

Carbocation Rearrangements: The Pinacol, Wagner–Meerwein, Demjanov, and Tiffeneau–Demjanov Rearrangements

The Pinacol Rearrangement

The first carbocation rearrangement to be observed and characterized was the pinacol rearrangement, discovered by German chemist Rudolph Fittig (1835–1910, Figure 1);^{1,2} an excellent account of the history of this reaction has been given by Berson.³ Fittig prepared pinacol (**2**) by the reaction of acetone (**1**), previously purified through its bisulfite addition product, with sodium metal, and he then prepared pinacolone (**3**) by dehydrating the pinacol with sulfuric acid (Scheme 1). Both syntheses were accomplished before atomic weights had been settled, and barely after Kekulé and Couper had proposed their versions of the structural theory of organic chemistry (in 1858).⁴

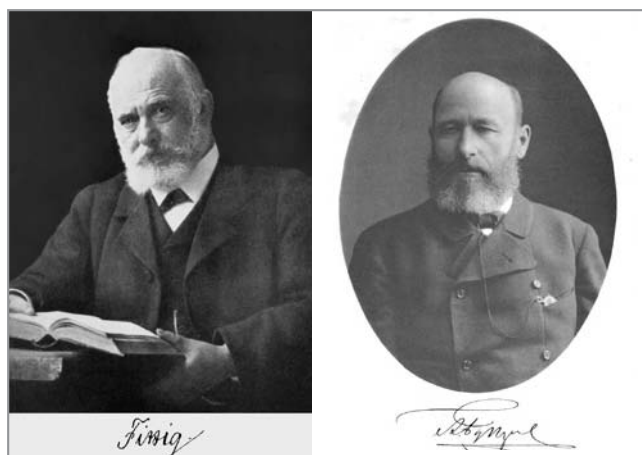
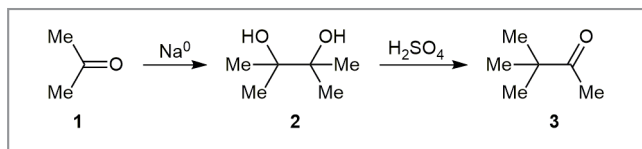


Figure 1 Fittig (left) and Butlerov (right)

The key to this reaction actually awaited the work of Aleksandr Mikhailovich Butlerov (1828–1886; Figure 1), the Russian professor of chemistry at Kazan Imperial University, and the pioneer of and ardent advocate for structural theory.

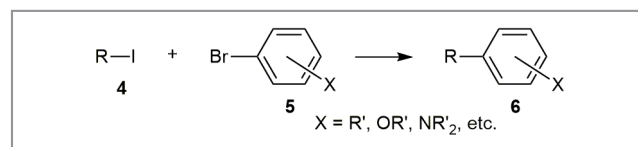


Scheme 1 Synthesis of pinacol and pinacolone

He was responsible for first proposing the correct structure of both pinacol and its acid rearrangement product.⁵

Fittig was born in Hamburg, and educated in Göttingen, where he took his Ph.D. under Heinrich Limpricht and Friedrich Wöhler. Following his graduation, Fittig remained at Göttingen, rising through the academic ranks (Assistant to Wöhler in 1858, Docent in 1860, Extraordinary (Associate) Professor in 1870). In 1870, he was appointed Ordinary Professor at Tübingen, and in 1876 he moved to Strasbourg as Professor. Here, the chemistry laboratories were constructed from his plans. He stayed at Strasbourg for the remainder of his life.

In addition to the synthesis and rearrangement of pinacol, Fittig reported a modification of the Wurtz coupling of alkyl halides⁶ with sodium, by replacing part of the alkyl halide with an aryl halide. The reaction, now known as the Wurtz–Fittig reaction,⁷ gives the corresponding alkylbenzene **6** (Scheme 2) by a cross-coupling pathway. Typically, the alkyl halide is an alkyl iodide, and the aryl halide is an aryl bromide.



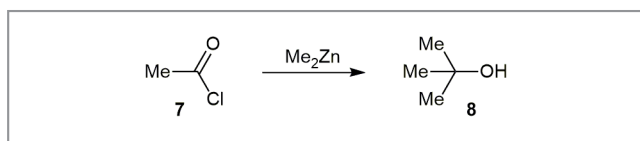
Scheme 2 Fittig's modification of the Wurtz coupling

Butlerov was born into the minor Russian nobility in Chistopol and educated at Kazan University in Russia. As a student at Kazan, he had been strongly influenced by Nikolai Nikolaevich Zinin (1812–1880), the discoverer of the reduction of nitrobenzene to aniline, and the subject of a later column in this series. Although Butlerov had begun his study of chemistry under Karl Karlovich Klaus (1796–1864, the discoverer of ruthenium), Klaus was a strong adherent of Berzelius's dualistic theory, and young Butlerov soon gravitated to Zinin with his more modern perspectives. In 1847, Zinin moved to the St. Petersburg Medical-Surgical Academy, and Butlerov reverted to entomology, his first love.

Following Zinin's departure, Kazan University needed a chemist, so, despite his personal preference for entomology, Butlerov was moved into chemistry as Klaus's assistant. He was quickly pushed through his *Magistr Khimii* (*M. Khim.*) and

Doktor Khimii (Dr. Khim.) degrees to allow him to be appointed as Extraordinary Professor of Chemistry. Neither his *M. Khim* nor his *Dr. Khim*. dissertation was more than marginally acceptable (his *Dr. Khim*. dissertation was failed when he presented it at Kazan); neither presaged the brilliant theoretician who would be developed by a *komandirovka* in Western Europe after his appointment as Extraordinary Professor.

Shortly after his return to Russia, he developed his own version of Structural Theory,⁴ thus becoming one of the young organic chemists at the forefront of the science. Unlike Couper and Kekulé, Butlerov used his theory to predict the existence of new compounds, *which he then prepared*. With his student Vladimir Vasil'evich Markovnikov (1838–1904), Butlerov took structural theory from an avant-garde theory to conventional wisdom.⁵ Structural theory, as modified by van't Hoff and Le Bel's stereochemical deductions, was critical to the study of rearrangement reactions. One of Butlerov's earliest successes was his synthesis of *tert*-butyl alcohol (Scheme 3).



Scheme 3 Butlerov's synthesis of *tert*-butyl alcohol

The Wagner–Meerwein Rearrangement

Carbocations and their rearrangements are almost ubiquitous in the biosynthesis of terpenoids and steroids and they are responsible for a dizzying array of natural products. Figure 2 shows representative monoterpenes [geraniol (**7a**) and fenchone (**8**)] and sesquiterpenes [farnesol (**9a**), nootkatone (**10**), modhephene (**11**), and isocomene (**12**)]. All of the cyclized terpenoids in Figure 2 are derived from the acyclic precursors [geranyl pyrophosphate (**7b**) and farnesyl pyrophosphate (**9b**)] by cationic cyclizations followed by one or more rearrangements in the biosynthetic pathway.

By far the most commonly encountered carbocation rearrangements are Wagner–Meerwein rearrangements.⁸ The first such rearrangement characterized, was reported by the Russian organic chemist, Yegor Yegorovich Vagner (1849–1903; Figure 3), who is better known in the west by the German form of his name, Georg Wagner. Towards the end of his career, Wagner had turned his attention to the structures of the bicyclic monoterpenes. In the course of this research, he was able to determine the relationship between the pinane, bornane and camphane ring systems (Figure 4).⁹ The lower

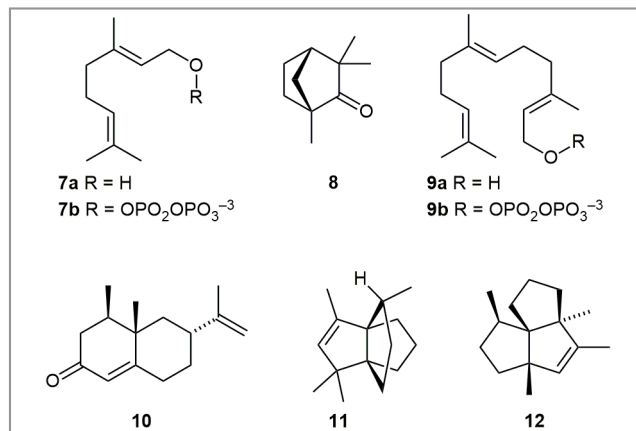


Figure 2 Representative terpenes with rearranged carbon skeletons

diagram in Figure 4 (in parentheses) clarifies the structural sequence in the original.

In 1914, Hans Lebrecht Meerwein (1879–1965, Figure 3) undertook a systematic study of carbocation rearrangements, publishing the first papers that established the link between the pinanes, camphanes and bornanes.¹⁰ The 1914 paper^{10a} is titled “Über den Reaktionsmechanismus der Umwandlung von Borneol in Camphen,” and it establishes the pattern of the 1,2- shift observed in the bicyclic terpenes. Only in 1922 did Meerwein and van Emster explicitly invoke a carbocation (Figure 5).¹¹

Wagner's family originated in East Prussia, but Wagner himself used the name ‘Yegor,’ a derivative of ‘Georgii’ that emphasized his Russian nationality. Wagner's father was a government official whose job entailed a great deal of traveling, so Wagner was entrusted to the care of his maternal grandparents after his mother died. When his grandfather died, he was sent to boarding school in modern Latvia, approximately 1700 km (1050 miles) west of Kazan.

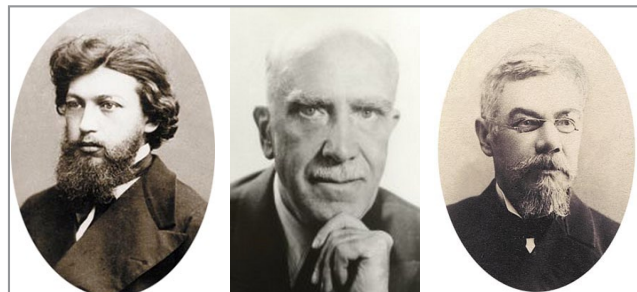


Figure 3 (left to right) Vagner (Wagner), Meerwein and Zaitsev

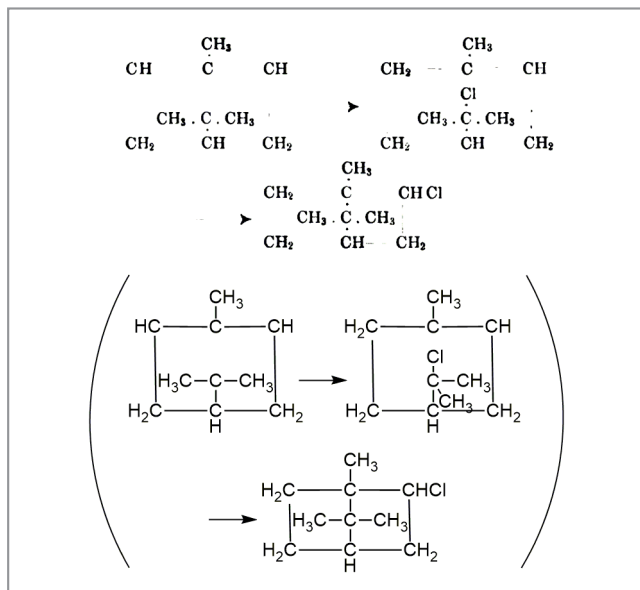


Figure 4 Wagner's description of the relationship between the pinane, camphane and bornane monoterpenes

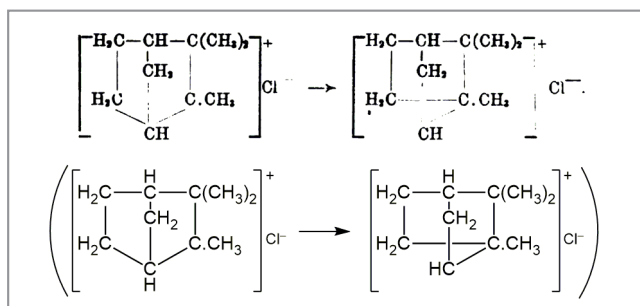
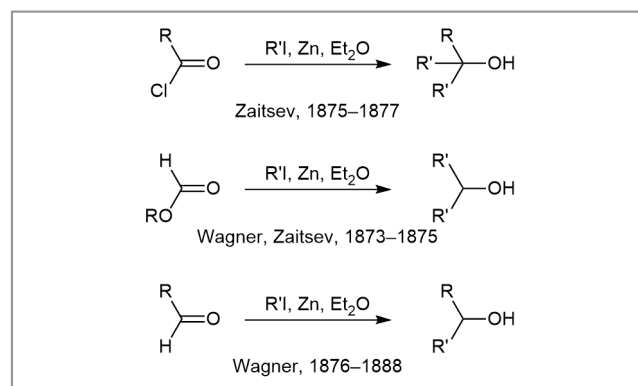


Figure 5 Meerwein and van Emster, 1922

He did not enjoy being at school, and he ran away to return to Kazan before graduating. He had enough money to cover only the first two thirds of the trip by train, so he completed the last 600 km (375 miles) on foot, begging for food along the way. Intensive home-schooling after his return permitted him to enter Kazan University in 1867. He entered the university as a student in law, but in 1869 (after his first classes in chemistry) he petitioned for a transfer to the Physics–Mathematics Faculty. The petition was granted, but at the cost of beginning his course of study from scratch.

As a student in chemistry, Wagner came under the influence of Aleksandr Mikhailovich Zaitsev (1841–1910, Figure 3). Zaitsev, who had continued the work of his own mentor, Butlerov, in the synthesis of alcohols from organozinc reagents,¹² oversaw Wagner's chemical research at Kazan.

Butlerov had prepared tertiary alcohols by the reaction between acid chlorides and dialkylzinc reagents,¹³ and Zaitsev had modified the procedure by using zinc metal and an alkyl (especially allyl) iodide (an alkylzinc iodide prepared *in situ*).¹⁴ Wagner's contribution was to substitute the acid chloride in the Zaitsev synthesis by aldehydes and formate esters, thus allowing the synthesis of symmetrical and unsymmetrical secondary alcohols.¹⁵ These developments in the organozinc synthesis of alcohols are summarized in Scheme 4.



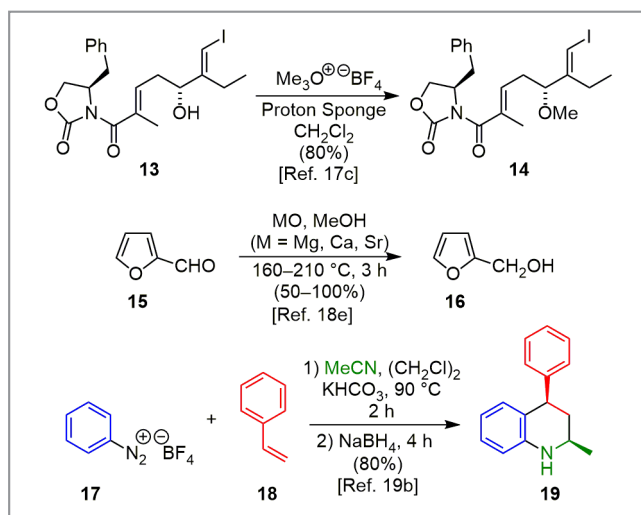
Scheme 4 Wagner's contributions to the synthesis of alcohols using organozinc compounds

Wagner graduated from Kazan in 1874 with the degree of *kandidat*. The next year, he was sent to St. Petersburg to study with Butlerov and Menshutkin as a salaried student. Following his move to Novo-Aleksandriya (now Puławy, Poland), Wagner turned his attention to the oxidation of alkenes with potassium permanganate, demonstrating that the oxidation with dilute permanganate solution ($\leq 2\%$) would give the diol without further oxidation. In Russia, this reaction is known as the Wagner oxidation. Later in his career, at Warsaw, he began the study of terpenes that led him to his description of the rearrangement that bears his name. One of his key deductions was the correct structure for α - and β -pinene,¹⁶ an achievement that brought Adolf Baeyer to concede that his own structure was incorrect, and to describe Wagner as 'a marvelously sharp-witted chemist.' Unfortunately for organic chemistry, Wagner died at 53 years of age due to complications of surgery for colorectal cancer.

The second chemist associated with this eponymous reaction, Hans Lebrecht Meerwein, was born in Hamburg and educated at the Fresenius University of Applied Sciences in Hesse. In 1900, he moved to the University of Bonn, where he eventually took his Ph.D. under Kekulé's student, Richard Anschütz. After a short term at Berlin, Meerwein became

Professor at Bonn in 1914, and then Professor of Organic Chemistry at the University of Königsberg until 1922. In 1922, he moved to Marburg as Professor, and he remained there until his retirement in 1953. He continued his research until his death twelve years later. Between 1948 and his death, Meerwein was nominated for the Nobel Prize in Chemistry twenty-seven times.

In addition to his work on rearrangement reactions, Meerwein also made other eponymous contributions to organic chemistry, including Meerwein's salt,¹⁷ the Meerwein–Ponndorf–Verley reduction,¹⁸ and the Meerwein arylation reaction.¹⁹ Some typical examples are gathered in Scheme 5: Meerwein's salt was used to effect methylation of alcohol **13** in the synthesis of nannocystin A analogues,^{17c} Group 2 oxides (MgO, CaO and SrO) catalyzed the reduction of furfural by methanol, which has the potential to be applied in the treatment of biomass,^{18e} and the Meerwein arylation of styrene **18** by diazonium ion **17** (which gives the aryl radical) and trapping of the resultant reactive intermediate provided a one-pot, metal-free, three-component assembly of aryltetrahydroquinolines such as **19**.¹⁹



Scheme 5 Applications of some of Meerwein's contributions to the field of organic chemistry

The Demjanov and Tiffeneau–Demjavov Rearrangements

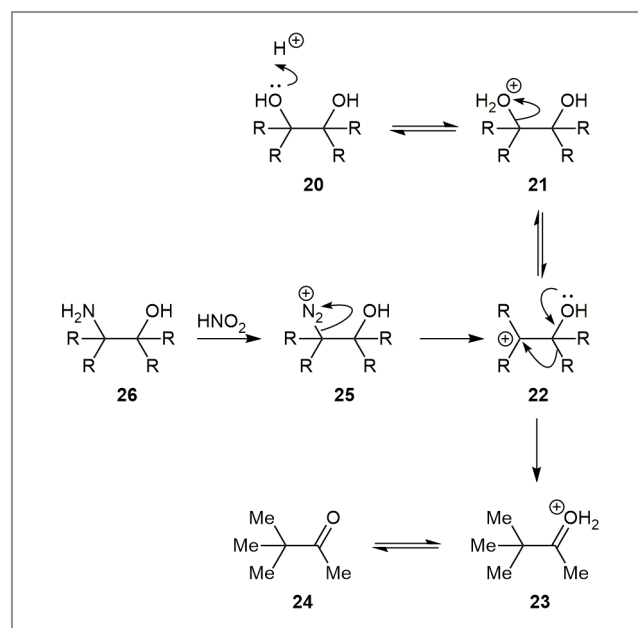
In 1903, Nikolai Yavkovlevich Dem'yanov (1861–1938; Figure 6) and his student, Mikhail Alekseevich Lushnikov, published the first paper describing the rearrangement of the cyclobutylcarbinyl system to the cyclopentyl system by the treat-

ment of (cyclobutylmethyl)amine with nitrous acid.²⁰ This was followed, four years later, by three papers in the *Zhurnal Russkago Fiziko-Khimicheskago Obshchestva*,^{21a–c} and three in the *Berichte der deutschen chemischen Gesellschaft* in which he expanded his studies to the cyclopropylcarbinyl and cyclobutyl systems.^{21d–f} In 1937, French chemist Marc Émile Pierre Adolphe Tiffeneau (1873–1945; Figure 6) published a paper with his students in which he described the rearrangement of 1-(aminomethyl)cyclohexanol to cycloheptanone by treatment with nitrous acid.²² This reaction, now known as the Tiffeneau–Demjanov rearrangement, has mechanistic elements of both the Demjanov and pinacol rearrangements (Scheme 6).

Nikolai Yavovlevich Dem'yanov was born in the city of Tver, northwest of Moscow, to Yakov Ivanovich Dem'yanov,



Figure 6 (left to right) Dem'yanov, Tiffeneau and Gustavson



Scheme 6

who was a member of the local nobility. Yakov Ivanovich died when his son was just three years old, and Nikolai was raised by his mother on their estate in Dievo, approximately 100 km north of the city. Dem'yanov was home-schooled until 11 years of age, and then he entered the prestigious 4th Moscow Classical Gymnasium. Little is known of this part of his life. He was an excellent student up to the 5th grade, but after that he found himself absorbed by physics and mathematics—much more so than by ancient languages; entering the 8th grade, he dropped out of the Gymnasium by request before graduating. He immediately applied to Moscow University as a volunteer, but he was denied admission for two years, while he completed his secondary education at the Tver Gymnasium.

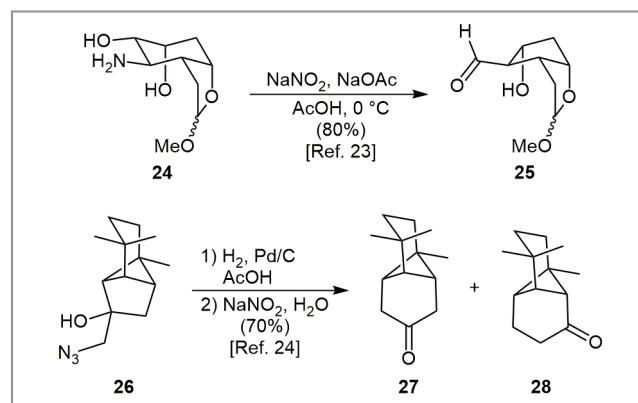
At the university, he quickly devoted himself to the intense study of chemistry. He showed an aptitude for research early on, and quickly became a student of Vladimir Vasil'evich Markovnikov (1838–1904), the great organic chemist who had built his research laboratory into one of the best in Europe. In 1886, Dem'yanov graduated from Moscow with the degree of 'authenticated student' and received an invitation from Markovnikov to remain with him for further training; he declined. Instead, he spent two years studying chemical technology and agronomic chemistry. He received a second diploma, in the physical sciences, for a report "On dextrans." This was not a *kandidat* degree.

In 1887, he was appointed Assistant in Inorganic and Analytical Chemistry at the Petrovskaya Academy of Agronomy and Forestry. Here, he met the organic chemist Gavriil Gavriilovich Gustavson (1842–1908; Figure 6), who was to become his mentor and friend. Under Gustavson's mentorship, Dem'yanov defended his dissertation for the *M. Khim.* degree at St. Petersburg in 1895, and for his *Dr. Khim.* at Moscow in 1899. In 1891, Gustavson retired from the Petrovskaya Academy, and accepted an appointment as Professor at the Higher Women's Courses (also known as the Moscow University for Women; now the Moscow State Pedagogical University). Gustavson's departure led to Dem'yanov's appointment to Extraordinary Professor, despite him being an *M. Khim.* student and not a graduate. In 1894, Dem'yanov became Head of Organic Chemistry at the Academy; he held this position until his death. In 1924, Dem'yanov was elected a Corresponding Member of the USSR Academy of Sciences, and in 1929 he was elected a Full Member.

Marc Tiffeneau was born in Mouy, 85 km north of Paris, and after leaving school he was apprenticed to an apothecary in Pont Sainte-Maxence, and a year later he moved to Paris, where he qualified as a pharmacist at the École de Pharmacie de Paris in 1899. After working as a pharmacy intern in several Paris hospitals, he was appointed head pharmacist at

the Hôpital Boucicaut in 1904; in 1927, he became head pharmacist at the Hôtel Dieu. Tiffeneau continued his graduate education after joining the Hôpital Boucicaut, and graduated Dr. ès Sciences in 1907 and obtained his degree in medicine in 1910. In 1924, he was elected to a Chair of Chemistry at the Hôtel Dieu, and two years later, to a Chair of Pharmacology and materia medica at the Sorbonne. In 1937, he became Dean of the Faculty of Medicine in the University of Paris. He was elected to the Académie de Médecine in 1927, and in 1939 he was elected to the Institut de France. He was elected Chevalier (1923) and Officier (1938) of the Légion d'honneur, and received the Prix Jecker twice: in 1911 (in part) and 1923 (full prize). At the time of his death, Tiffeneau was President of the Société chimique de France.

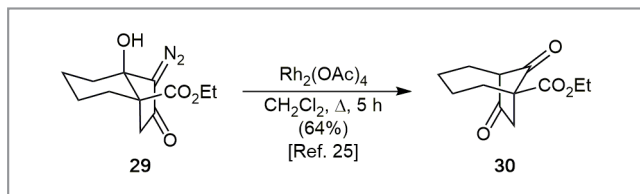
The Tiffeneau–Demjanov rearrangement has been used in synthesis for many years, as in Woodward's synthesis of prostaglandin $F_{2\alpha}$,²³ and Miyashita and Yoshikoshi's synthesis of longipinene²⁴ (Scheme 7).



Scheme 7 Applications of the Tiffeneau–Demjanov rearrangement

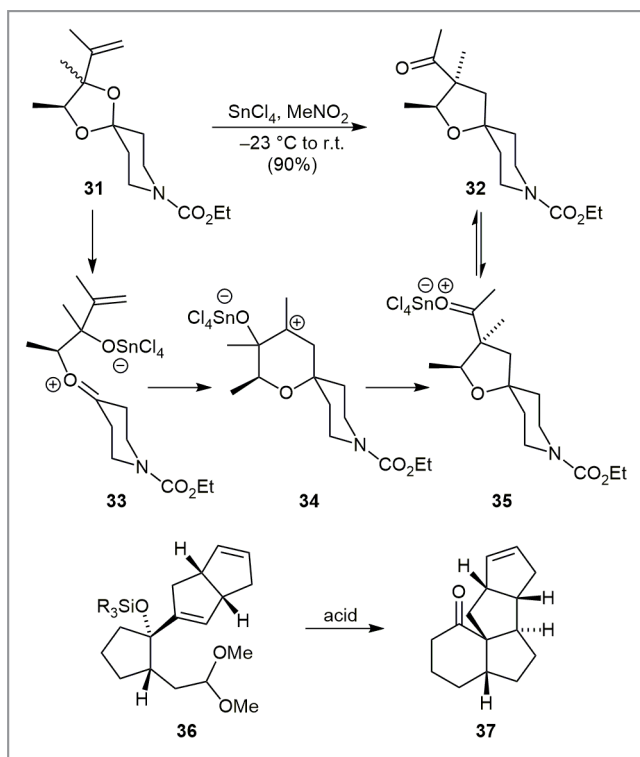
In the Woodward synthesis, the cyclopentane of the prostaglandin is assembled with the correct relative stereochemistry by the regioselective Tiffeneau–Demjanov ring contraction of cyclohexylamine derivative **24** to give cyclopentane **25**. The reverse operation, the Tiffeneau–Demjanov ring expansion of the tricyclic aminoalcohol obtained by reduction of azide **26**, gave a 95:5 mixture of the regioisomeric ketones **27** and **28**, respectively.

More recently, alternative methods for the formation of the deaminated carbocation have been developed. Several of these methods involve using a singlet carbene substitute as a carbocation surrogate, as illustrated by the rhodium–carbene complex formed from the fused-ring α -diazo ketone **29**, which rearranges into bridged-ring diketone **30** (Scheme 8).²⁵



Scheme 8 Rearrangement of fused-ring α -diazo ketone **29**

Recent applications of the pinacol rearrangement are provided by the pinacol-terminated Prins reaction shown in Scheme 9. Overman and Rishton²⁶ used the reaction for the stereospecific synthesis of spirotetrahydrofuranone derivative **32** from ketal **31**, and Overman and Pennington used the reaction to close the tetracyclic ring system of ketone **36** from acetal **37**.²⁷



Scheme 9 Recent applications of the pinacol rearrangement by Overman and co-workers

The use of carbocation rearrangements is of long standing in organic synthesis, and it is still likely that new carbocation rearrangement reactions will be developed in the future. I am one chemist who looks forward to seeing what that future holds.

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