical tool-box consisting of transition-metal catalysis, photocatalysis and radical chemistry to synthesize interesting molecular architectures, and perform late-stage functionalizations. All this is expected to facilitate drug discovery, materials science and agrochemical research.

SYNFORM *When did you get interested in synthesis?*

Dr. S. Murarka My initial interest in organic synthesis grew during my high school days. I was fascinated by the concept of chemical reactions and making new molecules. Organic chemistry seemed most exciting, logical and natural to me as I was able to understand the bond-breaking and bond-making phenomena. I must acknowledge the role of my chemistry instructor in igniting my interest in organic synthesis. I took no time to decide that I should pursue my undergraduate education in chemistry. Although I was studying different branches of chemistry along with mathematics and physics, I took a deep interest in organic chemistry and finally decided to pursue an M.Sc. with a major in organic chemistry. The courses in organic chemistry and the laboratory project on the synthesis and application of Morita-Baylis-Hillman (MBH) adducts during my M.Sc. further excited me, to the point where I decided to pursue doctoral research in organic and organometallic chemistry with Prof. Armido Studer at the Universi-

ty of Münster (Germany). Following my PhD, I did post-doc research with Prof. Herbert Waldmann at Max-Planck Dortmund (Germany), where I was involved in a highly interdisciplinary and collaborative research program focusing on the development of novel chemotypes to suppress oncogenic RAS signaling for the treatment of cancer. My PhD and post-doc research made me realize the potential of organic synthesis, which is not limited to making molecules, but has widespread utility in allied field of sciences.

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

Dr. S. Murarka In principle, organic synthesis is about making novel and interesting molecules through an innovative disconnection approach. Hence, development of efficient, green and sustainable synthetic methods will remain as the most sought-after area of research. The molecules that are being made by organic chemists have huge implications in the discovery and manufacturing of products that we encounter in our day-to-day lives, like medicines, materials, energy storage, agrochemicals, perfumes, polymers, food, etc. Accordingly, the true potential of organic chemistry will be unfolded

through endorsing interdisciplinary research and blurring cross-disciplinary boundaries. Discoveries and advances in research and development are more likely to happen at the borders between multiple scientific fields, which necessitates reinventing ourselves and engaging with researchers across the disciplines and sectors.

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

Dr. S. Murarka I started my independent career with a vision to develop a research program on cascade/domino/tandem annulations and direct C–H functionalizations utilizing base metal-catalyzed cross-couplings and photocatalysis as sustainable chemical tools (Figure 1). Cascade annulations allow rapid increment of molecular complexity leading to the synthesis of interesting molecular frameworks in an efficient fashion, and direct C–H functionalizations enable late-stage diversification of molecular scaffolds. In both these cases, our primary focus lies in the synthesis and late-stage functionalization of bioactive molecules, therapeutics and agrochemicals. On a mechanistic level, we are interested in the generation and study of reactive organic intermediates (car-

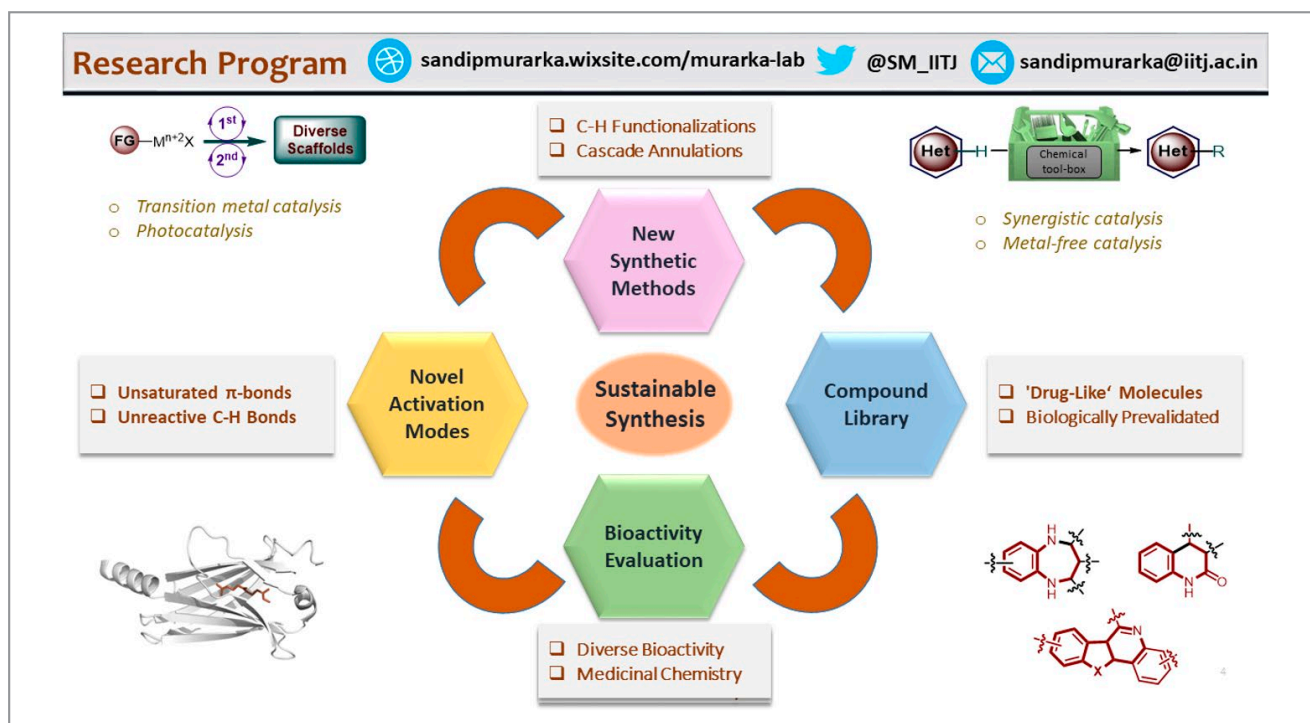


Figure 1 Ongoing research program

bocations, radicals, and carbenes) and electron-transfer processes in organic molecules through unique approaches. Since we aim to develop sustainable synthetic methods that work under amenable conditions, we utilized the synthetic potential of photoredox catalysis to generate structurally and electronically diverse alkyl radicals from *N*-(acyloxy)phthalimides (NHPI esters) under mild conditions and trigger those to forge a variety of carbon–carbon bonds through cascade annulations, leading to a plethora of highly substituted heterocyclic architectures. NHPI esters have emerged as a surrogate of alkyl halides and can easily be synthesized from carboxylic acid feedstock. They are predisposed to participate in single electron transfer (SET) processes, ultimately leading to the generation of alkyl radicals through reductive fragmentation and concomitant decarboxylation. We wrote the first concise (*Adv. Synth. Catal.* **2018**, 360, 1735; *Chem. Asian J.* **2021**, 16, 879) and comprehensive (*ACS Catal.* **2021**, 11, 1640) reviews on the diverse reactivity of NHPI esters and successfully synthesized alkylated chroman-4-ones (*Chem. Asian J.* **2020**, 15, 568), not so easily accessible *Z*-alkoxy-alkylidene succinimides (*Org. Chem. Front.* **2021**, 8, 2256), and alkylated indoles (*Chem. Commun.* **2021**, 57, 13130) through innovative radical cascade annulations involving NHPI esters under photoredox catalyzed conditions. Lately, we have also become interested

in the chemistry of diaryl iodonium reagents (DIARs) due to their ready availability, bench stability and low cost. We have successfully utilized DIARs as aryl cation equivalents under metal-free conditions to synthesize *S*-aryl dithiocarbamates (*Org. Lett.* **2021**, 23, 6401), and as aryl radical synthons under photoredox conditions to perform late-stage functionalization of quinoxalinones (*J. Org. Chem.* **2022**, 87, 10947). Currently, we are engaged in unraveling further applications of NHPI esters and DIARs in a diverse range of (non)photoinduced processes leading to the construction and functionalization of densely functionalized molecular frameworks.

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

Dr. S. Murarka At this early stage of my independent career, I feel that the ‘most awaited important scientific achievement’ is yet to arrive. Currently, I believe that the most impactful aspect of our research is about the approach we have adopted, which is basically about the development of sustainable methods with mechanistic rationale, and the synthesis of molecules of medicinal importance. In this way, we are able to amalgamate the fundamental understanding of a chemical transformation with potential applications. However, if I am pressed to pick one from my early career, that would be the development of a metal-free multi-component annulation between diaryliodonium salts, aliphatic amines, and carbon disulfide enabling access to *S*-aryl dithiocarbamates (*Org. Lett.* **2021**, 23, 6401). This methodology is scalable, exhibits broad scope, and most importantly, allows access to some of hitherto inaccessible dithiocarbamates (Figure 2). Gratifyingly, one of the *S*-aryl dithiocarbamates exhibited antiproliferative activity in cancer cells and affected tubulin dynamics by inducing microtubule bundling, which makes this class of compounds a promising scaffold for designing new anticancer drugs (*Bioorg. Med. Chem.* **2022**, 68, 116874).

S. Murarka



Figure 2 Graphical representation of the metal-free multi-component synthesis of *S*-aryl dithiocarbamates

Coming soon

— Literature Coverage

Palladium-Catalyzed *trans*-Hydroalkoxylation: Counter-intuitive Use of an Aryl Iodide Additive to Promote C–H Bond Formation

— Literature Coverage

S,O-Ligand Promoted *meta*-C–H Arylation of Anisole Derivatives via Palladium/Norbornene Catalysis

— Literature Coverage

Total Synthesis and Anti-inflammatory Activity of Stemoamide-Type Alkaloids Including Totally Substituted Butenolides and Pyrroles

Further highlights

Synthesis Review: The Properties, Synthesis, and Materials Applications of 1,4-Dithiins and Thianthrenes

(by S. I. Etkind, T. M. Swager)

Synlett Account: Unlocking Electrophilic *N*-Aryl Intermediates from Aryl Azides, Nitroarenes, and Aryl Amines in Cyclization–Migration Reactions

(by T. G. Driver)

Synfacts Synfact of the Month in category “Organo- and Biocatalysis”: Thioxanthone-Catalyzed Single-Step Synthesis of β - and γ -Amino Acid Derivatives

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