

Reaction Regiochemistry – Markovnikov, Zaitsev and Hofmann

In previous columns in this series, the focus has been on name reactions in organic chemistry. But two of the oldest synthetic reactions – addition and elimination – are also associated by name with empirical rules proposed by the pioneering chemists who observed their regiochemical and stereochemical outcomes. These named rules are a major part of the teaching of these reactions in introductory organic chemistry courses.

Additions: Markovnikov's Rule

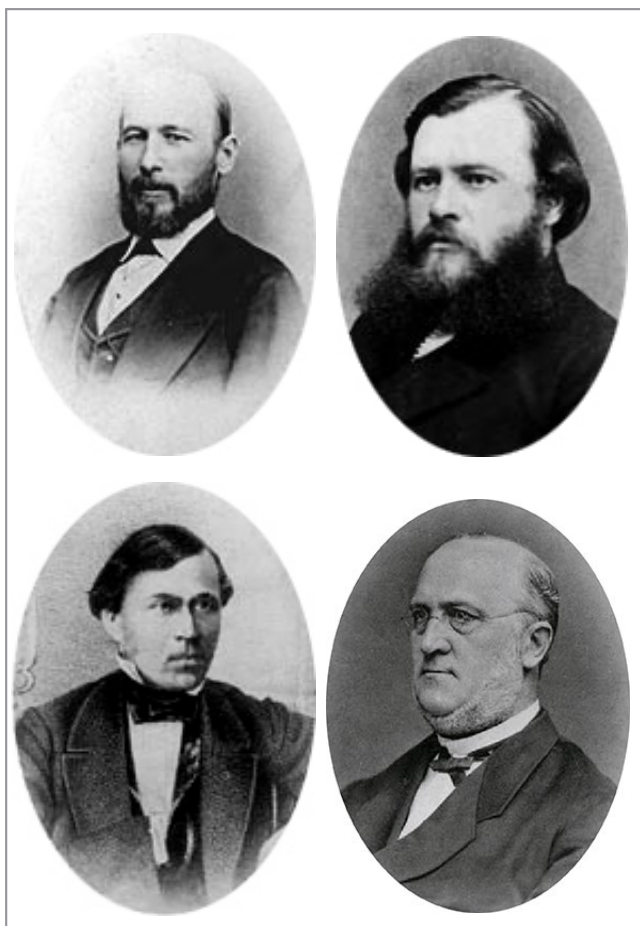
On November 6, 1869, Aleksandr Mikhailovich Butlerov (1828–1886), newly appointed as Professor at the St. Petersburg Medical-Surgical Academy, read a paper by his former student and colleague at Kazan, Vladimir Vasil'evich

Markovnikov (1837/8–1904),¹ to the meeting of the Russian Chemical Society. This paper, which appeared in the November issue of Volume 1 of the Journal of the Society,² contained the first disclosure of the empirical rule for predicting the outcome of addition reactions that has borne Markovnikov's name since.

Markovnikov was born into the Russian nobility near Nizhnii Novgorod in December, but sources vary as to the year and village of his birth.^{3,4} His father, Vasilii Vasil'evich, was a Lieutenant in the Belevskii Jaeger Regiment; shortly after his son was born, he retired from his military post and took his family to the estate near Knyaginino that he had procured as part of the dowry of his wife, Lyubov Nikolaevna. Markovnikov was first taught to read by the village priest, and he read so voraciously that by the time he left home at 10 years old, he could read both French and German. At 10 years of age, he was sent to the Nizhnii Novgorod Alexander II Nobles Institute to complete his secondary education. In 1856, he entered the Juridical Faculty of the Imperial Kazan University as a student in cameral (economic) science.

At that time, Russia was implementing the German cameral system in an attempt to educate government workers better qualified to deal with new technologies. Part of the cameral course of study was a requirement that all cameral students take two years of science. Markovnikov had come in contact early with Modest Yakovlevich Kittary (1825–1880), the Professor of Chemical Technology, and Kittary's lectures captivated him. However, before he could take chemical technology for his required science, Kittary had left for Moscow. As a consequence, Markovnikov came under the influence of Aleksandr Mikhailovich Butlerov (1828–1886), whom we encountered in an earlier column in this series.⁵ This was a fortuitous happenstance for both men. When Markovnikov took his first course in organic chemistry (1859–1860), Butlerov was the teacher, and Markovnikov not only took notes in the course, but also published them by the lithographic process.⁶ By the end of that year, the two men were firm friends; in fact, Markovnikov became a regular visitor to Butlerov's home. Upon his graduation with the *Diplom*, Butlerov immediately seconded him to train for the professoriate.

Four months later, Markovnikov submitted his dissertation, on the subject of aldehydes, for the degree of *kandidat*.⁷ Note the spelling of his name – he changed it to the modern form during his graduate studies.⁸ This degree permitted him to be appointed to a salaried position as a laboratory assistant. He immediately began work for his *Magistr Khimii* degree, the



Top row (left to right): Butlerov, Markovnikov; bottom row (left to right): Kittary, Kolbe

minimum qualification that would permit him to take a faculty position at a university. In 1865, he successfully defended his dissertation, on the topic of isomerism.⁹

After completing his *M. Khim.*, Markovnikov was sent abroad for further study and research. Beginning in Berlin, he traveled through Heidelberg to Leipzig, where he began work in the laboratory of Hermann Kolbe (1818–1884). As a student with a graduate degree already, Markovnikov was allowed considerable latitude in deciding what his project should be (Kolbe addressed him as ‘Herr Doktor’). In 1867, he returned to Kazan, to a position as Extraordinary (Associate) Professor of Chemistry. He immediately set to completing his *Dr. Khim.* work and passing the required examinations. In the dissertation,¹⁰ he furthered his study of isomerism, and began to consider the reasons why certain reactions (especially free-radical substitution of hydrogen by chlorine and bromine) exhibited predictable regiochemistry.

One important part of the dissertation was devoted to studies designed to demonstrate that the unsatisfied valences in alkenes were on adjacent carbon atoms. During this part of his work, when he was attempting to locate the unsatisfied affinities by adding hydrogen halides to unsymmetrically substituted alkenes (1-butene, 1-pentene and isobutylene; Scheme 1) he discovered the empirical rule that now carries his name.

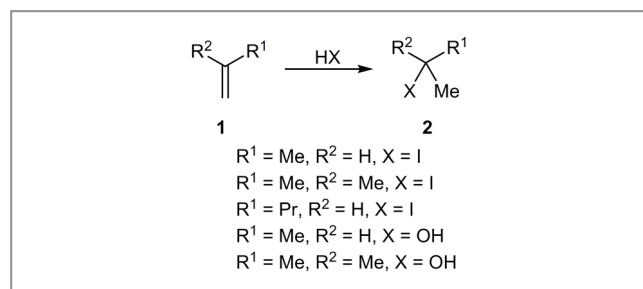
The Russian Chemical Society had been organized in 1868, and it published the first volume of its journal, the *Zhurnal Russkago Khimicheskago Obshchestva*, in 1869. Markovnikov published his Rule in the inaugural volume of the *Zhurnal*,² based on the research in his *Dr. Khim.* dissertation. The following year, he published the more widely cited paper containing his rule in *Liebigs Annalen der Chemie*.¹¹

The year after becoming *Dr. Khimii*, Markovnikov was promoted to Ordinary (Full) Professor, replacing his mentor, Butlerov, who had moved to St. Petersburg. Markovnikov continued at Kazan until 1872, when he, along with six colleagues, resigned from Kazan University to protest the treat-

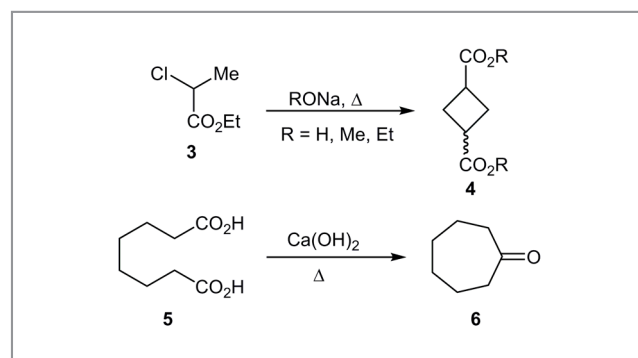
ment of Professor Pyotr Frantsevich Lesgaft (1837–1909), who had been barred from teaching physiology and denied promotion to Ordinary (Full) Professor because of his criticism of the unscientific methods used.

Markovnikov was not out of work long, however. Two weeks later, he received the call to Novorossiisk University in Odessa (now in the Ukraine) as Professor of Chemistry. In 1875, he accepted the call to Moscow, where he took a moribund program and built it into one of the best in Russia. At Moscow, he began research into the compositions of the Caucasus oils that led to the founding of the field of petrochemistry in Russia. In the course of this work, he was instrumental in developing the chemistry of the cycloalkanes (which he called ‘naphthenes’). He became the first to synthesize derivatives of cyclobutane,¹² by the serendipitous reaction between ethyl α -chloropropionate and base (Scheme 2). He also prepared suberone (**6**) by the pyrolysis of the calcium salt of suberic (octanedioic) acid (Scheme 2),¹³ and demonstrated its identity with cycloheptanone. This made Markovnikov the first organic chemist to make cyclic compounds with less than five and more than six atoms in the ring.

In 1893, twenty-five years after his first faculty appointment at Kazan, Markovnikov’s enemies orchestrated his ouster from his Professorship using an arcane provision of the University Statute. He was replaced by Nikolai Dmitrievich Zelinskii (1861–1953), and although he retained his laboratory, he was evicted from the professorial apartment. He continued research until his death in 1904.^{1b} His legacy was enhanced by his students from Moscow, who included Nikolai Matveevich Kizhner (1867–1935),¹⁴ Nikolai Yakovlevich Dem’yanov (1861–1938),⁵ and Aleksei Yevgen’evich Chichibabin (1871–1945),¹⁵ all of whom have their own eponymous reactions. In 2017, Lomonosov Moscow State University established the Markovnikov Medal (Figure 1) in honor of the great chemist.^{1a}



Scheme 1 Addition reactions carried out by Markovnikov



Scheme 2 Markovnikov’s syntheses of the first cyclobutene derivative (**4**) and suberone (**6**)

$$\left\{ \begin{array}{l} C_4H_5 \\ C_4H_5 \\ C_4H_5 \\ C_4H_5 \end{array} \right\} NO, HO=2HO + \left\{ \begin{array}{l} C_4H_5 \\ C_4H_5 \\ C_4H_5 \end{array} \right\} N + C_4H_5$$

(C=6, H=1, N=14, O=8)

$$\begin{array}{c} Et \\ | \\ Et-N^+-Et \\ | \\ Et \end{array} HO^- \xrightarrow{\Delta} \begin{array}{c} Et \\ | \\ Et-N-Et \\ | \\ Et \end{array} + H_2O + H_2C=CH_2$$

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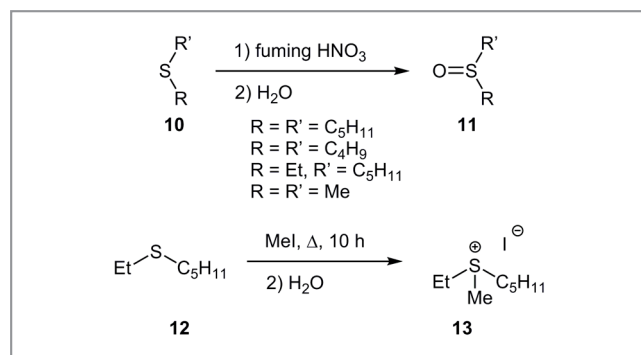
The Zaitsev Elimination

The alternative regiochemistry for elimination – giving the most substituted alkene as the major product – was reported by Zaitsev in 1875 for the eliminations of alkyl iodides by base.¹⁹

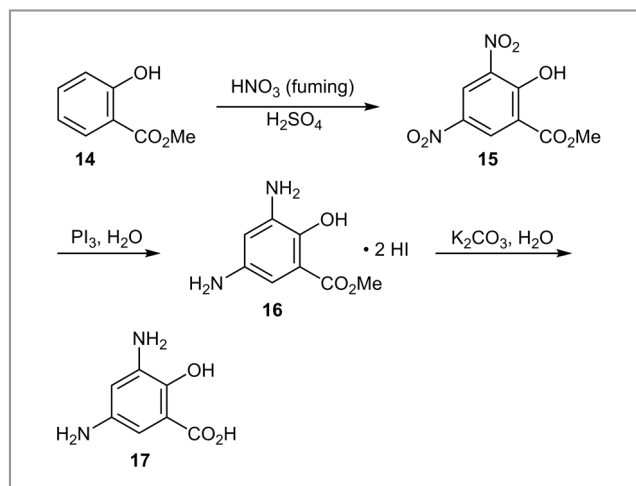
Zaitsev was born into a family that had held a prominent place in the trading guilds in the city of Kazan following the conquest of the Kazan khanate by Ivan IV ('The Terrible'). Zaitsev's father, Mikhail Savvich, had intended that his son enter the guilds after completing his studies at the Gymnasium, as his family had done for generations. Zaitsev, however, was determined to take another path. He entreated his maternal uncle, the astronomer Mikhail Vasil'evich Lyapunov (later Professor at Kazan University), to persuade his father to permit him to enter the university. Mikhail Savvich acquiesced to his brother-in-law's request, but only on the condition that Aleksandr enter the Cameral division of the Juridical faculty; in 1858, Zaitsev entered Kazan University as a cameral student.²⁰

As with Markovnikov before him, this decision brought him under the influence of Butlerov, who ultimately changed the course of his career... but not before some serious misadventures after his graduation with the *diplom* that came about because he flouted tradition. Zaitsev left Kazan immediately after receiving his *diplom*, using his inheritance (his father had died shortly before his graduation), to follow his older brother Konstantin Mikhailovich (born 1840) to the Marburg laboratory of Hermann Kolbe. He did not wait to complete the degree of *kandidat*, which was the minimum qualification for obtaining a salaried position at a Russian university.

In Marburg, Zaitsev worked with organic sulfur compounds (Scheme 4). In the process, he became the first to prepare both the sulfoxides (**11**)²¹ and the sulfonium salts (**13**),²² compounds that were to become useful compounds in organic synthesis.²³ During the 1864–1865 academic year,



Scheme 4 Zaitsev's sulfur chemistry



Scheme 5 Zaitsev's preparation of diaminosalicylic acid

Zaitsev worked in the Paris laboratory of Adolphe Wurtz; there he prepared diaminosalicylic acid (**17**) and its derivatives (Scheme 5).²⁴ At the end of this year, Kolbe had accepted the call to Leipzig, but Zaitsev had by then run out of money, so he could not follow; he returned to Russia.

As early as 1863, Zaitsev had come to the realization that he would need the degree of *kandidat* to return to a salaried position in Russia. He tried to rectify the situation by submitting a 76-page, handwritten dissertation '*The Theoretical Views of Kolbe on the Rational Constitution of Organic Compounds and Their Relationship with Inorganic Compounds*' for the degree.²⁵ The fact that he wrote a dissertation whose views were diametrically opposed to those of Butlerov, and submitted it to *Butlerov* (!) for examination is, in my opinion, indicative of two things. First, he failed to see the fundamental differences between Butlerov's and Kolbe's views on structure, and second, he was not particularly committed to Butlerov's structural theory at the time. It certainly brought the usually placid and gentlemanly Butlerov to a paroxysm of rage, which he made clear by his notes in the margin. Unsurprisingly, the degree was not awarded.

Having returned to Russia without the degree of *kandidat*, he could not occupy a salaried position at a university, but this master of ingratiation applied to Butlerov 'as a private (i.e., unsalaried) person.' Butlerov, who recognized the master synthetic chemist in this poor theoretician, accepted his offer, and immediately set him to work to submit his Paris work for the degree of *kandidat*.²⁶ This time, the degree was awarded, and he became a salaried Assistant in the Agronomy laboratory.

In order to become a professor, Zaitsev needed the degree of *Magistr Khimii* (*M. Khim.*), which was conferred by the

Physics-Mathematics Faculty. As a cameralist, he was not eligible to submit his dissertation to this Faculty, but by obtaining a doctoral degree from a western university he might become eligible. Markovnikov had relied on Butlerov's intercession, but Zaitsev was much more impatient. He submitted his work from Marburg to Kolbe at Leipzig, and was awarded the Ph.D. there in 1866. Even so, it still took Butlerov's intercession for him to receive permission to submit his dissertation for the *M. Khim.* He wrote up his work on sulfur compounds from Germany²⁷ and submitted it in 1867; he was awarded the degree in 1868. In 1869, he was promoted to Extraordinary Professor of Chemistry. In 1870, he successfully defended a dissertation for the *Dr. Khim.* degree,²⁸ containing work on the reduction of acid chlorides with sodium amalgam in ether buffered with carbon dioxide, and was promoted to Ordinary Professor.

As a Professor at Kazan, Zaitsev focused his research on the synthesis of alcohols by means of organozinc reagents. His own work had extended the work of Butlerov²⁹ to the use of alkylzinc iodides as nucleophiles with acid chlorides. This reaction gives tertiary alcohols with two identical alkyl groups (**19**; Scheme 6, top) provided that the alkyl group on the alkylzinc halide is methyl, ethyl or allyl.³⁰ With his students Innokentii Ivanovich Kanonnikov (1854–1902)³¹ and Yegor Yegorovich Vagner (Georg Wagner, 1849–1903),³² Zaitsev expanded the reaction to the synthesis of secondary alcohols by replacing the acid chloride with an aldehyde or formate ester (Scheme 6, middle). Zaitsev's next student to gain his own eponymous

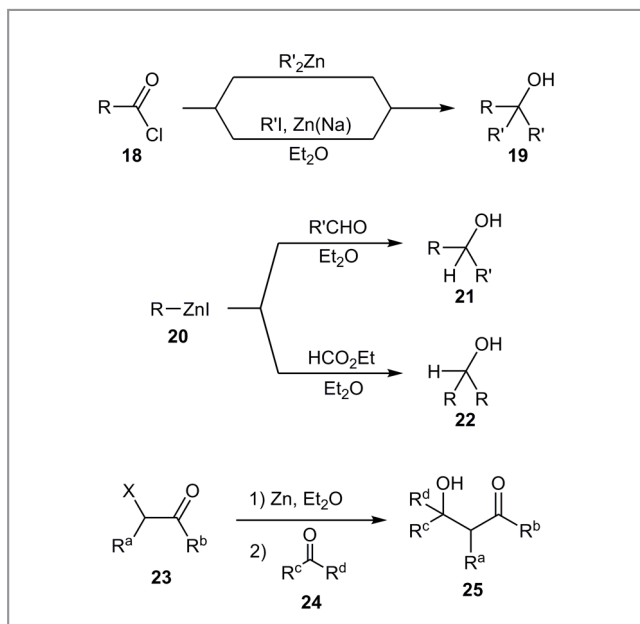
reaction was Sergei Nikolaevich Reformatskii (1860–1934). Reformatskii replaced the alkene π bond in the allylic iodide with a carbonyl group, thus using an α -halocarbonyl compound as the nucleophile (Scheme 6, bottom).³³



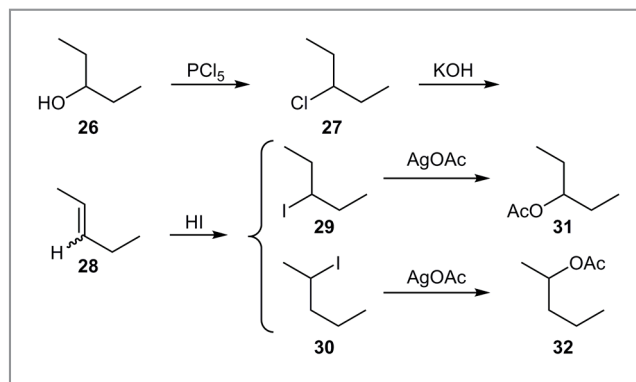
Left to right: Kanonnikov, Wagner (Vagner), Reformatskii

On October 12, 1875, a series of papers from Zaitsev's Kazan laboratory were received by the Editor of *Justus Liebig's Annalen der Chemie*, and published in the last part of that journal for 1875.^{19a,b} On November 6, the same year, the same series of papers were read by A. M. Butlerov and Ye. Ye. Vagner before the Russian Physical-Chemical Society, and appeared as the final articles published in volume 7 (1875) of the *Zhurnal Russkago Fiziko-Khimicheskago Obshchestva*.^{19c} A reading of these papers confirms that the German papers are verbatim translations of the Russian.

The first paper in each language^{19a,e} is largely a theoretical consideration of eliminations from unsymmetrical, straight-chain secondary halides. Zaitsev begins with Markovnikov's Rule, and then examines Markovnikov's experiments. From this, he reasoned that the elimination from a secondary or tertiary halide could give just one alkene only if all the alkyl groups attached to the halogen-bearing atom are identical,



Scheme 6 Organozinc syntheses by Zaitsev and his students



Scheme 7 Conversion of 3-pentanol into 2-pentanol

and should also give more than one alkene if the alkyl groups are not identical. In the paper by Vagner and Zaitsev, the conversion of 3-pentanol to 2-pentanol is described.^{19b,c,34} The sequence used is summarized in Scheme 7.

This work confirmed Zaitsev's summary of the literature precedents in terms of the most substituted alkene being the major product of the elimination.

Manipulating Regiochemistry

As organic synthesis entered the twentieth century, chemists moved to exert regiochemical control over reactions, over what had been the main emphasis of the nineteenth, chemoselectivity. Following the Lewis theory of bonding, this ultimately led to the intense research into the mechanisms of organic reactions by E. David Hughes (1906–1963) and Sir Christopher Kelk Ingold (1893–1970). Prior to these two giants of physical organic chemistry, it was Nikolai Aleksandrovich Menshutkin (1842–1907) who had first begun the systematic study of the effects of structure on reactivity. Although Hofmann had prepared quaternary ammonium hydroxides, it was Menshutkin who noted that the structure of the amine and the alkyl halide both had a major influence on the rate of the quaternization reaction. It was during these studies that he made the (for the time) profound observation that the solvent, which had theretofore been viewed as a non-participant in the reaction, had a dramatic effect on the rate of quaternization.³⁵ This solvent effect was to play an important part in the studies of substitution and elimination by Hughes and Ingold two decades later.³⁶

Among the substantial early studies of elimination reactions investigated by Hughes and Ingold, the origin of the Hofmann regiochemistry occupies an important part.³⁷ Based on their observations, Hughes and Ingold proposed a rationalization of the Hofmann orientation (although this was later shown to be too simplistic).

Markovnikov himself recognized that his empirical rule was not universally applicable, because he, himself, had observed that the regiochemistry of the addition of hydrogen bromide to alkenes was not consistent. The origin of this phenomenon was eventually clarified by Morris Selig Kharasch (1895–1957), who coined the term 'peroxide effect' and quantitated it.³⁸ The inversion of regiochemistry is now attributed to the change in mechanism from ionic to radical.

Negative Interpersonal Dynamics

We cannot leave the discussion of the Markovnikov and Zaitsev rules without considering the relationship between the two young Kazan men. Zaitsev and Markovnikov overlapped at



Top row (left to right): Hughes, Ingold. Bottom row (left to right): Menshutkin, Kharasch. (Image of Kharasch from University of Chicago Photographic Archive [apf1-03193])

Kazan, but they were far from friends. In fact, there was an intense antipathy – to the point that despite the prolific work of photographers recording the chemists of the Russian Empire, I have never seen a single photograph where both chemists are in the same frame. This feud lasted until Markovnikov's death. The possible origins of this feud have been discussed,³⁹ but the question of why the feud arose is still open to interpretation.⁴⁰

And Now?

Unfortunately for organic chemistry, H. C. Brown ignored the mechanism of addition when he termed the regiochemistry of hydroboration, 'anti-Markovnikov'. This has led to Markovnikov's rule becoming a source of controversy,⁴¹ because Brown's designation assumes that the hydrogen atom in the reagent is electrophilic.⁴² In borane, it is not. Nevertheless, the term is now in almost universal use. The regiochemistry of hydrometallation and carbometallation reactions that

are frequently key steps in a catalytic cycle is usually anti-Markovnikov, so the anti-Markovnikov regiochemistry has become a key target for synthetic chemists.^{1a}

In similar fashion, the preference for Zaitsev regiochemistry in E1 eliminations, and in E2 eliminations from conformationally flexible halides and sulfonates, has spurred research to obtain the Hofmann regioisomer from a precursor lacking an ammonium or sulfonium leaving group. The simplest method for doing this was shown by Hughes and Ingold to be simply using a sterically hindered base. Sterically hindered alkoxide bases such as potassium *tert*-butoxide, sterically hindered strong amide bases (e.g., LDA and similar amide bases), and non-nucleophilic amidine bases (e.g., DBN and DBU) have all been used to increase the percentage of the Hofmann regioisomer of the alkene in the product mixture.

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