Organic Synthesis—Where now?

By Dieter Seebach

This review article is an attempt to sketch the important developments in organic synthesis during the past 25 years, and to project them into the future.—The primary motivations that once induced chemists to undertake natural product syntheses no longer exist. Instead of target structures themselves, molecular function and activity now occupy center stage. Thus, inhibitors with an affinity for all the important natural enzymes and receptors have moved to the fore as potential synthetic targets.—New synthetic methods are most likely to be encountered in the fields of biological and organometallic chemistry. Enzymes, whole organisms, and cell cultures for enantioselective synthesis of new substances have already been incorporated into the synthetic arsenals of both research laboratories and industry. In addition, designing appropriate analogues to transition states and intermediates should soon make it possible, with the aid of the mammalian immune system and gene technology, to prepare catalytically active monoclonal antibodies for almost any reaction; perhaps more important, such processes will increasingly come to be applied on an industrial scale.—The discovery of truly new reactions is likely to be limited to the realm of transition-metal organic chemistry, which will almost certainly provide us with additional “miracle reagents” in the years to come. As regards main group elements (“organoelemental chemistry”), we can surely anticipate further stepwise improvements in experimental procedures and the broader application of special techniques, leading to undreamed of efficiency and selectivity with respect to known procedures. The primary center of attention for all synthetic methods will continue to shift toward catalytic and enantioselective variants; indeed, it will not be long before such modifications will be available with every standard reaction for converting achiral educts into chiral products.—Analysis, spectroscopy, structure determination, theory, and electronic data processing have all become indispensable in organic synthesis. Only with the aid of these “tools” will the methods of organic chemistry permit selective syntheses of ever larger and more complex systems on both the molecular and supramolecular levels.—Examples have been introduced throughout this discourse to illustrate its many themes, and a very comprehensive bibliography should help the interested reader become more familiar with important keywords and authors.[**]—This article will have served its intended purpose if it changes the minds of some of those who claim organic chemistry is a mature science, and if it causes students to discover the vitality and forcefulness with which organic synthesis is meeting new challenges and attempting to fulfill old dreams.

Er zeigt uns so in seinem wissenschaftlichen Leben, daß die Chemie nicht von einer Theorie, nicht von einer Methode aus zu erschöpfen ist, und daß Erkenntnis und Nutzen in ihr unternanbar verwoben sind.[***]

R. Koch, writing about Louis Pasteur

1. Introduction—a Difficult Subject!

1.1. On the Problems Associated with Prognostication

One can certainly plan research, but not the results!
(Adressed to all those engaged in the distribution of research grants?)

The task I have set myself, ten years before the end of the present century, is to take inventory of the field of organic chemistry and attempt to discern the nature of some of the developments that lie ahead.

It is obviously impossible to review such a broad topic in the space available without imposing certain limits. To begin with, all my prognostication is subject to the bounds imposed by one general consideration that arises out of the very nature of scientific progress, which results from a combination of discovery, invention, development, and explanation. By definition, a discovery is something totally unexpected—even to the discoverer. Thus, Columbus set out in search of a route to India, but instead discovered America. If one accepts the premise that organic chemistry entails discoveries, then one is also compelled to be somewhat wary of predictions. On the other hand, impeding inventions, explanations, and especially developments often can be foreseen through careful analysis of current trends and application of the time-tested scientific principle of extrapolation.

One additional imponderable is the effect of outside influences on the development of the discipline. No one in the mid-1960s would have anticipated the impending precipi-
tous decline in United States dominance of the field of mechanistic physical organic chemistry, which was in part a consequence of research-political decisions by the National Institutes of Health at the end of the decade to limit funding more strictly to health-related projects. Japan illustrates how quickly a new nation can come onto the playing field and completely change the course of the game. Thus it is tempting to hope that the forthcoming steps toward European unification will eventually produce a system of elite universities like those in the USA, which would be in a position to attract the most talented minds in a population reservoir of nearly 300 million.

There is one other limitation that must be recognized with respect to the present endeavor, and it relates directly to the author himself. I have necessarily treated the subject from my own personal vantage point, which reflects my particular range of experiences. This in turn implies an emphasis on organic synthesis, and a time span of direct observation encompassing only 25 years. Nevertheless, a quarter of a century should more than suffice, and synthesis is certainly at the center of the discipline. No matter what the narrow goal of any particular project, whether the work involved is ground-breaking or of a more routine nature, synthesis and analysis are crucial to every chemist’s activities.

1.2. Organic Chemistry in Crisis?

We are all very much aware of the fact—and also partly responsible for it!—that chemistry has a rather poor reputation in the media and within the public generally. Even so, it is somewhat surprising to see an educated layman like the editor of Nature, John Maddox, declaring that chemistry as a discipline has lost its identity, and citing as evidence the fact that the 1985 Nobel Prize for chemistry was actually awarded to two mathematicians. It is also sad to find respected colleagues referring to organic chemistry, and specifically to organic synthesis, as a “mature” science. There is no way this remark can be regarded as anything but an expression of resignation, of self-pitying nostalgia—indeed, as evidence of a “drop-out” mentality. A more accurate diagnosis would focus on the fact that discrete boundaries no longer exist between the various natural sciences (mathematics, physics, chemistry, biology, medicine) and especially between related subdisciplines (in this case inorganic, biological, organic, and physical chemistry). This has been the case for a long time in the world of applications, and it is just as true along the frontlines of research. Chemistry has not lost its identity: it has instead gained important footholds within the domains of other disciplines—albeit rarely at the initiative of chemists. Most of the real advances in the field of biochemistry, and increasingly in medicine as well, result directly from a deeper understanding of the processes of life at the molecular and supramolecular levels, and they must clearly be numbered among the accomplishments of chemistry. What is DNA sequencing? If not the structural analysis of a macromolecule? Is a DNA- or peptide-synthesizing machine anything more than an automaton for repetitively carrying out a particular series of high-yield synthetic steps, always relying on the same reagents and very similar subunits? In the field of polymers, block polymerization via O-silyl ketene acetals (intermediates that were developed originally for organic synthetic purposes) has led to materials with very remarkable properties,[9] and careful introduction of “functional groups” has made it possible to use chemical reactions and the resulting covalent bonds as a way of binding surfaces together.[10] It is also appropriate to point to the recent synthesis of palitoxin,[11] a substance with 68 stereogenic units; organic synthesis has been responsible for a number of monumental breakthroughs in the pharmaceutical industry, contributing daily to the saving of countless lives.

In summary, the crass contradiction between the accomplishments and the reputation of chemistry, of which organic synthesis and its industrial applications constitute a significant part, can only be characterized as remarkable.[12, 13]

That which follows is a descriptive look at the current goals of organic synthesis; recently developed approaches to the purification, isolation, and identification of organic substances; key considerations in the development of improved techniques and in research into synthetic methodology; new insights gained through further investigation of classic reactions; and a few industrial applications drawn from the field of pharmaceutical synthesis. The selection is a very personal one, based on a much larger pool of potential examples, but it should nevertheless demonstrate quite clearly the vitality and ferment that characterize organic chemistry and organic synthesis in our day.


La chimie crée son objet.
Cette faculté créatrice, semblable à celle de l’art lui même, la distingue essentiellement des sciences naturelles et historiques.[*]

M. Berthelot (1860)

2.1. From Natural Products to Supramolecular Structures

New synthetic methods have traditionally emerged from one of two sources: a) the deliberate attempt to perfect a known reaction or invent a new one in order to permit the preparation of a specific target molecule, which may be either a natural product or some structure that so far exists only in the imagination, or b) studies of the reactivity of some new class of carbon derivatives (organometallic compounds, perhaps, or the more classical “organoelemental” substances). To these traditional sources of innovation we

[*] “Chemistry creates its own object. This creative power, similar to that of the arts, distinguishes it fundamentally from the natural and historical sciences.”


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must add, thanks to the initiative of E. J. Corey, the directed search for reactivity, including attempts to realize specific desirable synthetic transformations (an approach that gave birth to the terms synthon, retron, and transform), as well as systematic umpolung of known modes of reactivity. A few examples taken from these three distinct breeding grounds are presented in Scheme 1.

The most celebrated aspect of synthesis has been the preparation of ever larger and more complex natural products, an endeavor in which creativity, intelligence, and endurance are prerequisites to success. The masters of the art have been immortalized in classic achievements, and their names can be found not only in the annals of chemistry but also among the ranks of Nobel Prize winners. Through their efforts, we have come to believe (like them) that virtually any molecule is amenable to synthesis. Together with non-natural products chemists as well as the pioneers of synthetic methodology and elemental (i.e., “main group”) organic chemists generally, they managed to discover almost every reaction there was to find; indeed, only transition-metal organic chemistry can still be regarded as a fertile field for synthetic surprises (see Sec. 6 below). Moreover, almost everything the study of unusual molecules could teach us about the nature of the chemical bond has probably already been learned. In other words, all the most important traditional reasons for undertaking a synthesis—proof of structure, the search for new reactions or new structural effects, and the intellectual challenge and pride associated with demonstrating that “it can be done”—have lost their validity. Exceptions only prove the rule (cf. Scheme 2).

Attempts are often still made to synthesize natural products with interesting biological properties or pharmacological activity, compounds unavailable from natural sources in quantities sufficient for thorough biological testing, but here there is an important financial motivation: such an effort stands a good chance of attracting research funds, either from government or industry. Multistep syntheses could also be said to provide the broadest possible training for graduate students in organic chemistry, and they certainly represent ideal preparation for jobs in the pharmaceutical industry, but sponsoring a project for this reason amounts to the fulfillment of a teaching responsibility rather than a commitment to the conduct of basic research within a university environment. In short, it really should come as no surprise that someone not prepared to adapt to new kinds of goals might refer to organic chemistry as a mature science.

How can we characterize the new generation of appropriate target structures for organic synthesis? In answering this
question it is useful to consider an observation of one of my colleagues in Zürich, a theoretical physical chemist who remarked during a 1982 lecture to the local chemical society: “Nowadays, the molecular program of chemistry has arrived at its successful termination” (H. Primas). What he meant is that research should no longer be directed primarily toward areas that lend themselves to treatment by simple molecular models. Instead, we should take the risk of attacking more complicated systems, ones whose structures and properties are determined by non-covalent interactions. This is precisely the shift in emphasis that has occurred in organic chemistry. In all aspects of the discipline—target structures, analysis, synthetic methodology, mechanistic investigations—discussions now tend to revolve around topics such as molecular recognition; supramolecular chemistry (or “supramolecules”, to use Lehn’s terminology); [53, 154] inclusion compounds (clathrates); [54] self-assembly, self-organization, [53, 55] even the self-reproduction or self-replication [56] of structures. Titles of lectures and publications now regularly include expressions like host–guest, [57] intertwining molecular threads, [58] information storage and processing, [53] molecular architecture, [59] molecular hole burning, [60] molecular computers, [60] molecular devices, [53] molecular cybernetics, [51] molecular cavities and clefts, [62] molecular Lego, [60] molecular mechanisms of biomineralization, [63] molecular robots, [12b, 64] molecular slits, [56] molecules within molecules, [57] nanochemistry, [53] programmed molecular systems, [53] spontaneous structure generation, [53] starburst dendrimers (control over size, form, and surface), [63] synthetic enzymes, [62, 66] template-associated synthetic proteins, [67] triple-helix formation in the non-enzymatic cleavage of DNA, [68] and van der Waals molecules. [57] The names of some of the key players on this new stage can be identified with the aid of the cited notes and literature references. An impressive example illustrative of the modern approach, particularly from the standpoint of “classical” catenane and rotaxane syntheses, [59] is summarized in Scheme 3. Scheme 4 compares the structure of the recently synthesized homo-DNA with that of normal DNA. Scheme 5 shows two self-orienting double helices in which bipyridyl-metal complex formation assumes the role of the familiar base-pairing interactions in DNA.

The exciting synthetic targets today are no longer molecules to be prepared “for their own sake”; instead, they are systems associated with particular functions or properties (cf. Scheme 6). Organic chemists are busy designing new materials, [10, 73, 74] and not only within the context of polymer chemistry, [19, 75] which—except in the case of certain biopolymers—is concerned largely with the preparation and investigation of products that show a Gaussian distribution in molecular weight. The molecular “design” of a (super)structure [76] now captures the spotlight, while the synthetic process itself may withdraw into the background. The very simple organic reactions often turn out to be appropriate for the purpose of synthesizing such structures: acetol formation, alkylation, etherification, esterification, the formation of amides and sulfamides, or electrophilic aromatic substitution. Nevertheless, it will still be the chemists skilled in synthesis who will succeed in preparing the most interesting targets and exploring the most challenging themes, also in this area!

Scheme 3. “Self-assembly” of a catenane and a rotaxane (the authors employ the term fabrication) [60]. The O–p-phenylene-O units (O–A–O) of the macrocyclic ether A “bind” the two p-bis(pyridinium) units (+ C) of B, one inside the ring and the other outside. This causes the two pyridine nitrogen atoms to be kept in close proximity, so they can be joined using dibromo-p-xylene to provide, in 70% yield, the catenane C. The crystal structure of C displays not only a layer-like packing of donor and acceptor aromatic units but also “edge-to-face” interactions [70] between benzene rings A and benzene rings D. A similar synthesis of a simple catenane was accomplished starting with components held together by metal complexation [58]. Rotaxane D [60] was constructed using the same principle that was applied to catenane C. Back-and-forth motion of ring I [a bis(pyridinium) dication unit] between the p-phenylene units G has been verified by NMR spectroscopy (AG = 34.3 kJ mol⁻¹ in D₂O, acetone). The authors [60] call the system a “molecular shuttle.”
Inorganic double helices constructed from doubly methylated, CH₂-O-CH₂ bridged bipyridine ligands and copper(1) ions (top) [33] or sexipyridine and cadmium(II) ions (bottom) [71]. In the first case it has been shown that (a) complex formation is attributable to positive cooperativity, (b) the mixing of bipyridine ligands with differing numbers of bpy units leads to "self-recognition" (i.e., complexes containing two ligands of the same length are favored), and (c) introduction of chiral substituents into one pyridine ring of a bpy unit causes preferential formation of one of the two possible enantiomeric helices (diastereoselectively!). In the second case, the double helix is probably stabilized by stacking interactions between superimposed pyridine rings. One of the ligands (top) was prepared by etherification, the other (bottom) through a Krohnke reaction [72].

Scheme 5.

An oligonucleotide that contains bis(desoxy)glucose (left) in place of the usual desoxyribose (right) carbohydrate units [55]. Perfect staggering about all the single bonds in the hexose derivative results in an inherently linear chain, along which the bases are arranged in parallel array. The tetrahydrofuran ring of DNA is characterized by incomplete staggering, leading to an intrinsically helical chain and greater conformational flexibility ("pseudorotation"). The most distinctive features of homo-DNA relative to normal DNA include stronger complexation between the strands, a much longer helix pitch, and pairing rules that differ from the Watson-Crick rules.

Scheme 4.

Scheme 6. Stoddart's list of objects and functions that are familiar from everyday life and for which he has proposed equivalents at the molecular level. (Taken from a lecture delivered by Prof. Stoddart at the ETH Zürich, 5 February 1990) [60].
2.2. Concerning Inhibitors, Suicidal Substrates, and Flustrates

Organofluorine compounds frequently play a role in the synthesis of inhibitors, substrate analogues, so-called enzymatic or metabolic probes, antimetabolites, "transition state analogues" [66a] and suicide substrates or inhibitors [66b]. Indeed, there has recently been a real "boom" in this field [67, 68] producing considerable research activity in both academia and industry. This will certainly lead to improved methods for the synthesis of organofluorine compounds [69, 70], but it will also provide a deeper understanding...

Another important new type of synthetic target is related to the active centers of biological catalysts (enzymes, receptors, transport and channel proteins, ribosomes). Recently there has been an explosive increase in the number of proteins whose structures have been characterized, proteins taken from throughout the realm of nature, beginning with viruses and proceeding through microorganisms, plants, and animals, all the way to man. This development can be attributed primarily to advances in gene technology and to modern methods of structure determination. Sequencing of the human genome is expected to be the key to all the proteins in our bodies, which should then become more readily available through expression in other organisms. Many proteins are already available on short notice and in substantial quantity, and this means that prospects are greatly improved for success in the crystallization experiments that of necessity precede X-ray structural analysis (see below) [71]. At the same time, NMR spectroscopy is being used to carry out protein studies in solution, an approach supported by powerful computer modeling and computer dynamics (see Sec. 3). Characterization of an active center, or perhaps a substrate–enzyme complex, is the step that opens the way to further study through organic synthesis. Once the interaction between enzyme and substrate has been clarified, the likelihood is increased that an effective inhibitor can be designed. Medicinal chemistry is on the way to targeted preparation of inhibitors for all the crucial enzymes in the mammalian organism. Even agricultural chemistry is turning increasingly to selective intervention in the cellular chemistry of plants and pests.

Success in these areas demands a great deal of fantasy, considerable knowledge of structure–reactivity relationships, and experience in the efficient assembly of complex molecules—but it also requires a willingness to learn the "languages" of biochemistry, biology, and medicine. [72, 73]

The importance of biological chemistry can easily be inferred from what has already been said in this section and from Sections 2.3 and 7.2.1 below. It is also apparent, however, from the number of relevant articles published in the new review journal Chemtracts (Organic Chemistry) [74], in 1988 such articles accounted for 90 of the 500 pages, and by 1989 the proportion had grown to 130 out of 400! Other representative examples can be drawn from recent Nobel Prize lectures [75, 76]. Effects of all this activity on the methodology of organic synthesis are evident, for example, in a series of innovative investigations of compactin and its analogues [77], useful for reducing cholesterol levels as well as in syntheses of statin [78] and other rhenin inhibitors (which act to lower the blood pressure). [79] Interest in the latter has resulted in an active demand for novel approaches to non-proteinogenic amino acids [80], peptides, and their analogues (cf. Sec. 7). [81]
of the effects of fluorine on physical properties and of the frequently unexpected reactivity of this class of compounds. A few aspects of the subject are illustrated in Scheme 7. The hectic state of activity in this field and the surprises that often emerge from what should be the simplest transformations of fluorine derivatives make it hard for me to resist coining a new term: *frustrates* (= fluorine-containing substrates).

Not quite so well developed, but still subject to similar types of investigation, are nitro- and sila-analogues of physiologically active compounds, a few examples of which are shown in Schemes 8 and 9.

**Properties of carboxyl and nitro groups**

\[
\begin{array}{c}
\text{O} \quad \text{OH} \\
\text{CH}_3 \\
\text{C} \quad \text{C} \\
\text{O} \quad \text{OH} \\
\text{CH}_3
\end{array}
\]

Dipole moment (CH₃COOH) 1.74 D

\[
\begin{array}{c}
\text{O} \quad \text{O} \\
\text{N} \quad \text{H} \\
\text{CH}_3
\end{array}
\]

Dipole moment (CH₃NO₂) 3.46 D

\[
\begin{array}{c}
\text{C} \quad \text{C} \\
\text{O} \quad \text{H} \\
\text{O} \quad \text{H}
\end{array}
\]

\[
\begin{array}{c}
\text{N} \\
\text{O}
\end{array}
\]

\[
\begin{array}{c}
\text{C} \\
\text{N}
\end{array}
\]

Relative binding constants of carboxylate enzyme substrates and their nitronate analogues

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Constant</th>
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<tbody>
<tr>
<td>HOOC-COONa</td>
<td>1</td>
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<tr>
<td>HOOC-COONa</td>
<td>65000</td>
</tr>
<tr>
<td>HOOC-COONa</td>
<td>1</td>
</tr>
<tr>
<td>HOOC-COONa</td>
<td>72000</td>
</tr>
</tbody>
</table>

Scheme 8. A comparison of the nitronate group with the carboxylate group. According to [103], nitronate effectively mimics the characteristics of carboxylate with respect to geometry, polarity, and charge. Despite the great polarity of the nitro group [102], nitroaliphatics behave as non-polar compounds—in chromatography over silica gel, for example (NO₂ is a poor candidate for hydrogen bonding; cf. the fluorine derivatives in Scheme 7); references [95, 96, 104, 165] provide access to some of the author's preparative work and recent reviews of the literature. The greatly increased enzyme affinity of nitronate analogues compared with carboxylate anion substrates results in (apparently very successful) competitive inhibition [103].

Sila-isosteres of carbon compounds in particular may someday become very important, but within an entirely different context. Although sila derivatives have the same geometries as their carbon counterparts, their van der Waals dimensions are somewhat greater. In certain cases they might therefore serve as transition-state analogues for the preparation of catalytic antibodies, which would then accelerate reactions leading to the corresponding carbon systems. The same principle should apply to other heteroatom derivatives as well, "organoelemental" compounds in which bonds to elements in the first row of the periodic table (such as C–H, C–N, C–C, C–O, R₃N, and R₅O bonds) are replaced by ones to elements displaying similar bonding geometries but greater bond lengths (bonds such as Si–H, Sn–H, C–P, C–Si, C–S, R₃P, R₃As, R₅S, R₅Se, etc.). The point is elaborated in the section that follows and in Schemes 10 and 11.

**2.3. Antibodies as Catalysts in Synthetic Reactions:**
from Abzymes to Diels–Alder-ases

The intended targets of the molecular probes discussed in the preceding section were active centers of enzymes and receptors. Four years ago, two groups [112, 113] in the USA showed that with the aid of the immune system [79] chemists can also prepare selective catalysts that have antibody-type structures (i.e., immunoglobulins, giant protein molecules with molecular weights of ca. 150 000 daltons), substances that have been referred to as "abzymes" (antibody enzymes). [112] Work in this area is particularly dependent on the chemist's imagination and knowledge. In one of the reported variants, the preparative procedure is essentially [114] as follows (Schemes 10 and 11): first, a molecule is synthesized with a shape resembling as closely as possible either a transition state or a short-lived intermediate in the reaction to be catalyzed. This substance is treated as a hapten and coupled with a carrier molecule (e.g., a protein) to produce a combination with immunogenic properties (an antigen). The antigen is then introduced into the circulatory system of
The reactions to be catalyzed:

1. $A + B \rightarrow A \cdot \cdot \cdot B \rightarrow A \cdot \cdot \cdot B'$
2. $A' \rightarrow A \cdot \cdot \cdot B \rightarrow A \cdot \cdot \cdot B'$

Desired stable molecule (hapten group)

$A^\# \cdot \cdot \cdot B^\#$ should resemble the transition state as closely possible

Transformation of the hapten into an antigen

Attachment of a spacer (6-8 Å long)

$A^\# \cdot \cdot \cdot B^\# \rightarrow X$

Attachment of a protein (carrier molecule)

$A^\# \cdot \cdot \cdot B^\# \rightarrow X \cdot \cdot \cdot Pr$ (Antigen)

Preparation of monoclonal antibodies against the antigen

for reaction (1) for reaction (2)

Prerequisites for an antibody effective as an enzyme-like catalyst

The "active center" must have a greater affinity for the transition state or intermediate than for the educt or product

Scheme 10. Preparation of monoclonal antibodies with "recognition potential" for the arrangement of transition states or intermediates; there also exist other methods by which catalytically active antibodies (abzymes) can be prepared [114b].

It would be unreasonable to suggest that synthetic chemists will soon be trying to make an abzyme for "the next step" in a multistep laboratory-scale synthesis. On the other hand, industrial chemists interested in the production of larger amounts of fine chemicals or pharmaceuticals are not likely to shy away from the effort required to prepare such custom-designed catalysts. Indeed, the day may come when attempts will be made to develop entire reaction cascades mediated by multi-abzyme systems, with a final, irreversible step ensuring the smooth operation of a complex sequence of abzyme-catalyzed reactions. Just as has happened with enzymatic transformations, abzyme procedures are likely soon to be extended beyond the constraints of aqueous media, and some abzyme-catalyzed processes will probably prove to be essentially substrate-independent (as in the case, for example, of lipase- and esterase-catalyzed enzymatic reactions; cf. also Section 7.2.1).

We have so far been dealing with considerations that impinge directly on the synthetic organic chemist, but recent developments also have the potential for deepening our over-
all understanding of molecular interactions. Examples have already been reported of structural investigations based on the use of catalytic antibodies and their complexes with transition-state analogues, permitting identification of the interactions that are at the root of hapten affinities. In the future, investigations of this type may compete successfully with the point-mutation methodology in protein studies ("site-specific mutagenesis"), especially since they offer the prospect of a much wider choice of potential substrates ("the whole of organic chemistry"). This potential may soon be further enhanced as a result of recent successes in the biosynthetic, targeted introduction of non-proteinogenic amino acids into proteins.

3. Analysis, Computers, and Theory—No Progress without Help

—citius, altius, fortius [*]

Pierre de Coubertin, father of the modern Olympic Games

Dramatic progress in organic chemistry has always been closely linked to the introduction of new methods in analytical chemistry generally. The pace of advances increases as a direct function of the speed, sensitivity, and precision of the methods available for following a reaction, for establishing a reaction's outcome, or for determining the constitution of [*] "Swifter, higher, stronger."

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**Fig. 1.** Selected examples of separations accomplished with the aid of modern analytical methods. A) Gas chromatogram from a mixture of all the proteinogenic amino acids (racemic mixtures, in the form of N-pentafluoropropionyl isopropyl esters); Chirasil®-L-Val column containing 5% Kovats phase [135]. B) Gas chromatogram from a preparation containing racemic cis- and trans-1-ethyl-2-methyl- and cis- and trans-1-methyl-2-propylcyclohexane; cyclodextrin column [136]. C) HPLC separation of a mixture of three racemic oxazolidinones for amino acid synthesis; Chiraspher® column [137]. D) HPCE separation of a poly(desoxothymidylate acid mixture, with an enlargement of the region near 160 nucleotide units; polyacrylamide gel, 3 × 10^7 plates [138].
a mixture or the structure of a complex molecule—up to and including antibodies, DNA, or supermolecules held together by non-covalent forces. It would be wrong in a presentation such as this not to acknowledge, at least, the dependency of organic chemistry upon analytical chemistry. Unfortunately, limits of time and space preclude my doing much more than “name-dropping”, although I will provide a few key citations and introduce a handful of impressive examples.

3.1. Chromatography, NMR, and Mass Spectroscopy

The last 35 years have witnessed the advent of remarkable new analytical techniques. These can be conveniently separated into three categories: chromatography, spectroscopy, and miscellaneous methods. With respect to the first, thin-layer and gas chromatography\[132\] appeared in the vanguard, then came HPLC, and finally chiral stationary phases for determining enantiomeric ratios\[133,134\] (Fig. 1). Very recent additions include HPCE (“high-performance capillary electrophoresis”)\[138\] and FFF\[139\] (“field flow fractionation”, which actually involves a different principle altogether). Now there is even talk of neochromatographic techniques\[139,140\].

The earliest of these developments in chromatography coincided with the introduction of NMR spectroscopy, a technique whose triumphal march through chemistry is far from exhausted. Accustomed originally to small instruments based on permanent magnets and applicable only to $^1$H measurements, we now take for granted sophisticated high-field spectrometers with magnetic coils fabricated from superconducting materials. Various pulse techniques and Fourier transform capability have been incorporated into versatile devices suitable for routine multi-element analysis. 2D\[141\] and 3D-spectroscopy\[142\] (Fig. 2) as well as the study of

![Fig. 2. 2D-NMR spectrum of the basic trypsin inhibitor from the pancreas][143]. A combination of X-ray structure analysis, NMR spectroscopy, and computer assisted modeling/dynamic calculation on proteins results in detailed information about both their structure and their enzymatic function (see Sec. 3.3 and Fig. 8).
dynamic processes have all become possible through the introduction of extremely clever pulse sequences,\textsuperscript{[144]} and accessories have been made available for automatic sampling and for low-temperature analysis of fast chemical processes [RI ("rapid injection") NMR methods, cf. Fig. 3].\textsuperscript{[145, 147]}

[Image 0x0 to 576x792]

Fig. 4. Analysis of the molecular weight distribution of polymers by mass spectrometry. A) Laser-desorption Fourier-transform mass spectrum (LD-FTMS) of a poly(ethylene glycol) sample (mean molecular weight 3550 dalton)\textsuperscript{[155]}. B) Plasma-desorption mass spectra (PDMS) of poly[(R)-3-hydroxybutyric ester] (PHB, mean molecular weight 2740 dalton (osmometric)) and C) of a copolymer consisting of 78\% PHB and 22\% poly[(R)-3-hydroxyvaleric ester] (BIO-POL'). The inserts show observed intensities and intensities calculated for a statistical distribution of HB and HV\textsuperscript{[156]}. Recently, a special laser-desorption mass-spectroscopic method was used to detect the molecular ion of the protein bovine albumin (67 000 dalton)\textsuperscript{[157]}. Coupled capillary-zone electrophoresis/ion-spray mass spectrometry permitted the detection of (multiply charged) molecular ions from proteins with molecular weights as high as 150 000 dalton\textsuperscript{[154]}.

Chiral shift reagents now permit the direct determination by NMR spectroscopy of enantiomer ratios,\textsuperscript{[134]} and difference-nuclear Overhauser effect measurements are used routinely as a source of information about configuration, once determined almost exclusively by "wet chemical" methods (i.e., chemical correlations). It seems quite likely that NMR will soon be providing structural resolution at the level of one C-C bond length (1.5 Å) with proteins containing over 100 amino acid residues. Indeed, bets have been placed on the question of whether NMR spectroscopists or X-ray crystallographers will be the first to establish a protein structure with a given degree of precision. The principal differences between the two methods are that NMR deals with structures as they exist in solution rather than in the crystalline phase, and only NMR is capable of probing dynamic processes.\textsuperscript{[141 - 152]} Solid-state NMR spectroscopy is also well on the way to becoming a routine technique.\textsuperscript{[153]}

Mass spectrometry has undergone developments comparable in importance to those of NMR. For example, FAB ionization has finally made it possible to apply this technique to the detection and study of molecules of ever-increasing size. Radically new ionization techniques\textsuperscript{[154]} have been introduced very recently, and these are currently undergoing tests (cf. Fig. 4). The combinations GC/MS, HPLC/MS, and HPCE/MS have facilitated analysis of the most complicated mixtures as well as high molecular mass materials—a major advance for chemistry, but one subject to serious abuse by those who ignore Paracelsus' still valid definition of a "poison".\textsuperscript{[158]}

The fact that organic synthesis is now preoccupied with increasingly complex systems has effectively brought an end to the days when a synthetic chemist could hope to identify a product with a "quick glance" at a set of IR, NMR, and mass spectra. Today, and even more in the future, such problems warrant the involvement of teams of specialists. The methods available for structural analysis are now so diverse that one can no longer aspire to be both an imaginative chemist who studies a wide range of reactions and an expert at analyzing the resulting products. On the other hand, a "super-spectroscopist" runs the risk of becoming little more than a sterile technician in the absence of contact and collaborative interaction with those in a position to recognize and investigate important chemical problems and isolate species with intriguing new structures.\textsuperscript{[159]}

3.2. X-Ray Structure Analysis—Also Valuable for Probing Reactivity!

The difference between a chemist and a crystallographer can be compared to two people who try to ascertain what furniture is present in a darkened room; one probes around in the dark breaking the china, while the other stays by the door and switches on the light!\textsuperscript{[160]}

Among the remaining analytical methods, X-ray structure analysis surely deserves to be mentioned first.\textsuperscript{[160]} It has
become impossible for a synthetic organic chemist to remain competitive without access to this technique. Tears well up in crystallographers’ eyes when they hear synthetic chemists assert that X-ray structure analysis is on the verge of becoming a type of spectroscopy. Instruments are indeed being developed that use more powerful X-ray tubes and incorporate faster mechanical devices for more rapid collection of reflections, and increasingly efficient computers and better software [161] are being incorporated for the solution of structures. It is now possible to carry out routine X-ray structural analyses of moderately complex molecules in the same amount of time that used to be set aside for NMR analysis. State-of-the-art technology for the solution of very large structures is soon likely to feature a synchrotron as the source of short-wavelength radiation, and to invoke nonmonochromatic radiation (as in the original Laue method, cf. Fig. 5).[162–164] The ability to grow perfect single crystals of pure compounds—one of the most ancient of chemical arts—will once again command respect in the laboratory. Chemists who display a combination of dexterity and devotion as they manipulate their products will stand the greatest chance of success in this endeavor. The foregoing generalization is equally applicable to small and large structures,[165, 166] compounds that are stable and those that are extremely air-sensitive,[167] and materials subject to decomposition well below room temperature,[168] loss of solvent,[169] or the development of plastic crystallinity.[170]

It has recently become apparent that X-ray diffraction can be important to the chemist not only for establishing the structures of isolated products, but also as a means of learning something about the structures of reactive intermediates—and therefore about reactivity in general. Many of the idiosyncrasies and imperceptibilities associated with the chemistry of polar organometallic compounds have become better understood, or have even been circumvented entirely, once the corresponding crystal structures were “seen”.[167, 171–174] Four recent examples are presented in Fig. 6. Other cases show how structural data can be correlated with the reactivity of compounds (the principle of structure-reactivity correlation)[179–181] or with force constants.[182] Three examples are presented in Fig. 7 in which pyramidalization of trigonal carbon atoms, determined in the crystalline phase, has been used to explain reactivities in solution. It is to be hoped that the future will bring more such non-routine applications of structure determination, and it is almost certain that X-ray results will continue to “open the eyes” of synthetic chemists. The crystallographic data bank in Cambridge (CSD)[189] already contains a wealth of uninterpreted information, a veritable treasure trove waiting to be exploited by the initiated!

It is difficult to predict which other analytical techniques will provide valuable information for synthetic chemists in the future.[190] We look with envy, for example, at tunneling electron microscopy,[191] which permits one to probe surfaces with a resolution sufficient to cause pyrrole and benzene rings—even individual xenon atoms—to become “visible”[192–194] and capable of revealing a piece of double-stranded DNA as a kind of “molecular braid”.[192b]

Fig. 5. Laue diffraction pattern of glycogen phosphorylase B. The use of high intensity, non-monochromatic synchrotron irradiation permits the collection within minutes of the data associated with a large protein or nucleic acid molecule—even an entire crystalline virus[162, 163]. Polychromatic irradiation permits a great many planes to fulfill the conditions of reflection, so that a single 100 μs “shot” can produce 150 000 measurable reflections. Employing a video camera as the recording device makes it possible to record the reflections generated by several pulses directed in rapid succession at a rotating crystal. This method is of course equally applicable to crystals of smaller molecules or even typical inorganic solids, although it requires crystals of higher quality than those typically used for monochromatic irradiation. J. Hajdu[164] has visions of employing pulse lengths of 10–40 ps, intervals of a few ns, and intensities equivalent to those produced by the highest energy synchrotrons to investigate on the ps time scale reactions occurring in the crystalline state. Nevertheless, enormous problems remain to be overcome (computer programs for the corresponding structural calculations, radiation damage, etc.). A: Laue photograph of glycogen phosphorylase B (space group P4₁2₁2, a = b = 128.8, c = 116.2 Å), taken at station 9.7 of the Daresbury synchrotron radiation source. The crystal was rotated 33.75° from the position with *a* antiparallel to the beam and *c* coinciding with the spindle of a one circle camera. Wavelength range: 0.20–2.10 Å; crystal to film distance: 133.8 mm; film radius: 59 mm; exposure time: 1 s; predicted total number of reflections: 49 570. B: Computer-generated Laue pattern of glycogen phosphorylase B (parameters as above) at 2.4 Å resolution. Reflections were color-coded to their wavelengths: blue signifies 0.20 Å and red is 2.10 Å (other wavelengths shown correspondingly in relation to the visible spectrum; computer program written by I. J. Clifton, Laboratory of Molecular Biophysics, Oxford University); total number of reflections: 49 570.
Fig. 6. Four structures of polar organometallic compounds of preparative significance. A) A tetrahydroisoquinoline derivative metallated in the 1-position; in contrast to the Li analogue, the Mg derivative whose crystal structure is shown here [174] adds with high diastereoselectivity to aldehydes [175]; structural data (Mg octahedral, Li tetrahedral; one of the THF solvent molecules is considerably further removed from the metal than the other two) were used in the development of a mechanistic model. B) Crystal structure [176] of an octameroid complex with the composition \([[\text{BuLi}]_4 \cdot (\text{t-BuOLi})_4]\). Complex bases derived from butyllithium and potassium tert-butyl alcololate (Lochmann–Schlosser bases [177]) prove to be much more efficient deprotonating agents than their components; it has been suggested that the uniqueness of such bases is a consequence of their complex structure. C) and D) Hexamer and octamer of lithiated benzoic acid isopropylamide [178]; the existence of such complex structures may be responsible for the remarkably selective reactions of polylithiated oligopeptides [172].

3.3. Quantum Mechanics and Force Fields: Ever Larger Pictures, Increasingly Reliable (a Contribution to Chemistry from Microchips)

Electronic data processing has played an important part in all the dramatic advances in instrumental analysis described above—a contribution of microelectronics to chemistry. The same applies to other areas of considerable interest to the synthetic chemist: literature searching, the organization of information about reactions, retrosynthetic analysis, structural data banks, structural and dynamic modelling of molecules and transition state geometries, and ab initio cal-
computable to experimental verification (cf. the examples in the cited works) and the ability of such predictions—judged on the basis of comparisons with structural parameters obtained through spectroscopy or diffraction—has caused even novices to trust computed results for systems that are not (or not yet!) susceptible to experimental verification (cf. the examples in Scheme 12). Virtually all the fundamental reactions of organicsynthesis—including nucleophilic addition to carbonyl groups, the Michael addition, the aldol addition, 1,3-dipolar cycloaddition, the Diels–Alder reaction, hydroboration, and addition to double bonds with stereogenic centers at their allyl positions—have been subjected to more or less elaborate calculations based on force field and/or ab initio methods. "Theoretical Chemistry en route to a Theory of Organic Chemistry" is a proclamation that pertains not only to very simple systems, and not just to reactants; it even embraces solvents (in modeling) as well as in the context of proteins and nucleic acids (cf. Fig. 8).

4. Experimental Design, Experimental Procedures, Types of Reactions, and Reaction Techniques—a Question of More Than Just the Scale of the Reaction

Necessity is the mother of invention!

Many of the modern techniques for carrying out reactions or purifying products still have a reputation for being somewhat exotic, and certainly inapplicable to large-scale work, but it is easy to foresee the day when these same methods will begin to play a significant role in the manufacture of organic compounds, opening the way to the synthetic reactions that depend on them. Meanwhile, other industrial processes that are now wide-spread will need to be abandoned because they are associated with indefensible levels of risk and the cost of retaining them will prove too high (e.g., reactions in hexamethylphosphorotriamide (HMPT), which has mutagenic properties). When I speak here of industry I am really referring to the preparation (usually in several steps) of specialty chemicals—particularly pharmaceutical agents, perfumes, vitamins, and agricultural products—not the bulk manufacture of petrochemicals, solvents, or polymer precursors.

Table 1. Sources of computer information, and computer-based tools useful to the synthetic chemist. Most of the programs and databases listed here are currently available in the organic chemical laboratories of the ETH Zürich. (To be fully effective, the programs must be immediately accessible within the laboratory itself.)

<table>
<thead>
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<td>CASP (Computer-Assisted Synthesis Planning) [198]</td>
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| Structures | CSD (Cambridge Structural Database) "Cambridge File"
| Modeling | MacMoMo [206] |
| ab initio calculations [210] | Monster-Gauss [211] |
| CAPDAC [212] | GAMESS [213] |
| MOPAC [214] | |

Fig. 7. Pyramidalization and reactivity at trigonal centers. A) In the crystalline state, cyclohexenones and similar derivatives with five atoms nearly in a plane and a sixth atom outside this plane ("sofa" conformation) often display pyramidalization as well as reactivity (183). B) Crystal structures of silylenol ethers from imidazolidinones, where R = C,H, or OCH,; the trigonal, methyl-substituted C atoms are displaced by 7.8 or 11.8 ° (A = 0.07, 0.11 Å) from the plane of the five-membered ring, and pyramidalization is in the direction from which reaction occurs with electrophiles for both the Si enol ethers and the corresponding Li enolates (184) (see also Scheme 12). C) The crystal structure of a norbornene derivative (determined using neutron diffraction) displays pyramidalization in the ex0 direction for the trigonal carbon atoms of the C–C double bond (185) (cf. the suggestion made in 1967 that the unexpectedly high ex0 selectivity in reactions of norbornenes might be due to torsional effects (186, 187), as well as Huisgen's "Factor X" (188)).

Table 1. Sources of computer information, and computer-based tools useful to the synthetic chemist. Most of the programs and databases listed here are currently available in the organic chemical laboratories of the ETH Zürich. (To be fully effective, the programs must be immediately accessible within the laboratory itself.)

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| CAPDAC [212] | GAMESS [213] |
| MOPAC [214] | |
A

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<tr>
<td>Calculated</td>
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<td>124.5</td>
<td>112.6</td>
<td>114.5</td>
<td>111.5</td>
</tr>
</tbody>
</table>

B

observed and calculated displacement of the substituents in the indicated direction: 0.2–4°

C

obs. 7.5°, calc. 3.4°

D

0.00 kJ / mol

44.8 kJ / mol

Scheme 12. A comparison of several structures obtained by crystal structure analysis with predictions based on ab initio calculations. A) Observed and computed (3-21G for the unsubstituted dioxinone R1= R2= R3= R4= H) pyramidalization of the trigonal C atoms of dioxinones (cf. Fig. 7); bond lengths in Å, angles in degrees [183]. B) Pyramidalization at the trigonal centers of norborne; comparison of observed parameters (Fig. 7) [185] with predictions (STO-3G) made many years earlier [215]. C) The acyliminium ion is found experimentally to be more stable than the oxonium ion, and it is also predicted to be more favorable by ab initio calculations (3-21G) [216]. Perhaps the most ambitious calculations to date (MP3/6-31+G**//6-31G*) are due to Wiberg [217], and they have shaken the foundations of our qualitative models of resonance stabilization.

In this context, many methods have already been introduced into large-scale practice that only a few years ago would have classed as truly bizarre (“the stuff of academia”). Consider the following examples, arranged alphabetically and supplemented with illustrations (or at least key literature references).

- Biological-chemical reactions (i.e., processes involving microorganisms and enzymes) are a good place to start, although some have actually been in limited use for years (cf. Reichstein’s vitamin C synthesis) [229]. BASF now prepares (R)-lactic acid and various fragrances by fermentative routes; ICI makes tons of poly[(R)-3-hydroxybutanoate] by fermentation [230], and the company has recently developed a process for the production of polyphenylene starting with cis-cyclohexa-3,5-dien-1,2-diol, an enzymatic oxidation product of benzene [231]. Amino acids are prepared in Japan with immobilized enzymes and microorganisms that display unbelievably long catalytic lifetimes; and enantioselective esterification and saponification with lipases are accepted as standard procedures in both large- and small-scale applications (cf. also “abzymes” and the EPC synthesis, Sections 2.3 and 7.2).

- Chromatography over aluminum oxide, silica gel, or ion exchangers has apparently proven to be economically feasible in the purification of products like cyclosporin [222].
and in the bulk isolation of amino acids from protein hydrolyzates.[233] About ten years ago, a synthetic chemist in the pharmaceutical industry reacted to a management directive stating that active ingredients were no longer to be developed as enantiomeric mixtures by exclaiming “Then from now on we’ll only study achiral compounds!” A decade later, chromatographic separation (by preparative HPLC) of a kilogram of an enantiomeric mixture is thought to be possible for less than 1000 DM (ca. $600).[1334]

- Clays, zeolites, and aluminum oxide have been recommended as catalysts or carriers for synthetic reagents.[234]
- Electrolysis is seeing increasing use both in industry[235, 236] and in the laboratory[237, 238] (cf. Scheme 13).

Scheme 13. Electrolysis of carboxylic acids and its application to the modification of peptides [239]. The great advantage of carboxylic acid electrolysis in particular is the fact that no electrolyte is required, and it is not necessary to employ divided cells. Addition of an amine causes the solution to become conductive; CO₂ is formed at the anode, and H₂ at the cathode. Equipment demands are minimal. “Normal” carboxylic acids afford Kolbe coupling products, while α-heterosubstituted acids undergo oxidative decarboxylation [237, 238]. In the case of oligopeptides (with up to six amino acid residues), electrolysis permits straightforward modification of the acid end of the molecule [239]; cf. the formation of phosphonic acid and allyl derivatives (polar vs. lipophilic end groups).

Indirect electrolysis[240] has proven particularly attractive, since it can be regarded as a catalytic process (e.g., an electrochemically generated oxidizing agent undergoes reduction in the course of a “perfectly normal” substrate oxidation, and is then regenerated at an electrode).[241]

- Fluorination with elemental fluorine is now a subject of active investigation even in industrial laboratories.[92]
- High- and very-high-pressure conditions (up to 20 kbar) permit the realization of reactions with negative activation volumes (ΔV*).[242] For example, Diels–Alder reactions between sterically hindered components become feasible under such conditions, whereas equilibrium consid-

...
day, when these same “deranged prophets” are invited to
tour the “holiest-of-holies”, they are likely to encounter a
perfectly ordinary-looking 1500 L reaction vessel—
cooled by liquid nitrogen!—to which is being added
150 L of butyl lithium solution. The result of such efforts
is often a considerable increase in selectivity, achieved
despite free energy of activation differences smaller than
one kcal mol\(^{-1}\) (cf. Fig. 9). An example of a continu-
ous low-temperature process is outlined in Fig. 10.\(^{244,247}\)
Even C–C bond formation with the aid of lithiated 1,3-
dithianes,\(^{188}\) now a standard laboratory method but one
that requires low temperatures,\(^{31,248}\) has been adapted
for large-scale application.

- **Microwaves are the answer**!—or so it would appear from
the increasing number of papers in which this approach to
introducing energy is described as the “method of choice”\(^{249}\)

- **Ozonolyses are being used in the manufacture of specialty
chemicals.**\(^{250}\) No one would have believed that possible
in the days when I was working on my dissertation with
Criegee!

- **Photoreactions (progeny of a venerable family of chemi-
cal transformations)**\(^{251}\) now are employed not only for
initiating chain reactions, but also under circumstances in
which the quantum yield is smaller than 1, especially if
they lead in a single step to structural changes that cannot
be realized in other ways\(^{252–254}\) (cf. Table 4G and
Scheme 20B).

- **Radical reactions** were viewed with considerable suspi-
cion by synthetic chemists as recently as 10 years ago,
attacking favor only among those interested in the study
of mechanisms.\(^{123,255}\) Today they are securely embedded in
the methodology of synthesis,\(^{256–258}\) and it is likely they
will become still more important, especially as tin deriva-
tives relinquish their roles as chain initiators and synthetic
reagents generally.\(^{256}\)

- **Salt effects** are as old as organic chemistry itself. It has
recently been discovered, however, that alkali metal and
alkaline earth salts in particular have extraordinary solu-
bilizing effects with respect to compounds otherwise in-
soluble in organic solvents (e.g., polylithiated deriva-
tives\(^{172}\) and oligopeptides;\(^{1260}\) cf. Table 2 and Fig. 11).

- **Solid-phase syntheses** have been achieved on a wide vari-
ty of carriers.\(^{8,263}\) Combination of the Merrifield pep-
tide synthesis with modern separation methods has even
made it possible to prepare relatively large peptide seg-
ments useful in the pharmaceutical industry for the pro-
duction of active ingredients.\(^{1264}\)

- **Solid–solid reactions** are not likely to evoke images that
are especially appealing. Nevertheless, close inspection of
the abstracts from a conference\(^{265}\) on the subject\(^{54,266}\)
reveals astonishing possibilities. A few examples are pre-
sented in Scheme 14.

- **Solvents** are more and more becoming the “problem chil-
dren” in applied organic chemistry. For instance, it is
absolutely necessary that new and safer techniques be
developed for the use of dichloromethane in those cases
where it cannot be avoided, techniques that will guarantee
the recycling of over 95% of the solvent. The urgency of
finding replacements for the equally unique HMPT has
already been noted.\(^{228}\) Easily recoverable chiral sol-
vents, especially ones available in both enantiomeric
forms\(^{226}\) would be useful for enhancing stereoselectivi-
ty.\(^{277,278}\)

- **Ultrasound** has been found to work wonders in many
heterogeneous reactions—sometimes in homogeneous
systems as well.\(^{249,279,280}\) It is especially effective for
activating surfaces (e.g., in virtually any reaction that in-
volves a dissolving metal) and has become a standard

---

Fig. 10. Example of a low-temperature reaction carried out as a continuous
process. Dihydrolysergic acid methyl ester is deprotonated to the Li enolate
using lithium diisopropylamide (LDA) generated in situ. Subsequent protona-
tion results in iso-9.10-dihydrolysergic acid methyl ester\(^{245,246}\). A) Schemat-
ic representation of the process, and B) photograph of the pilot facility\(^{244}\).

1–4 correspond to the stirred reactors in A.
Fig. 11. Use of LiX-containing solvents [260] in Merrifield peptide syntheses involving various anchoring groups and coupling methodologies. The peptides chosen were notorious for a tendency to undergo aggregation (β-pleated sheet), which normally implies a decrease in yield after a certain chain length has been attained. Experiments with Rapp and Wang resins [261] as well as with Kaiser oxime resin [262]. Polystyrene/1% divinylbenzene was the basis resin in each case. DCM = dichloromethane; NMP = N-methylpyrrolidone.

Table 2. Solubilization of oligopeptides in tetrahydrofuran and other organic solvents through the addition of salts and titanates. The reported maximum solubility is often achieved only after redissolving the residue from a much more dilute solution [260]. This method made it possible to obtain solutions of peptides soluble in no other solvent (example at the bottom of the table) [262]. For an application involving solid-state synthesis see Fig. 11.

<table>
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<th>Solvent</th>
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</tr>
<tr>
<td></td>
<td>DME</td>
<td>≥ 470</td>
</tr>
<tr>
<td></td>
<td>DCM</td>
<td>≥ 420</td>
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<tr>
<td></td>
<td>DCM</td>
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<tr>
<td></td>
<td>DCM</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td>DCM</td>
<td>≥ 440</td>
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<tr>
<td>Z-Ile-Gly-Gly-OH</td>
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<td>≥ 340</td>
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<tr>
<td>Boc-Gly-Gly-Nva-OH</td>
<td>THF</td>
<td>≥ 190</td>
</tr>
<tr>
<td>H$_2$N-Asp(OBz)-Val-Tyr-OBz-HCl</td>
<td>THF</td>
<td>≥ 470</td>
</tr>
<tr>
<td>H$_2$N-Lys(2)-Asp(OBz)-Val-Tyr-OBz</td>
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<td>≥ 510</td>
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<td></td>
<td>DME</td>
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<td></td>
<td>DME</td>
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<td></td>
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<td></td>
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<td>≥ 120</td>
<td>3.3 LiClO$_4$</td>
</tr>
<tr>
<td>Boc-Ala-Gly-Gly-OH</td>
<td>THF</td>
<td>≥ 300</td>
</tr>
<tr>
<td>HCl H$_2$N-Lys(Z)-Asp(OBz)-Val-Tyr-OBz</td>
<td>THF</td>
<td>≥ 380</td>
</tr>
<tr>
<td>Z-Arg(Lys)-Asp(OBz)-Val-Tyr-OBz-HCl</td>
<td>THF</td>
<td>≥ 230</td>
</tr>
<tr>
<td>H$_2$N-Leu-Met-Val-Gly-Gly-Val-Ile-Ala-OH</td>
<td>THF</td>
<td>insoluble</td>
</tr>
</tbody>
</table>

These examples have been selected to call attention to a number of unusual or at least (until recently) atypical ways of carrying out reactions. At the same time, they illustrate the principle that the feasibility of extreme conditions is limited in practice only by the value of the product to be synthesized.

5. Reactivity: the Age-Old and Uniquely Chemical Fascination.

New reactions—are any more waiting to be discovered?

For the great things are not done by impulse, but by a series of small things brought together.

Vincent van Gogh (1888, in a letter to his brother Theo) [*]

A great many synthetic chemists, whether devotees of natural products synthesis or simply interested in synthesis general...

rooted in general principles of reactivity. The challenge is still open! For my part, I am convinced that only in the area of transition-metal organic chemistry are there new reactions waiting to be discovered (see Sections 6 and 7.2.2). In terms of main-group elements, whether metallic (Li through Ca, Be through Ba, Al through Tl, Ge through Pb, or Bi), metalloid (B, Si, As, Sb, Se, Te), or non-metallic (N, P, O, S, the halogens, or the noble gases), carbon derivatives have been examined for so long and with such intensity that no fundamentally new types of reactivity can reasonably be anticipated (see the applications associated with silicon and a few elements from higher periods outlined in Table 3 and Schemes 15–17). This obviously does not mean that in the areas we have long regarded as the true domain of classical organic chemistry there will be no more progress. On the contrary! The achievements of the past 30 years indeed the past 10 years, have been quite remarkable. To a greater extent than in the past, however, progress has been not the product of solitary, revolutionary discoveries, but rather the cumulative effect of innumerable small steps taken by increasing numbers of researchers throughout the world.

Thus, we have not witnessed the discovery of new al- dol, Beckmann, Claisen, Cope, Diels–Alder, Mannich, Michael, or Wittig reactions (1330) but rather a steady increase in the number of known reactions of which the applications associated with silicon and a few elements from higher periods outlined in Table 3 and

<table>
<thead>
<tr>
<th>Example</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Si-acetylation</td>
<td>of aldehydes and ketones, Si-triflate catalysis (based on Noyori) [298–300]</td>
</tr>
<tr>
<td>Si-acyloin condensation</td>
<td>Rühlmann variant of the acyloin reaction [301,302]</td>
</tr>
<tr>
<td>Si-aldol additions</td>
<td>see Schemes 19 and 26</td>
</tr>
<tr>
<td>Si-alkene additions</td>
<td>see Schemes 19 and 26</td>
</tr>
<tr>
<td>Si-azide</td>
<td>&quot;the versatile reagent&quot; [303]</td>
</tr>
<tr>
<td>Si-Birch reduction</td>
<td>and other Si-modified reactions of dissolving metals [304]</td>
</tr>
<tr>
<td>Si-cyanohydrin reaction</td>
<td>see below, Si-umpolung</td>
</tr>
<tr>
<td>Si-diazomethane</td>
<td>sultam variant of the standard diazomethane reactions [305]</td>
</tr>
<tr>
<td>Si-Friedel-Crafts-type acylations</td>
<td>at aromatic, vinylic, and acetylenic C-atoms [109,289]</td>
</tr>
<tr>
<td>Si-Mannich</td>
<td>see below, Mannich reactions [336]</td>
</tr>
<tr>
<td>Si-Nazarov reaction</td>
<td>five-membered ring annelation [306], cf. also the Si-variant of the Robinson annelation [307]</td>
</tr>
<tr>
<td>Si-nitrilodiazides</td>
<td>diastereoselective to give products of I or u configuration [181,308]</td>
</tr>
<tr>
<td>Si-olefination</td>
<td>Peterson olefination [108,295,309]</td>
</tr>
<tr>
<td>Si-oxonitriles</td>
<td>with tri-hydroxyketones [310]</td>
</tr>
<tr>
<td>Si-pinacol rearrangements</td>
<td>migrating α-Si-vinyl group [311], see also Scheme 16 and [320] therein</td>
</tr>
<tr>
<td>Si-Pummerer rearrangements from sulfides</td>
<td>to Si-thioethers [312]</td>
</tr>
<tr>
<td>Si-radical chain reductions</td>
<td>see above, Scheme 15 D, ref. [259]</td>
</tr>
<tr>
<td>Si-umpolung with trimethylsilanolysiodine [34] or with Me3Si-thioazole [313]</td>
<td></td>
</tr>
</tbody>
</table>

Table 3. Examples for Si-modified reactions from A to U. Most of the cases offer more or less significant advantages relative to the corresponding "normal" procedures. The Si variants can also be implemented at reasonable cost provided commercial silylating agents are utilized. (Numerous silyl compounds are manufactured in bulk for use in the preparation of silicones [314].)
Scheme 15. R₃Si: more than just a "big, fat proton". In most of the organic synthetic applications of R₃Si derivatives, the Si group plays a role identical to that of the proton in analogous classical reactions (cf. A and B, as well as the aldol reactions in Scheme 19) [289]. The Si group can be introduced nucleophilically by way of Li or Cu derivatives (cf. C). Radical hydrogen transfer can be accomplished with SiH compounds in the presence of chain initiators such as AIBN (D). Stabilization by Si of α-anionic charges (E), as well as β-cationic charges (F, cf. Scheme 16) also leads to useful applications of Si derivatives in synthesis. The oxidative cleavage of Si-C bond indicated in G establishes synthetic equivalence between silyl groups and OH.

Scheme 16. Transformations facilitated by the stability of β-Si carbocations. The amount of stabilization associated with the β-Si effect has been estimated to be as great as 139 kJ mol⁻¹ [315]. Vinyl-[109] and allylsilanes [107, 316] have acquired considerable significance in organic synthesis. Thus, Si groups activate double bonds, control regioselectivity in electrophilic attack, ensure stereoselectivity during reaction (cf. the preference for retention in substitution of vinyl silyl groups [109, 296] and S₂,anti-substitution of allylic silyl groups [109, 317, 318]), and function—formally speaking—as leaving groups of the type R₃Si⁺.

A) Stereoselective (cis → Z, trans → E; ca. 95% de) rearrangement of silyloxa-
ranes to Si enol ethers [319, 320]. B) Attack of an oxonium ion on a vinyl silane, leading to an oxepane via substitution with retention (R = Bu, R' = H and
R = H, R' = Bu, > 98% de) [321]. C) Migration of an α-silylvinyl group in what amounts to a pinacol rearrangement (retention at the migrating carbon, inver-
sion at the migration terminus; this process may involve a β-Si stabilized cyclo-
propylmethyl carbocation) [311, 322] (BOM = benzylxymethyl). D) Allylation with allylsilane/TiCl₄(OCHMe₃) used to effect S₂ ring opening of a dioxanone with the (1R,6R) configuration, a process that entails subsequent elimination to provide a homoallylic alcohol (overall yield 76%, enantiomeric excess 94% ee) [299, 324].

6. Transition-Metal Derivatives—Always Good for a Discovery

Anyone who has attended one of the biennial conferences on organometallic chemistry directed toward organic synthesis (OMCOS), and sensed there the atmosphere of excite-

---

**Table**

<table>
<thead>
<tr>
<th>Reactivity</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Iodide [290] and triflate [291]; hydride transfer from R₂SiH</td>
</tr>
<tr>
<td>B</td>
<td>Formation of short-lived carbon derivatives [292]</td>
</tr>
<tr>
<td>C</td>
<td>(Me₅Si)₂Cu for Michael addition [292]</td>
</tr>
<tr>
<td>D</td>
<td>Radical chain reductions with (Me₅Si)₂SiH [292]</td>
</tr>
<tr>
<td>E</td>
<td>Metallated silanes for Peterson olefination [292]</td>
</tr>
<tr>
<td>F</td>
<td>Electrophilic vinyl substitution with retention [292]</td>
</tr>
<tr>
<td>G</td>
<td>Oxidative cleavage of the Si-C bond with reaction at carbon [292]</td>
</tr>
</tbody>
</table>
Scheme 17. Synthetic transformations involving organometallic compounds containing main group elements from higher periods. A) The Li enolate of propiophenone, prepared with the aid of LDA, was transmetallated to give the indicated Ge enolate, which in turn leads preferentially, depending on the reaction conditions, to either an $\alpha$- or a $\alpha$-aldol$^{325}$. B) Cu-catalyzed reaction of tetrahydroisoquinoline with aromatic $\text{Pb}^{(iv)}$ compounds, resulting in N-arylation $^{326}$. C) A first catalytic olefination following the scheme of the Wittig reaction proceeds via an arsenic ylid $^{327a}$. D) Phenylation of an indole with triphenylbismuth trifluoroacetate $^{327b}$. E) A type of mixed Wurtz coupling between adamantyl and $\text{p}$-methoxyphenyl, accomplished via a telluride $^{328}$. F) Use of $\text{XeF}_2$ as reagent for the addition of fluorine to a double bond $^{329}$ (cf. also Scheme 7).

It is worth noting that three of the six reactions shown are catalyzed by transition metals! (cf. also Sections 6 and 7.2).

Scheme 18. “Evolution” in the oxidation of an alcohol to a carbonyl derivative $^{355}$. A) A leaving group is first introduced, after which the actual oxidation at carbon takes place by HX elimination. This scheme characterizes, for example, chromic acid oxidation $^{355}$, the reaction with hypochlorite $^{356}$, corresponding reactions of peroxides $^{357}$—in principle, even the oxidation of amines to carbonyl compounds with the aid of an $\alpha$-quinone $^{358}$. B) Reaction by way of sulfoxonium salts can occur starting with educts of widely varying type $^{359-363}$, with the Kornblum oxidation itself $^{359}$ serving to convert an alkyl halide into an aldehyde. The currently most popular variant is the Swern oxidation $^{362}$, favored because of its mild conditions. There are numerous other possibilities for activating DMSO in the oxidation of alcohols to aldehydes and ketones (cf. the review articles cited under $^{362,363}$). DCC = di-cyclohexylcarbodiimide, NCS = N-chlorosuccinimide.

A few examples are presented in Table 5. (The author accepts full responsibility for incorrect classifications and missing names!) Scheme 20 illustrates several cyclizations that proceed via carbonyl complexes and are without precedent in classical organic chemistry.

Here, too, there have been significant developments with respect to well-known reaction types $^{408-411}$ for the practitioner, some of them amounting to genuine quantum leaps. Thus, by using transmetallation to go from classical Grignard or organolithium reagents to the easily prepared titanium $^{273-275,299,412}$, zirconium $^{273,274,413}$ or lanthanide derivatives $^{414-416}$ it is possible to experience selectivity increases during carbonyl addition that raise the yield of the desired product from less than 10% to over 90%. Examples of differentiation among several functional groups, preparation of specific diastereoisomers, and the realization of enantioselective transformations are provided in Scheme 21, Fig. 12, and Scheme 22, respectively.

Reductive coupling $^{320.342}$ of carbonyl derivatives and their thio and imino analogues has been greatly facilitated by the advent of low-valent derivatives of titanium, vanadium,
Table 4. In situ sequences [373] of classical reactions leading to the formation of up to five new stereogenic centers. Enthusiasm over successful “complexity-enhancement” has resulted in several dazzling descriptions [351, 374–376].

A) Carbonyl addition, oxy-Cope rearrangement [334b], proton transfer, and selenization leads to a tricyclic product with five stereogenic centers (where the educt contained only two); KHMDS=potassium hexamethyldisilazanide [343c]. B) Two bonds, two rings, and three stereogenic centers are formed in this sequence of radical reactions [377]. C) A C-acylation of 4-methylcyclohexanone enolate with 4-nitrobutyryl chloride, followed by an intramolecular nitroaldol addition, results in a trans-decalin derivative [378]. D) Michael addition of the di-enolate of 3,5-dioxohexanoic acid ester to a nitrostyrene, followed by nitroaldol addition, gives a cyclohexanone with four adjacent stereogenic centers [337d]. E) Intermolecular Michael addition (or S,S substitution?), intramolecular Michael addition, and proton transfer accomplishes diastereoselective generation of a total of five stereogenic centers [337e]. F) Iminium salt formation, aza-Cope rearrangement, a Mannich reaction, and condensation between the ortho amino group and the newly formed carbonyl function all occur in situ during synthesis of the alkaloid methoxytabersonine [336a, 379]. G) Light truly works wonders in this intramolecular cycloaddition between an olefinic double bond and a benzene ring [380] (Kaplan–Bryce-Smith reaction [254, 381, 382]). H) Ethoxycarbonylmethylation at the nitrogen of a shilazol, ylid formation, cycloduction to the C–C double bond of an enone, and tetrahydrofuran formation are the steps leading from two achiral educts to a tricyclic system with five centers of chirality [383]. I) Three-fold Michael addition produces four stereogenic centers [384]. K) Enamine acylation, followed by intramolecular Michael and Dieckmann reactions, transforms methacryl chloride and a cyclohexanone derivative directly into the adamantane skeleton [385]. L) A 1:2 intermediate trapped along the way toward polymerization in the reaction of cyclohexanone enolate with methacrylic ester [386]. M) Michael addition to methylcyclopentanone, trapping of the resulting enolate with a vinylphosphonium salt, and an intramolecular Wittig reaction—carried out as a one-pot sequence leading to the estrone skeleton, albeit in low yield [387].

and niobium, and the scope of the reaction has been broadened (e.g., to include nitriles), as shown in Scheme 23.

An application of allyl protective groups in DNA synthesis [430–434] provides a particularly impressive example of what can be achieved with organometallic methodology: Nitrogen atoms in the constituent bases were subjected to allyloxycarbonyl (AOC) protection, and O-allyl groups were incorporated into the added phosphoramidite units. In a dramatic final step, with the substrate still attached to the polymeric carrier, all the protective groups were removed at once by treatment with Pd⁰/Ph₃P/butyl amine/formic acid in THF. Oligonucleotides resulting from this “Nagoya method” are of unprecedented purity; this is illustrated in Fig. 13, which compares samples of nucleotides containing up to 60 nucleoside units prepared by the conventional method and by the new method.

Scheme 20. Four cases of cyclization accompanied by CO insertion and made possible by transition-metal derivatives. A) \(3+2+1\)-Carbocyclization in the Dotz reaction [397-399]. B) \(\beta\)-Lactam formation through photochemical addition of an aminoalkene complex to an imine (Hegedus [390, 394]). C) \(2+2+1\)-Carbocyclization via a cobalt carboxyl-acetylene complex (Magnus [390, 401, 403]). D) Lactone formation by CO insertion into a vinylloxirane (Ley [390]).

Scheme 19. Aldol addition—from humble origins to undreamed of heights (the enantioselective variant is included in Sec. 7, Scheme 26). A) Development of the aldol reaction from an unselective process in protic solvents to a diastereoselective variant in non-polar medium at low temperature. B) Directed aldol addition (and increased enolate nucleophilicity) with enamides and enhydrazides [369]. C) In situ generation of unstable or highly reactive enolates via \(\alpha\)-Si carbonyl compounds, exemplified by a cyclopropanecarboxylic acid derivative [292, 370]. D) Aldol adducts and condensation products from aldols via enolates of \((2R,6R)-\)dioxanones [371]. E) Aldol addition (or is it a hetero-Diels-Alder reaction?) cyclization, elimination, and desilylation leads to dihydropyrans with synthetic utility. The Lewis acid-induced addition (LAC-DAC = “Lewis acid-catalyzed diene-alkyde cyclocondensation”) of a “double enol ether” to an aldehyde (stereoselectively in the case of a 1-substituted enone or a chiral aldehyde) has proven to be a veritable gold mine in the hands of Danishefsky and his group [372].

The high price and/or toxicity of many transition metals adds urgency to the ongoing quest for catalytic approaches to such transformations, even on the laboratory scale; this particular problem has recently been addressed in a review article. [435]

Scheme 21. Highly selective nucleophilic addition of Ti, Zr, and Ce reagents to carbonyl groups (cf. also Fig. 12). A) \(\alpha\)-Fluorophenyl trimisopropoxytitanium, stable at room temperature, adds nearly quantitatively to a dinitrobenzaldehyde [417] (cf. case A in Fig. 12). B) The non-basic reagent tetrakis(diethylamino)titanium (synthesis described in [274]) adds selectively to the aldehyde group in a formyl ketone, leaving only the keto group accessible to attack by a polar nucleophile [412]. C) Neither electron transfer nor base-induced retroaldol addition interferes with diastereoselective (>98% ds) addition of the methylzirconium reagent (74% yield) [413]. D) If all else fails, or if an absolutely foolproof method is required, then the answer today is transmetalation of a Li or Mg derivative with CeCl₃, prior to introduction of a carbonyl compound! [414].

Table 5. A few examples of transition-metal name reagents or reactions that in the last 20 years have come to be regarded as standard procedures. Excluded from consideration here are primarily industrial methods, such as hydroformylation or the Ziegler-Natta polymerization. Some of the reactions shown require stoichiometric amounts of the organometallic reagents, whereas others are catalytic (in some cases involving polymer-bound catalysts). Enantioselective transformations are discussed further in Sec. 7. The book [394] by Colman, Hegedus, Norton, and Finke includes pertinent references to all the examples shown.

<table>
<thead>
<tr>
<th>Name</th>
<th>Reaction/Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birch-Pearson</td>
<td>Fe tricarbonyl complexes of cyclohexadiene and other dienes for C,C coupling [390,396]</td>
</tr>
<tr>
<td>Crabtree</td>
<td>Ir hydrogenation catalyst for C,C double bonds (in the presence of other reducible groups)</td>
</tr>
<tr>
<td>Dozzi</td>
<td>Cr carbonyl-carbene complexes for annelation of aromatic rings [397-399]</td>
</tr>
<tr>
<td>Heck-Stille</td>
<td>Pd-catalyzed amination, vinylation, and CO insertions [400]</td>
</tr>
<tr>
<td>Hegedus</td>
<td>Cr carbonyl-carbene complexes and imines lead photochemically to β-lactams [390]</td>
</tr>
<tr>
<td>Horner-Knoles</td>
<td>Rh complexes with chiral phosphines (Wilkinson catalysts) for enantioselective hydrogencations of C,C double bonds</td>
</tr>
<tr>
<td>McMurty</td>
<td>Tp (&quot;low-valent&quot;) Ti for the coupling of two carbonyl groups directly to olefins [342b-d]</td>
</tr>
<tr>
<td>Mukasyama</td>
<td>TiX₄-mediated reactions of silylenol ethers with aldehydes, acetals, and Michael acceptors [311a,b]</td>
</tr>
<tr>
<td>Nicholas-Pettit</td>
<td>Co carbonyl-acetylene complexes as protective groups and precursors for cyclizations [401]</td>
</tr>
<tr>
<td>Noyori</td>
<td>Fe₂(CO)₉ for preparing oxallyl cations for use in [3+2]- and [4+3]-cycloditions</td>
</tr>
<tr>
<td>Noyori-Takaya</td>
<td>Rh-, Ru-catalyzed enantioselective hydrogenations of C,C double bonds [402]</td>
</tr>
<tr>
<td>Pauson-Khand</td>
<td>Co carbonyl complexes for the preparation of cyclopentenones with CO insertion [390,403]</td>
</tr>
<tr>
<td>Schwartz-Negishi</td>
<td>Zr reagent (Cp₂ZrHCl) for hydrozirconation of C,C double and triple bonds [404]</td>
</tr>
<tr>
<td>Sharpless</td>
<td>Ti(O₃Bu)₄ or ROH or tartrate for enantioselective epoxidation of allyl alcohols</td>
</tr>
<tr>
<td>Suzuki</td>
<td>Pd-catalyzed coupling of aryl and vinyl boron compounds with halides [405]</td>
</tr>
<tr>
<td>Tebbe-Grubbs</td>
<td>Ti/Al-carbene complex for methylation of carbonyl compounds (also esters, amides) [29]</td>
</tr>
<tr>
<td>Tsuji-Trost</td>
<td>Pd allyl complexes for C,C coupling, especially for cyclizations [406,407]</td>
</tr>
<tr>
<td>Volhardt</td>
<td>Co complexes for cyclotrimerization of acetylenes (also with the participation of nitrites) to aromatic systems</td>
</tr>
</tbody>
</table>

7. The Preparation of Enantiomerically Pure Compounds (EPC)

There is nothing faster than the years.
Ovid (43 B. C.–17 A. D.)

At the present time, almost no aspect of organic synthesis is generating as many publications as the preparation of enantiomerically pure compounds. At the present time, almost no aspect of organic synthesis is generating as many publications as the preparation of enantiomerically pure compounds. It is easy to predict that by the year 2000 this flurry of activity will have provided us with all of the following: a) simple approaches to the synthesis of enantiomerically pure chiral compounds.

Fig. 12. Three examples of yield and selectivity increases that can be achieved by transmetallation of Li and Mg reagents to Ti derivatives. A) A glance at the NMR spectrum of the crude product betrays the high yield obtained upon addition of the methyltitanium reagent to m-nitrobenzaldehyde [418] relative to addition of a Grignard reagent. B) A comparison of crude product gas chromatograms reveals the perfect selectivity of Me₂Ti vs. Me₂Li with respect to aldehyde/ketone addition. With the Li reagent, the rate of addition at the ketone is comparable to that at the aldehyde [274]. C) Crotyltitanium adds more selectively than the crotyl Grignard reagent to a mixture of benzaldehyde and acetophenone [273a].
representing all the known classes of substances; b) catalytic variants for every reaction in which achiral precursors lead to at least one element of chirality; c) corresponding methods suitable for industrial use on any desired scale; and d) much wider understanding of intermolecular interactions and the detailed course of reactions.

Why is it that enantiomeric compounds have moved so decisively toward the center of attention? One important factor is certainly the general recognition that living systems, which are themselves made up of chiral components, interact with enantiomers in different ways (as a result of diastereomeric relationships). This awareness has led to increasingly restrictive guidelines with respect to the registration of racemic mixtures of active substances (by the FDA, for example), which has in turn forced industry to amend its ways. Anyone who has had the occasion to sniff samples of both enantiomers of certain fragrances will not be surprised to learn that the fragrance industry has been one of the leaders in this development.

Ever since stereochemistry was in its infancy, experts—or perhaps one should say “the educated”—have understood the profound difference between enantiomers and racemates; Pasteur himself was able to show that microorganisms have no trouble distinguishing between (R,R)- and (S,S)-tartaric acid (Scheme 24).

Actually, there has been nothing fundamentally new discovered in this area during the 140 years since Pasteur took the first steps along the three basic paths to pure enantioselective reductive [4 + 2]-carbocyclization of o-phthalaldehyde with an alkyne to give a naphthol [429] (rs = regioselectivity).
7.1. Separation, Selectivity, or Incorporation—That is the (Gretchen) Question![*]

Which of the three routes one chooses to prepare an enantiomerically pure compound depends essentially upon the task at hand. The substance in question may be required on a tons-per-annum basis (as in the case of phenylalanine, lactic acid, or menthol). On the other hand, a few hundred kilograms per year might suffice for an expensive pharmaceutical agent, and pharmacological screening can be carried out with much smaller amounts. A research laboratory is more likely to need a few grams of one enantiomerically pure substance today and a different one tomorrow. If the problem is one of developing a new stereoselective application, or of completing a mechanistic investigation, a few hundred milligrams of a pure substance will probably serve the purpose. The greater the quantity of material required, the more important it becomes to recycle the unwanted enantiomer after a resolution, to recover an auxiliary introduced in stoichiometric quantities, to choose natural (renewable) chiral building blocks, or to develop efficient catalytic methods. The more limited and diverse the needs, the more flexible must be the methods with respect to product structure and to the chemistry involved; cost is not then an issue, as exemplified by the extreme case of a radioactively labeled material for use in metabolic studies.

The examples shown in Schemes 25–27 have been selected to demonstrate all three of the basic methodologies. Thus, heterocyclic glycine derivatives obtained through separation of enantiomeric mixtures (Scheme 25) facilitate the synthesis of non-proteinogenic amino acids, and this method of preparation is quite competitive with other approaches. By the way, the tert-butyl group responsible here for selectivity came from BASF, which supported our work with a generous...
Scheme 25. Glycine derivatives that are readily accessible by the separation of racemates and are useful in the synthesis of (R) or (S) amino acids. The oxazolidinones ($R=OBn$, aryl) are obtained by the chromatographic separation of enantiomers [137] (Fig. 1), and the imidazolidinones by crystallization of their mandelic acid salts [450] (recycling by heating). A versatile series of transformations [137, 353, 450, 451] leads ultimately to branched and unbranched non-proteinogenic amino acids with a wide “structural bandwidth.”

ous gift of pivalaldehyde (a byproduct in the hydroformylation of isobutylene, previously disposed of by burning!).

The collage of auxiliary groups for stereoselective synthesis shown in Scheme 26 is only a small sample, representing a few of the most successful reagents; most were prepared from inexpensive chiral precursors such as amino acids, ephedrine, 3-amino-3-phenylpropan-1,3-diol, β-hydroxybutyric acid, mandelic acid, tartaric acid, pantolactone, men-

Scheme 26. A selection of chiral auxiliaries for multistep enantioselective syntheses. The chiral auxiliaries included in this collage are attached to the reactive center of an achiral molecule by way of a covalent bond in order to carry out the various transformations A–Z. The point is to ensure that a diastereoselective reaction, followed by removal of the auxiliary, will lead to the isolation of product enriched in a single enantiomer. No attempt has been made to provide a comprehensive list of such auxiliaries. Color has been used to emphasize the sources of the various auxiliary reagents. To the best of my knowledge, those auxiliaries not depicted in color result from the separation of racemic mixtures.

Scheme 27. Products obtained through transformations of (R)-3-hydroxybutyric acid derived from the biopolymer PHB. In a formal sense, the β-hydroxy acids shown at the top constitute αdialdadducts of aldehydes or ketones with acetic acid, higher acids, or α-branched acids. Directly below these are the nucleophilic and electrophilic intermediates utilized for CC bond formation [183, 294, 353, 354, 371, 474–476]. It is clearly apparent that substituents can also be introduced at C-3 and C-4 of the hydroxybutyric acid without the occurrence of racemization (principle of self-regeneration of a stereogenic center [353, 477, 478]).
The long list of suggested applications for Evans’ acyloxyazolidinone is testimony to the profound significance of this particular reagent (cf., for example, the total synthesis of fujimycin). [511]

Finally, Scheme 27 illustrates a few transformation products derived from poly[(R)-3-hydroxybutyrate], which is prepared on a commercial scale by fermentation. Some of the compounds even contain quaternary centers, rendering them inaccessible in enantiomerically pure form by alternative methods. [479] Other applications of the incorporation method can be mentioned here only in passing. [480-482]

7.2. Catalytic Enantioselective Reactions: from Enzymes to Chemzymes

Even after casting off the phlogiston theory, chemists were (and remain today) fascinated by the synthetic achievements of nature, many of which can now be appreciated at the molecular level. The synthetic organic chemist typically regards nature’s achievements not only as a standard to be emulated, but also as a formidable challenge, especially from the standpoint of selectivity (above all enantioselectivity). A single enzyme molecule is capable of supervising the transformation of millions and billions of substrate molecules before it loses its own activity. When an achiral educt is converted enzymatically into a chiral product, the enantiomeric yield is of the order of 10-7-10-9%, at least according to the way some chemists prefer to make calculations of this type!

Lurking between the lines of the following three more or less prosaic utterances is a subtle mixture of anxiety and fascination:

“Lord, I fall upon my knees
And pray that all my syntheses,
May no longer be inferior,
To those conducted by bacteria.” [483]

“These new catalysts will be better than enzymes in that they will work under more flexible conditions than biological systems. Also, they don’t need to work in water and don’t have complicated cofactors and all this other garbage around that has to be gotten rid of when the product is purified.” [484]

“Chemzymes are small, soluble organic molecules that can catalyze certain reactions in much the same way that natural enzymes catalyze biochemical reactions. . . . Think of a submicroscopic production-line worker: over and over again, the chemzyme grabs a pair of reactant molecules out of the surrounding solution, twists them into position, welds them together into a precise three-dimensional structure, and then tosses the product molecule away to free itself for the next pair of reactants.” [485]

It is no wonder that synthetic chemists have frequently tried to make direct use of biochemical catalysts and countless standard laboratory methods have been perfected for the biological-chemical synthesis of simple compounds. Increasingly, however, various research groups are turning their attention to non-biochemical catalysis. In fact, there is a real atmosphere of discovery surrounding the subject of catalysis in organic synthesis, as evidenced by the recently released collection of essays Catalysis of Organic Reactions. [491, 492] It would appear that most of the true sorcerers in this field are located in Japan. The following sections constitute brief discussions of enantioselective catalysis—first with enzymes, and then without.

7.2.1. Biological-chemical Transformations

Biological-chemical transformations on both an industrial scale and in the laboratory can be carried out using either whole cells or isolated enzymes. In certain industrial applications it has even proven feasible to “optimize” the required organisms or enzymes, sometimes carrying it to the point of preparing azymes (Sec. 2.3). [1144] Unusual types of reactions or conditions may be invoked (again, after extensive optimization) in the effort to prepare specific products. All the following substances are currently being synthesized on a more or less large scale by fermentation techniques: [493] alkaloids and dyes (in plant cell cultures), [494, 495] cis-3,5-cyclohexadien-1,2-diol (using a dioxygenase) [231, 496] cyclosporin (with Tolypocladium inflatum Gans) [132] a copolymer based on (R)-3-hydroxybutyric and valeric acids (PHB/PHV, Biopol, with Hydrogenomonas eutrophica) [230] 2-hydroxypropionic acid (by lactic acid fermentation; used by BASF in the production of an agricultural product), penicillin (and other antibiotics), proteins (such as insulin and interferon, using Escherichia coli modified with the aid of gene technology), hydroxysteroids (using oxygenases), [497] vitamin C (l-sorbos, from D-sorbitol, with Acetobacter suboxidans), [1224] and tartaric acid. [332] A recently conducted analysis of publications and patents dealing with preparative applications and included in the 1987/1988 “Warwick Biotransformation Abstracts” demonstrated on the one hand that 40% of the reported transformations involved syntheses or reactions of esters, 25% were dehydrogenase-related procedures, and 24% had to do with peptide or oligosaccharide syntheses. Of the ester-cleaving enzymes employed (proteases, esterases, and lipases, enzymes that are available commercially), by far the most prevalent was pig liver esterase. Almost all the applications related to reduction involved whole cells; according to this source, half were carried out with baker’s yeast (Saccharomyces cerevisiae). Enzymatic enantioselective esterifications, transesterifications, and saponifications can clearly be regarded today as standard laboratory procedures. The reduction of carbonyl groups requires the presence of NADPH as a hydride donor, and in this case it is more common to take advantage of the metabolic capabilities of whole cells. Yeast for this purpose can be managed successfully without a bioreactor [499-501] at least with small preparations [487]

There are, of course, a great many tricks and variations applicable to biological-chemical reaction steps, but this is true for the “classical” methods of organic synthesis as well. [502] For example, simple reductions with yeast alone sometimes fail to produce adequate enantioselectivity, usually because of competition between a number of oxidoreductases. [503] The situation can often be improved by carrying out the reaction in the presence of additives, or by an expedient such as pretreatment of the yeast (e.g., “starving”). [504]
temporary modification of the substrate (cf. protective group techniques), or switching to an organic medium (e.g., the "microemulsion" method). Use of the easily cultured thermophilic microorganism \textit{Thermoanaerobium brockii}, which is most comfortable at 70–80 °C, may lead to advantages in both selectivity and convenience (sterilization of the apparatus is not required).

Methods have also been devised for improving the yield, selectivity, and isolability of the product in applications involving isolated enzymes or enzyme concentrates (pig liver esterase is often employed as a concentrate); examples appear under the first two entries in the alphabetical list in Chapter 4. Biological-chemical methods are currently used for synthesizing amino acids both on a large and a small scale. Here the enzymes themselves are immobilized on a solid phase or trapped within a membrane (dialysis tubing or a bag—permeable, for example, to molecules with a molecular weight less than 1000 daltons, i.e., to educts and products). Aqueous medium is not a disadvantage with amino acids—indeed, it is essential—but in other applications of biological-chemical methods insufficient polarity or lack of water solubility on the part of educt and/or product can often be a serious limiting factor. Organic solvents sometimes help, especially in transformations involving isolated enzymes, but this alternative is usually associated with a significant retardation in the reaction rate.

The biological-chemical reactions with the strongest appeal for synthetic chemists are those capable of converting achiral educts (or chiral educts that rapidly equilibrate through achiral intermediates) into a single enantiomerically pure product containing as many stereogenic centers and functional groups as possible. It is therefore appropriate to conclude the discussion with a few examples that fall in this category (Schemes 28–30). The easiest to carry out are based on enzymes that require no cofactors (other than metallic ions).

Even a cursory examination of the many "unnatural" compounds that have been successfully subjected to biological-chemical transformations reveals a remarkable degree of diversity, and one is forced to conclude that enzymes are amazingly "tolerant." Perhaps it is no accident that the most frequently utilized biological reagents have assignments in nature that also demand flexibility.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme28}
\caption{Scheme 28. Biological-chemical reactions involving enantioselective hydroxylation or C–C bond formation. A) The microorganisms capable of hydroxylating arenes to cyclohexadienols were discovered in a landfill in which aromatic compounds had been deposited. B) MBL, extracted from almond flour, catalyzes the cyanohydrin reaction to give the nitriles of \(-\text{hydroxy} \text{carboxylic acids}, a\ procedure that is effective with both \(N\)-alkyl and aromatic aldehydes. C) Formally speaking, this is a Michael addition of trifluoroethanol (d\textsuperscript{4} reactivity) to methyl vinyl ketone (oxidation of trifluoroethanol to an aldehyde and thiamine pyrophosphate umpolung?). D) Analogous reaction involving 1, 2-addition of acetaldehyde to cinnamaldehyde.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Scheme29}
\caption{Scheme 29. Compounds with the \textit{meso} configuration and other achiral educts containing enantiotopic groups can be ideal substrates for biological-chemical transformations. Subsequent to the enzymatic reaction it is almost always possible to invoke straightforward synthetic manipulations in order to prepare either enantiomer of the desired product.}
\end{figure}
Thus, liver esterases come from the mammalian organ most responsible for detoxification, and they have been shown to consist of isoenzyme mixtures; monooxygenases ("hydroxylases") owe their existence in part to the need for making hydrocarbons "metabolizable"; lipases promote cleavage of all types of fatty acid esters; and yeasts have "evolved" in such a way that they grow on a wide variety of culture media and under diverse sets of conditions.

**7.2.2. Enantioselective Catalysis: Bases, Phase Transfer, and the Ligand Spheres of Metals**

So far, the only popular, standard laboratory reaction that is both enantioselective and catalytic in nature is the Sharpless epoxidation. Not only does it employ inexpensive reagents (tert-butylhydroperoxide, titanate, and ethyl tartrate) and involve educts (allyl alcohols) and products (epoxides) that are ubiquitous in organic synthesis, but it also enjoys an unusually wide range of applicability because of insensitivity to many aspects of substrate structure (constitution, configuration, chirality). Selection of the proper chiral form of the starting tartrate ester allows one to establish both the chirality of the product and/or its relative configuration. An example of a simple enantioselective epoxidation is presented in Scheme 31.

Enantioselective hydrogenations and hydrogen shifts catalyzed by phosphine complexes of rhodium and ruthenium (Scheme 31) are not quite so straightforward on a laboratory scale, nor are they as easy to reproduce, but they do have broad applicability. Looking at the conditions required for the reduction of acetoacetic ester to (R)-3-hydroxybutyrate (Scheme 31) one cannot help but wonder what process will triumph for large-scale preparation of this important hydroxy acid (useful, for example, in the synthesis of thienamycin): the catalytic transition-metal approach or one of the fermentative methods mentioned previously. The "volume yield" criterion (i.e., mass of product obtained per unit volume of reactor) argues for the non-biological procedure.

Scheme 32 illustrates a few other standard organic reactions that can be induced to proceed in a catalytic and enantioselective way by the addition of transition-metal complexes. Brief mention should also be made of two catalytic processes that do not involve the ligand spheres of metals: a phase-transfer route to enantioselective amino acid synthesis and the cycloaddition reaction of ketene with α-halogenated aldehydes to give β-lactones, catalyzed by cinchona alkaloids.
precisely those enantioselective catalytic reactions that are most successful were either discovered accidentally or resulted from years of effort devoted to optimization. Even though it has sometimes been possible to discern the mechanism of a catalytic reaction—the recently proposed mechanism for the Sharpless epoxidation is a case in point—the rational design of a structurally defined chiral catalyst is still in its infancy. A noteworthy example of such an effort is mentioned near the end of this discussion.

One group of enantioselective reactions has been the subject of special attention in recent years. I am referring to reactions in which organometallic compounds that are normally unreactive toward aldehydes and ketones can be activated by catalytic amounts of a chiral amino alcohol so that they undergo enantioselective carbonyl addition. Organometallic agents of this type include alkyl and alkyl lead derivatives, but most interesting perhaps are the boranes and borates. The latter have the advantage that their reactions seem to lend themselves best—to rationalization on the basis of mechanistic models. Alkyl, alkoxy, aryloxy, and dialkylamino groups are kinetically more tightly bound to boron than to other metallic centers, inhibiting dynamic processes that might otherwise result in ligand-exchange reactions. More important, however, one can rely on the fact (thanks to the octet rule!) that boron will never associate with more than four ligands, and that the ligands will be arranged tetrahedrally. With the single exception of beryllium, whose toxicity has so far prevented its application in organic chemistry, all other metals are capable of supporting as many as six (or more!) ligand sites, characterized (depending upon valence and placement in the periodic table) by tetragonal planar, tetrahedral, trigonal bipyramidal, tetragonal pyramidal, or octa-

![Scheme 32. Some examples of enantioselective reactions catalyzed by transition metals. A) Hydroxylation with osmium tetroxide, accelerated and made enantioselective by the presence of a cinchona alkaloid [544]. B) Hydrogenation of an α,β-unsaturated ester with NaBH₄/chiral-Co catalyst (ligand based on pyroglutamic acid) [490e]. C) Cyclopropanation with diazaacetic ester [copper(n)/chiral-semicorrin ligand] [490e]. D) The gold complex of a complicated chiral-ferrocene ligand catalyzes the addition of isocyanosacetic ester to benzaldehyde, leading to a three-phenylenediyil derivative [545]. E) A ligand derived from tartaric acid belonging to their discipline. It is also remarkable that...](image)

It is interesting to note that many reactions called “catalytic” in the literature actually require the addition of rather large amounts of the alleged catalyst. For example, consider a benzylated or benzoylated quinine derivative with a molecular weight of over 400 daltons. If 0.1 mole-equivalent of such a material were to be utilized in a transformation leading to a product with a molecular weight of 120, then the substrate/catalyst relationship would be such that few true catalysis chemists would be willing to regard the reaction as belonging to their discipline. It is also remarkable that...
Table 6. Reductions of ketones with the boranes a and b of Scheme 33 and the chiral catalysts c-g.[567] Even the purely aliphatic substrate cyclohexyl methyl ketone undergoes reduction with an enantioselectivity as high as 95:5. In the last case the borane in question (b) contained D in place of H.

<table>
<thead>
<tr>
<th>Product</th>
<th>Borane</th>
<th>Catalyst</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>formula</td>
<td>yield</td>
<td>ee</td>
<td>equiv.</td>
</tr>
<tr>
<td>H</td>
<td>&gt; 99%</td>
<td>97%</td>
<td>a</td>
</tr>
<tr>
<td>MeOCH(CH$_2$)$_2$</td>
<td>quart.</td>
<td>97%</td>
<td>a</td>
</tr>
<tr>
<td>HO</td>
<td>&gt; 90%</td>
<td>95%</td>
<td>a</td>
</tr>
<tr>
<td>HO</td>
<td>96%</td>
<td>97%</td>
<td>a</td>
</tr>
<tr>
<td>HO</td>
<td>&gt; 95%</td>
<td>93%</td>
<td>b</td>
</tr>
<tr>
<td>HO</td>
<td>91%</td>
<td>90%</td>
<td>a</td>
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<tr>
<td>HO</td>
<td>88%</td>
<td>93%</td>
<td>a</td>
</tr>
<tr>
<td>HO</td>
<td>90%</td>
<td>91%</td>
<td>b</td>
</tr>
</tbody>
</table>

hedral geometries. Finally, BC, BO, and BN bonds are shorter than the corresponding bonds to carbon,[556] so that the groups bonded to boron approach each other more closely than in the case of boron-free systems, and considerably more closely than in compounds with other metals, permitting steric (van der Waals repulsion) and polar interactions (Coulomb forces) to play a more effective role.[557] The currently favored mechanistic model for enantioselective borane reduction of aromatic and α,β-unsaturated ketones with various chiral catalysts has been proven so reliable in explaining all the observed experimental results that Corey allowed himself to be seduced into inventing the word “chemzyme”, a term already alluded to several times in this contribution.[12b, 64, 485, 558] Scheme 33 and Table 6 provide several examples of this type of borane reduction along with the proposed mechanism.

8. Concluding Remarks

Teach me the glorious lesson that occasionally it is possible that I may be mistaken
"Prayer of an ageing woman", ascribed to Teresa of Ávila (1515-1582)

In presenting a paper or a talk, nothing is worse than beginning with a bad title, and the worst titles are ones that promise too much! I hope my contribution does not fit in this category, though I confess that the last part of the title ("Where now?") caused me to lose a certain amount of sleep and suffer several crises of conscience.

The effort will not have been wasted if I have convincingly swept away the one-sided but prevalent notion that organic chemistry and organic synthesis are mature sciences. On the contrary: they are neither stagnating, nor are they on the decline! The general directions I expect our disciplines to take in the future are apparent in the structure of the presentation itself and in the summary at the beginning. The topic treated last—preparing enantiomerically pure compounds, in particular with the aid of enantioselective catalysis—is one I would especially like to have discussed in more detail, but time and space constraints have made this impossible.

My time will also have been well spent if the roughly 1000 literature references prove to be stimulating, especially for my younger colleagues. I hope those readers who find the limited and very personal selection of topics unbalanced, or who regard the mode of presentation as awkward or somewhat “gauche” (Fig. 14), will nevertheless take to heart what
extent of chemical methodology's contributions to other disciplines it is tempting to take the charge that chemistry is in danger of losing its identity[2] and turn it around, proclaiming instead that chemistry—today more than ever before—is "the central science" (Scheme 34) [56b] What a change from the days when Albertus Magnus (1193–1280) in his tract "De Alchemia" placed at the head of the list of essential characteristics for an alchemist:

He must be taciturn and circumspect, and should communicate to no one the results of his operations.

This article could not have been written without the help of a great many coworkers: Albert K. Beck (library), Silvia Sigrist (preparation of the manuscript), Linda Behrendt (figures, schemes, tables); Josef Meienberger (departmental librarian) and Christoph von den Bussche Hunnefeld (literature searches); Bernd Lamatsch and Dietmar Platter (structural data); Stefan Blank, Dennis Blaser, Richard Breitschuh, Urs Gysel, André Jeanguenat, Axel Neidlein, Christof Schickli, and Adrian Thaler (preparation of drawings and figures); as well as the rest of the group for checking in the library all the names and numbers in the bibliography. I offer all of you my heartfelt thanks; it is a real pleasure to be surrounded by such a host of talented and motivated young people.

I also wish to thank those colleagues who have supplied me with information, data, drawings, or figures for use in this article (see also the acknowledgments in the legends and the list of references): E. Bayer (Tübingen), G. Boche (Marburg), Z. Brich (Sandoz, Basel), E. C. Constable (Cambridge, U. K.), R. R. Ernst (Zürich), A. Eschenmoser (Zürich), E. Galantay (Sandoz, Basel), J. Hajdu (Oxford), D. Hilvert (La Jolla), B. L. Karger (Boston), P. T. Lansbury (Boston), R. Noyori (Nagoya), L. E. Overman (Irving), Sir D. Phillips (Oxford), J. F. Stoddart (Sheffield), W. F. van Gunsteren (Groningen), E. Vedejs (Madison), E. Zass (Zürich).

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Translated by Dr. W. E. Bussey, Huntington, PA (USA)


[11] In 1985 the Pimentel Report [12a] came to the conclusion that five priorities should be established within the areas of chemistry. The first two are related to synthesis: a) Understanding Chemical Reactivity: ("We propose an initiative to apply the full power of modern instrumental techniques and chemical theory to the clarification of factors that control the rates of reactions and to the development of new synthetic pathways for chemical change"). b) Chemical Catalysts: ("We propose an initiative to apply the techniques of chemistry to obtain a molecular-level and coherent understanding of catalysis that encompasses heterogeneous, homogeneous, photo-, electro- and artificial enzyme catalysis").


[14] a) Corey's original definition of synthetic [15] was very useful in the context of retrosynthetic analysis, but the expression has now degenerated into one that is applied to synthetic intermediates. As a result, Corey himself no longer employs it at all—in the book cited previously [16], for example, which deals with all of his work to date! b) "Retrosynthetic Thinking—Essentials and Examples" (Robert Robinson Lecture). E. J. Corey, Chem. Soc. Rev. 17 (1988) 111–133.


[16] "Sulfidkontraktion via alkylative Kupplung: eine Methode zur Darstellung von β-Dicarbonylderivaten": M. Roth, P. Dubs, E. Götschi, A.


[26] It is no wonder that one often leaves a lecture or a symposium in which “something else has just been synthesized” with a feeling of boredom coupled with a sense that the same lectures could just as well have been delivered 20 years ago! b) Nowadays the synthetic portion of a lecture is sometimes delivered almost in an apologetic tone: “it has to be done, but it’s not exciting, so let’s get it over with”. Not long ago a well-known young synthetic (organic) chemist observed as part of the introduction to a lecture that people like himself now represent “a dying breed”.


"Biopolymers" (1987) 23-42.


There recently appeared a book full of ideas and encouragement with respect to this theme, including nearly 100 key references: R. Hoffmann, Solids and Surfaces, A Chemist's View of Bonding in Extended Structures, VCH Verlagsgesellschaft, Weinheim 1988.


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As an outsider one has the impression that specialists take it for granted that reactions of "normal" compounds won't work with fluorine derivatives; if they do succeed, the astonishing news warrants immediate publication! A few personal experiences would suggest that one should be prepared for anything with even the simplest reactions—a thrilling prospect, see [94–97] (cf. also Chapter 4, "Aliphatic Fluoronitro Compounds", in [105a]).


[93] The physical and spectroscopic data listed here, as well as the bond angles and bond lengths, have been taken from standard textbooks, monographs, and reference works. Bond lengths from X-ray structural data: a) [95a].


1355


[90] The growing interest in fluorine chemistry is documented by the steadily increasing number of publications in the area. The following diagram was designed on the basis of publications covered by Chemical Abstracts in the period from Jan. to conformational fixation ("turn mimetics") in 1983. However, recent literature gives little indication that reactions of "normal" compounds won't work with fluorine derivatives; if they do succeed, the astonishing news warrants immediate publication! A few personal experiences would suggest that one should be prepared for anything with even the simplest reactions—a thrilling prospect, see [94–97] (cf. also Chapter 4, "Aliphatic Fluoronitro Compounds", in [105a]).

1184. Wiley, Chichesrer 1987, pp. 539-621; E. W. Colvin: Silicon in Organic Synthesis, Structure in Table 3; b) an extensive collection of pentakoordinierten Siliciumver-


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“Structural Studies on Macromolecules and Viruses with Laue Diffrac-

tion.” J. Hartel, Lecture in the Physical-Chemical Colloquium of the ETH Zürich, 28 March 1990. I wish to thank Dr. Hajdu and Professor Philips (Oxford) for stimulating discussions. I am grateful to Dr. Hajdu for the Laue diffraction pattern shown in Fig. 5 and the data in the caption.
The use of force field methods with the full set of parameters (Macro-
M. R. Peterson, R. A. Poirier. "The Cambridge Crystallographic Data Centre:
Sec. B 35 (1979) 829.

(1991)


(1982).

Evans-Sutherland Picture System)

M. R. Peterson, R. A. Poirier. "The Cambridge Crystallographic Data Centre:
Sec. B 35 (1979) 829.

(1982).

Evans-Sutherland Picture System)

M. R. Peterson, R. A. Poirier. "The Cambridge Crystallographic Data Centre:
Sec. B 35 (1979) 829.


[28] Chiral Li amides, used in preparing enolates and for other lithiations. Also references cited therein.


[30] For recent general reviews of Si chemistry in organic synthesis see [109].


[335] a) "Intramolecular [4+2] and [3+2] Cycloadditions in Organic Synthesi-


[1363]
**Enantiomerenreine Naturstoife und Pharmaka aus billigen Vorliiufern**


We suggested in 1980 use of the abbreviation "EPC synthesis" as a generic term for the preparation of enantiomerically pure compounds.

Stereochemical Control in Organic Synthesis": S. Masamune. W. Choy, Oochirul:


As if there were not already enough periodicals-and it were not already tolerates combinations like "married name" and "fishing pond"), they comparing the chirality of molecules in the unit cell of a crystal, but it is now considered appropriate to the chiral auxiliary [(q'-C,H,)Fe(CO)(PPh3)]:


I wish to thank Professor Royoi Noyori most sincerely for providing me with manuscript copies prior to their publication [42], as well as for the chromatogram of the "complex mixture" of "mixture compounds", or a pair of chiral molecules in the unit cell of a crystal, but it is now considered appropriate for describing a flask full of (+)-tartaric acid (lo3 molecules per mole)'.


We suggested [352] in 1980 use of the abbreviation "EPC synthesis" as a generic term for the preparation of enantiomerically pure compounds. While there might be disagreement over the definition of "purity" (which is dependent above all on the sensitivity of the analytical methods employed), the terminology is otherwise unambiguous. Expressions like "homochiral compounds" [437] or "sooichiral compounds" [438] are unfortunate in several respects. Thus, "homochiral" has long been used in describing the ratio of two similar compounds, or a pair of chiral molecules in the unit cell of a crystal, but it is now considered appropriate for describing a flask full of (+)tartaric acid (10^6 molecules per mole).

"Asymmetric synthesis" and "racemic synthesis" have also become common; while these may be permissible in English (which also tolerates combinations like "married name" and "fishing pond")", they certainly cannot be translated directly into German. The equally correct expression "chiral, not racemic" is more awkward than "enantiomerically pure". Finally, let me urge that the matter not be carried too far; in most cases all that is required is judicious use of R or S.


Stereochemical considerations with respect to preparation of a new edition of the classic textbook of stereochemistry by E. L. Eliel.


A missiological in this field is E. J. Arias [Ear J. Clin. Pharmacol. 26 (1984) 663], who has suggested the terms "eutomer" and "dutomer" (the good and the bad isoforms) to classify active and inactive enantiomers.


Numerous pheromones have been prepared by Mori and coworkers starting with 3-hydroxybutyric acid, as well as with 3-hydroxyvaleric acid, in the Pheromone Field (see also the preparation of polyphenylene [231] and enantiomerically pure diols of this type from substituted arenes by ICI in England. Recent review articles: D. W. Blackburn (Ed.): Catalysis of Organic Reactions, Marcel Dekker, New York 1990. See also the Journal of Molecular Catalysis, published since 1975, and a recent review article: "Enzyme as a tool in Catalytic Asymmetric Reactions Probed by Transition Metal Complexes"; I. Ojima, N. Clos, C. Bastos, Tetrahedron 45 (1989) 6901–6939; e) a particularly useful review because of the inclusion of representative procedures and numerous citations: "Enantioselective Catalysis with Chiral Cobalt and Copper Complexes": A. Pfaltz, Mod. Synth. Methods 5 (1989) 199–248.


Deugas utilizes membrane techniques [233, cf. also [511]. Nevertheless, much of the data of the amino acid output is derived from protein hydrolyzates (animal skin, hair, horn, or feathers, or protein-containing material from plants) [233].


An entirely different case in which the change to an organic solvent proved crucial is the enantioselective cyanohydrin reaction catalyzed by mandelonitrile benzaldehyde ylde (MBL) and discovered by Pfalz [252]. A. Fuchsberger, T. Ziegler, S. Föster, ibid 99 (1987) 491 and 25 (1987) 458; J. Brusewitz, E. C. Roos, A. Van Der Gen, Tetrahedron Lett. 28 (1987) 6391; see Scheme 28, B.

Another case I would prefer to regard as a “youthful sin” (cf. Scheme 24b) is my suggestion [352]—taken up by many others as well—that this process be designated the "meso trick". Such expressions really should be confined to the important—real laboratory jargon.

I now deliberately refrain from using the terms prochiral (let alone “pro-"prochiral”) and prostereogenic: They have contributed too much to a state of confusion (e.g., “prochiral hydrogen”, “prochiral ketones”), and they are unnecessary. See also the remarks in the caption to Scheme 24b, the comments in [529], and CIP nomenclature [552]. The thoughts expressed on the subject by Mislow [552] (“Stereoisomerism and Local Chirality”); K. Mislow, J. Siegel, J. Am. Chem. Soc. 106 (1984) 3139] derive more from fundamental and theoretical considerations than from practical concerns.


... or might one here employ the adjective promiscuous?" Cf. the classical picture of the "key and keyhole".


This has been designated as "reagent control" [357]; in contrast to "substrate control". In German it would have to be expressed as "durch das Reagens gesteuert". I well remember the sermon on a similar theme by my thesis advisor Rudolf Criegee, who was at that time editor of Chemische Berichte: "Es muß heißen kinetisch oder thermodynamisch gesteuert, nicht kontrollierte Reaktion, Kontrolle hat im Deutschen eine vom Englisichen 'control' verschiedene Bedeutung!" From the fact that the term "stereocontrol" is about to replace "stereoselectivity", we may conclude that now everything is "under control".


One should also note that it has become common to speak of Lewis acid-catalyzed reactions even when equimolar amounts or even large excesses of SrCl₂, TiCl₄, or BF₃-either are added, in which case the Lewis acid could be regarded as a "catalytic" component.


See, for example, the semicronic ligand proposed for transannular-metallic catalyzed reactions by Putter [490a], as well as the work of C. Schirmer and C in Scheme 32.

So far, the addition of alkylzinc compounds with high enantioselectivity has been successful only with aromatic aldehydes; a) first examples with very high selectivity: M. Kitamura, S. Koga, K. Kawai, R. Noyori, J. Am. Chem. Soc. 108 (1986) 6071; b) application of pyrrolidine ligands: E. J. Corey, P. W. Yuen, F. J. Hannon, J. Org. Chem. 59 (1994) 784; c) highly effective (down to 10⁻⁹ equiv.) catalysts for dialkylzincs reactions to benzaldehyde are prepared from tetraisopropylsilane and the diri-

With few exceptions, lithium also does not exceed the limit of four tetrahedrally oriented ligands; see [117] and references cited therein. Higher coordination numbers with this element appear to result largely from ionic interactions.

Mean lengths for the bonds [Å] between N, C, and O and a number of the metals that are important in synthetic applications:

- Li-N 2.11(8)
- Li-C 2.214
- Li-O 2.0(1)
- B-N 1.404
- B-C 1.597
- B-O 1.367
- C-N 1.469
- C-C 1.530
- C-O 1.426
- Mg-N 2.21(7)
- Mg-C 2.15
- Mg-O 2.11(6)
- Al-N 1.94(5)
- Al-C 1.97(3)
- Al-O 2.04(9)
- Ti-N 2.296 (Ti-C see below Ti-O 2.205)
- Zn-N 2.159
- Zn-C 1.964
- Zn-O 2.093
- Sn-N 2.24(6)
- Sn-C 2.12(2)
- Sn-O 2.7(1)

Commentary: The average bond lengths for pure B/C/N/O-compounds are taken from [102a]. Average bond lengths for Ti and Zn compounds are derived from [102b] and apply to compounds containing a metal bonded to a methyl group, or complexes with aliphatic amines or aliphatic ethers. In the case of the Ti-CH₃ group only two widely divergent values have been reported (1.969 and 2.206 Å). The rest of the data values have been reported (1.969 and 2.206 Å).

The amino alcohols used for preparing the catalysts were derived from N-protected proline esters and phenyl or naphthyl Grignard reagents. The diphenylmethanol group has proven effective as part of a chiral auxiliary in other cases as well (M. Brau in [331d], Schemes 14, 22 [275]). For the use of other 2-hydroxymethylpyrrolidine or "prolinol" derivatives in enantioselective synthesis see also Scheme 26, chapters 11 and 14 of [331a], and D. Seebach, H.-O. Kalinowski, B. Bastam, G. Crass, H. Daem, H. Dorr, W. P. du Preez, V. Ehrig, W. Langer, C. Nussler, H.-A. Schmidt, Heiz. Chem. Acta 60 (1977) 301.

The prophetic observations of Woodward in his famous 1956 essay on the subject of "Synthesis" [39] remain just as valid today. On the other hand, it was left to a magician like Stork to propose a time scale: "So it is not surprising that organic synthesis is far from the level that many people assume. Progress is continuing, but there will not be any dramatic developments. It is more like a glacier that gradually moves forward until it has

Additionally, it was noted that chemical Control of Organic Reactions with Chiral Organoboron Reagents": S. Masamune in W. Bartmann, K. B. Sharpless (Eds.): Stereochemistry of Organic and Bioorganic Transformations, Workshop Conference Hoestadt, Vol. 17, VCH Verlagsgesellschaft, Weinheim 1987, pp. 49–72.