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From Catalysis to Lewis Base Catalysis with Highlights from 1806 to 1970

Edwin Vedejs[1,2,3]

[1]*Leading Investigator, Latvian Institute of Organic Synthesis, Aizkraukles iela 21, Riga LV-1006, Riga, Latvia*
[2]*Professor Emeritus, University of Michigan, Department of Chemistry, 930 N. University Ave., Ann Arbor, MI 48109, USA*
[3]*Professor Emeritus, University of Wisconsin, Department of Chemistry, 1102 University Ave., Madison, WI 53706, USA*

1.1
Introduction

This chapter tracks several of the most informative developments involving Lewis base catalysis from the time of their discovery to the period when general features of the underlying mechanistic principles had been identified and had stimulated systematic investigation. By roughly 1960–1970, it had been widely recognized that many important reactions are triggered by new bonding interactions involving a pair of electrons from a Lewis base catalyst. A partial list of examples includes such classical reactions as the benzoin and Knoevenagel condensations, pyridine-catalyzed acylations, Walden's autoracemization, the Dakin–West reaction, cyanide- or thiamine-catalyzed Stetter reaction, and so on. It was also becoming clear that the events subsequent to electron pair donation could be exceptionally diverse, ranging from very simple scenarios involving Lewis base-promoted C—X bond heterolysis to other situations involving intriguing complexity over several stages, some of which feature the Lewis base in more than one role. These mechanistic insights did not begin to develop until the twentieth century, following a protracted period of confusing formulas and structures, fascinating discoveries, false starts, and controversies that began roughly at the same time as the science of organic chemistry.

1.2
Catalysis

Much of modern organic chemistry can be traced to the period immediately after the revolution in structural understanding that occurred between 1860 and 1875, but some important stories began earlier, before it was known that carbon is tetravalent and tetrahedral, and before consensus was reached regarding the atomic weights of the most common main group elements. Catalysis is one of those older stories, and the benzoin condensation will be our connection between the first

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attempts to classify the phenomenon of catalysis, the first example of catalysis by a Lewis base, and (nearly 70 years later!) the first example to be understood mechanistically.

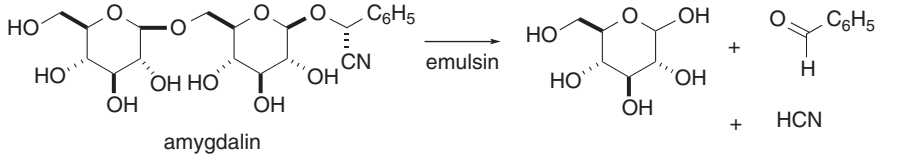
1.2.1 Berzelius Defines Catalysis

By 1835–1836, Berzelius had recognized a common feature among five very different chemical transformations that were initiated by another substance that could be recovered unchanged, including such familiar examples as the hydrolysis of starch or the ignition of a mixture of hydrogen and oxygen by a platinum surface [1]. Some sources also credit Berzelius with coining the word "catalysis" from Greek *kata* ("down") and *lysis* ("dissolution" of an object or a group, among other implied meanings), but certainly the word is older and was used in various contexts by the mid-seventeenth century [2]. One interesting source is *Alchimia*, authored by Libavius (1597), and sometimes referred to as the first chemistry textbook. However, Libavius connected the term *catalysis* with a "breaking down" of base metals in procedures intended to produce gold. Why this term resonated with Berzelius is not entirely clear, but a common theme in his writings and lectures over the years 1820–1843 is the notion that catalysis results from an unknown force exerted by the presence of the catalyst, and that this force acts upon the substrate(s) to cause a chemical transformation. "Breaking down" or chemically transforming the substrate is understandable in that context, but Berzelius was careful to reject any "breaking down" of the catalyst itself. It was not to be seen as a participant in the chemical changes initiated by catalysis, but as the source of an unknown "catalytic power."

1.2.2 Early Proposals for Intermediates in Catalytic Reactions

At about the same time that Berzelius formulated his definition of catalysis, Mitscherlich demonstrated conversion of ethanol to diethyl ether upon heating in the presence of a substoichiometric amount of sulfuric acid. He also made the connection with known cases in which a small amount of what he called a contact substance (*Contactsubstanz*) would cause chemical transformation of a large amount of substrate [3]. About two decades later, Williamson revisited the same method of ether synthesis and observed that monoethyl sulfate is formed initially and reacts with ethanol to form the final product [4]. These are probably the first systematic investigations of catalysis involving an organic substrate. Williamson's study is also important for documenting the first example in which catalysis of an organochemical reaction is associated with the formation of an intermediate (monoethyl sulfate) that is capable of reacting with the substrate (ethanol) to give the product (ether). An earlier (1806) study by Désormes and Clément had already implicated reactive intermediates in an *inorganic* reaction, the catalytic lead chamber process for manufacture of sulfuric acid from SO_2 and oxygen in the presence of potassium nitrate, and had attributed the formation of SO_3 to the involvement of intermediate nitrogen oxides [5]. Together with Williamson's result, these findings could have helped open the door to a general understanding of catalysis via reactive intermediates, but this did not happen. Instead, chemists interested in catalysis wavered between the influence of Berzelius, who had spoken out against any modification of catalysts during catalyzed reactions, and the skepticism of Liebig, who dismissed Berzelius' unknown catalytic force with the words ". . . creation of a new force with a new word that does not clarify the phenomenon . . ." [6].

Liebig's interest in catalysis had begun at least by 1837 when he and Wöhler reported the hydrolytic cleavage of amygdalin to benzaldehyde by "emulsin," a biological catalyst that is present in bitter almonds (Eq. (1.1)) [7]. Over the following years, Liebig proposed alternative explanations for catalysis that invoked the disturbance of existing bonds by heat and by physical contacts between molecules [8]. However, the argument between Berzelius and Liebig was not resolved, and other ideas regarding catalysis had limited impact.



amygdalin (1.1)

1.3 Progress with Catalysis in Organic Chemistry

The decades immediately preceding and following the Berzelius definition of catalysis produced a number of examples of lasting importance, starting with sulfuric acid production and continuing with other industrially important inorganic processes by the end of the nineteenth century. Even the public became aware of one of the earliest discoveries, the 1823 Döbereiner lamp, consisting of a Zn/H_2SO_4 chamber as hydrogen source and a Pt ignition catalyst [9]. Several important biological catalysts were also recognized by 1850, including diastase (hydrolysis of starch), emulsin (hydrolysis of glycosides), yeast, and various other "ferments" (later called enzymes following the 1878 suggestion of W. Kühne) [10] that attracted interest due to their connection with metabolism, nutrition, and, of course, brewing and wine making. The examples of nonbiological, organic catalysis were not at that level of visibility and the topic lagged behind other developments in organic chemistry. The work of Mitscherlich and Williamson is unusual because both authors were clearly aware of the catalytic aspects, and because they happened to combine a practical problem (preparation of ether) and a conceptual advance in organic reactivity (C—O bond formation). Curiously, the generation of organic chemists after Williamson made many discoveries involving catalysis but the topic was not mentioned, may not have been recognized, and might not have been a concern to the authors. The focus of organic chemistry had moved on to identifying new reactions, expanding the understanding of functional groups, and developing useful procedures.

By 1860, revolutionary advances in the understanding of organic structures were under way as a result of Kekule's 1858 structural proposals, and uncertainties regarding carbon valency, relative atomic weights for C, H, and O, and empirical formulas had been resolved [11]. However, almost none of the emerging classical organic reactions (acid, base, or metal-catalyzed) were subjected to mechanistic study until 1900. The timing may have been stimulated in part by Ostwald's redefinition of catalysis, based on his work beginning in the 1880s and finalized in 1901 [12]. Like Berzelius, Ostwald was initially skeptical of reaction intermediates in catalysis, so it is no surprise that intermediates were hardly mentioned in organic manuscripts appearing between 1850 and 1900. More surprising is the frequent absence of any mention of catalysis in manuscripts from this era.

One of the few publications to comment on catalysis is Williamson's paper on catalytic formation of ether from ethanol as already discussed [4]. Another example is Walden's 1898 publication describing what proved to be the first case of Lewis basic halide catalysis [13]. Walden reports the apparently spontaneous decrease in optical rotation (about 40%) for enantioenriched dimethyl

2-bromosuccinate, and the total racemization for *d*-$C_6H_5CHBrCO_2H$, both after 3 years of storage. Walden was Ostwald's student in Riga until 1887, and later (briefly) also in Leipzig, and shared his mentor's reluctance regarding hypotheses based on incomplete knowledge. His 1898 text largely avoids any rationale or comment beyond experimental observations, although the closing sentence cautiously states "It is not ruled out that a small amount of cleaved HBr as catalyst influences or controls the reaction." On the other hand, Walden is less cautious in a sentence supporting autoracemization, a word that also appears in the title of the paper. Walden implies that racemization is an intramolecular event because no evidence was seen for decomposition of the substrate. However, subsequent studies indicate that the racemization is in fact catalyzed, not spontaneous [14]. In 1929, Kuhn ruled out autoracemization (i.e., self-racemization via reversible heterolysis, homolysis, or elimination) by showing that highly purified bromosuccinate ester is configurationally stable [14b]. Racemization occurs in the presence of KBr and related halide salts, and appears to be a simple example of catalysis by a Lewis base (bromide). The most likely explanation for the partial loss of configurational homogeneity observed by Walden in 1898 involves reversible S_N2 displacement by traces of bromide ion, and not a new phenomenon such as autoracemization.

Many other now famous nineteenth century publications described reactions that must have been catalytic, but the authors paid attention mostly to reporting the procedures. Reports in which smaller, nonstoichiometric amounts of a key reagent were advantageous for yield, purification, or convenience certainly included suitable comments to alert the reader. Notable examples include Fischer's classical glycosidation [15] and esterification methods [16], an earlier (first) example of acid-catalyzed acetal formation [17], and Claisen's crossed aldol condensation to form benzylideneacetone in the presence of "a little $ZnCl_2$" [18]. Other examples of catalysis attracted attention if they made a good story. For example, Kekulé's 1870 manuscript describing the conversion of acetaldehyde to crotonaldehyde begins with commentary on prior work in which this reaction had been achieved by simply heating the aldehyde in ethylidenechloride [19]. However, Kekulé observed that no condensation occurred using purified solvent, but did take place in the presence of "traces of HCl" in control experiments. Apparently, the earlier report had used contaminated ethylidenechloride, and Kekulé made sure to start his story with this "teaser." Finally, a number of reports describe catalytic reactions in which the amounts of reagents are given but not discussed, as often happened in various base-induced carbonyl condensations [20], or in which the amounts are left unspecified, as happened in the first report of hydrogenation over a platinum catalyst [21].

One common feature among all of the classical publications cited in the prior paragraph is that *none* of them mention "catalysis," "catalyst," or analogous terms. Was the concept so familiar that mention was not necessary? Were the authors avoiding pointless conflicts over unknown forces? Or was the topic simply not in fashion? Most likely, all of these reasons played some small role, but a larger factor may have been the scientific culture during the second half of the nineteenth century. During this period, a massive influx of seemingly endless and often disconnected new facts was reported along with unsatisfactory, short-lived hypotheses and explanations. Many years later, Ostwald would characterize the controversies between supporters of Berzelius and supporters of Liebig and their role in the development of catalysis as part of his 1909 Nobel Prize lecture as follows:[1)] "Although neither Berzelius' good definition nor Liebig's bad definition promoted in any way this scientifically interesting and technically highly important field, the new definition (i.e., Ostwald's own definition) had this effect at once." Apparently, Liebig's "bad definition" was too familiar to merit any descriptive comment. From a current perspective, Liebig's writings about catalysis come

1) Nobel lectures may be accessed online at www.nobelprize.org/.

across more as commentary than definition [6,8], and connect catalysis with physical phenomena as already mentioned. However, Ostwald did provide an evaluation of the Berzelius interpretation: "Only the statement that the catalysts acted by their mere presence can be criticized." but proceeded to dismiss unknown catalytic forces or catalytic powers and to connect catalysis with the emerging fundamental principles of reaction kinetics and Gibbs energy.

1.4
Ostwald's Redefinition of Catalysis

Ostwald has been called the founding figure in physical chemistry, having contributed to several distinct and important advances and subdisciplines [22], but he received the Nobel Prize in Chemistry in 1909 specifically "for his work on catalysis and for his investigations into the fundamental principles governing chemical equilibria and rates of reaction." It was Ostwald who developed the modern definition of a catalyst in his publications and lectures between 1894 and 1901.

1.4.1
The Evolution of Ostwald's Views and Their Subsequent Refinement

Ostwald's views about catalysis developed during a decade of work involving acid-catalyzed hydrolysis, and his first definition was published under unusual circumstances in 1894. Quite remarkably, the definition appeared not in a typical research contribution, but in a one-page critique of a manuscript by F. Stohmann, as follows. "If this reviewer faced the task of characterizing the general phenomenon of catalysis, he would envision the following expression: the acceleration of a slowly occurring chemical change by the presence of a foreign substance." [23]. Together with the appended explanation saying (in part) that the foreign substance "is not necessary for the reaction," this definition encountered some resistance. If the catalyst is "not necessary," then apparently "a slowly occurring chemical change" would have a finite rate in the absence of catalyst. Is that different from a reaction that does not occur at all or is too slow to observe on some arbitrary laboratory timescale? Ostwald thought not, but others had doubts. Some took issue with Ostwald's earlier study of HCl-catalyzed hydrolysis of methyl acetate that began with a restatement of the Berzelius criterion for catalysis [24]. Having carefully proved that HCl is not consumed during the reaction, and that weaker acids catalyze hydrolysis more slowly, the paper closes with a statement that the catalytic acids ". . . remain in the free state throughout the course of the reaction . . . ." This was taken by some to imply that the acid catalyst acts by its mere presence, and does not participate directly. Whether or not that was Ostwald's intent can be questioned since he would not have speculated beyond the observable facts. In any event, his paper makes no specific proposal about how the catalyzed hydrolysis takes place.

Presumably, the mixed responses to the 1894 critique/definition may have stimulated Ostwald to take a much more careful approach in his definition published in 1901. This manuscript is the text of a lecture that summarizes the history of catalysis in depth, mentions alternative explanations, and comments on a possible catalytic role for reaction intermediates if they can be detected and their rate effects confirmed. The following simplified definition was given:

> "A catalyst is any substance that changes the rate of a chemical reaction without appearing in the final products." [25]

By the time of his Nobel Prize lecture in 1909,[1)] Ostwald's opinion of intermediates had evolved further. As he also did in 1901, he called attention to the 1806 work by Désormes and Clément [5], but refers to it with more weight as the "theory of intermediate reactions" followed by the words ". . . no other equally effective principle has hitherto been found in the theory of catalysis." Ostwald cautions against assuming that intermediates are always required, but does not comment on recent developments that had already implicated intermediates in heterogeneous as well as homogeneous catalysis, as discussed in Section 1.4.2 and Section 1.5.

1.4.2
Sabatier and "Temporary Compounds" in Heterogeneous Catalysis

During the evolution of Ostwald's views, Sabatier had begun his classical studies on heterogeneous catalysis. In 1897, he had already observed that changes in catalysts could change the outcome of reactions at a metal surface, and spoke out against contemporary ideas focusing on a role for physical proximity due to adsorption of gaseous reactants in porous catalysts [26]. Instead, Sabatier explained the conversion of ethylene into methane and carbon upon heating with nickel (obtained from the oxide and hydrogen) by saying that "It is possible that an unstable compound of nickel and ethylene is first formed and afterwards splits up into nickel, carbon, and methane." In other publications, Sabatier suggested the formation of distinct temporary compounds (i.e., intermediates) to account for differing catalyst-dependent outcomes [27]. The importance of intermediates was further underscored by Sabatier's 1912 Nobel Prize, awarded "for his method of hydrogenating organic compounds in the presence of finely disintegrated metals whereby the progress of organic chemistry has been greatly advanced in recent years" (in other words, for major developments in heterogeneous catalysis, including the hydrogenation of alkenes, alkynes, and even benzene derivatives). Sabatier's award address comments on his views regarding catalysis from 1897 onward: "I thought and I still think . . . that the decisive cause of the catalytic activity of porous platinum is not a simple process of physical condensation producing a local rise in temperature but that it is a real chemical combination of the surface of the metal with the surrounding gas".[1)] Later in the same lecture, Sabatier mentions the temporary formation of nickel hydrides under conditions of catalytic hydrogenation. He also draws an analogy between (i) Williamson's monoethyl sulfate intermediate in the reaction of ethanol with sulfuric acid to form ether and (ii) hypothetical alkoxide intermediates formed at the surface of metal oxide catalysts (Al_2O_3, ThO_2, or WO_2) acting as displaceable groups in high-temperature reaction of simple alcohols to form ethers.

1.4.3
A Curious Tangent: The Radiation Hypothesis for Catalysis

Ostwald rejected a role for any special catalytic force. Nevertheless, unusual candidates for the origins of catalytic reactivity continued to enter the literature until the 1920s, culminating in the so-called radiation theory [28]. This theory proposed, among other things, that infrared radiation emitted by catalysts, solvents, walls of reaction vessels, and so on was an energy source involved in reactivity, and thus also in catalysis. In one paper by Lamble and McCudmore Lewis (no connection with G.N. Lewis), infrared radiation by the hydrogen chloride molecule was discussed as an explanation for the acid-catalyzed inversion (i.e., hydrolysis) of sucrose [29], while the abstract of a publication by Barendrecht states "Since the change of activity of invertase with the change of pH

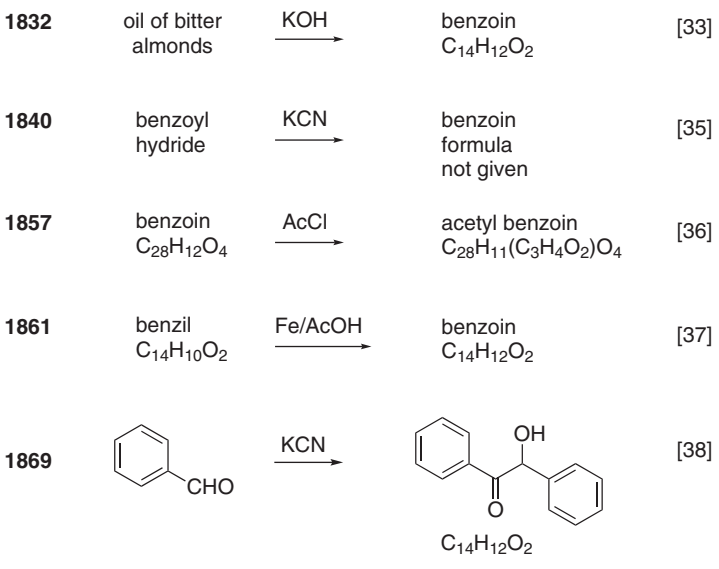
corresponds to that expected on the radiation hypothesis, it is concluded that invertase also works by a radiation." [30]. The radiation theory was originally phrased using the language and mathematics of early physical chemistry and attracted sufficiently serious attention to warrant a 1928 article by Daniels in *Chemical Reviews* that begins with the sentence "Few hypotheses in science have suffered such a rapid rise and fall as the radiation hypothesis." [31]. To be fair to the initiators of this idea (Trautz, Perrin, McCudmore Lewis), it arose partly over real concerns regarding some aspects of early collisional activation theory. In contrast to various attempts to explain catalysis during the nineteenth century, the radiation theory was presented in a scientifically testable context, was duly tested, and was soon refuted.

No one claimed to have identified the original catalytic force of Berzelius as part of the radiation episode, but the demise of this hypothesis may have helped to finally put an end to the quest for unknown forces. The new understanding of reaction kinetics and thermodynamics in the context of catalysis did not begin with Ostwald [32], nor did Ostwald bring it to the modern level. What he did do was to convince many chemists that no special forces were needed to understand catalytic phenomena, and that explanations could be found in physical chemistry.

Further discussion of catalysis is beyond the scope of this chapter, but more detailed accounts of the early developments are available in recent historical reviews [9] and the kinetic treatments are given in many textbooks. The account by Lindström and Pettersson also provides a summary of milestones in industrial catalysis from the nineteenth century up to 1970, including Ostwald's process for oxidation of ammonia to nitric acid, Haber's conversion of nitrogen into ammonia, the Fischer–Tropsch method for production of hydrocarbons by coal gasification, Houdry's petroleum cracking process, the Ziegler–Natta alkene polymerization chemistry, Wacker oxidation of ethylene to acetaldehyde, and many other developments that profoundly affect chemical technology [9a].

1.5
The First Example of Lewis Base Catalysis

Shortly before Berzelius' comments regarding catalysis were published in 1836, the first example that can be recognized as Lewis base catalysis appeared as a very small part of the famous 1832 paper by Wöhler and Liebig describing their investigation of oil of bitter almonds (benzaldehyde) [33]. Treatment of the naturally derived oil with KOH resulted in modest conversion to a crystalline product that was called "benzoin" (after gum benzoin, a source of benzoic acid, as well as the origin of traditional nomenclature of benzene derivatives). Elemental analysis gave the same % composition as determined for the starting material. The original Wöhler–Liebig publication was instrumental in correctly defining oil of bitter almonds as a "benzoyl hydride," although the exact identity of "benzoyl" remained elusive for some years. Of course, the benzoyl hydride was later identified as benzaldehyde, but benzoin came to be described as an *isomer* (not a dimer) and the correct empirical formulas remained uncertain [isomerism had already been encountered by Wöhler in 1827–1828 and was defined by Berzelius between 1830 and 1831 [34]. The formula of benzaldehyde given by Liebig happened to be incorrect ($C_{14}H_{12}O_2$) because the work was done well before the 1860 consensus regarding correct atomic weights, but this meant that the formula fits benzoin. Such formulas were in flux until 1869 [35–38], as shown in Scheme 1.1, but the more intriguing conclusion was entirely correct: benzoin is a different substance, but has the same elemental composition as the starting material, benzaldehyde.



Scheme 1.1 Benzoin condensation; 40 years to finalize formula and structure.

One other development having special significance for Lewis base catalysis occurred during the first decade following discovery of the benzoin reaction. In 1840, Zinin reported that formation of benzoin from benzaldehyde can be effected using potassium cyanide without any potassium hydroxide [35]. The original experiments of Liebig and Wöhler had unknowingly generated the true catalyst *in situ* because oil of bitter almonds is contaminated with HCN. Zinin must have understood this because he was working in Liebig's laboratory at the time. He comments that good conversion to benzoin depends on how much HCN is present in the naturally derived oil, and also mentions successful experiments using pure benzoyl hydride (presumably, distilled benzaldehyde) and dilute ethanolic KCN (no KOH), or ethanolic KOH plus "a few drops of HCN." The manuscript does not specify how much cyanide was used, so we cannot be certain whether Zinin knew what would happen using a substoichiometric quantity of cyanide. On the other hand, he certainly knew what would happen with an excess of HCN because the same paper describes isolation of the HCN adduct (cyanohydrin) of "benzoyl hydride" and comments on its somewhat variable presence in samples of oil of bitter almonds. Zinin also knew that cyanide did not become part of the benzoin product, a key criterion for catalysis.

Here was a case where a natural substrate contained at least two potential precatalysts (HCN and the cyanohydrin) for its own conversion to a new structure. A number of other phenomena were already recognized where chemical transformations were affected by the action of natural contaminants, but these examples would prove to be the result of "contaminating" enzymes (leavening of bread, fermentation of grapes, etc.). One of these, the 1837 report by Wöhler and Liebig describing the hydrolytic cleavage of amygdalin using emulsin (Eq. (1.1)), has already been discussed in connection with catalysis in Section 1.2.2. Perhaps these analogies between cyanide and biological catalysts escaped Zinin's notice, but more likely catalysis was not his concern and not his problem. Certainly, the possibility of biological as well as chemical catalysis was already explicit in the

Berzelius summation of known catalytic events in 1836, but Zinin did not raise that issue and the literature makes no connection between catalysis and benzoin condensation until much later.

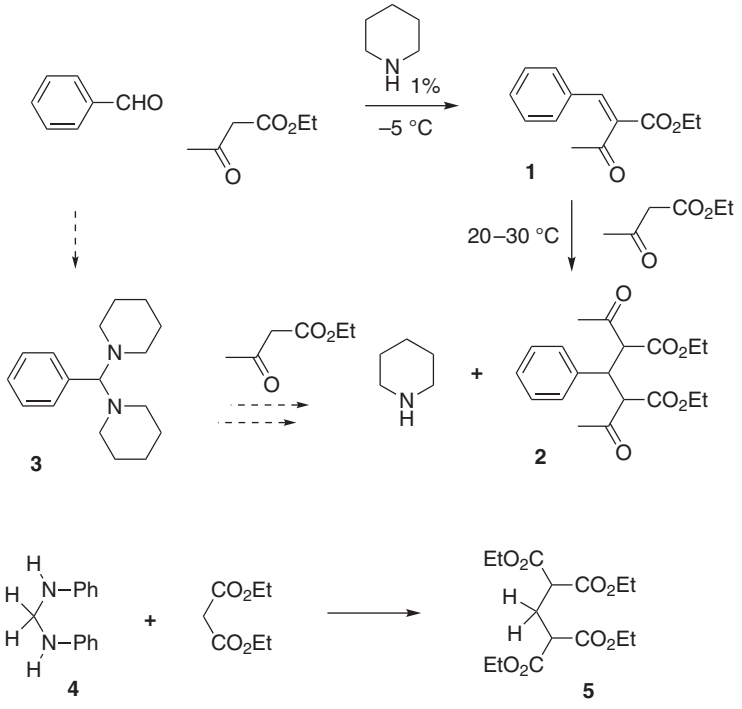
In 1861, the correct formula of benzoin appeared in a Zinin publication [37], without comment about a different formula in a paper by the same author a few years earlier (Scheme 1.1) [36]. On the other hand, the structural problem had not been solved. By then, benzoin had been correlated chemically with benzil (originally, "benzoyl") as well as diphenylethane, both of which were recognized to contain two phenyl substituents. However, the connectivity of benzil was clouded by its controversial base-induced rearrangement to benzylic acid, as discussed in the broader historical context by Berson [39]. At the time, many chemists followed Kekule's view that carbon skeletons could be degraded into simpler carbon segments, but could not be rearranged [39]. Nevertheless, these concerns were largely overcome by 1870 and all of the key structures relevant to the benzoin problem were understood by at least some of the principal players. In 1874, the structures were already correctly shown in a leading textbook of that era [40]. That is not to say that they were universally accepted [41], but consensus was near.

1.6
The Road to Mechanistic Comprehension; Multistage Catalysis by Lewis Base

The structural problems involving benzoin were solved, but little progress was forthcoming regarding the nature of the C—C bond-forming step. Further progress would have to await the emergence of mechanistic thinking in connection with the role of intermediates in catalysis, and also with amine catalysis as an important advance in preparative organic chemistry. This topic would eventually become one of the most broadly applicable categories of Lewis base catalysis, and currently is probably the most important one (see Chapters 6, 12, 13, 16, and 17). The point of entry in this account will be the 1894–1898 study by Knoevenagel describing the condensation between aldehydes and acetoacetate or malonate esters [42].

1.6.1
The Knoevenagel Condensation

In his first publications on the topic, Knoevenagel showed that primary or secondary amines promote the condensation of β-dicarbonyl compounds with aldehydes to give amine-free products (Scheme 1.2). His 1896 paper is especially significant because it shows that the reaction of ethyl acetoacetate with benzaldehyde in the presence of about 1% of piperidine can be controlled to give either a 1 : 1 adduct (**1**) or a 2 : 1 adduct (**2**), depending on the temperature [43]. The text shows the reaction scheme and comments "As one can see, the piperidine is regenerated during the reaction. That explains how 1% of piperidine effects the condensation of a large amount of acetoacetate and aldehyde." Importantly, this paper also offers a rationale (*chemismus*) suggesting that benzaldehyde is converted initially into benzylidenebispiperidine (the benzaldehyde aminal), which then condenses with acetoacetate by replacement of the "mobile" (*bewegliche*) methylene hydrogens. Two years later, another publication in the series describes the same events, ". . . it is not yet clarified how the amine plays the role of *contactsubstanz* whereby a small amount is sufficient to convert a large amount of aldehyde and acetoacetate . . ." [44]. However, later that year (1898) the most definitive paper in the series appeared demonstrating that the previously known crystalline aminals $CH_2(NHPh)_2$ and $CH_2(NC_5H_{10})_2$ react upon heating with an excess of dimethyl malonate to give



Scheme 1.2 Knoevenagel condensation.

the 2 : 1 adduct (**5**) [45]. The sequence of three publications from 1896–1898 is noteworthy not only for its preparative impact but also for its scientific approach: (i) catalysis was clearly recognized and emphasized, (ii) a mechanistic hypothesis based on a precedented intermediate was presented, and (iii) the hypothesis was tested and positive results were obtained.

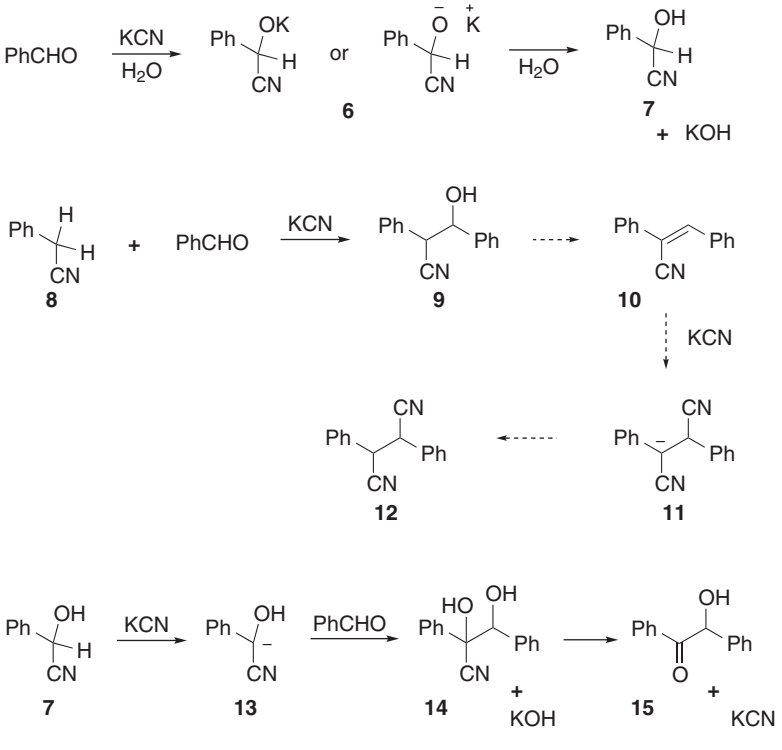
The special ability of primary and secondary amines to catalyze the reaction of aldehydes had been recognized and the "Knoevenagel mechanism" entered the literature. However, some aspects remained to be understood. Knoevenagel briefly mentioned aldimines (Schiff bases) in his papers, and even carried out a control experiment using "methyleneaniline" in an attempted reaction with malonate ester. However, no condensation product was obtained [45]. The same paper also shows that much better condensation yields can be obtained by adding small amounts of secondary amine catalyst to an aldehyde and malonate at room temperature compared to the control experiments with stoichiometric amounts of aminal reagents that required heating. The reasons for these discrepancies were not discussed, and were not fully understood for at least five decades when the first kinetic studies appeared implicating iminium intermediates [46]. Importantly, the preparative advantage of using an amino acid or acetic acid to generate cationic intermediates had been recognized earlier [47]. As recently as 1988, the "Knoevenagel mechanism" was mentioned in a mechanistic discussion without showing the iminium ion intermediates [48]. However, Knoevenagel's manuscripts did not say that a mechanism had been defined. Instead, he discussed *potential* intermediates (the aminal and the imine), performed key control experiments, and established catalysis. These were major steps toward modern mechanistic thinking.

1.6.2

Lapworth's Breakthrough; Benzoin Revisited

Arthur Lapworth was one of the first, if not the first, organic chemists to present his findings in a modern mechanistic perspective [49]. His early, intuitive classification of organic substructures as "anionoid" and "cationoid" anticipates Ingold's more definitive terminology (nucleophilic and electrophilic), as discussed in Chapter 2, and he also made important contributions to the understanding of carbonyl reactivity. For Lewis base catalysis, the breakthrough disclosure came in 1903 as part of Lapworth's publication regarding the formation of cyanohydrins using aqueous KCN [50].

Lapworth formulated several reasonable mechanistic options for cyanohydrin formation and settled on a pathway involving slow addition of cyanide followed by rapid proton transfer (Scheme 1.3). His analysis included anionic intermediates, discussed the proton transfer equilibria, and demonstrated reversibility in the cyanide addition. The investigation also addressed a puzzling 1884 Knoevenagel experiment involving the conversion of mandelonitrile (**7**) into 2,3-diphenylsuccinonitrile upon being heated with benzyl cyanide (**8**) and KCN. Since Lapworth had found that **7** undergoes reversible dissociation to benzaldehyde and cyanide in the presence of base, he recognized that condensation of benzaldehyde with **8** would become feasible to give the benzylidene intermediate **10** via an adduct **9**. Conjugate addition by cyanide to **10** would then form anion **11** and thus explain the formation of 2,3-diphenylsuccinonitrile (**12**). All of these steps were confirmed by control experiments, thereby explaining Knoevenagel's findings. More importantly, the addition step leading to **9** provided a key insight relevant to the benzoin problem. Lapworth realized that



Scheme 1.3 Lapworth's mechanism for benzoin condensation.

both mandelonitrile (**7**) and benzyl cyanide (**8**) contain "labile α-hydrogen" adjacent to cyanide. If **8** can be activated for condensation with benzaldehyde, then **7** might also be activated by deprotonation to **13**, and by analogy should afford **14** "which is simply the unstable cyanohydrin of benzoin; this would break up, reversibly, into benzoin (**15**) and hydrogen cyanide, which would then be available for further conversion of benzaldehyde." Lapworth's words, within the quotes, not only define the mechanism but also identify the catalytic cycle. One more control experiment was performed, probably because cyanide was not a typical base for use in condensation reactions. Thus, a mixture of **7** and benzaldehyde was treated with about 40% of tripropylamine, and formation of benzoin was confirmed after 20 days at room temperature, as expected for Brønsted base catalysis.

In short, Lapworth's 1903 paper presented and tested the mechanism in much the same way that is done now a century later. In his closing paragraph, Lapworth had more to say, ". . . the additive reactions of HCN occur under the same conditions as those of ethyl malonate, ethyl acetoacetate, and similar compounds. The mechanism is doubtless much the same in all these cases . . . ." In other words, those similar compounds react via the formation of anions. The word "enolate" was not yet in use to describe metalated carbonyl intermediates, but Lapworth's comment is a milestone in enolate condensation chemistry [50].

Lapworth's mechanistic insight solved the 70-year benzoin mystery, and it not only revealed the first mechanistic interpretation of a Lewis base-catalyzed process but also demonstrated how deeply one may need to look to fully grasp the role of the Lewis base. Cyanide plays four different roles in the mechanism: (i) Lewis base in the first nucleophilic addition, (ii) activating group for anion formation prior to the second nucleophilic addition, (iii) Brønsted base in the deprotonation step, and (iv) leaving group. Such mechanistic diversity within a single sequence is not uncommon in Lewis base catalysis, as will be shown in later chapters.

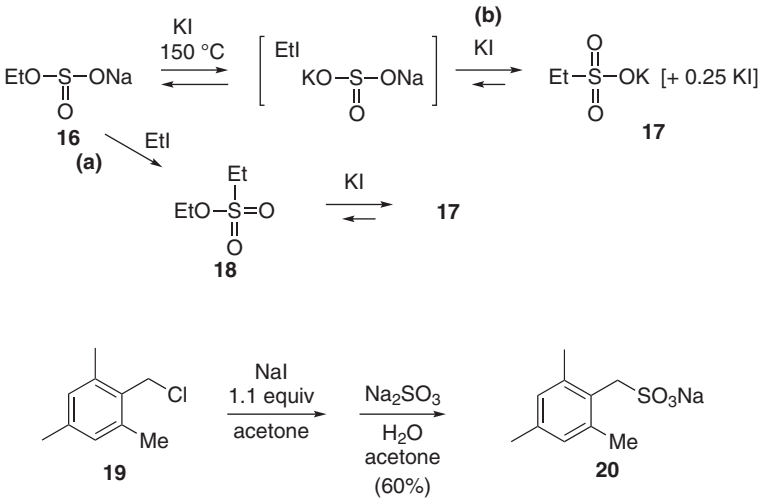
1.7
An Uneven Path to a Unifying Concept

The benzoin condensation can be regarded as an example of Lewis basic anion catalysis. As already described, it features cyanide anion in multiple roles, as also happens in an unusual multistage cyanide-catalyzed cleavage of benzil [51][2], but that level of complexity is not obligatory. Much simpler catalytic events can be initiated by a Lewis basic anion that can also serve as a good leaving group, and many of those transformations represent catalysis by halide anion. Not all of the mechanisms are simple, but all of the examples summarized below consistently involve nucleophilic attack and leaving group displacement at some stage in the overall mechanism. On the other hand, surprising diversity is encountered in the substrates, as shown in the following sections.

1.7.1
Halide Catalysis

In 1905, Rosenheim and Sarow reported one of the oldest examples of halide catalysis, the unusual transformation from sodium ethyl sulfite ($EtOSO_2Na$, **16**) to an isomeric sulfonate salt **17** using an excess of potassium iodide (150 °C, sealed tube; Scheme 1.4) [52]. A similar reaction

2) (a) Lapworth did not comment on a related mechanistic puzzle involving the cyanide (Lewis base)-catalyzed cleavage of benzil in alcoholic solution (ROH) to give equal parts of benzaldehyde and $PhCO_2R$.



Scheme 1.4 Alkylsulfonate salts from sulfite alkylations.

occurs with NaSCN as the catalyst. At first glance, these might appear to be rather esoteric examples, but subsequent developments will show that a second look is worthwhile (see Section 1.7.3). In contrast to the earlier Walden racemization [13], in which halide catalysis was not established until Holmberg's subsequent (1913) report [14a], and Walden's observations were finally explained in 1929 [14], Rosenheim and Sarow were able to provide a plausible explanation already in the original publication. Alternative pathways were evaluated, evidence regarding potential intermediates was obtained, and a reasonable case was made for catalysis by the Lewis basic iodide additive. Assuming that initial attack by iodide on the ethyl group cleaves the carbon oxygen bond in **16** to generate iodoethane and sulfite anion, the authors proposed that ethyl iodide formed in the first step would then react with **16** at sulfur to give ethyl ethylsulfonate **18** as an intermediate that is cleaved by iodide to afford **17**. In support of this proposal, an authentic sample of **18** was prepared and treated with KI under the usual conditions to generate the same product **17**, presumably following path **(a)**.

A more direct pathway (**b**) might also be invoked, proceeding by iodoethane alkylation of the nucleophilic sulfur electron pairs of SO_3^{2-} to give the more stable sulfonate **17**. The latter step is well known with sodium sulfite as the nucleophile, and one example is illustrated in Scheme 1.4 by the preparation of a benzylic sulfonate salt **20** from **19** [53]. The procedure also uses added NaI to enable a facile S_N2 displacement by generating an intermediate iodide (not shown) from the benzylic chloride **16**. Although the sequence is conducted in two stages and relies upon a stoichiometric amount of NaI, catalytic, one-pot variations of analogous Finkelstein displacements are known and have been used to facilitate the relatively sluggish S_N2 reactions of chlorides and sulfonates [54].

None of the proposals or control experiments addresses the reported catalysis of the conversion from **16** to **17** by NaSCN. However, there is some precedent that NaSCN can function in a similar way as a Lewis base catalyst as well as a good nucleophile and leaving group. The simplest case involves the isomerization of benzylthiocyanate (BnSCN) to the more stable isothiocyanate, (BnNCS), a process that has been interpreted as a simple equilibration initiated by nucleophilic

attack of the ambident nucleophile NaSCN [55]. In this system, the leaving group (SCN^-) is of course identical to the nucleophile.

An extensively studied example of halide catalysis and substrate activation for nucleophilic displacement is the iodide-assisted hydrolysis of bromomethane [56]. The rate constants for individual steps were determined, and it was shown that the rate of direct bromomethane solvolysis is small compared to the competing S_N2 displacement by iodide and subsequent solvolysis of iodomethane. Together with the earlier report that racemization of bromosuccinate takes place by analogous (reversible) S_N2 displacement [14], these findings could have been used to help make a general case for catalysis by Lewis basic anions, but that did not happen.

1.7.2
Ambident Nucleophile Intermediates in Halide-Catalyzed Rearrangements

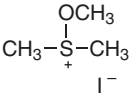
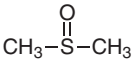
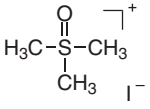
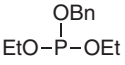
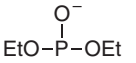
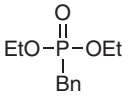
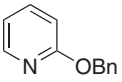
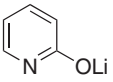
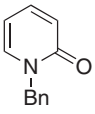
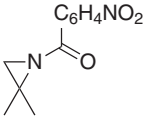
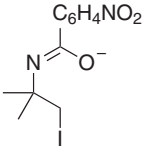
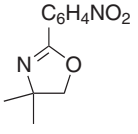
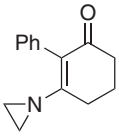
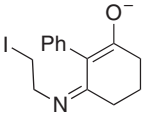
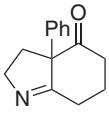
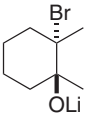
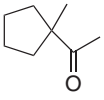
The key conceptual advance illustrated in Scheme 1.4 is related to the generation of an unusual nucleophile (SO_3^{2-}) that has electron pair density at sulfur as well as oxygen. In principle, this means that nucleophilic attack may occur involving either of the heteroatoms, sulfur or oxygen, resulting in eventual formation of the more stable product (sulfonate). In other words, sulfite anion is an ambident nucleophile. Many other anionic or neutral nucleophiles share that property, and can play a similar role as reactive intermediates in systems that undergo halide-catalyzed rearrangement. The structural diversity of substrates that undergo such rearrangements is remarkable (Table 1.1), and the outcomes range from very simple and transparent to more challenging. Mechanistic similarities between some of these events were not recognized until the 1960s, and even then, analogies between rearrangements involving different functional groups were seldom mentioned. For that reason, Table 1.1 includes representative recent examples as well as historical cases. The first three entries resemble the sulfite/sulfonate system in that a net alkyl migration occurs from one heteroatom to the other, likely due to initial cleavage to an intermediate alkyl halide followed by a bimolecular recombination step [57–59]. The first example is probably the most important, and illustrates the key rearrangement involved in preparation of trimethylsulfoxonium iodide [57]. The same report also mentions facile deuterium exchange upon exposure of the salt to D_2O, corresponding to sulfoxonium ylide generation. The other cases in Table 1.1 (entries 4–6) feature tethered systems where the final stage involves intramolecular attack by the ambident nucleophilic intermediate [60–62].

The halide-catalyzed epoxide rearrangement (entry 6) in Table 1.1 does not involve a typical ambident nucleophile intermediate and is included in the table partly for convenience, but there are some conceptual similarities with the other examples. The term "ambident nucleophile" typically refers to a strongly delocalized system having two interacting nucleophilic sites, each with substantial unshared electron pair density. By comparison, the epoxide-derived alkoxide intermediate (entry 6) lacks the strong delocalization (although its nucleophilic sites may interact by hyperconjugation), has one conventional Lewis basic site (alkoxide unshared pairs), and one unconventional site (the σ-electrons in the migrating ring C—C bond). The latter site serves as an intramolecular nucleophile in the rearrangement step leading to the cyclopentane product [62].

1.7.3
The First Recognition of Lewis Base Catalysis

The three decades following the 1903–1905 studies by Lapworth and by Rosenheim and Sarow were crucially important for the development of a conceptual basis for bonding and reactivity in

Table 1.1 Halide-catalyzed rearrangement via ambident nucleophilic intermediates.

Entry	Conditions	Substrate	Intermediate	Product
1	I^- 50 °C, DMSO, >50%			
2[a), b)]	Bu_4NI, $(EtO)_3P$, BnOH, 160 °C			
3	LiI, neat, 100 °C, >90%			
4	NaI/acetone, reflux 10 h, 93%			
5	NaI, neat, 110 °C, 37%			
6[b)]	$LiBr/Bu_3P{=}O$, benzene 80 °C			

a) The substrate is generated *in situ* by alkoxide exchange between $(EtO)_3P$ and BnOH.

b) Yield not reported.

organic chemistry. These advances cover such fundamental topics as Lewis structures, acid–base theory, and the definitions of Lewis base, Lewis acid, nucleophile, and electrophile, as discussed in Chapter 2. By comparison, rather modest advances were reported regarding Lewis base catalysis. Several additional categories of amine catalysis entered the literature, including isolated examples of amine-catalyzed decarboxylation [63–66] and anhydride activation [67–71]. By the mid-1930s, some of these reactions were the subject of mechanistic studies, but no one had identified a conceptual connection between cyanide catalysis, halide catalysis, and amine catalysis.

The Knoevenagel condensation did attract some comparisons over this time period, but only among cases involving primary or secondary amine catalysts where formation of aminals, hemiaminals (carbinolamines), or imines might play a role. This latter category was also more visible because similar chemistry had been observed with enzymatic catalysts and was being actively pursued (see Section 1.8). If any of the investigators had noticed that some or all of the amine catalysts

fit the recently defined categories of Lewis base (1923) or Lapworth's "anionoid" (1925) or Ingold's nucleophile (1933–1934) [72], then surely the discussion would have included amine catalysis. However, it was G.N. Lewis who noticed [73], and his classical 1938 paper mentions a single example, the "esoteric" case of halide catalysis from **16** to **17**.

The 1938 publication by Lewis is entitled simply *Acids and Bases*. A cursory look at the next to last page finds a heading "Acids and Bases as Catalysts," but the full context makes clear that the author is referring to *Lewis* acids and *Lewis* bases. Of course, that terminology would not have been used by G.N. Lewis, but the thrust of the entire manuscript is to underscore the common features between conventional acids and bases with those molecules that are basic because they can donate two electrons to form a new bond, while acids are those species that can accept two electrons. Lewis unifies acidic and basic substances under one generalized classification, and in that regard his usage is very distinct from contemporary (1938) usage. More discussion of the background along with precise versions of the Lewis definition can be found in Chapter 2, but for present purposes it is important to note that Lewis included the following operational criteria to describe *all acids and bases that fit his broader electronic definition*:

1) When an acid and a base can combine, the process of combination, or neutralization, is a rapid one.
2) An acid or a base will replace a weaker acid or base from its compounds.
3) Acids and bases can be titrated against one another by use of . . . indicators.
4) Both acids and bases play an extremely important part in promoting chemical processes *through their action as catalysts*.

The 1938 manuscript goes into considerable details to show that criteria (1)–(4) apply to what are now called Lewis acids and Lewis bases, and provides experimental evidence for each criterion. Regarding catalysis (criterion 4), his text comments ". . . in the many organic syntheses that are caused by strong acids such as the halides of many metals and of boron, we see more fully the scope of catalytic action." However, the text does not provide any specific cases of acid catalysis. On the other hand, Lewis uses the 1905 publication of Rosenheim and Sarow as the example describing a case of base catalysis in detail [52]. He invokes the reaction between the *base* iodide with the *acid* SO_2 as an analogy for the formation of $EtOSO_2Na$ (**16**) from EtONa and SO_2 (Scheme 1.4). The subsequent conversion to **17** is then described as ". . . a clear case of basic catalysis, due to the formation of temporary intermediates between $EtOSO_2^-$ and the basic ions." By this remarkable insight, Lewis recognizes and implicitly defines the principal topic of the current volumes: Lewis base catalysis.

Chapter 2 provides a more complete account of the fundamentals involved in the concept of Lewis base catalysis, so the current discussion of the 1938 publication will end by briefly considering a simple question: How did the Lewis manuscript influence the development of catalysis using Lewis basic species? Considering the publications represented in Table 1.1, listing the most closely related examples of halide catalysis following the Rosenheim and Sarow precedent that Lewis cited, one would have to conclude that there was little, if any, direct influence. None of those authors cited Lewis (or Rosenheim and Sarow) nor did they indicate a common conceptual basis for halide or anion catalysis until 1960.

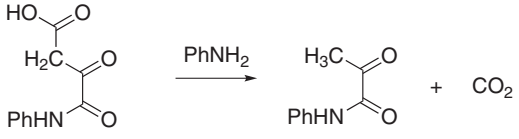
There can be no doubt that the Lewis paper was influential in other contexts because it has been cited nearly 200 times, mostly in connection with acid–base theory and Lewis acid–Lewis base complexation chemistry. However, only a few of the citations mention catalysis. One of the cited publications is Jensen's influential review of Lewis acid and Lewis base fundamentals [74], to be described in detail in Chapter 2, but that review gives no specific catalysis examples. None of the

other cited publications classify their findings as Lewis base catalysis according to the aforementioned criterion (4), and only a small handful of publications would fall into the category of organic chemistry. As noted by Jensen in his review [74], there were artificial divisions between organic chemistry and other disciplines in the 1930s and subsequent decades. This may be one reason, along with the readjustment of traditional acid/base terminology, why the Lewis classification of "basic catalysis" was largely ignored by the organic chemistry community. The same divide between disciplines may also be the reason why Lewis did not connect his arguments with the more visible (and "more organic") examples of halide or anion or amine catalysis discovered in the prior century.

1.8
Amine Catalysis

1.8.1
Amine-Catalyzed Decarboxylation

Soon after Knoevenagel's study of amine-catalyzed C—C bond formation, isolated instances of amine-catalyzed C—C bond cleavage were reported, involving decarboxylation of β-keto acid derivatives. In what may be the first encounter (Eq. (1.2)), an oxaloacetate anilide (mixture of tautomers) was converted into a pyruvate-derived anilide and CO_2 in the presence of excess aniline at temperatures above −10 °C [63]. Further details of the decarboxylation process were not explored, but the general features of aniline-catalyzed decarboxylation of the parent oxaloacetic acid and the role of carbinolamine and iminium intermediates using various amines have been addressed in more recent literature [75].

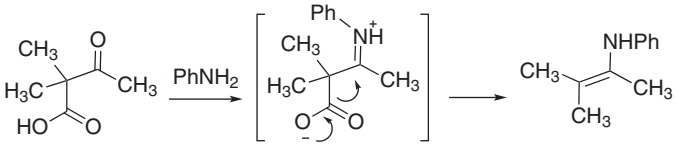


(1.2)

Several years later (1907), Pollak investigated the reaction of sodium acetoacetate under a variety of biologically relevant conditions to test for acetone formation, including treatment with simple amino acids [64]. The facile conversion to acetone and CO_2 was attributed to the intermediate formation of the corresponding imine or enamine, presumably after initial proton transfer to neutralize the sodium acetoacetate, but no other mechanistic aspects of the decarboxylation were mentioned.

In 1908, the first paper in an extensive series of investigations by Bredig and Fajans reported the decarboxylation of racemic camphorcarboxylic acid catalyzed by chiral amines [65]. These studies, along with subsequent work by Fajans [66], clearly established catalysis as well as modest, but measurable, levels of enantioselection in the kinetic resolution of the racemic substrate. The 1908 paper also mentioned formation of nitrogen-containing intermediates, but did not draw them and explicitly considered only the diastereomeric carboxylate ammonium salts and not the imines. No connection with Pollak's 1907 work was made, and again, an opportunity for mechanistic insight was lost. That did not come until 1929, when Pedersen compared the rates of amine-catalyzed and uncatalyzed β-keto acid decarboxylations [76]. His unique insight was to suggest that the uncatalyzed decarboxylation of acetoacetate proceeds directly to the product enol via formation of zwitterionic intermediates. The corresponding amine-catalyzed decarboxylation was also

considered and a similar zwitterionic intermediate was proposed (Eq. (1.3)) [76b], but the kinetic investigations indicated more than one amine-catalyzed pathway [76c,76d].



(1.3)

Additional kinetic studies by Westheimer *et al.* led to the conclusion that the amine-catalyzed decarboxylation can be explained by rate-determining formation of an imine intermediate or loss of carbon dioxide via a 6-center mechanism from the imine [77]. Furthermore, these authors demonstrated a closely related sequence in the mechanism for the enzymatic conversion from acetoacetic acid to acetone catalyzed by acetoacetate decarboxylase. The enzymatic process features nucleophilic attack by the free amino group of a lysine subunit of the enzyme at ketone carbonyl to form the iminium ion, followed by decarboxylation as before [78]. Westheimer also demonstrated that amines catalyze retro-aldol C—C cleavage of diacetone alcohol by way of an imine intermediate [79]. Together with Pedersen's findings, Westheimer's work provided definitive early evidence for the role of imines in enzymatic transformations, many examples of which are now known [80]. These studies also stimulated extensive mechanistic investigations of amine catalysis between 1933 and 1960 using simple model structures in processes that mimic some aspects of enzymatic reactivity. Further developments are beyond the scope of this chapter. An informative account of that first major era of amine catalysis is provided by Bruice and Benkovic that includes additional examples of amine-catalyzed decarboxylations [81]. Structural and mechanistic features of acetoacetate decarboxylase function are discussed in the recent literature [82].

1.8.2
The Thiamine Story: Amine Catalysis Is Slower Than *N*-Heterocyclic Carbene Catalysis

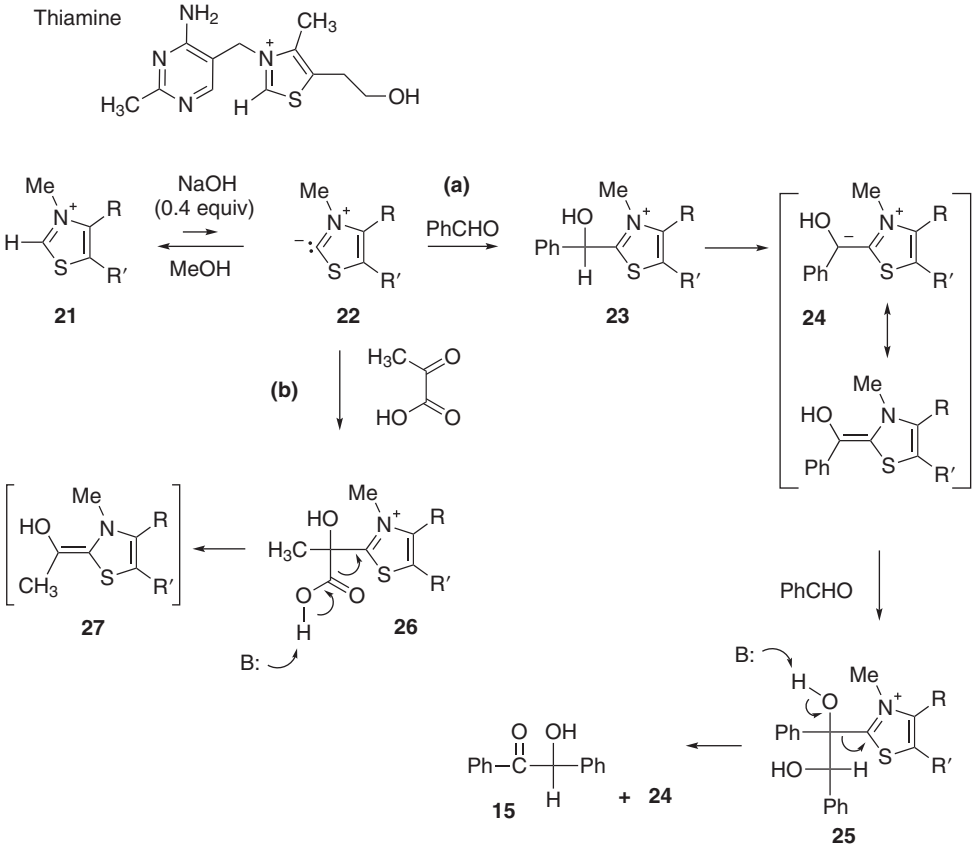
Amine-catalyzed C—C bond cleavage (decarboxylation; retro-aldol) played a major role in enzymology as mentioned above, while the implications for preparative chemistry (i.e., catalyst optimization to achieve the reverse reaction of C—C bond formation) were often recognized, but rarely studied in depth until about 2000 (iminium and enamine catalysis, see Chapters 16 and 17 of Volume 2). On the other hand, parallel investigations of thiamine-catalyzed decarboxylation attracted more preparative interest, probably because the early experiments encountered not only bond cleavage [83] but also catalytic C—C bond formation (benzoin condensation) [84]. This topic has become especially important in connection with the Lewis basic *N*-heterocyclic carbene catalysts, as described in Chapter 27 of Volume 3. It will be summarized very briefly here among the other historical examples of catalytic decarboxylation. Extensive reviews of the background and early development are available, and much of that material will not be repeated here [85,86].

The connection with amine catalysis has proven to be more historical than structural. Originally, it had been thought that the primary amino group attached to the pyrimidine subunit of thiamine is the catalytic site by analogy to the amino group of aniline [83a]. However, the pyrimidine amine is not an effective Lewis base because it is deactivated by the π-deficient heterocycle. On the other hand, in the presence of base, thiamine has the potential to generate a more Lewis basic site at the thiazolium C2 position, as recognized by Breslow in 1958 [87]. This activation pathway is

responsible for the decarboxylation and C—C bond-forming reactions catalyzed by thiamine, as described in the next paragraph.

Breslow proposed a mechanism for the thiazolium salt-catalyzed benzoin condensation that begins with thiazolium deprotonation (Scheme 1.5) [87]. After introducing evidence for the facile equilibration of the model thiazolium salt **21** with the *N*-heterocyclic carbene **22** in D_2O, the discussion presented a sequence of steps for the thiazolium-catalyzed benzoin condensation in methanol (containing 0.4 equiv NaOH) that parallels the Lapworth cyanide-catalyzed benzoin mechanism step-by-step. The only substantial difference is that **22** replaces cyanide in the key roles, including nucleophilic attack to form **23**, activation of the benzylic hydrogen in the deprotonation from **23** to **24**, and ultimate departure as a leaving group to produce benzoin (**15**). The important structure **24** has come to be known as the Breslow intermediate. Structure **24** is too labile for isolation, but analogous imidazolium- and triazolium-derived benzaldehyde adducts have recently been characterized [88].

The initially formed intermediate **22** can be invoked to explain the thiazolium-catalyzed decarboxylation of pyruvic acid (path **b**), as well as subsequent carbon bond-forming events that are catalyzed by thiamine [86]. Nucleophilic addition of **22** to pyruvic acid generates **26**, which is



Scheme 1.5 Thiazolium salt-catalyzed C—C bond formation and cleavage.

activated for decarboxylation in a manner analogous to the amine-catalyzed decarboxylation of β-keto acids via simpler iminium intermediates (compare with Eq. (1.3)). The resulting **27** is a nucleophile that can react with carbonyl substrates to form a new C—C bond via steps resembling the conversion from **24** to benzoin (**15**).

1.8.3 Amine Activation of Anhydrides

1.8.3.1 Early Examples of Anhydride Activation

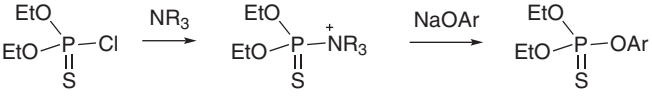
During the period when intermediates were increasingly recognized to play an essential role in catalysis (1895–1910), the first (1901) report appeared describing the acylation of alcohols using pyridine/acetic anhydride [67]. This paper was entirely focused on the preparative aspects of routine acylations. No mention was made of stoichiometry, catalysis, or the now familiar transient *N*-acetylpyridinium acetate intermediate. Thus was lost another opportunity for mechanistic comment and insight because the analogous *N*-acetylpyridinium chloride was already known and had been isolated as a crystalline, easily hydrolyzed substance [68]. The related *N*-benzoylpyridinium chloride was also known and had been shown to react with water to form benzoic anhydride [69] or acylate alcohols and phenols [70]. Furthermore, formic acetic anhydride had been prepared and was reported to decompose to acetic acid and carbon monoxide in the presence of pyridine, quinoline, or *N*,*N*-dimethylaniline [71], but the mechanistic connections between these related topics were not made. For example, a 1923 kinetic study of the catalytic decarbonylation of formic acetic anhydride by Lewis basic amines including pyridine concluded that the data point to an intermediate [89]. However, the author drew an unconventional structure for the intermediate where the pyridine nitrogen appears to be connected to anhydride oxygen and not to carbon as had been drawn in the earlier literature. Another example is Wegler's pioneering 1932 study on the enantioselective acylation of 1-phenylethanol using acetic anhydride and brucine as catalyst [90]. This work is an important milestone in the development of chiral Lewis base methodology, as discussed in Chapter 12 of Volume 2. Formation of an intermediate adduct (*doppelbindung*) by interaction of brucine with the anhydride was considered carefully, but no intermediate could be isolated or detected and no structure for the intermediate was drawn.

That all of these events are related to intermediate *N*-acyl salts generated from the Lewis base did not become clear until 1950–1960, when a more mechanistic approach clarified the role of simple pyridine catalysts in acyl transfer chemistry [91]. The stimulus came partly from enzymology and partly from the maturing discipline of physical organic chemistry (Sections 1.8.3.2 and 1.8.4).

1.8.3.2 Gold and Jefferson: The First Mechanistic Study

Judging from the above evidence and the dozens of publications between 1901 and 1950 that mention using amine additives to promote preparative acylations, the conclusion seems inescapable that there was at least some awareness of activated *N*-acyl intermediates for reactions wherein Lewis basic amines were used together with electrophilic halides or anhydrides. Nevertheless, the absence of intermediates in so many publications over several decades reminds of Hammett's interesting retrospective account regarding attitudes during the early twentieth century [92]. While summarizing several "obsessively held convictions" of that era, Hammett attributed the following "conviction" to the older generation: "it is scientifically immoral to talk about a reaction mechanism involving intermediates which cannot be isolated." Behind that smokescreen of exaggeration, Bunnett may well have been thinking of Ostwald's influence, but he does not say. Whatever the reason, explicitly

drawn *N*-acyl intermediates or analogous electrophiles (precedented since 1886 [68]) in acyl transfer or related reactions could not be found in the literature from 1898 [70] to a brief 1950 publication regarding thiophosphoryl transfer by Toy and Beck [93]. These authors developed a catalytic process for the preparation of Parathion and suggested a quaternary ammonium intermediate (Eq. (1.4)). Interestingly, the reaction of diethyl chlorothionophosphate with sodium 4-nitrophenoxide was catalyzed not only by tertiary amines but also by 3% of diamylphenylphosphine. Relative reactivities of the catalysts were not reported, but the catalyzed reactions were shown to proceed at 105 °C in chlorobenzene versus about 150 °C in the absence of catalyst. This may well be the first reported use of a phosphine Lewis base in catalysis.



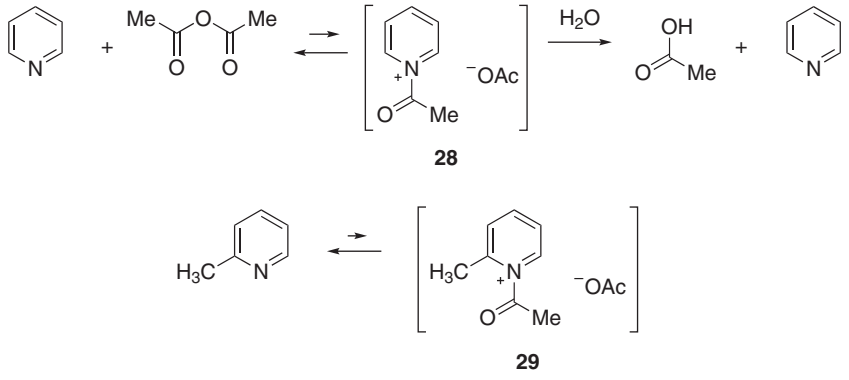
(1.4)

Three years later, a detailed mechanism for the Lewis base-catalyzed acylation using acetic anhydride finally appeared as part of the classical investigation by Gold and Jefferson [91]. For the first time, the familiar and extensively used pyridine/acetic anhydride method was subjected to a thorough kinetic study, and rate comparisons were made with substituted pyridines. Similar catalytic effects were observed for the 3-methyl and 4-methyl derivatives (picolines) compared to the parent pyridine, but 2-picoline and 2,6-dimethylpyridine were about 10-fold less reactive. This reactivity difference was attributed to a destabilizing steric effect by the 2-methyl group on the *N*-acetylpyridinium intermediate **29** compared to **28** (Scheme 1.6), and steric inhibition of delocalization in a geometry having coplanar pyridinium and acetyl π-systems was suggested as the reason. The kinetic behavior was interpreted on the basis of a two-stage mechanism involving rate-determining, reversible formation of **28**, followed by rapid hydrolytic cleavage.

1.8.4
Model Systems as Probes of Enzyme Function

1.8.4.1 Bender's Summary of "Nucleophilic" Catalysis

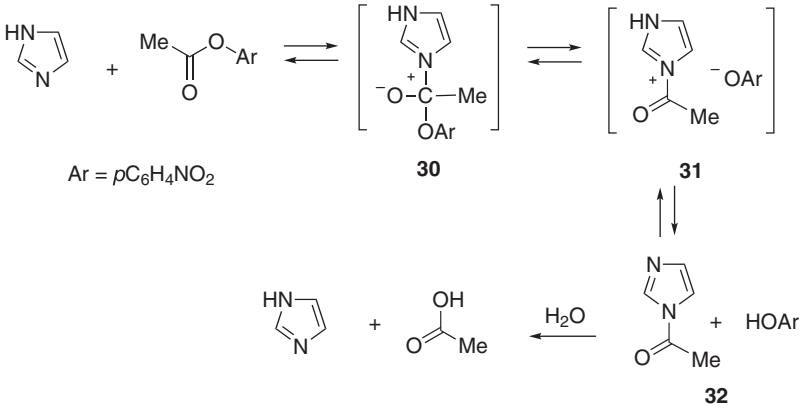
Several years after Gold and Jefferson's key publication [91], Bender and Turnquest investigated the imidazole-catalyzed hydrolysis of phenyl 4-nitrophenyl acetate as part of efforts to understand the



Scheme 1.6 *N*-Acetylpyridinium intermediates in anhydride hydrolysis.

active site of α-chymotrypsin, trypsin, and acetylcholinesterase [94]. Based on kinetic studies, a mechanism was proposed starting with nucleophilic attack by imidazole to generate the *N*-acetyl 4-nitrophenoxide **31** via a tetrahedral intermediate **30** (Scheme 1.7). The sequence resembles the pyridine-catalyzed hydrolysis of acetic anhydride, except for the deprotonation step from **31** to the *N*-acylimidazole **32**, a neutral intermediate that hydrolyzes more slowly than the analogous pyridinium salt **28** in Scheme 1.6. This sequence was regarded as a form of basic catalysis, but the terminology was modified a year later [95]. Conceptually related, but structurally distinct, chemistry was discussed in a paper describing intramolecular catalysis of phthalamic acid hydrolysis assisted by carboxylate anion as the internal nucleophile. Bender modified the basic catalysis phrasing as follows: ". . . it is suggested that nucleophilic catalysis be adopted as the proper term in order to distinguish a mechanism involving the addition of a nucleophile to the substrate producing an unstable intermediate from the classical mechanism of general basic catalysis involving a rate-determining proton transfer."

By 1960, Bender had gathered an extensive summary of related studies in an important review [96].[3), 4)] Most of the examples date back to the 1950s and reflect rapidly growing interest in enzymatic acyl transfer chemistry and in model studies using relatively simple nucleophilic amines and anions as catalysts. However, the review also includes representative cases of amine catalysis via iminium intermediates and even mentions the iodide-catalyzed hydrolysis of bromomethane [56], along with more biologically relevant examples of anion catalysis. This was the first comprehensive summary of catalysis by a broad range of Lewis basic species, and the first to cross the arbitrary divisions between organic chemistry and neighboring fields. Over the prior decades, such divisions had served as barriers to information flow and had worked against mechanistic understanding. Ironically, the review did not mention the 1938 Lewis paper or its classification of catalysis (see Section 1.7.3 and Chapter 2), so that specific casualty resulting



Scheme 1.7 Imidazole catalysis of 4-nitrophenyl acetate hydrolysis.

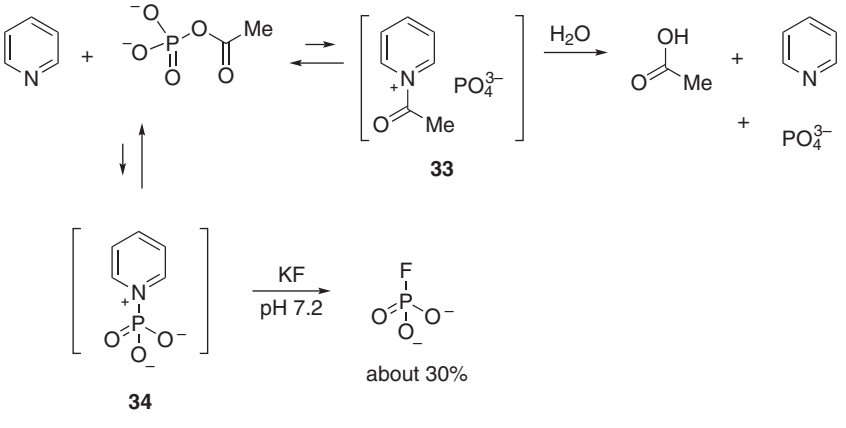
3) Bender's review uses the following, somewhat modified version of the 1958 definition: "Nucleophilic catalysis may be defined as the reaction of a nucleophilic substance with a substrate, leading to the formation of an unstable intermediate which in subsequent reaction yield the products of the reaction and regenerates the catalyst."

4) The nucleophilic catalysis terminology was also adopted in a 1959 paper on intramolecular Lewis base-induced acyl transfer [97] and in the influential text by Bruice and Benkovic [81].

from divisions among the disciplines was not remedied [96,97].[3), 4)] On the other hand, Bender's overview stimulated progress in several subdisciplines where the concepts of Lewis basicity are important, including organic synthesis applications.

1.8.4.2 Acetyl Phosphate Hydrolysis

A year prior to the definitive publication by Gold and Jefferson, the role of intermediates in acetyl transfer chemistry had been explicitly considered by Koshland in a less typical, but biologically significant setting [98]. Hydrolysis of acetyl phosphate was investigated as a model system for potentially catalytic enzyme functionality and pyridine was found to accelerate hydrolytic cleavage (Scheme 1.8). Although the intermediate could not be detected, selectivity differences between the uncatalyzed reaction and the presumably analogous reaction of isolable *N*-acetylpyridinium chloride [68] were invoked to suggest hydrolysis via an *N*-acetylpyridinium phosphate intermediate **33**, resulting from C—O cleavage. However, a subsequent isotopic labeling study proved that pyridine attack occurs primarily at phosphorus, resulting in the isomeric intermediate **34** (P—O cleavage) [99]. This structure happens to resemble the intermediate proposed for the Parathion process mentioned earlier (Section 1.8.3.2), but later work by Di Sabato and Jencks found that the regioselectivity of tertiary amine-catalyzed solvolysis of acetyl phosphate occurs via both the C—O and P—O cleavage pathways, depending on the Lewis base [100]. The latter authors also showed that amine catalysis promotes conversion of acetyl phosphate into different products in the presence of stoichiometric amounts of moderately nucleophilic additives. Thus, pyridine catalysis promoted both pathways, and trapping of the intermediate **34** with fluoride ion afforded the fluorophosphate ion according to paper electrophoresis identification and colorimetric assay. Furthermore, treatment of acetyl phosphate with DABCO (1,4-diazabicyclo[2.2.2]octane) and excess KF gave largely the fluorophosphate (P—O cleavage), whereas reaction with *N*-methylimidazole/MeOH under similar conditions afforded methyl acetate and phosphate (C—O cleavage). Both of the cleavage pathways involve Lewis base catalysis according to current terminology, but were called examples of nucleophilic catalysis, following the 1958 definition [95].



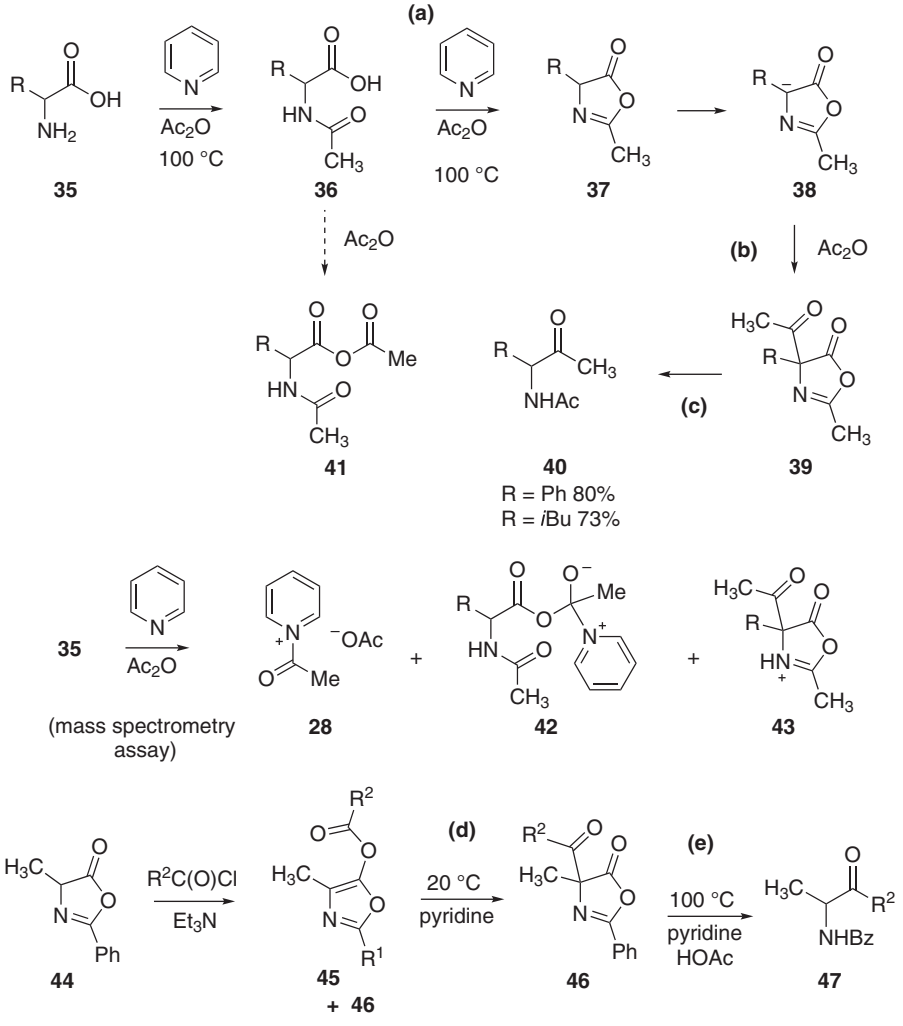
Scheme 1.8 Acetyl phosphate hydrolysis.

1.8.5 Miscellaneous Examples of Lewis Base Catalysis

1.8.5.1 Dakin–West Reaction

In their 1953 report, Gold and Jefferson recognized that their findings regarding anhydride activation by pyridine may also play a role in other reactions involving acyl transfer [91]. The last page of their manuscript comments on the Dakin–West reaction (conversion of acylamino acids into α-*N*-acylamino ketones using pyridine/acetic anhydride; see Scheme 1.9) and notes that the original 1928 study by Dakin and West had found 2-picoline to be much less effective than pyridine [101]. Gold and Jefferson had observed a similar effect in acetic anhydride hydrolysis, and had concluded that the 2-methyl group is a poorer catalyst because it inhibits formation of the corresponding *N*-acetyl-2-picolinium acetate intermediate. In view of this analogy, Gold and Jefferson proposed that the Dakin–West reaction may involve the *N*-acetylpyridinium acetate (**28**) in one or more acyl transfer steps, but provided no specifics. Further details regarding the Dakin–West reaction are included in a brief mechanistic sequence as part of the opening paragraph of a 1949 paper by Cleland and Niemann ". . . it appears that the overall reaction proceeds by acylation of the amino acid (**35** to **36**), cyclization to the azlactone (**37**), reaction with base to give a resonance-stabilized carbanion (**38**), the reaction . . . with acetic anhydride . . . to give **39** and subsequent conversion . . . to **40** and carbon dioxide." (Scheme 1.9) [102]. Dakin and West did not propose so detailed a sequence, but did show that azlactone **37** is a viable intermediate from **35** because independently prepared **37** reacts with acetic anhydride/pyridine to form the same product **40**. They also suggested that the mixed anhydride **41** may be involved. In any event, Cleland and Niemann's summary appears in subsequent literature along with added details and has been called the generally accepted mechanism, consistent with kinetic studies (first order in *N*-acylamino acid **36**, pyridine, and Ac_2O) [103], detection of ionic intermediates including identification of **28**, **41**, and **42** by mass spectrometry [104], and supported by computational studies [104].

Despite extensive effort [103,104], it is still not clear which, if any, of the several acyl transfer steps considered in 1949–1950 is catalyzed by pyridine as a Lewis base. Because at least some of the Dakin–West examples can also be catalyzed by sodium acetate in place of pyridine [102], simple general base catalysis remains a possibility. On the other hand, there can be no doubt that **28** is present in equilibrium under the Dakin–West conditions, and that it could serve as the acyl donor in steps **(a)**, from **36** to **37**, or **(b)**. Pyridine might also be involved as a Lewis base catalyst to promote step **(c)** by initiating C—O bond cleavage of the anhydride-like oxazolin-5-one lactone subunit. Furthermore, in 1969 Steglich and Hofle reported that *O*-acyl oxazoles **45** can be crystallized from the mixture of **45** and **46** obtained by reaction of **44** with acyl chlorides and trimethylamine [104]. The purified **45** rearranges to the *C*-acyl isomer **46** upon treatment with pyridine at room temperature – step **(d)**. This reaction has come to be known as the Steglich rearrangement, as described further in Chapter 12 of Volume 2. Since **45** ($R^1 = R^2 = CH_3$) may well be formed as an intermediate from the oxazolin-5-one enolate **38** (Scheme 1.9), the experimental evidence argues for the inclusion of **45** ($R^1 = R^2 = CH_3$) in the generally accepted Dakin–West mechanism unless further control experiments can rule it out. In this context, it should be noted that the computational work found similar activation barriers for the pathway via **45** and the alternative of direct *C*-acylation from **38** to **39** [105]. Steglich and Hofle also demonstrated that heating **45** with pyridine/acetic anhydride affords the Dakin–West ketone **46** in excellent yield – step **(e)**, so the differences in substituents shown in **46** and **39** do not play a major role in the overall conversion [104].



Scheme 1.9 Dakin–West Reaction.

1.8.5.2 Miscellaneous Catalytic Applications of Neutral and Anionic Lewis Bases

The first broad conceptual connections between different classes of Lewis base-catalyzed reactions were made by Bender in his 1960 review. He identified nearly all of the classes of catalysts known at the time, including amines (especially, imidazole) and various anions such as halide, alkoxide, formate, nitrite, and cyanide. Most of the examples feature the Lewis base as catalyst for hydrolytic cleavage of biologically significant carboxylic acid derivatives. Phosphines, mercaptans, and sulfides were not included, but they had barely emerged as catalysts until 1960 [93,106]. More recently, interest in phosphorus and sulfur Lewis base catalysis has increased in connection with enantioselective variants of the Morita–Baylis–Hillman reaction [107], as described in Chapters 14 and 15 of Volume 2, and also in the Corey–Chaykovsky epoxide synthesis, covered in an excellent review by Aggarwal and coworkers [108]. Some unusual applications of anionic catalysts also emerged later,

including the thiocyanate catalysis of nitrosation [109]. Organometallic applications of catalysis using iodide as the Lewis base also came later and are potentially quite important [110,111], but that topic is beyond the scope of this chapter. Finally, a number of examples of anion-induced double bond *E*/*Z* isomerization have been observed. Some of these probably date back to the nineteenth century, relating to the formation of α,β-unsaturated *E*-enones in alkoxide-catalyzed aldol condensations under equilibrium conditions, but explicit studies to address the isomerization step are rare. Two studies will be mentioned in passing because they focus on catalysis by glutathione and other mercaptans as the Lewis base catalysts [112]. Isomerization of *Z,Z*-hexadienal (muconaldehyde) to the *E,E* isomer was shown to occur by reversible 1,4-addition of the mercaptans. A similar addition–elimination mechanism has been proposed for the corresponding trialkylamine-catalyzed isomerizations [113].

1.9 Summary

The history of Lewis base catalysis intersects with the history of catalysis at several stages. This confluence began by coincidence because the first definition of catalysis was published within a year of the first relevant example of Lewis base catalysis (benzoin condensation). By the start of the twentieth century, the intersection was repeated as part of the struggle to show that intermediates are essential in catalysis. This effort coincided with some of the first examples of organic reactions that were investigated in mechanistic depth and that also happened to be catalyzed by a Lewis base. A third intersection occurred during the 1950–1960 period, driven mostly by the rise of bioorganic chemistry. This period featured in-depth studies of acyl transfer chemistry that impacted organic as well as bioorganic chemistry, and resulted in Bender's influential review [96].[3), 4)] A decade later, W.P. Jencks authored an important resource *Catalysis in Chemistry and Enzymology* that contains an informative chapter on covalent catalysis, including many of the examples of Lewis base catalysis known by 1969.

Lapworth's benzoin mechanism and subsequent (1925) definition of anionoid species did not unleash a wave of mechanistically informed investigations of "anionoid catalysis" [51] because Lapworth was too far ahead of his time. The 1938 generalized definition of base catalysis by Lewis did not make an immediate impact on Lewis base catalysis because his message did not reach enough of the organic chemistry community. In the near term, Lapworth's contributions initiated more change in the way that organic chemists thought about organic reactions, and stimulated a younger generation (most notably, Lapworth's colleague at Manchester, Robert Robinson). Mechanistic explanations began to succeed in the first years of the twentieth century. In the longer term, the fundamental contributions of Lewis were more important for reasons to be discussed in Chapter 2.

Together with the conceptual advances described in Chapter 2, the mechanistic approach changed the way that organic chemistry was taught and practiced, but it took at least another generation after Lapworth and Lewis before this became the norm. The current author learned his first organic chemistry in 1958. At that time, it was common to teach the first semester as a recitation of organic reactions without *any* mechanistic discussion, although that changed in the second semester, and changed more at the graduate level. However, the concepts introduced by Lewis between 1923 and 1938 were taught in the context of octet structures and formation of dative bonds, and Lewis bases were treated as unshared pair donors, that were not to be "confused" with traditional

bases. That premise has been slow to change, and it needs to change more. The transition to a more fundamental mechanistic approach to Lewis base catalysis is still under way in some areas (e.g., the treatment of nucleophilic and electrophilic reactivity in Chapter 4) and there is room for further growth.

Acknowledgment

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