

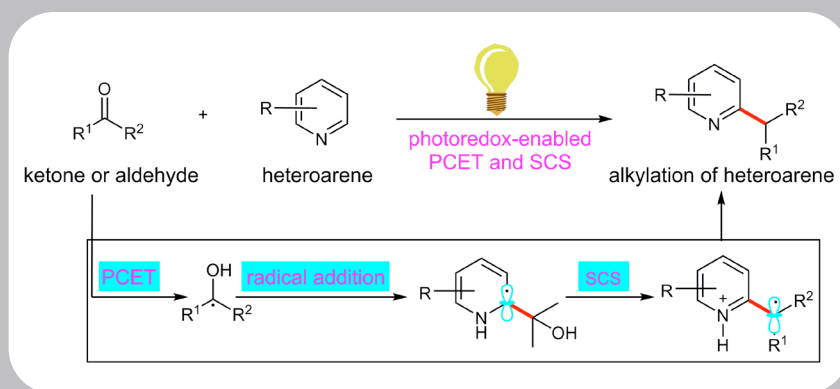
Synform

People, Trends and Views in Chemical Synthesis

2020/03

Ketones and Aldehydes as Alkyl Radical Equivalents for C–H Functionalization of Heteroarenes

Highlighted article by J. Dong, Z. Wang, X. Wang, H. Song, Y. Liu, Q. Wang



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marketing@thieme-chemistry.com

Dear Readers,

A recent non-peer-reviewed Perspective article published by Pumera et al. (“Will Any Crap We Put into Graphene Increase Its Electrocatalytic Effect” *ACS Nano* **2020**, *14*, 21–25), which attracted over 80,000 views in 2 months, has been causing a bit of a stir among the graphene research community and beyond. The authors – to make a point on the meaninglessness of publishing a myriad of papers on the doping of graphene with different elements and combinations thereof, instead of trying to understand why this leads to improved electrocatalytic performance – have shown that even chicken poop is able to cause the same effect. And this is not the only provocative aspect of the paper, the language used by the authors is indeed quite unusual for a research article, featuring a high degree of sarcasm with sentences like: “One may exaggerate only a little by saying that if we spit on graphene it becomes a better electrocatalyst.” A number of opinions have been already expressed on social media and in the scientific press about this Perspective, and although I fully respect the freedom of expression of all the authors and editors involved, I personally felt slightly uncomfortable with some of the expressions used and with this sort of high-octane sarcasm, which I am not entirely sure should find place in the primary scientific literature. Personally, I would not be overly enthusiastic if this became a precedent opening the way to a new comedian-style scientific language, after all having to deal with certain supposedly funny/argute graphical abstracts is already hard enough to take... Of one thing we can be sure: this style is not going to find a place in SYNFORM, first and foremost because it is already packed full with a lot of great science!! We start this March issue with a Young Career Focus interview with T. Iwasaki (Japan) who tells us about his research focused on multimetal catalytic systems. The

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following article covers the radical-chemistry-based functionalization of heterocycles developed by Q. Wang (P. R. of China). Next comes the intriguing hydrazone chemistry developed by Koh and Loh (Singapore), while the final article is a thorough overview of the Nazarov Cyclization in a new superb Name Reaction Bio article authored by David Lewis.

Enjoy your reading!!!



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

Young Career Focus: Professor Takanori Iwasaki (The University of Tokyo, Japan)

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 Takanori Iwasaki (The University of Tokyo, Japan).

Biographical Sketch



Prof. T. Iwasaki

Takanori Iwasaki was born and raised in Osaka, in the southern-central region of Japan. He finished his BSc in 2004 and MSc in 2006 at the Graduate School of Engineering Science, Osaka University (Japan), and received his PhD in 2009 from the same university under the supervision of Professors Kazushi Mashima and Takashi Ohshima, where he worked on the zinc-cluster-catalyzed transformations of esters. During his PhD course, he worked with Professor Karl Kirchner, Vienna University of Technology (Austria) in 2004. He became an Assistant Professor at the Graduate School of Engineering, Osaka University in 2009, working with Professor Nobuaki Kambe, and was promoted to Associate Professor in 2017, where he developed late-transition-metal-catalyzed cross- and multicomponent coupling reactions. In the summer of 2018, he was appointed Associate Professor at The University of Tokyo (Japan). He received the Japan Society for Process Chemistry (JSPC) Award for Excellence 2008, Asahi Kasei Pharma Award in Synthetic Organic Chemistry, Japan in 2011, The Ube Foundation Young Researcher Award in 2014, Special Lecture for Young Chemists in 96th the Chemical Society of Japan (CSJ) in 2016, CSJ Presentation Award 2017, Chemistry Award BCA 2018, Incentive Award in Synthetic Organic Chemistry, Japan in 2018, Thieme Chemistry Journals Award 2019, and The Japan Petroleum Institute Award for Encouragement of Research and Development in 2019. He was also selected as finalist of Reaxys PhD Prize 2010. His research interests include the development of multi-metallic catalytic systems for the cooperative activation of substrates toward challenging transformations.

INTERVIEW

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

Prof. T. Iwasaki My major research interest is the development of catalytic systems, which consist of multiple metal centers, and their application to challenging transformations.

Organic synthesis can create new molecules by repeating bond cleavage and formation. Organic chemists often use highly active reagents for bond cleavage and formation to activate one of the substrates. In this case, the counterpart reacts with the activated substrate based on its own reactivity. When the reaction is applied to multi-functionalized compounds, the chemoselectivity is difficult to control in many cases. To overcome this issue, I focus on the simultaneous activation of both substrates by catalysts to achieve the catalyst-controlled chemoselectivity.

In particular, I am interested in multinuclear metal complexes as catalysts and have achieved chemoselective reactions, such as *O*-selective acylation of amino alcohols, selective cleavage of the carbon–fluorine bond in the presence of more reactive chemical bonds, and so on. In addition, I have demonstrated that the simultaneous activation of two substrates on multinuclear metal complexes kinetically accelerates reactions to allow the use of less reactive chemical bonds as reacting sites.

SYNFORM *When did you get interested in synthesis?*

Prof. T. Iwasaki I started my research activities at Osaka University, where I tried to synthesize a new bimetallic complex supported by a novel multidentate ligand. The synthesis of the new multidentate ligand resulted in a litany of failures because of hidden pitfalls in the synthesis, such as lower efficiency of the reported reaction conditions for my target molecule and facile decomposition of molecules during

multistep manipulations. Eventually, I succeeded in synthesizing the ligand using a catalyst I newly developed myself. During the ligand synthesis, I was fascinated by synthetic organic chemistry using catalysis.

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

Prof. T. Iwasaki I believe that organic synthesis will retain its standing at the center of mainstream science and will continue to contribute to the progress of humankind through the supply of materials. Synthetic organic chemistry has developed much over the last 100 years. In my opinion, the advancement of analytical technology as well as catalyst technology represented by transition-metal catalyses has contributed greatly to the progress of organic chemistry. This progress will continue or even accelerate with the aid of these technologies, along with leading-edge informatics and automation technologies, to bring organic synthesis to a level unimaginable today. Although it is concerning that the rise of informatics and automation technologies will eliminate the need for organic synthetic chemists from both industry and academic positions, I am not so pessimistic over the future of organic synthetic chemists. Looking back on history, new technologies freed organic synthetic chemists from complicated manipulations and gave them time to focus on more creative works. I envisage a future where we can concentrate more on creative works and can try our own ideas easily using these new technologies. As a conclusion, I am confident that synthetic organic chemistry will continue to develop as a discipline that creates new molecules.

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

Prof. T. Iwasaki For now, my group is focusing on rational design of metal complexes, which have two catalytically active sites. An important concept for me is connecting these two functions flexibly. Although there are many reports on multi-functional catalysts, these catalytic sites are often connected by a rigid backbone of ligands to fix the relative positions of these catalytic sites. This may cause difficulty in the catalyst design and synthesis of supporting ligands. In my concept, electrostatic interaction between ion pairs of an ionic transition-metal complex is used as a flexible connection of two catalytic active sites. For example, ate complexes generated by the reaction of neutral transition-metal complexes with appropriate organometallic reagents such as Grignard reagents were employed for the C–C bond-forming reactions

as catalysts. In particular, the cross-coupling reaction of alkyl halides with tertiary alkyl Grignard reagents to construct quaternary carbon center was catalyzed by cobaltate complex **1** (Figure 1). It should be noted that alkyl fluorides could be used as a coupling partner in the Co-catalyzed cross-coupling reaction, and the C–F bond, which is the strongest single bond in organic compounds, was smoothly cleaved even under mild conditions. The unexpectedly facile cleavage of the C–F bond is due to its cooperative activation by the Lewis acidic counter cation in cobaltate complex **1**. Because alkyl fluorides are inert toward conventional catalyses and reagents, late-stage construction of a quaternary carbon center via the cross-coupling reaction was successfully demonstrated. Anionic Fe complex **2** bearing cyclopentadienyl ligand was found to catalyze a similar cross-coupling reaction.

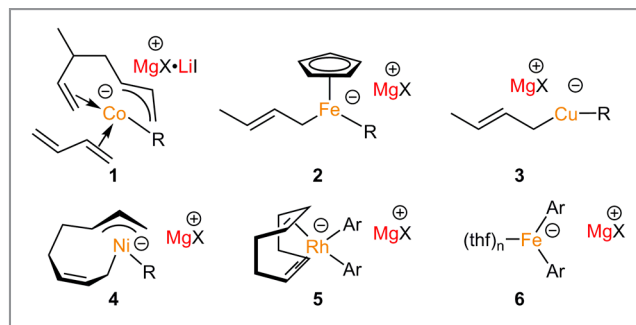


Figure 1 Structure of transition-metal ate complexes

Other examples of the use of alkyl fluorides as alkylating reagents are Cu-catalyzed internal-carbon-selective reductive alkylation of 1,3-dienes and Ni-catalyzed dimerization and alkylation of 1,3-dienes promoted by anionic allyl-metal intermediates **3** and **4**, respectively. In these reactions, alkyl fluorides are the best alkylating reagents, and other alkyl halides led to poor results.

The concept of ate-complex-mediated activation of less reactive chemical bonds could be expanded to the cross-coupling reaction of vinylic ethers with aryl Grignard reagents via C–O bond cleavage catalyzed by anionic diarylrhodate **5** and related Fe complex **6**.

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

Prof. T. Iwasaki My most important scientific achievement, I think, is the demonstration of the cooperative activation of alkyl electrophile and carbon nucleophile by ate complexes. As briefly mentioned above, I found Ni-catalyzed

four-component-coupling reaction of alkyl fluorides, aryl Grignard reagents, and two molecules of 1,3-butadiene. From exhaustive mechanistic studies and theoretical calculations on the reaction, I determined the reaction mechanism as follows: (1) actual catalytic species at the C–F bond-cleavage step are nickelate complex **4**, generated by the reaction of Ni(0) with two molecules of 1,3-butadiene and subsequent complexation with Grignard reagent, (2) entropy does not contribute to the C–F bond-cleavage step, and (3) the magnesium cation of nickelate coordinates to the fluorine atom, and the anionic nickel approaches from the opposite side at the transition-state-determined theoretical calculations. These observations clearly support my concept of cooperative activation of both nucleophile and electrophile on each metal center of the ate complex. I hope that the insight of the chemistry of ate complexes provides useful information for designing catalytic intermediates in organometallic and synthetic organic chemistry.

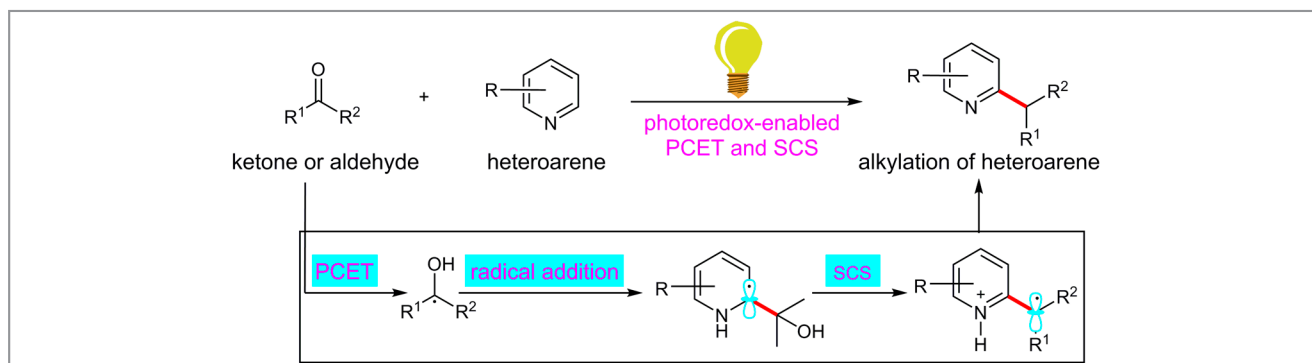
Mattias Forsell

Ketones and Aldehydes as Alkyl Radical Equivalents for C–H Functionalization of Heteroarenes

Sci. Adv. **2019**, DOI: 10.1126/sciadv.aax9955

The use of aldehydes as umpolung nucleophilic reagents is a classic strategy in synthetic organic chemistry, which has complemented the use of carbonyl compounds as electrophilic partners in countless reactions with a very broad range of organometallic reagents, ylides and other nucleophiles. There have also been reports of aldehydes used as alkyl radicals, resulting from oxidative decarbonylation (for references see the original article). However, the use of aldehydes and

ketones as radical equivalents in which the radical is centered on the carbonyl carbon is far less common, and the viability of such an innovative approach has been recently investigated in a paper published by the group of Professor Qingmin Wang at Nankai University (Tianjin, P. R. of China). These authors have developed a new catalytic activation mode that involves a combination of Proton Coupled Electron Transfer (PCET) and a RiboNucleotide Reductase (RNR) class I reaction to enable



Scheme 1 Proposed direct installation of alkyl groups using ketone or aldehyde under mild photoredox conditions. SCS = (3,2)-spin-center shift.

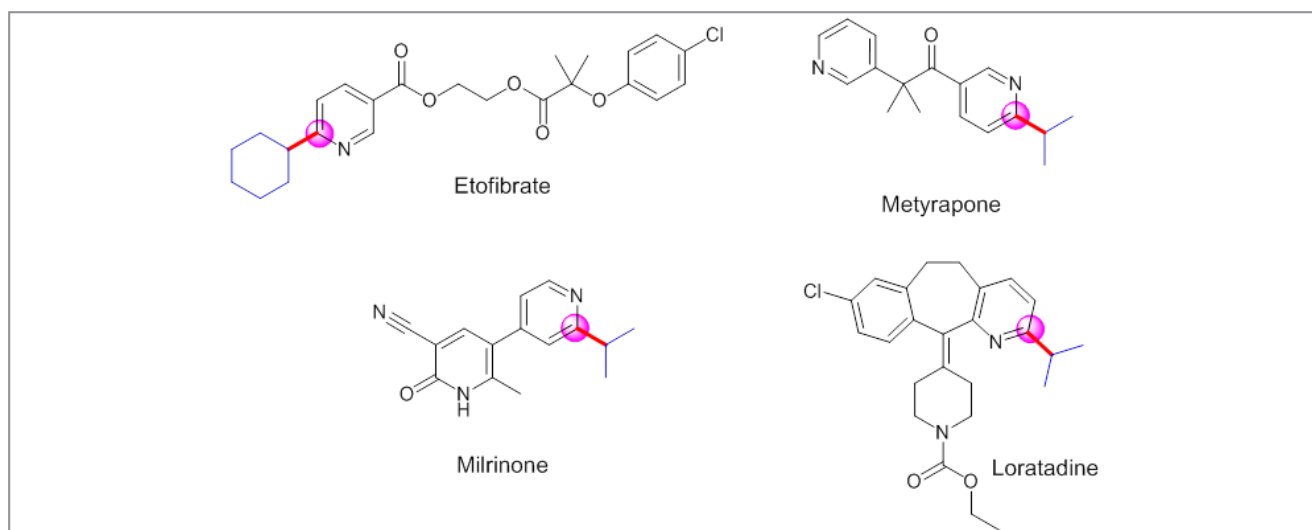


Figure 1 The new alkylation protocol for late-stage functionalization can be used to produce several complex natural products and drug molecules.

C–H alkylation of heteroarenes using ketones and aldehydes as alkyl radical sources under mild conditions, without the need for oxidants or high temperatures.

Professor Wang explained: “For the success of the transformation, we had to overcome two important challenges: first, ketones and aldehydes generally act as electrophilic alkyl groups and are difficult to couple to *N*-heteroarenes due to polarity mismatch. Second, it is difficult to get alkylation products that forge a new bond at the carbonyl carbon for aldehydes due to competing decarbonylation.”

According to Professor Wang, this mild protocol represents a general use of abundant commercially available ketones and aldehydes as latent alkyl radical equivalents, which greatly expands and enriches the portfolio of reactions that can be performed with carbonyl compounds.

“We have applied this new protocol for the late-stage functionalization of several complex nitrogen-containing natural products, organic materials, small-molecule drugs, and ligands,” said Professor Wang. He concluded: “We hope that this method can help the development of new drugs and new materials.”



About the authors



Dr. Q. Wang

the design, synthesis, and structure–activity relationships of pesticides and drugs.



J. Dong



Z. Wang

Qingmin Wang is currently a professor at the State Key Laboratory of Elemento–Organic Chemistry, Nankai University (P. R. of China). He obtained his B.Sc. degree (1994) from Lanzhou University (P. R. of China) and Ph.D. degree (2000) from Nankai University under the supervision of Prof. Runqiu Huang. His research interests mainly focus on the isolation, total synthesis, structural optimization, and bioactivity research of natural products and

Jiayang Dong obtained his B.Sc. degree (2016) under the supervision of Prof. Jianhan Huang at Central South University (P. R. of China). He then pursued a Master's degree in 2016 under the supervision of Prof. Qingmin Wang at Nankai University (P. R. of China) and in 2018 he began his Ph.D. studies. His research focuses on photoredox-catalyzed radical chemistry.

Zhen Wang obtained his B.Sc. degree (2017) under the supervision of Prof. Kunxian Shu at Chongqing University of Posts and Telecommunications (P. R. of China) before starting his current M.Sc. studies under the supervision of Prof. Qingmin Wang at Nankai University (P. R. of China). His research focuses on photoredox-



X. Wang

catalyzed radical chemistry.

Xiaochen Wang obtained her B.Sc. degree (2017) at Changchun University of Science and Technology (P. R. of China). She then started her M.Sc. studies under the supervision of Prof. Qingmin Wang at Nankai University (P. R. of China) in 2018. Her research focuses on photoredox-catalyzed radical chemistry.



Dr. H. Song

Hongjian Song obtained his B.Sc. degree in 2008 at Qufu Normal University (P. R. of China). He then obtained his M.Sc. degree (2011) and Ph.D. (2014) under the supervision of Prof. Qingmin Wang at Nankai University (P. R. of China), majoring in organic chemistry. Currently he is a lecturer at Nankai University. His research focuses on natural pesticide discovery.



Dr. Y. Liu

Yuxiu Liu obtained her B.Sc. (1994), Master's (1997) and Ph.D. (2003) from Nankai University (P. R. of China). She is currently an associate professor at the State Key Laboratory of Elemento–Organic Chemistry, Nankai University. Her research interests mainly focus on the isolation, total synthesis, structural optimization, and bioactivity research of natural products.

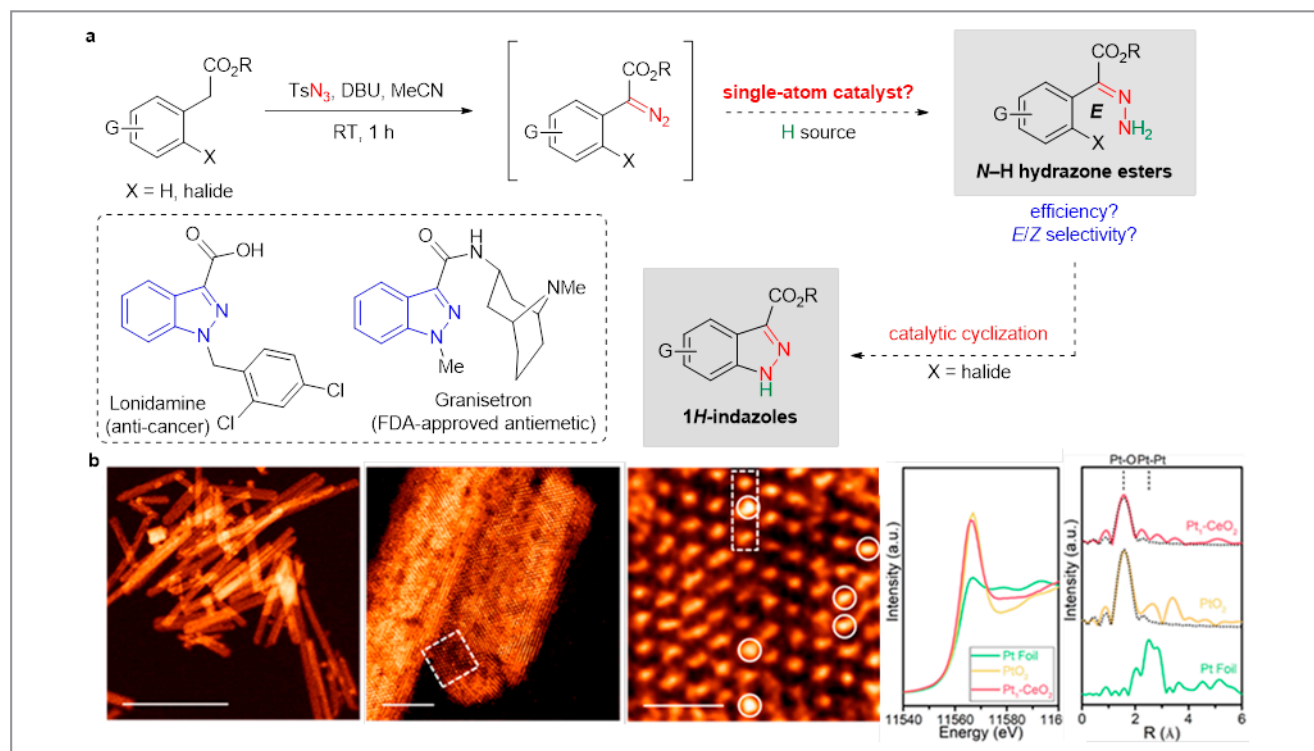
Expedient Synthesis of *E*-Hydrazone Esters and 1*H*-Indazole Scaffolds through Heterogeneous Single-Atom Platinum Catalysis

Sci. Adv. 2019, DOI: 10.1126/sciadv.aay1537

Single-atom catalysts (SACs) with the distinct advantage of ultra-high performance-to-metal ratios have been actively explored on many energy-related frontiers.^{1–3} “Despite their superior performance in gas-phase reactions, SACs are typically ineffective and rarely utilized to construct medicinally important structures under liquid-phase conditions,” said Professor Kian Ping Loh from the National University of Singapore. “One such class of medicinally relevant molecules is that of the 1*H*-indazole compounds.” Professor Ming Joo Koh, an expert in organic synthesis from the same school, remarked: “However, access to 1*H*-indazoles requires the synthesis of stereodefined and unprotected *E*- α -hydrazone esters, which

is often difficult to achieve by conventional strategies.” Both Professor Loh and Professor Koh then wondered whether it would have been possible to identify a stable SAC system that is capable of promoting stereoselective generation of *N*-*H* hydrazone esters en route to 1*H*-indazoles.

Recently, the groups of Professor Loh and Professor Koh demonstrated that Pt single atoms anchored on defect-rich CeO₂ nanorods (Pt₁/CeO₂) promote exceptionally *E*-selective hydrogenation of α -diazoesters to afford a wide assortment of *E*- α -hydrazone esters by the catalytic alcoholysis of ammonia borane (NH₃·BH₃) (Scheme 1a).



Scheme 1 The significance and challenges in developing heterogeneous single-atom metal catalysts that furnish *E*-hydrazones and 1*H*-indazoles. (a) 1*H*-Indazoles are common entities in medicinally relevant compounds and are conventionally derived from unprotected *E*-hydrazone precursors, the synthesis of which is non-trivial. An attractive approach to *E*-hydrazones involved *in situ* diazo formation followed by catalytic hydrogenation in one sequence. (b) STEM-HAADF images; atomic-resolution STEM-HAADF images of Pt₁/CeO₂ nanorods; Pt L₃-edge XANES; EXAFS spectra of Pt foil, PtO₂, Pt₁/CeO₂ nanorods; dashed lines represent the simulated EXAFS spectra.

“The support is the key for developing a highly stable SAC. Defective CeO₂ with paired Ce³⁺/Ce⁴⁺ redox couple and rich oxygen vacancies is the ideal candidate for anchoring and stabilizing metal single atoms,” said Dr. Cuibo Liu, the first author of this paper. He continued: “The Pt₁/CeO₂ catalysts were prepared by atomic layer deposition (ALD). The atomic feature of Pt SAC can be observed through scanning transmission electron microscopy.” Dr. Zhongxin Chen, the article’s co-first author, added: “By using X-ray absorption spectroscopy, we could confirm the Pt configuration in the catalyst, which has a coordination number of 4 and prominent Pt–O bonding (Scheme 1b).”

By using Pt₁/CeO₂ as catalyst and NH₃·BH₃ as a hydrogen source, a wide range of functionalized α -diazoesters were selectively hydrogenated to unprotected *E*- α -hydrazone esters with good efficiency. “Defective CeO₂ nanorods with atomically dispersed Pt single atoms favor the activation of substrates on surface and deliver the products in better yields and selectivity than conventional homogeneous synthetic methods,” said Professor Loh. “Other reducible functional groups are tolerated under the mild reaction conditions and the catalyst is stable owing to the unique features of the CeO₂ support.”

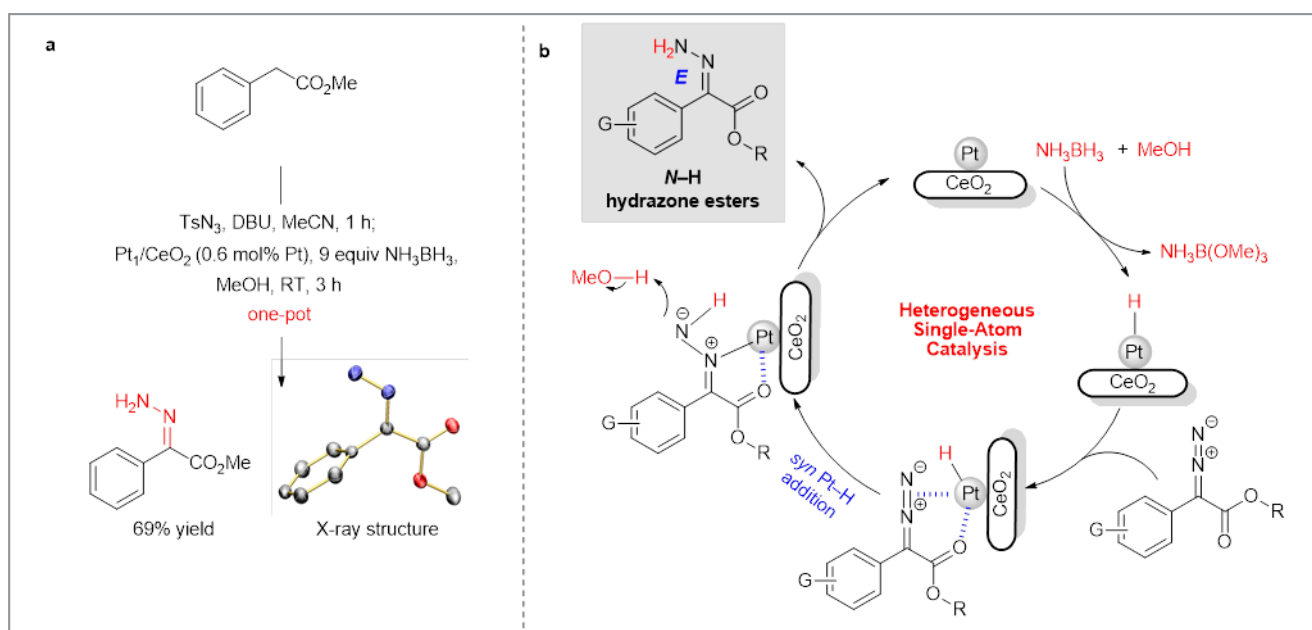
The direct synthesis of unprotected α -hydrazone esters in *E* configuration is a remarkable feature of this research work, which was very challenging to accomplish given that the *Z* isomers are thermodynamically favored over the *E* isomers.

Professor Loh explained: “Simultaneous coordination of a Pt site with the diazo N=N and ester carbonyl motifs plays a central role in controlling the selectivity.” The DFT calculations were used to verify the coordination effect of Pt sites and the favorable *E* configuration (Scheme 2).

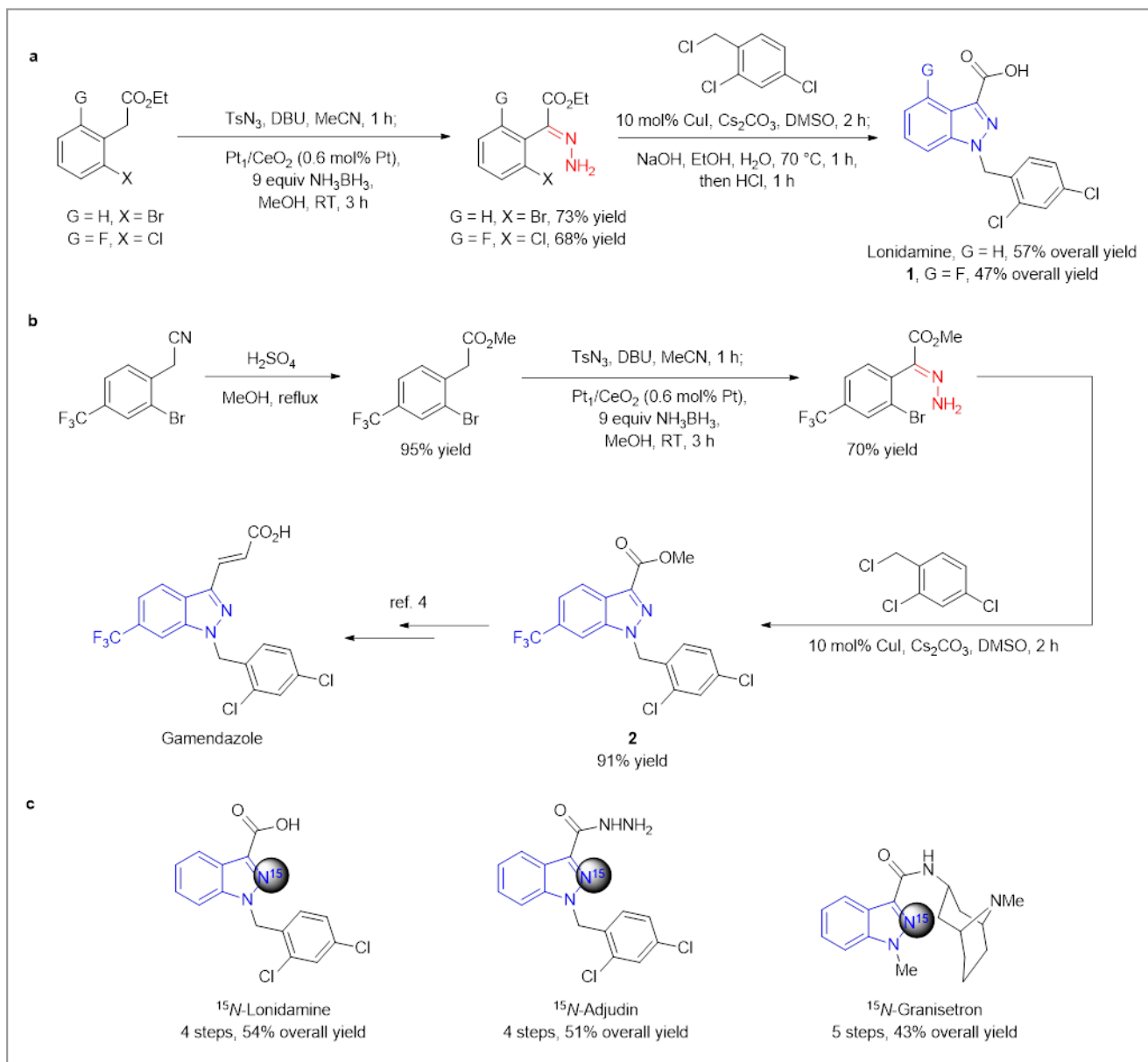
Professor Koh further remarked: “The diazo substrates can be generated in situ from readily available carboxylic esters in one-pot for subsequent hydrogenation to *E*- α -hydrazone esters, by-passing the tedious purification of diazo precursors. We have realized the gram-scale synthesis of *E*- α -hydrazone esters for preparing 1*H*-indazole related pharmaceuticals and their ¹⁵N-labeled derivatives” (Scheme 3).

Professor Loh concluded by examining future perspectives of this work: “By developing the highly efficient and robust Pt₁/CeO₂ SAC, we have not just provided a new platform for the expedient synthesis of *E*- α -hydrazone esters and 1*H*-indazole scaffolds. This work also serves to highlight that heterogeneous SACs can be successfully implemented in liquid-phase systems, which are typically dominated by homogeneous reactions, to facilitate the assembly of complex molecules. Further exploration of synthetic methods for scalable fabrication of SACs towards the rapid generation of molecular complexity has become more promising than ever.”

Mattias Fankle



Scheme 2 *E*-Selective synthesis of *N*-*H* hydrazone esters. (a) Direct conversion of readily available carboxylic esters into *N*-*H* *E*-hydrazones in a single vessel enhances the practicality of our catalytic method. (b) Proposed catalytic cycle highlighting the importance of the ester moiety in directing regio- and stereoselective Pt–H addition across the diazo N=N bond.



Scheme 3 Synthesis of 1*H*-indazole-derived biologically active compounds. (a) Anti-cancer lomidamine was assembled in 42% overall yield by a concise two-pot sequence, which may be used to prepare derivatives such as **1**. (b) Formal synthesis of gamendazole, a drug candidate for male contraception, was accomplished in 61% overall yield within 3 steps through 1*H*-indazole intermediate **2**. (c) The versatility of our protocol is further highlighted through facile preparation of ^{15}N -labelled analogues of key therapeutic agents.

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About the authors



Dr. C. Liu

Cuibo Liu obtained his Ph.D. from Tianjin University (P. R. of China) in 2015 (with Professor Bin Zhang). After that, he joined Professor Kian Ping Loh's group at the National University of Singapore for his postdoctoral research. His research interests are mainly focused on photocatalysis, single-atom-catalysis, as well as electrocatalysis by using nanomaterials for the selective synthesis of labelled molecules.



Dr. S. Xi

Shibo Xi obtained his B.S. degree from Sichuan University (P. R. of China) and his Ph.D. in OPTICS from Institute of High Energy Physics, Chinese Academy of Sciences (P. R. of China). He joined the Institute of Chemical and Engineering Sciences, Agency for Science, Technology and Research (Singapore) in 2012. Currently, his research interests involve the methodology and application of X-ray absorption fine structure.



Dr. Z. Chen

Zhongxin Chen obtained his Ph.D. with Professor Kian Ping Loh at the National University of Singapore in 2018. He continued his research on single-atom catalysis and confined catalysis for the transformation of small molecules into high-value chemicals in collaboration with Professor Ming Joo Koh.



Prof. K. P. Loh

Kian Ping Loh is a provost's chair professor in the department of chemistry at the National University of Singapore. He obtained his Ph.D. from Oxford University (UK) in 1996 and won the President's Science Award of Singapore in 2014. His research interests include single-atom catalysis, covalent organic frameworks, graphene and 2D materials, hybrid organic-inorganic materials and surface science.



Dr. H. Yan

Huan Yan received his Ph.D. in physical chemistry from the University of Science and Technology in China (USTC). Then he joined the National University of Singapore as a research fellow, focusing on the atomic design of heterogeneous catalysts via atomic layer deposition. In 2018, he joined the group of Professor Peter Stair at Northwestern University (USA), where he now focuses on the reforming of shale gas.



Prof. M. J. Koh

Ming Joo Koh is a President's assistant professor in the department of chemistry at the National University of Singapore. He obtained his Ph.D. with Professor Amir H. Hoveyda at Boston College (USA). His primary research focus is to develop sustainable and enabling catalytic solutions that address critical and unresolved problems in chemical synthesis by homogeneous base metal catalysis, heterogeneous single-atom catalysis and radical chemistry.

The Nazarov Cyclization

The Imperial era was a time of prolific discovery and development of new reactions and rules by Russian chemists: Zinin's reduction of nitrobenzene to aniline,¹ Markovnikov's Rule,² Zaitsev's Rule,³ the permanganate hydroxylation of alkenes (the Wagner oxidation),⁴ the Reformatskii reaction,⁵ the Wagner–Meerwein rearrangement,⁶ the Dem'yanov (Demjanow) rearrangement,⁷ the Arbuzov (Arbuzov) rearrangement,⁸ the Tishchenko reaction,⁹ the Zelinskii–Stadnikoff modification of the Strecker amino acid synthesis,¹⁰ the Wolff–Kishner reduction,¹¹ the Prilezhaev (epoxidation) reaction,¹² and the Chichibabin reaction¹³ among others. The impact of these imperial-era Russian organic chemists on the content of modern introductory organic chemistry courses can hardly be overstated. In contrast to this, the discovery and development of new organic reactions in Soviet Russia was almost non-existent. This dearth of creativity is what makes the subject of this Name Reaction Biography so remarkable.



Ivan Nikolaevich Nazarov

Ivan Nikolaevich Nazarov (1905–1957)¹⁴ was born in the village of Koshelevo in the Nizhny Novgorod district (oblast), approximately 100 km southwest of the capital city of the oblast. His parents were peasants who worked a small farm in the village. His childhood was a difficult one, and before he had graduated from the village school at age 16, he had been orphaned. His mother died when he was eleven, and he then lost

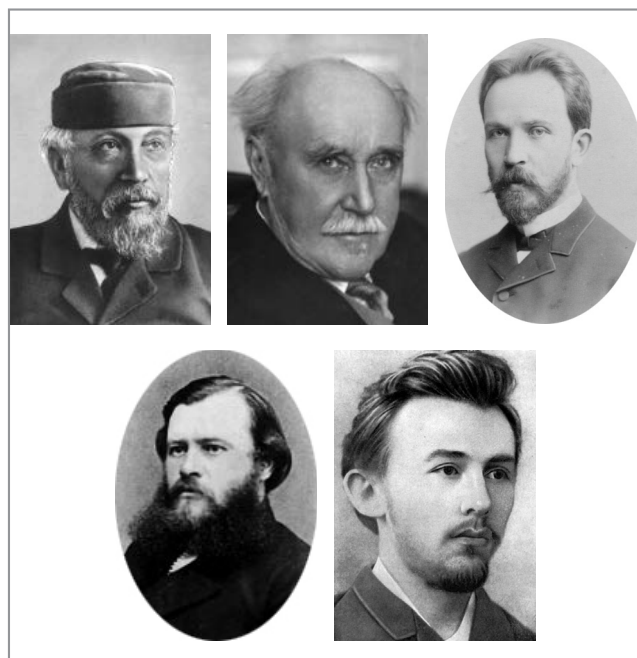
his father in the typhus epidemic of 1921. At fifteen, Nazarov was left to raise his orphaned younger brother and sister along with his older brother. Despite the hardships, he continued with his education. He graduated from the village school in 1922. In 1923, he was appointed to teach at the school, and he did such a good job that, in 1925, he was selected as Inspector of Schools in the County (uyezd) Department of Education in the city of Murom, 60 km southwest of Koshelevo. Then, as now, Murom was known for its concentration of monasteries.

As a young student at the beginning of his education, Nazarov had been strongly influenced by his biology teacher, who fostered his love for science. Consequently, it is no surprise that in 1925 he began his preparations for entry into the K. A. Timiryazev Agricultural Academy in Moscow. In 1927,



A photograph of the group of monasteries in the city center of Murom taken during the Imperial era

he was sent to Moscow to enter the Agricultural Academy. At this time, this institution was favored with the presence of some important chemists, including Academicians Ivan Alekseevich Kablukov (1857–1942) and Nikolai Yakovlevich Dem'yanov (1861–1938), both of whom had studied with Vladimir Vasil'evich Markovnikov (1837–1904). One of his



Nazarov's mentors (clockwise from top left): Kablukov, Dem'yanov, Favorskii, Pryanishnikov, Markovnikov

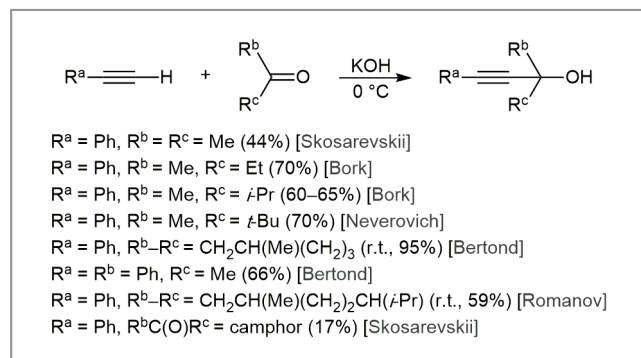
most influential instructors was the agronomist and biochemist, Dmitrii Nikolaevich Pryanishnikov (1865–1948).

Nazarov graduated from the Agricultural Academy in 1931, and was immediately appointed as a young researcher in the biochemical laboratory of the Nikitskii Botanical Garden. However, he fairly quickly decided that plant chemistry and agronomy was not the career for him, and he resolved to study organic chemistry. He therefore left Moscow for Leningrad (St. Petersburg), where he passed the entrance examinations and entered the laboratory of the great acetylene chemist, Aleksei Yevgrafovich Favorskii (1860–1945).

Nazarov was an extremely well-organized experimenter, and routinely carried out three or four experiments simultaneously. It did not take long for Favorskii to see the makings of an excellent research scientist in his new student. Nazarov quickly became his favorite student. Nazarov studied the reactions of aliphatic and aromatic metal ketyls for his research for the degree of *kandidat*, and he successfully defended his dissertation in 1934. That same year, the USSR Academy of Sciences moved from Leningrad to Moscow, and Nazarov moved his family to Moscow, where he was appointed to the newly organized Institute of Organic Chemistry of the Academy of Sciences. He spent the remainder of his career there.

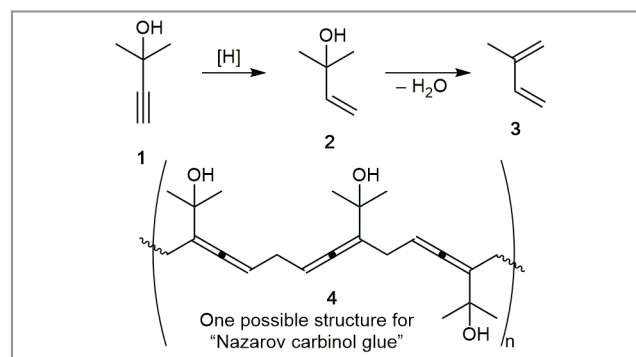
In 1905 Favorskii and his students had reported¹⁵ the synthesis of propargyl alcohols from alkynes and carbonyl compounds in the presence of solid potassium hydroxide (Scheme 1). Nazarov found that vinylacetylenes, obtained by the dehydration of these propargyl alcohols, underwent the Favorskii reaction more readily than acetylene itself, and in higher (typically above 90%) yields.

During World War II, Nazarov was seconded to the Russian war effort. His studies of the dehydration of alcohols such as 2-methylbut-3-yn-2-ol (**1**) were key in the synthesis of precursors to dienes such as isoprene (**3**) for the manufacture of



Scheme 1 The synthesis of propargyl alcohols by Favorskii's students reported in 1905

synthetic rubber (Scheme 2). At the same time, he discovered that partially polymerized 2-methylhex-5-en-4-yn-2-ol (**4**), obtained by treating the monomeric alcohol with benzoyl peroxide or nitric acid, was an excellent adhesive whose properties could be varied by changing the degree of polymerization. In 1942, he was awarded the Stalin Prize for this discovery, which proved to be critically important for front-line repairs of instruments, etc., by Russian soldiers.

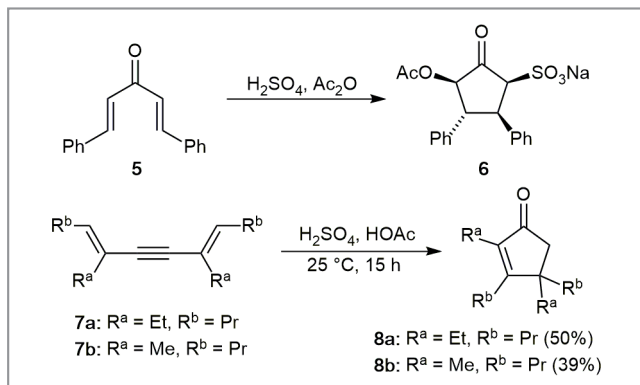


Scheme 2 Nazarov's war-related chemistry

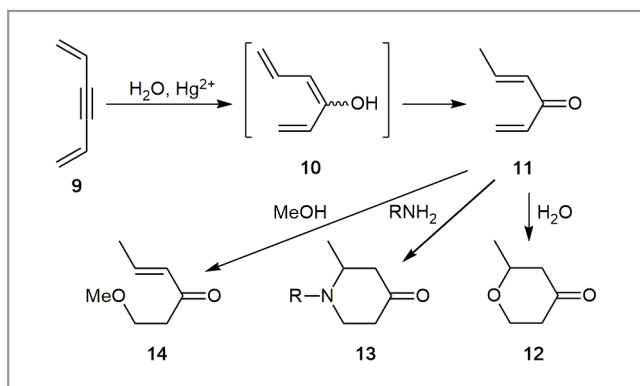
In 1936, Nazarov became head of a research group studying film-forming substances. In the course of this work, he began his work with vinylacetylenes. In 1941, he defended his Dr. Khim. dissertation, "Research in the field of acetylene derivatives. Synthesis of alcohols of the vinylacetylene series and their transformations."

Nazarov and his students were not the first to investigate the acid-catalyzed cyclization of divinyl ketones and divinylacetylenes. Vorländer and Schroedter had examined the reaction of dibenzalacetone (**5**) with concentrated sulfuric acid and acetic anhydride in 1903,¹⁶ but had not been able to identify the product (in 1974, Shoppee and Cooke elucidated its structure as **6**¹⁷). Three decades later, in 1933, Blomquist and Marvel reported their results from a study of the cyclization of dienyne **7** with sulfuric acid in acetic acid, but they assigned the structure of the cyclized product as being a cyclohexene derivative.¹⁸ The probable course of these early reactions is shown in Scheme 3. But it was not until the work of Nazarov and his students, that the outcome of the reaction was clarified; it is for this reason that the reaction now bears his name.

In 1941, Nazarov and his student, I. I. Zaretskaya, reported the synthesis of divinyl ketones (**11**) from divinylacetylenes (**9**) by mercury-catalyzed hydration and isomerization of the allyl vinyl ketone initially formed (Scheme 4). This paper is often quoted—incorrectly—as the first report of the Nazarov cyclization.¹⁹



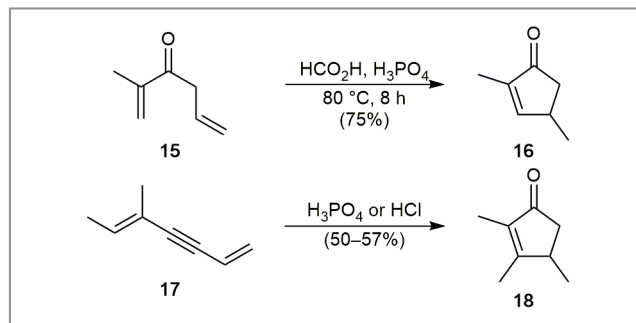
Scheme 3 Early experiments on the cyclization of divinyl ketones and dienes



Scheme 4 Divinyl ketones and heterocycles derived from them

This reaction made these previously inaccessible, cross-conjugated ketones readily available. Nazarov and Zaretskaya showed that these compounds could be readily converted into heterocycles such as 4-pyranones (**12**) and 4-piperidinones (**13**), as well as into conjugate addition products such as **14** (Scheme 4). The next year, the same authors published the first of a long series of reports on the hydration–cyclization of divinylacetylenes (Scheme 5).²⁰ They reported that when divinyl ketones were heated with a mixture of phosphoric and formic acids, or allowed to stand with a mixture of sulfuric and acetic acids, high yields of 2-cyclopentenones were obtained.

Despite numerous investigations, the mechanism of the Nazarov reaction remained an enigma until the 1960s, and the rise of the concept of the conservation of orbital symmetry first proposed by Japanese physical chemist, Kenichi Fukui (1918–1998) in 1952,²¹ and further developed by Robert Burns Woodward (1917–1979) and Roald Hoffmann (1937–).

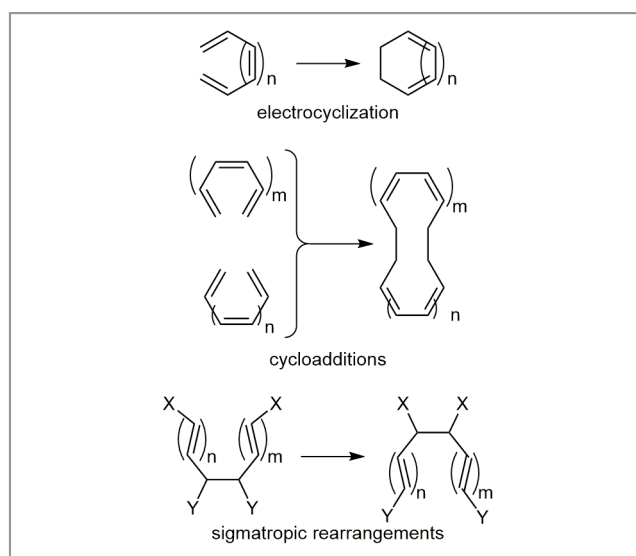


Scheme 5 Nazarov's first reported syntheses of cyclopentenones

In 1969,²² Woodward and Hoffmann revolutionized the use of pericyclic reactions in organic synthesis. Hoffmann and Fukui shared the Nobel Prize for Chemistry in 1981 for their work.

Nazarov's later work focused on the generation of carbocyclic products by exploiting acetylenes as synthons.

Woodward and Hoffmann defined pericyclic reactions as reactions occurring through a cyclic, delocalized transition state, and identified several classes of reactions, the most widely used of which are electrocyclizations, cycloaddition reactions and sigmatropic rearrangements (Scheme 6). As part of their work on the conservation of orbital symmetry, Woodward and Hoffmann characterized the Nazarov cyclization as a $[4n]$ electrocyclization of a substituted pentadienyl cation, which should proceed with conrotatory stereochemistry.



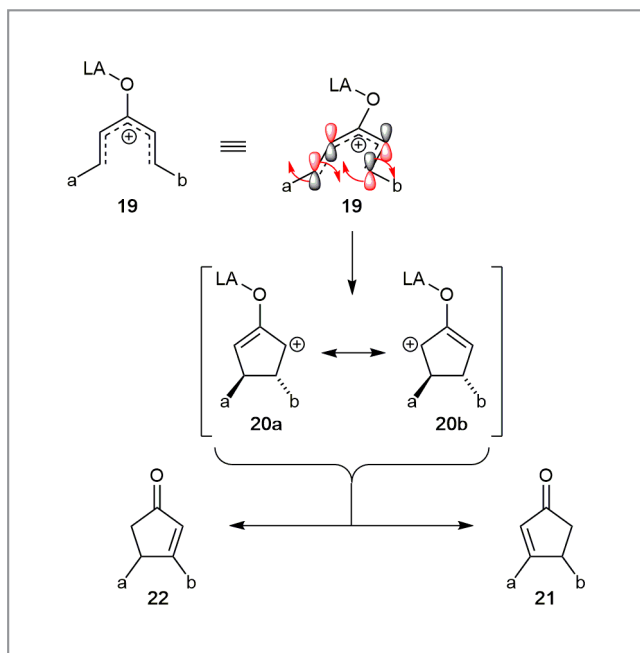
Scheme 6 Representative pericyclic reactions



From left: Fukui, Woodward, Hoffmann

In their early work, Nazarov and Zaretskaya showed that the cyclization of dienynes gave rise to regioisomeric products, often with low regioisomer preferences. Controlling the regiochemistry thus became the first major focus of research on the reaction. The accepted mechanism of the reaction is given in Scheme 7.

The reaction is initiated by the complexation of the carbonyl oxygen by a Lewis acid (LA). The conrotatory electrocyclicization of the resultant cation (**19**) gives a resonance-stabilized oxyallyl cation (**20**) that then loses a proton to give the enone (**21** or **22**). When groups “a” and “b” are similar (e.g., both alkyl), the equilibrium favors neither regioisomer

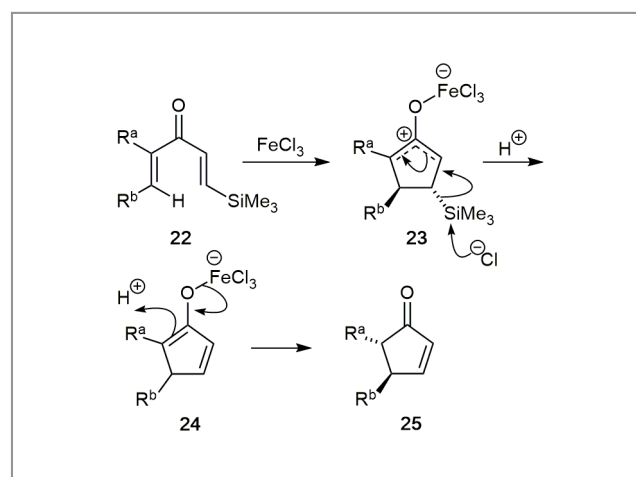


Scheme 7 The formation of regioisomers in the Nazarov cyclization

by a large amount. In 1977, the Nazarov cyclization figured prominently in the Merck synthesis of the indanone subunit of the diuretic, indacrinone.²³

The Nazarov reaction is not without its shortcomings, however.²⁴ The need for a strong protic or Lewis acid catalyst makes it unsuitable for use with compounds possessing acid-sensitive functional groups, and this problem is often exacerbated by the need to employ greater than stoichiometric amounts of the acid. One of the most successful approaches to controlling regiochemistry in the Nazarov cyclization has involved incorporating groups capable of stabilizing the intermediate oxyallyl cation, thus resulting in preferential deprotonation of the cation to give a preferred regioisomer of the product.

The silicon-directed Nazarov cyclization developed by Denmark and his research group is one such reaction.²⁵ In the Denmark approach, one of the vinyl groups was substituted at the β -position by a trialkylsilyl group; this allowed the stabilization of the oxyallyl cation by hyperconjugation with the C–Si σ bond.²⁶ It also leads to the alkene by elimination of the silyl group, overcoming the natural tendency of the carbocation to give the Zaitsev alkene as the major product. The course of the reaction is summarized in Scheme 8.



Scheme 8 The silicon-directed Nazarov cyclization

An alternative approach to controlling regiochemistry in the Nazarov cyclization was proposed by Frontier and her research group.²⁷ In this solution, the divinyl ketone carries an electron-releasing group (D:) at one α carbon and an electron-withdrawing group (E) at the other. The complementary nature of the two vinyl substituents makes one of the bipolar resonance contributors highly favored, as shown in Figure 1.

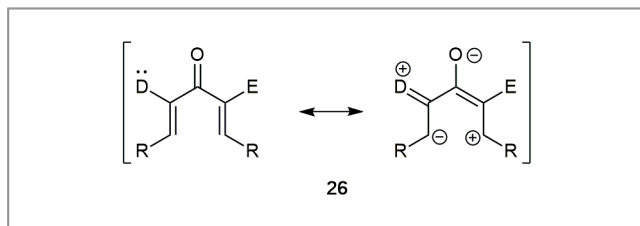
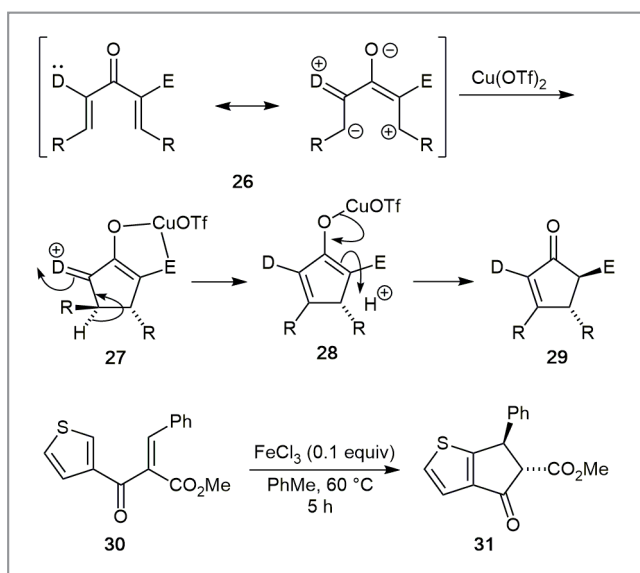


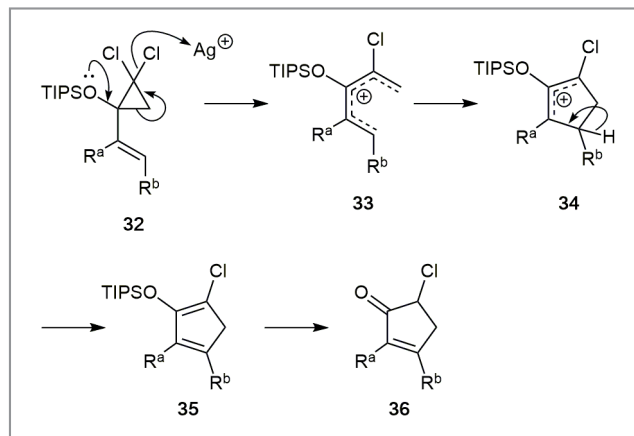
Figure 1 Resonance in a polarized dienone

This highly polarized dienone (**26**) is particularly amenable to the Nazarov cyclization under catalysis by mild Lewis acids such as copper(II) triflate (Scheme 9). This permits the reaction to be carried out with acid-sensitive groups. The application of this principle is illustrated by the FeCl_3 -catalyzed Nazarov cyclization of the thiophene **30** to the ketone **31**.²⁸



Scheme 9 The polarized Nazarov cyclization

A third option for forming the Nazarov cationic intermediate accomplished this by the reaction of a 2,2-dichloro-1-vinylcyclopropanol triisopropylsilyl ether **32** with a silver salt.²⁹ In this reaction, the abstraction of the halogen by the silver ion leads to a cyclopropyl cation that undergoes disrotatory ring opening to give the pentadienyl cation **33**, which then undergoes conrotatory electrocyclicization to **34** and subsequent deprotonation to give the cyclopentadiene **35**. Desilylation then gives the cyclopent-2-enone **36** with predictable regiochemistry (Scheme 10).



Scheme 10 The Nazarov cyclization from *gem*-dihalovinyl-cyclopropanes

The Nazarov cyclization has also been the subject of asymmetric synthesis; these efforts to control the absolute stereochemistry of the reaction are summarized in the reviews since 2011.³⁰

David Lewis

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