

A FUTURE HISTORY OF SELECTIVITY IN ORGANIC CHEMISTRY: WHENCE, WHERE AND WHITHER?

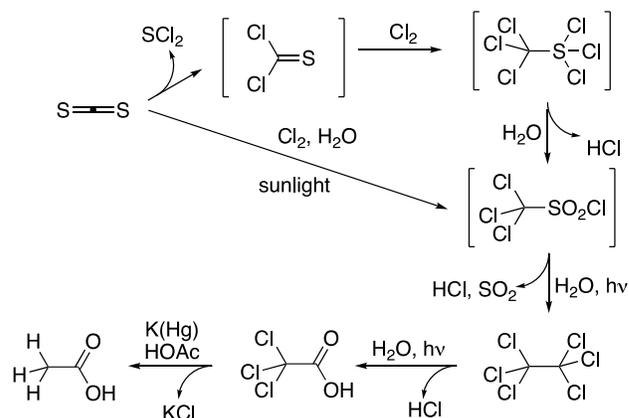
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Abstract

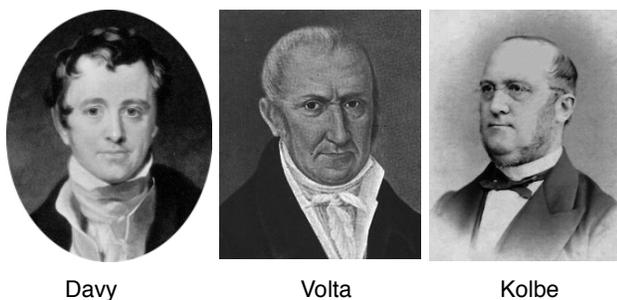
A series of historical snippets of milestones in the development of selectivity in organic synthesis is presented, followed by a few prognostications about future directions in selectivity in organic synthesis—contingent on the cautionary observation that major advances are not always recognized as such at the time. The historical snippets include the foundational landmarks: the unambiguous synthesis of acetic acid from only inorganic substances by Kolbe, the Structural Theory by Couper and Kekulé and its modification by Butlerov in 1861, and the tetrahedral carbon of van't Hoff and Le Bel. Physical chemists and physical organic chemists provided insights into rates and mechanisms of reaction. In the space of a century and a half, organic synthesis had passed through eras of chemoselectivity, regioselectivity, and diastereoselectivity, to enantioselectivity. Along with advances in spectroscopy and separations techniques, the rise of computational chemistry has added yet another tool to the arsenal of organic chemists.

Defining the concept of selectivity was not one of the first fundamental questions identified by organic chemists. The reason is simple: until the development of a good theoretical footing, the appropriate questions could not be formulated. In 1840, for example, many organic chemists were preoccupied with obtaining evidence to support the legitimacy of the new science, including evidence that organic compounds could be prepared from demonstrably inorganic precursors. Those who already accepted the new discipline, saw the exploration of organic chemical

reactivity as the prime task. The formal synthesis of acetic acid from its elements (Scheme 1) by Hermann Kolbe (1818-1884, Figure 1) (1) satisfied the former, but his accomplishment was only possible because of the results of other organic chemists whose exploration of organic reactivity yielded useful reactions such as the reduction of trichloroacetic acid with sodium amalgam, following Melsens' procedure (2). Its reducing power and ease of handling had quickly made sodium amalgam a popular reducing agent. Even this reagent had a debt to earlier chemists: by applying the Voltaic pile (3), which had been developed by Alessandro Volta (1745-1827, Figure 1), Humphry Davy (1887-1829, Figure 1) made metallic sodium available in 1808 by electrolysis of molten sodium hydroxide (4).



Scheme 1. Kolbe's synthesis of acetic acid (depicted in modern structures).



Davy

Volta

Kolbe

Figure 1. Scientists whose combined work provided the evidentiary basis for the legitimacy of organic chemistry as a new subdiscipline of the science.

The continued probing of organic reactivity (“What will react *with* what *to give* what?”) did give a diverse set of useful reactions by the middle of the nineteenth century. But... until the Structural Theory of Organic Chemistry emerged in 1858-1861, there was no framework for the systematic interpretation of the results of these experimental observations.

A major problem for early organic chemists was that the amount of information conveyed by the formulas then in use was very limited. Organic chemistry’s growth and the development of concepts such as “selectivity” required a representation that would show more granular detail than the Type formulas then in use. At the same time, the atomic weights of the elements also caused their own problems—until the Karlsruhe conference, most organic chemists used equivalent weights (C = 6, O = 8, S = 16, etc.), which led to confusing doubled atoms for these elements. In 1843, Gerhardt had proposed that doubling the atomic weights then in use would eliminate the double atoms of elements such as carbon, oxygen and sulfur, and so on (5). In his 1857 paper (6), August Kekulé (1829-1896, Figure 2) adopted Gerhardt’s values for the atomic weights (H = 1, C = 12, N = 14, O = 16, S = 32, etc.), indicating this by means of “barred” symbols (H̄, C̄, N̄, Ō, S̄, etc.), and gave evidence for the tetravalency of carbon, atomic weight 12. This change in symbology has been discussed in more detail by Rocke (7).

This paper presents snippet views of some milestones in the development of selectivity in organic synthesis from the advent of structural theory to recent catalytic approaches to asymmetric synthesis. The stories of several of these milestones have been told in more detail elsewhere, while others merit more detailed and contextualized study. This paper ends with a few prognostications about future directions in selectivity in organic synthesis.

Whence?

The Structural Theory of Organic Chemistry (8) was proposed independently in 1858 by Kekulé (9a), who had just been appointed Professor at Ghent, and a young Scot, Archibald Scott Couper (1831-1892, Figure 2) (9b-d), who was a student in the Paris laboratory of Adolphe Wurtz (1817-1884) at the time. This initial version of Structural Theory was refined in 1861 (10) by the Russian, Aleksandr Mikhailovich Butlerov (Бутлеров Александр Михайлович, 1828-1886, Figure 2), an entomology graduate who had been chosen by the Curator of the Educational District for transfer into chemistry—despite little formal chemical training—to meet the needs of Kazan University. This was the second time that Kazan had been lucky: the previous non-chemist to be forced into teaching chemistry there was Nikolai Nikolaevich Zinin (Зинин Николай Николаевич, 1812-1880), a physics-mathematics graduate who was teaching hydrostatics; both Zinin and Butlerov became internationally eminent nineteenth-century organic chemists and helped to propel Kazan to the forefront of chemistry schools in Russia.



Couper

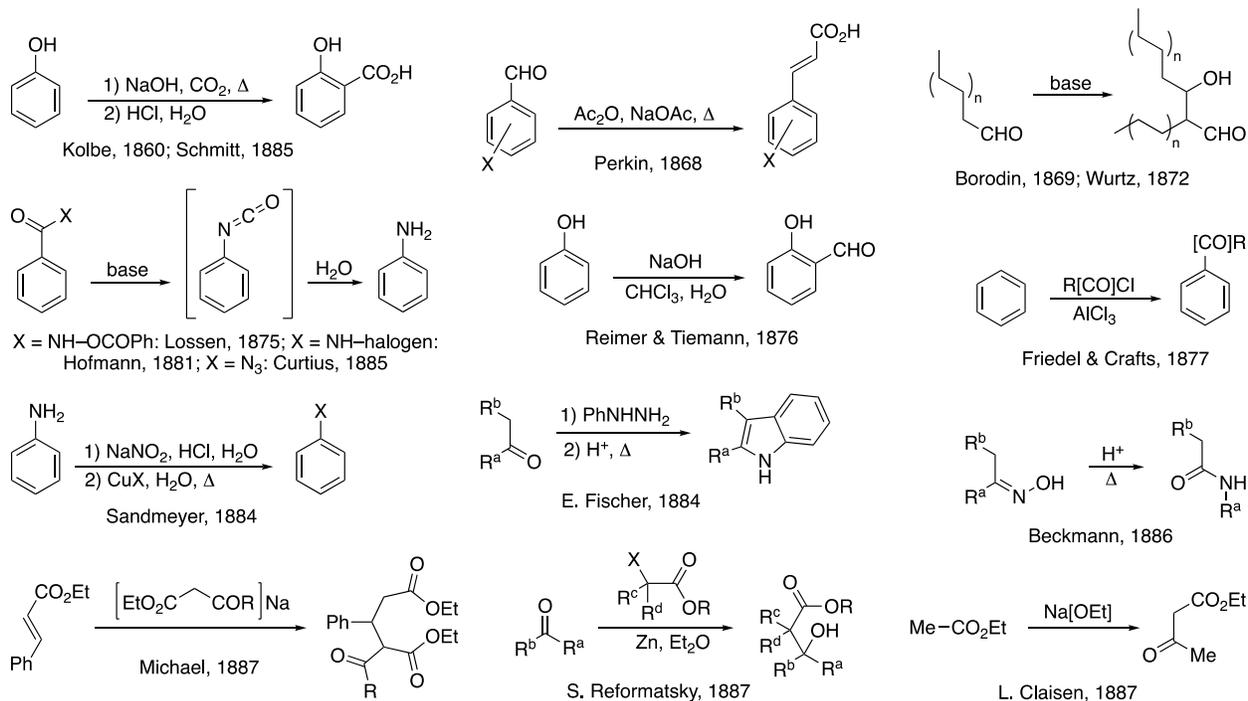
Kekulé

Butlerov

Figure 2. The developers of the Structural Theory of Organic Chemistry.

Structural Theory stimulated a wave of innovation in organic chemistry, most especially in organic synthesis. Between 1850 and 1900, over twenty well-known name reactions were discovered; representative examples from 1860-1890 are collected in Table 1. Why did this happen? And what guidance does it offer us today about where organic chemistry might go?

The answer to the first question is fairly obvious: The simple equivalent and molecular formulas that had been used since the early work of Wöhler and Liebig (11) were devoid of detail when it came to the structure of organic compounds. Now, for the first time, organic chemists had a framework that they could use to better understand the course of chemical reactions and, in the process, ask questions about how they might manipulate the reaction conditions to affect the reaction outcome.

Table 1. Representative name reactions developed between 1860 and 1890 (depicted in modern structural notation)

Organic chemistry had become a science formulated in visual, structural formulas rather than in simple molecular or empirical formulas.

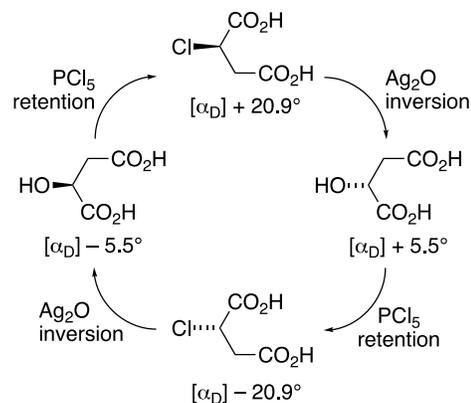
The second question is more subtle, and it may well be that its answer will appear trite, but Butlerov, in particular, had shown that Structural Theory had predictive potential by predicting the structures of previously unknown alcohols *and then confirming their existence by synthesis*. This was one of the first examples of what is now a *sine qua non*—today, a viable theory must have predictive potential.

Stereochemistry

The third dimension in organic chemistry also emerged at the end of the nineteenth century (12) with the stereochemical theories of Dutch chemist Jacobus Henricus van't Hoff (1852-1911, Figure 3) (13) and French chemist Joseph-Achille Le Bel (1847-1930, Figure 3) (14), and with the discovery of his eponymous inversion reaction by Latvian chemist Paul Walden (1863-1957, Figure 3) (15).

Empiricism and Regiochemistry

In addition to the Name Reactions, the nineteenth century also saw the publication of empirical rules to pre-

**Figure 3.** Key chemists in the rise of stereochemistry**Scheme 2.** The Walden cycle

dict reaction regiochemistry and to predict the strain in cyclic compounds (Figure 4). Prior to the emergence of Structural Theory, August Wilhelm [von] Hofmann

(1818-1892) had proposed his Rule for elimination from quaternary ammonium hydroxides (16), and had added the Ammonia Type to the dominant theory of the time, Type Theory. The search for clear experimental validation of Butlerov's version of Structural Theory drove the work of his student, Vladimir Vasil'evich Markovnikov (Markownikoff,



Hofmann



Markovnikov



Zaitsev



Baeyer

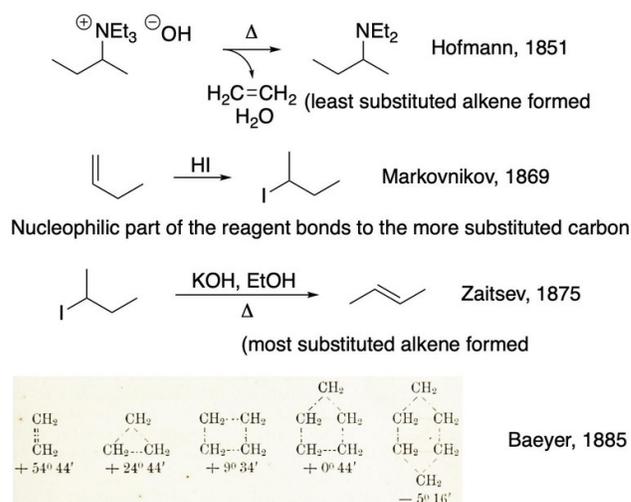


Figure 4. Organic chemists and their eponymous empirical rules and theories

Владимир Васильевич, 1837-1904, Figure 4), whose Rule for addition of acids to alkenes (17) emerged in 1869 as a logical offshoot of his graduate research (18). The motive for the development of the empirical rule

for elimination from alkyl halides (19) by another Butlerov student, Aleksandr Mikhailovich Zaitsev (Зайцев Александр Михайлович, 1841-1910, Figure 4), was hardly altruistic: Zaitsev and Markovnikov carried on a



Marcellin Berthelot



Nikolai Menshutkin

Structure	R = Me	26.53
$\text{R}-\text{C}(\text{OH})(\text{H})-\text{Me}$	R = Et	22.56
	R = <i>n</i> -C ₆ H ₁₃	21.19
	R = <i>i</i> -Pr	18.95

Structure	R = Et	16.93
$\text{R}-\text{C}(\text{OH})(\text{H})-\text{Et}$	R = CH=CH ₂	14.85

primary alcohols

R = Me	46.95
R = Et	46.92
R = <i>n</i> -Pr	46.85
R = <i>n</i> -C ₇ H ₁₅	46.85
R = <i>i</i> -Pr	44.36
R = HC=CH ₂	36.72
R = Ph	38.64
R = CH=CHPh	37.21

secondary alcohols

	20.53
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tertiary alcohols

R = Me	1.17
R = Et	0.68
R = <i>n</i> -Pr	2.15
R = <i>i</i> -Pr	0.86
R = H ₂ CCH=CH ₂	3.10

	1.04
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Figure 5. Marcellin Berthelot, Nikolai Menshutkin, and representative initial rates of acetylation of alcohols with acetic acid in a sealed tube at 155 °C as measured by Menshutkin.

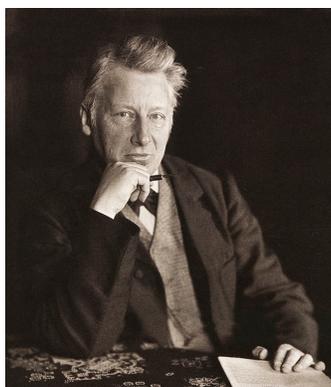
life-long feud. In 1885, Adolf von Baeyer (1835-1917, Figure 4) proposed the existence of ring strain in cyclic compounds (20). The eponymous rules and theories of these chemists are collected in Figure 4.

An additional question to be answered was a simple one: “What factors affect the reactivity of a functional group in an organic compound, and is the effect big enough to be exploited?” The answer to this question required answers from a new sub-discipline of organic chemistry: physical organic chemistry. The earliest work in this area consisted of rate studies of reactions. One of the first systematic reports of rate studies was disclosed in three papers between 1862 and 1863 by Pierre Eugène Marcellin Berthelot (1827-1907, Figure 5) and Léon Péan de Saint-Gilles, who were studying the rates of esterification of alcohols (21). In 1877 (22), the Russian chemist Nikolai Aleksandrovich Menshutkin (Меншуткин,

Николай Александрович, 1842-1907, Figure 5) began what eventually became a four decade-long study of the effects of reactant structure on the rates of organic reactions, beginning with esterification reactions (23) (Figure 5). Menshutkin followed his work on esterification by studies of the effects of amine and alkyl halide structure on the rates of alkylation of amines (24), which later became his eponymous reaction.

Following the model of Berthelot and Péan de Saint-Gilles, Menshutkin studied the initial rates of ester formation in equimolar mixtures of the alcohol and acetic acid in sealed tubes at 155 °C. These studies revealed consistent patterns of reactivity: for example, the initial rate of acetylation could be used to distinguish the alcohol as primary, secondary or tertiary.

Seven years after Menshutkin’s initial studies, Jacobus Henricus van’t Hoff (1852-1911, Figure 6)



J. H. van't Hoff



S. Arrhenius



J. B. Conant



J. F. Norris



E. D. Hughes



C. K. Ingold



L. P. Hammett



R. W. Taft, Jr.

Figure 6. Important early physical organic chemists. The new evidence was provided by kinetic isotope effects (30), which gave a direct measure of bonding changes between reactants and transition state. The deuterium kinetic isotope effect, defined as $^Hk/^Dk$, is defined as “normal” when $^Hk/^Dk > 1$, “inverse” when $^Hk/^Dk < 1$, and “null” when $^Hk/^Dk = 1$. Normal isotope effects arise when the bond to the labeled atom is weakened in the transition state, and inverse isotope effects arise when the bonding to the labeled atom is strengthened. The information gleaned from isotope effect studies provided a basis for modeling transition states (30d)

published his *Études de Dynamique chimique*, in which he first proposed his equation describing the temperature-dependence of the equilibrium constant (25).

$$\frac{d}{dT} \ln(K_{eq}) = \frac{\Delta_r H^\circ}{RT^2}$$

Five years later, Svante Arrhenius (1859-1927, Figure 6) proposed his equation relating the rate constant of a reaction and the temperature at which the reaction is carried out (26).

$$k = Ae^{\frac{-E_a}{RT}}$$

Menshutkin adopted these new approaches for his work in the 1890s and beyond.

The twentieth century saw a real blossoming of the field, with luminaries such as James Bryant Conant (1893-1978, Figure 6) and James Flack Norris (1871-1940, Figure 6), who made important contributions in the kinetics of organic reactions in the 1920s, Edward David Hughes (1906-1963, Figure 6) and Sir Christopher Kelk Ingold (1893-1970, Figure 6), and Louis Plack Hammett (1894-1987, Figure 6), whose contributions during the 1930s cemented physical organic chemistry's position as a legitimate subdiscipline of organic chemistry. The conclusions of Hughes and Ingold's sixty joint papers, collected in Ingold's monograph (27), gave us the terminology about the mechanisms of substitution and elimination reactions that is still in use today: S_N1 , S_N2 , E1 and E2. Hammett's simple equation (28) provided a productive springboard for the launch of modern physi-

cal organic chemistry; Robert W. Taft, Jr. (1922-1996, Figure 6), expanded the Hammett equation to include resonance and field effects (29). The work of Hammett, then Taft, shifted the focus of organic chemists to the transition state; this could not be completely successful without evidence for its possible structure.

Early Total Synthesis: Exploiting Chemoselectivity

The formal total synthesis of camphor was among the earliest successes in chemoselectivity in organic synthesis. This was accomplished by combining the conversion of α -campholide to camphor by Haller (31) with the total synthesis (32) of camphoric acid by Finnish chemist, Gustaf Komppa (1867-1949) in the form of three different reductions (Figure 7). The first, a dissolving metal reduction with sodium amalgam, reduces only the ketone carbonyl groups; the second, a Berthelot reduction (33) of the diol, leads first to hydrolysis of the diester to the diacid, which will be resistant to reduction, and then reduction to the alkene, probably through the vicinal diiodide; and the third is another dissolving metal reduction with zinc metal, which will reduce a bromide. The modern concepts of tandem or cascade reactions and biomimetic synthesis were showcased in 1917 with Robinson's classic synthesis of tropinone (34).

Diastereoselectivity in Cyclic Systems

The next major advances in organic synthesis led to the control of the relative stereochemistry of reactions. As part of this advance, the stereochemistry of organic reactions became a high-priority area of research. A

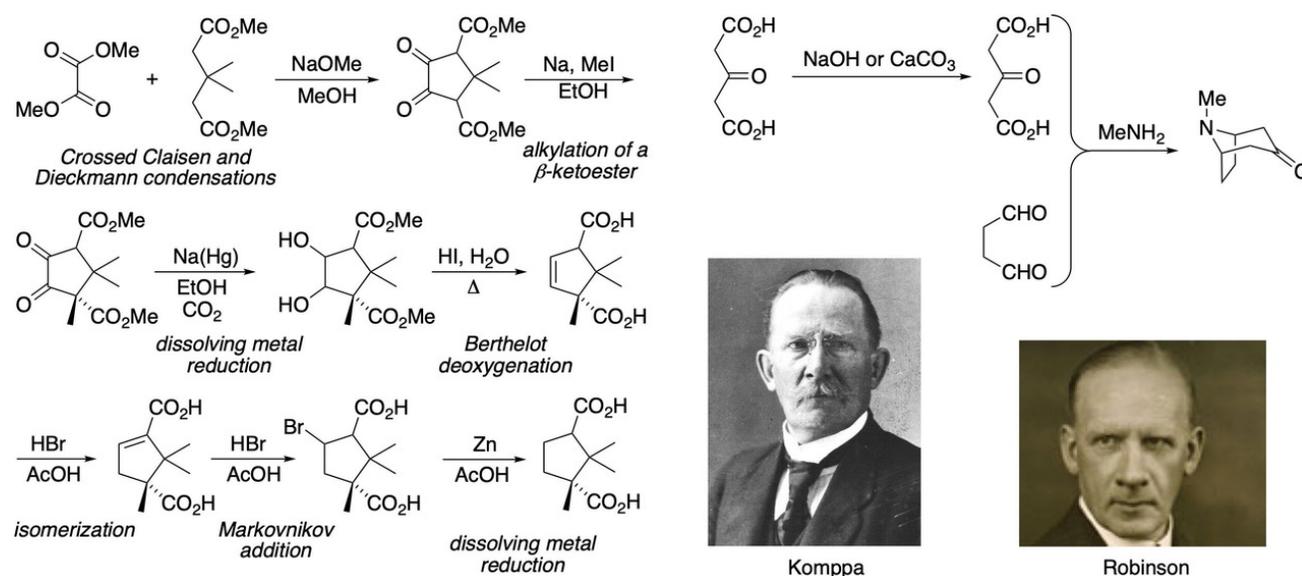


Figure 7. Komppa's total synthesis of (\pm)-camphoric acid, constituting a formal total synthesis of (\pm)-camphor, and Robinson's biomimetic synthesis of tropinone.

Acyclic Stereoselectivity

By the late 1960s, controlling the relative stereochemistry in cyclic systems had become a well-developed art. The next big hurdle was to move to acyclic systems. An early exploration of this problem by Donald James Cram (1919-2001) resulted in the empirical rule that bears his name for predicting the stereochemistry of the product of addition of a nucleophile to a chiral aldehyde (Figure 9) (44).

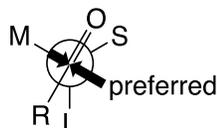


Figure 9. Cram's empirical Rule for predicting the direction of attack of a nucleophile on a carbonyl group.

The histories of acyclic diastereoselectivity and enantioselectivity are so intertwined that the two should be discussed together. Conformational analysis (45), for which Barton and Hassell shared the Nobel Prize for Chemistry in 1969, provided the basis for predicting the stereochemistry of transition states resulting from the preferred conformations of the reacting species. Although Cram's 1952 Rule had offered a tool for predicting the stereochemical outcomes in reactions of acyclic substrates, it took another two decades before serious efforts were made to exert stereochemical control in such systems. Why so long? It required the confluence of more advances from disparate directions before serious progress in this area could be realized:

First, methods for carrying out reactions under conditions of kinetic control needed to be developed. This paradigm shift in synthetic organic chemistry, from running reactions under thermodynamic control to running them under kinetic control, drew the attention of organic chemists to the structure and energy of the transition state for the reaction. This now highlighted the task of increasing activation energy difference between competing reactions. The solution to the problem came from the work of the early physical and physical organic chemists. Arrhenius' work, in particular, had shown that it should be possible to lower the reaction temperature to a point where even a small difference in activation energy might so retard one of two competing reactions that it would be possible to form the product of the other with a high degree of selectivity: the product of kinetic control would predominate.

Second, a vocabulary for describing the stereochemical outcome of a reaction needed to be developed. In 1971, Morrison and Mosher coined the term, "enantio-

meric excess (e.e.)," in their book, *Asymmetric Organic Reactions* (46), and this term is still in use, usually as a percentage. However, in 1969 Horeau showed that the value obtained for the e.e. depends on the method used to calculate it (47), which prompted Gawley to analyze the deficiencies in the terms, "% e.e." and "% d.e.," and propose their replacement by "enantiomer ratio, er," and "diastereomer ratio, dr," instead (48).

Measuring the values of e.r. and d.r. in organic reactions also required the development of methods for doing so. Modern organic chemistry has settled on chromatography and NMR spectroscopy as the techniques of choice. The chromatographic separation of enantiomers was pioneered by William H. Pirkle at the University of Illinois in the late 1970s and early 1980s (49); the growth of the technique is illustrated by the more than 17,000 hits on the search term, "chiral chromatography," in Google Scholar since January 2020. The pioneering work of Heathcock (50) on the aldol addition reaction provided an early example of the use of NMR spectroscopy to obtain the data to assign the relative configuration to chiral centers in a molecule. Today, a combination of experimental and computational NMR methods is used to determine absolute configurations and e.r. values for reactions.

Running reactions under conditions of kinetic control required the use of cryogenic baths: dry ice-acetone ($-78\text{ }^{\circ}\text{C}$), liquid nitrogen-ethanol ($-110\text{ }^{\circ}\text{C}$), and liquid nitrogen ($-196\text{ }^{\circ}\text{C}$). The manufacture of dry ice had been patented in France in May 1831 (51). An explosion in 1841 (52) served to dampen enthusiasm for its use; its use as a reaction coolant did not become routine until well into the twentieth century. The pioneering work of Heathcock, for example, could not have been accomplished without being able to access low temperatures that would suppress the isomerization of the lithium enolates. Because his work involved the correlation of product stereochemistry with reactant stereochemistry, it was imperative that the stereochemistry of the reactant not change during the course of the reaction.

Using very low reaction temperatures to moderate organic reactions also yielded another benefit: very low reaction temperatures permitted the use of extremely reactive reagents or thermally unstable reactants. Sterically hindered, strong amide bases such as lithium diisopropylamide, which can be formed by the reaction of butyllithium and diisopropylamine in tetrahydrofuran at $-30\text{ }^{\circ}\text{C}$, have become routine reagents for forming anionic nucleophiles such as enolates, azaenolates, ylides, etc., at $-78\text{ }^{\circ}\text{C}$.

The successes in controlling the relative stereochemistry obviously promoted interest in being able to meet the next stereochemical challenge: controlling the absolute, as well as the relative configuration of products formed from achiral precursors. The three successful strategies for accomplishing this (Figure 10) were, in chronological order: 1) chiral auxiliaries; 2) chiral reagents; and 3) chiral catalysts. All three of these approaches were based on having the reaction proceed through diastereomeric activated complexes of significantly different energy.

Where?

Chiral catalysis now falls in the mainstream of asymmetric synthesis; it is the work for which Sharpless (53), Noyori (54) and Knowles shared the Nobel Prize in Chemistry for 2001. This strategy for generating asymmetric induction, the *chiral catalyst* strategy, has taken the organic synthesis community by storm since the first reports of high levels of asymmetric induction in reactions catalyzed by metal complexes (55). The growth in the field can be gauged from the growth in size of the volumes in *Catalytic Asymmetric Organic Synthesis*, edited by Ojima (54a); the first edition (1993) had 476 pages, the second edition (2000) had 864 pages, and the third edition (2010) had 998 pages. No fourth edition has yet appeared, but it would not be unrealistic to expect that it will be more than 1500 pages. A recent search reveals that there have been 349 articles published in *Chemical*

Reviews since 2008, averaging 40-50 pages per review, and a Google Scholar search on May 20, 2021, returned 3,310 hits since January 1, 2021 hits on the search term, “catalytic asymmetric synthesis.”

The other area where catalysis has had a major impact has been on reaction regiochemistry. Every student of introductory organic chemistry was taught that halogens bonded to sp^2 -hybridized carbon atoms are inert to displacement except under extreme conditions. That changed in 1971. That year, Tsutomu Mizoroki (1933-1980) of the Tokyo Institute of Technology reported the palladium-catalyzed cross-coupling of iodobenzene with olefins (56). These kinds of reactions, now known as cross-coupling reactions, were the basis for the Nobel Prize in Chemistry in 2010 to Heck, Negishi and Suzuki, and the related olefin metathesis reaction, for the Prize in 2005 to Chauvin, Grubbs and Schrock. A Google Scholar search using the term, “cross-coupling reactions,” on May 20, 2021, returned approximately 10,000 hits since January 1, 2021. The results from searches on individual cross-coupling reactions for the same time period are gathered in Table 2.

Organocatalysis

The success of transition metal catalysts in stereoselective organic synthesis has prompted the search for efficient, metal-free catalysis of reactions (especially asymmetric reactions). Two major contributions in this area have come from the laboratories of MacMillan (57) and Shi (58), whose work first appeared around the turn

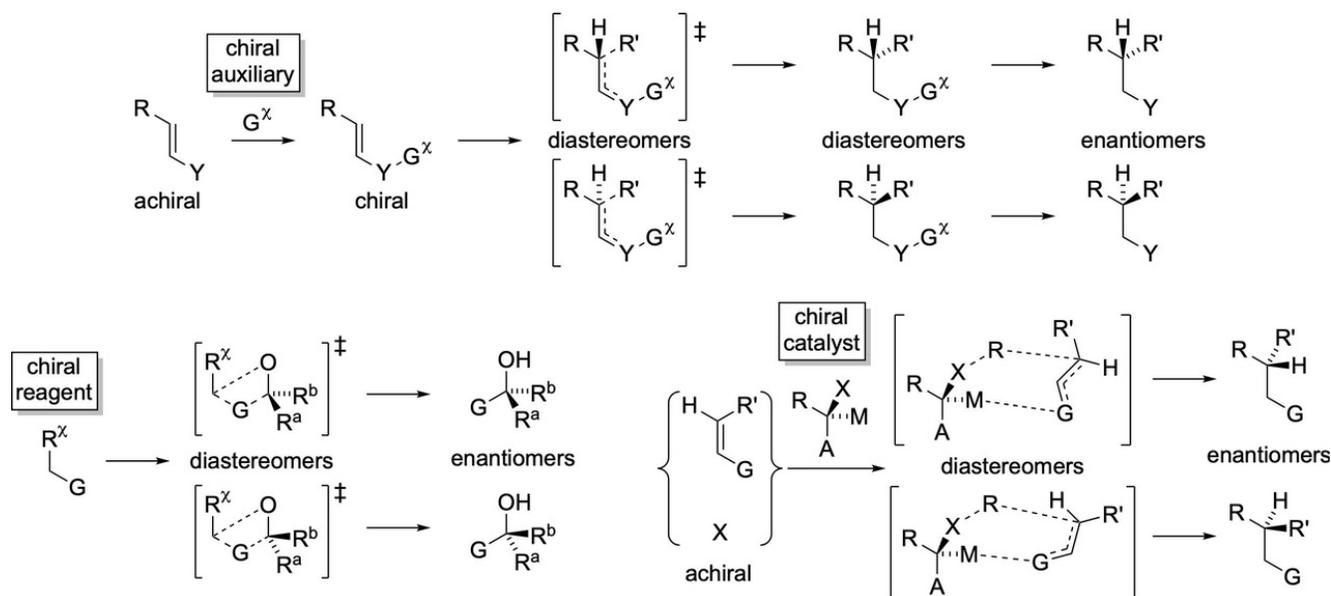


Figure 10. The three fundamental strategies for asymmetric synthesis. The superscript “x” indicates that the group is a single enantiomer.

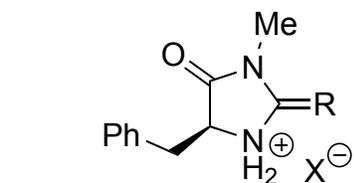
of the twenty-first century. Indeed, MacMillan and Benjamin List were awarded the 2021 Nobel Prize in Chemistry “for the development of asymmetric organocatalysis.”

MacMillan noted that iminium ions, nature’s acylium ion equivalents, offer enhanced electrophilicity compared to carbonyl compounds, but do so without the recourse to strong Lewis acid catalysts, and showed that this type of electrophilic enhancement would be successful *in vitro*; his imidazolinone organocatalysts are based on proline, which itself shows modest asymmetric organocatalytic effects. By clarifying how structural changes to proline influence the efficacy of the organocatalyst, he was able to identify the key structural moieties needed to give high levels of diastereoselectivity in the transition state, and high e.r.’s in the product.

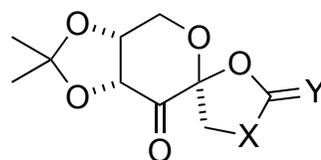
The asymmetric reduction of ketones has long been problematical for organic chemists. However, the search for new chiral organocatalysts for reduction has led to the development of the oxaborolidine catalyst for the asymmetric reduction of prochiral ketones by borane derivatives, first reported by Itsuno (59) and developed by Corey (60). The oxaborolidine and the MacMillan and Shi catalysts are shown in Figure 11.

Whither?

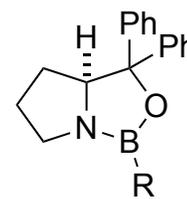
We have now arrived at the present, so now the job is to answer the question, “whither—*quo vadimus?*” Prognostication is a perilous pastime, but since that is the basis of this Special Issue, I can but do my best.



R = Me₂; X = OTFA, OTf
R = H, t-Bu, Ar; X = OTFA, OTf
MacMillan imidazolinones



X = O, Y = Me₂
X = N-Ar, Y = O
Shi ketones



Corey oxaborolidine

Table 2. Palladium-catalyzed Coupling Reactions Reported in 2021 (through May 20, 2021)

Reaction	Number of Hits	Reaction	Number of Hits
Suzuki-Miyaura	4,380	Heck	1,940
Sonogashira	1,380	Negishi	1,580
Olefin metathesis	1,440	Stille	1,190
Hiyama	961	Tsuji-Trost	172

As I see it, the first question to answer is, “What lessons have we learned in the past two centuries?” The second is, “What do these lessons teach us about where organic synthesis may evolve?”

The advances in the science that have led to major improvements in being able to control selectivity in organic chemistry have not necessarily achieved contemporaneous recognition. For example, did Mikhail Tsvet and his contemporaries see the truly transformative effect of his discovery of chromatography on the course of organic chemistry? If they did, why did he receive only one nomination for the Nobel Prize? Sometimes milestones become apparent only with the passage of time—a fact that complicates the writing of recent history, let alone prognostication.

Advances in selectivity in organic chemistry have almost always correlated with progress in physical or theoretical methods. Once discovered, new techniques have diverged and specialized under the intensive research that followed, as the proliferation of chromatographic techniques shows. Thanks to advances in instrument and software design, bench-top instruments for NMR spectrometry and X-ray diffraction are now widely available; when the author was a graduate student in the 1970s, neither proposition would have been taken seriously.

Beginning with the work of Hughes, Ingold and Hammett almost a century ago, our better understanding of reaction mechanisms has allowed the outcomes of reactions to be optimized by manipulating the reaction conditions over which the chemist has control: temperature, pressure, solvent, reagent power and concentration.

Figure 11. Chiral organocatalysts

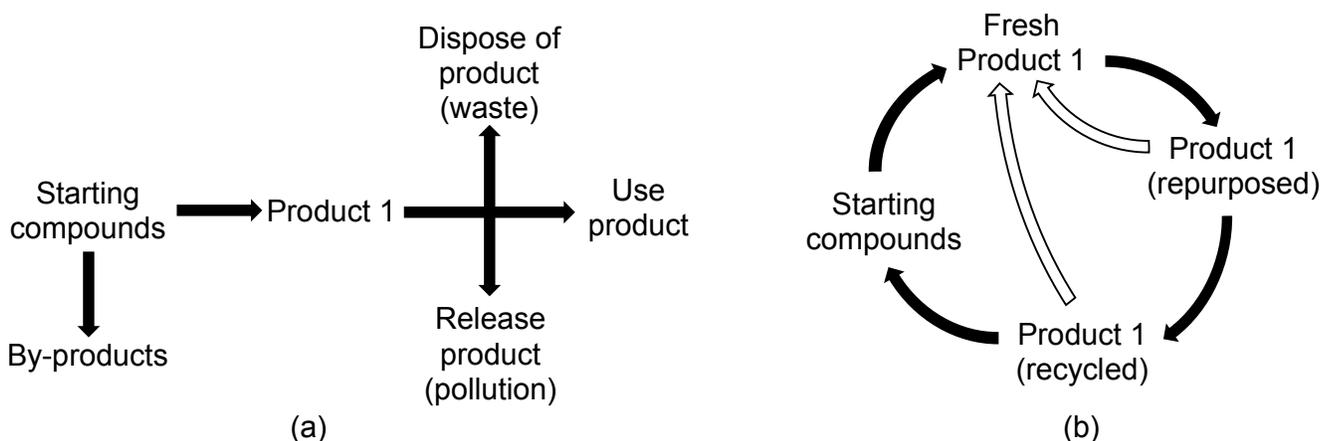


Figure 12. The linear (a) and cyclic (b) views of the progression from raw materials through organic chemistry.

One can select for the S_N1 reaction, for example, by using a low concentration of a weak nucleophile in a protic solvent. In the 1950s, conformational analysis was developed, giving the organic chemist a way to “see” the dynamic shapes of molecules. By using these concepts, organic chemists were able to design stereocontrolled total syntheses of complex natural products.

Today, computational chemistry is being used to reveal the basis for empirical rules that have long been a mainstay of organic chemistry—Hofmann’s Rule for elimination (16), Markovnikov’s Rule for addition (17, 18) and Zaitsev’s Rule for elimination (19). For example, the origins of Markovnikov regioselectivity (61) are being elucidated *in silico*.

Until the last decades of the twentieth century, useful, stereoselective catalytic organic reactions were few and far between. That changed with the Sharpless asymmetric epoxidation (53). For the first time, it was possible to prepare a chiral product from a prochiral starting compound and an achiral reagent with known absolute configuration and high e.r.’s and d.r.’s, an accomplishment previously limited to enzymes. Reactions catalyzed by transition metal complexes have made asymmetric syntheses that would not have been seriously contemplated half a century ago, fairly routine. At the same time, these reactions have also turned the conventional wisdom on its head: the categorical statement, that nucleophilic displacement of leaving groups from sp^2 -hybridized centers other than acyl groups is not easy to accomplish, is contradicted by reactions such as the Heck, Stille, Suzuki and Sonagashira cross-coupling reactions. The difficulties inherent in the synthesis of macrocyclic compounds have been circumvented by olefin metathesis.

So, once again, “whither?” I believe that Green Chemistry will have a major impact on organic chemistry, an opinion shared by Javier Garcia-Martinez, Vice-Chair of the Bureau of IUPAC (62). This vision sees the organic synthesis enterprise moving from the traditional linear progression through organic chemistry, where the trajectory is unidirectional, from starting materials through to the target product and waste; as we know, much of the final product ends up as waste, also. The alternative progression through the same lifespan is dramatically different. In the idealized system in Figure 12, there is no waste, but the starting material is cycled through useful products until it reaches the end of its useful lifetime, whereupon it is reconverted to the starting compounds, which are then used to re-form the original product. As drawn, this cyclic system has no losses or waste, but today that is still an unattainable, though not unworthy goal.

How does the history of organic chemistry provide a blueprint for how we move forward? It took the combined efforts—often not in intentional collaboration—of synthetic organic chemists, whose efforts added to the library of synthetic methods, physical organic chemists, whose efforts elucidated the detailed mechanisms of reactions, and analytical chemists and spectroscopists, who developed the techniques for separation, purification, and structure elucidation of organic compounds (again, often not recognized as paradigm-changing at the time) to get us to where we are now, and it is not unreasonable to expect that the next major advance may already have occurred, but may not yet have been appreciated. Increased collaboration between different subdisciplines, which we are already seeing to a higher degree than heretofore, will, in my opinion, be the most important circumstance allowing us to achieve the goal.

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