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 specific 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 untrennbar 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!
(Addressed 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, impending 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-

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[**] The list of references is also available upon request in the form of a Microsoft Word* file on diskette.

[***] "He showed us through his scientific life that chemistry cannot be exploited fully with the aid of a *single* theory or a *single* methodology, and that it is a field in which knowledge and application are inextricably linked." G. Bugge: *Das Buch der großen Chemiker, Vol. 2*, 4th reprint, Verlag Chemie, Weinheim 1974.

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 groundbreaking or of a more routine nature, synthesis and analysis are crucial to every chemist's activities.

1.2. Organic Chemistry in Crisis?

The biologists usually pick out the raisins, while the chemists are left to do the foot-work.
(The observation of a young researcher immediately after a postdoctoral experience in a research group concerned with the chemistry of DNA)

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.[1] Even so, it is somewhat surprising to see an educated layman like the editor of *Nature*, *John Maddox*, declaring[2] 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.[3] It is also sad to find respected colleagues referring to organic chemistry, and specifically to organic synthesis, as a "mature" science.[4] 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[5] if not the structural analysis of a macromolecule? Is a DNA-[6, 7] or peptide-synthesizing machine[8] 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.[14]

2. Old and New Target Structures in Organic Synthesis—Not Simply a Matter of Fashionable Trends!

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 (organo*metallic* compounds, perhaps, or the more classical "organo*elemental*" 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."

must add, thanks to the initiative of *E. J. Corey*,[15, 16] c) the directed search for reactivity, including attempts to realize specific desirable synthetic transformations (an approach that gave birth to the terms *synthon*,[17] *retron*, and *transform*[16]), as well as systematic *umpolung* of known modes of reactivity.[18] 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.[36–45] 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[46–51] only prove the rule (cf. Scheme 2).

Natural target molecule

Vitamin B 12

Non-natural target molecules

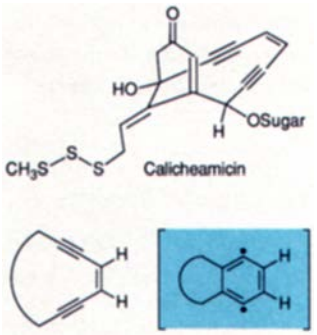
Olefination of a carbonyl compound

$$Y\text{–}CH_2X + O{=}CR_2 \longrightarrow H_2C{=}CR_2$$

Synthetically equivalent reagents

Umpolung of nitroolefin reactivity

Scheme 1. New synthetic methods have arisen as "by-products" of natural product syntheses (sulfide contraction [19, 20]), as well as in the course of preparing such unusual, non-natural substances as tetrahedrane [21], prismane [22], cubane [23], dodecahedrane [24], and centrohexaindane [25]. Olefinations have resulted from a preoccupation with heteroatom-substituted organometallic reagents [26–30]. Nucleophilic acylation via dithianes [31], doubly metallated nitroalkanes [32] or cyanohydrin derivatives [33, 34], and umpolung of a nitroalkene to a super-enamine [35] all owe their discovery to systematic searches.



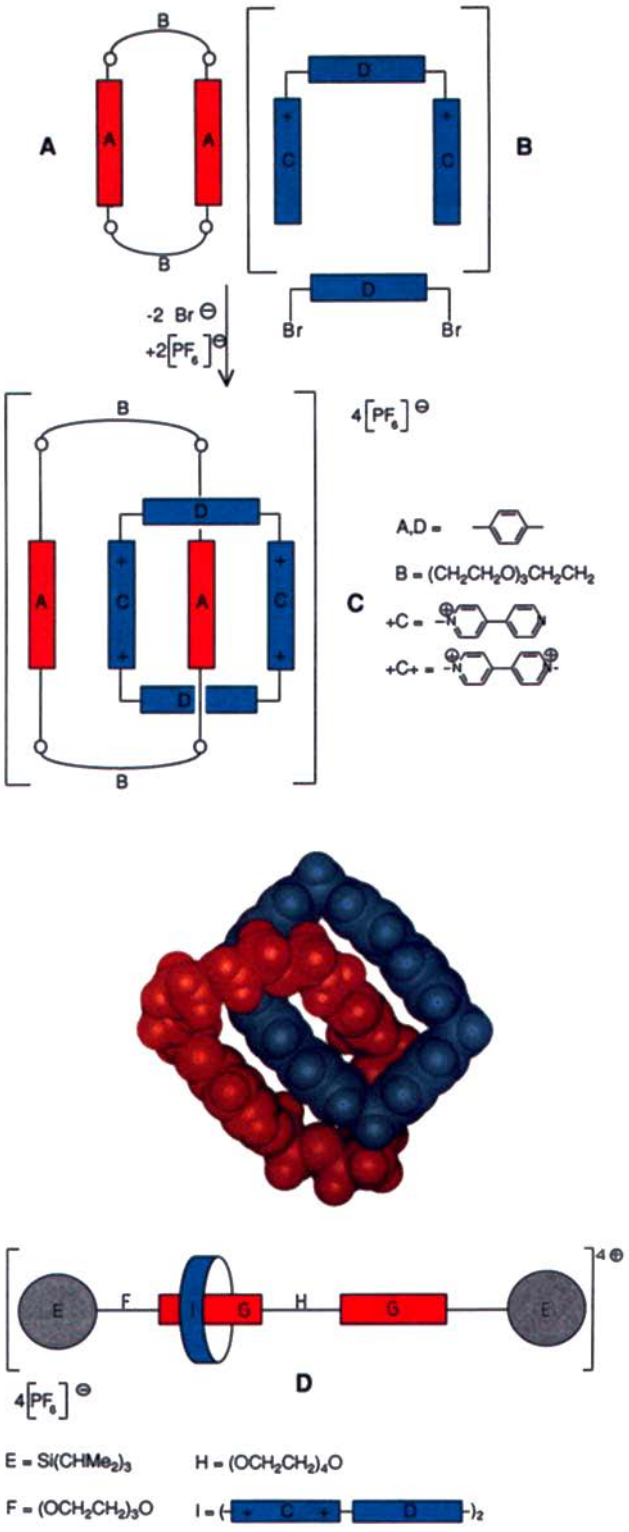
Scheme 2. A novel natural product system containing the *cis*-en-diyne moiety. Several derivatives with this characteristic skeleton have now been isolated (neocarcinostatin [46], esperamycin [47a], calicheamicin [47b], dynemicin A [47c]). The high antitumor activity of these compounds is based [48] on an elegant initiation of the illustrated ring-closure reaction to give an aromatic diradical (1,4-dehydrobenzene [49]), which reacts with a nucleotide unit of DNA to cause chain cleavage. Numerous synthesis-oriented research groups in the USA are busy trying to develop a synthesis of this natural system, and especially of simpler analogues [50].

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.[52a] 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.[52b]

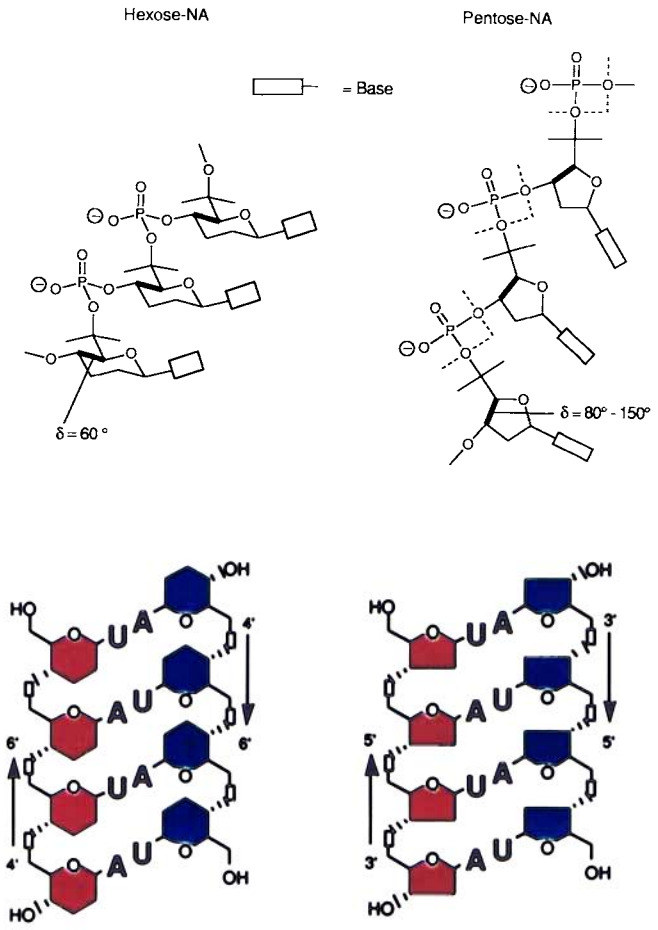
How can we characterize the new generation of appropriate target structures for organic synthesis? In answering this

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 "supermolecules", to use *Lehn*'s terminology);[53] 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,[61] 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),[65] synzymes,[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,[69] 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.

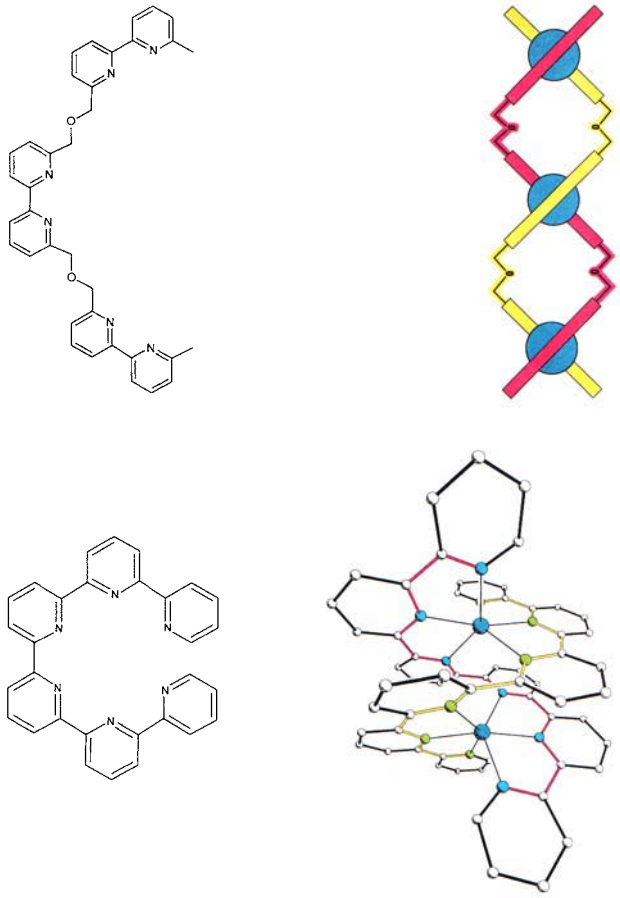
The exciting synthetic targets today are no longer molecules to be prepared "for their own sake"; instead, they are systems associated with particular functions or properties (cf. Scheme 6). Organic chemists are busy designing new materials,[10, 73, 74] and not only within the context of polymer chemistry,[9, 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: acetal 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 ($\Delta G^{\neq} = 54.3$ kJ mol^{-1} in [D_6]acetone). The authors [60] call the system a "molecular shuttle".



Scheme 4. 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 5. "Inorganic" double helices constructed from doubly methylated, CH_2–O–CH_2-bridged bipyridine ligands and copper(I) ions (top) [53] 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 Kröhnke reaction [72].

Molecules with the following

Form:		Function:	
- ball bearings	- knots	- abacuses	- nuts and bolts
- beads and threads	- ladders	- capacitors	- resistors
- belts	- nets	- catalysts	- screws
- cages	- springs	- circuits	- semiconductors
- chains	- stacks	- clocks	- sensors
- chimneys	- strips	- conductors	- shuttles
- clefts	- washers	- dynamos	- superconductors
- coils	- wires	- membranes	- switches
- collars		- motors	

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

Für die Biochemie braucht man mindestens so viel organische Chemie wie für die organische Chemie.[*]
L. Ruzicka (1964)

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).[77] At the same time, NMR spectroscopy is being used to carry out protein studies in solution, an approach supported by powerful computer modelling 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.[78, 79] 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)*:[80] 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.[81, 82] 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[83] (useful for reducing cholesterol levels) as well as in syntheses of statin[84] and other rhenin inhibitors (which act to lower the blood pressure).[85] Interest in the latter has resulted in an active demand for novel approaches to non-proteinogenic amino acids,[86] peptides, and their analogues (cf. Sec. 7).[87]

[*] "Biochemistry requires at least as much organic chemistry as does organic chemistry."

Organofluorine compounds frequently play a role in the synthesis of inhibitors, substrate analogues, so-called enzymatic or metabolic probes, antimetabolites, "transition state analogues",[88a] and suicide substrates or inhibitors.[88b] Indeed, there has recently been a real "boom" in this field,[89, 90] producing considerable research activity in both academia and industry. This will certainly lead to improved methods for the synthesis of organofluorine compounds,[91, 92] but it will also provide a deeper understanding

Bond energy *[kJ mol^{-1}]*

C-H 416 C-F 485 C-Cl 328

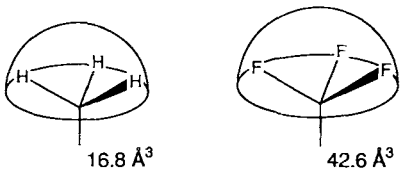
Bond length *[Å]*

C-H 1.09 C-F 1.38 C-Cl 1.78

Van der Waals radius *[Å]*

CH_3 2.0 CF_3 2.7 CCl_3 3.5 $C(CH_3)_3$ 3.5

Van der Waals volume *(hemisphere [Å^3])*



Electronegativity *(according to Pauling)*

H 2.1 C 2.5 Cl 3.0 F 4.0

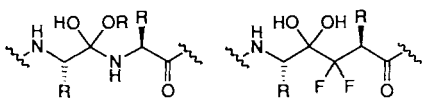
Polarizability *(for CH_3X [10^{-24} cm^3])*

H 2.59 F 2.97 Cl 4.72 Br 6.03

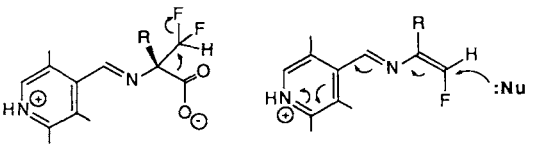
Magnetic properties *(relative sensitivity)*

^{1}H (Spin 1/2) 1.00 ^{19}F (Spin 1/2) 0.83 ^{13}C (Spin 1/2) 0.016

Competitive inhibition



Suicide inhibition

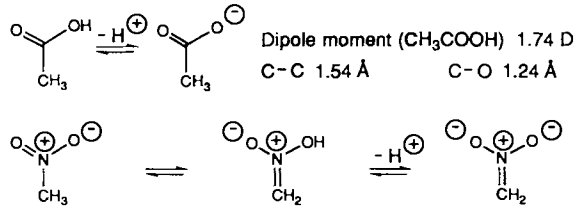


Scheme 7. Characteristic features of organofluorine compounds [91, 92]. The C–F bond is particularly strong; of all the bonds involving carbon, the C–F bond is the shortest apart from C–H; despite the fact that a CF_3 group has nearly twice the van der Waals volume of a CH_3 group, it is still capable of replacing the latter statistically in crystals (solid solutions [94a]); the C–F bond is extremely polar, but is nevertheless stable under most conditions; fluorine has a very high electronegativity, but fluorine compounds are very volatile; and substitution of CH, CH_2, or CH_3 by CF, CF_2, or CF_3 increases the lipophilicity of a compound (low polarizability of the fluorine electrons). On the other hand, fluorine substitution has enormous effects on the characteristics of functional groups: pK_a (C_2H_5OH) 16, (CF_3CH_2OH) 12.4; i.e., the trifluoro alcoholate is stabilized by 21 kJ mol^{-1} [92]; the introduction of F-substituted aromatic rings into pharmaceutical agents usually causes little change in general characteristics, but it leads to inhibition of oxidative metabolism (increased bioaccessibility, reduced dosage, patent "jumping"; the first fluorine-containing drugs were *Fried*'s fluorosteroids [98]); α-CF_2 ketones exist as hydrates in aqueous solution (cf. the similarity between the resulting hydrate and the tetrahedral intermediate of a peptide serinase-cleavage [92], 99]); α-difluoromethyl amino acids [91d] act as irreversible inhibitors ("suicide inhibitors") in that they lead to formation of a Michael acceptor at the active site of the enzyme responsible for pyridoxal phosphate metabolism (by nucleophilic addition to a neighboring group in the protein [100]). The magnetic properties of the ^{19}F nucleus facilitate the investigation of receptors and metabolic phenomena without interference from other magnetic nuclei [101]. (For sources of the data on fluorine compounds generally see [102].)

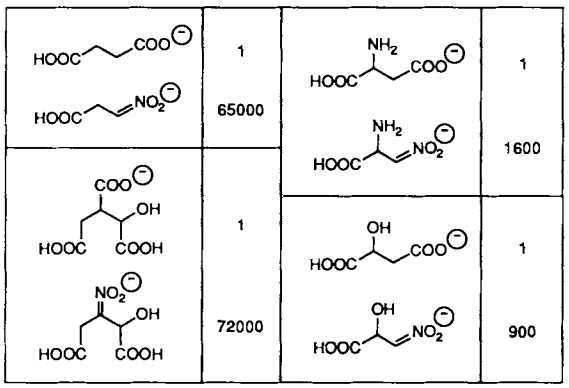
of the effects of fluorine on physical properties and of the frequently unexpected reactivity of this class of compounds.[91-97] A few aspects of the subject are illustrated in Scheme 7. The hectic state of activity in this field and the surprises that often emerge from what should be the simplest transformations of fluorine derivatives make it hard for me to resist coining a new term: *flustrates* (≡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



Relative binding constants of carboxylate enzyme substrates and their nitronate analogues



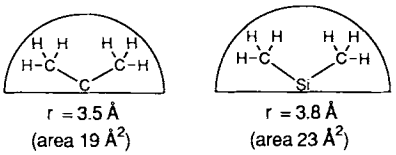
Scheme 8. A comparison of the nitronate group with the carboxylate group. According to [103], nitronate effectively mimics the characteristics of carboxylate with respect to geometry, polarity, and charge. Despite the great polarity of the nitro group [102], nitroaliphatics behave as non-polar compounds—in chromatography over silica gel, for example (NO_2 is a poor candidate for hydrogen bonding; cf. the fluorine derivatives in Scheme 7); references [95, 96, 104, 105] provide access to some of the author's preparative work and recent reviews of the literature. The greatly increased enzyme affinity of nitronate anion 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, R_3N, and R_2O 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, R_3P, R_3As, R_2S, R_2Se, etc.); the point is elaborated in the section that follows and in Schemes 10 and 11.

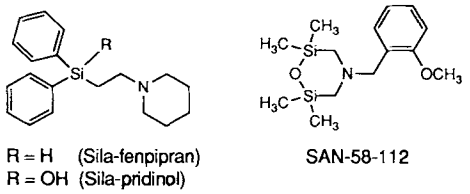
***Bond lengths** [Å] CX vs. SiX*

C-H 1.09	C-C 1.54	C-O 1.41
Si-H 1.48	Si-C 1.86	Si-O 1.50

***Van der Waals radii** [Å] $C(CH_3)_2$ vs. $Si(CH_3)_2$*



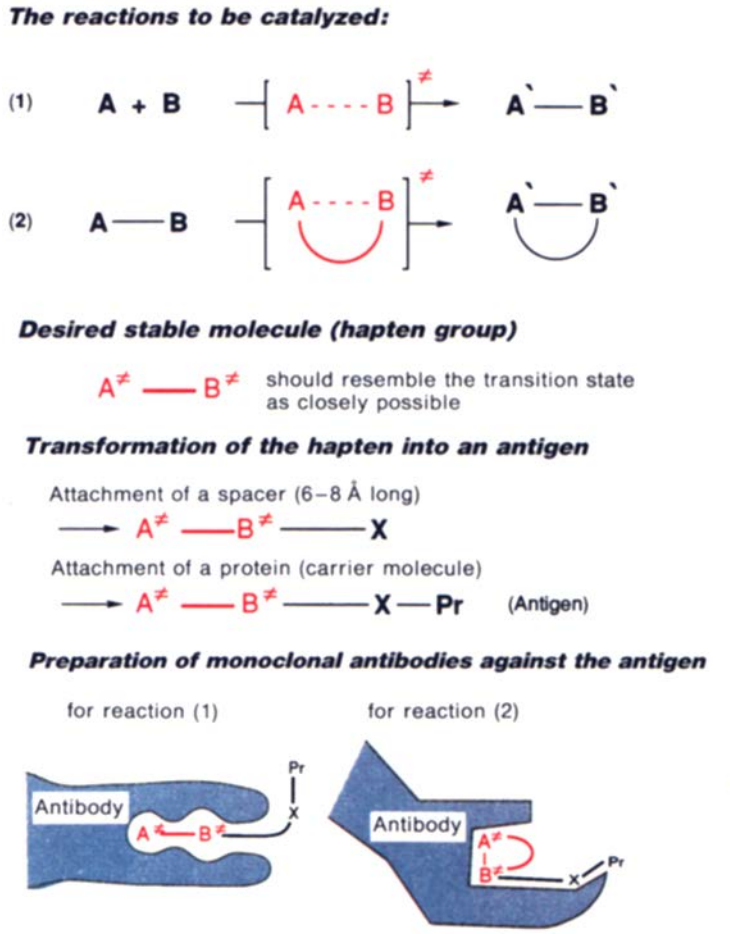
***Bioisosteric relationship** between C/Si analogues*



Scheme 9. Comparison of isosteric C and Si compounds. The illustrated Si isosteres of active substances [106] differ in interesting ways from the parent compounds; once again, the spatial arrangements [102, 107b] of the compounds are almost unaffected by incorporation of Si, but the reactivities (metabolizabilities) change considerably, as do electronic properties (possible formation of hypervalent species [107], σ-donor characteristics of the Si–C bond [108, 109]).—Deuterated derivatives have so far not been utilized, although the somewhat reduced size of CD_3 relative to CH_3 [110], for example, should have significant consequences, as should kinetic isotope effects [111] in interactions with receptors and in rates of metabolism (particularly on the physiological time scale).

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

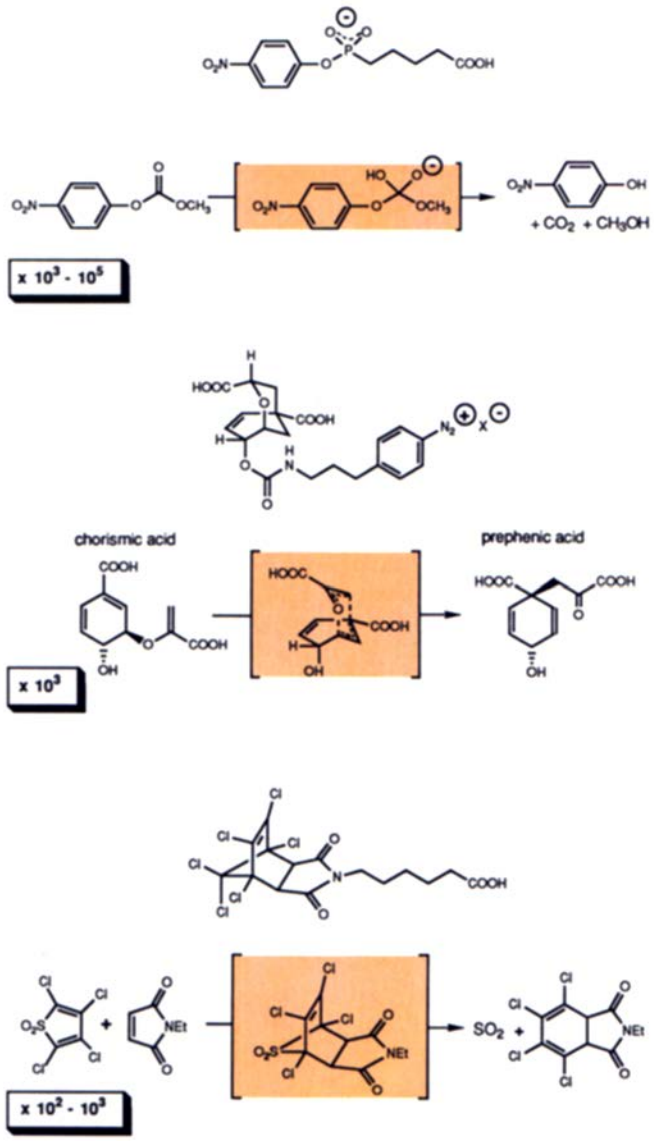


Scheme 10. Preparation of monoclonal antibodies with "recognition potential" for the arrangement of transition states or intermediates; there also exist other methods by which catalytically active antibodies (abzymes) can be prepared [114b].

a mammal,[119] which responds with an immune reaction leading to antibodies. The antibodies are isolated, and those with the highest affinity are separated and replicated monoclonally.[120] Finally, a test is performed for catalytic effectiveness in accelerating the target reaction. Abzymes prepared in this way[114] have been shown to accelerate by factors as great as 10^5 such reactions as ester-,[115, 121] amide-,[114b] and peptide-bond cleavages;[122] lactonizations;[123] and even Claisen rearrangements,[116] Diels–Alder reactions (catalysis by "Diels–Alder-ase"),[118] and redox reactions.[124] All such reactions of course display enantioselectivity.

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,[125] 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;[126] 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-



Scheme 11. Three examples of abzyme-catalyzed reactions. The observed rate enhancements in ester hydrolysis [114b, 115] and in the rearrangement of chorismic to prephenic acid [116] are significantly less than those produced by natural enzymes (esterases and chorismate mutase [117]). In the case of the Diels–Alder reaction [118], the antibody—generated in response to the hapten, and replicated monoclonally—must be methylated with $CH_2O/NaCNBH_3$ in order to keep it from reacting with tetrachlorothiophene dioxide (cf. suicide substrates). In each of the three examples, the hapten and the spacer are shown at the top, and directly below is the corresponding catalyzed reaction, including the transition state or intermediate and an indication of the observed extent of rate enhancement.

all understanding of molecular interactions. Examples have already been reported[114b] 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.[127–131]

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."

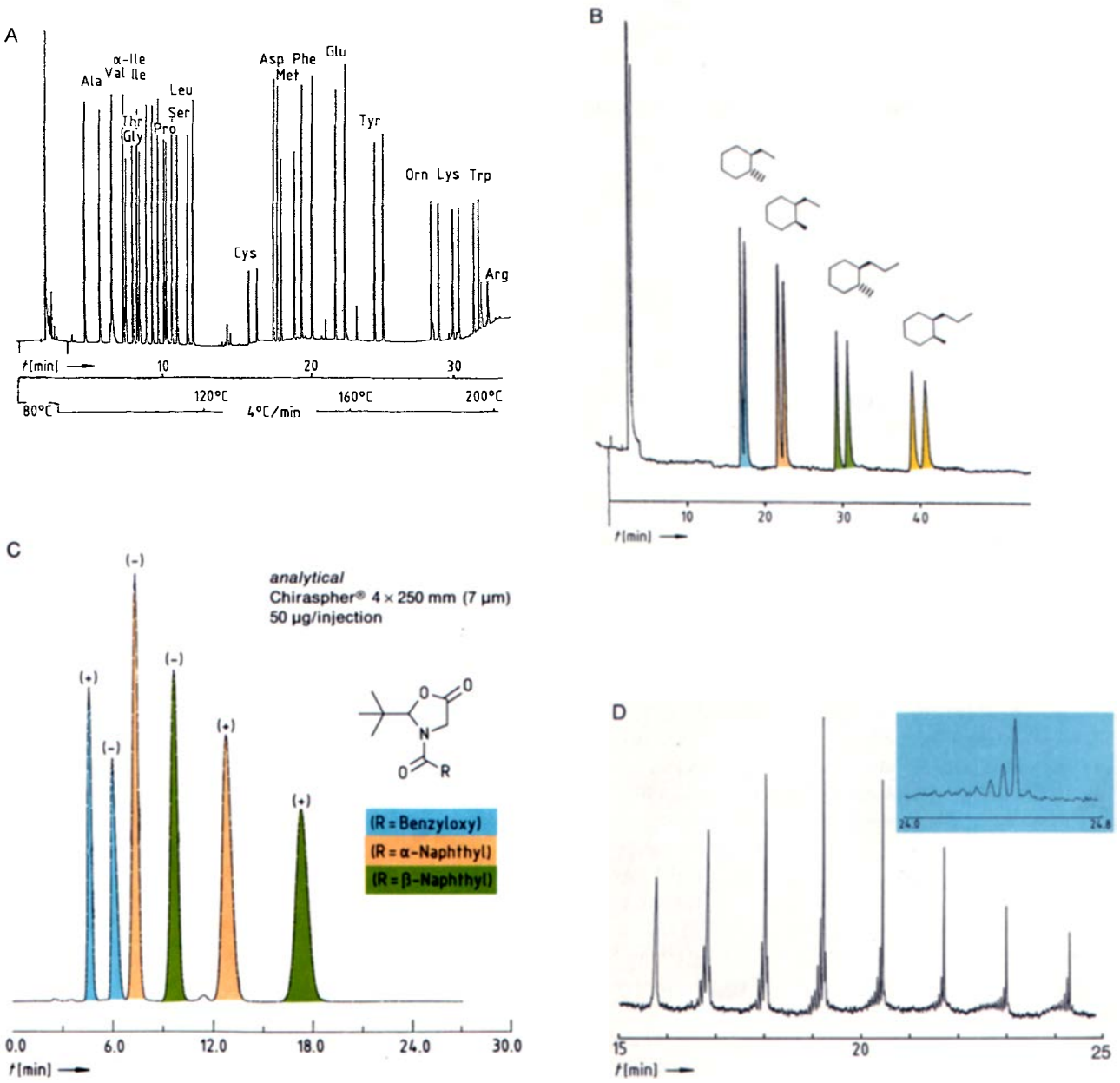


Fig. 1. Selected examples of separations accomplished with the aid of modern analytical methods. A) Gas chromatogram from a mixture of all the proteinogenic amino acids (racemic mixtures, in the form of *N*-pentafluoropropionyl isopropyl esters); Chirasil®-L-Val column containing 5% Kóvats phase [135]. 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(desoxy)thymidylic acid mixture, with an enlargement of the region near 160 nucleotide units; polyacrylamide gel, 3×10^7 plates [138].

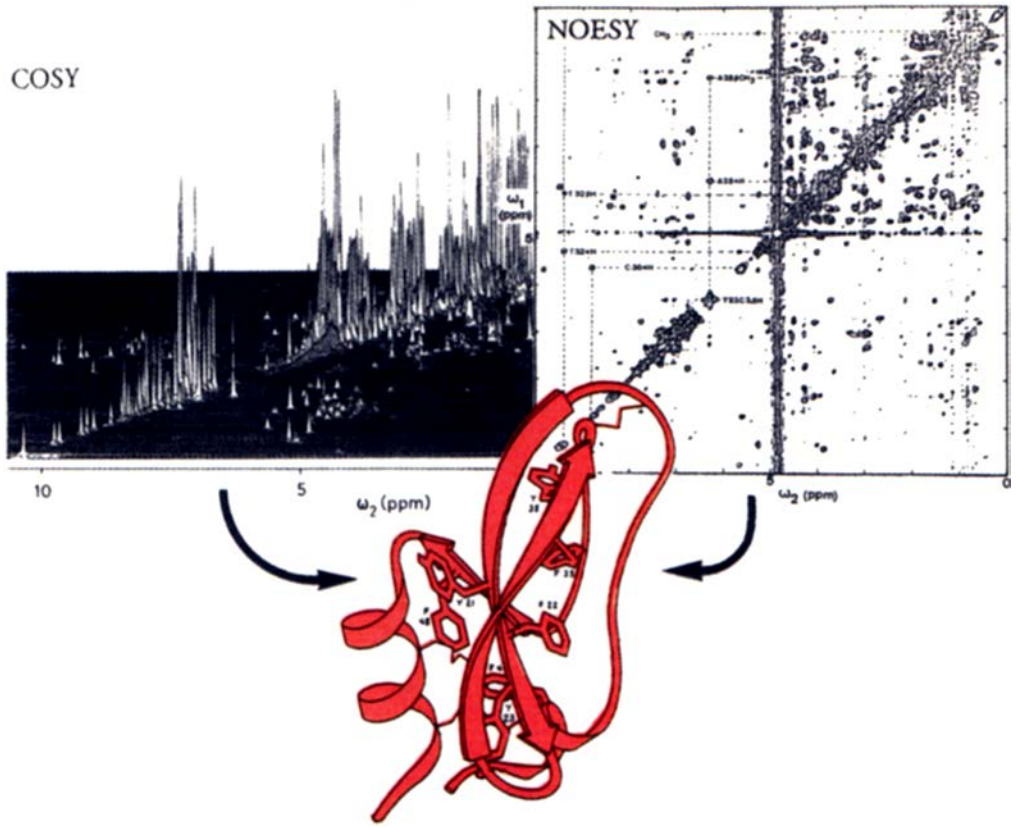


Fig. 2. 2D-NMR spectrum of the basic trypsin inhibitor from the pancreas [143]. A combination of X-ray structure analysis, NMR spectroscopy, and computer-assisted modeling/dynamic calculation on proteins results in detailed information about both their structure and their enzymatic function (see Sec. 3.3 and Fig. 8).

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

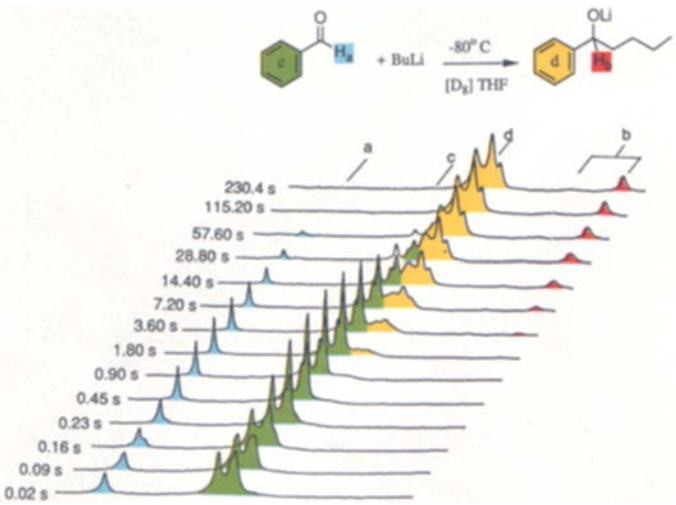


Fig. 3. Rapid-injection ^{1}H-NMR measurement (RI-NMR) [145] during the reaction of butyllithium with benzaldehyde at $-80\,^\circ$C in perdeuteriotetrahydrofuran. A benzaldehyde solution of the substrate (2.3 mg in 250 μL [D$_8$]THF) and butyllithium (15 μL, 2 M in hexane) were injected into a 5 mm NMR tube (rotation frequency 10 Hz). Pulses and Fourier transforms were applied after the indicated time intervals (Bruker model WH-360) [146]. Further applications of this method involve studies of reactions of other organolithium systems and of organomagnesium compounds [147, 148], and investigations of short-lived cations [149].

dynamic processes have all become possible through the introduction of extremely clever pulse sequences,[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].[145, 147]

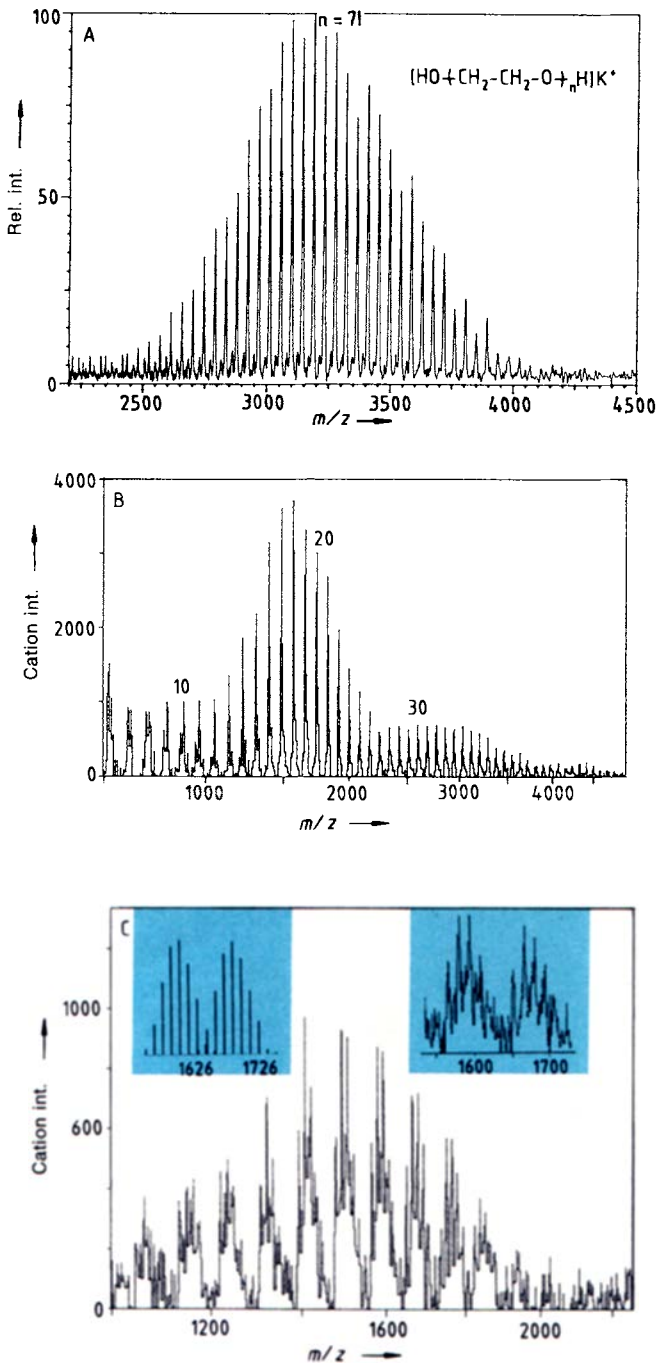


Fig. 4. Analysis of the molecular weight distribution of polymers by mass spectroscopy. A) Laser-desorption Fourier-transform mass spectrum (LD-FTMS) of a poly(ethylene glycol) sample (mean molecular weight 3550 dalton) [155]. B) Plasma-desorption mass spectra (PDMS) of poly[(*R*)-3-hydroxybutyric ester]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

Chiral shift reagents now permit the direct determination by NMR spectroscopy of enantiomer ratios,[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.[141–152] Solid-state NMR spectroscopy is also well on the way to becoming a routine technique.[153]

Mass spectroscopy 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[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".[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.[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!
J. D. Dunitz (1977)

Among the remaining analytical methods, X-ray structure analysis surely deserves to be mentioned first.[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 non-monochromatic 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;[167a] and materials subject to decomposition[167b] well below room temperature,[168] loss of solvent,[169] melting,[170] or the development of plastic crystallinity.[171]

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 imponderables 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",[192a] and capable of revealing a piece of double-stranded DNA as a kind of "molecular braid".[192b]

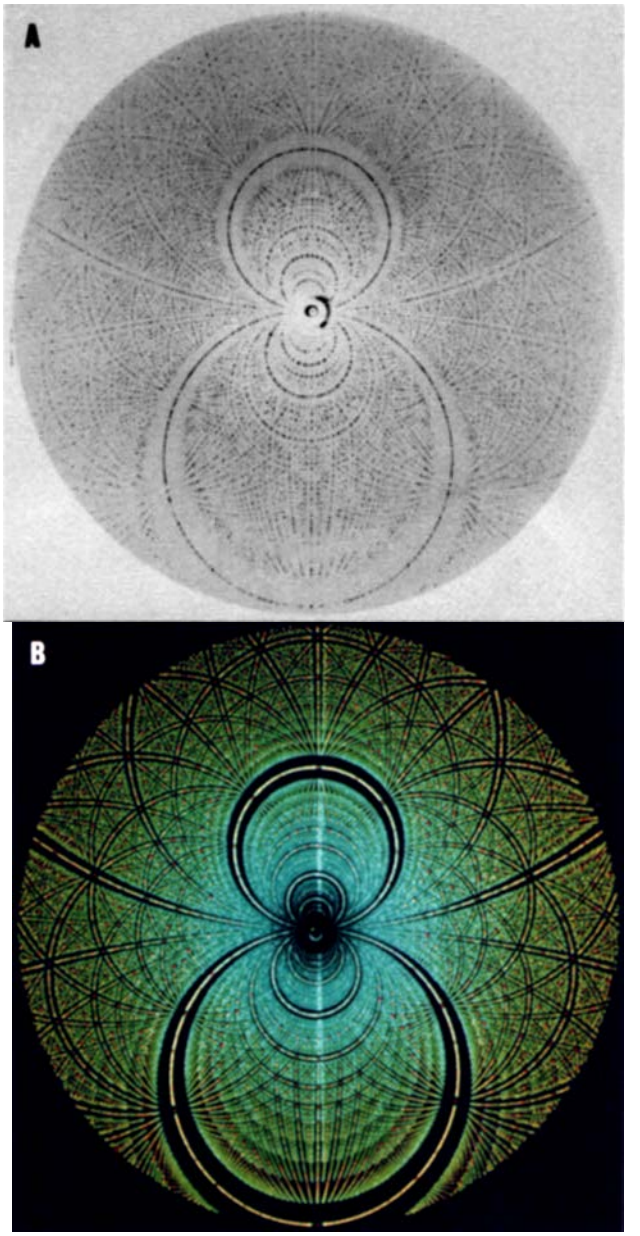


Fig. 5. Laue diffraction pattern of glycogen phosphorylase B. The use of high intensity, non-monochromatic synchrotron irradiation permits the collection within minutes of the data associated with a large protein or nucleic acid molecule—even an entire crystalline virus [162, 163]. Polychromatic irradiation 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 $P4_32_12$, $a=b=128.8$, $c=116.2$ 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.

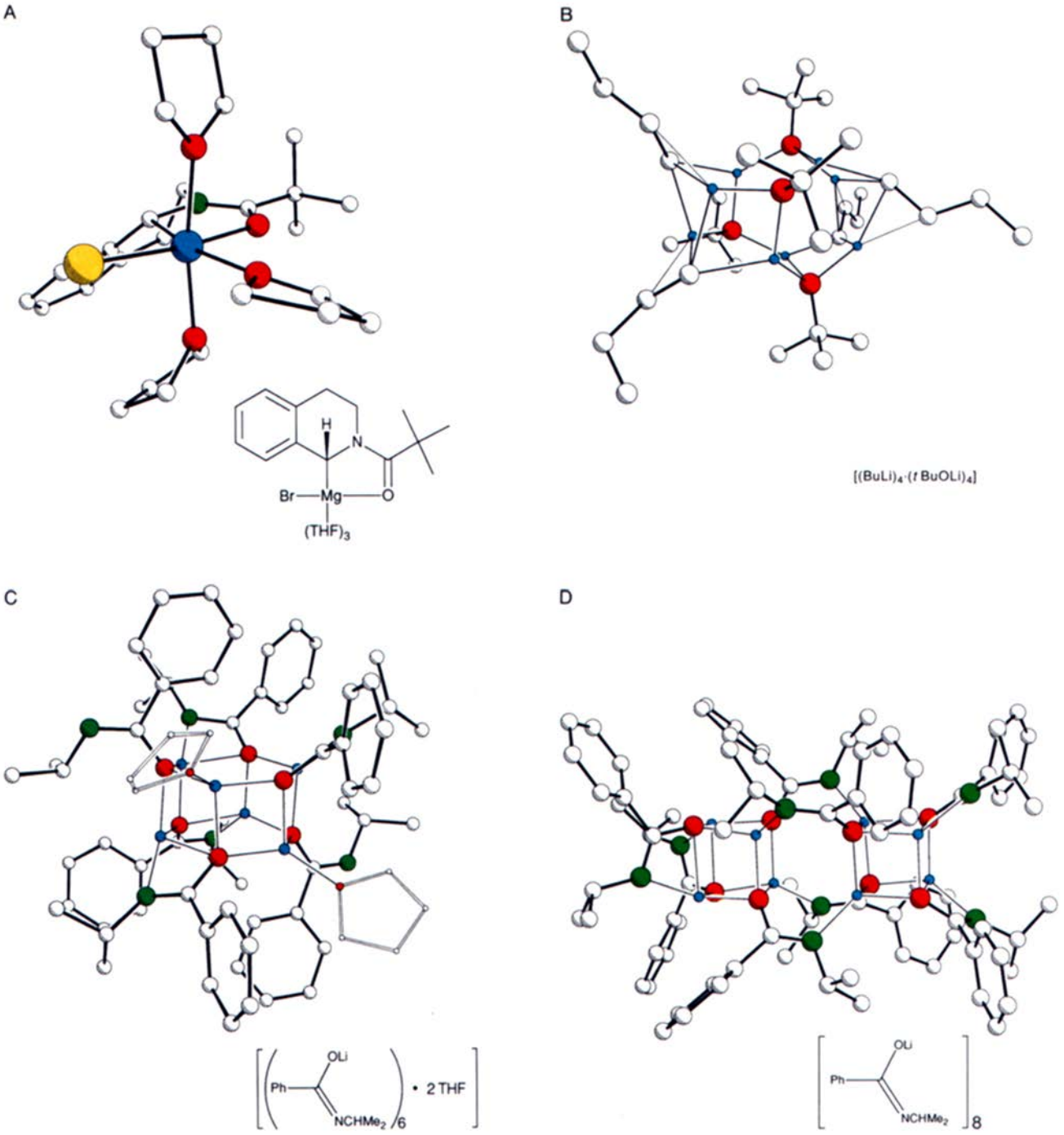


Fig. 6. Four structures of polar organometallic compounds of preparative significance. A) A tetrahydroisoquinoline derivative metallated in the 1-position; in contrast to the Li analogue, the Mg derivative whose crystal structure is shown here [174] adds with high diastereoselectivity to aldehydes [175]; 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 $[(BuLi)_4 \cdot (t\text{-}BuOLi)_4]$. Complex bases derived from butyllithium and potassium *tert*-butyl alcoholate (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[193]—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-

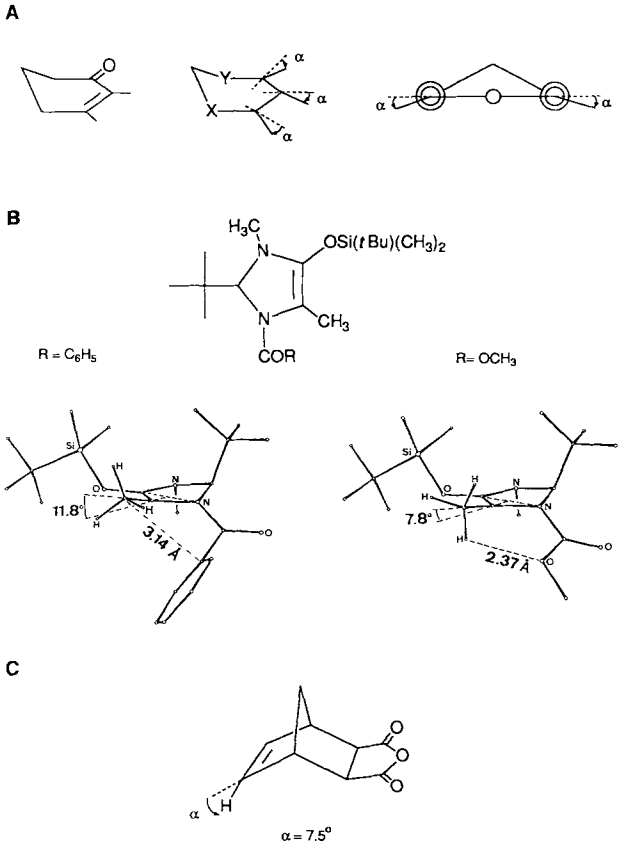


Fig. 7. Pyramidalization and reactivity at trigonal centers. A) In the crystalline state, cyclohexenones and similar derivatives with five atoms nearly in a plane and a sixth atom outside this plane ("sofa" conformation) often display pyramidalization of the trigonal centers in precisely that direction from which attack occurs during reactions transforming the trigonal centers into tetragonal centers [183]. B) Crystal structures of silylenol ethers from imidazolidinones, where $R = C_6H_5$ or OCH_3; the trigonal, methyl-substituted C atoms are displaced by 7.8 or 11.8° ($\Delta = 0.07$, 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 *exo* direction for the trigonal carbon atoms of the C–C double bond [185] (cf. the suggestion made in 1967 that the unexpectedly high *exo* selectivity in reactions of norbornenes might be due to torsional effects [186, 187], as well as *Huisgen*'s "Factor X" [188]).

culations, to name but a few. Computer technology and the advent of instantaneous worldwide data transfer have transformed the everyday life of the chemist, and their importance will certainly continue to grow. Table 1 contains a list of computer programs we have assembled for use in our research group. Most are for the Apple Macintosh computers that are running day and night in our laboratories and offices, serving also as terminals that can be used for tapping the extensive resources of the ETH computer center.

Product and transition-state geometries of increasingly large molecules and even supermolecules can be simulated effectively with the aid of computer programs that are also constantly increasing in their power. The demonstrated reliability 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 or-

Table 1. Sources of computer information, and computer-based tools useful to the synthetic chemist [194]. 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.)

Drawing	ChemDraw [195]	
Literature searching	*Chemical Abstracts* databases Substructure searches [196]	
Retrosynthesis [17b] **and reactivity**	CAMEO	(**C**omputer-**A**ssisted **M**echanistic **E**valuation of **O**rganic Reactions) [197]
	CASP	(**C**omputer **A**ssisted **S**ynthesis **P**lanning) [198]
	CHIRON	("**Chir**al **Syn**thons") [199]
	LHASA	(**L**ogic and **H**euristics **A**pplied to **S**yntheses **A**nalysis) [17b,200]
Reactions [201]	ORAC	(**O**rganic **R**eaction **A**ccess by **C**omputer) [202]
	REACCS	(**Reac**tion **C**ess **S**ystem) [203]
	SYNLIB	(**Syn**thetic **Lib**rary) [204]
Structures	CSD	(Cambridge Structural Database "Cambridge File") [189]
Modeling	MacMoMo [205] Chem 3 D Plus [206] Macro Model [207] (MM2 [208]) [209]	
ab initio calculations [210]	Monster-Gauss [211] CADPAC [212] GAMESS [213] MOPAC [214]	

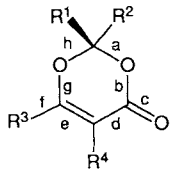
ganic synthesis[218]—including nucleophilic addition to carbonyl groups,[219] the Michael addition,[220] the aldol addition,[221] 1,3-dipolar cycloaddition,[222] the Diels–Alder reaction,[223] hydroboration,[224] and addition to double bonds with stereogenic centers at their allyl positions[219, 220–224]—have 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 Chemistry" is a proclamation[225] that pertains not only to very simple systems, and not just to reactants; it even embraces solvents (in modeling,[226] as well as in the context of proteins and nucleic acids;[227] 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 hexamethylphosphortriamide (HMPT), which has mutagenic properties].[228] 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 precur-

A



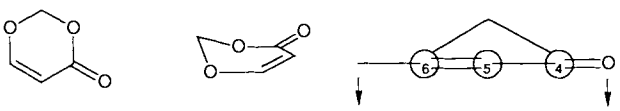
Bond	a	b	c	d
Average value	1.430	1.371	1.202	1.443
Calculated	1.422	1.383	1.195	1.467

Bond	e	f	g	h
Average value	1.336	1.487	1.359	1.427
Calculated	1.322		1.366	1.436

Angle	ab	bc	bd	cd	de
Average value	116.2	118.1	114.5	127.2	121.3
Calculated	118.6	120.0	113.8	126.2	120.5

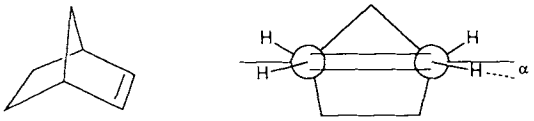
Angle	eg	ef	fg	gh	ah
Average value	119.9	127.8	112.3	114.4	110.0
Calculated	122.9	124.5	112.6	114.5	111.5

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 $R^1=R^2=R^3=R^4=H$) 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 norbornene; 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 (MP3/6-311++G**//6-31G*) are due to *Wiberg* [217], and they have shaken the foundations of our qualitative models of resonance stabilization.

sors. 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 al-

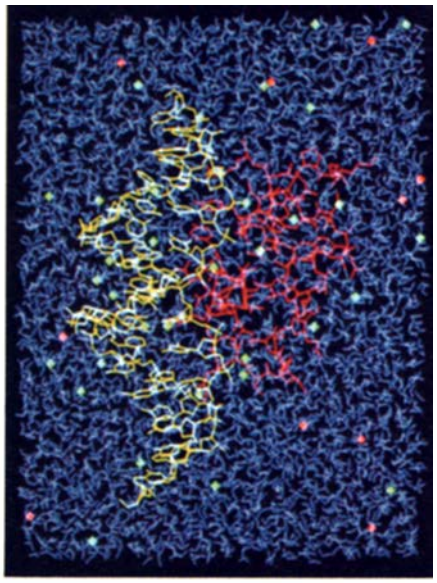


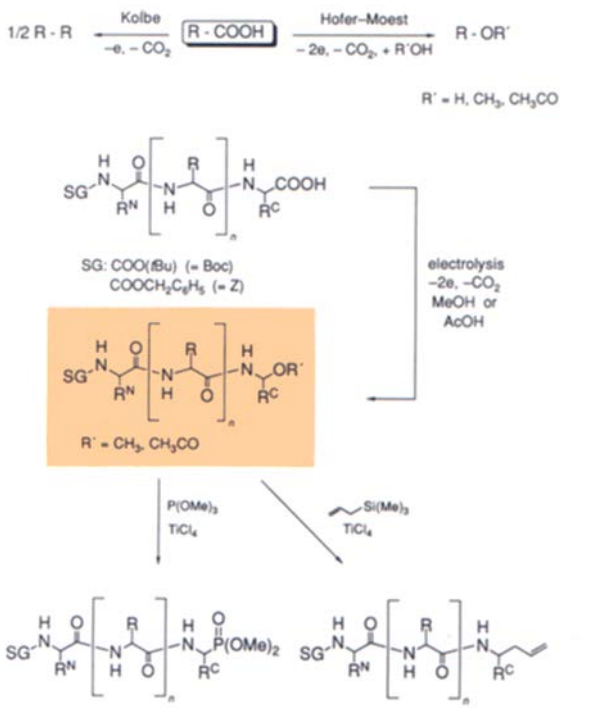
Fig. 8. Modelling in chemistry from the early days to the present. A) Calculations by *van Gunsteren* et al. (a complex of a DNA containing 14 base pairs with the lac-repressor protein from *Escherichia coli* in the presence of 34 $Na^{\oplus}$ ions, 10 $Cl^{\ominus}$ ions, and 3906 H_2O molecules; support provided by NMR data) [227]. B) "Match box" models of *van t'Hoff* (from the chemistry museum in the *Maison de chimie* of the French Chemical Society in Paris).

phabetically and supplemented with illustrations (or at least key literature references).

- *B*iological-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).
- *C*hromatography over aluminum oxide, silica gel, or ion exchangers has apparently proven to be economically feasible in the purification of products like cyclosporin[232]

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).[133d]

- *C*lays, zeolites, and aluminum oxide have been recommended as catalysts or carriers for synthetic reagents.[234]
- *E*lectrolysis 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; CO_2 is formed at the anode, and H_2 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]

- *F*luorination with elemental fluorine is now a subject of active investigation even in industrial laboratories.[92]
- *H*igh- and very-high-pressure conditions (up to 20 kbar) permit the realization of reactions with negative activation volumes ($\Delta V^{\neq}$).[242] For example, Diels–Alder reactions between sterically hindered components become feasible under such conditions, whereas equilibrium considerations preclude the usual approach of simply heating the mixture of starting materials to a high temperature.
- *L*ow and very low temperatures[243] under inert atmosphere have become commonplace even in large reactors—a source of some satisfaction for those who 20 years ago were telling industrial chemists about the remarkable selectivity of reactions with organometallic reagents at −100°C under argon, often to be greeted with smiles reflecting pity for the naiveté of "academic eggheads". To-

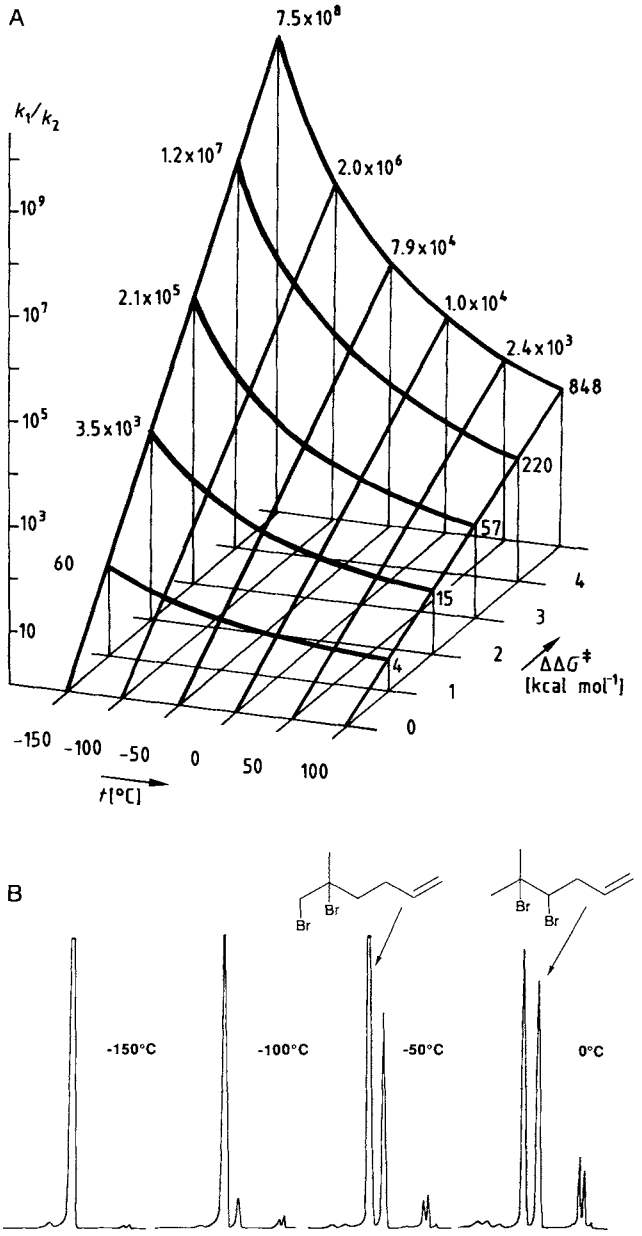


Fig. 9. Increase in the selectivity of reactions at extremely low temperature [243a]. A) 3D diagram showing the relationship between the yields of two products (from competing reactions, both first-order) as a function of difference in enthalpies of activation ($\Delta\Delta G^{\neq}$) and temperature. B) Gas chromatogram of the reaction mixture obtained on treatment of 2-methyl-1,5-hexadiene with bromine; ratios of the principal components at 0°C (in $CH_2Cl_2/CHCl_3$), −50°C (in CHF_2Cl), −100°C (in $CH_2Cl_2/CHCl_3$), and −150°C (in CHF_2Cl) 1:1, 2:1, 200:1, > 500:1. Of course, lower temperatures do not always result in greater selectivity [243b], since selectivity is a function of the relative temperature dependencies of competing reactions, which intersect at the isoselective temperature [243c]. Complex reactions (sequential reactions, pre-equilibria, systems with feedback) also lead to situations much more complicated than that depicted in diagram A [172, 243d–f, 253].

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}[243] (cf. Fig. 9). An example of a continuous low-temperature process is outlined in Fig. 10.[247] Even C–C bond formation with the aid of lithiated 1,3-dithianes,[18i] now a standard laboratory method but one that requires low temperatures,[31, 248] has been adapted for large-scale application.

- *M*icrowaves 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]
- *O*zonolyses 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*!
- *P*hotoreactions (progeny of a venerable family of chemical 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).
- *R*adical reactions were viewed with considerable suspicion by synthetic chemists as recently as 10 years ago, attracting favor only among those interested in the study of mechanisms.[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 derivatives relinquish their roles as chain initiators and synthetic reagents generally.[259]
- *S*alt 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 solubilizing effects with respect to compounds otherwise insoluble in organic solvents (e.g., polylithiated derivatives[172] and oligopeptides;[260] cf. Table 2 and Fig. 11).
- *S*olid-phase syntheses have been achieved on a wide variety of carriers.[8, 263] Combination of the Merrifield peptide synthesis with modern separation methods has even made it possible to prepare relatively large peptide segments useful in the pharmaceutical industry for the *production* of active ingredients.[264]
- *S*olid–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 presented in Scheme 14.
- *S*olvents are more and more becoming the "problem children" 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 solvents, especially ones available in both enantiomeric forms,[276] would be useful for enhancing stereoselectivity.[277, 278]
- *U*ltrasound 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 involves a dissolving metal) and has become a standard

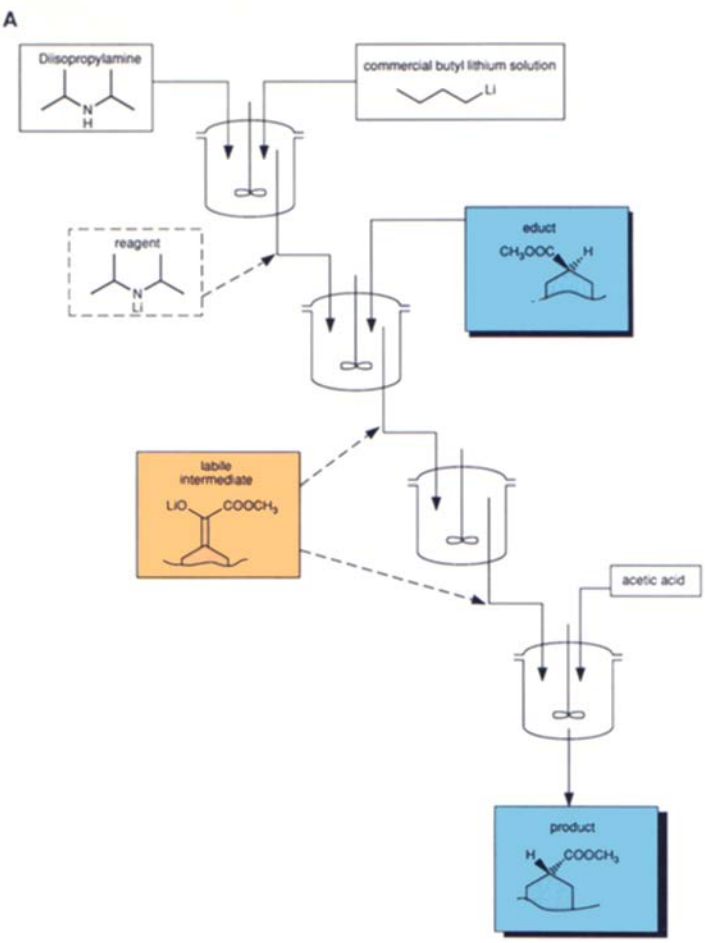


Fig. 10. Example of a low-temperature reaction carried out as a continuous process. Dihydrolysergic acid methyl ester is deprotonated to the Li enolate using lithium diisopropylamide (LDA) generated in situ. Subsequent protonation results in iso-9,10-dihydrolysergic acid methyl ester [245, 246]. A) Schematic representation of the process, and B) photograph of the pilot facility [244]. 1–4 correspond to the stirred reactors in A.

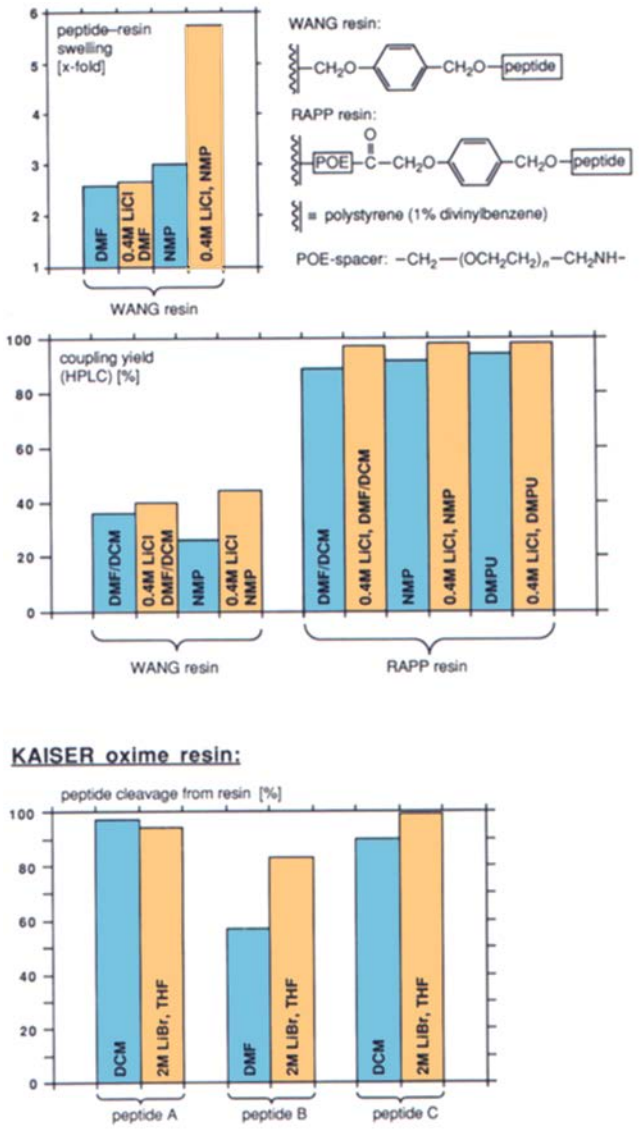


Fig. 11. Use of LiX-containing solvents [260] in Merrifield peptide syntheses involving various anchoring groups and coupling methodologies. The peptides chosen were notorious for a tendency to undergo aggregation (β-pleated sheet!), which normally implies a decrease in yield after a certain chain length has been attained. Experiments with Rapp andWang 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.

Peptide / Solvent	Solubility [mg mL^{-1}] without	with salt	[mol per mol peptide]
Z-Gly-Gly-Nva-OH			
THF	27	≥ 500	3.0 LiCl
		≥ 470	3.6 LiBr
		≥ 420	2.9 LiI
		≥ 360	3.0 $LiBF_4$
		≥ 340	3.0 $LiClO_4$
		≥ 510	3.0 $Ti(OEt)_4$
		≥ 440	3.0 $Ti(OCHMe_2)_4$
DME	10	> 145	3.2 $LiClO_4$
Z-Ile-Gly-Gly-OH			
THF	23	≥ 340	2.8 LiCl
		≥ 190	3.0 $Ti(OCHMe_2)_4$
Boc-Gly-Gly-Nva-OH			
THF	27		
		≥ 470	2.9 LiBr
H_2N-Asp(OBzl)-Val-Tyr-OBzl·HCl			
THF	1.5	≥ 510	2.9 LiCl
		≥ 520	2.9 $LiClO_4$
		≥ 140	3.0 NaI
		≥ 150	3.0 $MgBr_2 \cdot OEt_2$
		≥ 390	3.1 $ZnCl_2$
Dioxane	2.3	12	3.5 LiCl
DME	0.45	> 27	5.0 LiCl
DMF	≥ 200		
DMPU	≥ 410	70	2.9 LiCl
PEG	≥ 120	≥ 120	3.3 $LiClO_4$
Boc-Ala-Gly-Gly-Gly-OH			
THF	2.0	≥ 300	5.9 LiCl
HCl·H_2N-Lys(Z)-Asp(OBzl)-Val-Tyr-OBzl			
THF	3.8	≥ 380	3.1 LiCl
Z-Arg-Lys(Z)-Asp(OBzl)-Val-Tyr-OBzl·HCl			
THF	0.7	≥ 230	6.0 LiCl
H_2N-Leu-Met-Val-Gly-Gly-Val-Val-Ile-Ala-OH			
THF	insoluble	≥ 100	20 LiBr

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.

method in the research laboratory, where an ultrasonic cleaning bath will usually do the job. To the best of my knowledge, however, no technological solution has so far been found to the problem of adapting ultrasound techniques to a large reaction vessel.

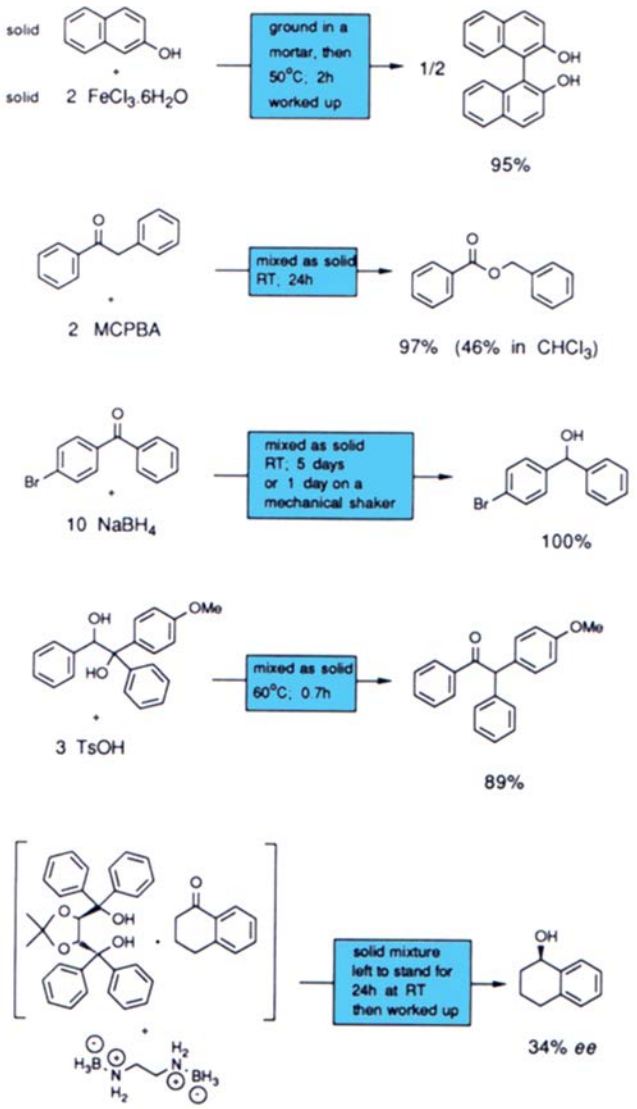
- *W*ater has been recommended[281–284] as a medium for organic reactions, even ones involving organometallic intermediates. The advantages of water as a solvent are self-evident.

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 gen-

[*] Quoted from Irving Stone (ed.): *Dear Theo*, Doubleday, New York 1969, p. 164.



Scheme 14. In certain cases, solid–solid reactions are superior to the corresponding transformations in solution with respect to yield and selectivity. The examples shown come from the laboratory of *Toda* [267], and illustrate a phenol coupling reaction [268a], a Baeyer–Villiger oxidation (MCPBA = *m*-chloroperbenzoic acid) [268b], a $NaBH_4$ reduction [269], a pinacol rearrangement [270], and an enantioselective reduction [271] [by mixing a crystalline clathrate from an achiral ketone and a chiral host [272–275] with the solid complex $(H_3B)_2 \cdot (CH_2NH_2)_2$].—To the best of my knowledge it is not yet known to what extent such reactions represent a safety risk in terms of large-scale adaptation. Nevertheless, it is reasonable to anticipate that a technical solution might be found if the approach proves its superiority in other ways (absence of solvent, high volume-efficiency!).

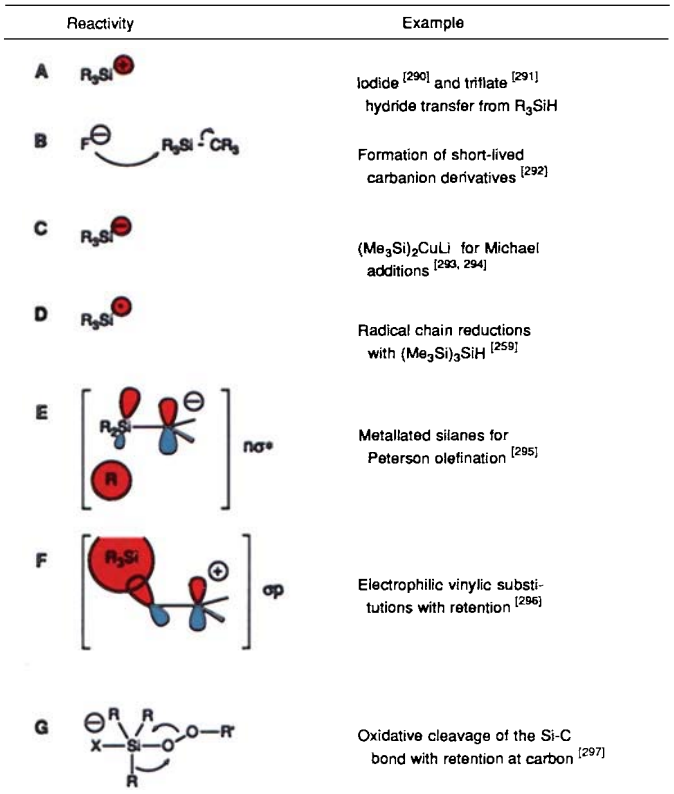
erally,[285, 286] list one of their areas of specialization as "new synthetic methods". It would be difficult, though, to develop a general consensus on the issue of what a "new" synthetic method really is. It has also become common to find words like *principle*, *strategy*, or even *protocol* linked with the adjectives "new" or "novel" (even "new *and* novel"!). But when one examines the piece of work to which such a description has been applied it often turns out to contain only a minor improvement on a well-known reaction, or a new *application* of an old technique. (Such observations tend to become more frequent as one grows older and wiser!) Years ago, a bet was made between one of my colleagues in Zürich and a chemist in Munich[287] about whether it is possible to find a truly new reaction with the help of a computer program[288] 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

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].)

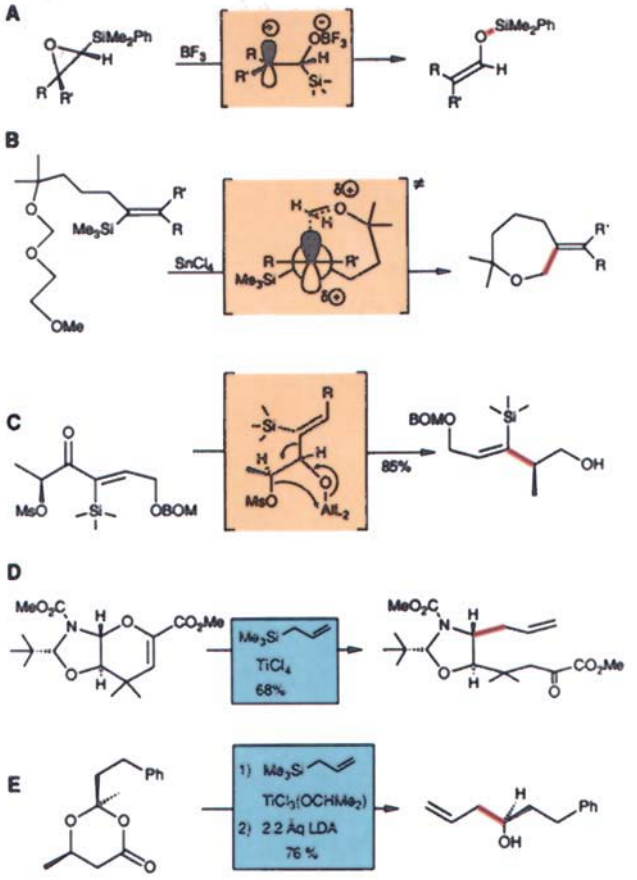
Si-acetalization	of aldehydes and ketones, Si-triflate catalysis (based on *Noyori*) [298–300]
Si-acyloin condensation	Rühlmann variant of the acyloin reaction [301,302]
Si-aldol additions	see Schemes 19 and 26
Si-azide	"the versatile reagent" [303]
Si-Birch reduction	and other Si-modified reactions of dissolving metals [304]
Si-cyanohydrin reaction	see below, Si-umpolung
Si-diazomethane	safer variant of the standard diazomethane reactions [305]
Si-Friedel–Crafts-type acylations	at aromatic, vinylic, and acetylenic C-atoms [109,289]
Si-Mannich	see below, Mannich reactions [336]
Si-Nazarov reaction	five-membered ring annelation [306], cf. also the Si-variant of the Robinson annelation [307]
Si-nitroaldol additions	diastereoselective to give products of *l* or *u* configuration [18f,308]
Si-olefination	Peterson olefination [108,295,309]
Si-ozonolysis	with triethylsilyl-hydrotrioxide [310]
Si-pinacol rearrangements	migrating α-Si-vinyl group [311], see also Scheme 16 and [322] therein
Si-Pummerer rearrangement	from sulfoxides to α-Si-thioethers [312]
Si-radical chain reductions	see above, Scheme 15 **D**, ref. [259]
Si-umpolung	with trimethylsilylcyanide [34] or with Me_3Si-thiazole [313]

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,[330] 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 aldol,[331] Beckmann,[332] Claisen,[333] Cope,[334] Diels–Alder,[335] Mannich,[336] Michael,[331a, 337] or Wittig[26, 27, 338]



Scheme 15. R_3Si: more than just a "big, fat proton". In most of the organic synthetic applications of R_3Si 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 SiC bonds indicated in G establishes synthetic equivalence between silyl groups and OH.



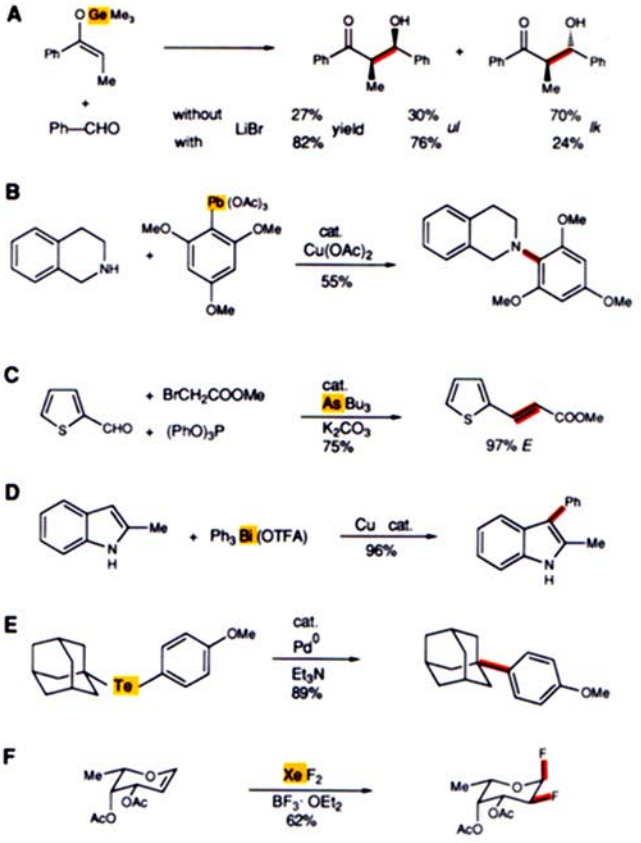
Scheme 16. Transformations facilitated by the stability of β-Si carbocations. The amount of stabilization associated with the β-Si effect has been estimated to be as great as 159 kJ mol^{-1} [315]. Vinyl- [109] and allylsilanes [107, 316] have acquired considerable significance in organic synthesis. Thus, Si groups activate double bonds, control regioselectivity in electrophilic attack, ensure stereoselectivity during reaction (cf. the preference for retention in substitution of vinylic silyl groups [109, 296] and S_E-*anti*-substitution of allylic silyl groups [109, 317, 318]), and function—formally speaking—as leaving groups of the type $R_3Si^{\oplus}$. A) Stereoselective (*cis* → *Z*, *trans* → *E*, ca. 95% *ds*) rearrangement of silyloxiranes 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% *ds*) [321]. C) Migration of an α-silylvinyl group in what amounts to a pinacol rearrangement (retention at the migrating carbon, inversion at the migration terminus; this process may involve a β-Si stabilized cyclopropylmethyl carbocation) [311, 322] (BOM = benzyloxymethyl). D) Allylation with allyltrimethylsilane via an acyliminium ion, accompanied by retention of configuration [323]. E) Allylsilane/$TiCl_3(OCHMe_2)$ used to effect S_N2 ring opening of a dioxanone with the (1*R*,6*R*) configuration, a process that entails subsequent elimination to provide a homoallylic alcohol (overall yield 76%, enantiomeric excess 94% *ee*) [299, 324].

reactions; even the exploitation of strain effects in small rings[339] and the broader application of 1,3-dipolar cycloadditions,[340] dithiane methodology,[18i] ortho metallation ("new arene chemistry"),[341] the acyloin[342a] and pinacol condensations,[274, 342b–d], photochemical[251–254, 343] and radical reactions,[255–259, 344–346] nucleophilic substitution,[347] and "umpolung" of reactivity[18, 31–35, 313, 348] took place without the discovery of new modes of reactivity. Nevertheless, each of the transformations cited[349] has, in a sense, been raised to a much higher level of sophistication. Major thrusts of recent activity have centered around catalytic modifications, diastereoselectivity,[350] enantioselectivity, and the linking together of series of reactions into multistep in situ sequences.[351]

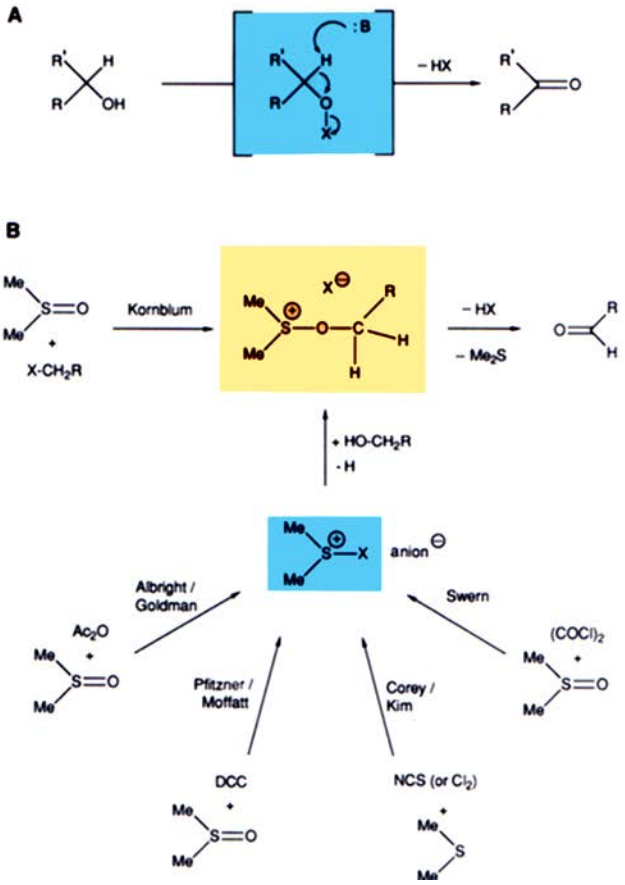
It is obviously quite impossible within the confines of this paper to present an account that even begins to describe the true extent of the efforts and accomplishments of the research groups responsible for these many developments. Instead, I have chosen the following course: First, two Schemes (18 and 19) present selected examples of stepwise improvements to certain standard reactions, and Table 4 highlights some diastereoselective reaction sequences in which a few steps suffice to generate surprisingly complex molecules. These representative samplings are followed by two chapters more directly related to my own interests,[273, 274, 342d, 352–354] illustrating the application of transition-metal derivatives in organic synthesis and the preparation of enantiomerically pure compounds, with an emphasis on catalytic methods. It is my conviction that precisely these two areas will become increasingly important over the next few years.

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

Anyone who has attended one of the biennial conferences on *o*rgano*m*etallic *c*hemistry directed toward *o*rganic *s*ynthesis (OMCOS), and sensed there the atmosphere of excite-



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 *lk*- or a *ul*-aldol [325]. B) Cu-catalyzed reaction of tetrahydroisoquinoline with aromatic 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 *p*-methoxyphenyl, accomplished via a telluride [328]. F) Use of 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).



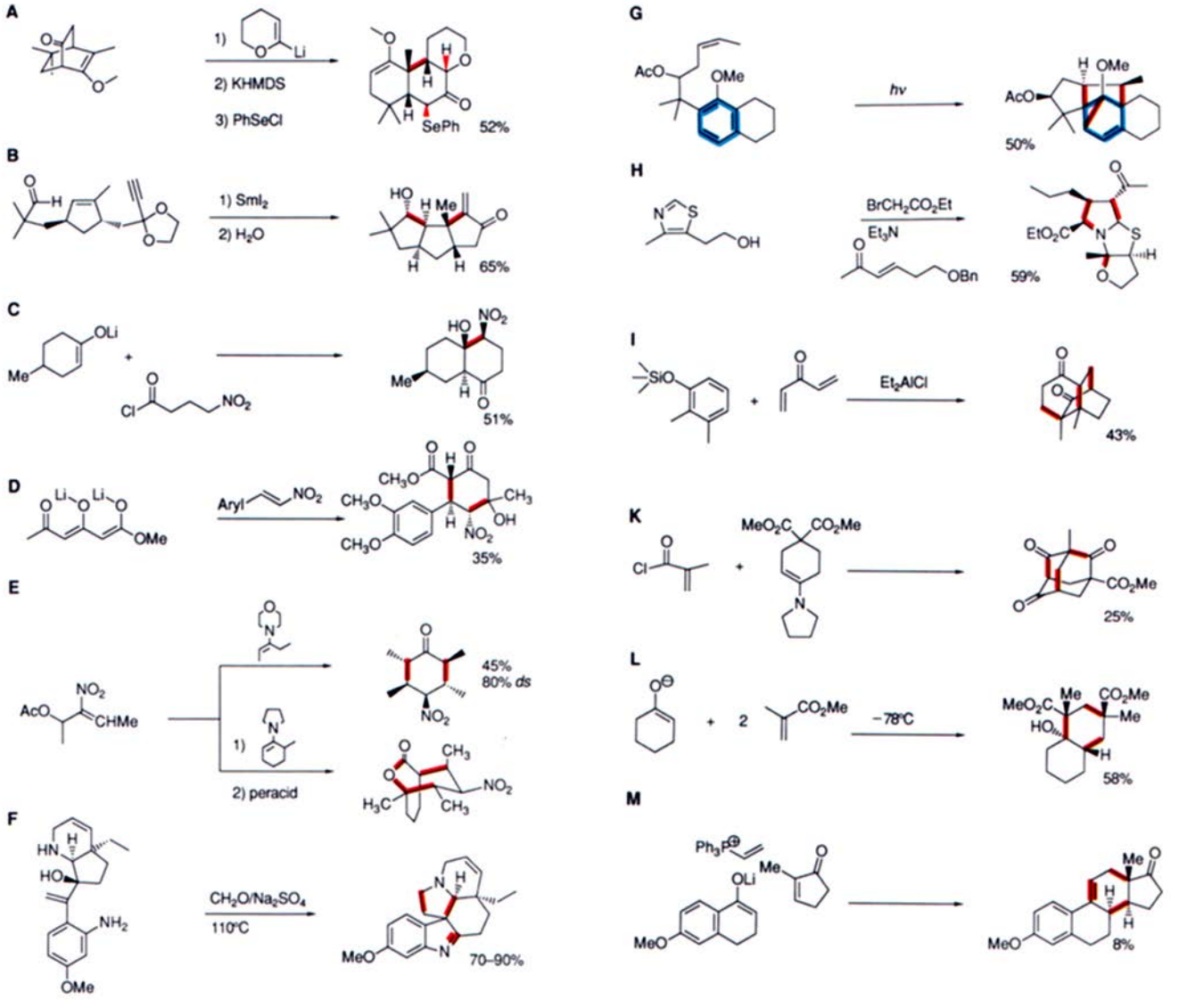
Scheme 18. "Evolution" in the oxidation of an alcohol to a carbonyl derivative [355]. A) A leaving group is first introduced, after which the actual oxidation at carbon takes place by HX elimination. This scheme characterizes, for example, chromic acid oxidation [355], the reaction with hypochlorite [356], corresponding reactions of peroxides [357]—in principle, even the oxidation of amines to carbonyl compounds with the aid of an *o*-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 = dicyclohexylcarbodiimide, NCS = *N*-chlorosuccinimide.

ment enveloping both speakers and audience, will surely find it inconceivable that organic chemistry could be described as a "mature" science. At the last of these OMCOS conferences (in Florence) the air was full of the way "we OMCOS people" would tackle something—and do it better! Many general treatises[388] and reviews, of which only two will be cited here,[389, 390] as well as the even more numerous monographs and articles dealing with specific reactions of the derivatives of particular metals,[391] demonstrate the increasing role of transition metals in the field of organometallic synthesis. Relevant papers may appear in general, inorganic, organic, organometallic, or even more specialized chemical journals, and it is difficult to maintain a satisfactory overview.[392] Furthermore, the reactions themselves are often not easy to classify, and despite great progress in both theory and formalism[393] they do not always lend themselves to detailed formulation, frequently leaving the reader to puzzle over the marvelous transformation of educt into product. One indication of activity in the field is the fact that most of the new organic name reactions of the last decades trace their origins to transition-metal chemistry;[394, 395] 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 amount 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.

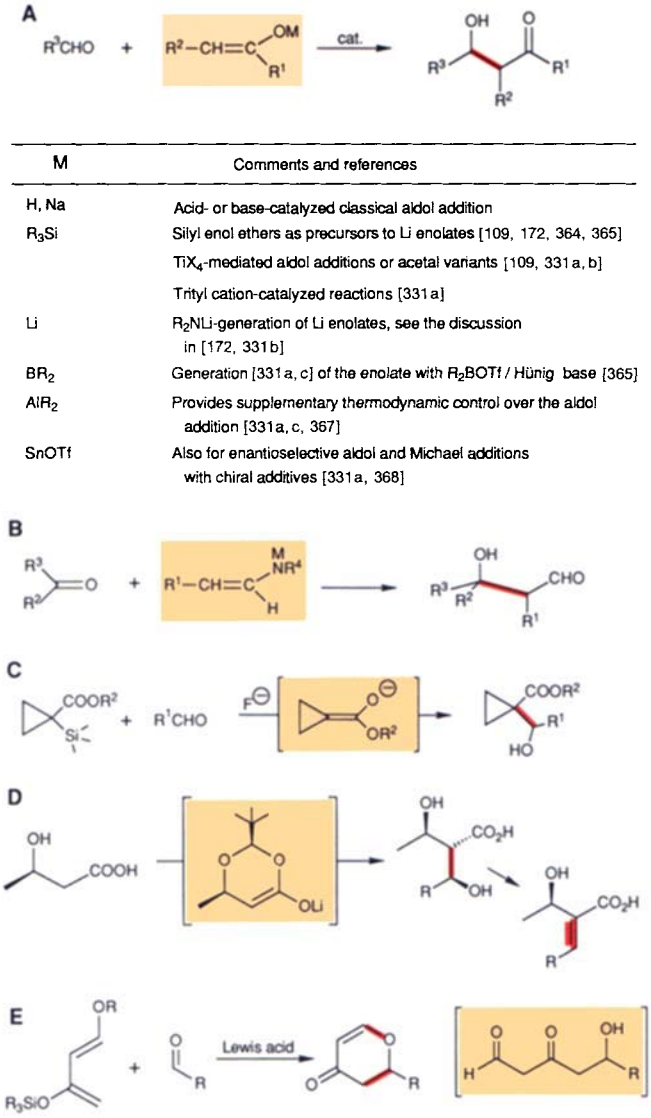
Reductive coupling[301, 342] of carbonyl derivatives and their thio and imino analogues has been greatly facilitated by the advent of low-valent derivatives of titanium, vanadium,

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_N 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 thiazole, ylid formation, cycloaddition 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 methacrylyl chloride and a cyclohexanone derivative directly into the adamantane skeleton [385]. L) A 1:2 intermediate trapped along the way toward polymerization [9] 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].



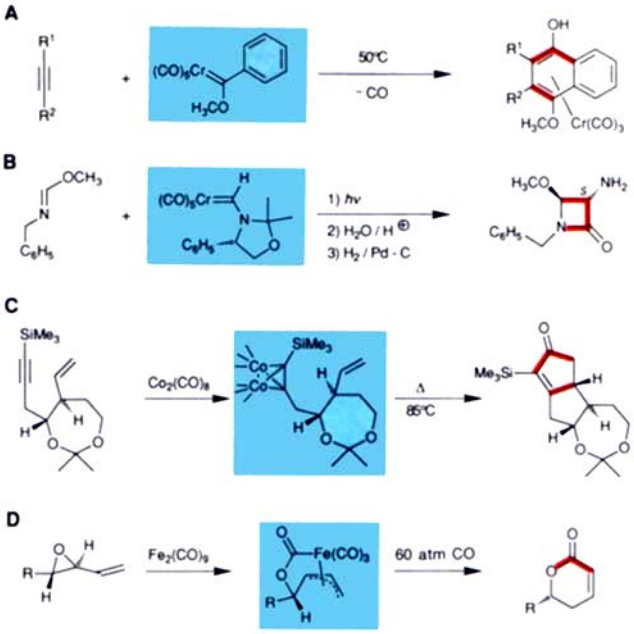
and niobium, and the scope of the reaction has been broadened (e.g., to include nitriles), as shown in Scheme 23.

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 Pd^0/Ph_3P/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.

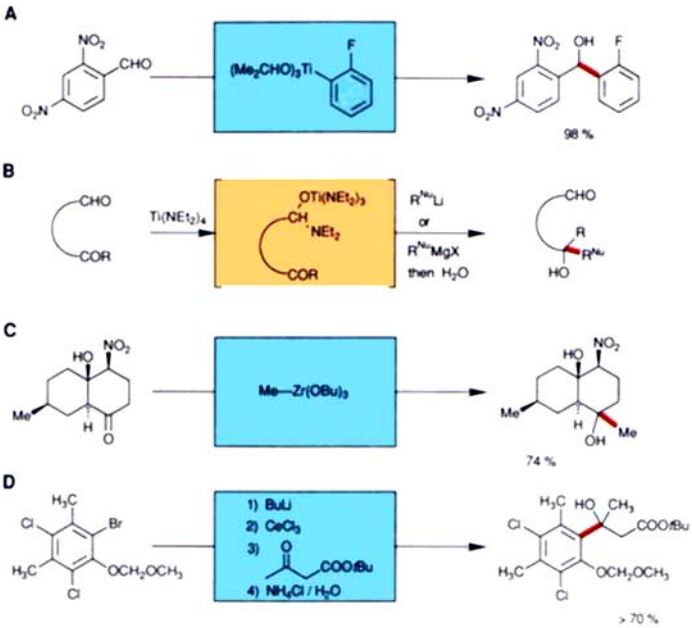


M	Comments and references
H, Na	Acid- or base-catalyzed classical aldol addition
R_3Si	Silyl enol ethers as precursors to Li enolates [109, 172, 364, 365]
	TiX_4-mediated aldol additions or acetal variants [109, 331a, b]
	Trityl cation-catalyzed reactions [331a]
Li	R_2NLi-generation of Li enolates, see the discussion in [172, 331b]
BR_2	Generation [331a, c] of the enolate with R_2BOTf / Hünig base [365]
AlR_2	Provides supplementary thermodynamic control over the aldol addition [331a, c, 367]
SnOTf	Also for enantioselective aldol and Michael additions with chiral additives [331a, 368]

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 α-Si carbonyl compounds, exemplified by a cyclopropanecarboxylic acid derivative [292, 370]. D) Aldol adducts and condensation products from aldols via enolates of (2*R*,6*R*)-dioxanones [371]. E) Aldol addition (or is it a hetero-Diels–Alder reaction?), cyclization, elimination, and desilylation leads to dihydropyran units with synthetic utility. The Lewis acid-induced addition (LACDAC = "*L*ewis *a*cid-catalyzed *d*iene–*a*ldehyde *c*yclocondensation") of a "double enol ether" to an aldehyde (stereoselectively in the case of a 1-substituted diene or a chiral aldehyde) has proven to be a veritable gold mine in the hands of *Danishefsky* and his group [372].



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



Scheme 21. Highly selective nucleophilic addition of Ti, Zr, and Ce reagents to carbonyl groups (cf. also Fig. 12). A) *o*-Fluorophenyl triisopropoxytitanium, 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 retro-nitroaldol 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 transmetallation of a Li or Mg derivative with $CeCl_3$ prior to introduction of a carbonyl compound! [414].

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]

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 *Collman, Hegedus, Norton,* and *Finke* includes pertinent references to all the examples shown.

Birch-Pearson	**Fe** tricarbonyl complexes of cyclohexadiene and other dienes for C,C coupling [390,396]
Crabtree	**Ir** hydrogenation catalyst for C,C double bonds (in the presence of other reducible groups)
Dötz (Scheme 20)	**Cr** carbonyl–carbene complexes for annelation of aromatic rings [397–399]
Heck-Stille	**Pd**-catalyzed arylation, vinylation, and CO insertions [400]
Hegedus (Scheme 20)	**Cr** carbonyl–carbene complexes and imines lead photochemically to β-lactams [390]
Horner-Knowles	**Rh** complexes with chiral phosphanes (Wilkinson catalysts) for enantioselective hydrogenations of C,C double bonds
McMurry (Scheme 23)	**Ti^0** ("low-valent" Ti) for the coupling of two carbonyl groups directly to olefins [342b–d]
Mukaiyama (Scheme 19)	**TiX_4**-mediated reactions of silylenol ethers with aldehydes, acetals, and Michael acceptors [331a,b]
Nicholas-Pettit (Scheme 20)	**Co** carbonyl–acetylene complexes as protective groups and precursors for cyclizations [401]
Noyori	**$Fe_2(CO)_9$** for preparing oxallyl cations for use in [3+2]- and [4+3]-cycloadditions
Noyori-Takaya	**Rh**-, **Ru**-catalyzed enantioselective hydrogenations of C,O double bonds [402]
Pauson-Khand (Scheme 20)	**Co** carbonyl complexes for the preparation of cyclopentenones with CO insertion [390,403]
Schwartz-Negishi	**Zr** reagent (Cp_2ZrHCl) for hydrozirconation of C,C double and triple bonds [404]
Sharpless	**Ti**(OR_4) / ROOH / tartrate for enantioselective epoxidation of allyl alcohols
Suzuki	**Pd**-catalyzed coupling of aryl and vinyl boron compounds with halides [405]
Tebbe-Grubbs	**Ti** / Al–carbene complex for methylenation of carbonyl compounds (also esters, amides) [29]
Tsuji-Trost	**Pd** allyl complexes for C,C coupling, especially for cyclizations [406,407]
Vollhardt	**Co** complexes for cyclotrimerization of acetylenes (also with the participation of nitriles) to aromatic systems

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.[436–438] 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

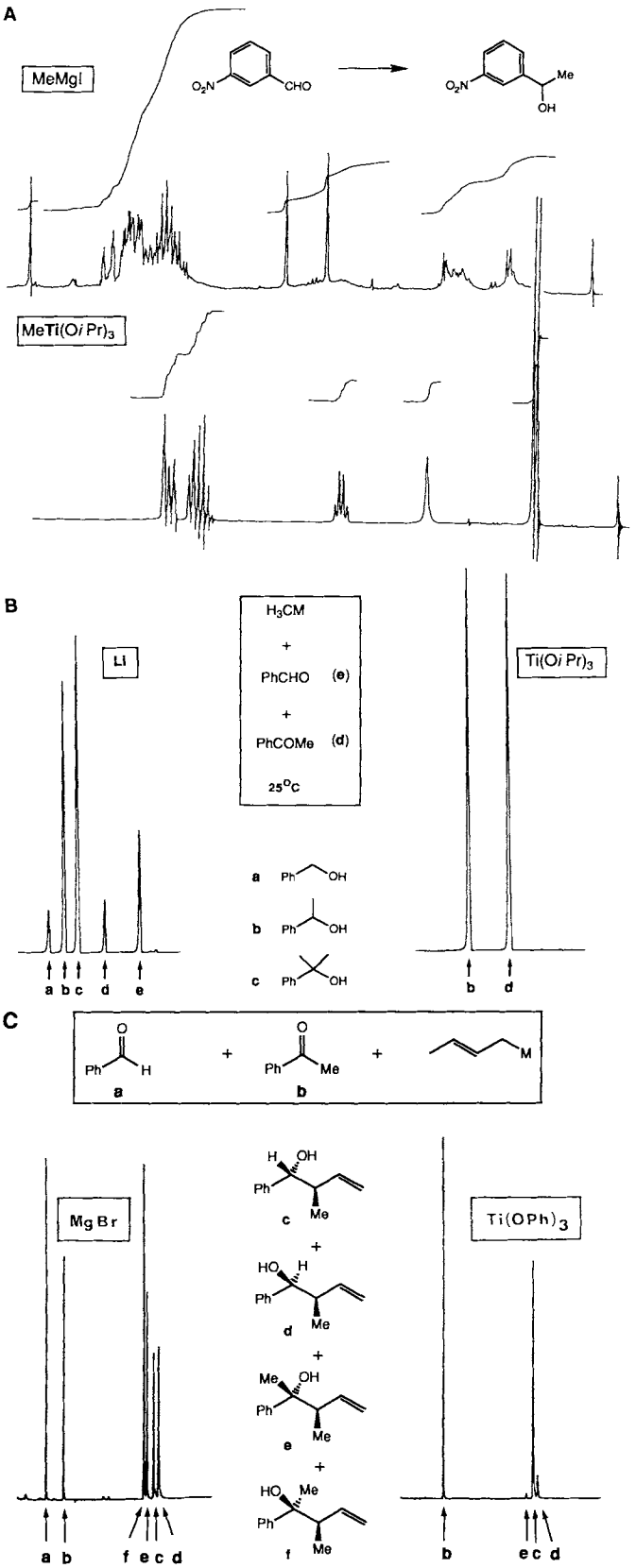
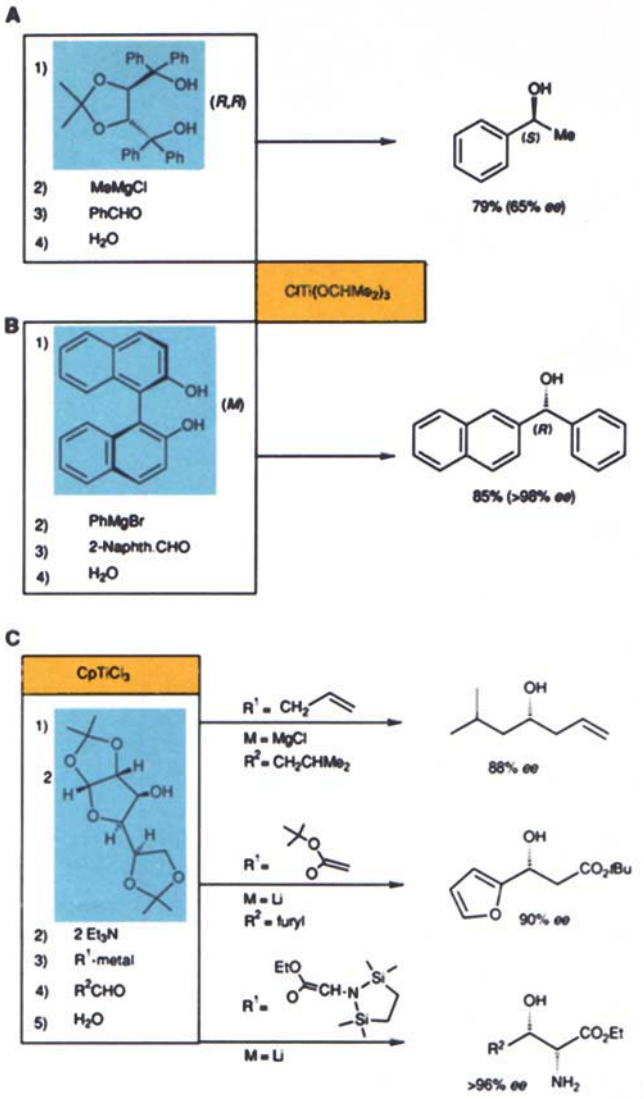
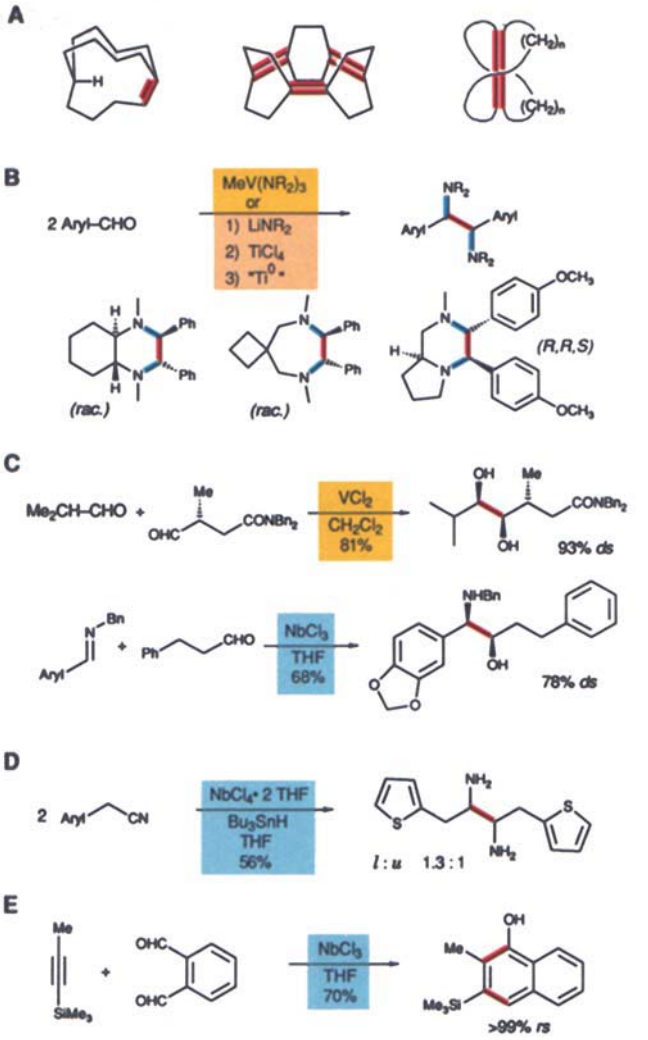


Fig. 12. Three examples of yield and selectivity increases that can be achieved by transmetallation of Li and Mg reagents to Ti derivatives. A) A glance at the NMR spectrum of the crude product betrays the high yield obtained upon addition of the methyltitanium reagent to *m*-nitrobenzaldehyde [418] relative to addition of a Grignard reagent. B) A comparison of crude product gas chromatograms reveals the perfect selectivity of MeTi vs. MeLi 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].



Scheme 22. The in situ generation of chiral alkyl, allyl, aryl, and vinyloxytitanium derivatives bearing $(R^*O)_2$ ligands, followed by addition to aldehydes. A) The chiral diol derived from tartaric acid [272–274] ensures fair-to-good enantiomeric excesses in the addition of alkyl groups to aldehydes (in this example, 79% yield, 65% *ee*) [273a, 275]. B) Particularly useful for the preparation of enantiomerically pure benzhydrol derivatives [419, 420] is the binaphthol ligand (here providing an 85% yield, > 98% *ee*) [402]. C) The use of CpTi derivatives in which the R*O group is derived from glucose offers distinct advantages (recoverability of $CpTiCl_3$; inexpensive, commercially available auxiliary; reproducible results); this method has been successfully utilized for allyl transfer (*lk* combination, cf. Fig. 12c) and aldol additions [421]. The diol shown in A has also been allowed to react with $CpTiCl_3$, providing access to both enantiomers of products of the type illustrated in C [422].



Scheme 23. Reductive coupling of carbonyl compounds and their analogues using derivatives of low-valent metals from the fourth and fifth subgroups. A) Three (attractive!) unsaturated hydrocarbons prepared from the corresponding diketones and a ketoaldehyde via the McMurry reaction (reviews: [342b–d]). B) Reductively aminating one-pot coupling of aromatic aldehydes to 1,2-diarylethan-1,2-diamines using either a vanadium(IV) derivative [423] or "titanium(0)" [342d, 424]. C) Diastereoselective crossed coupling with VCl_2 of two different aldehydes [425], and of an imine and an aldehyde using $NbCl_5$ [426] (cf. also the *like*-selective coupling of aromatic aldehydes with $TiCl_4$/BuLi [427]). D) 1,2-Diamines from nitriles and $NbCl_4$/Bu_3SnH [428]. E) Regioselective reductive [4 + 2]-carbocyclization of *o*-phthalaldehyde with an alkyne to give a naphthol [429] (rs = regioselectivity).

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,[439] 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),[440] which has in turn forced industry to amend its ways.[435, 441, 442] 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 enan-

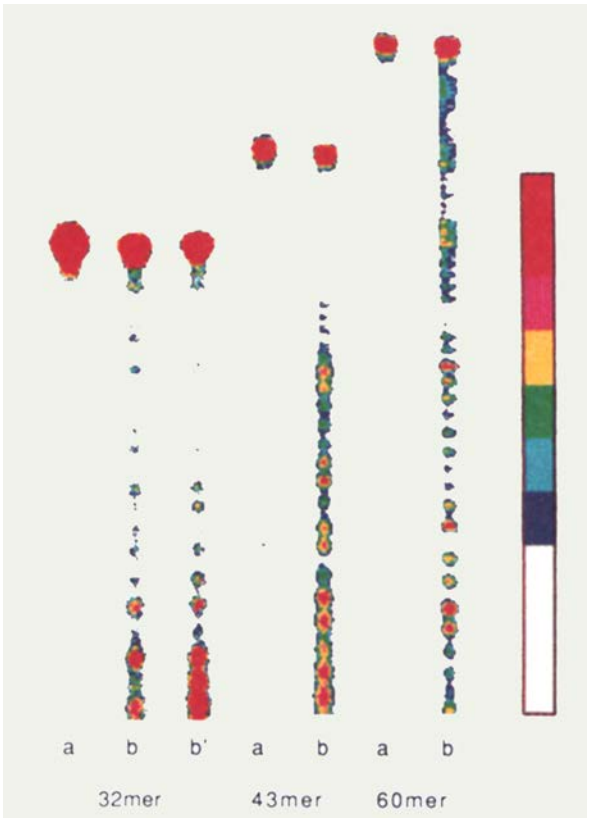
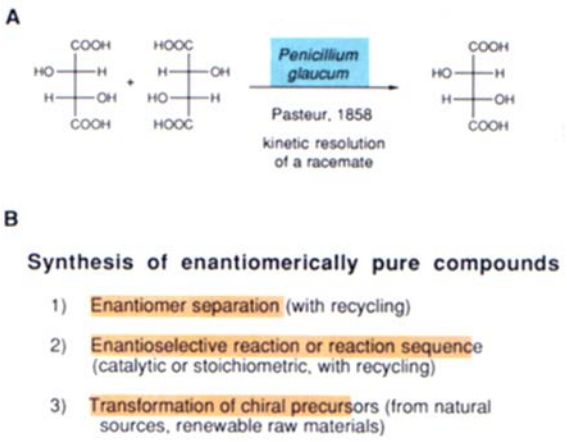


Fig. 13. "Bio-image" chromatogram of oligo-DNA crude products [430–433]. Track a: products prepared via the new (allyl–allyloxycarbonyl) protective group method. Track b: products obtained by what are now the standard routes. Color scale: red (high intensity) to blue (lower intensity) [434].



Scheme 24. *Pasteur*'s kinetic separation of the tartaric acid enantiomers with the aid of a microorganism (an enantioselective biological-chemical reaction!), and the three techniques for synthesis of enantiomerically pure compounds. A) If *Penicillium glaucum* is permitted to grow on racemic tartaric acid (*acidum racemicum*), fermentation ceases as soon as the (*R*,*R*)-(+)-tartaric acid has been consumed; *Pasteur* succeeded in isolating residual (−)-enantiomer from the growth medium. B) The following review articles on the three methods of preparing enantiomerically pure compounds (EPCs) have already been cited in Sections 2–5: separation of racemates [133–137, 343a], enantioselective reaction [125, 126, 331a, c, 353, 354, 402, 435], incorporation of chiral building blocks [199, 352–354] (the author of the present article accepts responsibility for the widespread use of the term "chiral pool" [443]—a sin from the days of his youth, of which he first became fully aware in *Vlado Prelog*'s circle [444, 445]; a "readily available supply" cannot be chiral! See the remarks in [436]).

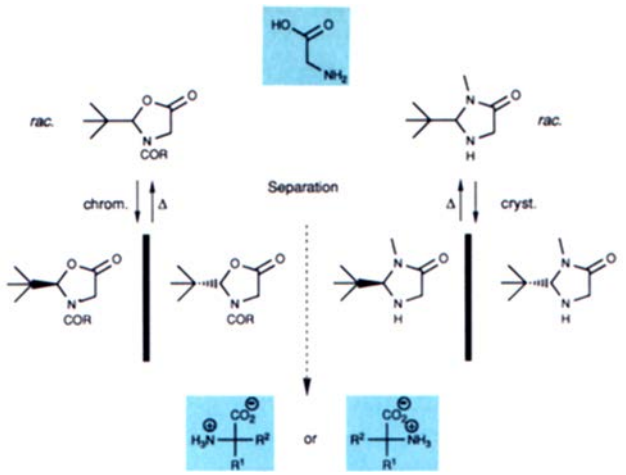
tiomers: separation of a racemic mixture, enantioselective reaction, and synthesis based on chiral starting materials isolated from natural sources. Quite properly, synthetic chemists devoted themselves first to the subject of reactivity in general, and natural products chemists nearly always synthesized their targets in racemic form. After all, a complex synthesis must be seen basically as the struggle to arrive at a correct constitution containing many stereogenic units; enantioselective generation of the first center of chirality, or separation of some intermediate into its enantiomers ("resolution"), represented the least of the worries! Times have changed, however, and interest in this subject has now become so intense that entire conferences have been devoted to it.[442, 446] Some have hailed enantioselective synthesis as *the* challenge,[447] and new publications have been established with titles like *Asymmetry* and *Chirality*.[448] In the present context it will be possible to touch upon only a few highlights.[449] Moreover, the subject itself is such that it precludes the offering of general prescriptions or advice regarding, for example, which of the three general approaches to enantiomerically pure compounds is "the best".

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.[86] By the way, the *tert*-butyl group responsible here for selectivity came from BASF, which supported our work with a gener-

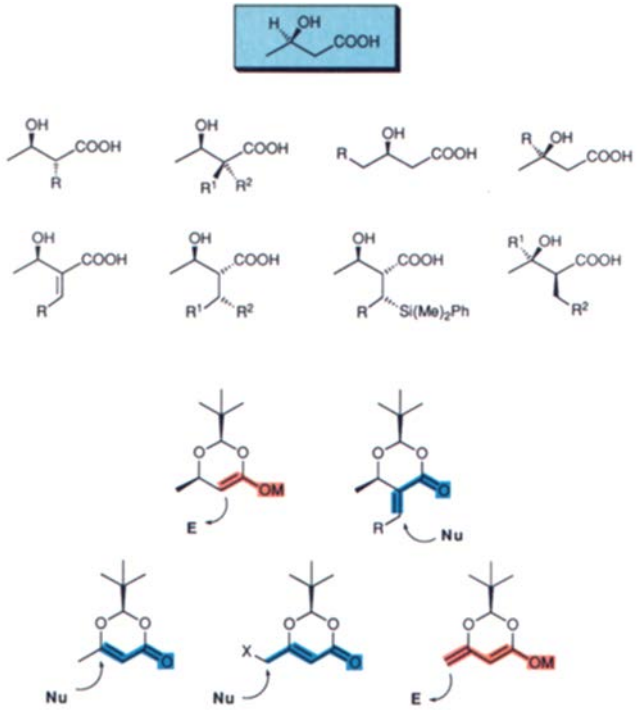
[*] An allusion to Margaret's (Gretchen's) famous query of Faust: "How do you feel about religion?" (Goethe).



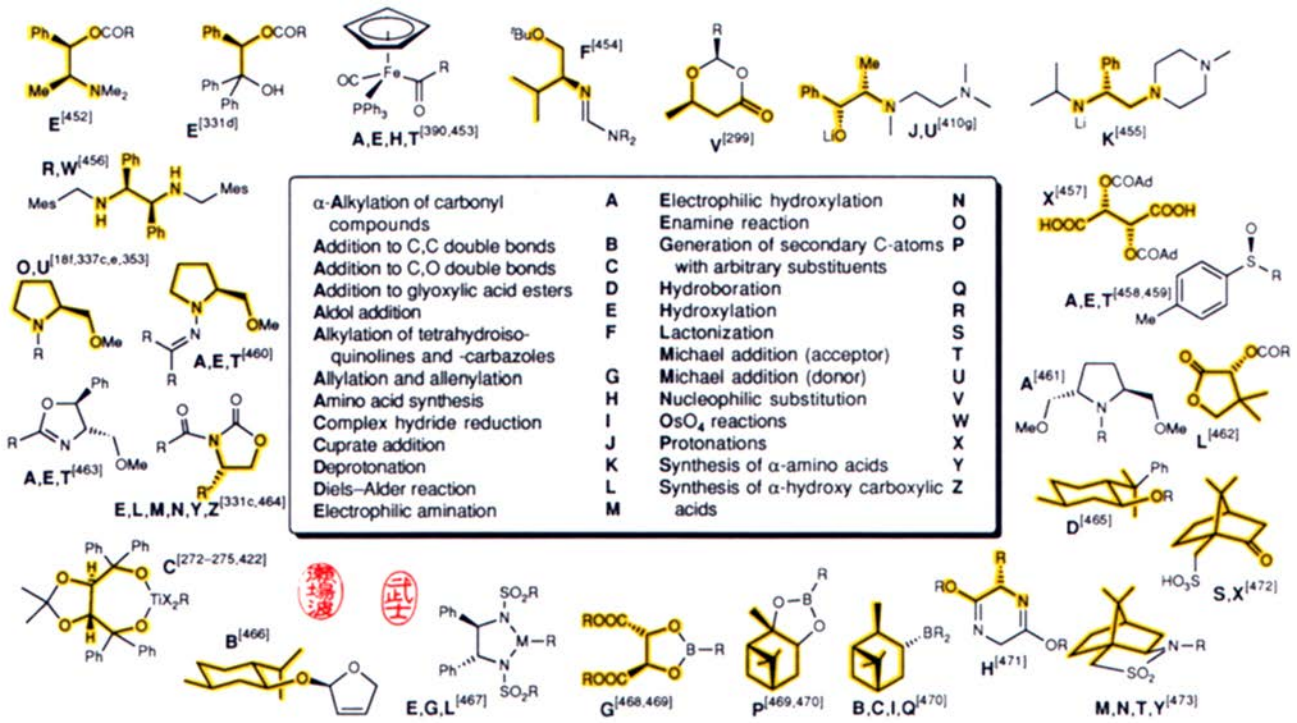
Scheme 25. Glycine derivatives that are readily accessible by the separation of racemates and are useful in the synthesis of (*R*) or (*S*) amino acids. The oxazolidinones (R = OBn, aryl) are obtained by the chromatographic separation of enantiomers [137] (Fig. 1), and the imidazolidinones by crystallization of their mandelic acid salts [450] (recycling by heating). A versatile series of transformations [137, 353, 450, 451] leads ultimately to branched and unbranched nonproteinogenic 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 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 aldol adducts 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]).



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.

thol, pinene, or camphor. The long list of suggested applications for *Evans*' acyloxazolidinone is testimony to the profound significance of this particular reagent (cf., for example, the total synthesis of fujimycin).[51]

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 10^6–10^9%, 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."[64b, 485]

It is no wonder that synthetic chemists have frequently tried to make direct use of biochemical catalysts,[486] and countless standard laboratory methods[487–489] have been perfected for the biological-chemical synthesis of simple compounds. Increasingly, however, various research groups are turning their attention to non-biochemical catalysis.[490] 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*

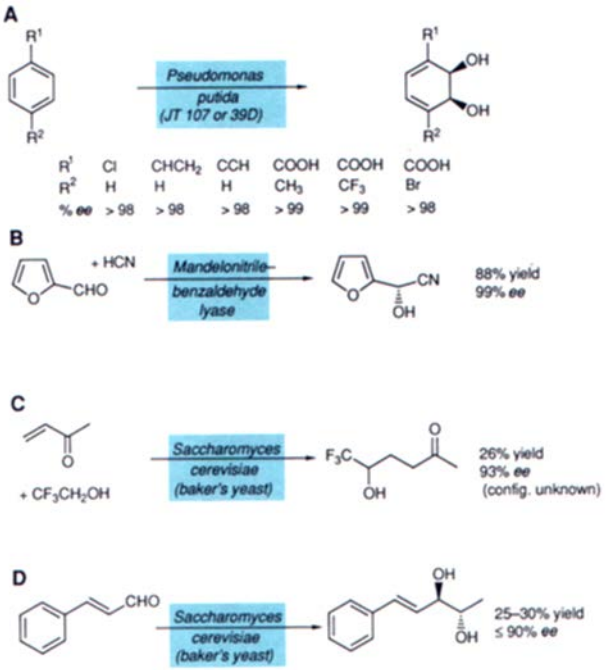
Biological-chemical transformations on both an industrial scale and in the laboratory can be carried out using either whole cells or isolated enzymes. In certain industrial applications it has even proven feasible to "optimize" the required organisms or enzymes, sometimes carrying it to the point of preparing abzymes (Sec. 2.3).[114] 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),[232] a copolymer based on (*R*)-3-hydroxybutyric and valeric acids (PHB/PHV, Biopol®, with *Hydrogenomonas eutropha*),[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 *Escherichiia coli* modified with the aid of gene technology), hydroxysteroids (using oxygenases),[497] vitamin C (L-sorbose, from D-sorbitol, with *Acetobacter suboxydans*),[229] and tartaric acid.[352] A recently conducted analysis[498] 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[488b] 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"),[504a]

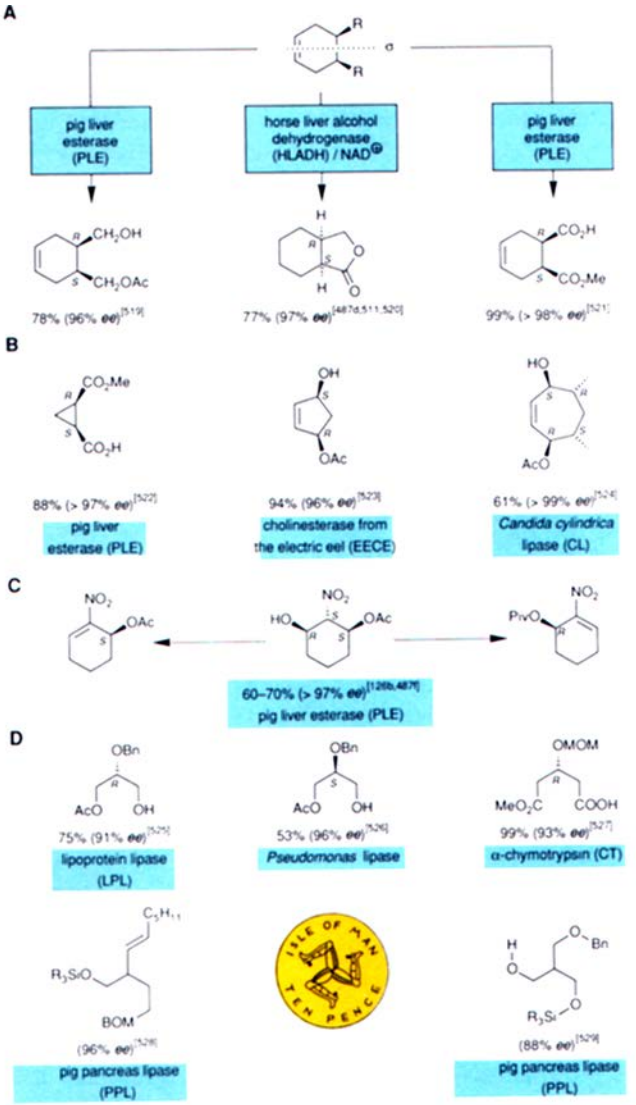
temporary modification of the substrate (cf. protective group techniques),[503] or switching to an organic medium (e.g., the "microemulsion"[504b] method).[505] Use of the easily cultured thermophilic microorganism *Thermoanaerobium brockii*, which is most comfortable at 70–80 °C, may lead to advantages in both selectivity and convenience (sterilization of the apparatus is not required).[506, 507] 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[126]); 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[508–510] and a small[511] scale. Here the enzymes themselves are immobilized on a solid phase or trapped within a membrane[509–511] (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,[125, 512, 513] 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 metal ions).

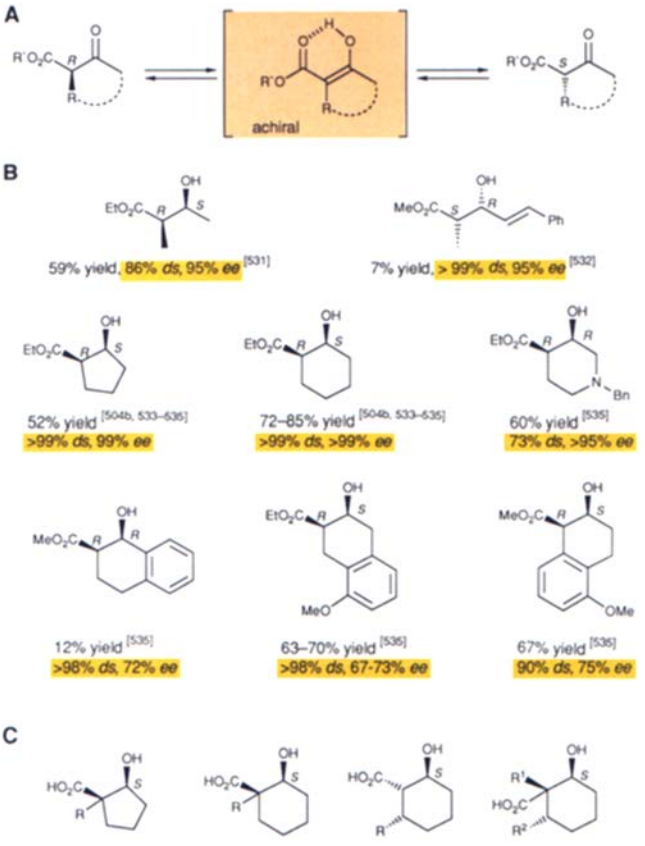
Even a cursory examination of the many "unnatural" compounds that have been successfully subjected to biological-chemical transformations[486–489, 496, 512] reveals a remarkable degree of diversity, and one is forced to conclude that enzymes are amazingly "tolerant".[536] Perhaps it is no accident that the most frequently utilized biological reagents have assignments in nature that also demand flexibility.



Scheme 28. Biological-chemical reactions involving enantioselective hydroxylation or C–C bond formation. A) The microorganisms capable of hydroxylating arenes to cyclohexadiendiols were discovered in a landfill in which aromatic compounds had been deposited [231, 496, 514]. B) MBL, extracted from almond flour, catalyzes the cyanohydrin reaction to give the nitriles of (*R*)-2-hydroxycarboxylic acids, a procedure that is effective with both aliphatic and aromatic aldehydes [513]. C) Formally speaking, this is a Michael addition of trifluoroethanol (d^1 reactivity [18g]) to methyl vinyl ketone (oxidation of trifluoroethanol to an aldehyde and thiamine pyrophosphate umpolung !?) [515]. D) Analogous reaction involving 1,2-addition of acetaldehyde to cinnamaldehyde [516].



Scheme 29. Compounds with the *meso* configuration [517] and other achiral educts containing enantiotopic groups [518] 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 (e.g., C). A) Products derived ultimately from the Diels–Alder adduct of butadiene with maleic ester; in the first case, R = CH_2OAc; in the second, CH_2OH (hydrogenation of the double bond!); in the third, CO_2Me. B) Three-, five-, and seven-membered ring derivatives containing up to four stereogenic centers and prepared from *meso* precursors. C) Three adjacent functional groups and stereogenic centers in a cyclohexane and enantiomeric nitrocyclohexenyl esters. D) Chiral derivatives of compounds with C_s and C_{3v} symmetry—versatile educts!

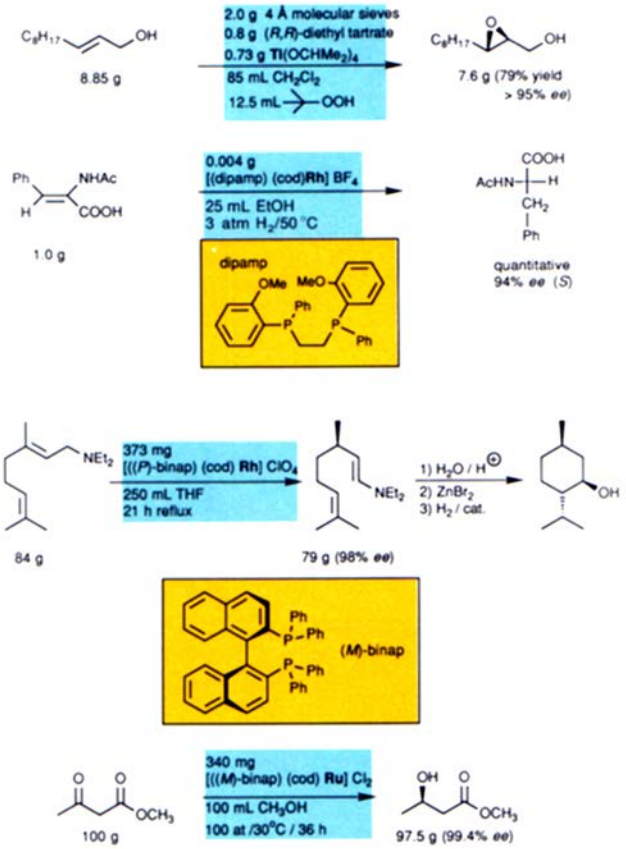


Scheme 30. Baker's yeast will do it [530]! Yeast reduction of 3-oxo esters with stereogenic centers at the 2-position is preceded by keto–enol tautomerization. Yeast reduces the (*R*) enantiomer, thereby removing it from the equilibrium; the process can thus be described as a kinetic resolution of enantiomers with in situ recycling, followed by diastereoselective reduction. The relative topicity [444] of the carbonyl reduction is consistent with the Prelog rule; that is, hydride is transferred from the *Re* side of the trigonal center in R_tCOR_s (with the priority $R_t > R_s$; in the case of styryl derivatives the styryl group assumes priority—although with a yield this low it is questionable whether any such consideration is permissible!). A) Equilibrium between enantiomeric 3-oxo esters. B) Yeast reduction products of the corresponding 3-oxo esters. C) Enantiomerically pure hydroxycyclopentane- and hydroxycyclohexanecarboxylic acid derivatives from the corresponding yeast reduction products [534].

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

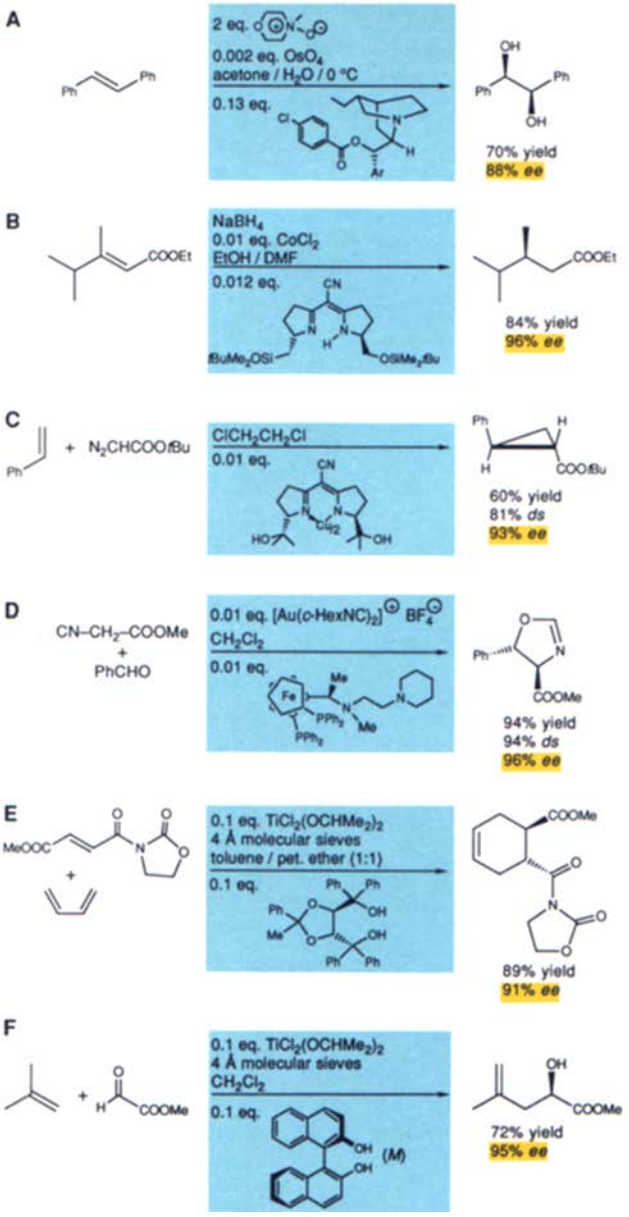
So far, the only popular, standard laboratory reaction that is both enantioselective and catalytic in nature is the Sharpless epoxidation.[537] Not only does it employ inexpensive reagents (*tert*-butylhydroperoxide, titanate, and ethyl tartrate) and involve educts (allyl alcohols) and products (epoxides) 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.[538] An example of a simple enantioselective epoxidation is presented in Scheme 31.



Scheme 31. Four examples of enantioselective transformations catalyzed by transition metals: Sharpless epoxidation of 2-undecen-1-ol [537d], Knowles hydrogenation to phenylalanine [435, 539], the Otsuka synthesis of menthol [540], and Noyori reduction of acetoacetic ester [402a].

Enantioselective hydrogenations and hydrogen shifts catalyzed by phosphane complexes of rhodium and ruthenium[402, 539–541] (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[402a] 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.[230] The "volume yield" criterion (i.e., mass of product obtained per unit volume of reactor) argues for the non-biological procedure.

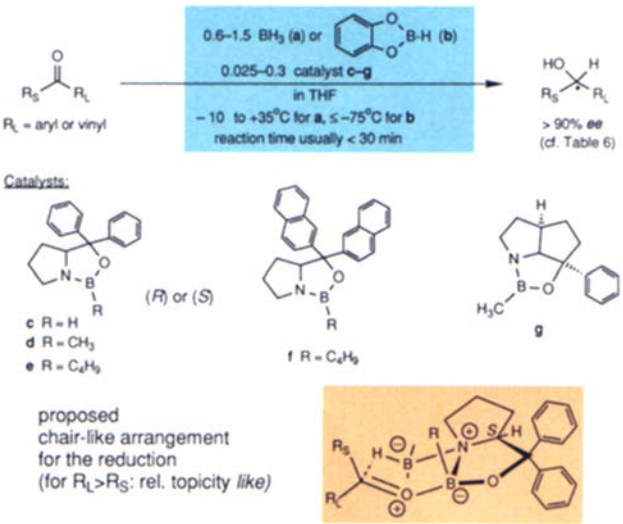
Scheme 32 illustrates a few other standard organic reactions[542] that can be induced to proceed in a catalytic and enantioselective way by the addition of transition-metal complexes. Brief mention should also be made of two catalytic processes that do not involve the ligand spheres of metals: a phase-transfer route to enantioselective amino acid synthesis[543a] and the cycloaddition reaction of ketene with α-halogenated aldehydes to give β-lactones, catalyzed by cinchona alkaloids.[543b]



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 $NaBH_4$/chiral-Co catalyst (ligand based on pyroglutamic acid) [490e]. C) Cyclopropanation with diazoacetic ester [copper(II)/chiral-semicorrin ligand] [490e]. D) The gold complex of a complicated chiral-ferrocene ligand catalyzes the addition of isocyanoacetic ester to benzaldehyde, leading to a *threo*-phenylserine derivative [545]. E) A ligand derived from tartaric acid [272–275] provides a Ti complex capable of catalyzing the Diels–Alder reaction in an enantioselective way [546, 547]. F) A derivative prepared from binaphthol/$TiCl_2(OCHMe_2)_2$ causes differentiation between the enantiotopic faces of the aldehyde in the ene reaction of isobutylene with glyoxylic ester [548].

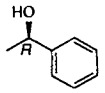
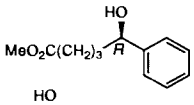
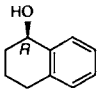
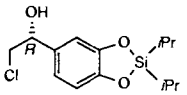
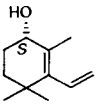
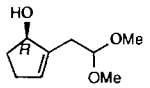
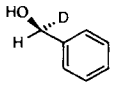
It is interesting to note that many reactions called "catalytic" in the literature actually require the addition of rather large amounts of the alleged catalyst. For example, consider a benzylated or benzoylated quinine derivative with a molecular weight of over 400 daltons. If 0.1 mole-equivalent of 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.[549] It is also remarkable that 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[550]—the recently proposed mechanism for the Sharpless epoxidation is a case in point[537f]—the rational design of a structurally defined chiral catalyst is still in its infancy.[551] 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 zinc[552] and alkyl lead[553] derivatives, but most interesting perhaps are the boranes and borates.[554] The latter have the advantage that their reactions seem to lend themselves best—before or after the fact—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[555] 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 33. The catalytic enantioselective reduction due to *Corey* et al. [559]. Several examples and references are collected in Table 6. As suggested by the analogy to an assembly line worker (see text), the authors believe that the bi- or tricyclic boron derivative functions at the boron atom as a Lewis acid, which is capable of activating the ketone that is to be reduced. The neighboring bridgehead nitrogen atom in turn binds to borane, activating it for the hydride transfer. The two achiral reaction partners are brought together in a chiral environment such that one of the enantiotopic sides of the carbonyl group is preferentially directed toward the hydride-transferring boron atom. Nevertheless, it is also important for the catalytic course of the reaction that the product alcoholate group is transferred from the boron atom in the ring to another boron atom, thereby removing it from the catalyst.

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.

Product from the corresponding ketone (or aldehyde)			Borane		Catalyst		Ref.
formula	yield	*ee*		equiv.		equiv.	
	> 99%	97%	**a**	1.2	(*S*)-**c**	0.1	[559]
	quant.	97%	**a**	0.6	(*S*)-**d**	0.1	[560]
	> 90%	95%	**a**	0.6	**g**	0.1	[561]
	96%	97%	**a**	0.6	(*R*)-**f**	0.1	[562]
	> 95%	93%	**b**	1.5–2.0	(*S*)-**e**	0.1	[563]
	91%	90%	**a**	0.6	(*R*)-**d**	0.2	[564]
	88%	93%	**a**	0.6	(*S*)-**d**	0.1	[565]
	90%	91%	**b**	1.5	(*S*)-**f**	0.3	[566]

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)

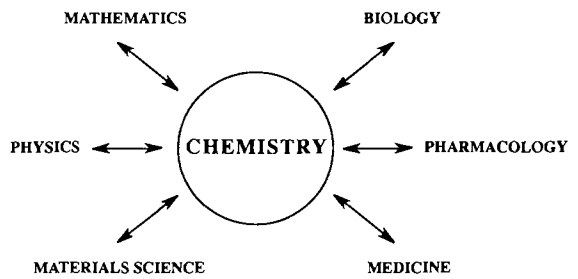
In presenting a paper or a talk, nothing is worse than beginning with a bad title, and the worst titles are ones that promise too much! I hope my contribution does not fit in this category, though I confess that the last part of the title ("Where now?") caused me to lose a certain amount of sleep and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

Fig. 14. Color plate based on an ancient Egyptian pattern [and distributed by the Franklin Mint AG, Zug (Switzerland)]. Hunter and huntress are shown with homochiral pairs of left hands, despite which they achieve their goal. The author hopes–despite taking controversial positions, passing judgments, and making difficult decisions regarding the research areas and research groups to be mentioned–that no friendships or feelings have been hurt, and that (unlike the archer in this picture) he has not put his neck into the "noose".

I consider the most important message: that organic synthesis continues to react forcefully and with vitality to new challenges, still ready to pursue old dreams. Considering the



Scheme 34. Chemistry—including organic synthesis—at the center of the natural and technical sciences.

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).[568] 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 (bibliography); Silvia Sigrist (preparation of the manuscript); Linda Behrendt (figures, schemes, tables); Josef Meienberger (departmental librarian) and Christoph von den Bussche Hünnefeld (literature searches); Bernd Lamatsch and Dietmar Plattner (strucural data); Stefan Blank, Denis 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 privilege 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 acknowledgements 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 (Irvine), 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. Russey*, Huntingdon, PA (USA)

[1] *Roald Hoffmann* is currently working on a 26-part television series entitled "The World of Chemistry" for broadcast in the USA in 1991. He has also planned a series of three one-hour broadcasts entitled "The Molecular World"! [S. C. Stinson, *Chem. Eng. News 67* (1989) No. 23, pp. 19–21].

[2] *J. Maddox*, editor of the journal *Nature*, made the following assertion during a speech in Maastricht (Netherlands) in March 1988: "Chemists have done wonders in losing their identity in the rest of science. Some might argue the point, but it is a fact that the Nobel committee awarded its 1985 chemistry prize to a pair of mathematicians.—Meanwhile, the practice of what still passes for chemistry seems to have been largely preempted by outsiders—physicists, quantum theoreticists, computer mavens, statisticians, instrument designers, laser experts, genetic engineers, medical researchers, psychiatrists, astronomers, material specialists and a host of other species. Truly, the science of chemistry has lost its identity." (These sentences have been quoted with Mr. *Maddox*'s permission, cf. also [12b].)

[3] *H. A. Hauptman* and *J. Karle*, for developing the direct methods of solving X-ray structures of molecules containing no heavy atoms. "Direct Methods and Anomalous Dispersion" (Nobel Lecture): H. Hauptman, *Angew. Chem. 98* (1986) 600–610; *Angew. Chem. Int. Ed. Engl. 25* (1986) 603–613; "Recovering Phase Information from Intensity Data" (Nobel Lecture): J. Karle, *ibid. 98* (1986) 611–626 and *25* (1986) 614–629.

[4] It is worth reading in this context an editorial by R. Scheffold with the title "Synthese: Jugendstil oder Postmoderne" [*Chimia 43* (1989) 37]; cf. also the thoughts expressed by B. Giese on the theme "Perspektiven der organischen Chemie" [*Merck-Spektrum (Darmstadt) 1/90* (1990)]. A troubled analysis of the situation of our discipline bears the title "What's wrong with chemistry?" [M. Heylin, *Chem. Eng. News 68* (1990) No. 5, p. 3].

[5] "DNA Sequencing and Gene Structure" (Nobel Lecture): W. Gilbert, *Science (Washington D.C.) 214* (1981) 1305–1312.

[6] Monograph: W. Saenger: *Principles of Nucleic Acid Structure*, Springer, New York 1984.

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[13] A recently published book that illustrates how the products of chemistry have transformed everyday life in the past 135 years: E. Bäumler: *Farben Formeln Forscher. Hoechst und die Geschichte der industriellen Chemie in Deutschland*, Piper Verlag, München 1990.

[14] 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 Catalysis* ("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").

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[36] The "Habilitationsschrift" of *R. Neier*, Universität Freiburg (Switzerland) 1989, contains an interesting discussion (with extensive bibliography) of the history of natural product synthesis and the role it has played in the discovery of new synthetic methods. I wish to thank Dr. *Neier* for providing me with a copy of this work.

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[52] a) 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 beast".

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[73] As, for example, conductive organic materials, or even superconductors, liquid crystals, ferroelectrics, materals for non-linear optics and information storage, layers and coatings, fibers, membranes, vesicles, and much besides. A recently published article bears the prognosis-rich title: "Materials for the Next Millenium": E. D. Hondros, E. Bullock, *Angew. Chem. Adv. Mater. 101* (1989) 1114–1123; *Angew. Chem. Int. Ed. Engl. Adv. Mater. 28* (1989) 1088–1097; *Adv. Mater. 1989*, 260–269; for a delightful presentation of "Organische Magnete, Idee und Realität" see L. Dulog, *Nachr. Chem. Tech. Lab. 38* (1990) 445–451; "Materials for Optical Data Storage": M. Emmelius, G. Pawlowski, H. W. Vollmann, *Angew. Chem. 101* (1989) 1475–1502; *Angew. Chem. Int. Ed. Engl. 28* (1989) 1445–1471.

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[77] "Pharmaceutical Proteins": D. Blohm, C. Bollschweiler, H. Hillen, *Angew. Chem. 100* (1988) 213–231; *Angew. Chem. Int. Ed. Engl. 27* (1988) 207–225.

[78] *Leopold Ruzicka*'s vision with respect to the development of organic chemistry in the direction of biological chemistry has been documented in two recent articles: "Leopold Ruzicka: von der Isoprenregel zur Frage nach dem Ursprung des Lebens": A. Eschenmoser, *Rad Jugosl. Akad. Znan. Umjet. Kem.* [443] *7* (1989) 21–68 and "Leopold Ruzicka—From the Isoprene Rule to the Question of Life's Origin": A. Eschenmoser, *Chimia 44* (1990) 1–21.

[79] a) An excellent introduction, even though more than ten years old, is the monograph by A. Fersht: *Enzyme Structure and Mechanism*, W. H. Freeman & Co., Reading 1977. A more mechanistically oriented book is: C. Walsh: *Enzymatic Reaction Mechanisms*, W. H. Freeman & Co., San Francisco 1979. More "chemical" is: "Stereospecificity in Organic Chemistry and Enzymology": J. Rétey, J. A. Robinson in H. F. Ebel (Ed.): *Monographs in Modern Chemistry*, Verlag Chemie, Weinheim 1982. Probably *the* textbook of molecular biology is: B. Lewin: *Genes III*, 3rd ed., Wiley, New York 1987; b) see also the article about enzymatic reactions in S. M. Roberts (Ed.): *Molecular Recognition: Chemical and Biochemical Problems*, The Royal Society of Chemistry, Cambridge 1989.

[80] *Chemtracts: Organic Chemistry* (ISSN 0895-4445), co-published by Data Trace Inc. and Wiley, New York.

[81] "Drugs from Emasculated Hormones: The Principle of Syntopic Antagonism" (Nobel Lecture): J. W. Black, *Angew. Chem. 101* (1989) 910–919; *Angew. Chem. Int. Ed. Engl. 28* (1989) 886–894.

[82] "Selective Inhibitors of Dihydrofolate Reductase" (Nobel Lecture): G. H. Hitchings, Jr., *Angew. Chem. 101* (1989) 903–909; *Angew. Chem. Int. Ed. Engl. 28* (1989) 879–885.

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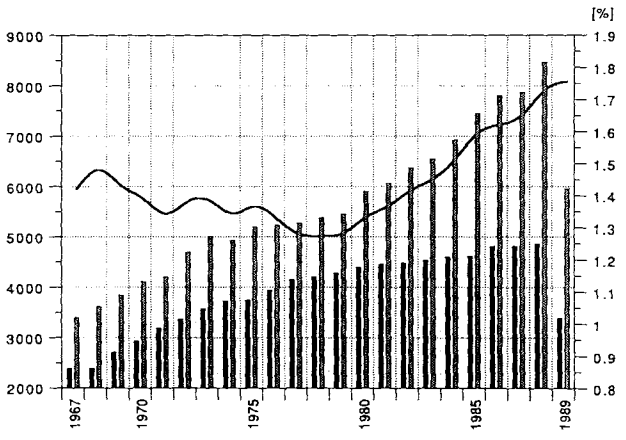
[87] The design of building blocks that mimic the turns in peptides and lead to conformational fixation ("turn mimetics") is subject to a great deal of phantasy; a few recent examples are described in the following publications: M. Kahn, B. Chen, *Tetrahedron Lett. 28* (1987) 1623; D. S. Kemp, W. E. Stites, *ibid. 29* (1988) 5057; M. G. Hinds, N. G. J. Richards, J. A. Robinson, *J. Chem. Soc. Chem. Commun. 1988*, 1447; amino acid isosteres for incorporation into peptides are intended to mimic the geometry and/or functionality of amino acids, but inhibit cleavage by peptidases: "Peptide Backbone Modifications: A Structure–Activity Analysis of Peptides Containing Amide Bond Surrogates, Conformational Constraints, and Related Backbone Replacements": A. F. Spatola in B. Weinstein (Ed.): *Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins, Vol. 7*, Marcel Dekker, New York 1983, pp. 267–357; "The Synthesis of Peptide Analogues with a Modified Peptide Bond": D. Tourwé, *Janssen Chim. Acta 3* (1985) No. 1, pp. 3–18.

[88] a) W. P. Jencks: *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York 1969; "Analog Approaches to the Structure of the Transition State in Enzyme Reactions": R. Wolfenden, *Acc. Chem. Res. 5* (1972) 10–18; b) S. Ghisla, H. Ogata, V. Massey, A. Schonbrunn, R. H. Abeles, C. T. Walsh, *Biochemistry 15* (1976) 1791.

[89] At the Chemical Congress of Pacific Basin Countries in Honolulu (17–22 Dec. 1989), 12% of all the contributions (lectures and posters) in the Organic Chemistry Section contained the five letters *fluor* in their titles; there were two symposia on organofluorine compounds, with the titles "Symposium on Modern Synthetic Methods in Fluorine Chemistry" and "Symposium on Biologically Active Organofluorine Compounds" (The 1989 International Chemical Congress of Pacific Basin Societies, Book of Abstracts II). The following fluorine symposia were arranged in the course of 1990 ACS conventions: 199th National ACS Meeting, 22–27 April 1990, Boston, MA: Symposium on the Effects of Selective Fluorination on Reactivity, Symposium on Fluorine Containing Polymeric Materials; 200th National ACS Meeting, 21–31 Aug. 1990, Washington, D.C.: Symposium on Mass Spectrometry of Fluorinated Compounds, Symposium on Fluorine Chemistry for Organic Chemists.

[90] The growing interest in fluorine chemistry is documented by the steadily increasing number of publications in the area. The following diagram was constructed on the basis of publications covered by *Chemical Abstracts* in the period from Jan. 1967 to March 1990 (solid bars: total number, in units of 100; dotted bars: publications indexed under "fluorine"; black line: contribution of "fluorine" publications in terms of percent).



[91] Monographs: a) M. Hudlicky: *Chemistry of Organic Fluorine Compounds, 2nd Edition*, Ellis Horwood, Chichester 1976; b) R. D. Chambers: *Fluorine in Organic Chemistry*, Wiley-Interscience, New York 1973; c) "Fluorinated Organic Molecules": B. E. Smart in J. F. Liebman, A. Greenberg (Eds.): *Molecular Structure and Energetics, Vol. 3*, VCH Publishers, Deerfield Beach 1986, pp. 141–191; d) J. F. Liebman, A. Greenberg, W. R. Dolbier, Jr.: *Fluorine-Containing Molecules—Structure, Reactivity, Synthesis and Applications*, VCH Publishers, New York 1988; e) J. T. Welch, S. Eswarakrishnan: *Fluorine in Bioorganic Chemistry*, Wiley, New York 1990.

[92] Recent review articles with an emphasis on synthetic aspects of the chemistry of organofluorine compounds: a) "Modern Synthetic Procedures for the Fluorination of Organic Molecules": A. Haas, M. Lieb, *Chimia 39* (1985) 134–140; b) "Präparative Fluorierung mit molekularem Fluor": H. Vyplel, *ibid. 39* (1985) 305–311; c) "Fluorination with Diethylaminosulfur Trifluoride and Related Aminofluorosulfuranes": M. Hudlicky, *Org. React. (N. Y.) 35* (1988) 513–637; d) "A Guide to Modern Organofluorine Chemistry": R. E. Banks, J. C. Tatlow, *J. Fluorine Chem. 33* (1986) 227–284; e) "Exploration into Selective Monofluorination Methods and Their Application to the Synthesis of Fluorinated Bio-active Compounds": M. Shimizu, H. Yoshioka, *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem. Jpn.) 47* (1989) 27–39; f) "Fluor in der organischen Synthese" (Synthese im Blickpunkt): R. Bohlmann, *Nachr. Chem. Tech. Lab. 38* (1990) 40–43; g) "Drucklose Direktfluorierung—eine einfache Methode zur präparativen Synthese von neuen Fluorierungsreagenzien": K. Auer, E. Hungerbühler, R. W. Lang, *Chimia 44* (1990) 120. A few reviews that have appeared since 1987 and which focus on the biological activity of F-derivatives: h) "Modern Methods for the Introduction of Fluorine into Organic Molecules: An Approach to Compounds with Altered Chemical and Biological Activities": J. Mann, *Chem. Soc. Rev. 16* (1987) 381–436; i) "A New Approach to Synthetic Pyrethroids Having a Trifluoromethyl Group": M. Fujita, T. Hiyama, *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem. Jpn.) 45* (1987) 664–671; j) "New Catalytic Reactions of the Hydrolytic Enzymes in Fluorine Chemistry": T. Kitazume, T. Yamazaki, *ibid. 45* (1987) 888–897; k) "Advances in the Preparation of Biologically Active Organofluorine Compounds": J. T. Welch, *Tetrahedron 43* (1987) 3123–3197; l) "Synthetic Fluoropeptides as Pharmacologically Useful Compounds": B. Imperiali, *Adv. Biotechnol. Processes 10* (1988) 97–129.

[93] 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]).

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[96] "Fluorierte Nitro- und Aminoalkohole": D. Seebach, A. K. Beck, *DOS 3 540 332* (1987), Bayer AG; *Chem. Abstr. 107* (1987) 115 246e; "Verfahren zur Herstellung von fluorierten Nitroalkylverbindungen": D. Seebach, A. K. Beck, *DOS 3 808 276* (1988), Bayer AG; *Chem. Abstr. 112* (1990) 98013k; "Synthesis of Fluorinated Nitro- and Aminoalcohols": B. Baasner, M. J. Negele, A. K. Beck, D. Seebach, *12th Int. Symp. Fluorine Chem.* 7–12 Aug. 1988, Santa Cruz, CA (USA), Abstr. 331.

[97] M. Ács, C. von dem Bussche, D. Seebach, *Chimia 44* (1990) 90; A. K. Beck, M. Gautschi, D. Seebach, *Chimia 44* (1990), 291.

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[101] T. Shimizu, M. Hatano, *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem. Jpn.) 43* (1985) 371–381.

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[103] T. A. Alston, D. J. T. Porter, H. J. Bright, *Acc. Chem. Res. 16* (1983) 418–424.

[104] Examples of recent reviews on nitroaliphatics: a) H. Feuer, A. T. Nielsen (Eds.): *Nitro Compounds—Recent Advances in Synthesis and Chemistry*, VCH Publishers, New York 1990; b) G. A. Olah, R. Malhotra, S. C. Narana: *Nitration—Methods and Mechanisms*, VCH Publishers, New York 1989; c) K. B. G. Torssell: *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis—Novel Strategies in Synthesis*, VCH Publishers, New York 1988; d) "Functionalized Nitroalkanes are Useful Reagents for Alkyl Anion Syntheses": G. Rosini, R. Ballini, *Synthesis 1988*, 833–847.

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(1990) 257; M. Kira, K. Sato, C. Kabuto, H. Sakurai, *ibid. 111* (1989) 3747; "Selektive Tranformationen mit pentakoordinierten Siliciumverbindungen" (Synthese im Blickpunkt): D. Schinzer, *Nachr. Chem. Tech. Lab. 37* (1989) 28–30; see also the references in Schemes 15 and 16 and in Table 3; b) an extensive collection (*ca.* 2000 literature references) of structures of organosilicon compounds (including pentacoordinate cases) can be found in: E. Lukevics, O. Pudova, R. Sturkovich: *Molecular Structure of Organosilicon Compounds*, Wiley, New York 1989.

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[124] N. Janjic, A. Tramontano, *J. Am. Chem. Soc. 111* (1989) 9109; K. M. Shokat, C. H. Leumann, R. Sugasawara, P. G. Schultz, *Angew. Chem. 100* (1988) 1227; *Angew. Chem. Int. Ed. Engl. 27* (1988) 1172.

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[464] "Stereoselective Aldol Condensations": D. A. Evans, J. V. Nelson, T. R. Taber, *Top. Stereochem. 13* (1982) 1–115; other transformations of Evans enolates: D. A. Evans, M. M. Morrissey, R. L. Dorow, *J. Am. Chem. Soc. 107* (1985) 4346; D. A. Evans, E. B. Sjogren, A. E. Weber, R. E. Conn, *Tetrahedron Lett. 28* (1987) 39; D. A. Evans, J. A. Ellman, R. L. Dorow, *ibid. 28* (1987) 1123; D. A. Evans, K. T. Chapman, J. Bisaha, *J. Am. Chem. Soc. 110* (1988) 1238; D. A. Evans, T. C. Britton, R. L. Dorow, J. F. Dellaria, Jr., *Tetrahedron 44* (1988) 5525.
[465] "New Perspectives in Asymmetric Induction": J. K. Whitesell, *Acc. Chem. Res. 18* (1985) 280–284.
[466] B. de Lange, F. van Bolhuis, B. L. Feringa, *Tetrahedron 45* (1989) 6799; J. F. G. A. Jansen, B. L. Feringa, *Tetrahedron Lett. 30* (1989) 5481.
[467] a) E. J. Corey, R. Imwinkelried, S. Pikul, Y. B. Xiang, *J. Am. Chem. Soc. 111* (1989) 5493; b) E. J. Corey, C.-M. Yu, S. S. Kim, *ibid. 111* (1989) 5495; c) E. J. Corey, C.-M. Yu, D.-H. Lee, *ibid. 112* (1990) 878.
[468] W. R. Roush, R. L. Halterman, *J. Am. Chem. Soc. 108* (1986) 294; W. R. Roush, L. Banfi, J. C. Park, L. K. Hoong, *Tetrahedron Lett. 30* (1989) 6457 and earlier cited work by the same research group.
[469] "Boronic Esters in Stereodirected Synthesis": D. S. Matteson, *Tetrahedron 45* (1989) 1859–1885; "Asymmetric Synthesis with Boronic Esters": D. S. Matteson, *Acc. Chem. Res. 21* (1988) 294–300; "The Use of Chiral Organoboranes in Organic Synthesis": D. S. Matteson, *Synthesis 1986*, 973–985.
[470] "Development of a Simple General Procedure for Synthesis of Pure Enantiomers *via* Chiral Organoboranes": H. C. Brown, B. Singaram,

Acc. Chem. Res. 21 (1988) 287–293; "Asymmetric Synthesis Made Easy": H. C. Brown, *Chemtracts: Org. Chem.1* (1988) 77–88; A. Pelter, K. Smith, H. C. Brown: *Borane Reagents*, Academic Press, London 1988.

[471] U. Schöllkopf, T. Tiller, J. Bardenhagen, *Tetrahedron 44* (1988) 5293 and earlier cited work related to the bislactim-ether method.

[472] K. Fuji, M. Node, S. Terada, M. Murata, H. Nagasawa, T. Taga, K. Machida, *J. Am. Chem. Soc. 107* (1985) 6404.

[473] "Camphor Derivatives as Chiral Auxiliaries in Asymmetric Synthesis": W. Oppolzer, *Tetrahedron 43* (1987) 1969–2004; "Metal-directed Stereoselective Functionalizations of Alkenes in Organic Synthesis": W. Oppolzer, *Pure Appl. Chem. 60* (1988) 39–48; W. Oppolzer, J. Blagg, I. Rodriguez, E. Walther, *J. Am. Chem. Soc. 112* (1990) 2767.

[474] J. Zimmermann, D. Seebach, T.-K. Ha, *Helv. Chim. Acta 71* (1988) 1143.

[475] Y. Noda, D. Seebach, *Helv. Chim. Acta 70* (1987) 2137.

[476] D. Seebach, U. Mißlitz, P. Uhlmann, *Angew. Chem. 101* (1989) 484; *Angew. Chem. Int. Ed. Engl. 28* (1989) 472.

[477] D. Seebach, R. Naef, *Helv. Chim. Acta 64* (1981) 2704.

[478] "Synthesis of Chiral Non-Racemic Compounds", Tetrahedron Symposia-in-Print Number 15: D. Seebach, R. Naef, G. Calderari, *Tetrahedron 40* (1984) 1313.

[479] "Methodology for the construction of quaternary carbon centers": S. F. Martin, *Tetrahedron 36* (1980) 419–460.

[480] Numerous pheromones have been prepared by *Mori* and coworkers starting with 3-hydroxybutyric acid, as well as with 3-hydroxyvaleric acid, which is also accessible from biopolymers: "Chiral Synthesis: Examples in the Pheromone Field": K. Mori, *Spec. Publ. R. Soc. Chem. 53* (1985) 293–306; "Chiral synthesis of bioactive natural products employing the building blocks of microbial origin": K. Mori, *Stud. Nat. Prod. Chem. 1* (1988) 677–712; "Recent Progress in Pheromone Chemistry": K. Mori, S. Kuwahara, *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem. Jpn.) 46* (1988) 467–477; "Synthesis of optically active pheromones": K. Mori, *Tetrahedron 45* (1989) 3233–3298.

[481] There continues to be a role for such old standbys as derivatives of glycerol and glyceraldehyde, which remain convenient and versatile sources of a *single* center of chirality: "Der 2,3-Isopropyliden-glycerinaldehyd—eine Modeverbindung" (Synthese im Blickpunkt): *Nachr. Chem. Tech. Lab. 32* (1984) 146–149; "Optisch aktive Glycerinderivate" (Synthese im Blickpunkt): H.-J. Altenbach, *ibid. 36* (1988) 33–38.

[482] Finally, sugars are still "in" as sources for the "pool" of chiral synthetic building blocks: "Chirale Bausteine aus Kohlenhydraten" (Synthese im Blickpunkt): K. Krohn, *Nachr. Chem. Tech. Lab. 35* (1987) 1155–1160; "New Chiral Synthons Derived from D-Glucose": H. Hashimoto, N. Kawaguchi, *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem. Jpn.) 45* (1987) 408–420; "Synthesis of Versatile Chiral Building Blocks Starting from D-Mannitol": S. Takano, K. Ogasawara, *ibid. 45* (1987) 1157–1170.

[483] "The Microbiological Production of Industrial Chemicals": D. E. Eveleigh, *Sci. Am. 245* (1981) No. 3, p. 120; *Spektrum Wiss. 1981*, No. 11, p. 88.

[484] T. H. Maugh II, *Science (Washington, D. C.) 221* (1983) 351.

[485] Even a general-circulation newspaper like DIE ZEIT (R. Schwerthöffer, *Die Zeit* No. 10, 2 March 1990, p. 96) recently devoted a half page in its science section to the subject *The Art of Catalysis* ("Die Chemie nutzt natürliche Vorbilder"), mentioning among other things *Corey*'s "Chemzymes".

[486] Previously cited books and reviews covering biological-chemical synthetic methods [79, 114, 125, 126, 241, 354]. A few additional, more recent articles: a) "Enzymes in Organic Syntheses": J. B. Jones in *F. E. C. S. Int. Conf. Chem. Biotechnol. Biol. Act. Nat. Prod. (3.)*, VCH Verlagsgesellschaft, Weinheim 1987, pp. 18–39; b) "Microbial and Enzymatic Processes for the Production of Biologically and Chemically Useful Compounds": H. Yamada, S. Shimizu, *Angew. Chem. 100* (1988) 640–661; *Angew. Chem. Int. Ed. Engl. 27* (1988) 622–642; c) "General Aspects and Optimization of Enantioselective Biocatalysis in Organic Solvents: The Use of Lipases": C.-S. Chen, C. J. Sih, *ibid. 101* (1989) 711–724 and *28* (1989) 695–707; d) "Resolution of Enantiomers *via* Biocatalysis": C. J. Sih, S.-H. Wu, *Top. Stereochem. 19* (1989) 63–126; e) "Baker's Yeast as a Reagent in Organic Synthesis": S. Servi, *Synthesis 1990*, 1–25.

[487] The following biological-chemical procedures have so far been incorporated into *Organic Syntheses*: a) yeast reduction of hydroxyacetone to (*S*)-propan-1,2-diol [P. A. Levene, A. Walti, *Coll. Vol. 2* (1943) 545]; b) emulsin-catalyzed dimerization of glucose to gentobiose [B. Helferich, J. F. Leete, *Coll. Vol. 3* (1955) 428]; c) yeast reduction of acetoacetic ester to ethyl (*S*)-3-hydroxybutyrate [D. Seebach, M. A. Sutter, R. H. Weber, M. F. Züger, *Vol. 63* (1985) 1]; d) the lactone from (1*S*,2*R*)-2-hydroxymethylcyclohexane carboxylic acid using horse liver alcohol dehydrogenase/NAD/FMN [J. B. Jones, I. J. Jakovac, *Vol. 63* (1985) 10]; e) yeast reduction of 2,2-dimethylcyclohexan-1,2-dione to (*S*)-3-hydroxy-2,2-dimethylcyclohexanone [K. Mori, H. Mori, *Vol. 68* (1989) 56]; f) (1*S*,2*S*,3*R*)-3-hydroxy-2-nitrocyclohexyl acetate by hydrolysis of the corresponding *meso*-nitrodiacetate with pig liver esterase [M. Eberle, M. Missbach, D. Seebach, *Vol. 69* (1990), 19].

[488] Numerous procedures for carrying out biological-chemical reactions can be found in the articles by *Fischli* as well as *Crout* and *Christen* (*Vol. 2* and *5* in the series *Modern Synthetic Methods*). A comparison reveals the progress in this field between 1980 and 1989: a) "Chiral Building Blocks in Enantiomer Synthesis Using Enzymatic Transformations": A. Fischli, *Mod. Synth. Methods 2* (1980) 269–350; b) "Biotransformations in Organic Synthesis": D. H. G. Crout, M. Christen, *ibid. 5* (1989) 1–114.

[489] A truly outstanding new book treating all the biological-chemical methods of preparative interest: H. G. Davies, R. H. Green, D. R. Kelly, S. M. Roberts: *Biotransformations in Preparative Organic Chemistry (The Use of Isolated Enzymes and Whole Cell Systems in Synthesis)* from the series *Best Synthetic Methods* [A. R. Katritzky, O. Meth-Cohn, C. W. Rees (Eds.)], Academic Press, London 1989.

[490] Previously cited books and reviews on the topic of organometallic catalysis [263b, 388, 390, 394, 400, 402, 405–407, 433, 435], above all the articles by *J. K. Stille, L. S. Hegedus* and *R. Scheffold* in [389] and citations in Scheme 17. A few additional more recent articles: a) "Enantioselective Synthesis with Optically Active Transition-Metal Catalysts": H. Brunner, *Synthesis 1988*, 645–654; b) "Enantioselective Synthesis of Organic Compounds with Optically Active Transition Metal Catalysts in Substoichiometric Quantities": H. Brunner, *Top. Stereochem. 18* (1988) 129–247; c) "Asymmetric homogeneous catalysis": J. M. Brown, *Chem. Br. 25* (1989) 276–280; d) "Recent Advances in Catalytic Asymmetric Reactions Promoted 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.

[491] D. W. Blackburn (Ed.): *Catalysis of Organic Reactions*, Marcel Dekker, New York 1990.

[492] See also the *Journal of Molecular Catalysis*, published since 1975, and a recent review article: "Catalysis from the perspective of an organic chemist: common problems and possible solutions": C. A. Maryanoff, J. E. Mills, R. C. Stanzione, J. T. Hortenstine, Jr., *Chem. Ind. (Dekker) 33* (1988) 359–379.

[493] In other words, biotechnology really *is* just an "old hat with new feathers" (H. Metz in *Merck-Spektrum*, Switzerland, No. 2, 1987).

[494] For example, shikonin from the firm Mitsui Petrochemical Industries, Ltd., Iwakuni, Yamaguchi-ken 740 (Japan).

[495] Recent brief review: "Cultured Plant Cells—the Factory Within": F. DiCosmo, P. J. Facchini, M. M. Kraml, *Chem. Br. 25* (1989) 1001–1004.

[496] See also the preparation of polyphenylene [231] and enantiomerically pure diols of this type from substituted arenes by ICI in England. Recent example: D. W. Ribbons, A. E. G. Cass, J. T. Rossiter, S. J. C. Taylor, M. P. Woodland, D. A. Widdowson, S. R. Williams, P. B. Baker, R. E. Martin, *J. Fluorine Chem. 37* (1987) 299; examples in Scheme 28.

[497] W. Charney, H. L. Herzog: *Microbial Transformations of Steroids*, Academic Press, New York 1967; see also non-steroidal cyclic compounds: K. Kieslich: *Microbial transformations on non-steroid cyclic compounds*, Thieme, Stuttgart 1976.

[498] Only papers of interest to the synthetic chemist have been considered [488b].

[499] B. Wipf, E. Kupfer, R. Bertazzi, H. G. W. Leuenberger, *Helv. Chim. Acta 66* (1983) 485.

[500] The yeast reduction of acetoacetic ester in a "chemostat": M. Rohner, T. Münch, B. Sonnleitner, A. Fiechter, *Biocatalysis 3* (1990) 37.

[501] "Bioreaktoren—Einführung in die Technik": W. F. Hess, M. B. Gatzemeier, *Chem. Ing. Tech. 60* (1988) A554–A559.

[502] One need only consider the many possible conditions for an aldol addition (see [331] and Scheme 26), or for reduction with a complex hydride $M^1(M^2H_{4-n}X_n)_b$, in which M^1 = Li, Na, K, Zn, Bu_4N, M^2 = B, Al, X = RO, RCOO, R_2N with $n = 1-3$ (there are entire books on the subject!).

[503] B. Zhou, A. S. Gopalan, F. VanMiddelsworth, W.-R. Shieh, C. J. Sih, *J. Am. Chem. Soc. 105* (1983) 5925; W.-R. Shieh, A. S. Gopalan, C. J. Sih, *ibid. 107* (1985) 2993.

[504] a) J. Ehrler, F. Giovannini, B. Lamatsch, D. Seebach, *Chimia 40* (1986) 172; b) T. Haag, T. Arslan, D. Seebach, *ibid. 43* (1989) 351, and references cited therein.

[505] For extensive, competent discussions of the subject containing numerous literature citations see [486b,e; 488b].

[506] a) D. Seebach, M. F. Züger, F. Giovannini, B. Sonnleitner, A. Fiechter, *Angew. Chem. 96* (1984) 155; *Angew. Chem. Int. Ed. Engl. 23* (1984) 151; b) D. Seebach, F. Giovannini, B. Lamatsch, *Helv. Chim. Acta 68* (1985) 958; c) C. H. Wong, D. G. Drueckhammer, H. M. Sweers, *J. Am. Chem. Soc. 107* (1985) 4028; d) "Synthetic Applications of Alcohol-Dehydrogenase from *Thermoanaerobium brockii*": E. Keinan, K. K. Seth, R. Lamed, *Ann. N. Y. Acad. Sci. 501* (1987) 130–149.

[507] Cubes of concentrated cell masses of the anaerobic microorganism *Thermoanaerobium brockii* can be kept wrapped in aluminum foil in a freezer—like baker's yeast in a refrigerator—for long periods of time without loss of reductase activity [506b].

[508] Proteinogenic amino acids are produced in Japan either by fermentative techniques or by the enantioselective cleavage of amino acid derivatives with immobilized microorganisms or peptidase enzymes: "Production of

Optically Active Amino Acids Using Immobilized Biocatalysts": T. Tosa, *Int. Chem. Congr. Pacific Basin Societies,* 17–22 Dec. 1989, Honolulu, HI, Abstr. ORGN 615.

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

[510] α-Branched amino acids are manufactured [for example, by DMS Research, Bio-organic Chemistry Section, Geleen (Netherlands)] through the enantioselective cleavage of amino acids with *Mycobacterium neoaurum*: W. H. Kruizinga, J. Bolster, R. M. Kellogg, J. Kamphuis, W. H. Boesten, E. M. Meijer, H. E. Schoemaker, *J. Org. Chem. 53* (1988) 1826; J. Kamphuis, H. F. M. Hermes, J. A. M. van Balken, H. E. Schoemaker, W. H. J. Boesten, E. M. Meijer in G. Lubec, G. A. Rosenthal (Eds.): *Amino Acids,* Escom, Leiden 1990, pp. 119–125.

[511] Application of membrane techniques (cf. [509]) on a laboratory scale ("*M*embrane-enclosed *e*nzymatic *c*atalysis = MEEC): M. D. Bednarski, H. K. Chenault, E. S. Simon, G. M. Whitesides, *J. Am. Chem. Soc. 109* (1987) 1283.

[512] C. Laane, J. Tramper, M. D. Lilly (Eds.): *Biocatalysis in Organic Media,* Elsevier, Amsterdam 1987.

[513] An entirely different case in which the change to an organic solvent proved crucial is the enantioselective cyanohydrin reaction catalyzed by mandelonitrile benzaldehyde lyase (MBL) and discovered by *Pfeil* [W. Becker, H. Freund, E. Pfeil, *Angew. Chem. 77* (1965) 1139; *Angew. Chem. Int. Ed. Engl. 4* (1965) 1079], a process that was long thought impractical due to its reversibility. Three years ago it was demonstrated that the problem can be circumvented with immobilized enzyme in ethyl acetate, permitting the large-scale preparation of cyanohydrins in > 98% *ee* and high yield: F. Effenberger, T. Ziegler, S. Förster, *ibid. 99* (1987) 491 and *26* (1987) 458; J. Brussee, E. C. Roos, A. Van Der Gen, *Tetrahedron Lett. 29* (1988) 4485; see Scheme 28, B.

[514] J. J. De Frank, D. W. Ribbons, *Biochem. Biophys. Res. Commun. 70* (1976) 1129; *J. Bacteriology 129* (1977) 1356; S. J. C. Taylor, D. W. Ribbons, A. M. Z. Slawin, D. A. Widdowson, D. J. Williams, *Tetrahedron Lett. 28* (1987) 6391; T. Hudlicky, H. Luna, G. Barbieri, L. D. Kwart, *J. Am. Chem. Soc. 110* (1988) 4735.

[515] T. Kitazume, N. Ishikawa, *Chem. Lett. 1984,* 1815.

[516] "Baker's Yeast Mediated Preparation of Carbohydrate-like Chiral Synthons": C. Fuganti in M. P. Scheider (Ed.): *Enzymes as Catalysts in Organic Synthesis,* D. Reidel, Dordrecht 1986, pp. 3–17.

[517] 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!–realm of laboratory jargon.

[518] 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 [353], and CIP nomenclature [444, 445]. The thoughts expressed on the subject by *Mislow* ["Stereoisomerism and Local Chirality": K. Mislow, J. Siegel, *J. Am. Chem. Soc. 106* (1984) 3319] derive more from fundamental and theoretical considerations than from practical concerns.

[519] G. Guanti, L. Banfi, E. Narisano, R. Riva, S. Thea, *Tetrahedron Lett. 27* (1986) 4639.

[520] H. B. Goodbrand, J. B. Jones, *J. Chem. Soc. Chem. Commun. 1977,* 469; I. J. Jakovac, H. B. Goodbrand, K. P. Lok, J. B. Jones, *J. Am. Chem. Soc. 104* (1982) 4659.

[521] H.-J. Gais, K. L. Lukas, W. A. Ball, S. Braun, H. J. Lindner, *Liebigs Ann. Chem. 1986,* 687.

[522] G. Sabbioni, J. B. Jones, *J. Org. Chem. 52* (1987) 4565.

[523] D. R. Deardorff, A. J. Matthews, D. S. McMeekin, C. L. Craney, *Tetrahedron Lett. 27* (1986) 1255.

[524] A. J. Pearson, H. S. Bansal, Y.-S. Lai, *J. Chem. Soc. Chem. Commun. 1987,* 519.

[525] D. Breitgoff, K. Laumen, M. P. Schneider, *J. Chem. Soc. Chem. Commun. 1986,* 1523.

[526] Y.-F. Wang, C.-H. Wong, *J. Org. Chem. 53* (1988) 3127.

[527] R. Roy, A. W. Rey, *Tetrahedron Lett. 28* (1987) 4935; cf. also the corresponding 3-aminoglutaric acid derivative: M. Ohno, S. Kobayashi, T. Imori, Y.-F. Wang, T. Izawa, *J. Am. Chem. Soc. 103* (1981) 2405 and [126a].

[528] G. Guanti, L. Banfi, E. Narisano, *Tetrahedron Lett. 30* (1989) 2697.

[529] J. Ehrler, D. Seebach, *Liebigs Ann. Chem. 1990,* 379.

[530] The title of a contribution in the series *Synthese im Blickpunkt*: H.-U. Reißig, *Nachr. Chem. Tech. Lab. 34* (1986) 782–84.

[531] R. W. Hoffmann, W. Ladner, K. Steinbach, W. Massa, R. Schmidt, G. Snatzke, *Chem. Ber. 114* (1981) 2786.

[532] H. Akita, H. Koshiji, A. Furuichi, K. Horikoshi, T. Oishi, *Tetrahedron Lett. 24* (1983) 2009.

[533] B. S. Deol, D. D. Ridley, G. W. Simpson, *Aust. J. Chem. 29* (1976) 2459.

[534] B. Herradon, D. Seebach, *Helv. Chim. Acta 72* (1989) 690.

[535] D. Seebach, S. Roggo, T. Maetzke, H. Braunschweiger, J. Cercus, M. Krieger, *Helv. Chim. Acta 70* (1987) 1605.

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

[537] a) Discovery: T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc. 102* (1980) 5974; b) kinetic separation of enantiomers: V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda, K. B. Sharpless, *ibid. 103* (1981) 6237; c) overviews: "Synthetic Aspects and Applications of Asymmetric Epoxidation": B. E. Rossiter in J. D. Morrison (Ed.): *Asymmetric Synthesis, Vol. 5,* Academic Press, Orlando, FL 1985, pp. 194–246; "Asymmetric Epoxidation of Allylic Alcohols: The Sharpless Epoxidation": A. Pfenninger, *Synthesis 1986,* 89–116; "Die Sharpless-Epoxidierung" (Synthese im Blickpunkt): D. Schinzer, *Nachr. Chem. Tech. Lab. 37* (1989) 1294–1298; d) catalytic variant: R. M. Hanson, K. B. Sharpless, *J. Org. Chem. 51* (1986) 1922; e) cyclic sulfonate esters of 1,2-diols (available from epoxides): Y. Gao, K. B. Sharpless, *J. Am. Chem. Soc. 110* (1988) 7538; f) most recent suggestion regarding the mechanism of the Sharpless epoxidation: "On the Origin of Enantioselectivity in the Katsuki–Sharpless Epoxidation Procedure": E. J. Corey, *J. Org. Chem. 55* (1990) 1693.

[538] This has been designated as "reagent control" [437]–in contrast to "substrate control". In German it would have to be expressed as "durch das Reagens gesteuert". I well remember the sermons 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 *gesteuerte*, nicht kontrollierte Reaktion; Kontrolle hat im Deutschen eine vom Englischen 'control' verschiedene Bedeutung!" From the fact that the term "stereocontrol" is about to replace "stereoselectivity", we must conclude that now everything is "under control".

[539] "Asymmetric Synthesis using Organometallic Catalysts": H. B. Kagan in [388], *Vol. 8,* chap. 53, pp. 463–498, and the original literature cited therein.

[540] "Asymmetric Catalytic Isomerization of Functionalized Olefins": S. Otsuka, K. Tani in J. D. Morrison (Ed.): *Asymmetric Synthesis, Vol. 5,* Academic Press, Orlando, FL 1985, pp. 171–191, and the original literature cited therein.

[541] "Directed Homogeneous Hydrogenation": J. M. Brown, *Angew. Chem. 99* (1987) 169–182; *Angew. Chem. Int. Ed. Engl. 26* (1987) 190–203; see also [490c].

[542] "Synthetic Applications of Enantioselective Organotransition-Metal-Mediated Reactions": S. L. Blystone, *Chem. Rev. 89* (1989) 1663–1679.

[543] a) PTC catalyst is an ammonium ion derived from cinchonine: M. J. O'Donnell, W. D. Bennett, S. Wu, *J. Am. Chem. Soc. 111* (1989) 2353; cf. also the enantioselective allylation of an indanone carried out by Merck Sharp & Dohme: D. L. Hughes, U.-H. Dolling, K. M. Ryan, E. F. Schoenewaldt, E. J. J. Grabowski, *J. Org. Chem. 52* (1987) 4745; b) H. Wynberg, E. G. J. Staring, *J. Am. Chem. Soc. 104* (1982) 166; *J. Org. Chem. 50* (1985) 1977; P. E. F. Ketelaar, E. G. J. Staring, H. Wynberg, *Tetrahedron Lett. 26* (1985) 4665.

[544] E. N. Jacobsen, I. Markó, W. S. Mungall, G. Schröder, K. B. Sharpless, *J. Am. Chem. Soc. 110* (1988) 1968.

[545] Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc. 108* (1986) 6405; Y. Ito, M. Sawamura, M. Kobayashi, T. Hayashi, *Tetrahedron Lett. 29* (1988) 6321.

[546] K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima, J. Sugimori, *J. Am. Chem. Soc. 111* (1989) 5340.

[547] a) The most recent essay about stereoselective Diels–Alder reactions contains sections on the following topics: chiral dienophiles and heterodienophiles, chiral dienes, chiral catalysts, and asymmetric intramolecular Diels–Alder reactions: "Asymmetric Diels–Alder Reactions": M. J. Taschner in T. Hudlicky (Ed.): *Organic Synthesis–Theory and Applications, A Research Annual, Vol. 1,* JAI Press, Greenwich 1989, pp. 1–101; b) "Asymmetrische Induktion bei Diels–Alder-Reaktionen" (Synthese im Blickpunkt): K. Krohn, *Nachr. Chem. Tech. Lab. 35* (1987) 836–841; see also the article by *Helmchen* et al. [462]; c) recent example: K. Furuta, S. Shimizu, Y. Miwa, H. Yamamoto, *J. Org. Chem. 54* (1989) 1481.

[548] K. Mikami, M. Terada, T. Nakai, *J. Am. Chem. Soc. 111* (1989) 1940.

[549] 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 $SnCl_4$, TiX_4, or BF_3–ether are added, in which case the Lewis acid could be regarded as part of the solvent!

[550] "Asymmetric Catalytic Hydrogenation: Mechanism and Origin of Enantioselection": J. Halpern in J. D. Morrison (Ed.): *Asymmetric Synthesis, Vol. 5,* Academic Press, Orlando, FL 1985, pp. 41–69.

[551] See, for example, the semicorrin ligand proposed for transition-metal-catalyzed reactions by *A. Pfaltz* [490e], as well as B and C in Scheme 32.

[552] 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. Suga, K. Kawai, R. Noyori, *J. Am. Chem. Soc. 108* (1986) 6071; b) application of pyrrolidine ligands: E. J. Corey, F. J. Hannon, *Tetrahedron Lett. 28* (1987) 5233, 5237; E. J. Corey, P.-W. Yuen, F. J. Hannon, D. A. Wierda, *J. Org. Chem. 55* (1990) 784; c) highly effective (down to 10^{-4} equiv.) catalysts for dialkylzinc additions to benzaldehyde are prepared from tetraisopropyltitanate and the ditri-

flate of (*R,R*)-*trans*-1,2-cyclohexanediamine: M. Yoshioka, T. Kawakita, M. Ohno, *Tetrahedron Lett. 30* (1989) 1657.

[553] Y. Yamamoto, J. Yamada, *J. Am. Chem. Soc. 109* (1987) 4395; J. Yamada, Y. Yamamoto, *J. Chem. Soc. Chem. Commun. 1987*, 1302.

[554] A review article summarizing the results obtained through 1986: "Catalytic Asymmetric Reduction Using Optically Active Amino Alcohol–Borane Complex": S. Itsuno, *Yuki Gosei Kagaku Kyokaishi (J. Synth. Org. Chem. Jpn.) 45* (1987) 101–111.

[555] With few exceptions, lithium also does not exceed the limit of four tetrahedrally oriented ligands; see [172] and references cited therein. Higher coordination numbers with this element appear to result largely from ionic interactions.

[556] 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-CH_3 group only two widely divergent values have been reported (1.969 and 2.206 Å). The rest of the data resulted from a search in the CSD [189] for comparable bonds (only trimethyl compounds in the case of Al-C and Sn-C). If more than twenty values were found, the average has been supplemented (in parentheses) with the standard deviation applicable to the last reported digit. Since the reported values were obtained on the basis of differing criteria they should be regarded only as points of reference.

[557] The most selective aldol additions with boron enolates [331,437,464]. See also the chiral 2,5-dimethylborolanes, which are of little practical utility but are nonetheless "reliable" in their reactivity and selectivity: R. P. Short, S. Masamune, *J. Am. Chem. Soc. 111* (1989) 1892; "Stereochemical Control of Organic Reactions with Chiral Organoboron Reagents": S. Masamune in W. Bartmann, K. B. Sharpless (Eds.): *Stereochemistry of Organic and Bioorganic Transformations, Workshop Conferences Hoechst, Vol. 17*, VCH Verlagsgesellschaft, Weinheim 1987, pp. 49–72.

[558] E. J. Corey, *Proc. 31st Natl. Org. Symp. Am. Chem. Soc.*, June 1989, pp. 1–14.

[559] E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc. 109* (1987) 5551.

[560] E. J. Corey, R. K. Bakshi, S. Shibata, C.-P. Chen, V. K. Singh, *J. Am. Chem. Soc. 109* (1987) 7925.

[561] E. J. Corey, C.-P. Chen, G. A. Reichard, *Tetrahedron Lett. 30* (1989) 5547.

[562] E. J. Corey, J. O. Link, *Tetrahedron Lett. 31* (1990) 601; E. J. Corey, S. Shibata, R. K. Bakshi, *J. Org. Chem. 53* (1988) 2861.

[563] E. J. Corey, R. K. Bakshi, *Tetrahedron Lett. 31* (1990) 611.

[564] E. J. Corey, P. Da Silva Jardine, T. Mohri, *Tetrahedron Lett. 29* (1988) 6409; E. J. Corey, P. Da Silva Jardine, J. C. Rohloff, *J. Am. Chem. Soc. 110* (1988) 3672.

[565] E. J. Corey, A. V. Gavai, *Tetrahedron Lett. 29* (1988) 3201.

[566] E. J. Corey, J. O. Link, *Tetrahedron Lett. 30* (1989) 6275.

[567] The amino alcohols used for preparing the catalysts **c**–**f** 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. Braun* 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. Bastani, G. Crass, H. Daum, H. Dörr, N. P. du Preez, V. Ehrig, W. Langer, C. Nüssler, H.-A. Oei, M. Schmidt, *Helv. Chim. Acta 60* (1977) 301.

[568] 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 finally covered an entire region, but it will still be *centuries* before synthesis has acquired the status that many people already ascribe to it today" [44].