

Rearrangement to Electron-Deficient Nitrogen: August Wilhelm von Hofmann (1818–1892), Wilhelm Lossen (1838–1906) and Theodor Curtius (1857–1928)

Between 1872 and 1890, three closely related reactions that involve a stereoselective (or stereospecific) rearrangement of an alkyl group from an acyl carbon to nitrogen were reported by Wilhelm Clemens Lossen (1838–1906), who reported a base-promoted rearrangement of hydroxamic acid derivatives, by August Wilhelm von Hofmann (1818–1892), who reported the base-promoted rearrangement of *N*-haloamides, and by Julius Wilhelm Theodor Curtius (1857–1928), who reported the rearrangement of acyl azides.



Wilhelm Clemens Lossen (1838–1906) | August Wilhelm von Hofmann (1818–1892) | Julius Wilhelm Theodor Curtius (1857–1928)

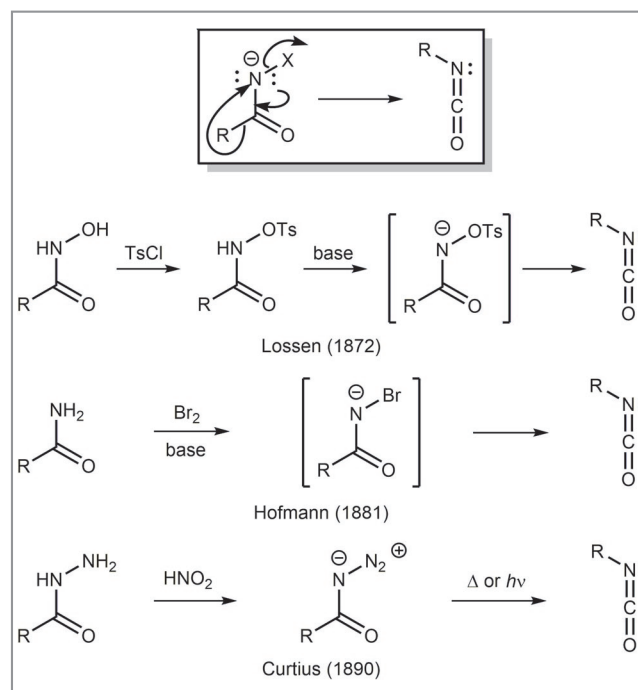
In chronological order of their publication, the reactions are the Lossen rearrangement,¹ the Hofmann rearrangement,² and the Curtius rearrangement³ (Scheme 1). The reactions share a common mechanism, where the rearrangement occurs in the same step with the loss of a leaving group from the nitrogen, to give an isocyanate.

Lossen⁴ was born in Kreuznach, and graduated from the Gymnasium in 1857. He then began his studies in chemistry at Giessen in 1857; two years later, he transferred to Göttingen, where he studied under Friedrich Wöhler. He graduated with his Ph.D. in 1862 for a dissertation on the structure of cocaine.⁵ During this same period, he began his studies of atropine.⁶ He immediately moved to Karlsruhe to work with Karl Weltzien (1813–1870), and then he moved to Halle in 1864 to study under Wilhelm Heinrich Heintz (1817–1880). Opportunities for Docents to deliver lectures were limited at Halle, so Lossen moved to Heidelberg, where he earned his *habilitation* in 1866, and promotion to Extraordinary Profes-

sor in 1870. In 1877, he accepted a call to the University of Königsberg as Ordinary Professor of Chemistry. He spent the next 26 years there, until his retirement as Professor Emeritus in 1903. Following his retirement, Lossen spent the last three years at Aachen.

Lossen discovered hydroxylamine in 1855,⁷ and spent much of the rest of his career devoted to the chemistry of hydroxylamine and its derivatives:⁸ added to his papers on his rearrangement reaction, hydroxylamine figures in some 20% of his publications.

In contrast to the situation with Lossen, there is a vast biographical literature about Hofmann.⁹ Arguably one of the most productive and influential organic chemists of the nineteenth century, Hofmann entered Giessen University to study philology and law. But, early in his student days, he met Justus von Liebig, who persuaded him to study chemistry instead. His life-long study of organic nitrogen compounds began with his Ph.D. project on aniline. Following his graduation in



Scheme 1

1841, he became one of Liebig's assistants in 1843. In 1845, he was appointed the first director of the Royal College of Chemistry in London, which had been established by several distinguished chemists and Prince Albert, Queen Victoria's German-born husband, who was a strong advocate for science and technology in Britain. He remained there for the next two decades but, after Prince Albert's death, support for science in Britain declined. This may well have led to Hofmann returning to Bonn in 1864. In 1865 he moved to Berlin, where he remained until his death in 1892.

Hofmann was responsible for some of the most brilliant teaching and research seen in London. In his view, organic chemistry lectures without experimental demonstrations were incomplete, so he had assistants perform the demonstrations in class. After his return to Germany, Hofmann founded the German Chemical Society; his home was preserved as headquarters of that society. He was a prolific researcher, and his laboratories produced over 1,000 papers, more than 300 of them his own work. Some idea of his contributions may be gauged from the number of reactions named after him: the Hofmann elimination,¹⁰ the Hofmann rearrangement, and the Hofmann–Löffler–Freitag reaction¹¹ (Scheme 2) are the most important. Hofmann was ennobled in 1888.

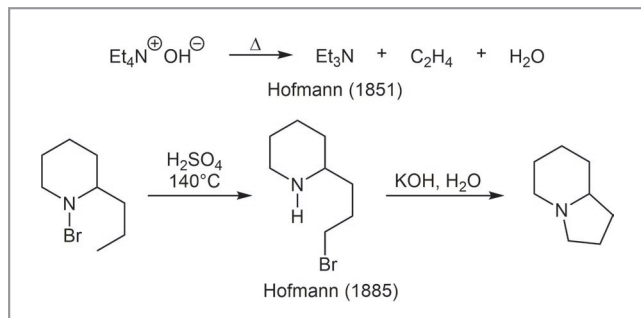
Curtius was born into a scholarly family at Duisburg, and entered Heidelberg University to study music and science. He studied chemistry under Robert Bunsen at Heidelberg until his required military service. Following his discharge as a first lieutenant, Curtius moved to Leipzig, where he took his Ph.D. under Kolbe in 1882 for a dissertation on hippuric acid. In 1884, he moved to Munich to study under Baeyer, and then qualified for his *habilitation* under Otto Fischer at Erlangen in 1886. On attaining this qualification, he became director of the analytical laboratories at Erlangen. In 1889, he was offered positions at Worcester Polytechnic in the U.S. and at Kiel. Curtius chose Kiel, where he was Professor of Chemistry and Director of the Chemical Institute. His career at Kiel was

very productive, and in 1895 he was appointed to the rank of *Geheimrat* (Privy Councillor).

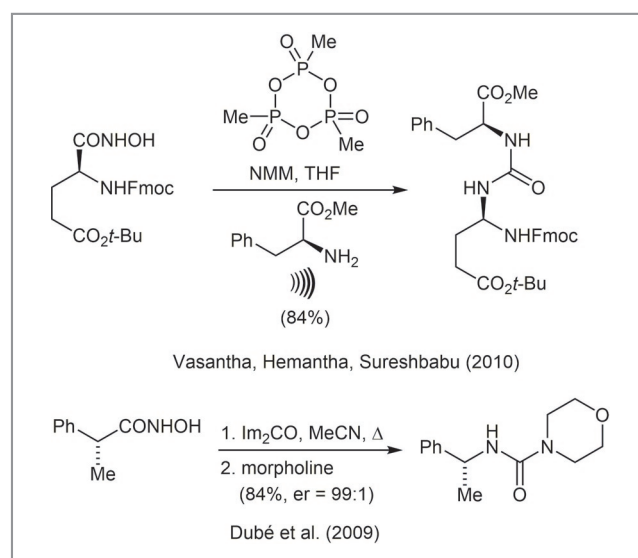
In 1897, Curtius succeeded Kekulé at Bonn, and the next year, he returned to Heidelberg as Professor of Chemistry, succeeding Victor Meyer. Curtius spent the rest of his career there, succeeding his Ph.D. mentor, Kolbe, as editor of the *Journal für praktische Chemie*. From the beginning, much of his research concerned the reactions of nitrogen compounds, especially amides and imides. The Curtius reactions named for him were discovered in 1894 (degradation to the amine) and 1911 (formation of the isocyanate). Curtius never lost his love for music, and he entertained himself and his friends by playing the piano, singing, and composing (although he never reached the heights of another organic chemist—Borodin—as a composer). Curtius was also an avid mountain-climber.

All three rearrangements share the common feature that the reaction occurs with retention of configuration, which has made them highly useful in stereocontrolled synthesis. An idea of how these reactions have been used in synthesis, where their stereospecificity has been crucial, are gathered in Schemes 3 (Lossen), 4 (Hofmann) and 5 (Curtius).

The first entry in Scheme 3^{12a} illustrates the use of the trimeric anhydride of methylphosphonic acid (T3P®) to form the hydroxamic acid *O*-phosphonate, *N*-methylmorpholine as the base, and heating by ultrasonic irradiation. In the same paper, the authors demonstrated that, to the limits of detection by 400 MHz ¹H NMR spectroscopy, the rearrangement is stereospecific. The second entry^{12b} also shows that the rearrangement occurs with retention of configuration to the extent of



Scheme 2



Scheme 3

99:1. Carbonyldiimidazole was the acylating reagent, and, by releasing imidazole, it also provides the base for the reaction.

The original version of the Hofmann rearrangement often gave relatively poor yields due to over-oxidation or the poor

solubility of some amides in aqueous base. Developments over the last two decades, in particular, have focused on refining both of these factors affecting the reaction. Radlick and Brown^{13a} showed that methyl hypobromite in methanol made a useful modification of the reaction, giving the urethane, which is relatively resistant to further oxidation, rather than the free amine. During the first decade of the 21st century, hypervalent iodine compounds^{13b,c} have emerged as reagents that avoid both the strong base, and the free halogens in the reaction. The final entry in Scheme 4 contains another alternative source of the halogen oxidant: trichlorocyanuric acid.^{13d}

Scheme 5 illustrates the usefulness of the stereospecificity of the Curtius rearrangement. In 1980, Massy-Westropp and coworkers^{14a} used the Curtius rearrangement of an acyl azide derived from L-proline as a key step in the determination of the absolute stereochemistry of odorine. In 2005, Overman used the Curtius rearrangement as a key step in the synthesis of (±)-gelsemine.^{14b} Hayashi's synthesis used a Curtius rearrangement of an acyl azide in acetic acid to give a key intermediate in the synthesis of (–)-oseltamivir.^{14c}

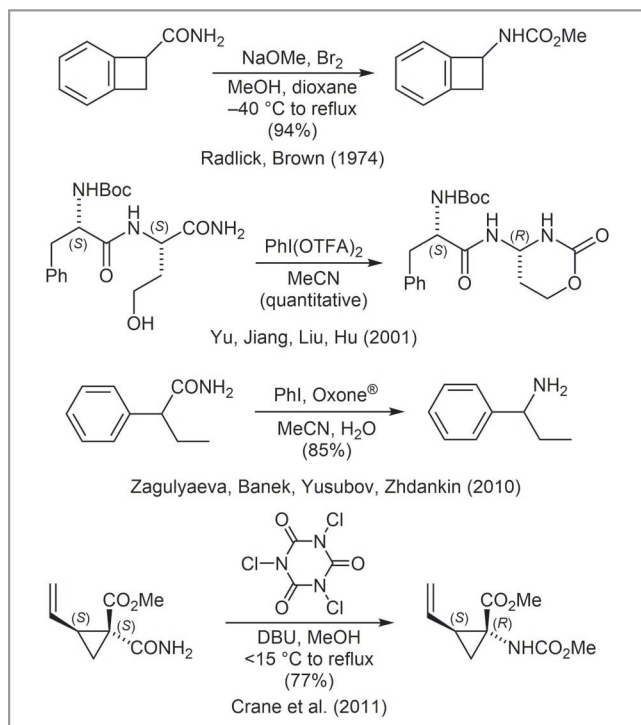
David Lewis

DEDICATION

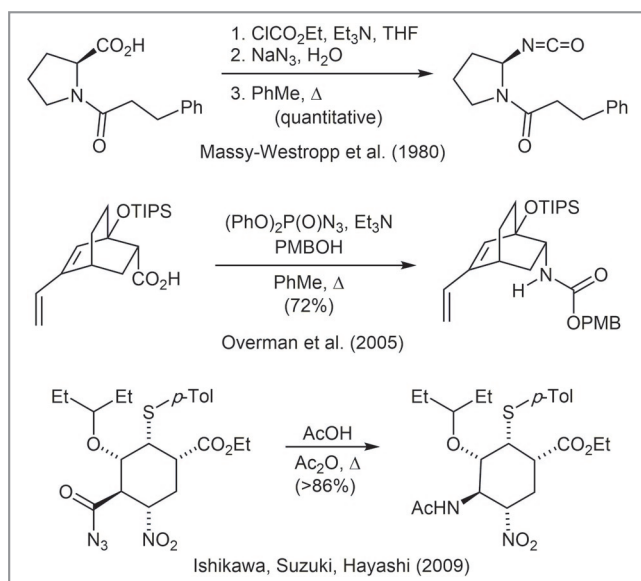
This article is dedicated to the memory of the great pioneer of aniline chemistry, August Wilhelm von Hofmann, on the bicentenary of his birth.

REFERENCES

- (1) (a) W. Lossen *Justus Liebig's Ann. Chem.* **1872**, 161, 347–362. (b) H. Rotermund *Justus Liebig's Ann. Chem.* **1875**, 175, 257–270. (c) W. Lossen *Justus Liebig's Ann. Chem.* **1875**, 175, 271–304. (d) F. Pieschel *Justus Liebig's Ann. Chem.* **1875**, 175, 305–313. (e) W. Lossen *Justus Liebig's Ann. Chem.* **1875**, 175, 313–325. (f) W. Lossen *Justus Liebig's Ann. Chem.* **1877**, 186, 1–74. (g) C. Klein, Ch. Trechmann *Justus Liebig's Ann. Chem.* **1877**, 186, 76–110. (h) W. Lossen *Justus Liebig's Ann. Chem.* **1889**, 252, 170–224.
- (2) (a) A. W. Hofmann *Ber. Dtsch. Chem. Ges.* **1881**, 14, 2725–2736. (b) A. W. Hofmann *Ber. Dtsch. Chem. Ges.* **1882**, 15, 407–416. (c) A. W. Hofmann *Ber. Dtsch. Chem. Ges.* **1882**, 15, 762–775. (d) A. W. Hofmann *Ber. Dtsch. Chem. Ges.* **1883**, 16, 558–560. (e) A. W. Hofmann *Ber. Dtsch. Chem. Ges.* **1884**, 17, 1406–1412. (f) A. W. Hofmann *Ber. Dtsch. Chem. Ges.* **1885**, 18, 2734–2741.



Scheme 4



Scheme 5

- (3) (a) T. Curtius *Ber. Dtsch. Chem. Ges.* **1890**, 23, 3023–3033. (b) T. Curtius *J. Prakt. Chem.* **1894**, 50, 275–294.
- (4) For biographies of Lossen, see: (a) Lassar-Cohn *Ber. Dtsch. Chem. Ges.* **1907**, 40, 5079–5086. (b) C. Priesner *Neue Deutsche Biographie* **1987**, 15, 202–202.
- (5) (a) In 1862, Wöhler reported the results of Lossen's dissertation: F. Wöhler, W. Lossen *Justus Liebigs Ann. Chem.* **1862**, 121, 372–375. (b) W. Lossen *Justus Liebigs Ann. Chem.* **1865**, 133, 351–371.
- (6) (a) W. Lossen *Justus Liebigs Ann. Chem.* **1864**, 131, 43–49. (b) W. Lossen *Justus Liebigs Ann. Chem.* **1866**, 138, 230–241. (c) W. Lossen *Justus Liebigs Ann. Chem.* **1869**, 149, 255–256. (7) W. Lossen *Z. Chem.* **1865**, 8, 551–553.
- (8) (a) W. Lossen *J. Prakt. Chem.* **1865**, 96, 462–465. (b) W. Lossen *Justus Liebigs Ann. Chem. Pharm* **1872**, 161, 347–362. (c) W. Lossen, J. Zanni *Justus Liebigs Ann. Chem. Pharm.* **1876**, 182, 220–230. (d) W. Lossen *Ber. Dtsch. Chem. Ges.* **1883**, 16, 873–878. (e) W. Lossen *Ber. Dtsch. Chem. Ges.* **1884**, 17, 1587–1589. (f) W. Lossen *Ber. Dtsch. Chem. Ges.* **1891**, 24, 4059–4062.
- (9) (a) J. Volhard, E. Fischer *August Wilhelm von Hofmann: ein Lebensbild*, Deutsche Chemische Gesellschaft: Berlin, 1902; This biography also appeared as two long papers in a special edition of the *Berichte*: (b) J. Volhard, E. Fischer *Ber. Dtsch. Chem. Ges.* **1902**, 35, 1–196. (c) J. Volhard, E. Fischer *Ber. Dtsch. Chem. Ges.* **1902**, 35, 197–284. (d) C. Meinel *Angew. Chem., Int. Ed. Engl.* **1992**, 31, 1265–1282. (e) A. S. Travis *Endeavour* **1992**, 16, 59–65. (f) G. Ronge *Neue Deutsche Biographie* **1972**, 9, 446–450.
- (10) (a) A. W. Hofmann *Ann. Chem. Pharm.* **1851**, 78, 253–286. (b) A. W. Hofmann *Ber. Dtsch. Chem. Ges.* **1885**, 18, 5–23. (c) A. W. Hofmann *Ber. Dtsch. Chem. Ges.* **1885**, 18, 109–131.
- (11) (a) See 10c. (b) K. Löffler, C. Freytag *Ber. Dtsch. Chem. Ges.* **1909**, 42, 3427–3431. (c) K. Löffler, S. Kober *Ber. Dtsch. Chem. Ges.* **1909**, 42, 3431–3438. (d) K. Löffler *Ber. Dtsch. Chem. Ges.* **1910**, 43, 2035–2048.
- (12) (a) B. Vasantha, H. P. Hemantha, V. V. Sureshbabu *Synthesis* **2010**, 2990–2996. (b) P. Dubé, N. F. Fine Nathel, M. Vetelino, M. Couturier, C. Larrivée Aboussafy, S. Pichette, M. L. Jorgensen, M. Hardink *Org. Lett.* **2009**, 11, 5622–5625.
- (13) (a) P. Radlick, L. R. Brown *Synthesis* **1974**, 290–292. (b) C. Yu, Y. Jiang, B. Liu, L. Hu *Tetrahedron Lett.* **2001**, 42, 1449–1452. (c) A. A. Zagulyaeva, C. T. Banek, M. S. Yusubov, V. V. Zhdankin *Org. Lett.* **2010**, 12, 4644–4647. (d) Z. D. Crane, P. J. Nichols, T. Sammakia, P. J. Stengel *J. Org. Chem.* **2011**, 76, 277–280.
- (14) (a) P. J. Babidge, R. A. Massy-Westropp, S. G. Pyne, D. Shienthong, A. Ungphakorn, G. Veerachat *Aust. J. Chem.* **1980**, 33, 1841–1845. (b) W. G. Earley, J. E. Jacobsen, A. Madin, G. P. Meier, C. J. O'Donnell, T. Oh, D. W. Old, L. E. Overman, M. J. Sharp *J. Am. Chem. Soc.* **2005**, 127, 18046–18053. (c) H. Ishikawa, T. Suzuki, Y. Hayashi *Angew. Chem. Int. Ed.* **2009**, 48, 1304–1307.