

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

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

Peter Griess and Aryldiazonium Ions

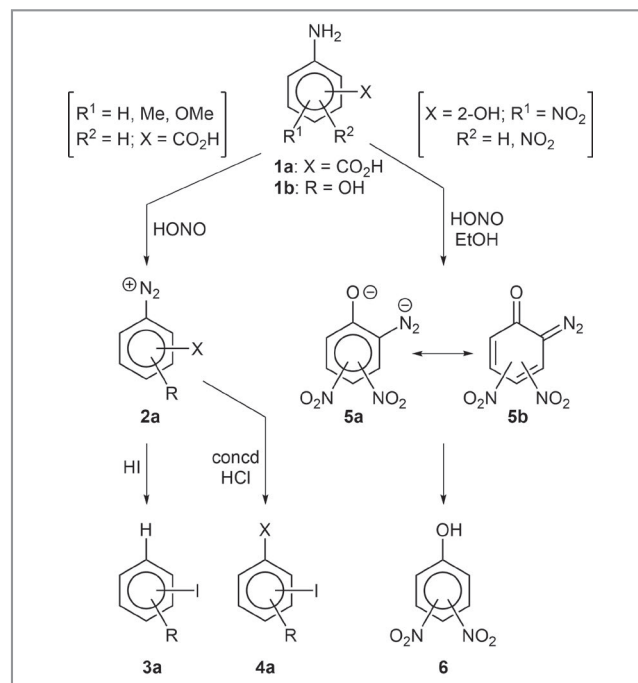
The aryldiazonium ions were discovered in 1858 by Johann Peter Griess, FRS,^{1a} a German-born British brewer working for Samuel Allsop & Sons in Burton-on-Trent, and the Pschorr reaction is named for its discoverer, Robert Franz Pschorr,^{1b} the fourth son of Georg Pschorr, Jr., the owner of the Hacker-Pschorr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



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

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

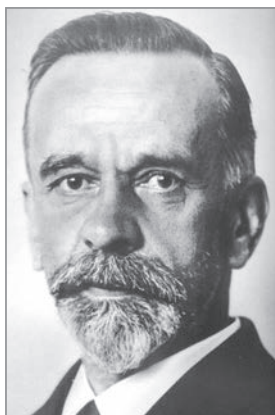
Griess' main chemical duties were as a brewer, and he was prohibited from disclosing his results, which were kept as



Scheme 1 Peter Griess' work with diazonium ions

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

Traugott Sandmeyer and His Eponymous Reaction



Traugott Sandmeyer
(1854–1922)

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

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

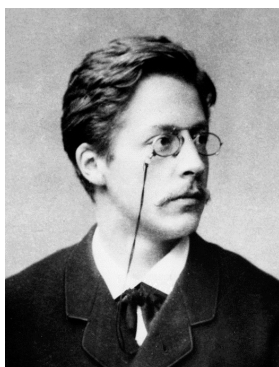
after she became a widow, she was appointed to the 5th and 6th grades of the girls' school in Aarau.

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

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

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

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



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

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

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

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

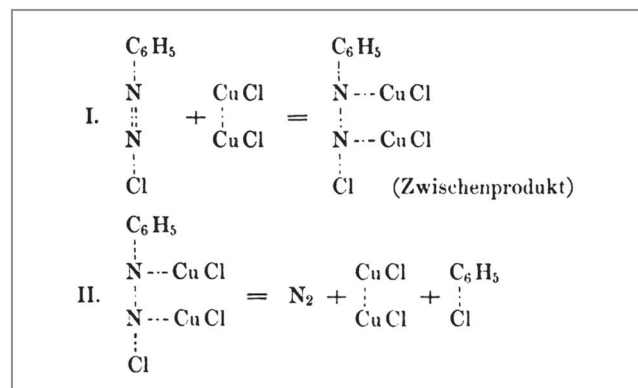
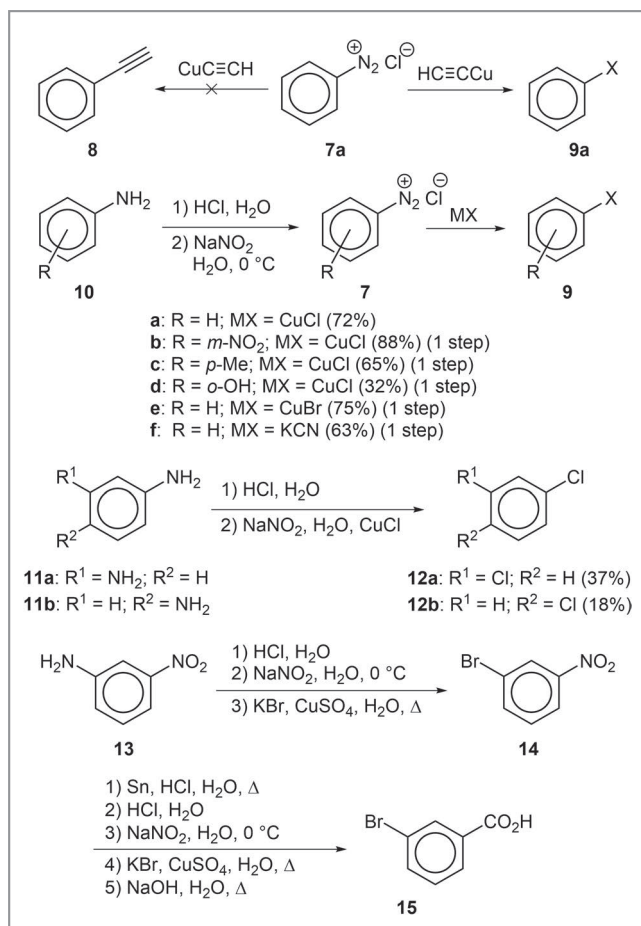
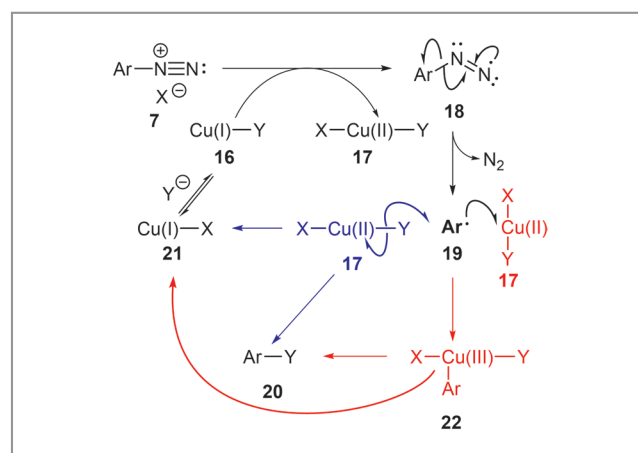


Figure 1 Sandmeyer's model for the displacement of the diazonium ion by the copper salt



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

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



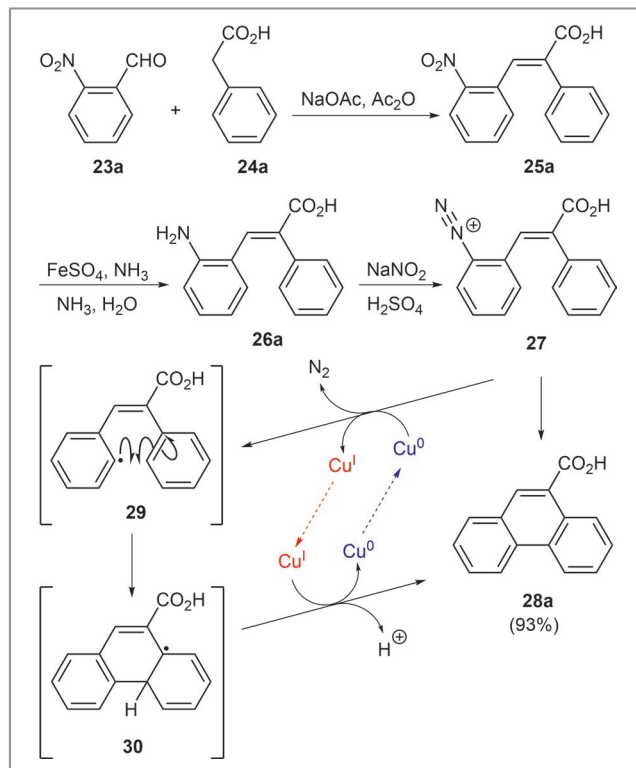
Scheme 3 The mechanism of the Sandmeyer reaction

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

The Pschorr Reaction¹⁶

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

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



Scheme 4 The Pschorr reaction to give a phenanthrene derivative

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

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



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

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

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

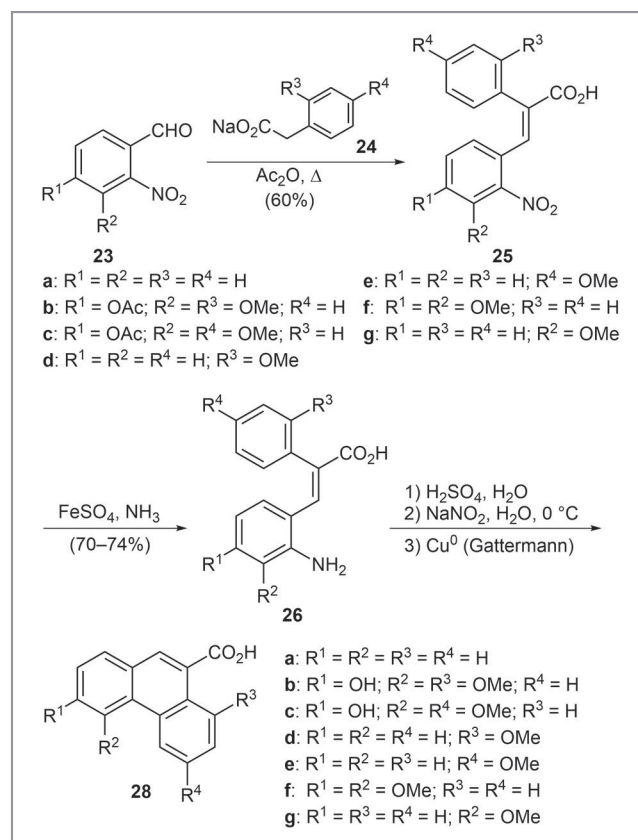
The war had reduced the German population to penury, and Pschorr well knew the economic hardship of students returning to their homes after their years of military service. He had means, so he did what he could to mitigate the situation by subsidizing the fees they had to pay. His philanthropy extended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

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

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

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

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

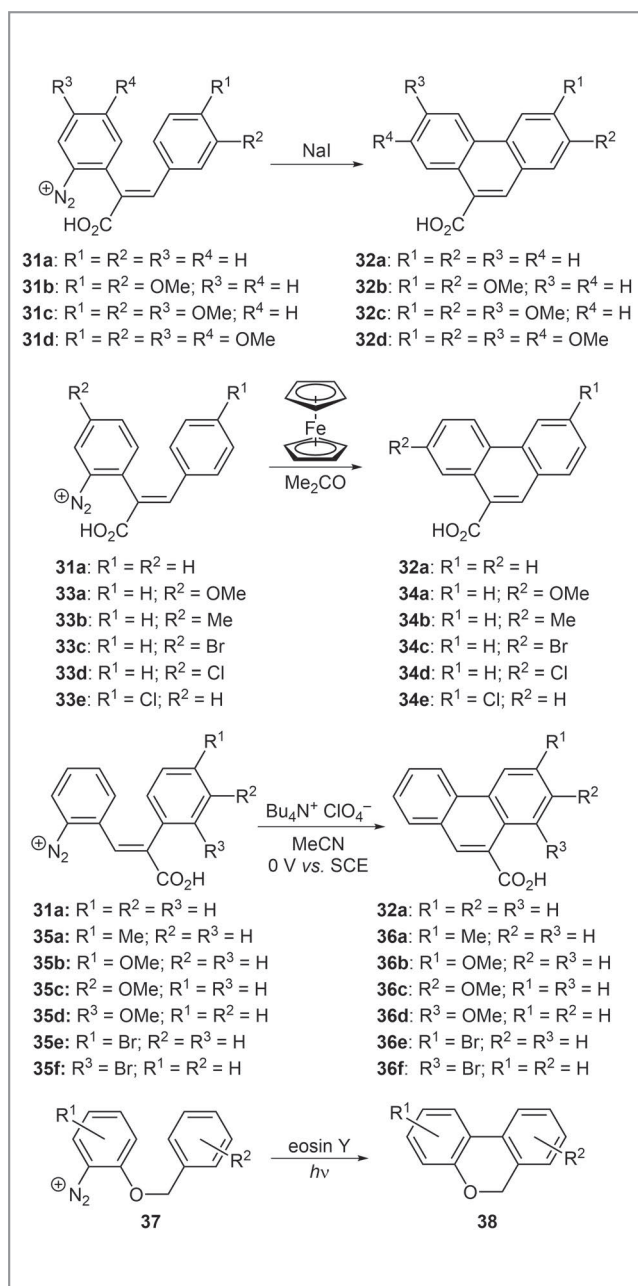


Scheme 5 The synthesis of other phenanthrene derivatives by Pschorr

Later Research on the Pschorr Reaction

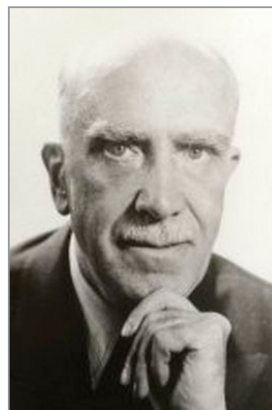
Efforts to improve the synthetic utility of the Pschorr cyclization have mainly focused on methods for the generation of the aryl radical intermediate. There have been three major avenues for accomplishing this: redox catalysis, photoredox catalysis, and electrochemical reduction of the diazonium ion.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

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



Scheme 6 Modern adaptations of the Pschorr cyclization

Meerwein Arylation



Hans Lebrecht Meerwein
(1879–1965)

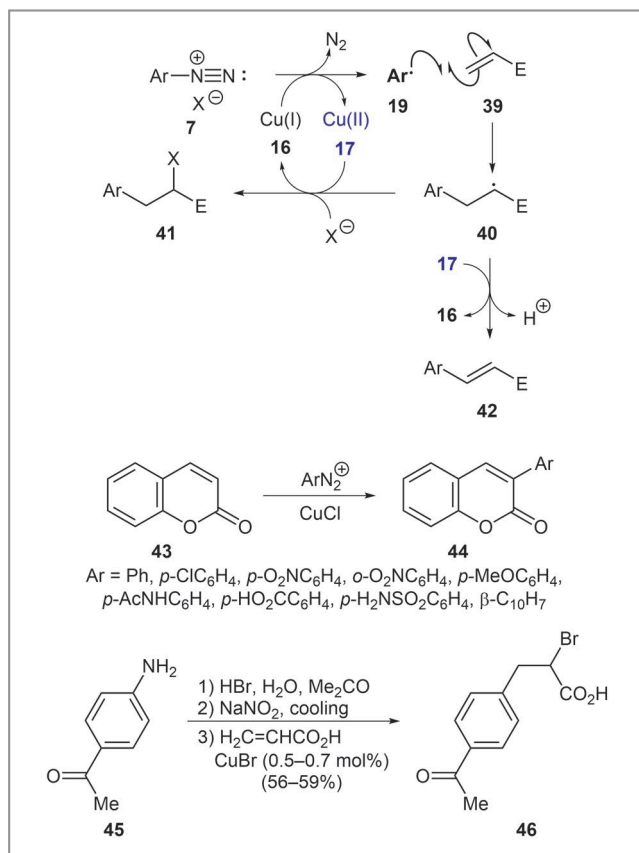
The name of Hans Lebrecht Meerwein (1879–1965) is associated with an eponymous reaction, the Wagner–Meerwein rearrangement of carbocations, which has been the subject of an earlier column in this series,²⁵ and with Meerwein's salt.²⁶ In 1939, Meerwein, Büchner and van Emster reported the addition of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

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

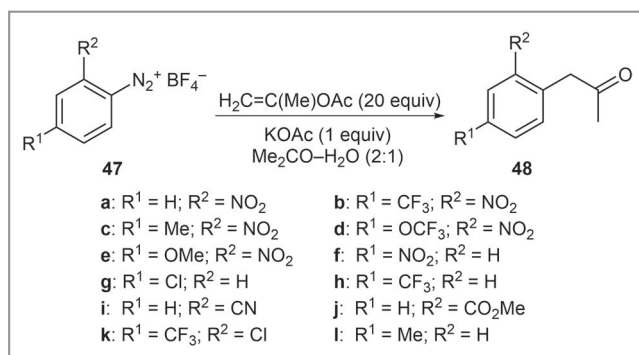
As with the Pschorr cyclization, the Meerwein reaction has been particularly amenable to research aimed towards developing a transition-metal-free version of the reaction. To this end, workers at Merck²⁸ reported a study of the Meerwein reaction of isopropenyl acetate with arene-diazonium tetrafluoroborates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

An analogous reaction was developed five years later, using $Ru(bpy)_3^{2+}$ in DMF as the redox-active photocatalyst.²⁹

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



Scheme 7 The Meerwein arylation reaction



Scheme 8 A transition-metal-free Meerwein reaction

David Lewis

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