

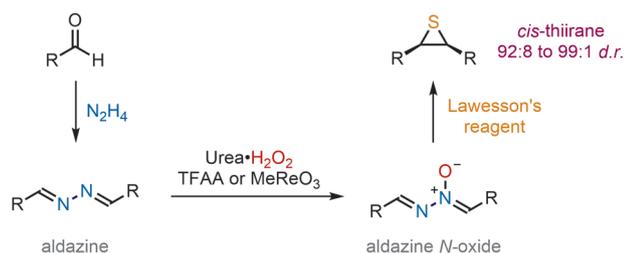
Synform

People, Trends and Views in Chemical Synthesis

2023/02

Synthesis of *cis*-Thiiranes as Diastereo-selective Access to Epoxide Congeners via 4π -Electrocyclization of Thiocarbonyl Ylide

Highlighted article by S.-m. Song, J. Jin, J.-H. Choi, W.-J. Chung



Contact

Your opinion about Synform is welcome,
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Dear Readers,

This is the first editorial I am writing since moving to Brussels, and I have to say that this February issue of SYNFORM looks a lot like my life: very diverse, vibrant and articulated!

The opening article is an interview with a new member of the Thieme Chemistry family, specifically Professor Tiansheng Mei (Shanghai Institute of Organic Chemistry, P. R. of China), who joined the Editorial Board of *SynOpen* on 1 October 2022. The groups of J.-H. Choi and W.-J. Chung (Republic of Korea) are protagonists of the first Literature Coverage article, covering the innovative and diastereoselective synthesis of cis-thiiranes via 4π -electrocyclization of thiocarbonyl ylides. The third article – a new Name Reaction Biography authored by David Lewis – takes us back in time to the discovery of aryldiazonium ions and their reactivity, through an intriguing perspective linking organic chemistry and... beer! The highly poisonous and structurally fascinating tetrodotoxin is the subject of the next Literature Coverage article, focussing on the new synthetic approach to the puffer fish toxin developed by the group of D. Trauner (USA), who also happens to be an Editor of SYNFACTS. The fifth and closing article is another interview, this time a Young Career Focus with the 2022 Thieme Chemistry Journals Awardee Jaideep Saha (India), who answers our questions about his group's research interests and perspectives.

Enjoy your reading!



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Contact

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

Editorial Board Focus: Professor Tiansheng Mei (Shanghai Institute of Organic Chemistry, P. R. of China)

Background and Purpose. From time to time, SYNFORM portraits Thieme Chemistry Editorial Board or Editorial Advisory Board members who answer several questions regarding their research interests and revealing their impressions and views on the developments in organic chemistry as a general research field. This Editorial Board Focus presents Professor Tiansheng Mei (Shanghai Institute of Organic Chemistry, P. R. of China) who joined the Editorial Board of *SynOpen* with effect of 1 October 2022.

Biographical Sketch



Prof. T. Mei

Tiansheng Mei received his B.S. degree in chemistry from Lanzhou University (Beijing, P. R. of China) in 2001. For the following four years he worked at Lanzhou University as Research Associate before joining the group Yin-Quan Yu at Brandeis University (USA) for his M.S. degree which he obtained in 2007. Together with the Yu group he then moved to The Scripps Research Institute in La Jolla (USA) and received his Ph.D. in 2012. After a postdoctoral stay from 2012–2014 in the group of Matthew Sigman at the University of Utah (USA) he returned to China and was appointed as Professor at the Shanghai Institute of Organic Chemistry at the end of 2014. His main research focus is on transition-metal-catalyzed electrosynthesis reactions including C–H and C–X functionalization, asymmetric synthesis, and the activation of small molecules. He has published more than 60 papers with over 9000 citations. He is the recipient of numerous awards and honors for his work in organometallic electrochemical synthesis, including the Thieme Chemistry Journals Award in 2016, the Bayer Investigator in 2020, and the Distinguished Lectureship Award of the CSJ Asian International Symposium in 2020. As of October 1, 2022, he became an Editorial Board member of *SynOpen*.

INTERVIEW

SYNFORM Please comment on your role as a member of the Editorial Board of *SynOpen*.

Prof. T. Mei I am responsible for taking part in developing topics, inviting manuscripts for the journal, managing individual manuscripts, and overseeing outreach activities in East Asia.

SYNFORM How do you describe the value of an open access resource such as *SynOpen* to the chemistry community?

Prof. T. Mei As Prof. Laurence M. Harwood said, *SynOpen* has a strap line of “**fast, fair, and flexible**”. I totally agree with him. Select Crowd Review has allowed for the manuscripts to be reviewed not only quickly, but and also fairly. As a wholly online journal, *SynOpen* is flexible in the type, format, and content of articles, including Letters, Papers, Reviews, Short Reviews, Graphical Reviews, Practical Synthetic Procedures, and Spotlights.

SYNFORM What is the focus of your current research activities?

Prof. T. Mei My current research activities focus on transition-metal-catalyzed electrosynthesis reactions including C–H and C–X functionalization, asymmetric synthesis, and the activation of small molecules.

SYNFORM You are a leading researcher with regard to electrosynthesis reactions and transformations using transition metals. Could you tell us more about how important you perceive this particular topic to be?

Prof. T. Mei Electrochemical synthesis is not only a sustainable alternative compared to conventional approaches via replacing stoichiometric chemical oxidants or reductants in organic synthesis, but also it shows huge potential to adjust and control the reactions for its tunability of the potential and electric current. The merger of transition-metal catalysis and electrochemistry provides a particularly promising means to realize high chemoselectivity, regioselectivity, and stereoselectivity within an electrochemical process. Three specific advantages for employing transition metals as molecular electrocatalysts are: (1) The redox potential of the transition-metal catalyst may be tuned by ligands; (2) Modification of the ligand can dictate the reaction stereoselectivity (and chemoselectivity and regioselectivity); and (3) Well-established metal-catalyzed methodologies provide a rigorous foundation for the development of electrochemical variants.



Synthesis of *cis*-Thiiranes as Diastereoselective Access to Epoxide Congeners via 4π -Electrocyclization of Thiocarbonyl Ylides

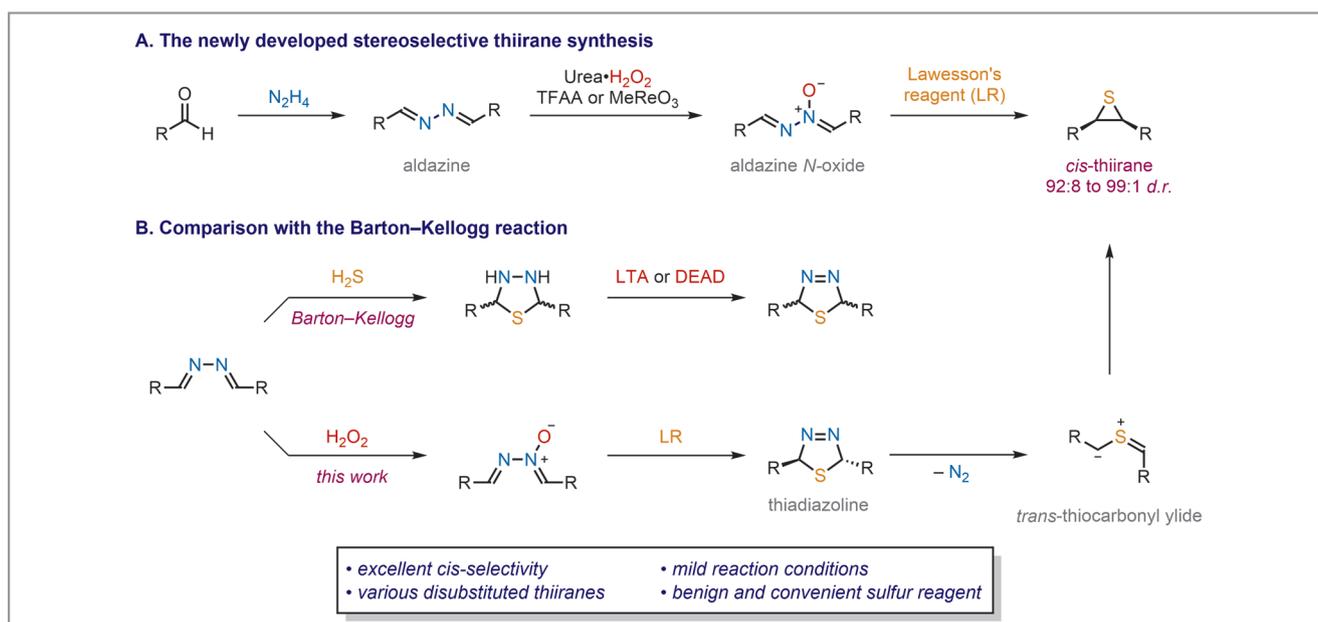
Nat. Commun. **2022**, *13*, 4818

Thiirane can be regarded as a cousin of a much more well-established congener, oxirane. However, while a myriad of synthetic methods – including enantioselective variants – have been extensively developed for oxiranes, thiirane synthesis is considerably underdeveloped, despite the structural similarity and the potential synthetic utility. “All four stereoisomers of stilbene oxide can be easily prepared and are even commercially available. In contrast, few synthetic methods are known for stilbene sulfides, and the processes typically employ stilbene oxides as the precursors,” said Professor Won-jin Chung from Gwangju Institute of Science and Technology (GIST, Republic of Korea). He continued: “In fact, thiiranes are most commonly prepared from the corresponding oxiranes via chalcogen exchange with thiocyanate or thiourea as sulfuring reagents. Stereoselective thiirane synthesis is an even more challenging task. Although a few notable examples including asymmetric catalysis have appeared recently, the reaction type and the substrate scope are still very limited.”

The group of Professor Chung has been intrigued by the unique structure-reorganizing characteristics of 1,2-diazines.

“For instance, we serendipitously discovered an unusual ring-contraction of electrophilically activated phthalazines, which are a kind of cyclic 1,2-diazine (*Synthesis* **2021**, *53*, 1760–1770),” explained Professor Chung. He added: “Then, as a continuation of our research program, acyclic 1,2-diazines such as aldazine derivatives were examined. While conducting exploratory experimentations, i.e., heuristic survey of various electrophiles, thiirane was obtained unexpectedly upon treatment of aldazine *N*-oxide with Lawesson’s reagent (Scheme 1A). We quickly realized that this kind of disubstituted thiirane is not easily accessible in a stereo-defined form, and thus we were pleased to see the outstanding *cis*-diastereoselectivities, as well as high chemical yields featured by our reactions with a wide range of diaryl substrates.”

The group hypothesized the intermediacy of *trans*-thiocarbonyl ylide which could be generated from putative *trans*-thiadiazoline. “Our newly developed process resembles the classic Barton–Kellogg reaction (Scheme 1B), in which sulfur is introduced first using hydrogen sulfide to form a fully saturated heterocyclic intermediate, and then the nitrogens are



Scheme 1 Title reaction discovery and comparison with the precedent

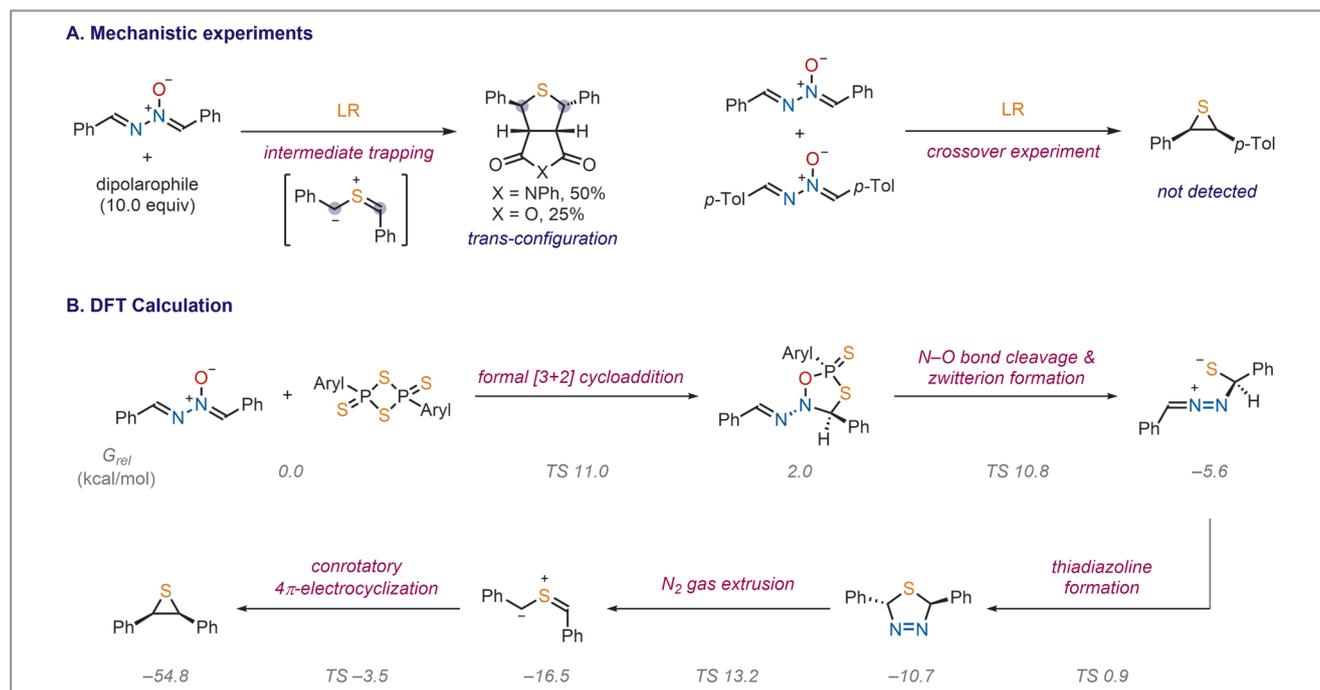
oxidized under harsh reaction conditions with toxic, and not exactly pleasant, reagents such as lead tetraacetate or DEAD,” remarked Professor Chung. He continued: “In contrast, our reaction sequence is reversed. The nitrogen part is pre-oxidized prior to the sulfuration, which – we believe – allows the use of a much more convenient, less toxic oxidant and sulfuring reagent. Furthermore, the exceptional diastereoselectivity is also a notable advantage that cannot be obtained from the Barton–Kellogg reaction.”

The key aspects of the reaction mechanism were elucidated by mechanistic experiments (Scheme 2A). “The putative thiocarbonyl ylide was successfully trapped by the dipolarophile to give the corresponding [3+2] cycloadduct, which clearly showed the *trans*-configuration around the sulfur. In addition, from a crossover experiment with a mixture of two different aldazine *N*-oxides, the aryl group scrambling was not detected at all, demonstrating the intramolecular nature of the thiirane formation,” explained Professor Chung. Then, through a collaboration with Professor Jun-Ho Choi at GIST, the DFT calculation was conducted to support the group’s proposal (Scheme 2B). Professor Chung said: “It was suggested that the processes toward the thiadiazoline formation take place on one side of the flat *E,E*-aldazine *N*-oxide, which should be responsible for the high stereospecificity. Then, the stereospecific nitrogen extrusion to *trans*-thiocarbonyl ylide

and the subsequent conrotatory 4 π -electrocyclization furnish the observed *cis*-disubstituted thiirane product.”

“Our work constitutes a rare example of stereoselective thiirane synthesis, through which an array of thermally stable *cis*-diaryl thiiranes became available,” said Professor Chung, continuing: “Currently, we are trying to expand the reaction scope to the *trans*-diastereomers as well as unsymmetrical structures. Furthermore, we are curious to find out whether other elements such as selenium-, nitrogen-, and carbon-containing moieties could be incorporated through similar processes.” Professor Chung concluded: “Eventually, we hope to develop a general synthetic platform for three-membered heterocycles utilizing azines and azine *N*-oxides.”

Matters female



About the authors



SM Song

Su-min Song received his MS degree from Gwangju Institute of Science and Technology (GIST, South Korea) in 2018 under the supervision of Prof. Won-jin Chung. He is continuing his PhD studies in the same research group. His research interests include the synthetic utilization of unusual reactivity of organonitrogen compounds and the development of stereoselective heterocycle synthesis.



J Jin

Jaeseong Jin obtained his B.S. degree in chemistry from Gwangju Institute of Science and Technology (GIST, South Korea) in 2016. After receiving his MS degree in organic chemistry from GIST under the supervision of Prof. Won-jin Chung in 2018, he continued his PhD studies in the same group. His research interests include the development of new synthetic methods for halogenated compounds and stereoselective synthesis of heterocycles.



Prof. JH Choi

Jun-Ho Choi has been on the faculty of Gwangju Institute of Science and Technology (South Korea) since 2018. He received his B.S., M.S., and Ph.D. degrees in chemistry from Seoul National University (South Korea) in 1990, 1992 and 1996, and worked as a research professor at the IBS Center for Molecular Spectroscopy and Dynamics (South Korea) from 2014 to 2018. He is a computational chemist, using DFT calculation, MD simulation and graph theory to explore molecular systems. His main research interests are chemical reaction mechanism prediction, computational spectroscopy, computer-aided molecular design and water structure and dynamics in solutions.



Prof. WJ Chung

Won-jin Chung received his B.S. degree from Korea Advanced Institute of Science and Technology (South Korea) in 2002 and his Ph.D. from University of Illinois at Urbana-Champaign (USA) under the supervision of Prof. Scott E. Denmark in 2008. After conducting postdoctoral studies with Prof. Christopher D. Vanderwal at the University of California, Irvine (USA), Won-jin began his independent career at Gwangju Institute of Science and Technology (South Korea) in 2014. His research group has been investigating various aspects of halogenations and molecular reorganizations of 1,2-diazines.

The Griess, Sandmeyer, and Pschorr Reactions: Arenediazonium Ions and Copper (and Beer)

It is often said in jest that there appears to be a natural affinity between organic chemists and beer. This is even more apparent in two of the name reactions in this Name Reaction Biography.

Peter Griess and Aryldiazonium Ions

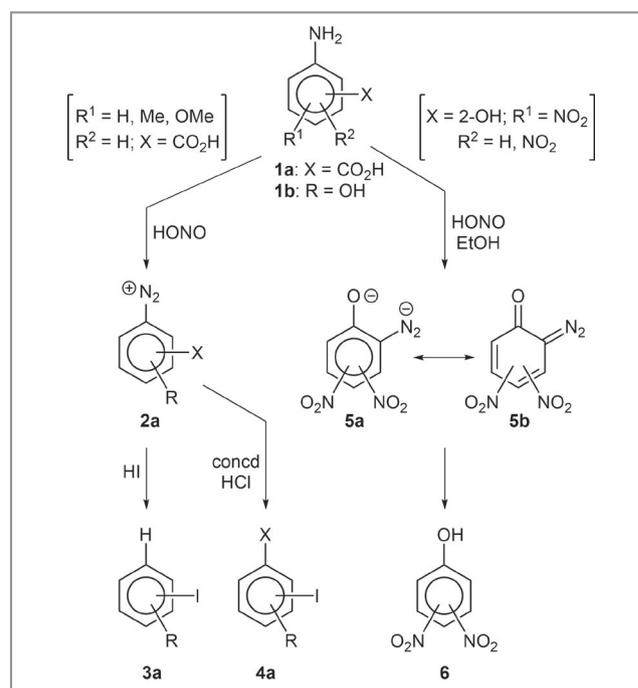
The aryldiazonium ions were discovered in 1858 by Johann Peter Griess, FRS,^{1a} a German-born British brewer working for Samuel Allsop & Sons in Burton-on-Trent, and the Pschorr reaction is named for its discoverer, Robert Franz Pschorr,^{1b} the fourth son of Georg Pschorr, Jr., the owner of the Hacker-Pschorr brewery in Munich.



Chemists connected to beer: (top) Johann Peter Griess (1829–1888) and (bottom) Robert Franz Pschorr (1868–1930). Their associated beverages are shown to their right.

Griess was born in the small town of Kirchhosbach, near Waldkappel in northern Hesse, and educated at a private agricultural college. However, he was not interested in an agricultural career, so after his graduation, he spent about three years in the Hessian cavalry. In 1851 he left the military for the University of Jena. In 1852, he transferred to Marburg, where he came under the influence of Herman Kolbe. He was a somewhat rebellious student—he served three terms in the *Karzer* (the student “prison,” or detention room)—and at one point he was banned from the city for a year. His student record meant that it required the recommendation of Kolbe for him to be hired by the Oehler chemical factory in Offenbach. In 1857, the factory burned down, and Griess returned to Marburg to work with Kolbe. His discovery of the diazonium salts in 1858² prompted Hofmann to invite him to the Royal College of Chemistry in London. In 1862, Griess left London for Burton-on-Trent, where he became the chemist at the Samuel Allsop & Sons brewery, where he worked until his retirement.

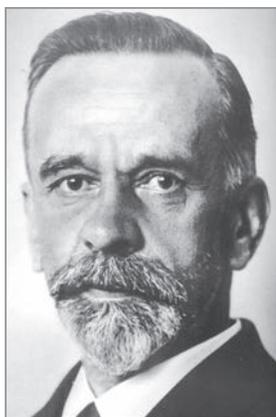
Griess' main chemical duties were as a brewer, and he was prohibited from disclosing his results, which were kept as



Scheme 1 Peter Griess' work with diazonium ions

trade secrets. However, in addition to his brewing duties, he was permitted to carry out research in organic chemistry that he was permitted to publish. Between 1859 and 1860, Griess had published three papers describing new compounds, diazonium salts that he made by treating aromatic amines with nitrous acid or N_2O_3 .³ His earliest results are summarized in Scheme 1. The coupling of an arenediazonium ion with an electron-rich aromatic compound—the Griess reaction—gives colored azo dyes that can be used as a colorimetric method for the determination of nitrite.⁴

Traugott Sandmeyer and His Eponymous Reaction



Traugott Sandmeyer
(1854–1922)

Traugott Sandmeyer⁵ was the youngest of seven children born to Melchior Sandmeyer, the Swiss educator, editor and author. At the time of his son's birth, he was teaching natural history and agriculture at the Wettingen Seminar (Teacher's College) in Seengen, in the Swiss Canton of Aargau. Just the day after Sandmeyer was born, his father died, at the age of only 41 years, of what is described as an incurable, chronic, typhoid eye disease. After the death of her husband, Sandmeyer's mother, Margarethe

Carolina (née Martin), moved to Aarau, the capital of the Canton, with her children. For the three years before her marriage, she had been a teacher at the top girls' school in Sofingen, in North Rhine-Westphalia (Nordrein-Westfalen, Germany) and

after she became a widow, she was appointed to the 5th and 6th grades of the girls' school in Aarau.

Sandmeyer attended the community and district school in Aarau. Reading scientific works from his father's library led to him developing a fondness for precision-engineered physical apparatus. Instead of proceeding to the Canton School after his graduation from school, he decided to take up the profession of precision mechanic. He spent the next three years as an apprentice in the precision engineering and optical workshops of J. F. Meyer in Zurich, following this with an additional year of residency.

For a time, he had to stop working due to poor health, so he set up a small workshop in his home. While delivering apparatus to the analytical and technical-chemical laboratory of the Federal Polytechnic, he had become acquainted with the professors there, especially Victor Meyer, and had become the close friend of Meyer's student, J. Gustav Schmidt, of eponymous condensation fame.⁶

Meyer arranged Sandmeyer's appointment to the position of permanent Lecturer Assistant at the Federal Polytechnic, despite him being self-taught in chemistry and lacking either a formal education or a university degree. Sandmeyer took advantage of this opportunity to acquire a thorough knowledge of inorganic and organic chemistry, as well as to carry out independent scientific research which he published in the *Berichte*.⁷ In 1885, he followed Victor Meyer to Göttingen, but after the summer semester he returned to Zurich, where he joined Arthur Rudolf Hantzsch, Meyer's successor. After working in Hantzsch's laboratory for three years, Sandmeyer moved from academia to industry.

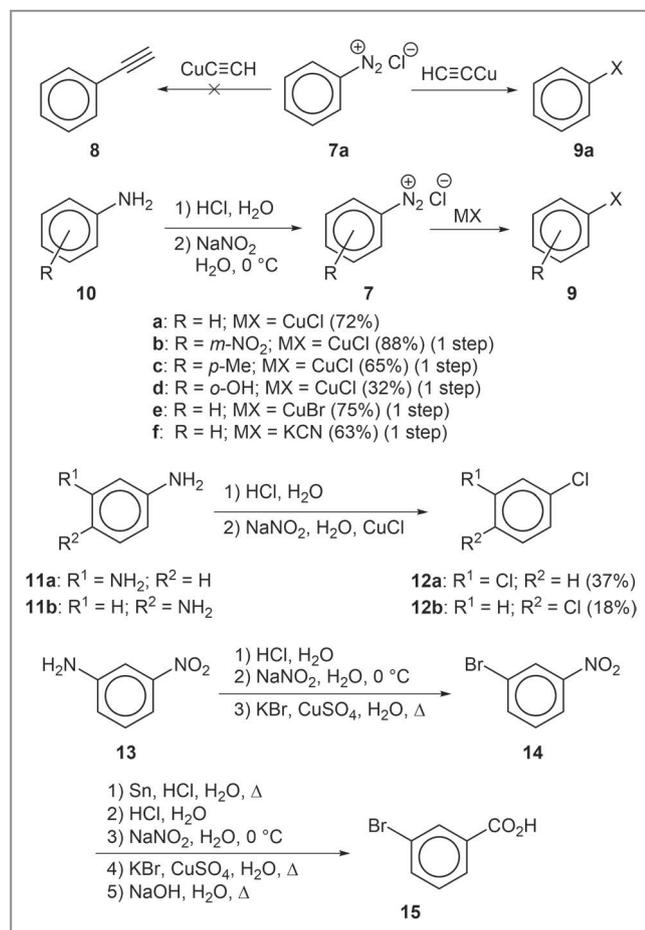
In 1888, he received offers from three coal-tar paint factories and chose to accept the offer from Johann Rudolf Geigy & Cie. in Basel, where J. R. Geigy-Merian had built a dyeworks in 1857. This company evolved, first by the merger with CIBA



Left to right: Victor Meyer (1848–1997), Arthur Rudolf Hantzsch (1857–1935), Johann Rudolf Geigy-Merian (1830–1917)

to form Ciba-Geigy, and then by the merger with Sandoz to become the Swiss pharmaceutical giant, Novartis. In part, Sandmeyer's decision was driven by what he saw as the opportunity to move into the field of technology. He eventually rose to become a Director of the company.

Sandmeyer's first publication was on the topic of synthetic thiophene, with Meyer as the lead author.⁷ He published two single-author papers in 1884,⁸ and two more in 1885.⁹ These papers give experimental conditions for carrying out the reaction that now bears his name.¹⁰ In the paper where he first disclosed the discovery of the reaction, he was attempting to couple copper(I) acetylide with phenyldiazonium chloride (**7a**) to give phenylacetylene (**8**) in a reaction analogous to the Glaser coupling;¹¹ he obtained chlorobenzene (**9a**) instead (Scheme 2). Early on, Sandmeyer pre-formed the aryldiazonium salt at low temperature, and then undertook its reaction with copper(I) salts.^{8a} He subsequently carried out the reac-



Scheme 2 Representative examples of reactions reported by Sandmeyer in 1884 and 1885

tions by adding a solution of sodium nitrite to an acid solution of the aromatic amine and the copper(I) salt at or above room temperature. Representative results from these experiments are summarized in Scheme 2. Sandmeyer proposed the model in Figure 1^{8a} to account for the formation of the product. In 1887, Sandmeyer reported the conversion of arylamines to nitroarenes by means of copper(I) nitrite.¹²

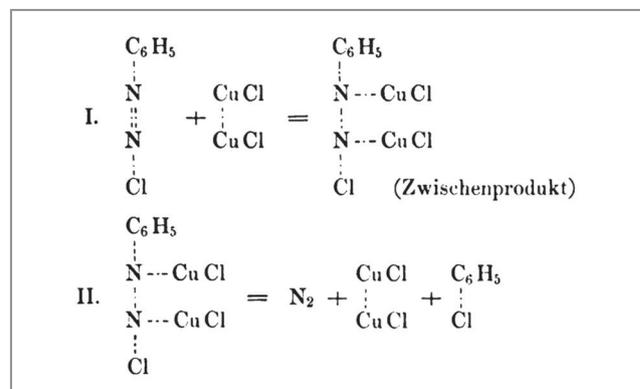
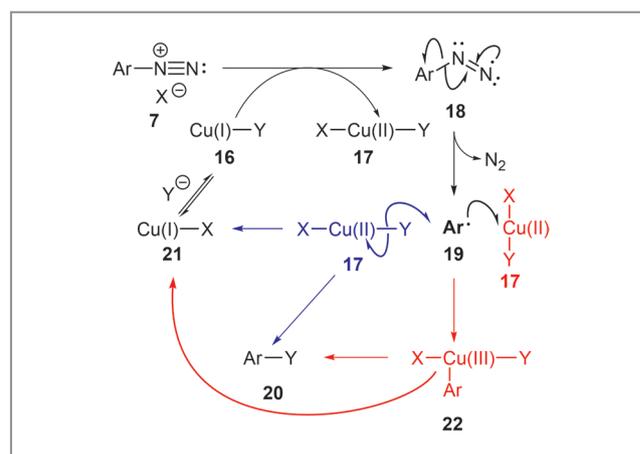


Figure 1 Sandmeyer's model for the displacement of the diazonium ion by the copper salt

Pfeil and Velten reported the involvement of free radicals in the mechanism of the Sandmeyer reaction in 1949.¹³ Additional evidence was provided in 1957 by American chemist Jay Kochi.¹⁴ The mechanism is now believed to proceed through aryl radicals derived by one-electron reduction of the arenediazonium ion **7** by the copper(I) salt **16**, giving the copper(II) salt **17** and the arenediazonium radical **18**, which loses nitrogen to give the key aryl radical **19** (Scheme 3).¹⁵



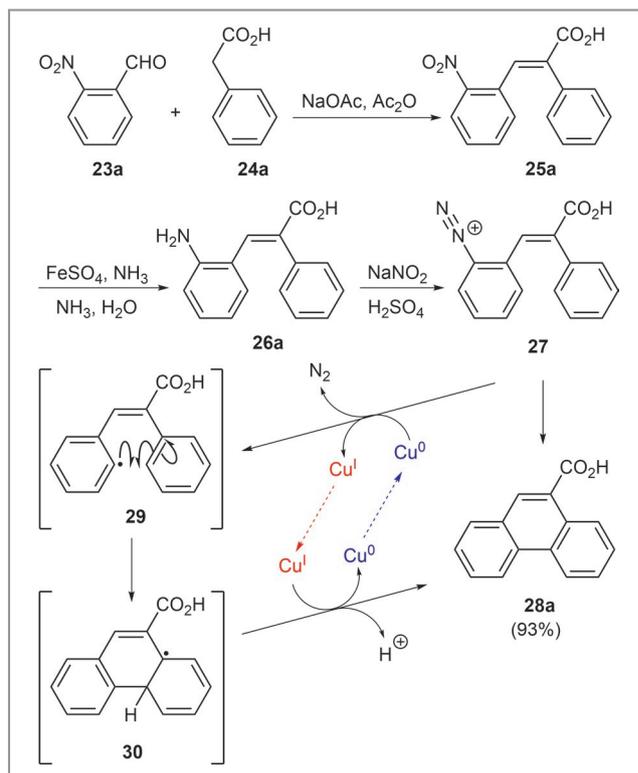
Scheme 3 The mechanism of the Sandmeyer reaction

The direct halogen atom transfer to this radical by **17** (shown in blue) gives the product **20** and copper(I) salt **21** that can be converted back into **16**. The alternative pathway, in red, involves the formation of copper(III) intermediate **22**, which undergoes reductive elimination to **20** and **21**.

The Pschorr Reaction¹⁶

It did not take long for the use of copper as a catalyst in other reactions of aryldiazonium ions to emerge. In 1896, German chemist Robert Pschorr reported a cyclization of *o*-substituted aryldiazonium ions in the presence of copper metal (Scheme 4).¹⁷ The starting α -phenyl-*o*-aminocinnamic acid (**25**) was obtained by the Perkin reaction¹⁸ of *o*-nitrobenzaldehyde (**23**) and phenylacetic acid (**24**), followed by reduction to the amine **26**. Pschorr carried out the diazotization to give the arenediazonium ion **27**. The reaction of **27** with Gattermann copper paste,¹⁹ a finely divided form of the metal produced by the reduction of copper(II) sulfate with zinc dust, resulted in loss of nitrogen to give phenanthrene-9-carboxylic acid (**28**). As shown in Scheme 4, the reaction may proceed by single-electron reduction of **27** to give the aryl radical **29**. Cyclization of **29** leads to the cyclized radical **30**, which undergoes oxidation by copper(I) and loss of a proton to give phenanthrene-9-carboxylic acid (**28**).

Robert Pschorr^{1b} was born in Munich in 1868 as the youngest of four sons of Georg Pschorr, Jr. (1830–1894), the owner of the important Hacker–Pschorr brewery. He studied chemistry at the Ludwig-Maximilians-Universität in Munich and in 1889 he was admitted to the Corps Franconia in Munich, a student fraternity founded in 1836. He later studied in Zurich, Jena and Berlin. He received his Dr. phil from Jena on September 8, 1894, with a dissertation, *Ueber einige neue Derivate des 1-Phenyl-3-methylpyrazolons und Antipyryns*,^{1b} under the direction of Ludwig Knorr. In his doctoral thesis, Pschorr dealt



Scheme 4 The Pschorr reaction to give a phenanthrene derivative

with heterocycles, specifically the pyrazoles, and with opium alkaloids.

In 1896, Pschorr suspended his academic work, and took a world tour with his fellow student, Herbert von Meister (1866–1919). Von Meister had also received his Ph.D. at Jena under Knorr in 1894, and eventually became Chairman of the Board of Farbwerke vorm. Meister Lucius & Bruning AG (later Farbwerk Hoechst AG, which became a unit of I. G. Farben AG).



The four Pschorr brothers and their wives, with Robert and Tilla on the left

After his return, Pschorr found the opportunity for independent research in Emil Fischer's laboratory in Berlin and resumed his experimental work. In 1899, he earned his Habilitation in Berlin. In April the same year he married Otilie (Tilla) Scherer. The couple had three children.

From April 1914, Pschorr was a professor of organic chemistry at the Technical University of Charlottenburg, succeeding Carl Liebermann. Shortly after the start of the First World War, he was commissioned as a reserve captain of the Royal Bavarian 1st Field Artillery Regiment "Prinzregent Luitpold". He moved as head of the 4th Infantry Ammunition Column from III Royal Bavarian Army Corps into the field. Promoted to major on July 8, 1915, he ended his four years of military service as Head of the Fliegerabwehr-Schule (Anti-Aircraft School); among other awards, he received the Iron Cross, 1st class. After the war, Pschorr returned to Charlottenburg, being elected Dean in 1919, and Rector in 1920.

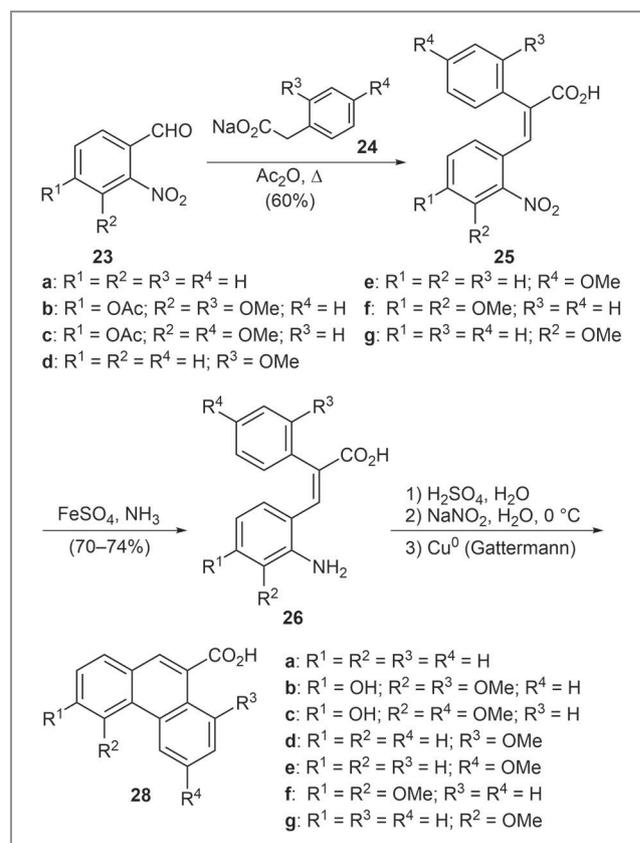
The war had reduced the German population to penury, and Pschorr well knew the economic hardship of students returning to their homes after their years of military service. He had means, so he did what he could to mitigate the situation by subsidizing the fees they had to pay. His philanthropy extended to providing financial aid to many needy academics. Ultimately, thousands of students and academics benefited from his beneficence. The students showed their gratitude by creating the Robert Pschorr medallion. His generosity with both his time and his money to the welfare institutions of the university continued until the end of his life.

His many official and honorary obligations took up most of his work in the last ten years of his life. Still, he remained a fully active scientist—his last work in the *Berichte* appeared in 1929 on the synthesis of apomorphine dimethyl ether. His influence on the scientific productivity of the Technical University of Berlin, which he headed, lasted well after his death.^{1b}

Pschorr was well known for his skills as a manager, and this made him sought after as an advisor by a number of technical companies, such as B. Riebeck-Montan. He was also held in high esteem by his colleagues and was repeatedly elected to the University senate from Chemistry and Metallurgy. In 1929, he was elected president of the Märkischer section of the Association of German Chemists in Berlin. He was a member of the Board of Pschorrbräu AG in Munich.

Pschorr was a close maternal cousin of the composer Richard Strauss, and he also inherited a rich musical talent. He was a master of the piano and violin, composed songs for children and marches for his field comrades, and as a conductor of an orchestra, he could bear comparison with his celebrated cousin.

Over the four years following his initial disclosure of the synthesis of phenanthrene-9-carboxylic acid,¹⁷ Pschorr extended this work to the synthesis of other substituted phenanthrenes (Scheme 5).²⁰

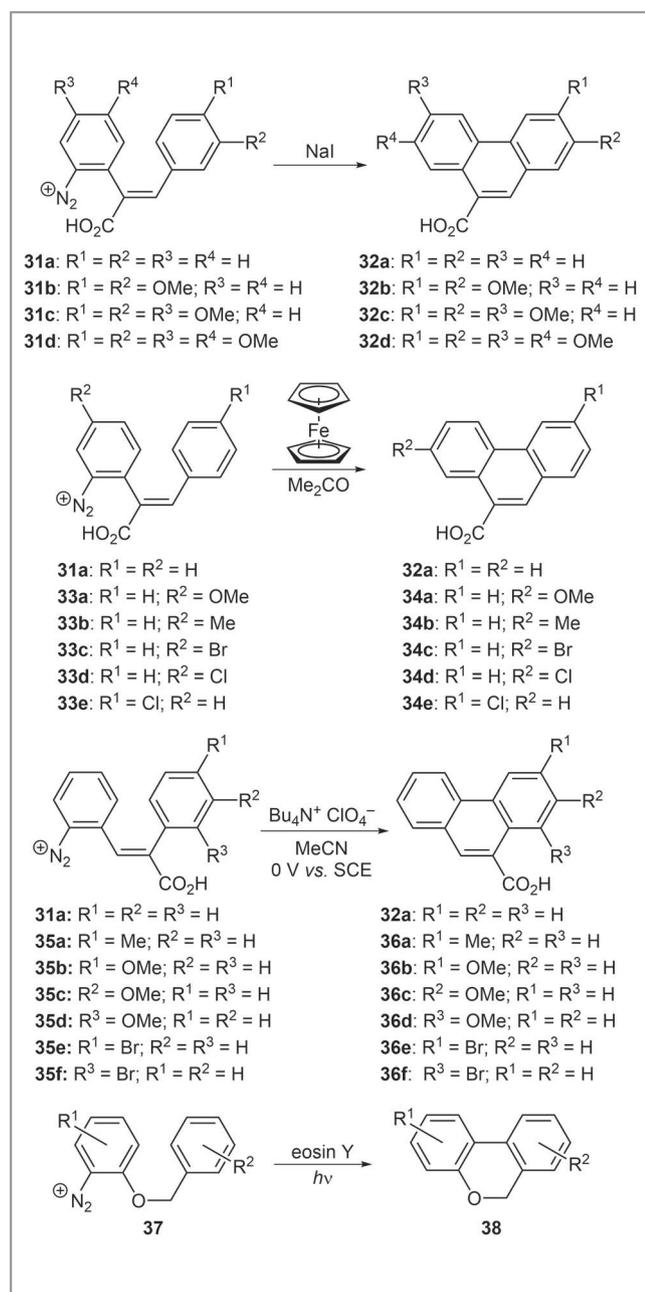


Scheme 5 The synthesis of other phenanthrene derivatives by Pschorr

Later Research on the Pschorr Reaction

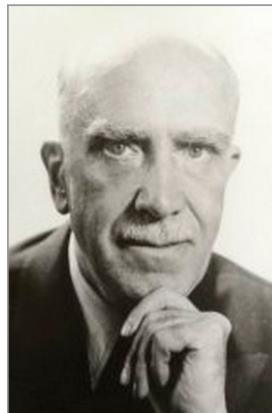
Efforts to improve the synthetic utility of the Pschorr cyclization have mainly focused on methods for the generation of the aryl radical intermediate. There have been three major avenues for accomplishing this: redox catalysis, photoredox catalysis, and electrochemical reduction of the diazonium ion. In 1969, iodide anion was shown to function as a soluble catalyst for the Pschorr cyclization of diazonium salts to the phenanthrene-9-carboxylic acids **32**, with improvements in the overall yield of the cyclization product.²¹ In 1995, a systematic study of compounds with potential to be soluble catalysts for the Pschorr reaction identified ferrocene as a useful soluble redox catalyst for the conversion of diazonium ions

into phenanthrenes (**32a**, **34**).²² The electrochemical reduction of diazonium tetrafluoroborates in acetonitrile occurred at 0 V vs. SCE, providing the corresponding phenanthrene-9-carboxylic acids (**32a**, **35**).²³ A photochemical cyclization using eosin Y as a redox-active photosensitizer was recently reported to promote cyclization of arenediazonium tetrafluoroborates **37** into benzochromenes **38**.²⁴



Scheme 6 Modern adaptations of the Pschorr cyclization

Meerwein Arylation



Hans Lebrecht Meerwein
(1879–1965)

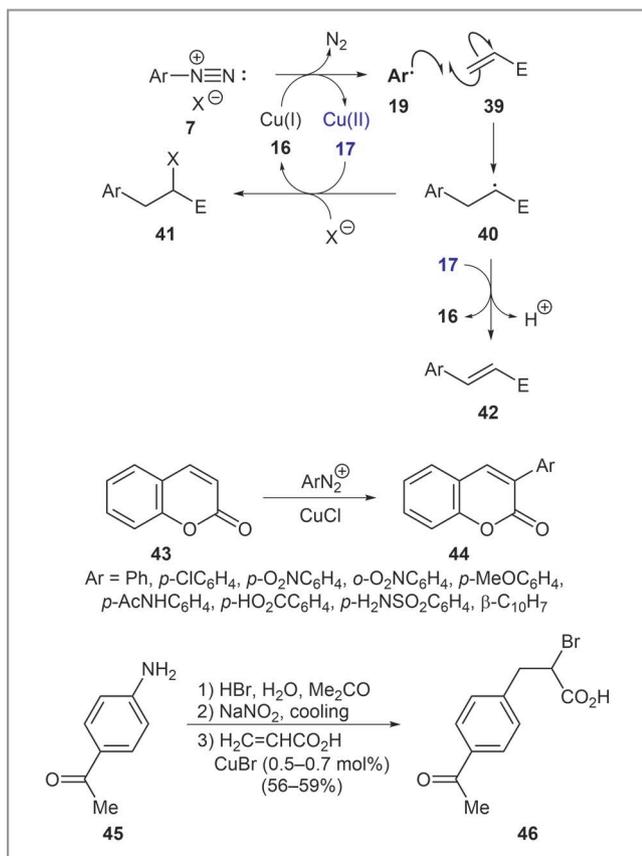
The name of Hans Lebrecht Meerwein (1879–1965) is associated with an eponymous reaction, the Wagner–Meerwein rearrangement of carbocations, which has been the subject of an earlier column in this series,²⁵ and with Meerwein's salt.²⁶ In 1939, Meerwein, Büchner and van Emster reported the addition of an aryldiazonium salt to an olefin in the presence of a metal (usually copper) catalyst. The reaction is now known as the Meerwein arylation.²⁷ The reaction differs from the Sandmeyer

reaction by the addition of the aryl radical **19** to an alkene (**39**), which usually carries a conjugating, electron-withdrawing substituent, to give the substituted 2-arylethyl radical **40** before the final coupling with the halide to give the final addition product **41**, or loss of hydrogen as a proton following oxidation of the radical to give the arylated alkene **42** (Scheme 7). Meerwein found that, when there was a choice between benzylic and α -carboxy radicals, the benzylic radical was preferred: the reaction of coumarin (**43**), for example, gave the 3-arylcoumarin **44** as the major product. The overall addition reaction is illustrated by the coupling of 4-acetylphenyldiazonium bromide, derived from **45**, with acrylic acid to give the α -bromo- β -aryl propionic acid **46**.

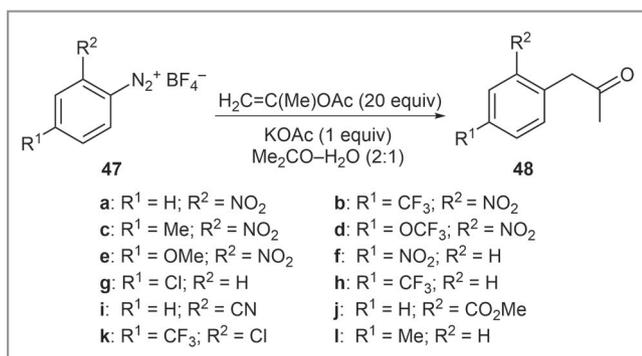
As with the Pschorr cyclization, the Meerwein reaction has been particularly amenable to research aimed towards developing a transition-metal-free version of the reaction. To this end, workers at Merck²⁸ reported a study of the Meerwein reaction of isopropenyl acetate with arenediazonium tetrafluoroborates **47** in the presence of acetate ion, which led to α -arylated acetone derivatives **48**.

An analogous reaction was developed five years later, using Ru(bpy)₃²⁺ in DMF as the redox-active photocatalyst.²⁹

The use of potassium acetate in this reaction is highly suggestive that this version of the Meerwein reaction shares mechanistic details with the Gomberg–Bachmann reaction for the synthesis of unsymmetrical biaryls.³⁰



Scheme 7 The Meerwein arylation reaction



Scheme 8 A transition-metal-free Meerwein reaction

David Lewis

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A Concise Synthesis of Tetrodotoxin

Science **2022**, 377, 411–415

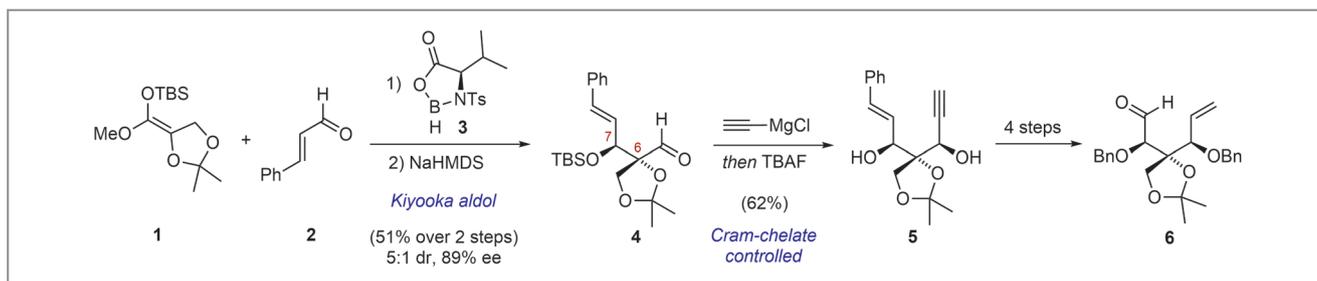
Tetrodotoxin (TTX) is an extremely potent poison found in different organs of some fish, such as puffer fish, as well as in some amphibian, octopus, and shellfish species, acting as a selective sodium channel blocker. Chemically, TTX is a complex quinazoline alkaloid, whose structure was elucidated by Hirata, Tsuda, Amakasu, and Woodward and later confirmed by X-ray crystallography. Its first synthesis – in racemic form – dates back to the work of Yoshito Kishi (1972), whereas the synthesis of the stereopure compound was first accomplished over three decades later. Recently, the group of Professor Dirk Trauner (New York University, USA) reported in *Science* a conceptually new and extremely concise stereoselective synthesis of TTX, which could also be amenable to readily accessing biologically active TTX derivatives of pharmaceutical interest.

Professor Trauner said: “Since my undergraduate days, I have been fascinated by the chemistry and biology of TTX, and I have always admired how Kishi solved this synthetic challenge more than five decades ago. For many years, I had been teaching his synthesis in comparison with more recent work in my graduate courses on “Synthetic Design” and “Chemical Neuroscience”. Browsing through an issue of *Org. Lett.* after one of my classes, I realized that the product of a Kiyooka aldol reaction reported by Marcus Kalesse, compound **4**, mapped onto C5, C6, C7 and C11 of TTX (Scheme 1) (*Org. Lett.* **2011**, 13, 6038–6041). This prompted us to work on TTX in hopes that we could adopt this powerful opening step, “somehow” forge the central cyclohexane ring, and then install the missing carbons, the all-important α -tertiary nitrogen, the remaining hydroxy groups, and the heterocycles of TTX.” The group found that a Cram-chelate controlled acetylide addition to **4** indeed set the C5 stereocenter with the correct configuration and they were able to access a key aldehyde intermediate **6** within

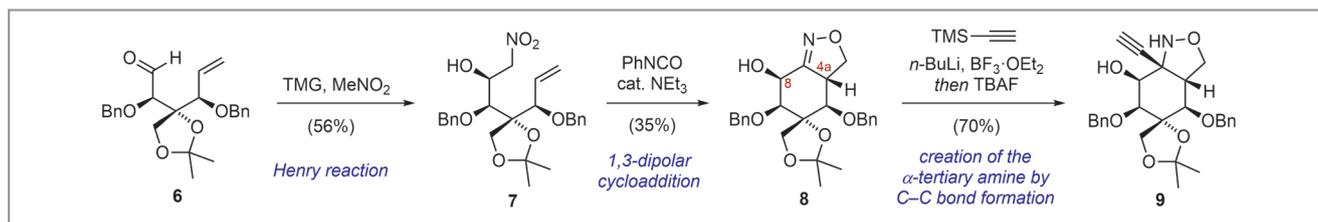
seven steps. David Konrad, the graduate student with whom Professor Trauner started this project, also used an intermediate similar to **5** in the first total synthesis of kweichowenol A (*Synlett* **2019**, 30, 383–386).

Mr. Konrad then went ahead and investigated a subsequent Henry reaction, dehydration and cycloaddition sequence (Scheme 2). “Despite extensive experimentation, the diastereoselectivity of the Henry reaction remained low,” said Professor Trauner. He continued: “Dehydration of the unprotected nitro-aldol product **7** to form a nitrile oxide with subsequent (3+2) cycloaddition afforded an isoxazoline product **8** in moderate yields. We confirmed the wrong configuration at C4a by X-ray crystallography; however, we were optimistic that we could epimerize this stereocenter at a later stage. Another distinct strategic difference of our approach was the establishment of the α -tertiary amine.” Indeed, all previous syntheses of TTX established this stereocenter by C–N bond formation using intramolecular rearrangements [Beckmann (Kishi), Overman (Isobe), Fukuyama or Curtius (Fukuyama)], an intramolecular nitrene insertion (Du Bois) or nucleophilic substitution with an azide (Sato). Professor Trauner’s group, however, instead aimed to create this stereocenter by formation of a C–C bond, specifically by addition of a C2 nucleophile into the isoxazoline. They found that steric hindrance prevented the addition of many nucleophiles, but TMS-acetylide formidably performed the addition into the isoxazoline after activation with a Lewis acid. Importantly, the C8-alcohol needed to be unprotected to promote an efficient nucleophilic addition.

Professor Trauner explained: “Although our route was scalable, the material throughput was limited by the necessity to use high volumes of carcinogenic HMPA as a cosolvent



Scheme 1 Initial attempts to access aldehyde **6** using a Kalesse–Kiyooka aldol approach



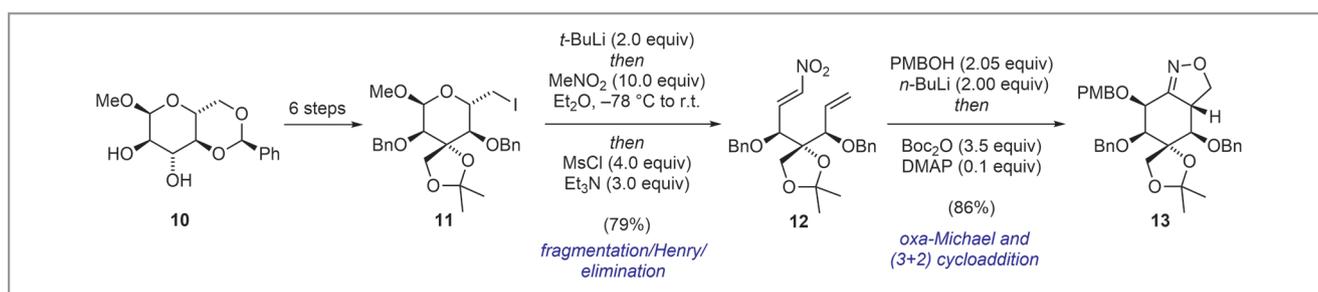
Scheme 2 Henry reaction, 1,3-dipolar cycloaddition and ATA formation

for the formation of silyl ketene acetal **1** and stoichiometric amounts of the oxazaborolidinone **3** for the Kiyooka aldol reaction.” At this stage, Bryan Matsuura joined the project as a postdoc and investigated alternative, more scalable strategies towards the key aldehyde **6**. Together with Hiroyasu Ando, he developed a highly scalable (100 g scale) and reliable route towards an iodoglycoside (**11**), starting from commercially available methyl 4,6-*O*-benzylidene- α -D-glucopyranoside (**10**). “With this new strategy, we no longer had any issues of material supply,” commented Professor Trauner. He added: “Initially, we used original Bernet–Vasella fragmentation conditions (Zn, I_2) to obtain crude aldehyde **6** and used the same Henry and cycloaddition conditions as before. Trying to optimize this low-yielding two-step sequence, Peter Rühmann followed conditions reported by Soengas and Silva and found that a tandem fragmentation/Henry reaction sequence successfully yielded nitroaldol products **7**, albeit still with low diastereoselectivities after extensive experimentation” (*Eur. J. Org. Chem.* **2013**, 5022–5027). The group’s solution to this problem was to eliminate the secondary alcohol in the same pot, which exclusively yielded (*E*)-nitroalkene **12** (Scheme 3). They were delighted to find that an oxa-Michael addition into this nitroalkene system solely yielded a single diastereomer. Professor Trauner said: “We could extend this finding by trapping the intermediate nitronate with Boc anhydride, which triggered the dehydration and subsequent 1,3-dipolar cycloaddition cascade in a single reaction step. Using phenyl iso-

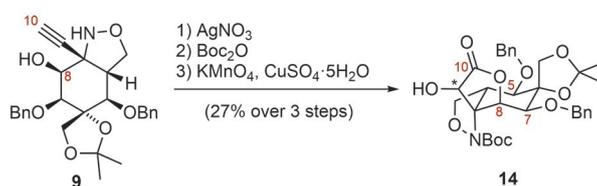
cyanate, we observed similar results, however obtained lower yields. Intrigued by the selectivity of this oxa-Michael attack and curious about which would be the actual 1,3-dipole that undergoes the cycloaddition (nitronate vs. nitrile oxide), we approached Prof. Ken Houk and Nina Strassner (UCLA) for computational assistance. Nina calculated diastereomeric transition states for the oxa-Michael attack which validated the lowest-energy transition state to yield an addition from the desired face. She further confirmed the pathway of the (3+2) cycloaddition to proceed via a nitrile oxide 1,3-dipole as the elimination occurs much faster than a competing cycloaddition of the Boc-nitronate intermediate.”

With a satisfying solution towards the hydroxy alkyne **9**, the group’s initial plan was to convert this intermediate into a hydroxylactone of type **14**, which they believed, after debenzilation, would transactonize and form the dioxo-adamantane core of TTX spontaneously. “Silver-based π -acids initiated the desired 5-*endo*-dig cyclization towards an enol ether, which after Boc-protection of the isoxazolidine could be converted into hydroxylactone **14** (Scheme 4), whose configuration at C9 we were unable to firmly establish,” said Professor Trauner. He continued: “Deprotection of the C5 and C7 benzyl ethers was possible, yet all attempts to isomerize the five-membered lactone to the desired dioxo-adamantane core of TTX proved futile.”

These results forced the group to adopt a new strategy, which sought to establish a hydroxylactone bridge to the C5



Scheme 3 The glucose-derived iodoglycoside **11** and its cascade transformations towards isoxazoline **13**

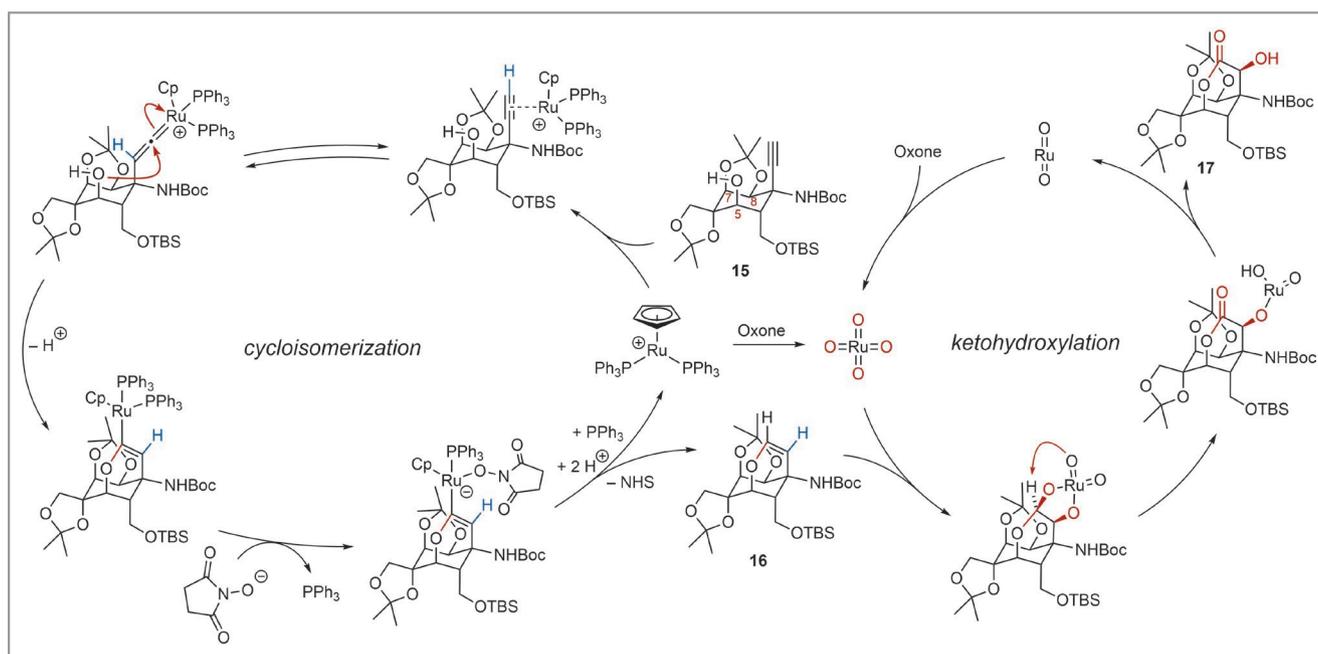


Scheme 4 Initial attempts to establish a hydroxylactone of type **14**

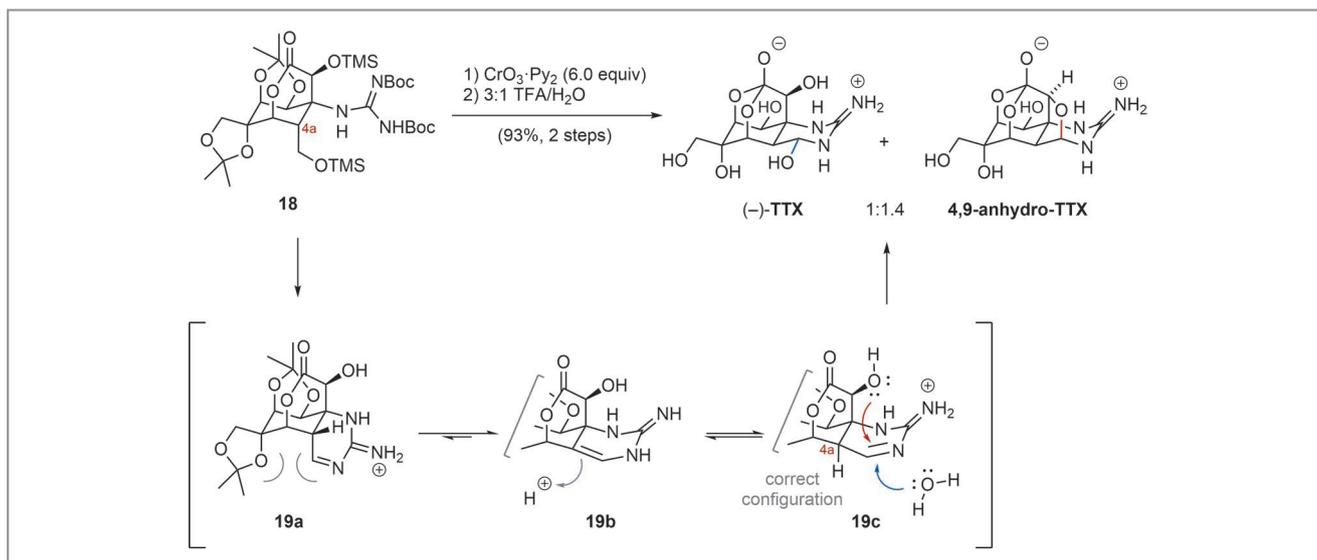
hydroxy group. “Such a maneuver would avoid a risky and unprecedented transactonization step,” Professor Trauner explained, adding: “To this end, intermediate **15** was synthesized from **9** in 6 steps, which took advantage of a novel photochemical debenzoylation methodology (*Org. Lett.* **2021**, *23*, 514–518). Initially, gold or silver π -acids exclusively yielded 5-*exo*-dig cyclization products of **15**. The breakthrough came with the identification of a Ru(II) catalyst that cleanly converted hydroxy alkyne **15** through a 6-*endo*-dig cyclization into enol ether **16** (Scheme 5), presumably through the intermediacy of a metalvinylidene carbene. Based on scarce literature precedence, Bryan then reasoned that addition of Oxone™ to this reaction mixture would oxidize our Ru(II) catalyst in situ to RuO₄ and dihydropyran **16** to the desired hydroxylactone **17**. After several rounds of optimization, we found that this transformation indeed was possible, requiring careful moni-

toring of the reaction mixture in order to avoid overoxidation to the ketolactone side product. I believe that this reaction is a nice example for on-demand methodology development in the spirit of Sam Danishefsky’s saying: “Sometimes you have to be a bit desperate to do something really interesting.” We currently are investigating this chemistry further and plan to apply it towards other natural products.”

Deprotection of **17**, followed by silylation/guanidinylation, yielded the penultimate intermediate **18** (Scheme 6). This compound bears all of the atoms and stereocenters of TTX, albeit with the wrong configuration at C4a. “Our final transformation required the chemoselective oxidation of the primary silyl ether at C4, epimerization of the C4a stereocenter, global deprotection of the remaining protecting groups, and spontaneous formation of the cyclic guanidine and *ortho*-acid,” said Professor Trauner. He continued: “This was achieved



Scheme 5 Proposed mechanism for the hydroxylactonization



Scheme 6 Global deprotection and epimerization of the C4a center afforded TTX and 4,9-anhydro-TTX

by exposure to Collins reagent followed by treatment with aqueous TFA, affording the desired product as a mixture of TTX and its naturally occurring 4,9-anhydro-TTX isomer. The handling and purification of this toxic mixture required much expertise, awareness, and patience. Belinda Hetzler and Peter Rühmann investigated the purification of the crude mixture using different HPLC columns and ultimately found conditions that could separate all impurities, affording a clean mixture of TTX and 4,9-anhydro-TTX. Since these interconvert in aqueous solution, we refrained from separating them.”

“Finally, as another, albeit imprecise, measure for the identity of our compound, we have tested the ability of our synthetic TTX/anhydro-TTX mixture to block action potentials in mouse brain slices (Figure 1),” said Professor Trauner. He added: “These measurements were done in collaboration with Dr. Jingjing Liu and Prof. Richard Tsien (NYU Neuroscience Institute), with whom we will pursue selective NaV1.7 (and NaV1.8) inhibitors as next-generation analgesics in the future.” Professor Trauner concluded: “We believe that our efficient approach provides a good platform for the synthesis of simplified TTX analogues and could even be used to procure TTX itself should supply ever become a concern.”

Mattes Fank

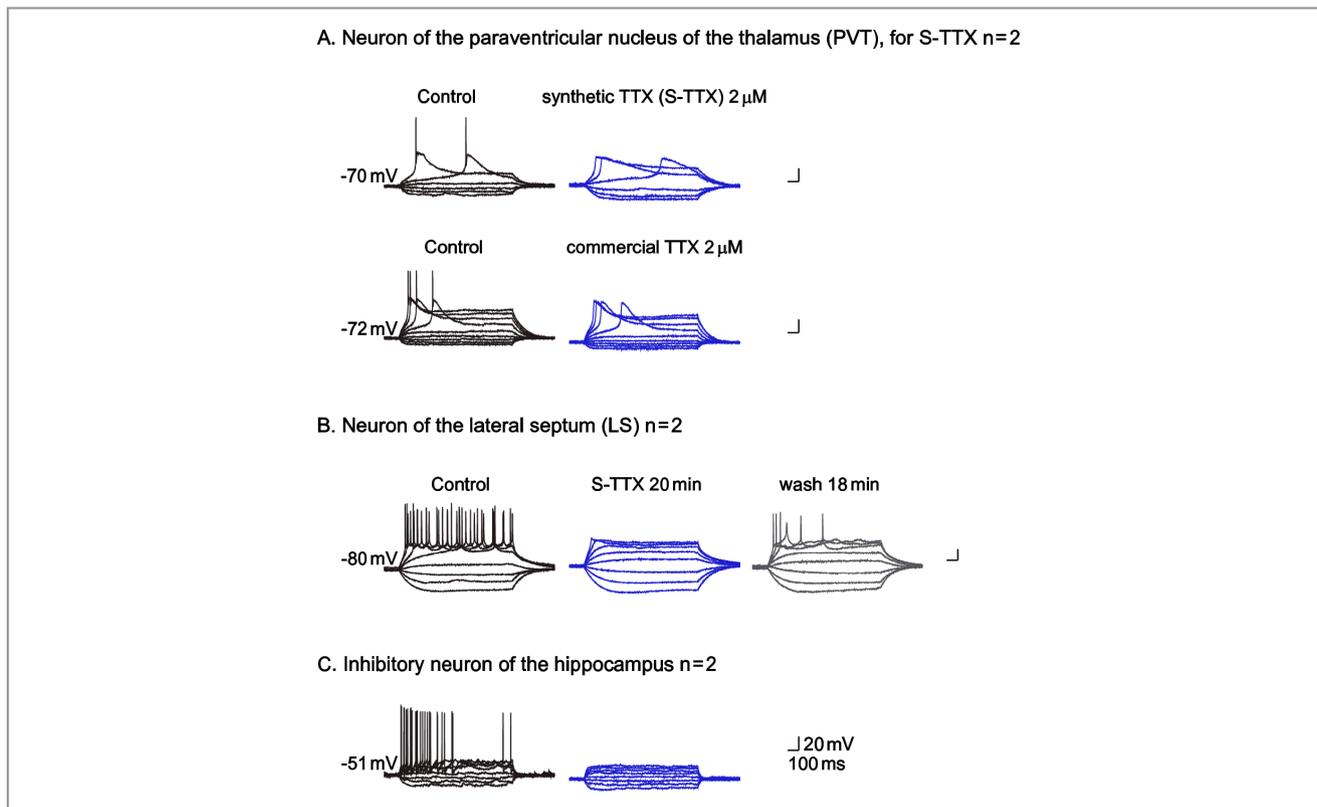


Figure 1 Electrophysiology traces of different neurons from mouse brain slices demonstrate successful inhibition of action potentials

Matthew Fenske

About the authors



Dr. D. B. Konrad

David B. Konrad is a Liebig fellow and research group leader at the Department of Pharmacy of the Ludwig Maximilian University of Munich (LMU Munich, Germany). He obtained his M.Sc. degree in chemistry and biochemistry at the LMU in 2013 which included research stays in the group of Prof. Dean Toste at the University of California, Berkeley (USA) and the group of Prof. Benjamin List at the Max Planck Institute for Coal Research in Mülheim an der Ruhr (Germany). In 2014, he joined the group of Prof. Dirk Trauner for his graduate studies to work on an asymmetric synthesis of tetrodotoxin and methods to red-shift

photopharmaceuticals. After graduating in 2018, he moved to the Scripps Research Institute in La Jolla (USA) as a postdoctoral fellow focusing on (chemo)proteomics-guided fragment-based ligand discovery using cysteine-targeted and photoaffinity probes under the guidance of Prof. Benjamin Cravatt. As part of the second phase of his fellowship, he returned to LMU Munich to join the group of Prof. Ivan Huc to analyze interactions of foldameric B-DNA mimics with the drosophila proteome before transitioning to an independent group leader in 2021. His research is focused on the development of covalent drugs that target advanced non-small cell lung cancers by working at the interface of chemical biology, (chemo)proteomics, medicinal chemistry, and synthetic methodology development.

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K.-P. Rühmann

Klaus-Peter Rühmann obtained his Bachelor's and Master's degrees at LMU Munich (Germany) in chemistry and biochemistry. He completed his Master's thesis research in the group of Prof. Andrew G. Myers at Harvard University (USA) before he joined the graduate program at New York University (USA) where he is conducting synthetic studies towards different medicinally relevant natural products under the guidance of Prof. Dirk Trauner.



Dr. B. E. Hetzler

Belinda E. Hetzler received her B.Sc. in chemistry from Heidelberg University (Germany). She then moved to LMU Munich (Germany) and joined Prof. Dirk Trauner's lab, where she completed her M.Sc. She then continued as a MacCracken Graduate Fellow at New York University (NY, USA), also in the group of Prof. Dirk Trauner. There, she worked on synthetic methodology for complex natural product synthesis and the design of novel molecular switches for the control of protein function. After receiving her Ph.D. in 2022, Belinda joined Vir Biotechnology (USA), where she is currently working in the infectious disease space as a Scientist in Medicinal Chemistry.



N. Strassner

Nina Strassner received her B.Sc. degree in chemistry from the University of Erlangen-Nuremberg (Germany) in 2021. She then spent seven months in Prof. Kendall N. Houk's lab at the University of California, Los Angeles (USA) as a Visiting Graduate Researcher doing computational studies of stereoselective (bio-)organic mechanisms. Supported by a scholarship of the Studienstiftung des deutschen Volkes, she is currently working toward her M.Sc. degree in Erlangen.



Prof. K. N. Houk

K. N. Houk received his A.B., M.S., and Ph.D. degrees at Harvard University (USA), working with R. B. Woodward on experimental tests of orbital symmetry selection rules. In 1968, he joined the faculty at Louisiana State University (USA), moved to the University of Pittsburgh (USA) in 1980, and to UCLA (USA) in 1986. From 1988–1990, he was Director of the Chemistry Division of the National Science Foundation (USA). He was the UCLA Saul Winstein Chair in Organic Chemistry from 2009–2021 and is now a Distinguished Research Professor. Beginning as an experimental organic chemist, he evolved over his career into a theoretical and computational organic chemist, involved in collaborations with groups all over the world. He has been elected as a member of both the US and Chinese Academies of Science. He has published almost 1500 refereed publications.



Dr. B. S. Matsuura

Bryan S. Matsuura received his B.A. from Boston University (USA) in 2009, after which he went on to the University of Michigan (USA) to study under the guidance of Prof. Corey R. J. Stephenson. He received his Ph.D. in 2015 which focused on photoredox catalysis, natural products total synthesis, biomass processing, and methodology development. He then joined the group of Prof. Dirk Trauner as an Alexander von Humboldt postdoctoral research fellow at LMU Munich (Germany), where he studied natural product total synthesis and photopharmacology. In 2021, Bryan joined Merck South San Francisco (USA) as a Senior Scientist, where he is currently working in the cardiometabolic disease area.



Prof. D. Trauner

Dirk Trauner was born and raised in Linz, Austria, studied biology and chemistry at the University of Vienna (Austria) and received his undergraduate degree in chemistry from the Free University of Berlin (Germany). He then pursued graduate studies in chemistry under the direction of Prof. Johann Mulzer and became a postdoctoral fellow with Prof. Samuel

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J. Danishefsky at the Memorial Sloan-Kettering Cancer Center (USA). Subsequently Dirk joined the Department of Chemistry at the University of California, Berkeley (USA), where he rose through the ranks to become an Associate Professor of chemistry (with tenure) and a member of the Lawrence Berkeley National Laboratory. In 2008, he moved to LMU Munich (Germany) as a Professor of Chemistry and Chemical Genetics. In the Spring of 2017, he returned to the United States as the Janice Cutler Chair in Chemistry at New York University. In July 2022, Prof. Trauner moved to the University of Pennsylvania (USA) as a Penn Integrates Knowledge Professor, holding joint appointments in the Department of Chemistry at the School of Arts and Sciences and the Department of Systems Pharmacology and Translational Therapeutics in the Perelman School of Medicine.

Young Career Focus: Professor Jaideep Saha (Centre of Biomedical Research, 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 Professor Jaideep Saha (Centre of Biomedical Research, India).

Biographical Sketch



Prof. J. Saha

Jaideep Saha obtained his B.Sc. (Hons) in Chemistry from S.A. Jai-puria College, Calcutta University (India) in 2003 and his M.Sc. (Chemistry) from IIT Madras (India) in 2005. He pursued his doctoral studies with Prof. Mark W. Peczu at the University of Connecticut (USA) where he worked in synthetic method development for the synthesis of unnatural carbohydrates and phosphine-catalyzed transformations. He was a research intern at Boehringer-Ingelheim Pharmaceutical Inc. CT (USA) in the chemical development department, where he worked with Dr. Chris Senanayake and Dr. Daniel Fandrick. After completing his PhD in 2012, he moved to the University of Pittsburgh (USA) as a post-doctoral fellow to work with Prof. Peter Wipf (2012–2013). He worked on medicinal chemistry projects and synthesized selective small-molecule inhibitors of NOX-2 enzyme. At that time he was also a Vascular Medicine Institute Fellow at the school of medicine. For his second post-doc, he moved to the University of Oxford (UK) as a Marie-Curie Post-doctoral Fellow in 2013 to work with Prof. Stuart Conway, where he developed small-molecule probes for targeting hypoxia. In December 2016, he began his independent career at the Centre of Biomedical Research (India) as an Assistant Professor, later promoted to Associate Professor (2019), where his group is involved in the development of new synthetic methodologies and the preparation of compounds for application in medicinal chemistry and drug discovery.

Recently he was awarded the Thieme Chemistry Journals Award (2022). He has been inducted as an early career advisory board member of *Bioorganic & Medicinal Chemistry* and *Bioorganic & Medicinal Chemistry Letters* (2022). He is also the recipient of a Marie-Curie Fellowship (2013), an INSPIRE faculty award from Department of Science and Technology, India (2013), a Dr. K. S. Krishnan Research Fellowship, BRNS India (2015), and a Discovery Early Career Research Award (DECRA) by ARC in 2017.

INTERVIEW

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

Prof. J. Saha Our current research activities have several overlapping themes, all of which are directed to synthetic method development using various catalytic approaches or radical-based chemistry. We are particularly interested in using strained organic molecules as synthons in our methodologies. These compounds can be stipulated for various strain-release-driven transformations or functionalizations and thus can deliver very interesting scaffolds which are otherwise not very easy to synthesize. For the last couple of years, we have been using several of them, including donor-acceptor cyclopropanes or vinyl cyclopropanes, aziridines, (aza)-bicyclobutanes, propellanes, etc. Depending on the activation modalities – i.e., whether metal or Lewis acid activation or radical conditions are used – these molecules can be engaged in many exciting transformations. Besides this, we are also actively working on exploiting azaoxyallyl cations or similar types of reactive intermediates in developing new synthetic transformations. In the same vein, we have become interested in developing ways to intercept the reactive intermediates that are generated during different chemical transformations; for example, oxypentadienyl cation is known to form during the course of the Piancatelli rearrangement or Nazarov reaction. We look for strategies that can intercept the original manifold and this can be achieved by taming the reactive intermediate involved. Such an exercise can give access to new reactivity, which can be translated into unconventional synthetic transformations.

In a nutshell, our motivation and goals behind all the research endeavors in our laboratory is to unfold new reactivity, develop sustainable chemical transformations and ultimately to leverage our findings in various contexts of medicinal chemistry and chemical biology.

SYNFORM *When did you get interested in synthesis?*

Prof. J. Saha It first struck me when I was studying for my bachelor's degree in chemistry (B.Sc.) at college. While I had to take all types of chemistry courses, organic chemistry became my favorite subject in no time. I was fascinated by the principles of organic synthesis, its mechanisms and the concept of chirality. I became even more passionate when I started my M.Sc. dissertation project in carbohydrate synthesis, with the late Prof. Loganathan at Indian Institute of Technology Madras in 2004. It was my first opportunity to work in an organic chemistry research lab.

From that point on, I began to appreciate the power of organic synthesis and it was very thrilling for me that with smart retrosynthetic logic and well-articulated design plans, synthetic chemists can synthesize complex natural products, including oligomeric carbohydrates, in the lab.

After completing my M.Sc., I decided to pursue doctoral studies in the field of synthetic organic chemistry and I entered the Ph.D. program at the University of Connecticut, USA with Prof. Mark W. Pecuh. I spent the most rewarding and most memorable time in graduate school in the process of becoming a trained organic chemist. After finishing my Ph.D., I pursued two consecutive post-doctoral studies in different areas of organic synthesis as I wanted to expand my expertise more into the applied areas.

I was fortunate that I came across some excellent teachers and mentors (Prof. Loganathan, Prof. Mark Pecuh, Prof. Peter Wipf, Prof. Stuart Conway, Prof. Amy Howell) who inspired and motivated me at different stages of my career and those were the push for which, today, I am one of the practitioners of this wonderful scientific discipline.

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

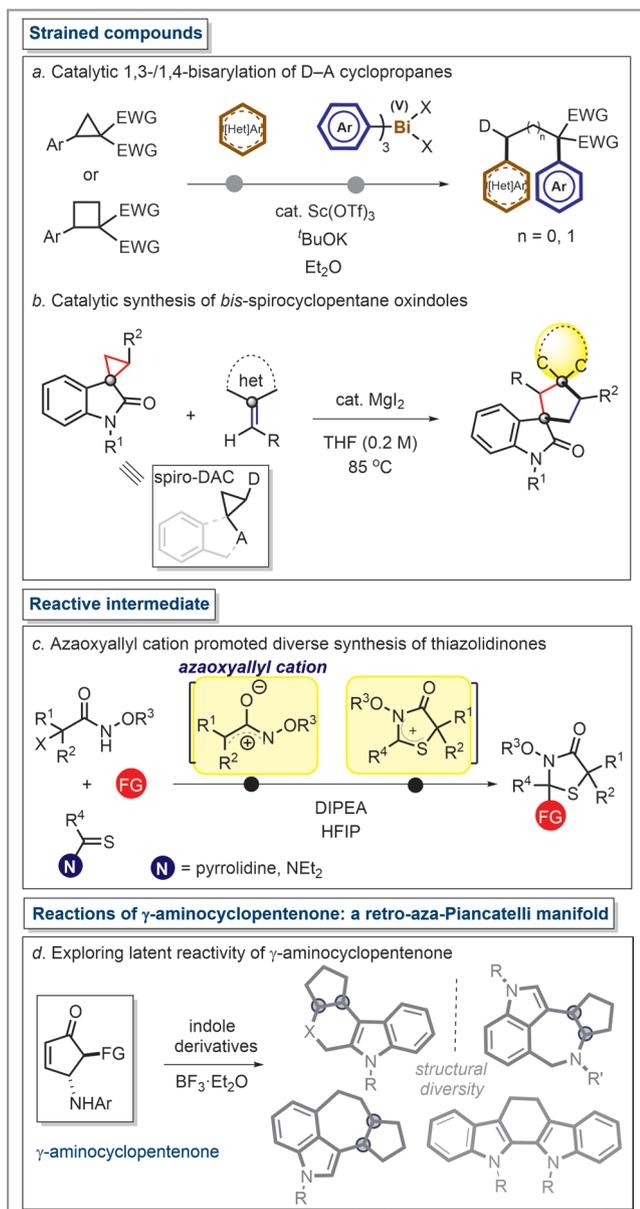
Prof. J. Saha In my opinion, organic synthesis is one of the most creative and important scientific disciplines which has had a great impact on human life and society on various fronts ranging from medicines, agrochemicals, cosmetics, and vitamins to materials, energy fuels and polymers. Over time, this field has undergone a massive transformation and now its role in enabling science and technology is truly remarkable as many allied disciplines – such as chemical biology, biotechnology, materials science and nanotechnology – benefit enormously from the discoveries of organic synthesis. A great example to cite in this very context would be the 2022 Noble Prize in Chemistry, that highlights the impact of click chemistry and biorthogonal chemistry in several cross-disciplinary research areas.

Since organic synthesis is, at its core, about practicing the means to create new chemical bonds involving carbon atoms, the development of creative and sustainable organic transformations will always be the essence of this field. However, it is also of paramount interest to extend the skillset of organic synthesis to interdisciplinary domains in order to foster new innovations and discoveries, especially in human health and medicine.

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

Prof. J. Saha Broadly speaking, we use various strained organic molecules or reactive intermediates and develop useful synthetic methodologies, and we particularly focus on nitrogen heterocycles or scaffolds that have medicinal relevance (Scheme 1). The reason we became interested in exploring strained compounds, or those that can form reactive intermediates, is their rich and diverse pool of reactivity which can be tapped for new synthetic transformations. For example, we have explored the reactivity of donor–acceptor (D–A) cyclopropanes/cyclobutanes for ring-opening 1,3-/1,4-bisfunctionalization reactions and through such a strategy we were able to incorporate two distinct functional groups on the resulting acyclic system in tandem (*J. Org. Chem.* **2019**, *84*, 710–725; *Org. Lett.* **2020**, *22*, 5115–5120). Further, we were able to append the “strain” to the oxindole ring and show the use of such an oxindole-activated D–A cyclopropane in a de novo synthesis of spirocyclopentane oxindole frameworks with an all-carbon quaternary center (*Chem. Commun.* **2019**, *55*, 7069–7072).

Developing the azaoxyallyl cation promoted transformation is another active area of research in our group. We found this transient intermediate particularly fascinating as it can be generated under extremely mild conditions (metal-free), yet the scope of the transformation is truly diverse and valuable. We have shown this chemistry can be tactically used for preparing some very important classes of heterocycles and other important compounds (*Org. Lett.* **2019**, *21*, 5848–5852; *J. Org. Chem.* **2022**, *87*, 613–627). These include morpholines, thiazolidinones, six-membered saturated S,N- and Se,N-heterocycles and organic peroxides. Structure–reactivity relationship of this transient intermediate always made us curious and recently we uncovered a distinct reactivity pattern when an α -aryl group is present. Such a system is suitably poised to undergo an intramolecular nucleophilic N-arylation [Ar(Csp²)–N cyclization] step, leading to oxindoles (*Chem. Eur. J.* **2022**, *28*, e202201208). There are other exciting ongoing projects based on this theme.



Scheme 1 Selected work from the research group

In the same vein, we are interested in those organic transformations that proceed through reactive intermediates. Our interests lie in tweaking of the normal manifold of those reactions (basically we look to intercept the underlying reactive intermediate with different trapping agents) and forging new and elusive chemical transformations. We have explored the Piancatelli rearrangement and Nazarov reaction and so far, we have contributed to some very interesting developments in this context (*Angew. Chem. Int. Ed.* **2021**, *60*, 8808–8812; *Chem. Commun.* **2022**, *58*, 2504–2507).

I should also point out that sometimes we become actively engaged in projects that are purely curiosity-driven, even when we do not possess the core competence or prior experience in those areas. In my experience, such projects always teach us new chemistry, irrespective of the outcomes.

In the next couple of years, we are planning to be more engaged in developing synthetic transformations based on radical chemistry. Besides the new objectives, we like to employ our favorite “strained compounds” or reactive intermediate in such regimens.

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

Prof. J. Saha Within the first two to three years of my independent research career at CBMR Lucknow, the world was hit by the COVID-19 pandemic. It is not so hard to imagine how it could have impacted any early career researcher to stay on the track of ongoing research projects. Therefore, each of the research projects that we were able to pursue or even complete during that uncertain time stands for an important scientific achievement to me and to our research group. I also believe that as we are a young research group, all of us are in the process of constant learning and every time we cross a milestone, we celebrate it as one of the most important scientific achievements in that time point. However, if I still have to choose one, I would like to talk about the work in particular that we had published in 2021 (*Angew. Chem. Int. Ed.* **2021**, *60*, 8808–8812). This study revealed an unexpected latent nucleofugal reactivity of the γ -aminocyclopentenone system, which was leveraged to gain access to many functionalized indole derivatives and indole-alkaloid-like structures, more in the fashion of diversity-oriented synthesis. Most importantly, the starting material used in this study was the end product of an aza-Piancatelli rearrangement and mechanistically the transformation indicated the feasibility of a retro-aza-Piancatelli manifold, which is unprecedented in the context of this venerable name reaction.

Animesh Saha

Coming soon

Literature Coverage

An Enzyme-Mimic Single Fe-N₃ Atom Catalyst for the Oxidative Synthesis of Nitriles via C–C Bond Cleavage Strategy

Literature Coverage

Peptide Carbocycles: From –SS– to –CC– via a Late-Stage “Snip-and-Stitch”

Literature Coverage

Ring Contraction of Metallacyclobutadiene to Metallacyclopentene Driven by π - and σ -Aromaticity Relay

Further highlights

Synthesis Review: Recent Developments in Isoindole Chemistry

(by R. A. Weintraub, X. Wang)

Synlett Account: Stereo- and Regioselective Synthesis of (*E,E*)-Dienes: Evolution from the Transition-Metal-Catalyzed Cross-Coupling to Titanium Alkoxide-Based Alkyne–Alkyne Reductive Coupling

(by J. Wu, J. S. Panek and co-workers)

Synfacts Synfact of the Month in category “Metals in Synthesis”: Atroposelective Ring-Closing Metathesis of Stereodynamic Trienes to Access Chiral Binaphthalenes

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