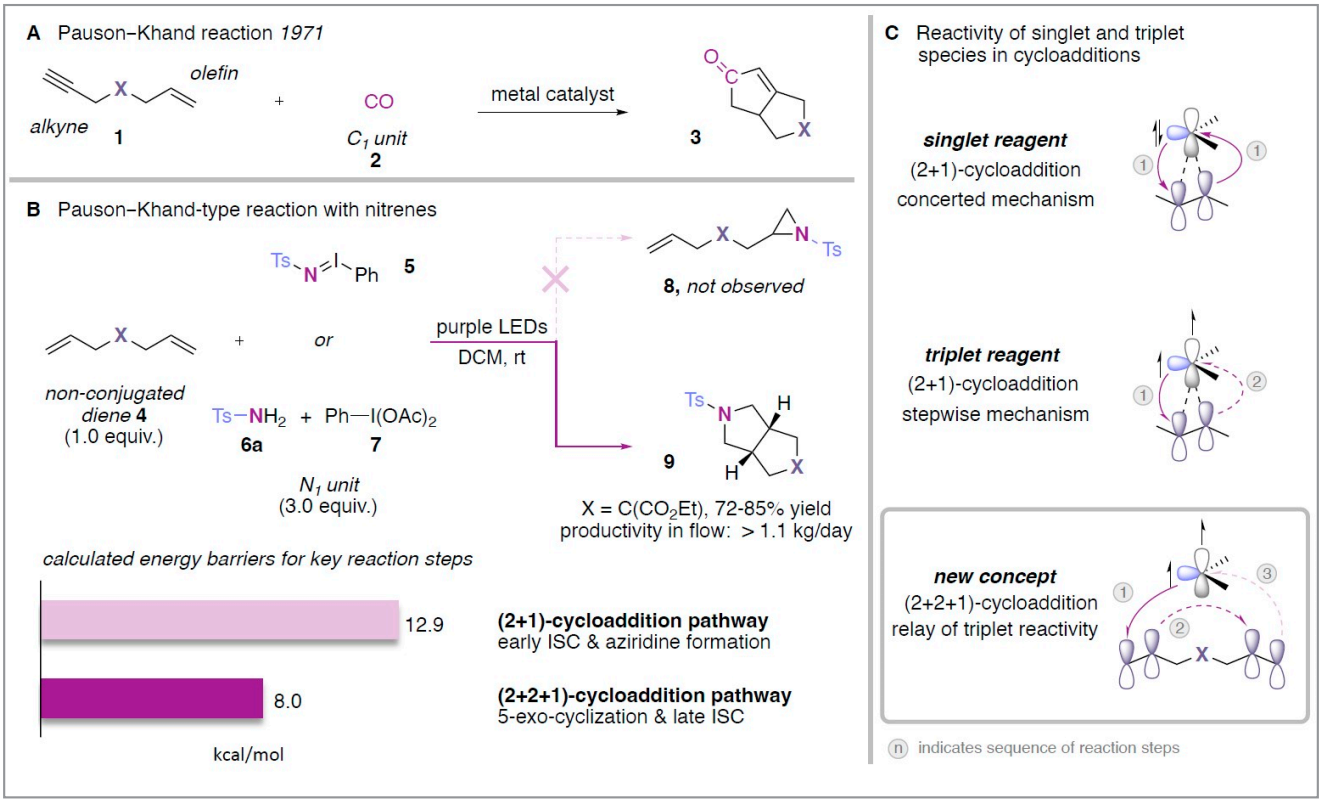
Photosensitization Enables Pauson–Khand-type Reactions with Nitrenes

Science **2024**, *383*, 498–503

Even 50 years after the landmark discovery of cobalt-catalyzed (2+2+1) cycloaddition reactions, the Pauson–Khand reaction remains one of the most synthetically intriguing among this type of processes. It features the reaction of an alkyne and an olefin with carbon monoxide to furnish cyclopentenones (Scheme 1A), and significant developments with regards to both unsaturated reaction partners and the catalyst were made. Nowadays, the Pauson–Khand reaction finds widespread applications, ranging from total synthesis towards applications in drug synthesis and bulk chemical synthesis. The most significant limitation of Pauson–Khand reactions, however, lies within the necessity to use carbon monoxide as a C_1 building block.

For the last few years, Professor Rene Koenigs' group at RWTH Aachen University (Germany) has been particularly interested in the development of metal-free carbene and nitrene chemistry, where photochemical or photocatalytic applications and spin-state-dependent reactivity are in the spotlight. Professor Koenigs said: "The spin state of carbene or nitrene reagents plays a key role in the reaction outcome of cycloaddition reactions; for example, singlet reagents react in a concerted, stereospecific cycloaddition, whereas triplet reagents react in a stepwise mechanism, which for example allows the development of stereoconvergent cyclopropanation reactions as recently described by our group."

Professor Koenigs went on to explain that when considering nitrene intermediates, the triplet spin state is often the preferred spin state and as such, nitrenes – in the absence of a stabilizing metal complex – commonly react on the triplet spin surface via initial formation of an initial triplet addi-

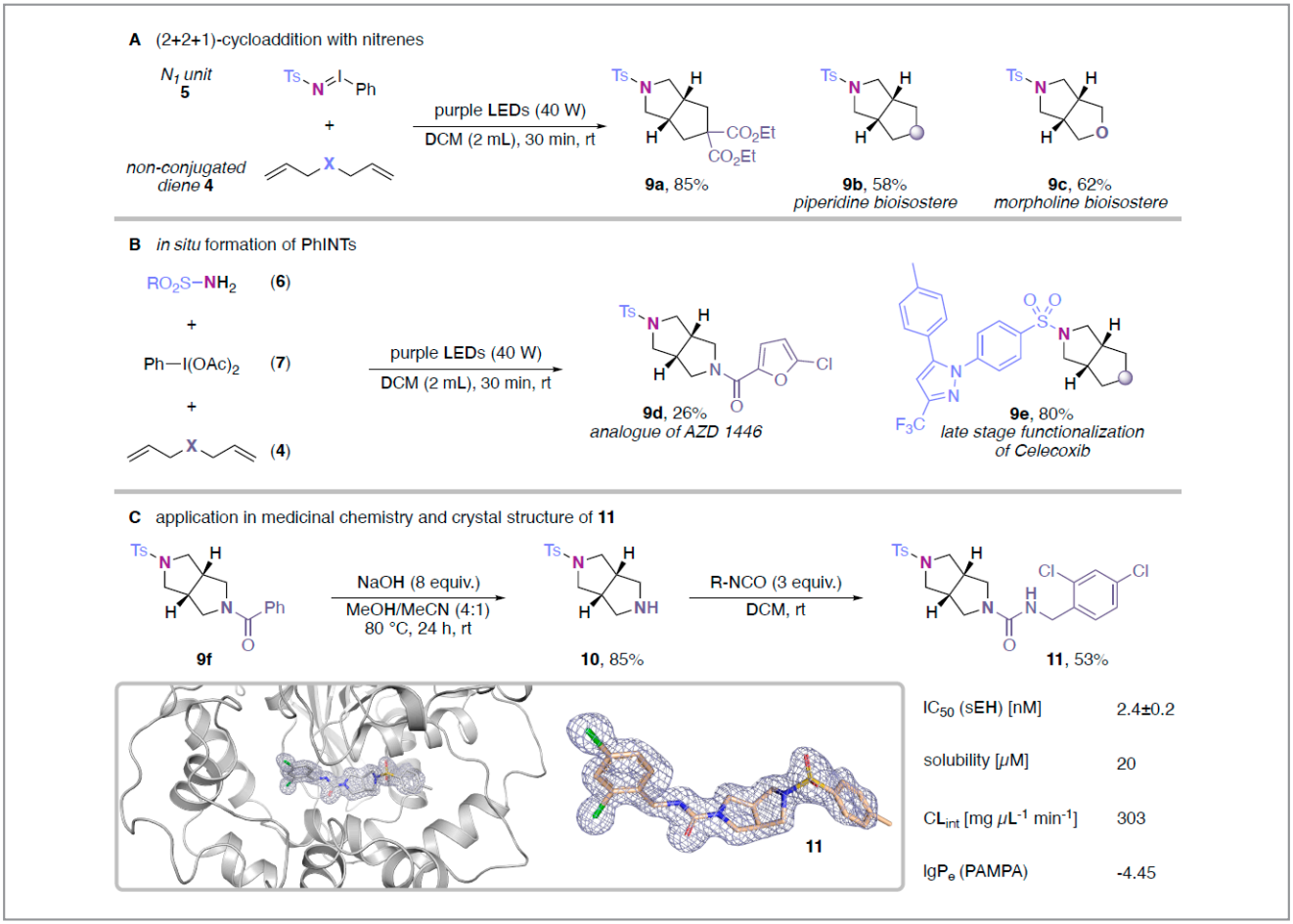


Scheme 1 Pauson–Khand reaction and Pauson–Khand-type reactions with nitrenes

  • Published online: April 15, 2024 • DOI: 10.1055/s-0040-1720630

tion product. To achieve cycloaddition reactivity, intersystem crossing from triplet to singlet spin surface is mandatory and must occur before the final bond/ring forming event. Professor Koenigs hypothesized that: "The triplet reactivity of the initial addition product can be used to forge a new C–C bond instead of intersystem crossing." Such a strategy thus relays the triplet reactivity, as he continued to explain: "A late intersystem crossing then sets the stage to forge a third bond-forming event and results in the product of a (2+2+1) cycloaddition reaction – or a Pauson–Khand-type reaction with a nitrene (Scheme 1B, 1C)."

When examining the reaction of a non-conjugated diene and an iminoiodinane, the Koenigs group indeed observed a high selectivity leading to a (2+2+1) cycloaddition product (Scheme 2A). Further simplification was achieved by the observation that iminoiodinane can be intermittently accessed under purple light irradiation (Scheme 2B). Professor Koenigs stated: "The reaction products are bicyclic bioisosteres of common saturated heterocycles such as piperidine, morpholine, and piperazine. The starting materials are really simple reagents: a non-conjugated diene, a sulfonamide and diacetoxy-iodobenzene." Following a collaborative research strategy, a research team with scientists from Enamine Ltd. (Ukraine), Kyiv Taras Shevchenko University (Ukraine), and Goethe University in Frankfurt/M. (Germany) was formed to translate this groundbreaking discovery to industrial scale and medicinal chemistry applications. "This is a really exciting discovery and it shortens synthesis routes from more than 5 steps to a single step," said co-author Dr. Sci. Pavel Mykhailiuk (Enamine Ltd.). Together with a team of researchers at Enamine Ltd., a flow synthesis was then achieved, which allows the synthesis of more than 1 kg of such bicycles per day. Ewgenji Proschak, from Goethe University, commented: "These are ideal bioisosteres for many applications in medicinal chemistry." Together with a team of researchers, a set of novel and highly potent inhibitors of soluble epoxide hydrolase were synthesized



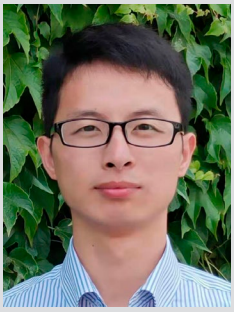
Scheme 2 (2+2+1)-Cycloaddition reactions with nitrenes towards application in medicinal chemistry

 Synform **2024/05**, A81–A85 • Published online: April 15, 2024 • DOI: 10.1055/s-0040-1720630

and tested in a typical medicinal chemistry screening setting (Scheme 2C).

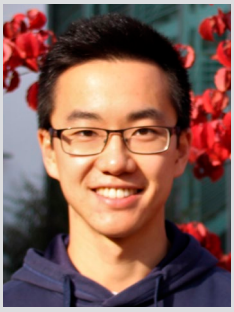
A combination of experimental and computational mechanistic analysis revealed that the initial hypothesis of an early intersystem crossing vs. late intersystem crossing is key to driving either conventional (2+1) or (2+2+1) cycloaddition chemistry. "Specifically, the barrier for an early intersystem crossing is simply unfavored and instead a 5-*exo*-cyclization reaction occurs and leads to the (2+2+1) reactivity. This concept opens up a plethora of new applications of advanced cycloaddition reactions and we are really excited about new developments in this area," concluded Professor Koenigs.

About the authors



Dr. F. Li

Fang Li obtained his B.A. in chemical engineering and technology from West Anhui University (P. R. of China) in 2012. He completed master's research on design, synthesis and characterization of cyclic conjugated molecules for optoelectronic nanomaterials with Prof. Shengxiong Xiao and earned an M.S. in 2016 from Shanghai Normal University (P. R. of China). He obtained his Ph.D. in organic chemistry in 2022 from RWTH University (Germany), working with Prof. Rene M. Koenigs. After a one-year postdoctoral stay at the RWTH University in 2023, he started his independent career at Shanghai Normal University. Recently, he has focused on molecular electronics and single-molecule electronics.

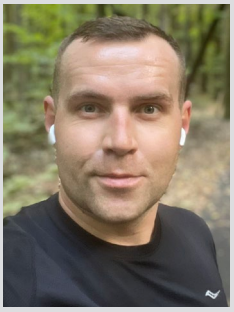


Dr. W. F. Zhu

Wenxin Felix Zhu received his B.Sc. and M.Sc. in chemistry from Goethe University of Frankfurt, Germany. He then joined the group of Prof. Eugen Proschak as a doctoral candidate, where his studies focused on the synthesis of bioactive heterocycles for pharmacological applications. He worked on target validation of ion channels as well as new chemical reactivities to assemble polycyclic heterocycles. In regard of the latter, he also completed a visiting stay in the laboratory of Prof. Rene Koenigs at RWTH Aachen (Germany) to study nitrene chemistry experimentally and computationally.

Dr. C. Empel

Claire Empel studied chemistry at the RWTH Aachen University (Germany) and the University of New South Wales (Sydney, Australia), and obtained her M.Sc. in 2020. In March 2020 she started her PhD in the group of Prof. Rene M. Koenigs, focusing on experimental and theoretical studies of carbene transfer reactions. She was initially funded by an RWTH Scholarship for Doctoral Students and since late 2020 by a Kekulé Scholarship from the Fonds der Chemischen Industrie and obtained her PhD in January 2023. She is now working as a PostDoc in the group of Prof. Rene M. Koenigs in collaboration with Prof. Debabrata Maiti (IIT Bombay, India), focusing on theoretical studies of metal-catalyzed C–H functionalization and light-mediated carbene and nitrene transfer reactions.



Dr. O. Datsenko

Oleksandr Datsenko was born in Ukraine. In 2006, he graduated from Taras Shevchenko National University of Kyiv (Ukraine) with a speciality in inorganic chemistry. Until 2012, he worked as a head of laboratory in the Ukrainian Organic Synthesis (UOS). During 2012–2015, he worked on a PhD project with Prof. Igor Komarov. In 2015, Oleksandr joined Enamine as a head of the photochemical laboratory. His research interests include photochemistry, 3D-shaped scaffolds and radical chemistry.

>>

  • Published online: April 15, 2024 • DOI: 10.1055/s-0040-1720630

Dr. A. Kumar

Adarsh Kumar was born and raised in India. He obtained his Ph.D. in 2018 at the CSIR-Institute of Microbial Technology, Chandigarh, India, under the mentorship of Dr. Karthikeyan Subramanian. His doctoral research focused on characterizing hypothetical essential proteins from *Mycobacterium tuberculosis* using structural biology and biophysical methods. Continuing his interest in mechanistic studies, he moved to The Florida State University, Tallahassee, Florida, USA, as a postdoctoral researcher, where his research focused on elucidating the mechanisms of enzymes involved in human DNA base excision repair pathways through time-resolved crystallography. In 2021, he joined The Structural Genomics Consortium, Frankfurt am Main, Germany, under the guidance of Prof. Dr. Stefan Knapp, where he is currently involved in structure-based drug discovery, with a particular emphasis on determining the structures of target–ligand complexes and conducting structure-based fragment screening to identify novel binding sites on the target proteins.

J.H.M. Ehrler

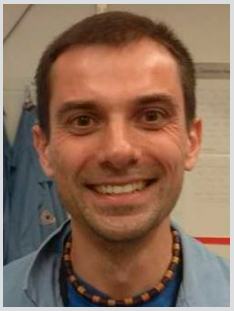
Johanna H. M. Ehrler received her B.Sc. and M.Sc. in chemistry from the Goethe University Frankfurt (Germany), where she studied photolabile protecting groups as well as proteins from antibiotic-resistant bacteria. She then joined the laboratory of Prof. Ewgenij Proschak as a Ph.D. student. Her doctoral research focuses on lipid signal transduction cascades along with G-protein-coupled receptors as therapeutic targets.

Dr. I. Atodiresei

Iuliana Atodiresei studied chemistry at the Al. I. Cuza University of Iasi, Romania and TU Braunschweig, Germany where she spent 9 months as a Socrates exchange student, performing research in the field of cross-conjugated compounds in the group of Professor H. Hopf. After obtaining her M.Sc. degree in 2001, she joined the group of Professor C. Bolm at the RWTH Aachen University, Germany where she carried out her doctoral studies in the field of asymmetric synthesis. In 2005 she joined the group of Professor G. Raabe, focusing on the determination of the absolute configuration of organic molecules by means of CD spectroscopy and theoretical investigations. In 2010 she joined the group of Prof. M. Rueping, widening her research interests and expanding her expertise towards X-ray crystal structure analysis. Currently, she is a senior scientist at the RWTH Aachen involved in the structure elucidation of organic molecules by spectroscopic, crystallographic, and theoretical means.

Prof. Dr. S. Knapp

Stefan Knapp studied chemistry at the University of Marburg (Germany) and the University of Illinois (USA). He received his Ph.D. in protein crystallography from the Karolinska Institute in Stockholm. He joined Pharmacia (Nerviano, Italy) in 1999 and left the company in 2004 to establish a research group at the Structural Genomics Consortium at the University of Oxford. From 2008 to 2015 he was Professor of Structural Biology at Oxford University (UK) and from 2012 to 2015 Director of Chemical Biology at the Target Discovery Institute at Oxford University. In 2015, he joined the University of Frankfurt as Professor of Pharmaceutical Chemistry. Since 2017, he is also the CSO of the SGC (Structure Genomics Consortium) node at Goethe University Frankfurt. His research interests are the elucidation of molecular/structural mechanisms of kinase regulation using high-resolution structures, the design of selective kinase inhibitors, and the inhibition of protein interaction domains such as bromodomains, which are the main readers of the epigenetic acetylation code, and E3 ubiquitylating ligases.



Dr. P.K. Mykhailiuk

Pavel K. Mykhailiuk was born in Kerch, Ukraine. In 2008 he received a Ph.D. in biochemistry from the Technical University of Karlsruhe (KIT, Germany) with Prof. Anne Ulrich, and a Ph.D. in organic chemistry from Taras Shevchenko National University of Kyiv (Ukraine) with Prof. Igor Komarov. In 2009 he returned to Ukraine and joined Enamine company, where he is currently involved in the discovery of novel building blocks for medicinal chemistry and agrochemistry. During his stay at Enamine, he

  • Published online: April 15, 2024 • DOI: 10.1055/s-0040-1720630

visited the groups of Prof. Thorsten Bach (TUM, Germany), Prof. Janine Cossy (ESPCI, France), and Prof. Phil Baran (Scripps, U.S.) as a research scientist to deepen his knowledge of organic chemistry. His research interests include fluoroorganic chemistry, diazo compounds, photochemistry, and bioisosteric replacements.

Prof. E. Proschak

Ewgenij Proschak is a Professor of Drug Design at the Institute of Pharmaceutical Chemistry at the Goethe University (GU) of Frankfurt (Germany). After his doctoral and postdoctoral studies at Goethe University, he became an Independent Group Leader at the Lipid Signaling Research Center (LIFF) in Frankfurt. The German Research Council (DFG) awarded him a Heisenberg Professorship, which was tenured by the GU. He has worked on hit identification and hit-to-lead optimization for fatty acid mimetics targeting enzymes, nuclear receptors and G-protein coupled receptors. His current research interests are the design and synthesis of multitarget drugs for the treatment of inflammatory conditions and metabolic syndrome.

Prof. R.M. Koenigs

Rene M. Koenigs obtained his PhD in 2011 from RWTH Aachen University (Germany) under the guidance of Prof. Magnus Rueping. He subsequently moved to Grünenthal GmbH (Germany), working as a medicinal chemist on GPCR and ion channel targets in pain and inflammation research under the supervision of Dr. Paul Ratcliffe and Dr. Henning Steinhagen. In 2015, he was appointed as junior professor at RWTH Aachen University and was promoted to full professor in 2022. His research interests focus on carbene and nitrene chemistry, photochemistry and photocatalysis, continuous-flow chemistry and fluorine chemistry.

  • Published online: April 15, 2024 • DOI: 10.1055/s-0040-1720630