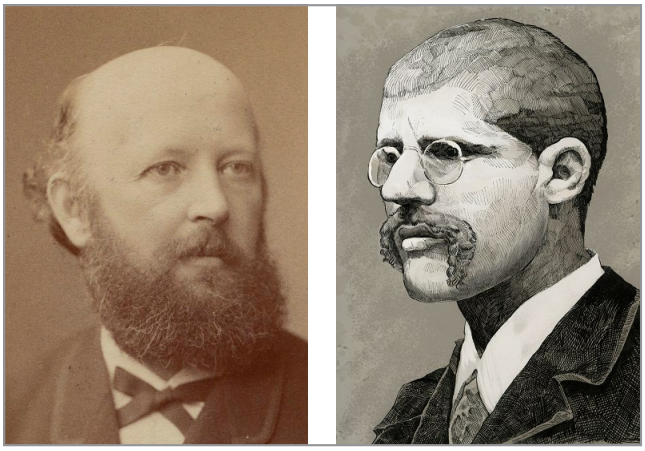
Johann Wilhelm Friedrich Adolf von Baeyer (1835–1917) and Victor Villiger (1868–1934): Peracid Oxidation of Ketones

The reaction between ketones and peracids, now known as the Baeyer–Villiger reaction, was first reported by Adolf von Baeyer (1835–1917) and his student and collaborator, Victor Villiger (1868–1934) in 1899.[1] Of the two men, von Baeyer is by far the better known, having won the Nobel Prize in Chemistry in 1905.



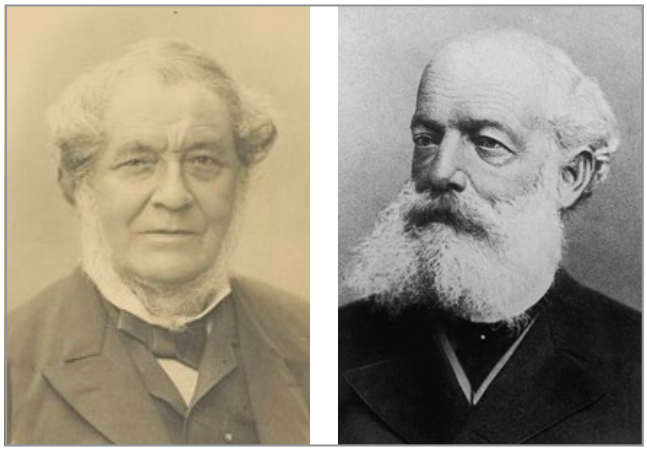
von Baeyer (left) and Villiger (right). *Image of von Baeyer courtesy of Science History Institute. The image of Villiger ©2019, Matthew A. Bergs; all rights reserved. Reproduced by permission of the artist.*

Johann Friedrich Wilhelm von Baeyer[2] was born to Lieutenant-General Jakob Baeyer and Eugenie, née Hitzig, on October 31, 1835. From a young age, he demonstrated his interest in science by his exploration of chemistry. When just 9 years old, he was conducting plant nutrition experiments, and just three years later[3] he isolated a new double salt of copper, whose formula was established as $CuCO_3 \cdot Na_2CO_3 \cdot 3H_2O$ by Struve in 1851.[4]

At age 17, Baeyer entered the University of Berlin, where he began his study of physics and mathematics. In his two years there, however, neither physics nor mathematics excited him as much as chemistry. Both physics and chemistry were taught as complete sciences, looking backwards. Chemistry, on the other hand, was taught as a new, vibrant science, and it was this that changed Baeyer's mind.

In 1855, Baeyer left the University for a year of military service, and after he had satisfied his obligation he returned to his studies, this time in chemistry at the University of Heidelberg, where Robert Bunsen (1811–1899) was one of the most important chemists in Germany working in one of the most modern laboratories. While with Bunsen, he published two papers, one on idiochemical induction,[5] and a second on methyl chloride.[6]

In 1840, Bunsen had begun research on cacodyl compounds,[7] and Baeyer continued that research in Bunsen's laboratory. However, the relationship between student and mentor deteriorated, and an argument between the two men led to Baeyer leaving Bunsen's research group and joining that of August Kekulé (1829–1896). The two men became life-long friends.



Bunsen (left) and Kekulé (right). *Image of Bunsen courtesy of Universitätsbibliothek Heidelberg. Public domain image of Kekulé downloaded June 2020 from https://commons.wikimedia.org/wiki/File:Frkekulé.jpg.*

Despite his break with Bunsen, Baeyer continued his research on organic arsenic compounds of the cacodyl (Me_2As) series.[8] In 1858, he submitted his work on cacodylic acid, $Me_2As(O)OH$, done in Kekulé's laboratory, to Berlin University, where he was awarded his Ph.D. in 1858. This dissertation[9] was written in Latin. During this time, Kekulé had become Professor at Ghent, and as soon as he held the Ph.D., Baeyer followed him there.

In 1860, Baeyer presented his *habilitation* lecture (again, in Latin), then returned to Berlin as a Privatdozent in the Berlin Gewerbeinstitut (The Royal Trade Institute, later the Königliche Technische Hochschule Charlottenburg). There he

© Georg Thieme Verlag Stuttgart • New York – Synform **2020/12**, A173–A178 • Published online: November 17, 2020 • DOI: 10.1055/s-0039-1691219

began his work with coloring matters, including indigo and alizarin, the red dye from madder root. In 1871, the Alsace–Lorraine region was ceded to France as a result of Prussia's victory in the Franco–Prussian War of 1870–1871. This event was accompanied by the University of Strasbourg becoming the Kaiser-Wilhem-Universität, and an influx of new, young German-speaking staff members. One of these was 36-year-old Adolf von Baeyer, who became Professor in 1871. Four years later, Baeyer became the successor to Justus von Liebig at the University of Munich, where he spent the rest of his career.

Baeyer's research made a huge impact on the field of organic chemistry. His major contributions to organic chemistry include the Baeyer strain theory (Figure 1),[10] and a series of papers on indoles, indoxyl, and isatin,[11] culminating in the synthesis of indigo (**1**; Scheme 1).[12]

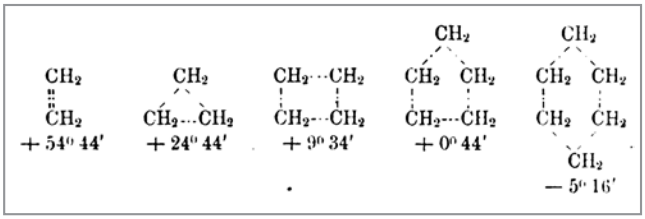
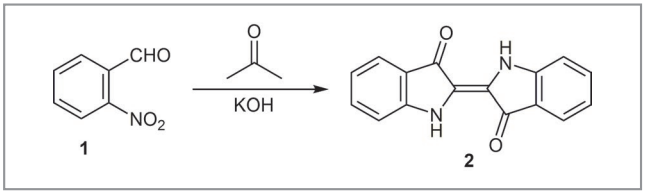


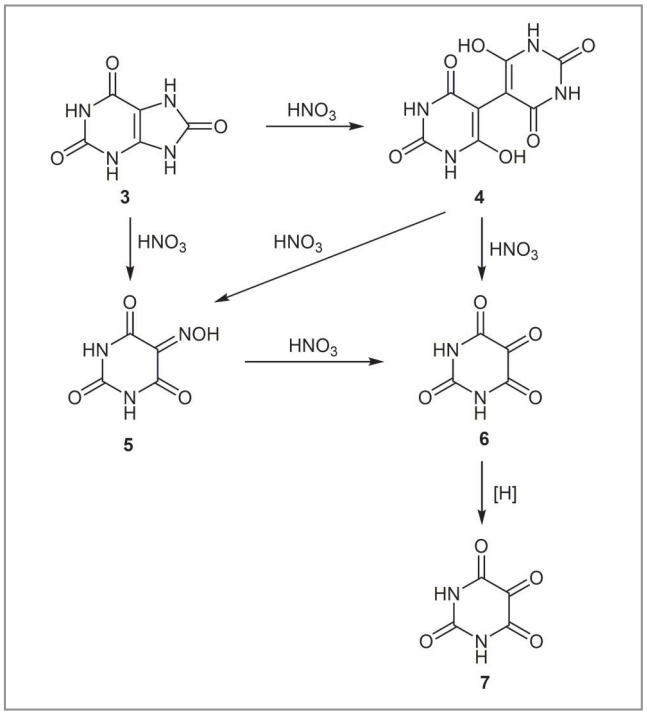
Figure 1 Baeyer's strain theory *(image taken from Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2269–2281*)*



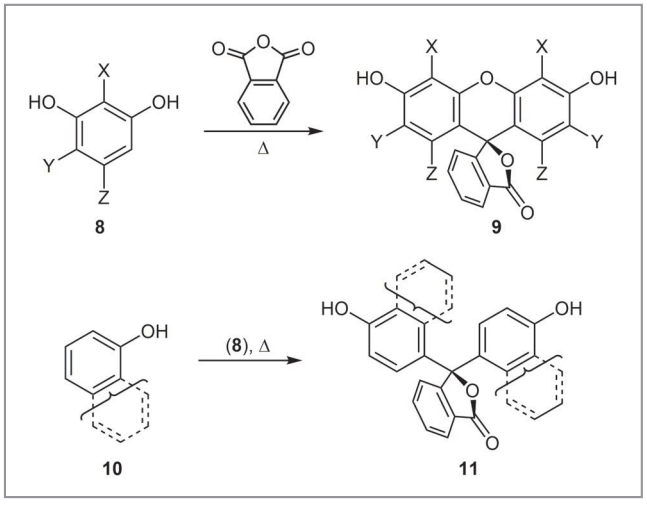
Scheme 1

In his degradation studies of uric acid (**3**), he obtained the dimeric pyrimidinetrione, hydriluric acid (**4**), as well as monomeric pyrimidinetrione derivatives **5** (violuric acid), **6** (alloxan), and **7** (barbituric acid (Scheme 2), along with several other pyrimidine derivatives.[13] In 1871, he reported the discovery and synthesis of the phthalein dyes (Scheme 3);[14] in 1900, he published a paper that proposed a system of nomenclature for polycyclic and spirocyclic compounds.[15]

Later he brought his chemical knowledge to the University of Munich, where the true synthesis of indigo developed alongside some of his other projects, such as his work with acetylene and polyacetylene which later developed into the Baeyer strains theory of carbon rings. More specifically, he



Scheme 2



Scheme 3

proposed that the stability of carbocyclic compounds was dependent on the angles' deviation from the commonly accepted 109° standard. In 1905, he received the Nobel Prize in Chemistry, further distinguishing himself in his field.

The other member of the team was Swiss chemist Victor Villiger (1868–1934), the son of a lawyer and later City Administrator of Lenzburg, and grandson of the Swiss Aarau po-

litician and reformer, Augustin Kweller (1805–1883). He was born in the small village of Cham am Zuger See and educated at the Aarau Canton School. In 1888, he entered the University of Geneva, where he studied chemistry for a year and a half under Carl Graebe (1841–1927) before completing his compulsory year of military service.

Carl Graebe ca. 1860 (left) and Heinrich Caro ca. 1900 (right). *Public domain images retrieved from https://commons.wikimedia.org/wiki/File:Carl_Graebe_1860-07-13.jpg (accessed July 10, 2020) and https://commons.wikimedia.org/wiki/File:Heinrich_Caro_ca1900.jpg (accessed July 10, 220).*

After completing his military service, Villiger volunteered for several months in the laboratory of the Research Chemist of the City of Zürich. Then, in the spring of 1890, he moved to Munich, where he entered Baeyer's laboratory. He began his Ph.D. studies there in 1893, focusing on the structure of the benzenoid and hydrobenzenoid compounds that had led to Baeyer's 1888 paper[16] on the structure of benzene, where he had first reported his centric formulas (Figure 2). Villiger received his Ph.D. in 1893 for his studies on hexahydroisophthalic acid.[17]

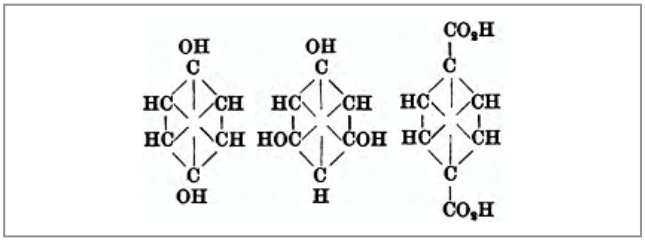
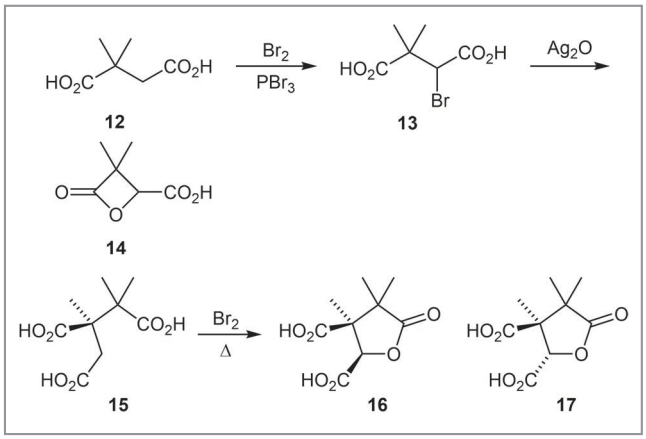


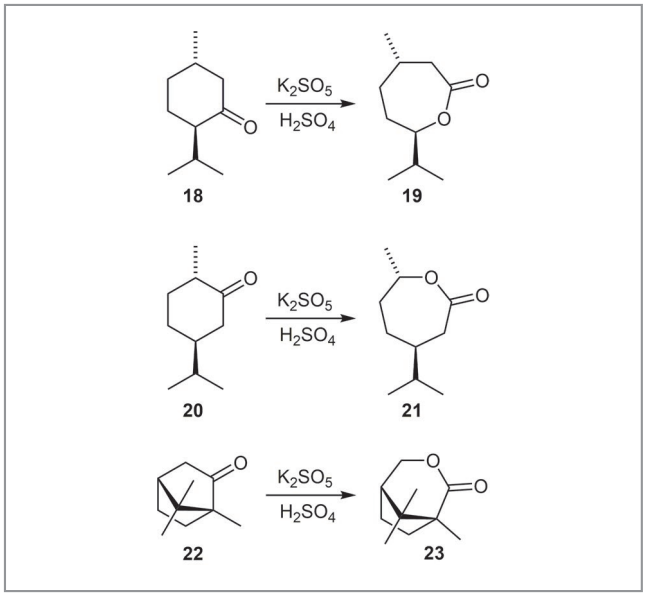
Figure 2 Baeyer's centric formulas for the structures of (l–r) hydroquinone, phloroglucinol and terephthalic acid (images taken from *Justus Liebigs Ann. Chem.* **1888**, *245*, 103–190)

Baeyer was very much impressed by the young Villiger, and therefore retained him as an assistant for another eleven years after his graduation. Initially, Villiger worked with Baeyer on the 'hot topic' at the time – the structure of terpenoid compounds.[18] During this work, the β-lactam **14** and stereoisomeric lactones **16** and **17** from camphoronic acid (**15**) were prepared.[19]

Literature searches using any search engine and the names Baeyer or Villiger, separately, return more hits on the Baeyer–Villiger reaction than on anything else. This important reaction was first described in the last two years of the nineteenth century,[1] and has remained an important synthetic organic



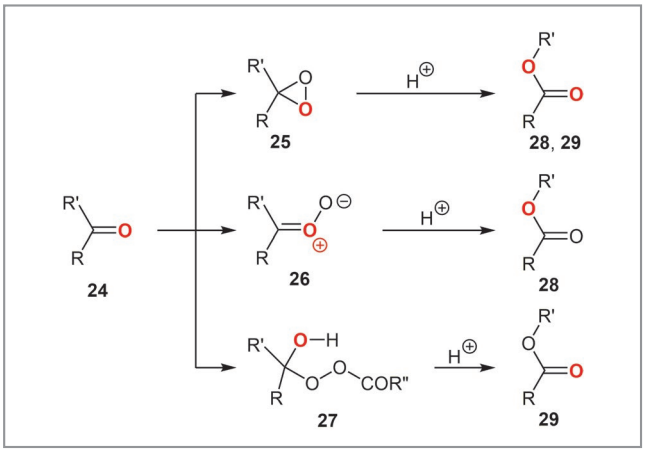
Scheme 4



Scheme 5

method.[20] The first examples of the Baeyer–Villiger oxidation of cyclic ketones were carried out using menthone (**18**), tetrahydrocarvone (**20**), and camphor (**22**); they are collected in Scheme 5.

The first reagent used in the reaction was Caro's acid (monopersulfuric acid), developed by the pioneering dye chemist, Heinrich Caro (1834–1910), who had worked with Baeyer on the synthesis of indole.[21]



Scheme 6

Three distinct mechanisms for the reaction were proposed (Scheme 6). The first, by Baeyer and Villiger themselves,[1a] passes through a dioxirane (**25**), the second, proposed by Wittig and Pieper,[22] passes through a carbonyl oxide (**26**), and the third, proposed by Criegee,[23] involves an α-hydroxyalkyl perester (the Criegee intermediate, **27**).

Evidence confirming the Criegee mechanism was obtained by Doering and Dorfman,[24] who used ^{18}O-labeled benzophenone (marked in red in Scheme 6) as the substrate for the reaction. The carbonyl-^{18}O-labeled ester (**29**) was obtained as the exclusive product, which is consistent with the Criegee mechanism, but neither of the others. A series of studies[25] established the migratory aptitudes of alkyl substituents as shown in Figure 3. The relative reactivities of commonly used peracids are summarized in Figure 4.

The Baeyer–Villiger oxidation of C-20 steroidal ketones was shown quite early on to give a single diastereoisomer of the product;[26] shortly thereafter, the rearrangement was shown to occur with retention of configuration.[27] This was effected by Turner as shown in Scheme 7. Thus, catalytic hydrogenation of 1-acetyl-2-methylcyclohexene (**30**) gave *cis*-1-acetyl-2-methylcyclohexane (**31**); this ketone was readily epimerized by base to the *trans* isomer (**32**). The treatment of these two ketones with perbenzoic acid in chloroform gave the diastereoisomeric acetates **33** and **34**, showing clearly that the rearrangement had occurred with retention of configuration.

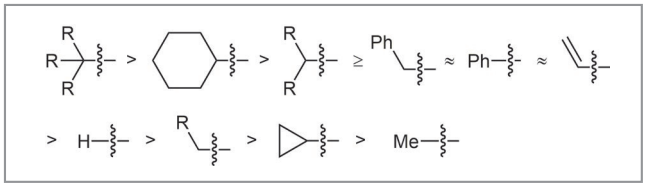


Figure 3 The migratory aptitudes, in the Baeyer–Villiger oxidation, of groups attached to the carbonyl carbon

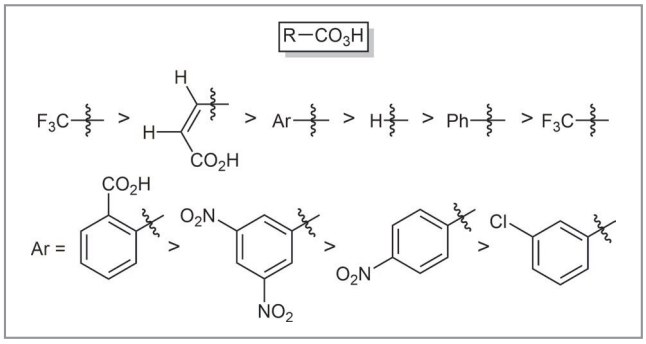
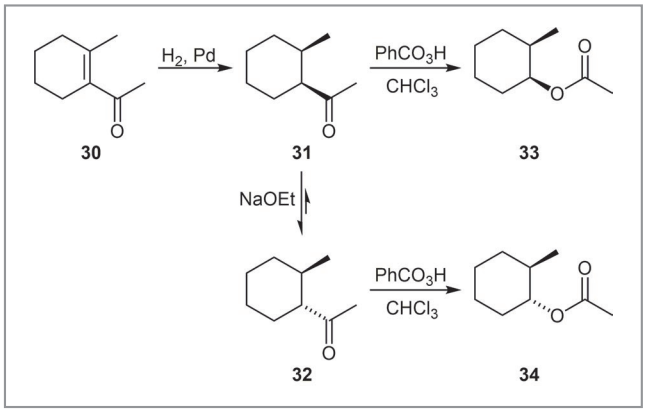


Figure 4 The relative reactivities of peracids in the Baeyer–Villiger reaction

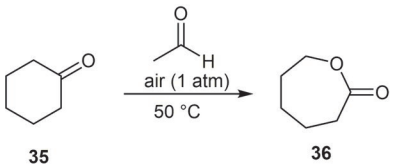


Scheme 7

The Baeyer–Villiger reaction has been a valuable synthetic method for nearly a century and a quarter, and it should come as no surprise that the reaction has come under intense research directed at 'greening' the reaction.[28] Under the standard conditions, the reaction poses several problems that need

to be addressed if it is to be carried out under green conditions: 1) Organic peracids are shock-sensitive, and oxidation hazards, covered by special regulations in their transportation and disposal. 2) The stoichiometric reaction generates one mole of the carboxylic acid per mole of peracid; this must be recycled or disposed of as hazardous waste. 3) The reaction involves the use of solvents that are not generally environmentally benign.

To address these problems, considerable effort has gone into identifying catalytic methods for the reaction. These include the catalytic generation of the peracid from aldehydes and molecular oxygen, a reaction known under the general name of the Mukaiyama oxidation (Scheme 8).[29a] The Mukaiyama oxidation was quickly expanded by the use of catalysts[29b–d] and forms the basis for an industrial synthesis of ε-caprolactone (Scheme 8),[30a] which was still under investigation nearly two decades later.[30b]

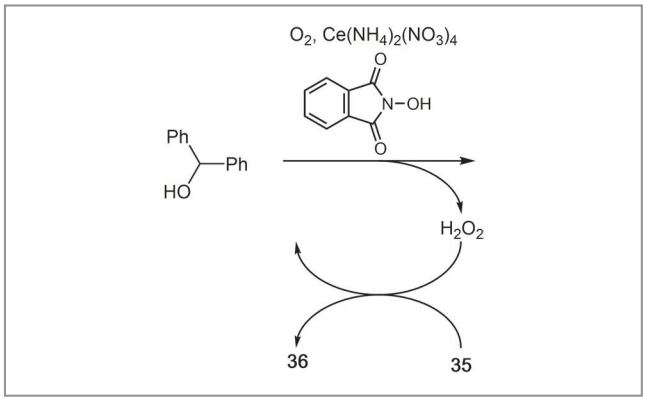


Scheme 8 The Mukaiyama oxidation of cyclohexanone to ε-caprolactone

Hydrogen peroxide also remains one of the most favored terminal oxidants for the greening of the Baeyer–Villiger oxidation. A search of Google Scholar for 2020 using the keywords 'Baeyer–Villiger' and 'hydrogen peroxide' returned 303 results as of October 20. One recent report[31] details the *in situ* generation of hydrogen peroxide and coupled Baeyer–Villiger oxidation in the presence of molecular oxygen under catalysis by cerium(IV) ammonium nitrate and *N*-hydroxypyridine (Scheme 9).

Other researchers have studied methods for reducing the shock sensitivity of the oxidant. A representative example of recent work in this area[32] has identified perdecanoic acid as a non-toxic, shock-resistant replacement for the more sensitive and toxic lower-molecular-weight peracids.

The most recent research aimed at making the reaction enantioselective is being addressed by examining biocatalysis. Baeyer–Villiger monooxygenases (BVMO) are flavoprotein monooxygenases that have been widely exploited for carrying out the asymmetric Baeyer–Villiger oxidation (a Google Scholar search, in July 2020, for the period 2016–2020 returns



Scheme 9 Coupled catalytic alcohol oxidation and Mukaiyama oxidation with oxygen as the terminal oxidant

over 460 hits). The enzyme structure and sequence have both been determined, and the enzyme has become a popular target for modification.[33] Several reviews[34] of the uses of these enzymes for asymmetric Baeyer–Villiger oxidations have been published since 2011.

REFERENCES

(1) (a) A. Baeyer, V. Villiger *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3625–3633. (b) A. Baeyer, V. Villiger *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 124–126. (c) A. Baeyer, V. Villiger *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 858–864.
(2) For biographies of Baeyer, see: (a) R. Huisgen *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 297–311.
(b) A. de Meijere *Angew. Chem. Int. Ed.* **2005**, *44*, 7836–7840.
(c) G. Nagendrappa *Resonance* **2014**, *19*, 489–522.
(3) W. H. Perkin *J. Chem. Soc., Trans.* **1923**, *123*, 1520–1546.
(4) Abstract (Referate) *Ann. Chem. Pharm.* **1851**, *80*, 253–255.
(5) A. Baeyer *Ann. Chem. Pharm.* **1857**, *103*, 178–181.
(6) A. Baeyer *Ann. Chem. Pharm.* **1857**, *103*, 181–184.
(7) (a) R. Bunsen *Ann. Chem. Pharm.* **1839**, *31*, 175–180.
(b) R. Bunsen *Ann. Chem. Pharm.* **1841**, *37*, 1–57.
(c) R. Bunsen *Ann. Chem. Pharm.* **1842**, *42*, 14–46.
(d) R. Bunsen *Ann. Chem. Pharm.* **1843**, *46*, 1–48.
(8) A. Baeyer *Ann. Chem. Pharm.* **1858**, *105*, 265–276.
(9) A. Baeyer *Inaugural-Dissertation*, University of Berlin, Germany, **1858**.
(10) A. Baeyer *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 2269–2281.
(11) For a history of Baeyer's work that culminated in the synthesis of indigo, see: A. v. Baeyer, In *Adolf von Baeyer's gesammelte Werke*, Vol. 1; A. v. Baeyer, V. Villiger,

V. Hottenroth, R. Hallensleben, Eds.; Friedrich Vieweg u. Sohn: Braunschweig, **1905**; XXXVIII–LV.
(12) A. Baeyer, V. Drewson *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 2856–2864.
(13) (a) A. Baeyer *Ann. Chem. Pharm.* **1863**, *127*, 199–236. (b) A. Baeyer *Ann. Chem. Pharm.* **1864**, *130*, 129–175.
(14) (a) A. Baeyer *Ber. Dtsch. Chem. Ges.* **1871**, *4*, 555–558. (b) A. Baeyer *Ber. Dtsch. Chem. Ges.* **1871**, *4*, 658–665. (c) A. Baeyer *Polytech. J.* **1871**, *201*, 358–362.
(15) A. Baeyer *Ber. Dtsch. Chem. Ges.* **1900**, *33*, 3771–3775.
(16) A. Baeyer *Justus Liebigs Ann. Chem.* **1888**, *245*, 103–190.
(17) (a) V. Villiger *Inaugural-Dissertation*, University of Munich: Germany, **1893**. (b) A. Baeyer, V. Villiger *Justus Liebigs Ann. Chem.* **1893**, *276*, 255–265.
(18) (a) A. Baeyer, V. Villiger *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 1923–1929. (b) A. Baeyer, V. Villiger *Ber. Dtsch. Chem. Ges.* **1898**, *31*, 2067–2079. (c) A. Baeyer, V. Villiger *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 2429–2447.
(19) A. Baeyer, V. Villiger *Ber. Dtsch. Chem. Ges.* **1897**, *30*, 1954–1958.
(20) (a) C. H. Hassall *Org. React.* **1957**, *9*, 73–106. (b) P. A. S. Smith, In *Molecular Rearrangements*, Vol. 1; P. DeMayo, Ed.; Interscience Publishers, Inc.: New York, **1963**; 577–591. (c) J. B. Lee, B. C. Uff *Q. Rev. Chem. Soc.* **1967**, *21*, 429–457. (d) G. R. Krow *Comprehensive Organic Synthesis* **1991**, *7*, 671–688. (e) G. R. Krow *Org. React.* **1993**, *43*, 251–798. (f) M. Renz, B. Meunier *Eur. J. Org. Chem.* **1999**, 737–750.
(21) (a) A. Baeyer, H. Caro *Ber. Dtsch. Chem. Ges.* **1877**, *10*, 692–693. (b) A. Baeyer, H. Caro *Ber. Dtsch. Chem. Ges.* **1877**, *10*, 1262–1265.
(22) G. Wittig, G. Pieper *Chem. Ber.* **1940**, *73*, 295–297.
(23) R. Criegee *Justus Liebigs Ann. Chem.* **1948**, *560*, 127–135.
(24) W. v. E. Doering, E. Dorfman *J. Am. Chem. Soc.* **1953**, *75*, 5595–5598.
(25) (a) S. L. Friess *J. Am. Chem. Soc.* **1949**, *71*, 14–15. (b) W. v. E. Doering, L. Speers *J. Am. Chem. Soc.* **1950**, *72*, 5515–5518. (c) S. L. Friess, N. Farnham *J. Am. Chem. Soc.* **1950**, *72*, 5518–5521. (d) S. L. Friess, A. H. Soloway *J. Am. Chem. Soc.* **1951**, *73*, 3968–3972. (e) R. R. Sauers, R. W. Ubersax *J. Org. Chem.* **1965**, *30*, 3939–3941.
(26) (a) R. E. Marker *J. Am. Chem. Soc.* **1940**, *62*, 2543–2547. (b) V. Burckhardt, T. Reichstein *Helv. Chim. Acta* **1942**, *25*, 821–832. (c) V. Burckhardt, T. Reichstein *Helv. Chim. Acta* **1942**, *25*, 1434–1443. (d) L. H. Sarett *J. Am. Chem. Soc.* **1947**, *69*, 2899–2901.
(27) (a) R. B. Turner *J. Am. Chem. Soc.* **1950**, *72*, 878–882. (b) T. F. Gallagher, T. H. Kritchevsky *J. Am. Chem. Soc.* **1950**, *72*, 882–885.
(28) (a) Y. Zhou, X. Chen, X. Ling, W. Rao *Green Chem.* **2019**, *21*, 5611–5615. (b) M. Uyanik, K. Ishihara *ACS Catal.* **2013**, *3*, 513–520. (c) C. Jiménez-Sanchidrián, J. R. Ruiz *Tetrahedron* **2008**, *64*, 2011–2026. (d) G.-J. ten Brink, I. W. C. E. Arends, R. A. Sheldon *Chem. Rev.* **2004**, *104*, 4105–4124.
(29) (a) T. Yamada, K. Takahashi, K. Kato, T. Takai, S. Inoki, T. Mukaiyama *Chem. Lett.* **1991**, *20*, 641–644. (b) S.-I. Murahashi, Y. Oda, T. Naota *Tetrahedron Lett.* **1992**, *33*, 7557–7560. (c) M. Hamamoto, K. Nakayama, Y. Nishiyama,Y. Ishii *J. Org. Chem.* **1993**, *58*, 6421–6425. (d) K. Kaneda, S. Ueno, T. Imanaka, E. Shimotsuma, Y. Nishiyama, Y. Ishii *J. Org. Chem.* **1994**, *59*, 2915–2917.
(30) (a) H. A. Wittcoff, B. G. Reuben *Industrial Organic Chemicals*; John Wiley & Sons: New York, **1996**; 254. (b) J. Zang, Y. Ding, Y. Pei, J. Liu, R. Lin, L. Yan, T. Liu, Y. Lu *React. Kinet. Mech. Catal.* **2014**, *112*, 159–171.
(31) R. Du, H. Yuan, C. Zhao, Y. Wang, J. Yao, H. Li *Mol. Catal.* **2020**, *490*, 110947.
(32) M. Sitko, A. Szelwicka, A. Wojewódka, A. Skwarek, D. Tadasiewicz, L. Schimmelpfennig, K. Dziuba, M. Morawiec-Witczak, A. Chrobok *RSC Adv.* **2019**, *9*, 30012–30018.
(33) For a recent example, see: R. D. Ceccoli, D. A. Bianchi, M. A. Carabajal, D. V. Rial *Mol. Catal.* **2020**, *486*, 110875.
(34) (a) H. Leisch, K. Morley, P. C. K. Lau *Chem. Rev.* **2011**, *111*, 4165–4222. (b) R. Wohlgemuth *Comprehensive Organic Synthesis II* **2014**, *7*, 121–144. (c) M. J. L. J. Fürst, A. Gran-Scheuch, F. S. Aalbers, M. W. Fraaije *ACS Catal.* **2019**, *9*, 11207–11241. (d) E. Romero, J. R. G. Castellanos, G. Gadda, M. W. Fraaije, A. Mattevi *Chem. Rev.* **2018**, *118*, 1742–1769.