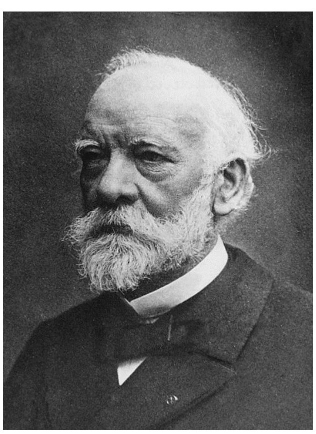
Charles Friedel (1832–1899) and James Mason Crafts (1839–1917): The Friedel–Crafts Alkylation and Acylation Reactions

In 1877, the first two papers of a series of nine appearing over the following four years,[1] were published by French chemist Charles Friedel,[2] and his American collaborator James Mason Crafts.[3] The reaction between a carbon electrophile and an aromatic hydrocarbon now bears the name of both chemists, and has become one of the foundational electrophilic aromatic substitution reactions.

Charles Friedel was born in Strasbourg (France), to a banker. On graduation from the Protestant Gymnasium, he enrolled in the Science Faculty at the University of Strasbourg, where Pasteur was a member of the faculty. Pasteur assigned him work in chemistry and crystallography, thus setting him on his career course: Friedel would make major contributions in both organic chemistry and mineralogy.



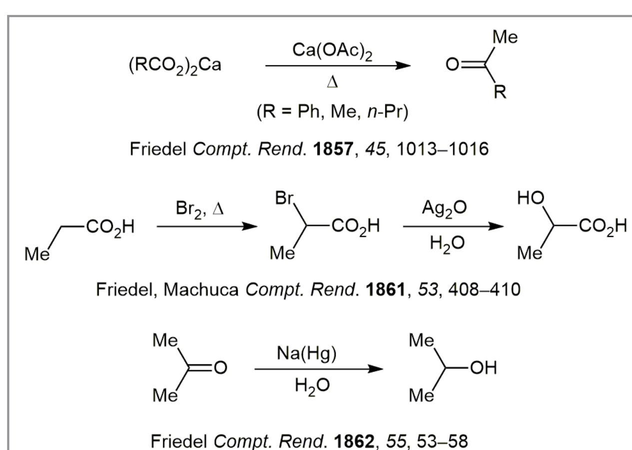
Charles Friedel (1832–1899) **I** *Louise Jeanne Salomé Combes [Friedel] (1838–1908)*

Friedel graduated with the baccalauréat de lettres in 1849 and the baccalauréat en sciences physique, with distinction, in 1850. He spent the year after his graduation working in his father's banking house, but it soon became apparent that he did not have the temperament to work in finance. So, at 20 years old, he was sent to Paris to live with his grandfather, the zoologist Georges Louis Duvernoy (1777–1855). On his arrival in Paris he entered the Lycée Saint-Louis to study for the baccalauréat de mathématique. In 1854, he obtained the licence mathématique. In 1855, he received the licence physique.

In 1856, Friedel was chosen to be Conservator of Collections at the École de Mines, a position he held for the next 20 years. The same year, he married Émilie Salomé Koechlin (1837–1871), who became mother of his four daughters and his first son. When she was a young girl near Nîmes, Émilie had lived in a house where the coffins of her ancestors were held – as Protestants, they had been denied Christian burial. At the beginning of the Franco-Prussian War, in 1870, Friedel sent Émilie and the children to Switzerland for their safety while he worked for the defense of the city of Paris. He did not learn of his young wife's death from pneumonia until after the capitulation.

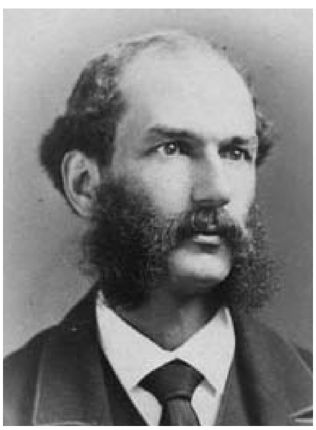
In 1854, Friedel entered the laboratory of Charles Adolphe Wurtz (1817–1884), another Strasbourg native with whom he became a lifelong friend. During his work with Wurtz, Friedel synthesized lactic acid, and established the chemistry of the two hydroxy groups in α-hydroxy acids. His studies of aldehydes and ketones led to him becoming the first to prepare isopropyl alcohol, by reduction of acetone with sodium amalgam, and thus establishing the existence of secondary alcohols as a class (Scheme 1).

In 1873, Friedel married Louise Jeanne Salomé Combes (1838–1908), who became the mother of his youngest son. The Friedel family produced several important French scientists. His son Georges (1865–1933) became an important crystallographer (Friedel's law is named for him) and his second son, Jean (1874–1941), became a biologist in Nancy. Georges' grandson (Friedel's great-grandson), Jacques (1921–2014), was an important physicist and materials scientist.



Scheme 1

The other partner in the discovery and development of this reaction, James Mason Crafts, was born in Boston (USA), and studied at the Lowell Academy; he graduated S.B. from the Lawrence Scientific School of Harvard University in 1858. Despite his long career and number of research publications, he never earned a doctoral degree. After his graduation, he spent a short time studying with E. N. Horsford (1818–1893) at Harvard, and then moved to Germany. There, he spent much of his first four years at Heidelberg, studying with Robert Bunsen (1811–1899). In 1862, he moved to France, where he spent another four years in the laboratory of Charles Adolphe Wurtz at the Sorbonne.



James Mason Crafts (1839–1917) **I** *Clemence Haggerty Crafts (1841–1912)*

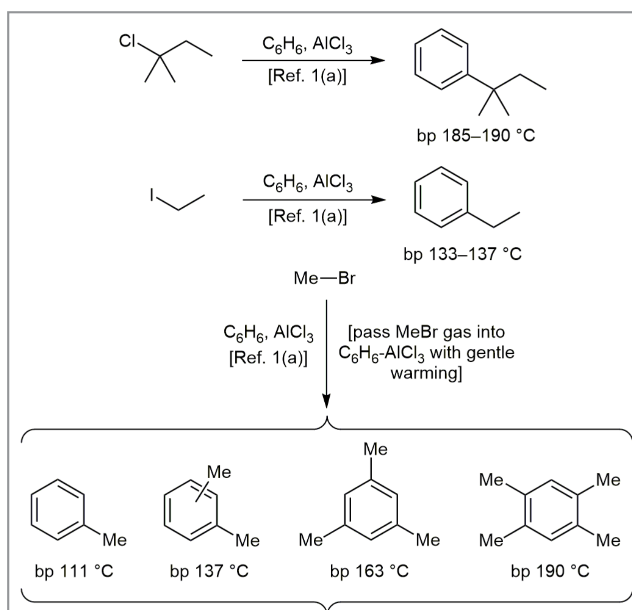
During Crafts' period in Heidelberg, Bunsen was heavily engaged in his systematic spectroscopic studies of the elements with Gustav Robert Kirchoff (1824–1887), and Crafts had the good fortune to become Bunsen's assistant during his time in Heidelberg. Despite this opportunity, Crafts published no papers during his time in Bunsen's laboratory.

In Wurtz' laboratory, Crafts was initially assigned to a problem on ethylene sulfide, and Crafts' first papers were in the area of organosulfur chemistry. Four years later, in 1865, he returned to the United States, and in 1866 he became mine examiner in Mexico – a perilous position at that time because of the physically difficult terrain and the dangers posed by bandits. Although very modest, Crafts occasionally told friends of his adventures in Mexico. In 1867, he took up a position as Professor of Chemistry and Dean of the Chemical Faculty at Cornell University, which had been founded just two years earlier. The next year, he married Clemence Haggerty (1841–1912); the couple had four children.

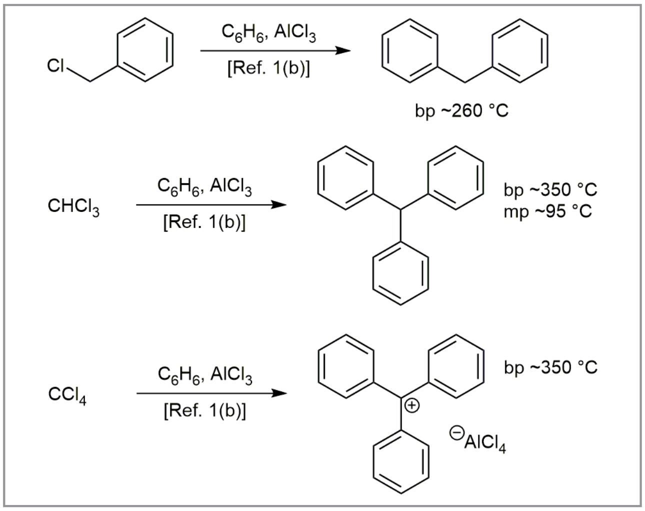
In 1870, Crafts moved to the Massachusetts Institute of Technology (MIT) as Professor. His work here was so demanding that his health suffered; in 1874, he changed his title to non-resident professor, and returned to France. It was during this sojourn in France that he began his incredibly fruitful collaboration with Friedel. In 1880, he resigned his non-resident professorship at MIT. He remained in France for another decade – possibly the most productive years of his scientific career. It was not until 1891 that he returned permanently to the United States, and MIT. From 1892–1897 he served as Professor of Chemistry, and then in 1897 he became Acting President, and then President of MIT. In 1900, he resigned his position, and returned to his research work.

Crafts' accomplishments were honored by his election to the National Academy of Sciences in 1872. Until the end of the nineteenth century, Crafts was a frequent visitor to the Sorbonne, where he became a close personal friend of his coworker, Charles Friedel. In 1885, he received the Prix Jecker of the Académie des Sciences de Paris, and became a Chevalier de la Légion d'Honneur. He was awarded an honorary LL.D. from Harvard University in 1898, and the Rumford Medal of the American Academy of Sciences in 1911. His last years were rendered difficult by his health, but he remained mentally vigorous to his death in 1917.

Friedel and Crafts first met in 1861, when Crafts entered Wurtz' laboratory after his time in Heidelberg. The two men quickly became firm friends and close collaborators. In their first joint paper,[1a] which was based on their joint research after



Scheme 2



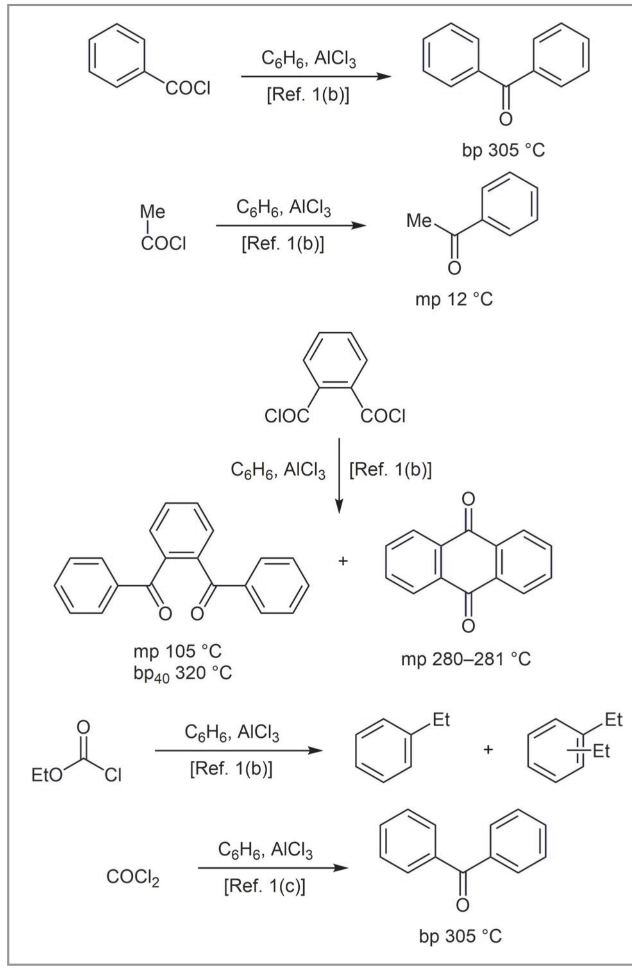
Scheme 3

Crafts had returned to France, Friedel and Crafts described what is now known as the Friedel–Crafts alkylation (Scheme 2). In the next two,[1b,c] they extended their study of alkylation into polyarylmethanes, described the acylation reaction (Scheme 3), and identified which metal halides would catalyze the reaction.[1d] Much more detailed accounts of their joint research appeared in the *Annales de chimie et de physique*.[4]

Their initial observations that *tert*-amyl chloride [which they called *amyl* chloride in the original paper] reacted with aluminum foil to give a wide range of saturated and unsaturated hydrocarbons, along with hydrogen chloride, led the two investigators to test if it was the metal or the metal halide that promoted the reaction; it proved to be the aluminum halide. They concluded that the alkyl halides might react with highly unsaturated compounds such as benzene in the presence of the aluminum halide. They were right (Scheme 2). They also showed how polymethylation could be easily accomplished, and the polymethylbenzenes separated on the basis of boiling point.

In their second paper, Friedel and Crafts extended their results to the formation of polyarylmethanes (Scheme 3; they did, however, misidentify the product with carbon tetrachloride as tetraphenylmethane). In the same paper, they introduced the acylation reaction (Scheme 4) with benzoyl chloride, acetyl chloride, and phthaloyl chloride. In a subsequent paper,[1c] they showed that phosgene produces benzophenone.

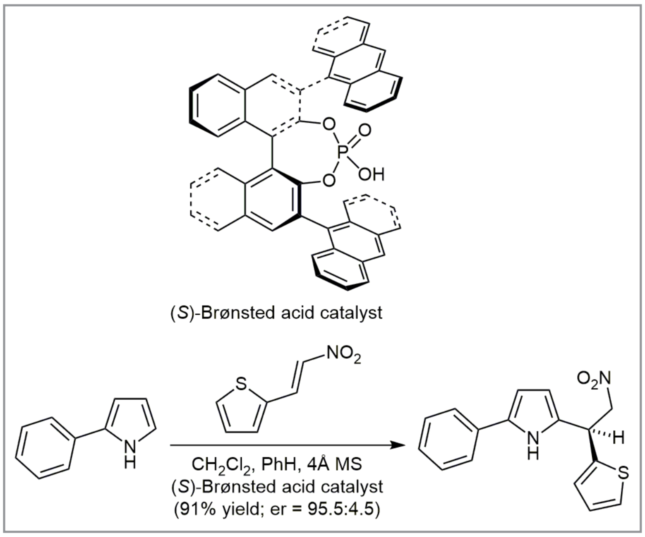
The thorough early work of Friedel and Crafts established their reaction as a premier method for the formation of carbon–carbon bonds to aromatic rings, and the reaction has been a staple in the synthetic organic chemist's toolbox. Like other venerable synthetic reactions, the Friedel–Crafts reaction has become the basis for any number of improvements and unforeseen applications. During the 1970s and 1980s, titanium tetrachloride became popular as a Lewis acid, and with the development of enol silyl ethers as surrogates for enolate anions, reactions such as the tertiary alkylation of the enol trimethylsilyl ethers[5] were developed.



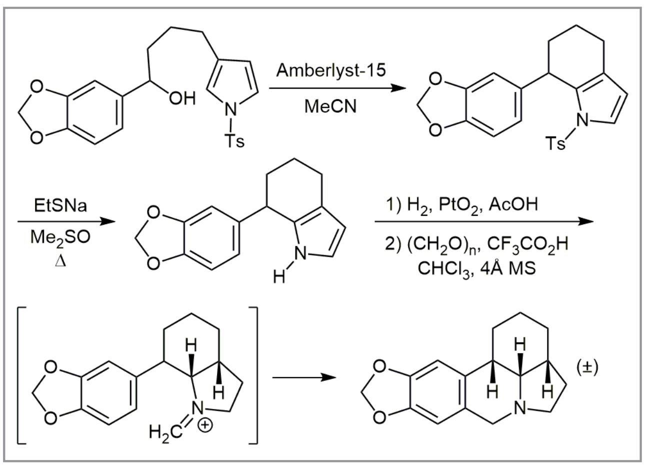
Scheme 4

The 21st century has seen the focus of research on this reaction move to the asymmetric Friedel–Crafts alkylation of electron-rich aromatic heterocycles by means of chiral organocatalysts and chiral Lowry–Brønsted acids,[6] such as the C_2-symmetric phosphoric acid derivative[7] in Scheme 5, which catalyzes the substitution of 2-phenylpyrrole by nitroalkenes.[8] This phosphoric acid can serve alone as a chiral catalyst, or as a chiral adjuvant with a Lewis acid catalyst.

The reaction has recently been applied to the synthesis of γ-lycorane by two sequential intramolecular Friedel–Crafts reactions (Scheme 6).[9]



Scheme 5



Scheme 6

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