

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 (Arbuzow) 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

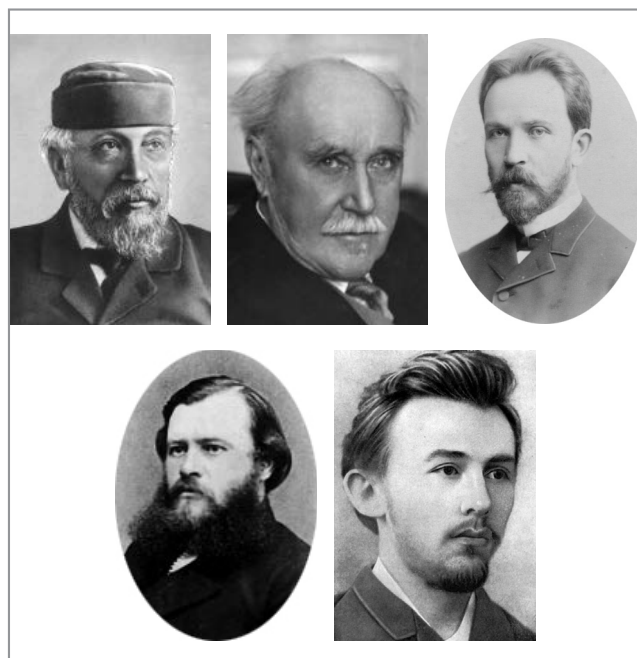
his father in the typhus epidemic of 1921. At fifteen, Nazarov was left to raise his orphaned younger brother and sister along with his older brother. Despite the hardships, he continued with his education. He graduated from the village school in 1922. In 1923, he was appointed to teach at the school, 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).

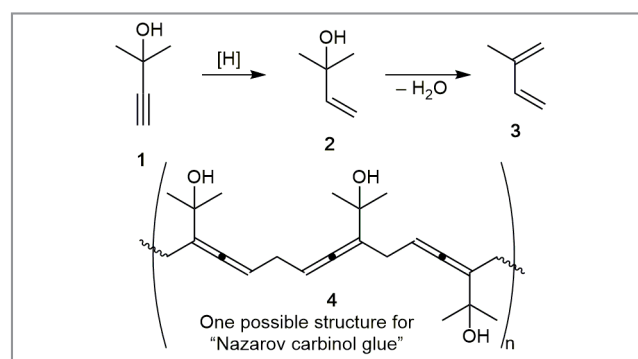
Nazarov graduated from the Agricultural Academy in 1931, and was immediately appointed as a young researcher in the biochemical laboratory of the Nikitskii Botanical Garden. However, he fairly quickly decided that plant chemistry and agronomy was not the career for him, and he resolved to study organic 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 propargylic 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

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.

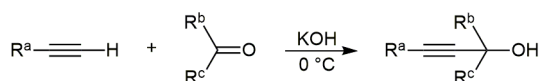


Scheme 2 Nazarov's war-related chemistry

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.*”

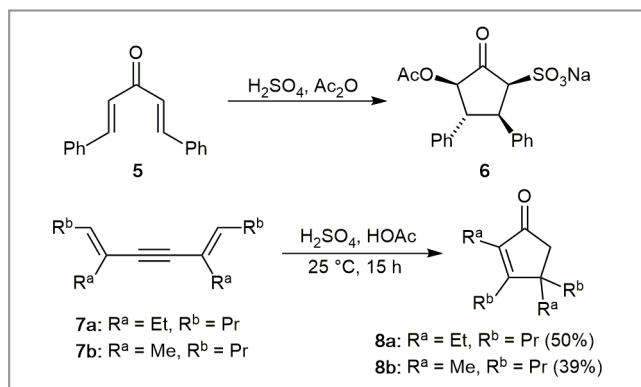
Nazarov and his students were not the first to investigate the acid-catalyzed cyclization of divinyl ketones and divinylacetylenes. Vorländer and Schroedter had examined the reaction of dibenzalacetone (**5**) with concentrated sulfuric acid and acetic anhydride in 1903,¹⁶ but had not been able to identify 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

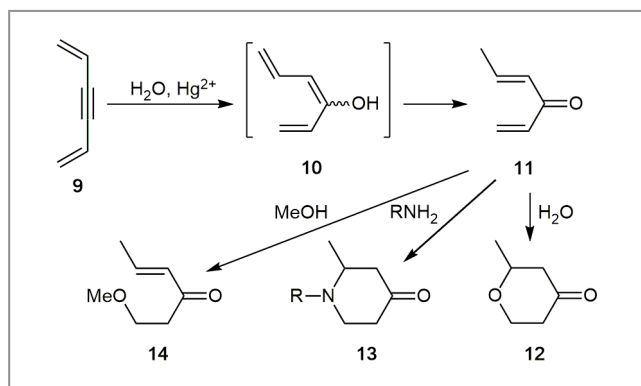


$R^a = \text{Ph}$, $R^b = R^c = \text{Me}$ (44%) [Skosarevskii]
 $R^a = \text{Ph}$, $R^b = \text{Me}$, $R^c = \text{Et}$ (70%) [Bork]
 $R^a = \text{Ph}$, $R^b = \text{Me}$, $R^c = i\text{Pr}$ (60–65%) [Bork]
 $R^a = \text{Ph}$, $R^b = \text{Me}$, $R^c = t\text{Bu}$ (70%) [Neverovich]
 $R^a = \text{Ph}$, $R^b-R^c = \text{CH}_2\text{CH}(\text{Me})(\text{CH}_2)_3$ (r.t., 95%) [Bertond]
 $R^a = R^b = \text{Ph}$, $R^c = \text{Me}$ (66%) [Bertond]
 $R^a = \text{Ph}$, $R^b-R^c = \text{CH}_2\text{CH}(\text{Me})(\text{CH}_2)_2\text{CH}(i\text{Pr})$ (r.t., 59%) [Romanov]
 $R^a = \text{Ph}$, $R^b\text{C(O)}R^c = \text{camphor}$ (17%) [Skosarevskii]

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



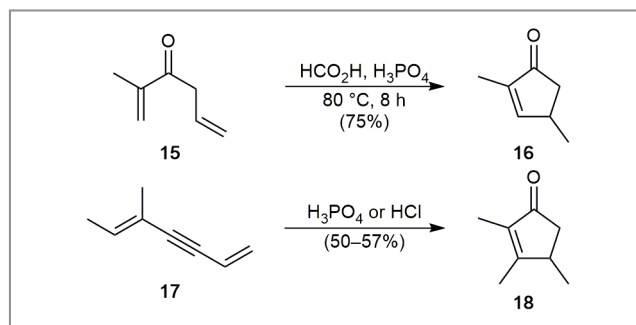
Scheme 3 Early experiments on the cyclization of divinyl ketones and dienes



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–).

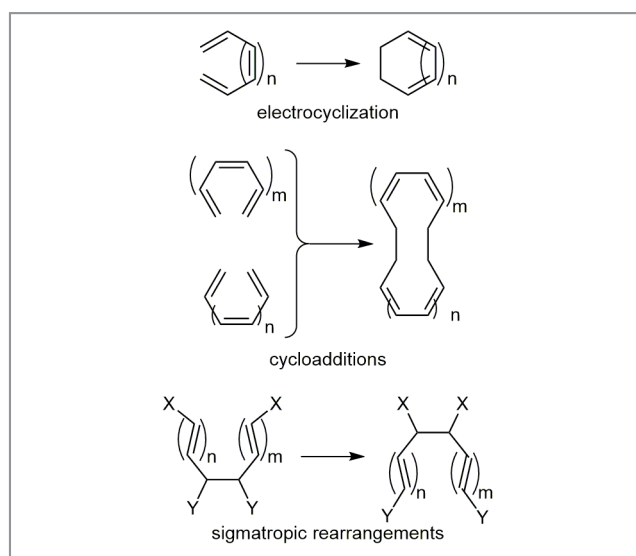


Scheme 5 Nazarov's first reported syntheses of cyclopentenones

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.



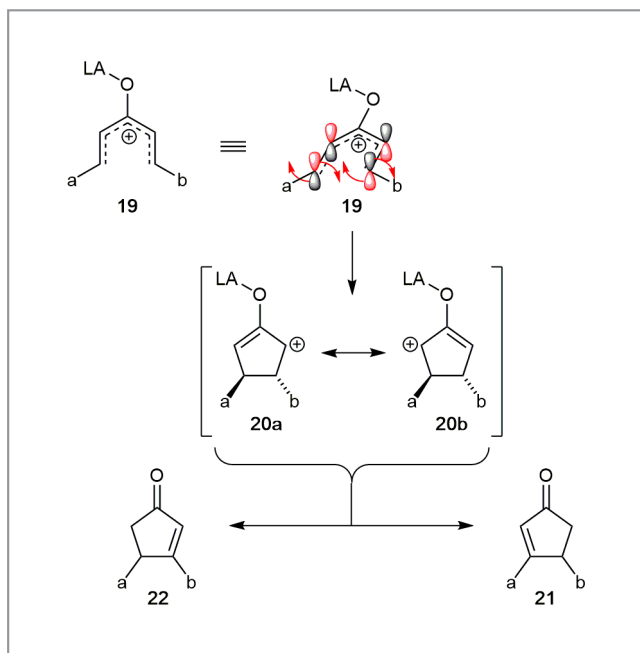
Scheme 6 Representative pericyclic reactions



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 electrocyclic cyclization 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

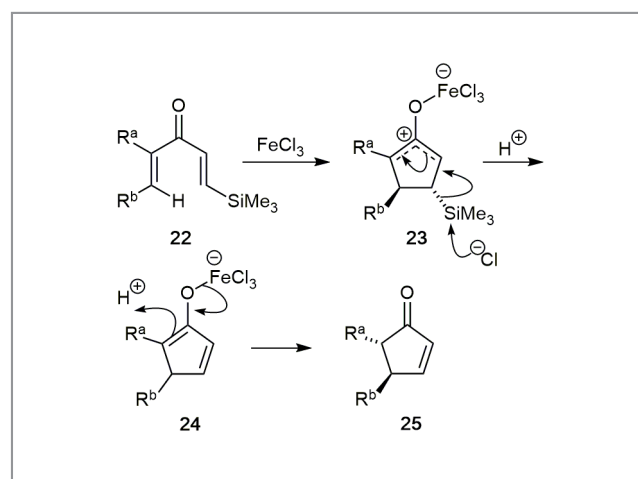


Scheme 7 The formation of regioisomers in the Nazarov cyclization

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.

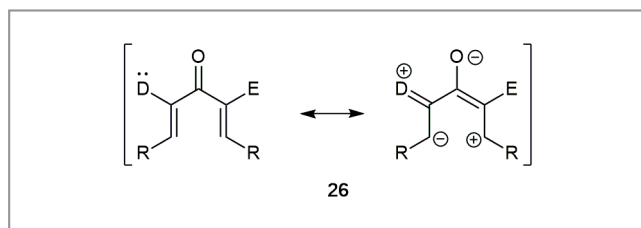
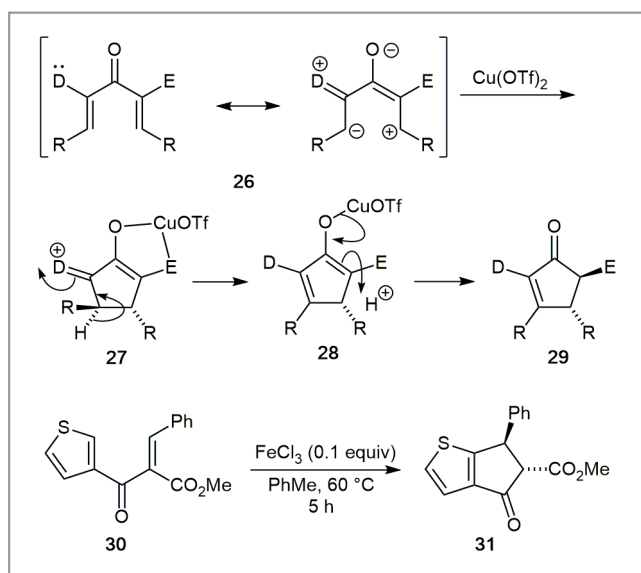


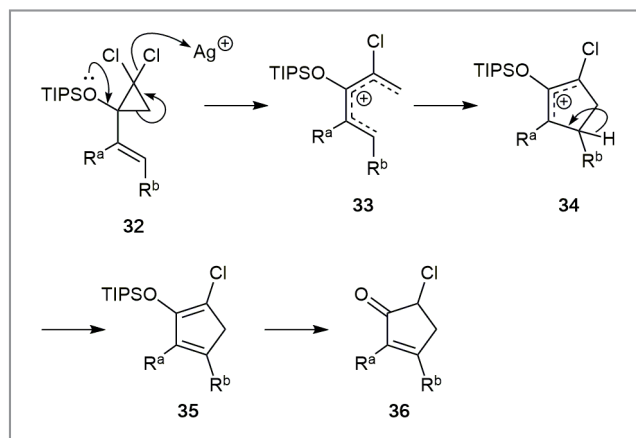
Figure 1 Resonance in a polarized dienone

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*-dihalovinylcyclopropanes

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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