

In the same manner that the Nasobem, Stümpke's mythical creature, teaches his child the peculiar way of life of the species *Nasobema lyricum*, the work of Seebach et al. on the self-regeneration of stereocenters has been governed by a fanciful idea. On the way, many tricks have been learned and much knowledge gained. Finally, they have come back down to earth and find themselves once again in the unimaginative world of enantiomer separation for the synthesis of enantiomerically pure compounds.

## Self-Regeneration of Stereocenters (SRS)—Applications, Limitations, and Abandonment of a Synthetic Principle

Dieter Seebach,\* Andrea R. Sting, and Matthias Hoffmann

*Dedicated to our much-admired teacher and mentor, Professor Dr. Vladimir Prelog, on the occasion of his 90th birthday*

In order to replace a substituent at a single stereogenic center of a chiral molecule without racemization, a temporary center of chirality is first generated diastereoselectively, the original tetragonal center is then trigonalized by removal of a substituent, a new ligand is introduced, again diastereoselectively, and finally, the temporary center is removed. By means of these four steps (the "Self-Regeneration of Stereocenters", SRS), 2- and 3-amino-, hydroxy-, and sulfanylcarboxylic acids have been successfully alkylated with formation of tertiary carbon centers and without the use of a chiral auxiliary. Use of this methodology has allowed the potential of these inexpensive chiral building blocks to be expanded considerably. This article aims to demonstrate (using, in part, examples from natural product syntheses) that chiral heterocyclic acetals with enamine, enol ether, enolate, dienolate, enoate, radical, and acyliminium functionalities and also those that are potential reactants for Michael additions and pericyclic processes (for example, electron-rich and electron-poor dienophiles and dienes) are now easily accessible, more often than not, in both enantiomeric forms. Stereogenic nitrogen atoms of aziridines, boron

atoms of cyclic or linear systems, and stereogenic planes of  $\pi$ -complexes can also be used as the temporary chirality element in other approaches to the realization of the SRS principle. Enantiomerically pure derivatives of, for example, glycine, hydroxy- and sulfanylacetic acid, 3-aminopropanoic acid, and 3-oxocarboxylic acids can be prepared by resolution of racemic mixtures via diastereoisomeric salts or by chromatography on a chiral column. Hence, the extensive reactivity of compounds developed to test the SRS principle and, above all, the outstanding stereoselectivities of the reactions can be put to good use even when no suitable chiral precursor is available—even though this amounts to an abandonment of the principle! The readily available 2-*tert*-butyl-1,3-imidazolidin-3-one, -oxazolidin-5-one, -dioxin-3-one, and -hydropyrimidinone (all of which contain a single stereogenic center at the acetal C atom) can thus be used in the preparation of a vast range of 2-amino- and 3-hydroxycarboxylic acids, and no chiral auxiliary has to be removed or regenerated during these procedures. (One example is the synthesis of 4-fluoro-MeBmt, a derivative of the C<sub>9</sub> amino acid found in cyclosporin.) In the final chapter we will

discuss the most useful findings gained from investigations into both the self-regeneration of stereocenters and the use of chiral acetals in the synthesis of enantiomerically pure compounds (EPC synthesis): the formation and characteristics of complexes obtained from Li-enolates and other Li compounds with secondary amines; the application of  $\alpha$ -alkoxy and  $\alpha$ -amino-Li-alkoxides as in situ bases and sources of aldehydes in C–C bond forming reactions with unstable enolates or nitronates; the significance of A<sup>1,3</sup> effects on the stereochemical course of nucleophilic, radical, and electrophilic reactions of *N*-acylated heterocycles and homo- or heterocyclic carboxylic ester enolates; and the effects of the amide protecting group on the reactivity of neighboring centers and on the stereoselectivity of the reactions at those centers. At the end of this article we have included an appendix containing tables, which are intended to summarize all the examples known in as complete a fashion as possible.

**Keywords:** asymmetric syntheses · chiral synthetic building blocks · enolates · lithium compounds

### 1. Introduction and Definition of the Problem

*Was nicht sein kann,  
das nicht sein darf!*<sup>[\*\*]</sup>

It is a fundamental part of every basic lecture course in organic chemistry that a reaction at a trigonal center bearing three different substituents in an achiral molecule results, if neither

[\*] Prof. Dr. D. Seebach, Dr. A. R. Sting, Dipl.-Chem. M. Hoffmann  
Laboratorium für Organische Chemie  
der Eidgenössischen Technischen Hochschule  
ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich (Switzerland)  
Fax.: Int. code +(1)632-1144  
e-mail: seebach@org.chem.ethz.ch

[\*\*] "Surely the impossible is just not possible."

the other reactants nor the surroundings are chiral, in the formation of a racemic product containing one center of chirality. The consequence of this is that a substitution that proceeds in either a homolytic or heterolytic manner at a solitary stereogenic center of a molecule yields enantiomeric products in a 1:1 ratio and hence, a racemic mixture is formed (Scheme 1 a). If the trigonal center in the intermediate is cationic or part of a  $\pi$ -system, it will have a trigonal-planar geometry and if it is radical or anionic in nature, it may have a trigonal-pyramidal geometry but will be capable of rapid inversion, particularly in noncyclic systems.

There are, of course, exceptions that can be of practical significance. These include the  $S_Ni$  substitution of OH by Cl using thionyl chloride (Scheme 1 b),<sup>[1]</sup> which proceeds with retention of configuration, and the cationic cyclization of linalol *p*-nitrobenzoate to terpineol (Scheme 1 c).<sup>[2]</sup> Stereoselective reactions proceeding via carbanionic intermediates are also known. For example, the D/H exchange with retention of configuration shown in Scheme 1 d,<sup>[3]</sup> which is really of rather academic interest, and the decarboxylation, with retention, of an intermediate used in the preparation of the anaesthetic Desfluran<sup>[4]</sup> (Scheme 1 e). Once it had been appreciated that within so-called

carbanion chemistry, there is also a cation, more often than not a metal ion, which can be sufficiently strongly bound<sup>[5]</sup> to allow the formation of configurationally stable organometallic derivatives<sup>[6-8]</sup> such as those shown in Scheme 1 f, a whole new branch of stereoselective synthesis developed.<sup>[9-14]</sup>

Even in enolate chemistry there are exceptions to the rules formulated above (see the examples in Scheme 2). Although the sole center of chirality in the starting material is removed, enantiomerically pure or enantiomerically enriched products may result. This can be attributed to the formation of aggregates of achiral enolates with chiral components in the reaction mixture (Scheme 2 a)<sup>[15]</sup> or also to sufficiently conformationally stable enolate intermediates which possess axes of chirality (Scheme 2 b-e).<sup>[16-20]</sup> The cation also plays a decisive role in the reactions of enolates. Owing to the successful creation of a variety of alternatives, today practically any type of imaginable reactivity or selectivity of these nucleophiles, which are of central importance in organic synthesis, can be achieved. Possibilities include the participation of aggregates ("supramolecular" structures) of Li-, Na-, K- and Mg-enolates<sup>[21-25]</sup> and their complexes with salts,<sup>[26, 27]</sup> amides,<sup>[28]</sup> and amines,<sup>[21-24, 29, 30]</sup> the reduction of the coordination sphere of the participating metal

*Andrea Rolf Sting was born in Samedan, Canton Graubünden (Switzerland) in 1963. After an apprenticeship and then a further three years working in the chemistry laboratories of Ciba-Geigy in Basel (Dyes and Chemicals Division), he studied from 1986 to 1989 at the "Ingenieurschule*



A. R. Sting

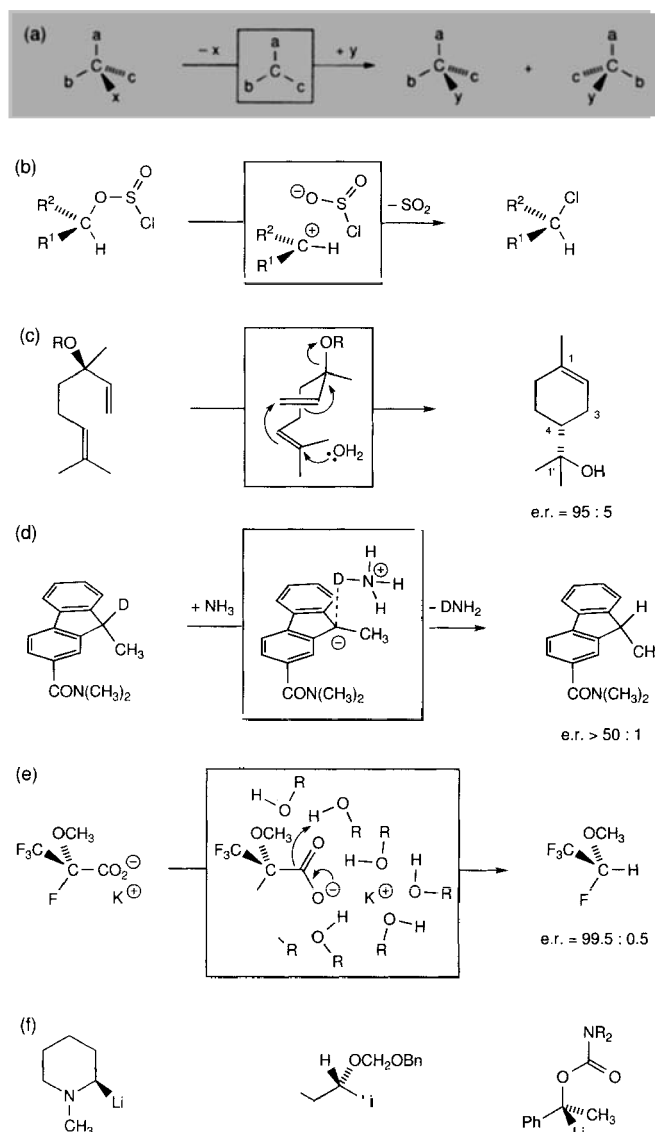
D. Seebach

M. Hoffmann

*Beider Basel" (IBB) in Muttenz (Canton Basel-Land), where he earned the title Dipl.-Chem. HTL. Subsequently, he moved to the ETH in Zürich to continue his chemistry studies (Diploma 1992). In the spring of 1993 he began working in the group of Prof. D. Seebach and completed his Ph.D. thesis on the synthesis of 4-fluoro-MeBmt in the spring of 1996. He is now working in the Division of Crop Protection of Ciba-Geigy in Basel.*

*Dieter Seebach was born in Karlsruhe (Germany) in 1937. He studied chemistry at the University of Karlsruhe and completed his Ph.D. thesis on small rings and peroxides under the supervision of Prof. R. Criegee in 1964. After a two-year stay at Harvard University as postdoctoral co-worker (with Prof. E. J. Corey) and lecturer, he returned to Karlsruhe and, in 1969, completed his "habilitation" on the topic of S- and Se-stabilized carbanion and carbene derivatives. In 1971 he moved to the University of Giessen as a full professor and then in 1977 to the Eidgenössische Technische Hochschule (Swiss Federal Institute of Technology) in Zürich. He has been a visiting professor at the Universities of Wisconsin-Madison, Strasbourg, Munich (TU), and Kaiserslautern and also at Caltech (Pasadena) and the Max Planck Institute in Mülheim. A main emphasis of his research is the development of new synthetic methods; in the last decade the subject discussed here and the Ti-TADDOLates have been major interests. His work also involves mechanistic studies and determination of structures. More recent research topics include chiral dendrimers, the short-chain oligomers of 3-hydroxybutanoic acid, the biopolymer PHB, and backbone-modified peptides.*

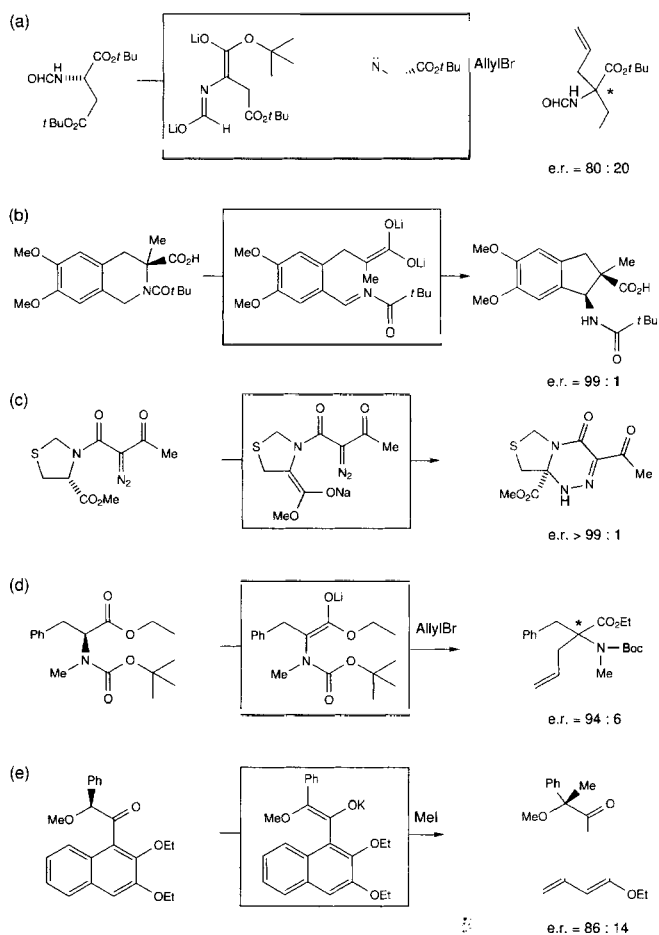
*Matthias Hoffmann was born in Zürich (Switzerland) in 1969. He completed his Diploma studies in chemistry at the ETH in Zürich in 1993 with research conducted in the group of Prof. D. Seebach. Later that year, he began working on his Ph.D. thesis in the same area. His research focuses on the development of methods for the preparation of enantiomerically pure, non-proteino-genic amino acids.*



Scheme 1. Dissociative reactions at stereogenic centers (a–e) and chiral organolithium compounds (f). In this article, the enantiomeric purity of compounds will be given exclusively in the form of enantiomer ratios (e.r.), which are typically determined by NMR, GC, or HPLC analysis. a) Racemization during dissociative substitution at a stereogenic center proceeding via a trigonal intermediate. b) OH/Cl substitution using thionyl chloride with retention of configuration [1]. c) The highly stereoselective cyclization of linalol to terpineol. The use of appropriately labeled derivatives has shown that the carbon atoms C4, C3 (H/D), and C1' (CH<sub>3</sub>/CD<sub>3</sub>) are present in only one configuration in the product [2]. d) D/H exchange, with retention, in a fluorene derivative using ammonia as the base; the ratio of the rate of isotope exchange ( $k_e$ ) to the rate of racemization ( $k_r$ ) is greater than 50:1 [3]. e) Decarboxylation, with retention of configuration, of (R)-2,3,3,3-tetrafluoro-2-methoxypropanoate to give (R)-1,1,1,2-tetrafluoro-2-methoxyethane [4]. f) Configurationally stable organolithium compounds described by Gawley et al. [6], Still et al. [7], and Hoppe et al. [8].

center in boron enolates<sup>[31]</sup> and its enlargement in titanium enolates,<sup>[32–34]</sup> the activation of the reaction partners with a variety of Lewis acids,<sup>[34]</sup> and the generation of enolates by the use of metal-free bases such as F<sup>−</sup> in Bu<sub>4</sub>NF<sup>[35]</sup> and phosphazenes,<sup>[36–38]</sup> from silyl enol ethers,<sup>[39]</sup> or by direct deprotonation.

Within the framework of our work over many years devoted to the incorporation of inexpensive, simple, chiral, naturally occurring compounds (the “pool of chiral building blocks”<sup>[40]</sup>) into complex target molecules, we wondered whether it would

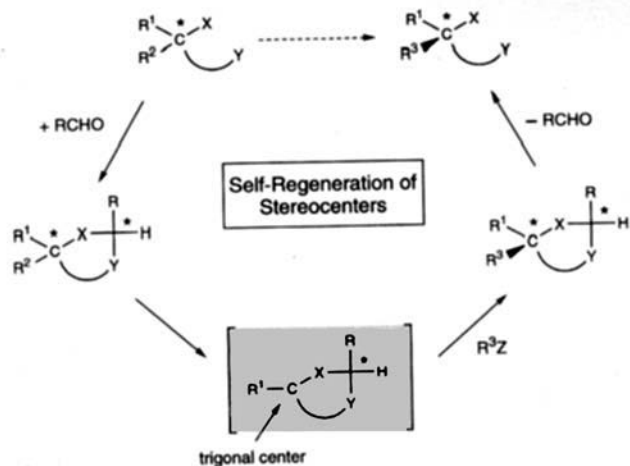


Scheme 2. Some reactions of enantiomerically pure esters and a ketone, which have only one center of chirality in the  $\alpha$ -carbonyl position, giving enantiomerically pure or enriched products via the appropriate enolate. a) Enantioselective reaction of an achiral enolate in the presence of a chiral enolate [15]. b) Tetrahydroisoquinoline/ aminoindane ring contraction without loss of enantiomeric purity, presumably via an imino-enediolate [16]. Strictly speaking, this is the nitrogen analog of the Wittig rearrangement, with retention of configuration at the migrating C atom (cf. the Stevens, Sommelet, and Hauser rearrangements [17]). c) Stereoselective intramolecular trapping of an enolate by a diazooxoketo group with retention [18]. d) Preparation of an  $\alpha,\alpha$ -disubstituted N-methylamino acid derivative without the aid of a chiral auxiliary and without a temporary stereogenic center [19]. e) H/Me exchange with inversion of configuration of a 1-naphthylketone (via an axially chiral intermediate?) [20].

be possible to develop some sort of “trick” for producing enolates of  $\alpha$ -amino or  $\alpha$ -hydroxy acids such that subsequent reactions with electrophiles yield nonracemic products. This led us to a simple yet broadly applicable synthetic principle<sup>[41–43]</sup> that we call the “Self-Regeneration of Stereocenters” (SRS).<sup>[44–48]</sup>

*Wenn zwei das Gleiche tun,  
ist es noch lange nicht Dasselbe.<sup>[\*]</sup>*

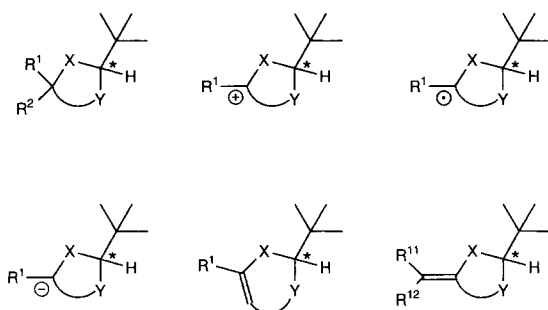
The principle is extremely simple (Scheme 3): The chiral starting material possessing two functional groups but one (and only



Scheme 3. The principle of the self-regeneration of a stereogenic entity illustrated with the example of a chirality center. In fact, the replacement of one of the four substituents at a single stereogenic center of the starting material requires four steps and is achieved without formation of a racemic product. The auxiliary is an achiral aldehyde.

one) stereogenic center is allowed to react with an aldehyde to form an acetal, with preference for one isomer. Annihilation of the original stereogenic center and concomitant formation of a trigonal center yields an intermediate, which, due to the stereogenic center of the acetal, is chiral. Subsequent reaction at the trigonal center proceeds diastereoselectively under the influence of this temporary stereogenic center, and finally, cleavage of the acetal unit leads to a product in which one of the substituents at the stereogenic center of the starting material has been replaced by a new one. The reaction sequence proceeds by dissociative, enantioselective substitution at a center of chirality and without the need for a chiral auxiliary—hence, the name “Self-Regeneration”. Of course, an auxiliary is necessary—the aldehyde, which is introduced at the acetalization step and is then regenerated by hydrolysis.

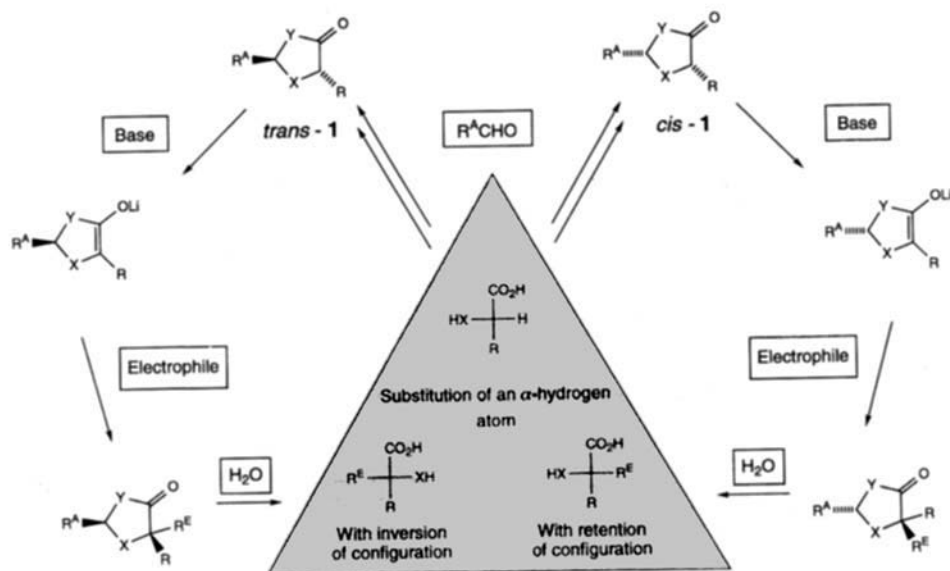
Naturally, an unsymmetrical ketone<sup>[49–52]</sup> or some other achiral compound can be used in place of the aldehyde such that reaction with the precursor occurs diastereoselectively, and



Scheme 4. Chiral species with cationic, radical, and anionic trigonal centers and also those with a  $\pi$ -system, all of which can act as the intermediate in the self-regeneration of a stereocenter (see Scheme 3).

hence, the stereogenic center of the precursor can be destroyed with no cause for concern. The temporary center of chirality can also be replaced by an alternative, but again temporary, element of chirality (axis or plane<sup>[53–56]</sup>, see Section 6).

An illustration of the breadth of possible applications of the SRS principle is given in Scheme 4. It shows suitable reactive intermediates or derivatives, in which the original stereocenter is destroyed by removal of one of the ligands ( $R^2$ ). Cationic (electrophilic), radical, or anionic (nucleophilic) reactivity can be generated, and endocyclic or exocyclic  $\pi$ -systems can be formed in which one or more trigonal centers with diastereotopic faces are present. In Scheme 4, a *tert*-butyl group is shown as the substituent at the acetal temporary stereogenic center. In our own work in this area, we prefer to use pivalaldehyde as the acetalization reagent for a number of reasons: a) the bulky *t*Bu group results in particularly high diastereoselectivity in the acetalization step (Scheme 3); b) the yields of acetalization are generally good (indeed, they are practically quantitative when the new transition metal catalysts<sup>[52]</sup> developed by Venanzi et al.<sup>[57]</sup> are employed); c) the *t*Bu group also leads to high diastereoselectivities in subsequent reactions at the trigonal center; d) the *t*Bu group is completely unreactive (in contrast to the Ph group introduced by the use of benzaldehyde) and enol derivatives cannot be formed; e) since the NMR signal of the



Scheme 5.  $\alpha$ -Alkylation of an  $\alpha$ -amino,  $\alpha$ -hydroxy-, or  $\alpha$ -sulfanylcarboxylic acid without racemization. Depending on whether a *cis*-substituted heterocycle **1** (when  $Y = \text{NH}$ ,  $\text{NCH}_3$ ,  $\text{O}$ ) or the other isomer *trans*-**1** (when  $X = \text{NH}$ ,  $Y = \text{NCH}_3$ ) is formed, heterochiral enolates are formed in the deprotonation step, and subsequent diastereoselective alkylation leads to the enantiomerically pure products resulting from electrophilic substitution of the  $\alpha$ -carbonyl proton. The letter A in  $R^A$  on the aldehyde reagent and at the acetal temporary stereogenic center stands for auxiliary.  $R^E$  represents the group in the product introduced by way of the electrophile. Specific examples can be found in Table A in the appendix. Short review articles on imidazolidinones [75] and oxazolidinones [66] derived from amino acids and dioxolanones [67] derived from  $\alpha$ -hydroxycarboxylic acids have been published in the *Encyclopedia of Reagents for Organic Synthesis* (see also the reviews in refs. [48, 68]).

*t*Bu group is one sharp singlet, it does not overlap with signals in large areas of the spectrum, and it can also serve as a useful reference in NMR analysis of the crude product; f) pivalaldehyde is available on a large scale (it is obtained as a side-product during the hydroformylation of isobutylene<sup>[58]</sup>) and is also used in the synthesis of fragrances<sup>[59]</sup>; g) as pivalaldehyde has a low boiling point (74 °C), it can be readily removed after the last step of the reaction sequence shown in Scheme 3, the hydrolysis.<sup>[60]</sup>

### 3. Chiral Heterocyclic Enolates of 2-Amino-, 2-Hydroxy-, and 2-Sulfanylcarboxylic Acids

*It's the exception that proves the rule!*

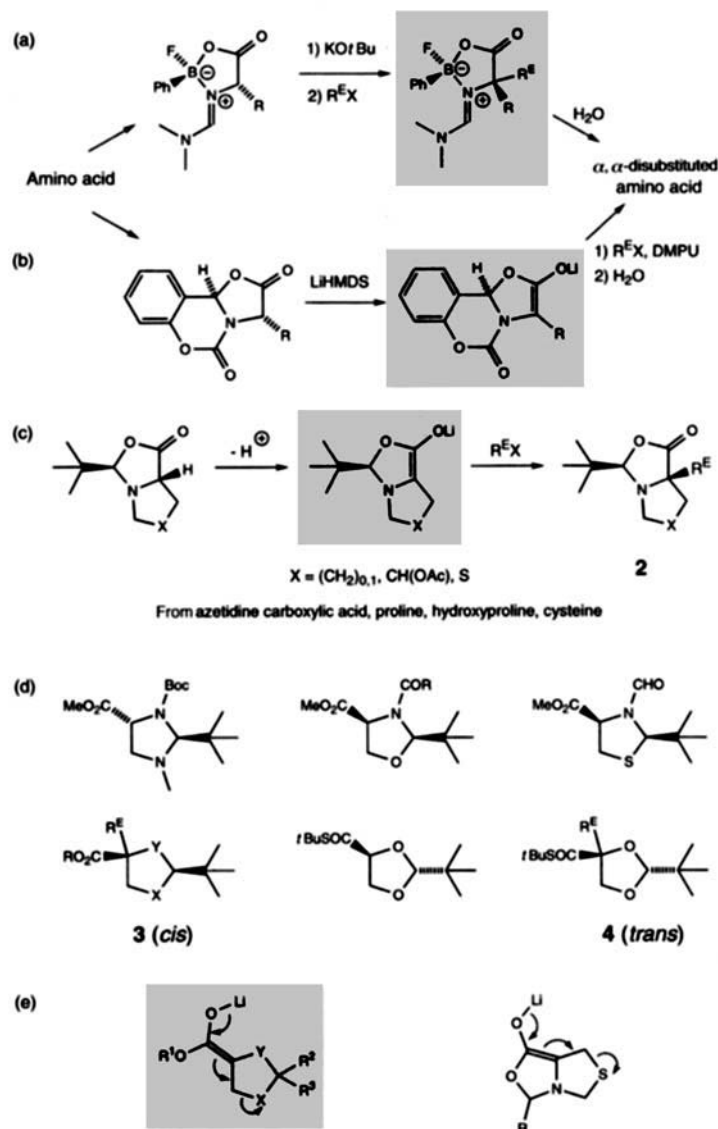
The twenty proteinogenic amino acids and the related  $\alpha$ -hydroxy acids (which are formed by diazotization of the amino acids in aqueous media with retention of configuration), as well as other naturally occurring members of this class of compounds—for example lactic acid, glyceric acid, malic acid, and mandelic acid—provide us with vast reserves of chiral building blocks. By applying the SRS principle these compounds can be alkylated at the stereogenic center to yield products containing a tertiary C atom.<sup>[61]</sup>

In the acetalization (the first step of the reaction sequence), the *cis*-substituted oxazolidinone, dioxolanone, or thioxolanone usually results from the thermodynamically controlled reaction of the carboxylic acid derivatives listed above.<sup>[62]</sup> The *cis*-substituted product is also formed in the case of the imidazolidinone derivative,<sup>[63, 64]</sup> which is obtained from an amino acid amide, and this is the precursor of a particularly reactive Li-enolate. Under kinetic control the reaction leads to the *trans*-imidazolidinone. Hence, acetals derived from (*S*)-amino-, -hydroxy-, and -sulfanylcarboxylic acids can be produced with (*R*) and/or (*S*) configuration at the acetal center. Subsequent formation of the Li-enolate, reaction with an electrophile, and finally cleavage of the acetal results in a wide variety of  $\alpha$ -branched,  $\alpha$ -heterosubstituted carboxylic acids (see Scheme 5<sup>[65–68]</sup> and Table A in the appendix, which contains numerous references.<sup>[47, 48]</sup>)

The *cis*-heterocycle **1** is formed with a selectivity that is usually over 90%, and clearly the enantiomeric purity of the intended substitution product cannot exceed the diastereoisomeric purity of the cyclic acetal. It is, therefore, usually necessary to purify these acetals by recrystallization or chromatography.<sup>[69]</sup> Detailed procedures are available for the preparation of the imidazolidinones (**1**, X = NCOPh, Y = NMe)<sup>[63]</sup> and oxazolidinones (**1**, X = NCOPh, Y = O)<sup>[70, 71]</sup> from alanine, phenylalanine, valine, and methionine.<sup>[71, 72]</sup> The synthesis of the dioxolanone (**1**, X = Y = O, R<sup>A</sup> = *t*Bu, R = Me) from lactic acid and pivalaldehyde has also been described.<sup>[46, 47]</sup> (This compound is obtained with a *cis/trans* ratio of 96:4 after crystallization.) Finally, the acid-catalyzed acetalization of malic acid, which yields a dioxolanylacetic acid and not a dioxanone carboxylic acid, has been published.<sup>[47, 73, 74]</sup>

The Li-enolates of the imidazolidinones have the greatest stability and tolerate reactions with electrophiles at temperatures above 0 °C, whereas enolates of the dioxolanones<sup>[46, 47, 75–79]</sup> can only be handled at low temperatures. The most successful

method for formation of the enolates relies on the use of lithium diisopropylamide (LDA) or hexamethyldisilazide (LHMDS). All the common electrophiles such as H<sup>+</sup>, D<sup>+</sup>, alkyl, allyl, and benzyl halides,  $\alpha$ -haloesters and amides, aldehydes, ketones,  $\alpha,\beta$ -unsaturated carbonyl compounds, and nitroolefins together with the more unusual ones such as tricarbonyl(benzene)-



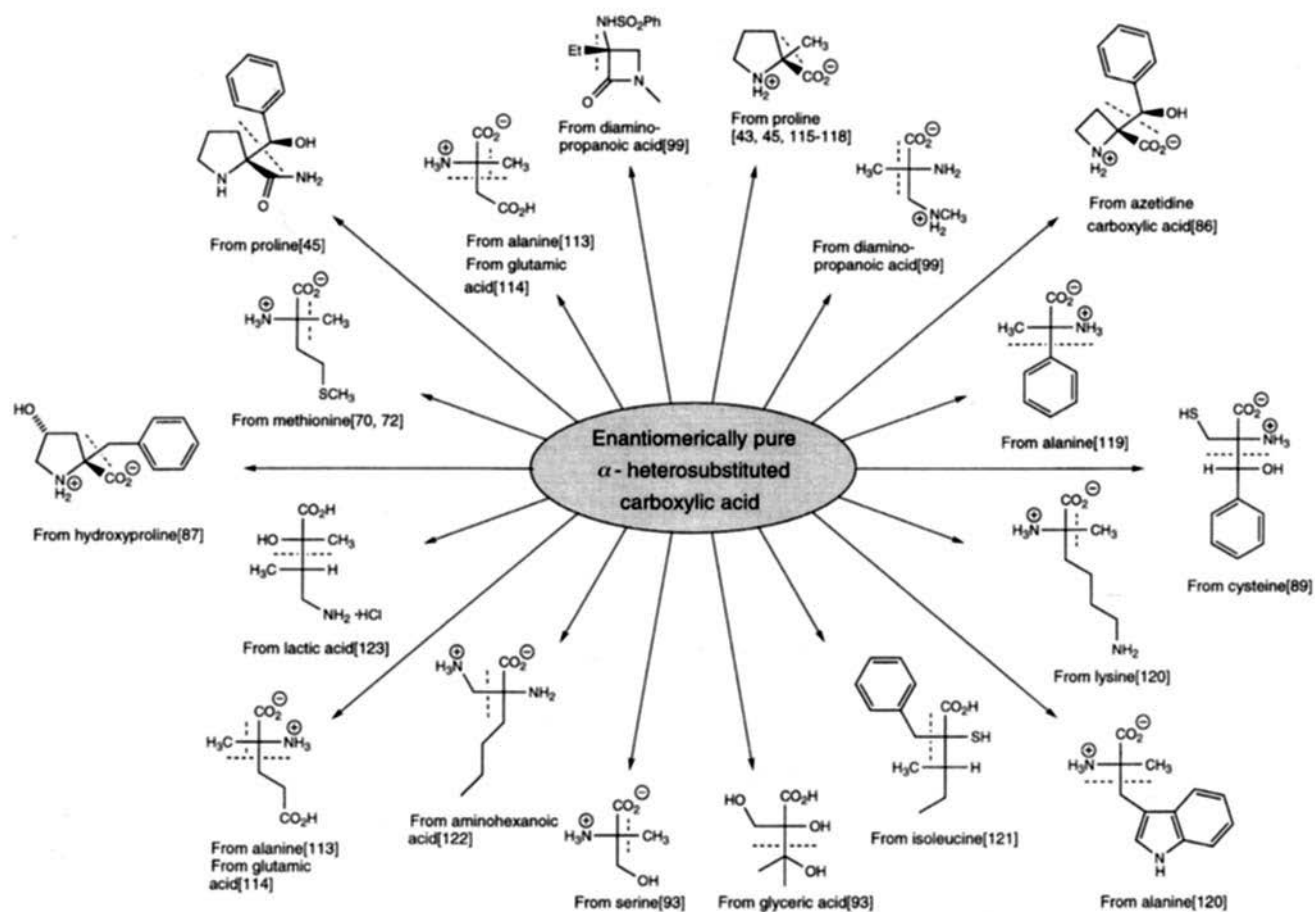
Scheme 6. Further  $\alpha$ -alkylations of amino acids following the SRS principle. a) A boraoxazolidinone [84] is alkylated via its K-enolate, and the boron atom serves as the stereogenic center. (This has been applied to phenylalanine, phenylglycine, and valine, which were allowed to react with methyl and propyl iodide, and allyl and benzyl bromide.) b) The amino acids alanine, phenylalanine, and leucine have been methylated and allylated via a tricyclic compound (derived from salicylaldehyde) [85]. c) Alkylation of a cyclic amino acid via a bicyclic enolate [43, 45, 86–89]; enolization of the cysteine derivative (X = S) without  $\beta$ -elimination (see e)) is successful only when a special trick is used (see Section 9) [89, 90]; with *O*-acetyl-hydroxyproline (X = CHOAc), the acetate group is also enolized [87, 88]. d) Branching of 2,3-diaminopropanoic acid [99], serine [93, 100, 101], cysteine [103–109], and glyceric acid [93, 102] via the geminal-disubstituted intermediates **3** and **4**; the Li-enolate intermediate (see e)) with an exocyclic double bond is fairly stable despite the (endocyclic)  $\beta$ -leaving group [93, 102–109]; as can be seen in the case of the cysteine derivative, the stability is very sensitive to the nature of the *N*-acyl group. Only the enolate formed from the formyl derivative is stable enough to undergo alkylation [93, 105–109] (see also Scheme 33 in Section 9). Further examples are given in Scheme 7 and in Tables B and C in the appendix. LiHMDS = lithium hexamethyldisilazide, DMPU = *N,N'*-dimethyl-*N,N'*-propylurea, Boc = *tert*-butoxycarbonyl.

chromium have been employed (see the  $R^E$  groups in Table A of the appendix and the accompanying references). The reactions proceed with high selectivity at the face of the enolate double bond<sup>[80]</sup> opposite to that shielded by the *tert*-butyl substituent on the acetal center. Furthermore, the products are usually highly crystalline or are easily purified by chromatography, such that a single diastereoisomer may be subjected to the final hydrolysis step. As the stereogenic center in the final product (the  $\alpha$ -heterosubstituted  $\alpha,\alpha$ -disubstituted carboxylic acid) is stable, rather drastic conditions may be used for the hydrolysis of the heterocycles in the last step of the SRS sequence of Scheme 5.<sup>[64, 81–83]</sup>

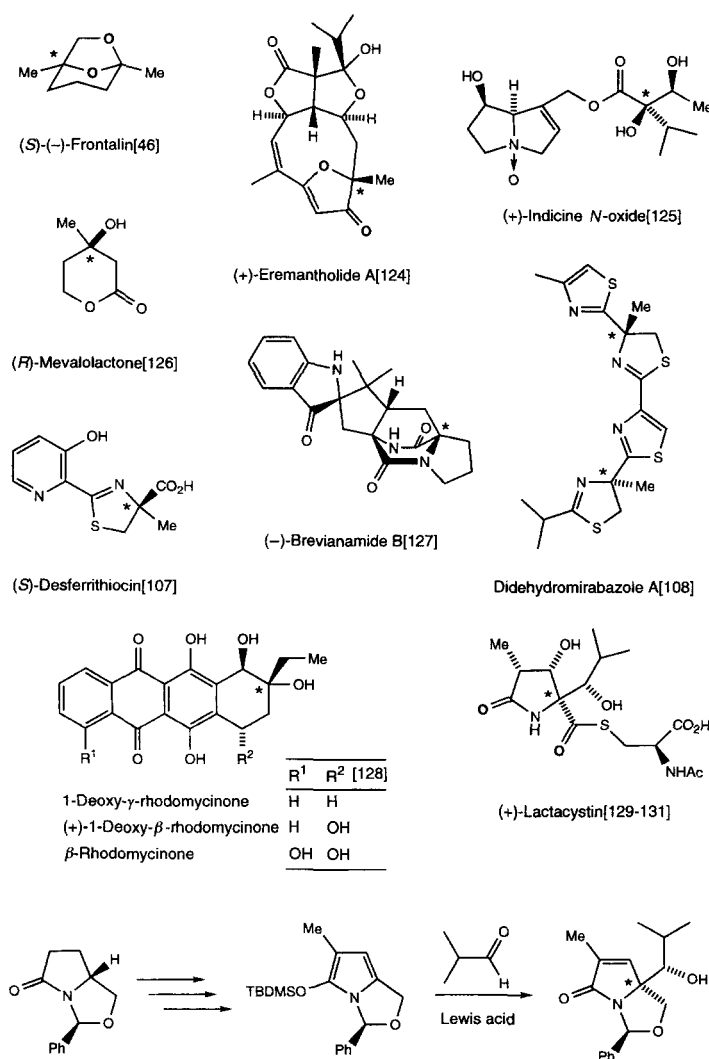
$\alpha$ -Substituents have also been introduced to simple amino acids via other heterocyclic derivatives and their enolates. In the particularly clever “trick” outlined in Scheme 6a the temporary stereogenic center is a boron atom, and, of course, hydrolysis after the alkylation can be achieved under very mild conditions in this case.<sup>[84]</sup> Salicylaldehyde has also been employed as an achiral auxiliary for the SRS alkylation of amino acids (see Scheme 6b).<sup>[85]</sup> Cyclic amino acids such as azetidine carboxylic acid,<sup>[86]</sup> proline,<sup>[43, 45]</sup> hydroxyproline,<sup>[87, 88]</sup> and the cysteine derivative 4-thiaproline<sup>[89, 90]</sup> may be alkylated via bicyclic enolates, which react with a wide variety of electrophiles at the *exo* face exclusively (see **2** in Scheme 6c and Table B in the appendix).<sup>[91–98]</sup>

The heterocycles derived from 2,3-diamino-,<sup>[99]</sup> 2-amino-3-hydroxy-,<sup>[93, 100, 101]</sup> and 2,3-dihydroxycarboxylic acids<sup>[93, 102]</sup>

(Scheme 6d) are of particular interest. *cis/trans* Mixtures are formed during acetalization and the diastereoisomeric purity is highly dependent upon reaction conditions (thermodynamic control for acid catalysis,<sup>[62, 93, 101–109]</sup> kinetic control for  $Rh^{3+}$  catalysis<sup>[52, 57]</sup>), upon the substitution of the ring, and upon the nature of the heteroatoms in the ring. Both the oxazolidine<sup>[93, 100, 101]</sup> and the thiazolidinecarboxylic esters<sup>[103–109]</sup> are normally formed as 1:1 *cis/trans* mixtures. However, the subsequent *N*-acylation results in the formation of only the *cis* derivative.<sup>[62, 93, 100, 101, 103–110]</sup> The enolates of the N,N-, N,O- and N,S-heterocycles are alkylated from the side opposite to that shielded by the *tert*-butyl group to give the products *cis*-**3** (Scheme 6d<sup>[100, 104–109]</sup>). The reactivity of the glyceric acid derivative is somewhat different: the *tert*-butylthiol ester cyclizes preferentially (5:1) to give the *trans* product, and subsequent alkylation occurs *cis* to the *t*Bu group ( $\rightarrow$  **4**).<sup>[93, 102]</sup> The enolates of the heterocyclic carboxylic esters have a range of stabilities with regard to  $\beta$ -elimination (Scheme 6e left), which should, in fact, be stereoelectronically unfavorable.<sup>[111]</sup> In spite of this problem, very high yields of the required product can be obtained under suitable reaction conditions. Examples with references can be found in Table C of the appendix and in Schemes 7 and 8, in which structures of some amino acids and natural products are shown that have been prepared using the intermediates shown in Schemes 5 and 6c,d,e or by different applications of the SRS principle.<sup>[112–131]</sup>



Scheme 7. Selected examples of  $\alpha,\alpha$ -disubstituted  $\alpha$ -heterocarboxylic acids prepared following the SRS principle described in Schemes 5 and 6. TBDMS = *tert*-butyldimethylsilyl.



#### 4. Using the SRS Principle in the Preparation and Reactions of $\alpha,\beta$ -Unsaturated, $\alpha$ - and/or $\beta$ -Heterosubstituted Carboxylic Acid Derivatives (Dienolates, Radicals, Michael Acceptors, and Components for Cycloadditions)

*Ich habe nicht mehr Glück als Sie,  
aber ich probiere mehr als Sie!\**

Adolf von Baeyer

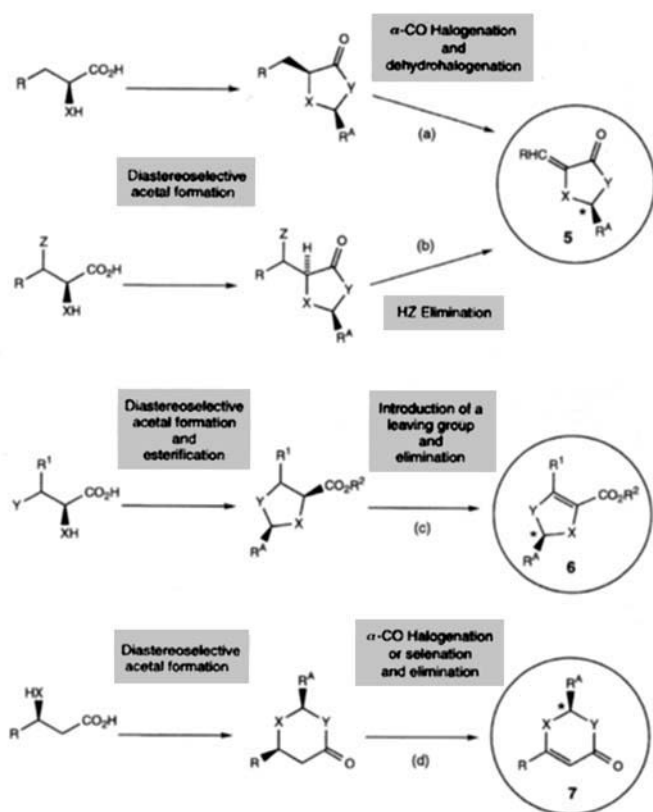
Cyclic acetals with endo- or exocyclic C–C double bonds must be prepared in order to introduce new substituents at the position  $\beta$  or  $\gamma$  to a carbonyl group of a chiral, heterosubstituted carboxylic acid, as was described in the previous scheme for the  $\alpha$ -position. This can be achieved in a number of ways (Scheme 9). Firstly, the familiar five-membered cyclic acetal is prepared diastereoselectively from an aldehyde  $R^A\text{CHO}$  and the  $\alpha$ - or  $\alpha,\beta$ -amino-, -hydroxy-, or -sulfanylcarboxylic acids. Subsequently, the resulting dioxolanones, oxazolidinones, and imidazolidinones can be, for example, brominated by means of a radical process. Such brominations display a

[\*] "I am not luckier than you, I simply try harder!"

Scheme 8. At least one step in the syntheses of the natural products shown here follows the principle of self-regeneration of stereocenters; the tertiary carbon atoms formed in this way are marked by an asterisk. (S)-(-)-Frontalin was obtained by alkylation of the enolate of *cis*-1 ( $X=Y=O$ ,  $R^A=t\text{Bu}$ ,  $R=\text{Me}$ , Scheme 5, derived from lactic acid) with 1-iodo-4,4-dimethoxypentane, reduction with lithium aluminium hydride, and interchange of acetals. The key step in the synthesis of (+)-cremantholide A was the reaction of the same lactic acid enolate with 2,3-dibromopropene; the final product was obtained after many more steps. In the alkaloid (+)-indicine *N*-oxide the carboxylic acid unit in the ester side chain was prepared by hydroxyalkylation of *cis*-1 ( $X=Y=O$ ,  $R^A=t\text{Bu}$ ,  $R=i\text{Pr}$ ) with acetaldehyde in 43% yield. (R)-Mevalolactone was prepared from both lactic acid (via *cis*-1 ( $X=Y=O$ ,  $R^A=t\text{Bu}$ ,  $R=\text{Me}$ )) and malic acid (1,  $X=Y=O$ ,  $R^A=t\text{Bu}$ ,  $R=\text{CH}_2\text{CO}_2t\text{Bu}$ ) following the SRS principle. The important point about this synthesis is that labels ( $^{13}\text{C}$ ,  $^2\text{H}$ ,  $^3\text{H}$ ) can be introduced at numerous positions to produce derivatives suitable for biosynthetic investigations. Proline was the starting point for an elegant total synthesis of brevianamide B. The synthesis proceeded via compound 2 ( $R^E=\text{allyl}$ ), which was prepared by the reaction of the bicyclic compound shown in Scheme 6c ( $X=\text{CH}_2$ ) with allyl bromide. The mirabazoles are a group of alkaloids that all contain an  $\alpha$ -methylcysteine functionality. Dehydromirabazole A was synthesized from the methyl ester of  $\alpha$ -methylcysteine, which was obtained from the appropriate heterocycle of type *cis*-3 ( $Y=\text{NCHO}$ ,  $X=\text{S}$ ,  $R=\text{Me}$ ,  $R^E=\text{Me}$ , Scheme 6).  $\alpha$ -Methylcysteine was employed in the same way in the synthesis of (S)-desferrithiocin. The synthesis of rhodomycinone began with enantiomerically pure (S)-aminobutanoic acid, which was converted into the hydroxy acid by diazotization. Subsequent reaction of the enolate of 1 ( $X=Y=O$ ,  $R^A=t\text{Bu}$ ,  $R=\text{Et}$ , Scheme 5) with allyl bromide proceeded in the normal manner. Reduction of the carbonyl functionality with DIBALH, acetal interchange, and ozonolysis led to the 1,4-dialdehyde, which was suitably protected such that a Marschalk reaction with the appropriately substituted anthrahydroquinones could then be carried out. This resulted in the formation of the rhodomycinones. The total synthesis of (+)-lactacystin was achieved by three different routes; two [129, 130] followed the SRS principle and the third used the strategy described in ref. [92]. The synthesis carried out by E. J. Corey and co-workers [129] began with the oxazolidine derived from serine, which was hydroxyalkylated with isobutyraldehyde to yield a product of type *cis*-3 ( $X=O$ ,  $Y=\text{BnN}$ ,  $R=\text{Me}$ ,  $R^E=\text{Me}_2\text{CHCH}(\text{OH})$ ), Scheme 6); J. E. Baldwin and co-workers described an extremely sophisticated application of the SRS principle. Pyroglutamic acid was allowed to react with benzaldehyde and then reduced to the bicyclic compound, shown in the last line. A series of subsequent steps led to the silyloxyproline shown, which reacted stereoselectively with isobutyraldehyde in the following key step.

surprisingly high preference for the CH-position adjacent to the carbonyl group (captodative radical stabilization<sup>[132]</sup>) over the acetal center (this has a bulky  $R^A$  substituent,  $t\text{Bu}$ , and is therefore sterically hindered).<sup>[133–136]</sup> Diastereoselectivity was observed early on in brominations that proceed via an  $\alpha$ -carbonyl radical intermediate<sup>[133]</sup> (see Section 9.3) rather than via an enolate (Schemes 5 and 6). Elimination of HBr then leads to acetals 5, which have an exocyclic double bond (Path a in Scheme 9). In the simplest case ( $R=\text{H}$ ), these are chiral non-racemic derivatives of  $\alpha$ -hydroxy- or  $\alpha$ -aminoacrylic acid, in other words, of pyruvic acid! An alternative method (Path b in Scheme 9) begins with a carboxylic acid bearing functional groups in the  $\alpha$ - and  $\beta$ -positions. After the necessary functional group manipulations, a five-membered cyclic acetal with a leaving group in the exocyclic position  $\beta$  to the carbonyl group is obtained and hence, the alkylidene derivative 5 can now be readily prepared.<sup>[137–139]</sup> Furthermore, the oxazoline and thiazoline carboxylic esters 6, heterocycles with conjugated endocyclic C–C double bonds, can be prepared from the appropriate acetals of serine, threonine,<sup>[140]</sup> and cysteine<sup>[103, 104]</sup> (Schemes 6d and 9c). Finally, perhydropyrimidinones<sup>[62, 141–149]</sup> and dioxanones<sup>[150–162]</sup> can be prepared diastereoselectively from  $\beta$ -amino- and  $\beta$ -hydroxycarboxylic acids, respectively, by a variety of

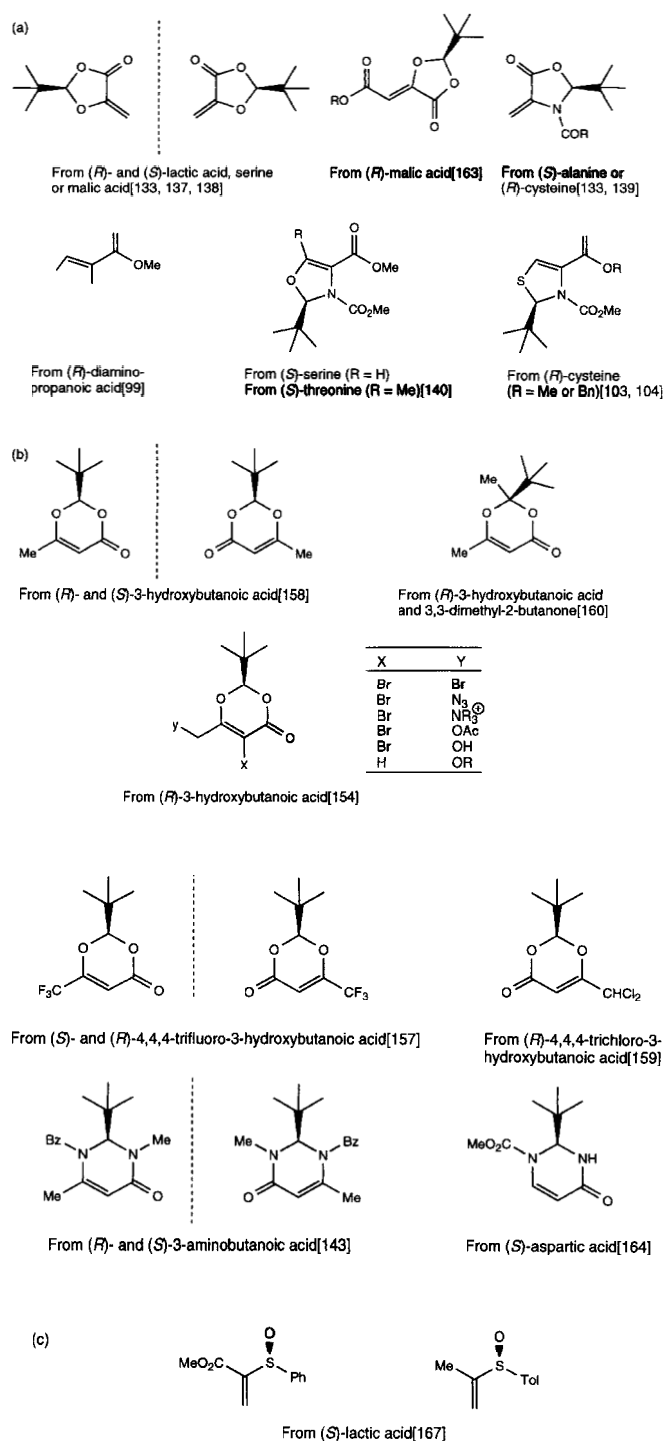




Scheme 9. Preparation of chiral  $\alpha,\beta$ -unsaturated carbonyl compounds from amino-, hydroxy-, and sulfanylcarboxylic acids with destruction of the original stereogenic center in the position  $\alpha$  or  $\beta$  to the carbonyl group. (For specific examples, see Scheme 10; for further reactions, see Schemes 11–14. See the text for a discussion of pathways (a)–(d). Tables D1–D4 in the appendix give examples of the applications of these heterocycles.)

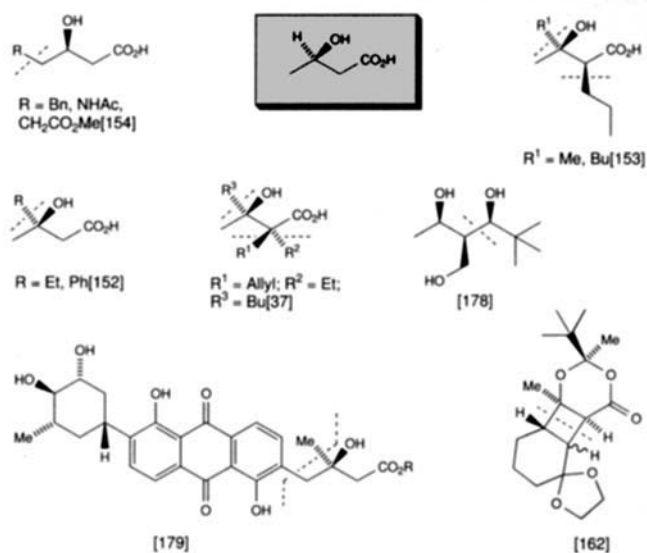
methods. Subsequent formal dehydrogenation leads to the heterocyclic  $\alpha,\beta$ -unsaturated carbonyl compounds 7 (Scheme 9d), which are, in fact, chiral, nonracemic acetals of, for example, acetoacetic acid and other  $\beta$ -ketocarboxylic acids.

The formulas of several five- and six-membered cyclic heterocycles with  $\alpha,\beta$ -unsaturated carbonyl functionality, together with the appropriate precursors and literature references are given in Schemes 10a and b.<sup>[163–166]</sup> An  $\alpha$ -sulfinylacrylate and a 2-propenylsulfoxide are depicted in Scheme 10c; here, the stereogenic center of a sulfoxide, rather than that of an acetal, is utilized to preserve the chirality of the Michael acceptor.<sup>[167, 168]</sup> These readily prepared  $\alpha,\beta$ -unsaturated carbonyl compounds can be used as chiral building blocks in a variety of processes: the Michael addition of nucleophiles (such as cuprates or  $\text{Cu}^{\text{I}}$ -doped Grignard reagents), the addition of radicals, in cycloadditions (photochemical [2+2] cycloadditions, Diels–Alder reactions), and catalytic *cis*-hydrogenations or deuterations. Reactions with electrophiles are also possible (via the dienolates shown in Scheme 11), and in this way new substituents can be introduced at the position  $\alpha$  or  $\gamma$  to the carbonyl group (see the examples in Schemes 11a–c). An assortment of products, which may be prepared by various types of additions at the C–C double bond of the heterocyclic acceptors discussed above, is shown in Scheme 12.<sup>[169–176]</sup> Structures derived from

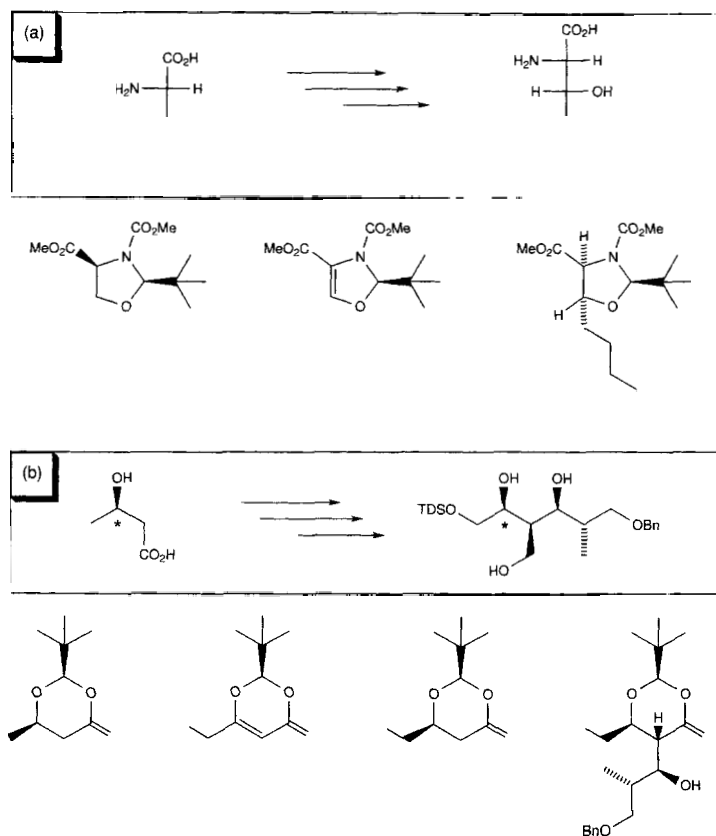


Scheme 10. Chiral products of formal dehydrogenation derived from lactic acid, malic acid, 3-hydroxybutanoic acid, and the amino acids alanine, serine, threonine, cysteine, aspartic acid, and 3-aminobutanoic acid. a) Five-membered ring heterocycles from  $\beta$ -hydroxy and  $\beta$ -amino acids. b) Six-membered ring heterocycles from  $\alpha$ - and  $\alpha,\beta$ -disubstituted carboxylic acids. c) Chiral, noncyclic sulfoxides from lactic acid. Subsequent products are depicted in Schemes 11–14 and in Tables D1–D4 in the appendix. For short review articles with information on methylene derivatives of dioxolanones [67], oxazolidinones [66], oxazolidine dicarboxylates [165], and dioxinones [166] see the *Encyclopedia of Reagents for Organic Synthesis*. Bz =  $\text{COC}_6\text{H}_5$ , Tol =  $\text{C}_6\text{H}_4\text{CH}_3$ .





Scheme 13. Products prepared from (*R*)-3-hydroxybutanoic acid in which the preparation involves the temporary destruction of the original stereogenic center; see the dioxinone derivatives in Schemes 9d, 10b, 11b, 14b and in Tables D3 and D4 of the appendix. Of course, the methods used here are not only applicable to both enantiomers of hydroxybutanoic acid but are also generally applicable to 3-hydroxycarboxylic acids (for example, see ref. [180]).



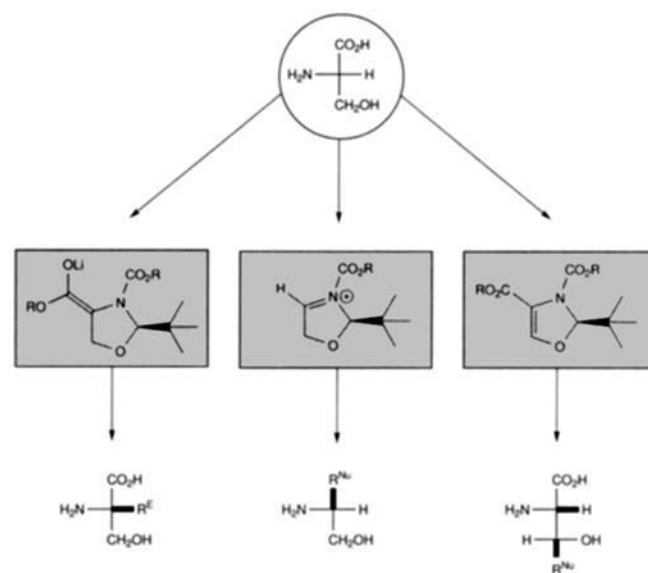
Scheme 14. Reactions of serine (a) [140] and (*R*)-3-hydroxybutanoic acid (b) [181] with substitution of the hydrogen atom in the position  $\beta$  or  $\gamma$  to the carbonyl functionality by  $C_4H_9$ , or RO groups. The formulas of the most important intermediates are shown. The original stereogenic center is temporarily destroyed in order to achieve the necessary reactivity at the 3- or 4-position of the carbon skeleton. In both products, an H atom (at C2 of serine and at C3 of hydroxybutanoic acid) is stereoselectively replaced (with retention!) by a new one; this could have been proved by deuterolysis in case (a) and by the use of  $D_2$  in case (b).

tionalization of the terminal  $CH_3$  group of the hydroxybutanoic acid is only possible via the dioxinone derivative, and the hydrogen atom at the C atom marked by the asterisk is derived from the  $H_2$  used in a catalytic hydrogenation step!

## 5. SRS via Acyliminium Ions and the Resulting Products

*Umpolung doubles the possibilities.*

In the previous two sections we have shown that new substituents can be introduced, without racemization, at the 2- or 3-position of carboxylic acids by means of enolate and enoate chemistry with the aid of electrophilic and nucleophilic reagents. The crucial intermediates derived from serine for the preparation of modified 2-amino-3-hydroxycarboxylic acids are depicted in Scheme 15. In all of the previous examples, it has been a hydrogen atom that has been replaced by a new substituent.

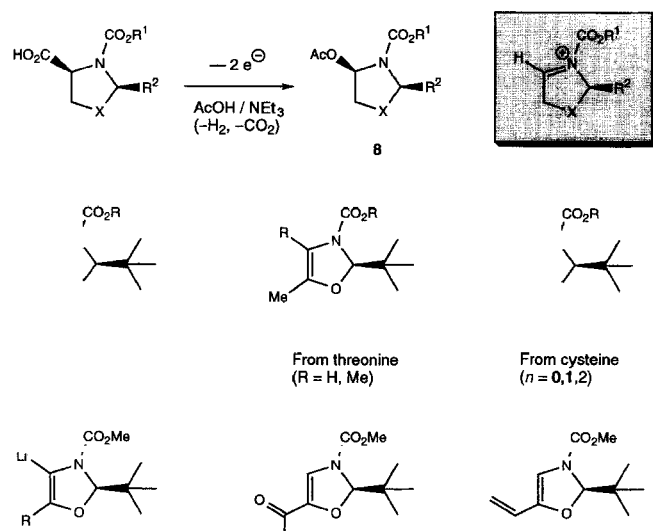


Scheme 15. Stereoselective replacement of H atoms and of the  $CO_2H$  group of serine by new substituents following the SRS principle. Bonds marked in bold are those resulting from this transformation and do not break the convention used for the depiction of Fischer projections (see center and right). The alkylation yielding the  $\alpha,\alpha$ -disubstituted amino acid (left) and the modification resulting in chain extension at the C atom in  $\beta$ -position (right) are also possible with simple amino acids such as alanine (Schemes 5, 9a, 10a), whereas the decarboxylation (center) [182] is not.

However, in the case of the trifunctional amino acids such as serine, threonine, cysteine, and aspartic acid the SRS principle can be applied to replace the carboxyl functionality with other groups. For example, in the case of aspartic acid, the reaction sequence proceeds via the dihydropyrimidinone<sup>[145–149]</sup> (shown in Scheme 10b), and for serine, the acyliminium ion<sup>[182]</sup> (shown in the center of Scheme 15) is involved. As can be seen, the carboxyl group is replaced by a new substituent  $R^{Nu}$ , which is introduced by the use of a nucleophilic reagent (umpolung of the nucleophilic reactivity of the Li-enolate to produce electrophilic reactivity at the former C2 of the acid). Interestingly, these reactions often proceed in a far superior fashion when an *i*Pr rather than the usual *t*Bu substituent is present at the tempo-

rary stereogenic center, and generally the new substituent enters *cis* to the substituent at the acetal C atom!<sup>[183]</sup>

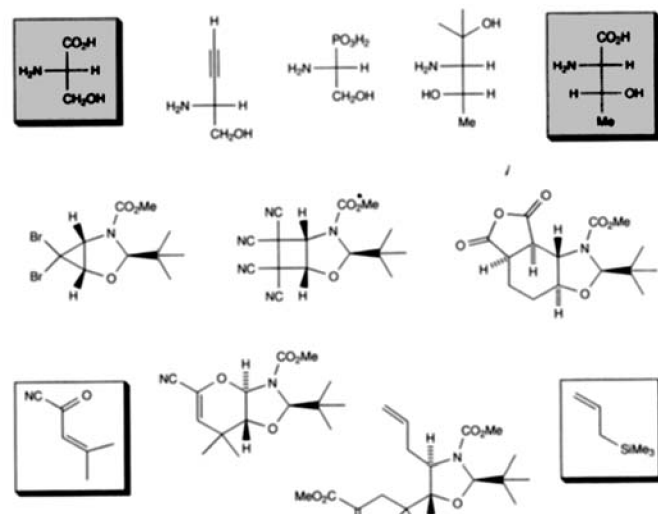
The key step in the removal of the carboxyl group from the derivatives of serine, threonine, and cysteine is the electrolytic anodic oxidation of the carboxylic acid. Faraday<sup>[184]</sup> and Kolbe<sup>[185]</sup> demonstrated that simple carboxylic acids are coupled under these conditions ( $2\text{RCO}_2\text{H} \rightarrow \text{R}-\text{R} + 2\text{CO}_2 + \text{H}_2$ ), and Hofer and Moest<sup>[186]</sup> showed that oxidative decarboxylation occurs with carboxylic acids when R is a cation-stabilizing substituent ( $\text{RCO}_2\text{H} + \text{R}'\text{OH} \rightarrow \text{ROR}' + \text{CO}_2 + \text{H}_2$ ). The reaction of the amino acids mentioned occurs as shown at the top of Scheme 16. In contrast to most other electrolysis procedures,



Scheme 16. Electrolysis of the oxazolidine and thiazolidine carboxylic acids (e.g. **8**) derived from L-amino acids, elimination of HOAc to yield the oxazoline and thiazoline derivatives (e.g. **9**), and electrophilic substitution at the C–C double bond by means of lithiation or by direct Vilsmeier formylation (subsequent Wittig olefination produces the electron-rich diene **10**) [101, 103, 140, 182, 190]. A short review article about **9** has been published in the *Encyclopedia of Reagents for Organic Synthesis* [165].

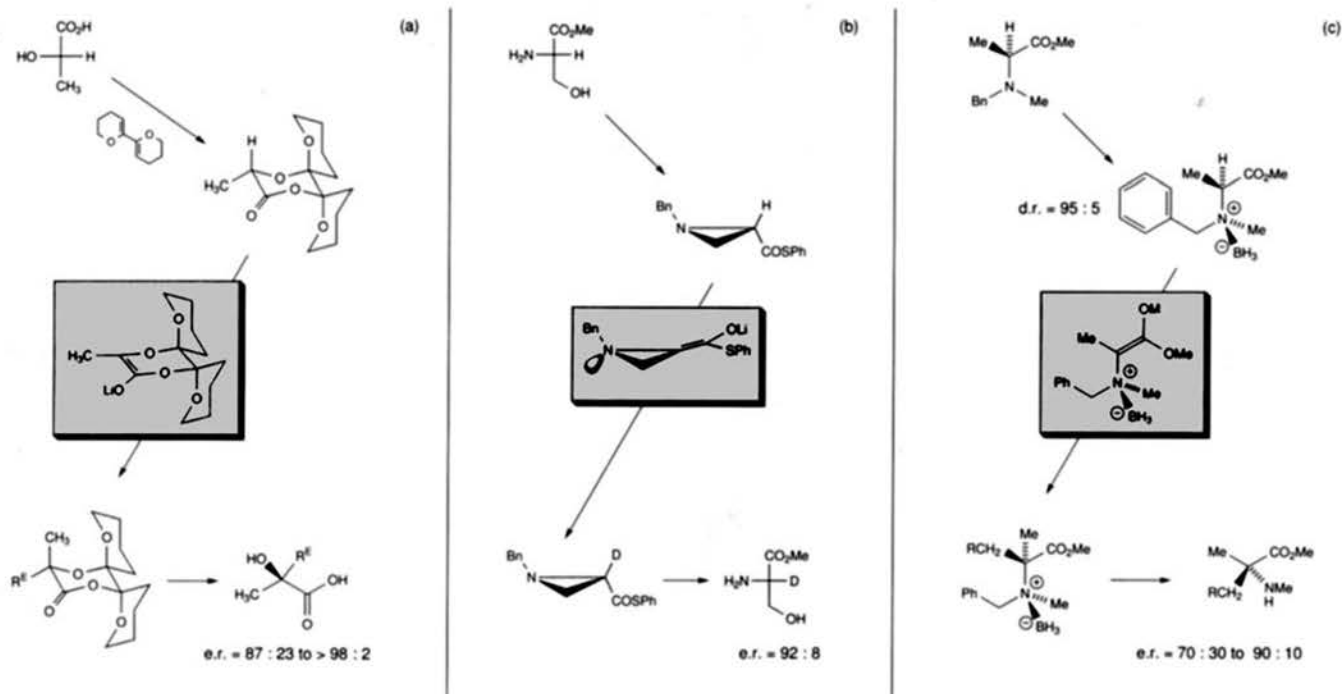
this decarboxylation is a simple, easily conducted reaction. The electrodes need not be separated by diaphragms and the addition of a supporting electrolyte is also not required. A solution of the oxazolidine<sup>[101]</sup> or oxidothiazolidine carboxylic acid<sup>[103]</sup> in a protic solvent such as acetic acid (this is much less susceptible to decarboxylation!) or methanol is mixed with triethylamine (formation of the supporting electrolyte,  $\text{RCO}_2^- \text{Et}_3\text{NH}^+$ ) and then electrolyzed in an undivided cell until the gas evolution ceases and the conductivity falls due to complete consumption of the carboxylate. This reaction can be carried out at high concentrations of the carboxylic acid on a multigram scale and results in excellent yields of the decarboxylated product (**8**, X = O, R<sup>1</sup> = Me, R<sup>2</sup> = *t*Bu, ca. 90% yield for the decarboxylation step, ca. 55% yield from serine over four steps;<sup>[101]</sup> the 2-isopropyl derivative can be prepared analogously). Here again, the *cis*-acetoxyoxazolidine is produced, which results from attack of the acyliminium salt (shown in the box in Scheme 16) at the apparently more sterically hindered face.<sup>[183]</sup> Lewis acid assisted nucleophilic substitution of

the AcO group of the useful, readily available, enantiomerically pure derivatives **8**<sup>[140, 187–194]</sup> can be performed, and once again, this proceeds via the acyliminium ion. Products obtained from the reaction with bis(trimethylsilyl)acetylene or from the Michaelis–Arbuzov reaction (triphenylphosphite/TiCl<sub>4</sub>) (yields of 80 and 95%, respectively; diastereoselectivities of 90 and 80%, respectively) are shown at the top of Scheme 17.<sup>[182, 195]</sup>



Scheme 17. Top: An acetylenic amino alcohol and a phosphoserine derived from heterocycle **8** [182, 195], which is shown in Scheme 16 and derived from serine; an amino diol prepared by addition of the Li threonine derivative from Scheme 16 to acetone, hydrogenation of the double bond, and hydrolysis [140]. Middle: Compounds resulting from addition of dibromocarbene, tetracyanoethylene, and an acyl cyanide to heterocycle **9**; a product with four neighboring stereogenic centers (two of which are derived from serine) results from hydrogenation of the Diels–Alder adduct of maleic anhydride and diene **10** [192]. Bottom: The addition of the  $\alpha,\beta$ -unsaturated acyl cyanide to **9** apparently proceeds via a zwitterion (enolate/acyl iminium ion) and results in the formation of a *trans*-fused bicyclic compound. The allylation of this compound (allylsilane/TiCl<sub>4</sub>, Sakurai method) proceeds *cis* to the *tert*-butyl group with formation of a 6-amino-5-hydroxy-4,4-dimethyl-2-oxonon-8-ene carboxylic acid derivative (the two C atoms derived from serine in the C<sub>9</sub> chain are both stereogenic centers).

Nucleophilic substitution of the electrolysis products **8**, derived from serine, threonine, and cysteine, gives these intermediates a wide-ranging potential in synthesis. Elimination of acetic acid yields the heterocycles shown in the center of Scheme 16, which have highly reactive C–C double bonds. The oxazoline **9** contains the structural features of both an enol ether and an *N*-acyl-enamine.<sup>[101, 140, 182, 190, 192]</sup> The hydrogen atoms at the double bond of **9** can be substituted by means of an *N*-acyl-directed metalation (next to the N atom) and by the use of a Friedel–Crafts type reaction (next to the O atom). Here, once again, the stability of the acyliminium ion is responsible for the regioselectivity of the kinetically controlled reaction with electrophiles<sup>[140, 192, 196]</sup> (see the formyl- and vinyloxazoline carboxylic acid ester **10** in Scheme 16 and the bicyclic and tricyclic species in Scheme 17, resulting from cycloaddition reactions). The relative configuration of the products, which are frequently formed with complete diastereoselectivity, was assigned by chemical correlation or NMR spectroscopy. All products are enantiomerically pure and all are also available in the enantiomeric form by the use of D- instead of L-serine, -threonine, or -cysteine.



Scheme 18. Three applications of the SRS principle in which the temporary stereogenic center is a) a spiroacetal C atom [205], b) an aziridine nitrogen atom [208], and c) a nitrogen atom of a boron–amine adduct  $R^1R^2R^3N^+BH_3^-$  [211].

## 6. Other “Tricks” for the Self-Regeneration of Stereocenters

*Phantasie ist wichtiger als Wissen.*<sup>[\*]</sup>

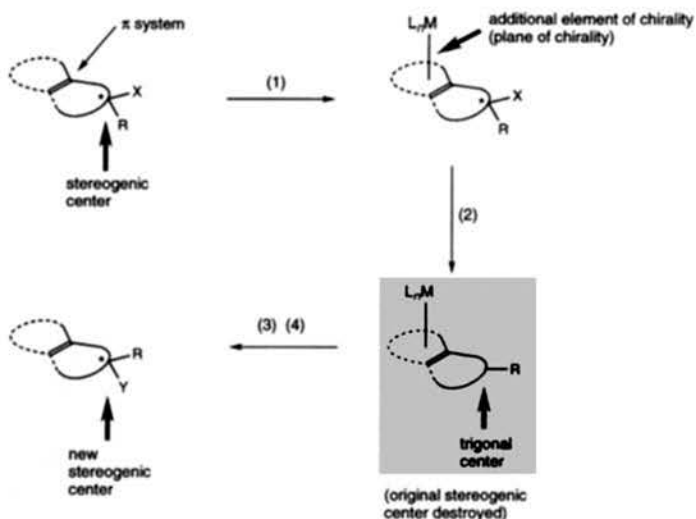
Albert Einstein

Once a synthetic principle has been understood, only the chemist’s imagination sets the limits! In recent years numerous reactions have been described that intentionally or unintentionally make use of the self-regeneration of stereocenters.<sup>[197, 198]</sup> We describe only a few here.

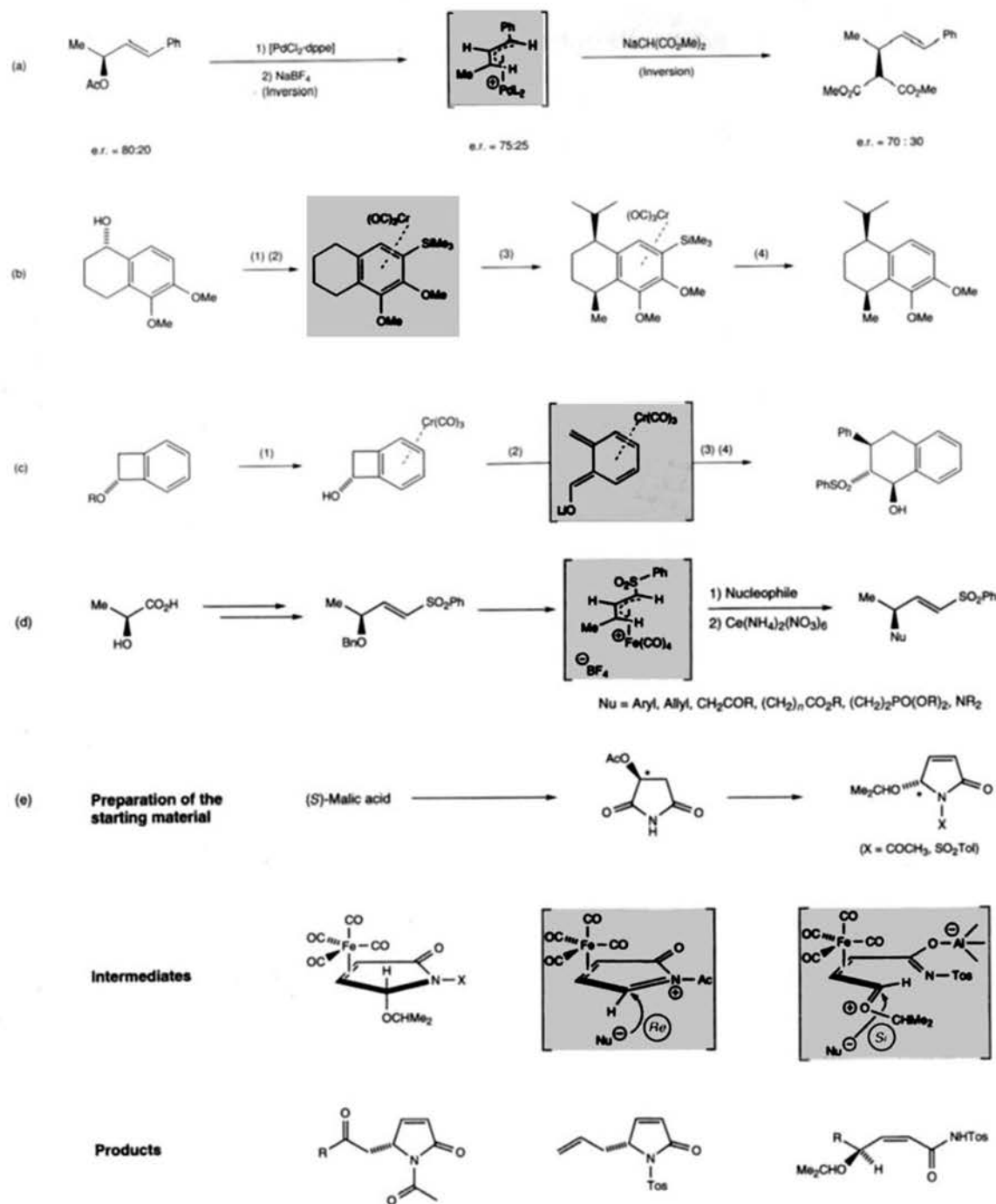
In Scheme 18 a the key step<sup>[205]</sup> is the diastereoselective formation of a dispirodiacetal from 1,1'-bis(dihydropyran) and lactic acid, a procedure that is useful in a variety of other transformations.<sup>[199–204]</sup> In Scheme 18 b the configurationally stable stereogenic center at the nitrogen atom of an aziridine facilitates the introduction of new substituents at the 2-position of serine<sup>[206]</sup> via enolates of the aziridine carboxylic ester.<sup>[207–209]</sup> Scheme 18 c depicts a highly refined, and yet conceptually simple  $\alpha$ -allylation of an amino acid derivative: After diastereoselective formation of a Lewis acid/Lewis base complex from  $BH_3$  and *N*-benzyl-*N*-methylalanine methyl ester, an enolate is formed, which is chiral owing to the stereogenic center at the nitrogen atom. This intermediate reacts diastereoselectively with alkyl halides such that removal of  $BH_3$  and debenylation leads to  $\alpha,\alpha$ -disubstituted *N*-methylamino acids with enantiomer ratios of up to 9:1.<sup>[210, 211]</sup>

Obviously, not only stereogenic centers but also stereogenic axes and planes are able to self-regenerate. Hence, it is also clear that not only temporary stereogenic centers but also every other chirality element (axis, plane, helix) can be employed in self-

regeneration. The application of chirality planes within transition metal complexes is well-documented. The principle is described in Scheme 19 (cf. Scheme 3) and some specific examples are given in Scheme 20.<sup>[212–217]</sup> As can be seen, the single stereogenic center of the starting material is destroyed in the process. Simultaneously, a plane of chirality is formed<sup>[218]</sup> or preserved. The metal center, together with its



Scheme 19. Self-regeneration of stereocenters with the assistance of transition metal  $\pi$ -complexes. An enantiomerically pure compound with only one stereogenic center is complexed diastereoselectively (1). The configurationally stable plane of chirality ensures that the subsequent destruction of the stereogenic center results in the formation of a nonracemic intermediate (2). Hence the next reaction (3) proceeds diastereoselectively and the destruction of the  $\pi$ -complex (4) results in the formation of an enantiomerically pure or enriched compound [212–217] (cf. Scheme 3).



Scheme 20. SRS processes via  $\pi$ -complexes with planes of chirality. Steps (1)–(4) in (b) and (c) correspond to steps (1)–(4) in Scheme 19. a) Nucleophilic substitution, with two inversions of configuration, at the allylic position via a stoichiometrically or catalytically generated Pd- $\pi$ -allyl complex [213] (dppe = ethane-1,2-diylbis(diphenylphosphane)). b) Substitution of an OH by an *i*Pr group with inversion. The intermediate is a benzene-chromium(tricarbonyl) complex, which is Me<sub>3</sub>Si-protected in the position on the benzene ring *ortho* to the methoxy group. This complex is first lithiated and methylated next to the methoxy group, and then an isopropyl group is introduced at the second benzylic position in an analogous fashion. The sequence shown is part of the total synthesis of the sesquiterpene *cis*-7,8-dihydroxy-11,12-dehydrocalamenene [214]. c) Diels-Alder reaction of an *ortho*-quinodimethane with  $\omega$ -phenylsulfonystyrene. The starting alcohol is produced by enzymatic kinetic resolution. The lithium alkoxide of the benzene-chromium(tricarbonyl) complex ring opens to the planar-chiral quinodimethane at approximately  $-30^\circ\text{C}$  [215]. d) Reaction of one of the  $\pi$ -allyl(carbonyl)iron complexes, available by transformation of lactic acid, with nucleophiles. This reaction was used in the synthesis of simple natural products such as pheromones and terpenes [216a]; analogous reactions are also possible with the complex derived from benzyloxy-2-pentenoic acid [216b]. e) Substitutions via cationic tetracarbonyliron complexes, in which the organic ligand is formally a derivative of maleic aldehyde but actually derived from malic acid [216c] (cf. the substitution reactions of **8**, Schemes 16 and 17). Similar reactions have been carried out with the tricarbonyliron complexes of 2-alkoxy-4-vinyl-2,5-dihydrofurans [217].

ligands, acts as a temporary substituent and hence, influences the stereochemical course of subsequent reaction(s) and the formation of new centers of chirality. Once the metal complex has been destroyed, the organic ligand is released in an enantiomerically pure or enriched form. The result of this reaction sequence

is that a new substituent is introduced stereoselectively at the original stereogenic center. Since this is achieved without the aid of a chiral auxiliary, this sequence can also be considered to follow the general concept of the self-regeneration of stereocenters.

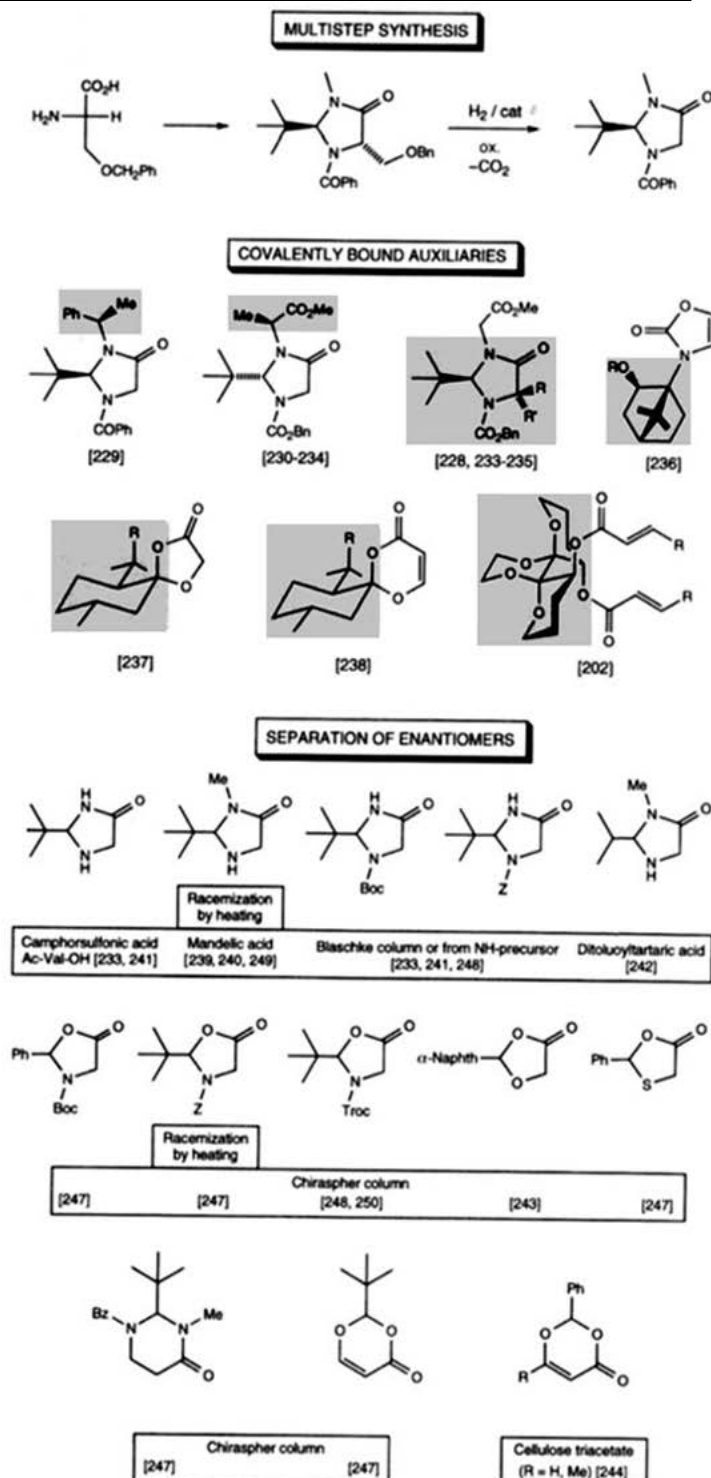
## 7. What Can Be Done When No Suitable Precursor for the Self-Regeneration of a Stereocenter Is Available?

*Nothing is worse than harping on principles!*

The heterocyclic products described in Sections 3–5 (Li-enolates, Michael acceptors, radical intermediates, acyliminium salts) display high reactivity, and their reactions usually proceed with outstanding diastereoselectivity. Availability, reactivity, and stereoselectivity are the marks of quality of synthetically useful compounds. For this reason we aimed to make such enantiomerically pure dioxolanones, oxazolidinones, imidazolidinones, perhydropyrimidinones, and dioxinones readily available, even when no suitable, inexpensive chiral precursors were available. The solution to this problem is illustrated with examples from the synthesis of  $\alpha$ -amino acids.<sup>[219, 220]</sup> As was shown in Section 3, amino acids can be substituted at the  $\alpha$ -position by applying the principles of SRS. This approach provides relatively easy access only to compounds in which one of the substituents at the stereogenic center is derived from one of the 20 proteinogenic amino acids. It is, however, impossible to produce an amino acid with a single, “unnatural” side chain in the  $\alpha$ -position by this method. Clearly what is needed is a chiral glycine derivative with an oxazolidinone or imidazolidinone structure. Reaction of this compound either once or twice with appropriate electrophiles and subsequent hydrolysis would lead to the desired amino acid. There are three ways to prepare a glycine derivative of this type, and we wish to denote them as the *laborious*, the *fashionable*, and the *classical* approach.

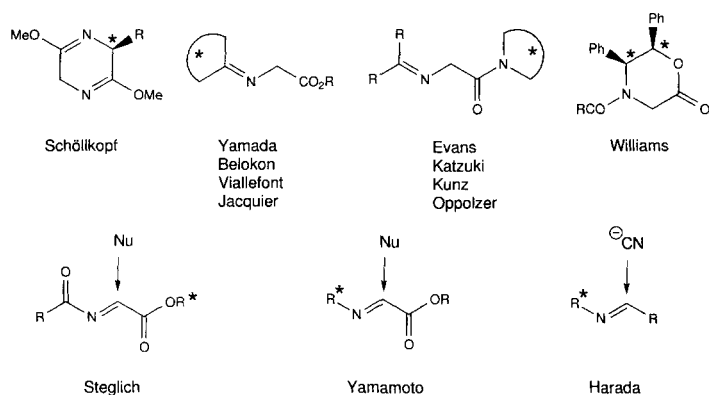
If you want to strictly follow the SRS principle then you have to use the laborious approach<sup>[221]</sup> (see Scheme 21 top). Serine is O-benzyl-protected and the imidazolidinone is formed by the usual methods (Scheme 5). This is then debenzylated, oxidized to an aminomalonic acid derivative,<sup>[222, 223]</sup> and then decarboxylated. A chiral, nonracemic glycine derivative results owing to the acetal center, and it can be alkylated via the Li-enolate in the usual manner.<sup>[71, 224]</sup>

Today, the most commonly used method (the fashionable approach) for the synthesis of enantiomerically pure compounds (EPC synthesis)<sup>[225]</sup> on a laboratory scale relies on covalently bound chiral auxiliaries which force the reaction to proceed in a diastereoselective fashion. In the extremely successful approach based on chiral auxiliaries, a readily available, enantiomerically pure compound is attached to the achiral compound that is to be modified enantioselectively in the overall process. The reaction is then carried out with as high a diastereoselectivity as possible and finally, the chiral auxiliary is cleaved. On a laboratory scale, the chiral auxiliary is commonly sacrificed, but in industrial applications, the auxiliary, which is used in a stoichiometric amount, must be recovered for further reactions.<sup>[226]</sup> Evans's method employing an oxazolidinone, which is usually derived from an amino acid, with an appropriate substituent in the 4-position is perhaps the archetype of this form of EPC synthesis.<sup>[31, 227]</sup> There are numerous examples of compounds derived from glycine and a chiral auxiliary; Scheme 22 shows the different types together



Scheme 21. Three possible routes to chiral acetals of achiral amino- and hydroxycarboxylic acids (glycine, glycolic acid, thioglycolic acid, formyl- and acetoacetic acid, 3-aminopropanoic acid). *Multistep syntheses* that “uphold” the SRS principle [71, 221–224]; the *auxiliary approach* via covalently bound auxiliaries (see text for further references; the auxiliary component is highlighted in each case). The *separation of enantiomers* via diastereoisomeric salts or by preparative chromatography on a chiral solid support. Short review articles on imidazolidinones [65], oxazolidinones [66], dioxolanones [67], and dioxinones [166] can be found in the *Encyclopedia of Reagents for Organic Synthesis*.  $\alpha$ -Naphth =  $\alpha$ -naphthyl, Bn =  $\text{CH}_2\text{C}_6\text{H}_5$ , Bz =  $\text{COC}_6\text{H}_5$ , Boc =  $\text{CO}_2t\text{Bu}$ , Z =  $\text{CO}_2\text{Bn}$ , Troc =  $\text{CO}_2\text{CH}_2\text{CCl}_3$ .

with the names of their creators and references.<sup>[228]</sup> Some of the chiral imidazolidinone-containing derivatives of glycine are shown in Scheme 21, which also contains references to the use of the chiral auxiliary approach in the reactions of oxazolines (cf.



Scheme 22. Some glycine, dehydroglycine, and imine derivatives that have been used (or proposed for application) in the auxiliary approach to *C-C* bond formation in amino acid synthesis. Due to the wide variety of different systems and the large number of research groups working in this field, the names of only a few of the authors are listed here. For further information, see Williams's book [219] and the recent review articles [220, 228]. The method developed by Williams is in some respects very similar to the "Separation of Enantiomers" method outlined in Scheme 21 as the 2-amino-1,2-diphenylethane used is obtained by resolution of a racemic mixture. However, in the latter case the stereogenic center is actually eliminated at the end ( $\rightarrow$  aldehyde), whereas here the auxiliary, which initially also had to be prepared, is destroyed by hydrogenolysis ( $\rightarrow$  1,2-diphenylethane!).

9 in Scheme 16), dioxolanones (glycolic acid, cf. Scheme 5), dioxinones (cf. 7 in Scheme 9 and Schemes 10 b, 11 b, 13, 14) and the dispiro-THP derivative (cf. Scheme 18 a).<sup>[229–238]</sup>

The third, so-called *classical* approach is the route we have chosen to adopt: either the resolution of a racemic mixture through diastereoisomeric salts or, the more recently developed approach, the separation of enantiomers by preparative HPLC on a chiral column. The structures of the heterocyclic acetals separated in this way are shown at the bottom of Scheme 21.<sup>[239–250]</sup> The following advantages rapidly became clear:

- 1) Large quantities of both enantiomers are readily available. Hundreds of grams, even several kilograms, of 2-*tert*-butyl-3-methyl-1,3-imidazolidin-4-one (BMI) can, for example, be prepared by crystallization of the mandelate salt.<sup>[240, 249, 251]</sup> The chromatographic separation of enantiomers (for example, benzyloxycarbonyl (Z) protected 2-*tert*-butyl-oxazolidin-5-one on a 100  $\times$  400 mm Chiraspher column) is possible on a multigram scale.<sup>[246, 247]</sup>
- 2) The enantiomer that is not required for a particular synthetic target can be easily recycled by thermally induced racemization (BMI,<sup>[240]</sup> oxazolidinone<sup>[246]</sup>).
- 3) Since the enantiomerically pure cyclic acetals are obtained by resolution (Scheme 21 bottom), an auxiliary does not have to be recovered. The aldehyde (ArCHO, *i*PrCHO, *t*BuCHO) formed during the hydrolysis step is cheap and can be discarded. In this case, the chiral auxiliary is the carboxylic acid or chromatography column used for the separation of the enantiomers. This is done at a very early stage of the overall process and of course, further use of this type of auxiliary ("recycling") is not a problem.
- 4) The reactivity of the heterocyclic glycine enolates and other intermediates is outstanding; the *t*Bu group is the source of the high diastereoselectivity.
- 5) The majority of the products are not only solid but also have a high tendency to crystallize. If necessary, the major product can be further purified by recrystallization in most cases.

- 6) Those heterocycles that are not derived from glycine (the dioxolanones, thioxolanones, perhydropyrimidinones, and dioxinones, see Scheme 21 bottom) can also be separated on chiral columns.<sup>[243, 244, 247]</sup>

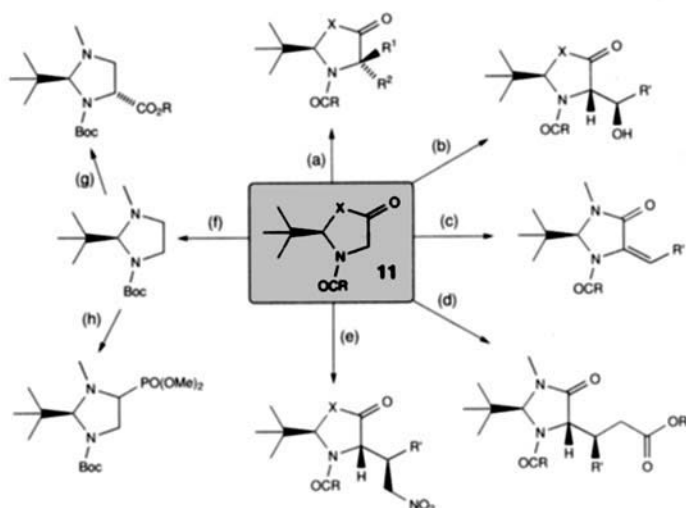
## 8. The Synthesis of Amino Acids via Chiral, Glycine-Derived Imidazolidinones and Oxazolidinones—Even Better than the SRS Principle

*Le mieux est l'ennemi du bien.*<sup>[\*]</sup>

Voltaire

In this section, we aim to demonstrate the wide variety of possibilities now open to us by using the glycine derivatives produced by the resolution of a racemic mixture as an example. Only the 2-*tert*-butyl-*N*-acyl-1,3-imidazolidinones and -oxazolidinones will be considered because they have proved to be particularly useful and their chemistry has been investigated in the most depth.<sup>[252]</sup>

The heterocycles described by the general formula **11** in Scheme 23 can be either mono- or dialkylated (a). The yield of



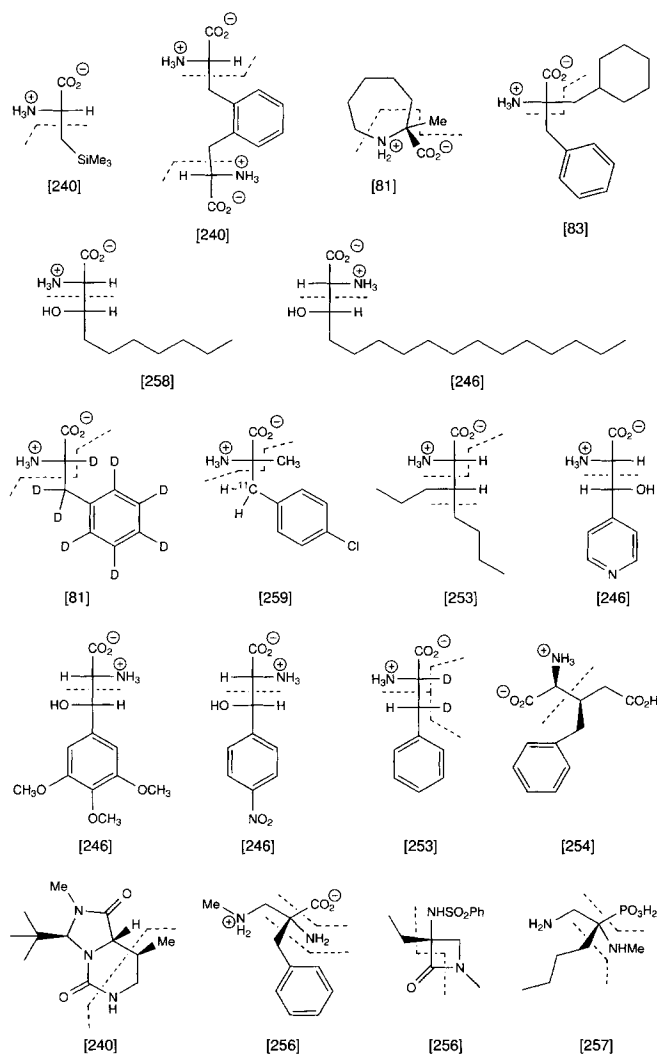
Scheme 23. Reactions (a)–(h) of acyl-*tert*-butyl oxazolidinones **11** (X = O) and acyl-*tert*-butyl methylimidazolidinones **11** (X = NMe) to give a variety of amino acid derivatives. See text for references; short review articles can be found in refs. [65, 66]; specific examples are shown in Schemes 24 and 25 and also in Table E (appendix). Compound **11** (X = NMe, RCO = Boc) is also known as Boc-BMI and oxazolidinone **11** (X = O, RCO = Z) is also known as Z-BOX.

the first alkylation<sup>[81, 240]</sup> is usually so high with a wide variety of alkyl halides that the second alkylation can be carried out immediately *in situ*.<sup>[82, 83]</sup> The order of addition of the two different electrophiles determines the absolute configuration of the  $\alpha$ -branched amino acid isolated at the end of the procedure. Good procedures<sup>[83]</sup> now exist for the hydrolysis of imidazolidinones with even the bulkiest substituents (derived from Boc-BMI, **11**, X = NMe, R = *t*BuO). This method has also been applied frequently for the synthesis of radiolabeled amino acids (examples in Table E in the appendix). The aldol addition (b) of

[\*] "The best is the enemy of the good."



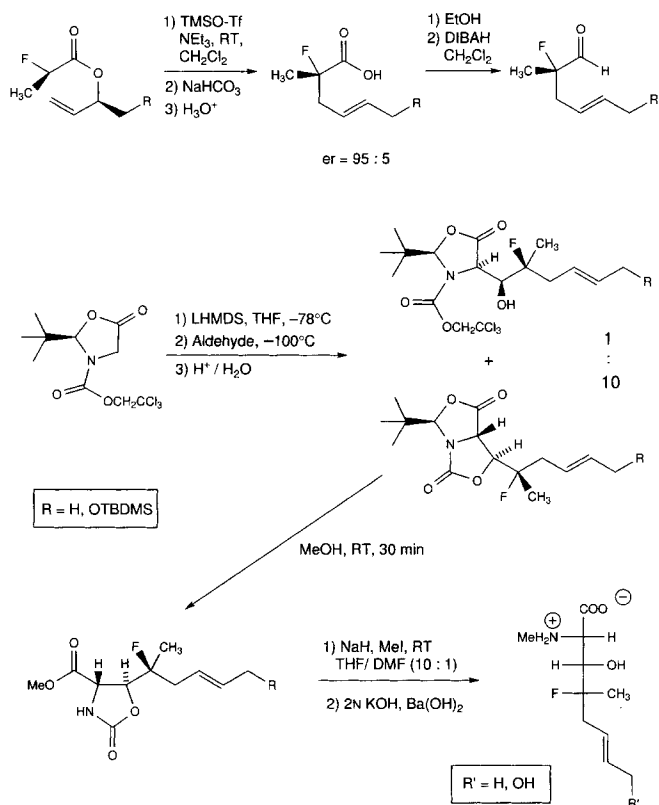
oxazolidinone **11**, X = O, R = BnO (Z-BOX),<sup>[245, 246]</sup> to aldehydes proceeds with high diastereoselectivity. If the aldehyde is chiral, the relative topicity is almost always determined by the enolate component.<sup>[71, 245, 250]</sup> (See the notes on the mechanism in Section 9.3, Scheme 29 and Table F.) Aldol condensations (c) are best brought about by a Wittig–Horner olefination using Boc-BMI. The imidazolidinone is brominated with NBS, the bromide is then converted by the Michaelis–Arbuzow procedure into a phosphonic ester (PO(OMe)<sub>2</sub> *cis* to *t*Bu), and this is condensed with an aldehyde to yield the (*E*)-alkylidene derivative.<sup>[134]</sup> These compounds are superb Michael acceptors and the addition of cuprates followed by aqueous workup yields pure derivatives of  $\beta$ -branched  $\alpha$ -amino acids with almost complete diastereoselectivity (R'' and H add to the exocyclic double bond in a *cis* fashion from the face opposite to that occupied



Scheme 24. Amino, diamino, and aminohydroxy acids derived from Boc-BMI and Z-BOX (**11**, X = NMe, RCO = Boc and X = O, RCO = Z, respectively, Scheme 23). The C–H, C–D, C–N, C–C, and C–P bonds resulting from connections to the skeleton of building block **11** are marked with dashed lines. These components were introduced by enolate protonation, deuteration, alkylation, by aldol condensations (to give (*S*)- or (*R*)-threonines or allothreonines), by aldol condensations and Michael additions, by catalytic hydrogenation of C–C double bonds, and by carboxylation and phosphonylation. See also Table E in the appendix, where many further examples can be found.

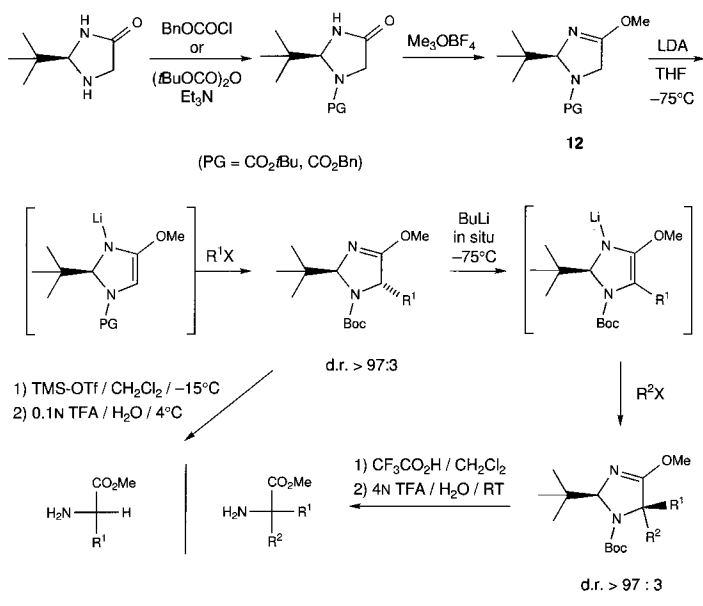
by the *t*Bu group).<sup>[253]</sup> Michael additions of enolates derived from **11** to enoates<sup>[254]</sup> and enones (d)<sup>[255]</sup> and to nitroolefins (e)<sup>[240]</sup> proceed selectively with respect to both of the newly formed stereogenic centers. Finally, the oxygen atom on the ring of Boc-BMI can be smoothly removed with LiBH<sub>4</sub> (Scheme 23 (f)) and the resulting chiral 1,2-diaminoethane derivative can be alkoxy-carbonylated (g) or phosphonylated (h). This methodology provides  $\alpha$ -branched  $\alpha,\beta$ -diaminopropanoic<sup>[99, 256]</sup> and -ethanephosphonic acids,<sup>[257]</sup> respectively, in enantiomerically pure form. Selected examples of such amino acids are shown in Scheme 24,<sup>[258, 259]</sup> and Table E in the appendix contains a complete list. The synthesis of (*S,S,S*)-2-amino-4-fluoro-3-hydroxy-*N*,4-dimethyl-(*E*)-6-octenoic acid (MeBmt) is outlined in Scheme 25.<sup>[250]</sup> This synthesis follows a route very similar to that used for the preparation of the parent compound MeBmt,<sup>[245]</sup> the unique amino acid found in the immunosuppressant cyclosporin. The preparation of MeBmt once again underlines the peculiar effects of a fluorine substituent on the properties and reactivities of organic compounds.<sup>[260, 261]</sup>

All of the advantages of the glycine derivative **11** have been emphasized, but the conditions necessary for the hydrolysis of



Scheme 25. Synthesis of fluorinated analogs of MeBmt (formula bottom right, R' = H and H in place of F), the unique amino acid in cyclosporin. A modified Ireland–Claisen rearrangement of the 2-fluoropropanoic acid allyl esters shown led to the appropriate (2*S*,4*E*)-2-fluoro-2-methylhex-4-enoic acid (R = H, OTBDMS) with enantiomer ratios of 95:5 (yields 45–52%). Esterification and subsequent reduction yielded the aldehydes (formula top right), which were allowed to react with the enantiomerically pure (*R*)-oxazolidinone Troc-BOX to give the products shown (65%). Methanolysis of the bicyclic major product, followed by methylation at nitrogen, yielded the *trans*-substituted cyclic carbamates. Finally, these carbamates were converted to the free, 4-fluoro-substituted amino acids under the mildest possible conditions (danger of epoxide formation via the intermediate alkoxide with loss of F<sup>−</sup>) [250].

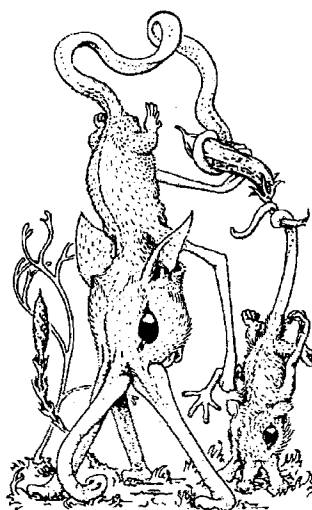
the amino acid precursors prepared from Boc-BMI still leave a lot to be desired. As the last step is the cleavage of an *N*-alkylcarboxylic acid amide, the highly acidic conditions required are not surprising. These conditions range (according to the substituent in the  $\alpha$ -position) from 0.75 N HCl/acidic ion-exchange resin/reflux,<sup>[240]</sup> to 4 N HCl/dioxane/H<sub>2</sub>O/80 °C, to 6 N HCl/10% MeOH/reflux,<sup>[83]</sup> to conc. HCl/100 °C<sup>[83]</sup> and finally up to 6 N HCl/180 °C/sealed tube.<sup>[64, 81, 262]</sup> A solution to this problem has now been found with the imidazolines **12** shown in



Scheme 26. 2-*tert*-Butylimidazolidin-4-one, which is unsubstituted at both nitrogen atoms and available by the resolution of a racemic mixture with camphor sulfonic acid and *N*-acetylvaline, can be converted into the methoxyimidazoline **12** by protection of the amine nitrogen with either a Boc or Z group and then O-methylation with Meerwein's salt. The enolate—or to be more precise, enamine—is an extremely reactive nucleophile particularly when the nitrogen is Boc-protected. Here too, the yields of alkylation are so high that a second alkylation can be carried out immediately in situ. The stereoselectivity of both steps is outstanding, and the 5-monosubstituted products can be hydrolyzed with 0.1 N aqueous trifluoroacetic acid at 4 °C; hydrolysis of the 5,5-disubstituted products requires 4 N trifluoroacetic acid in water at room temperature.<sup>[233, 241]</sup> It is, therefore, now possible to produce amino acids with highly acid-sensitive side chains (see the lower section of Scheme 26) by this procedure.

The reactions of the glycine derivatives, which are prepared by resolution of racemic mixtures, proceed so well that these synthetic building blocks are now preferred even for the synthesis of  $\alpha,\alpha$ -disubstituted amino acids derived from natural amino acids, in other words when the side chain is “proteinogenic” and the principles of SRS could also be applied.

## 9. What Have We Learned?

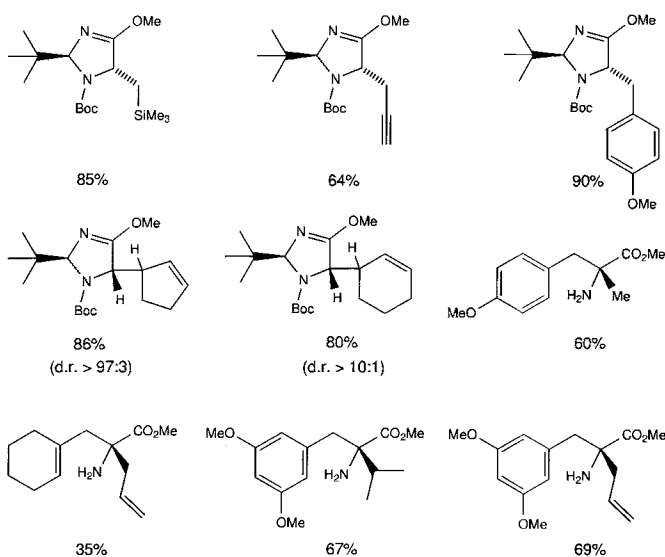


*There is no disgrace  
in not knowing,  
but there is in not wanting  
to learn.*

Socrates

“Nasobem with Child” (from H. Stümpke, *Bau und Leben der Rhinogradentia*, Copyright© Gustav Fischer, Stuttgart, 1961).

There have been a few record-breaking cases of stereoselectivity resulting from long-range effects (with up to six atoms between the “inducing” and the newly formed stereogenic center!)<sup>[263–266]</sup> and spectacular effects of fluorine substitution (reversal of the regio- and stereochemical course of the reaction on replacement of a CH<sub>3</sub> group by CF<sub>3</sub> in a reactant).<sup>[267]</sup> In the past we have somewhat cautiously speculated (sometimes only in footnotes) about the causes of these observations. They have, however, led us to become interested in the nucleophilic, radical, and electrophilic reactivity of the heterocycles prepared in stud-

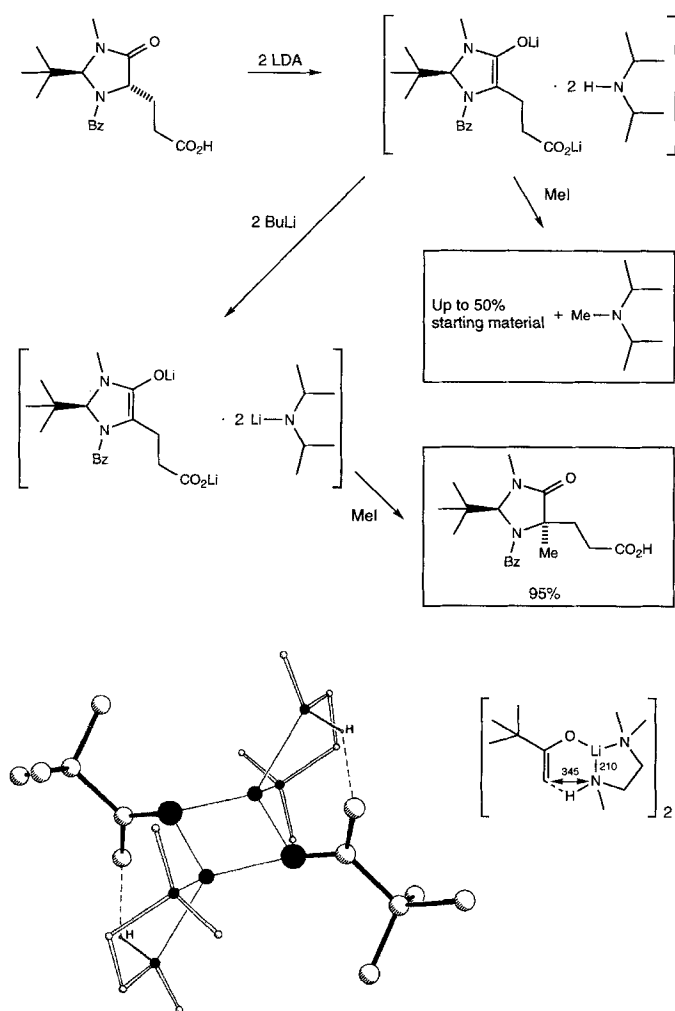


Scheme 26. 1-Boc- and 1-*Z*-2-*tert*-butyl-3-methoxy- $\Delta^3$ -imidazoline **12** (PG = Boc and Z, respectively) as chiral, nonracemic, glycine-derived, synthetic building blocks [233, 241]. Reactions with alkyl halides proceed with high selectivity; the use of an excess of the racemic allylation reagents bromocyclopentene and -hexene results in an efficient kinetic resolution (as in the reaction of Boc-BMI-enolate with 1-bromo-1-phenylethane [240, 254]); the absolute configuration at the cycloalkenyl C atom is not yet known. The quoted diastereoisomer ratio, d.r. > 97:3, means that the second isomer is not detectable in the high-field NMR spectrum of the crude product. The yields listed below the imidazolines refer to the alkylation step and those below the amino acids refer to the hydrolysis step. Addition of the deprotonated iminoester Li-**12** to the aldehyde does not result, after hydrolysis, in threonine (as observed with the enolate of heterocycle **11**) but gives allothreonine derivatives instead. LDA = lithium diisopropylamide, TFA = trifluoroacetic acid.

ies of the SRS principle, and this in turn has led to some insights into the reactivity that are of general importance and not simply confined to this area. These topics will be discussed in the following sections.

### 9.1. The Effect of Secondary Amines

We first stumbled upon this effect while studying the reactions of the lithium enolates of oxazolidinones and imidazolidinones, and it is now clear that this effect is particularly marked for polyolithated derivatives.<sup>[29, 45, 114, 268]</sup> One example is the reaction of the enolate derived from glutamic acid<sup>[269]</sup> (Scheme 27). The enolate-carboxylate forms a complex with the diisopropylamine that results from the enolate formation. (The structure of such a complex has been determined by X-ray crystallography.<sup>[29]</sup>) Subsequent reaction of the complex with electrophiles results in the recovery of up to 50% of the starting material. It

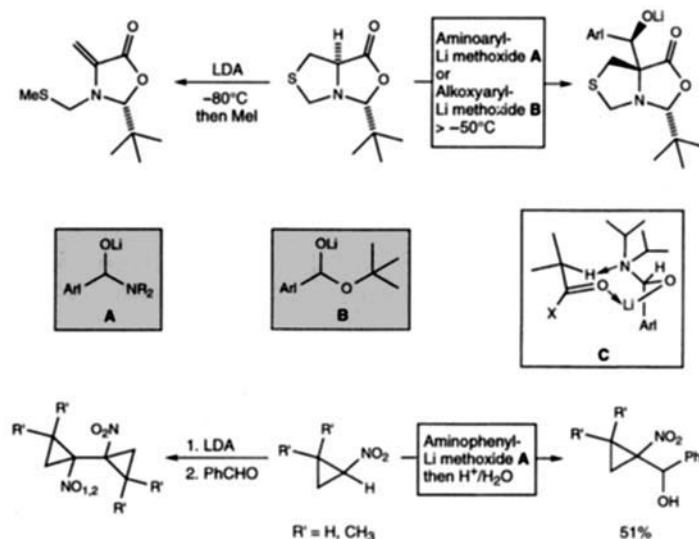


Scheme 27. The effect of secondary amines on the reactivity of Li-enolates and other Li derivatives. In a complex formed between an enolate and an amine, the nucleophilicity of the amine is enhanced, and hence, in the ensuing reaction with electrophiles, it acts as a proton source! Similarly, the reactivity of the Li-enolate-Li-amide complex is very different from that of the enolate alone [269]. The structure shown is that of a complex between the Li-enolate of pinacolone and *N,N,N*-trimethylethylenediamine, which contains a hydrogen bond between the NH hydrogen atom and the enolate C atom [29]. (The numbers on the formula in the bottom right-hand corner are the interatomic distances in pm.)

was proved that the proton of the amine was actually donated back to the enolate (apparently contrary to the relative  $pK_a$  values of a lactam and an amine!) and that the amine was *N*-methylated under these conditions, although, in the absence of the Li-enolate, it would not normally react. Irreversible removal of the NH proton with BuLi leads to the formation of a new complex between the Li-enolate and the Li-amide, and subsequent alkylation now proceeds in excellent yield.<sup>[269]</sup> Today it is now commonplace to attempt to improve poor results of reactions between lithiated compounds, generated with LDA and an electrophile, by adding BuLi prior to the electrophile; it often, but not always, helps.<sup>[270]</sup>

### 9.2. LiX Adducts with Aromatic Aldehydes—In Situ Sources of Bases and Electrophiles

During attempts to  $\alpha$ -alkylate cysteine via a bicyclic acetal in an analogous fashion to the proline derivative, it became clear to us that the (expected?)<sup>[271]</sup>  $\beta$ -elimination interferes in any reaction with LDA under all the conditions tested.<sup>[45]</sup> However, when a complex of an aromatic aldehyde and LDA<sup>[272]</sup> or lithium *tert*-butoxide is employed, the aldol products shown in Scheme 28 are formed in good yield.<sup>[48, 89]</sup> Transformations of



Scheme 28. In situ generation and trapping of unstable enolates [48, 89] and nitronates [273, 274] with aromatic aldehydes with the assistance of the aldehyde adducts **A** [272] and **B** (lithiated hemi-aminal and lithiated hemi-acetal [89], respectively); the Li derivative **A** is usually used for the orthometalation of aromatic aldehydes [272]. In light of the instability of the enolates formed from the bicyclic compound shown, we conclude that this does not result from reaction of the free LiNR<sub>2</sub>, which exists in equilibrium with **A**, but that deprotonation, generation of the aldehyde, and aldol or nitroaldol addition result in a "collision complex" (see for example **C** and the accompanying caveat in the text). Arl = aryl.

other unstable anionic derivatives such as those derived from nitrocyclopropane<sup>[273]</sup> are possible when functionalized, lithiated hemi-aminals or hemi-acetals are used as both base and electrophile.<sup>[274]</sup> Fully realizing the complexity of the reactions of lithiated compounds<sup>[5, 21–29]</sup> and hence with all due caution, we have proposed a mechanistic model for this process.<sup>[275]</sup>

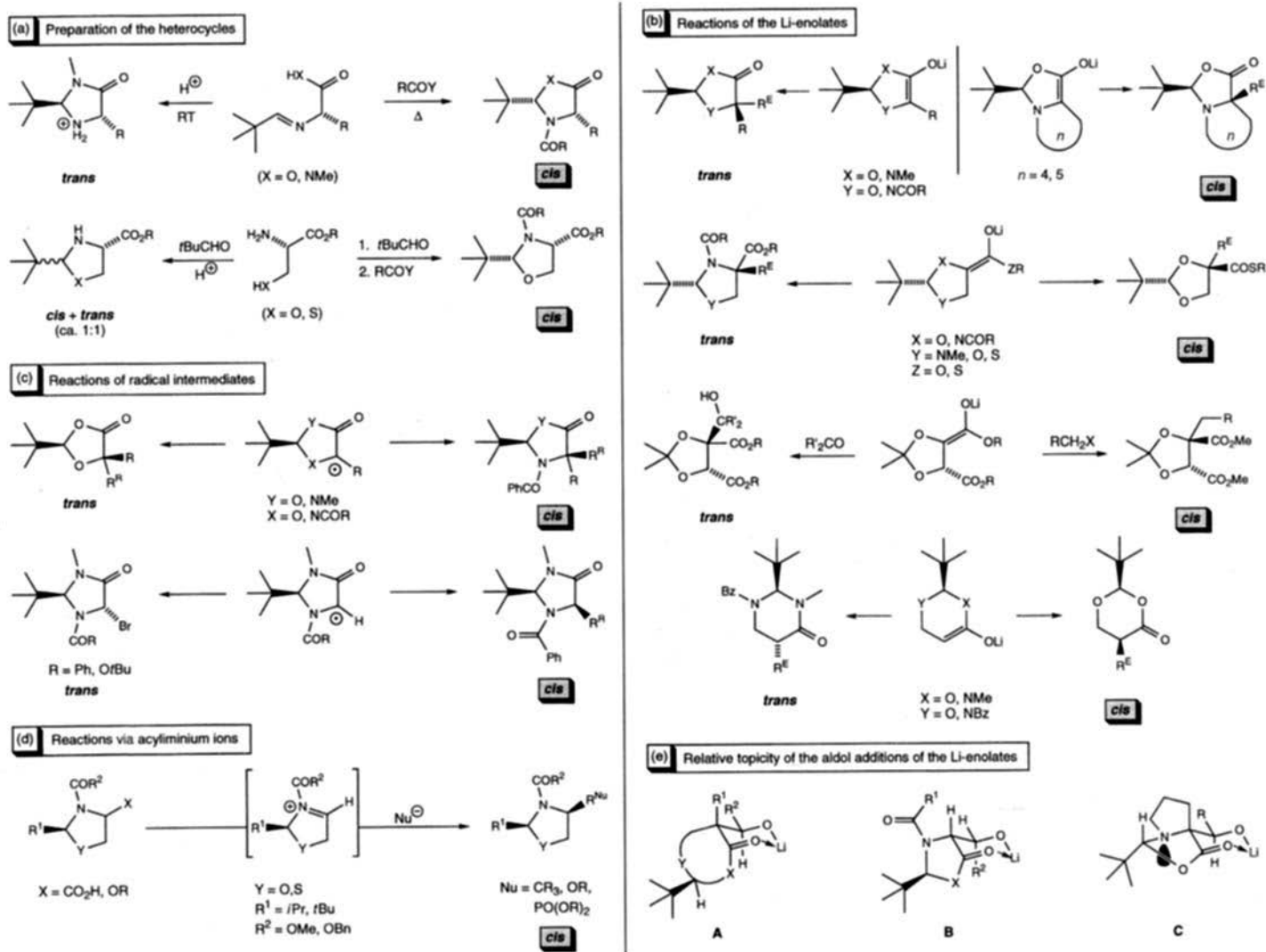
### 9.3. *cis* Selectivity Here, There, and Everywhere—The Power of the A<sup>1,3</sup> Effect

An observant reader of Sections 3 through 8 and the accompanying schemes can hardly have failed to notice that numerous, at first sight surprising, stereochemical outcomes of reactions have been presented; these could all be collected together loosely under the heading “the *cis* effect” and they are summarized in Scheme 29. Except for a few examples from the early publications, we have interpreted<sup>[276]</sup> and summarized these results in more recent articles.<sup>[62, 196, 254]</sup>

First of all, it must be stressed that the level of stereoselectivity found in the alkylations and hydroxyalkylations of our heteromonocyclic enolates has still not been achieved with the carbocyclic analogs.<sup>[277]</sup> For example, the reactions of the Li-enolates of 4- and 3-*tert*-butylcyclohexanone with CH<sub>3</sub>I proceed

with diastereoselectivities of 55:45 and 80:20, respectively.<sup>[278]</sup> The addition of the Li-enolate of cyclohexanone to PhCHO proceeds with a maximum diastereoselectivity of 92:8,<sup>[279]</sup> whereas the equivalent reactions of the five- and six-membered ring enolates of dioxolanones, dioxanones, oxazolidinones, imidazolidinones, thioxolanones, and perhydropyrimidinones with alkyl halides, aldehydes, and Michael acceptors are so highly selective that the second diastereoisomer cannot normally be seen in the high-field NMR spectrum of the crude product. The same is true for Michael additions to alkylidene derivatives (for example, that from Boc-BMI<sup>[253]</sup> or from dioxanones<sup>[153, 280]</sup>).

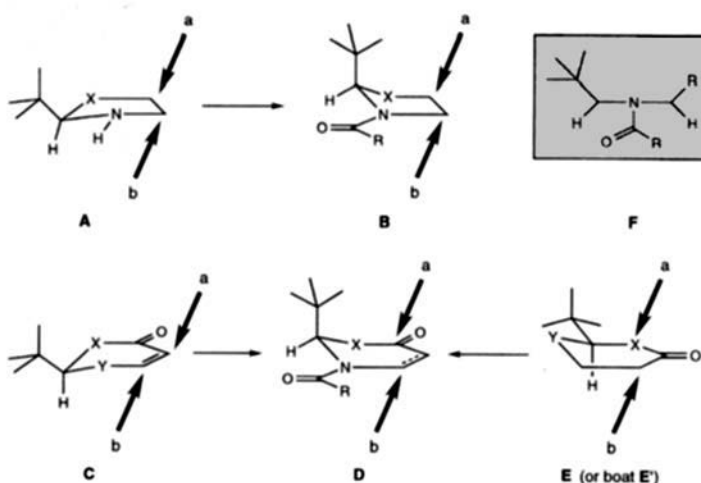
Together with these questions of the degree of stereoselectivity, the direction of selectivity has also always surprised us, in other words, both the type and manner of the influence on the relative topicity of the reaction process of certain substituents on the heterocycle. Scheme 29 summarizes reactions in which an



Scheme 29. Examples of reactions which, during the SRS process, result in substitution *cis* to the original substituent on the heterocycles (see Sections 3–5 for references). a) *cis*-Disubstituted five-membered ring heterocycles that are more stable than the *trans* isomers. b) Reactions of Li-enolates of the five- and six-membered ring N,N-, N,O-, N,S-, and O,O-acetals that often lead preferentially to the *cis* products; the geometry of the exocyclic enolate double bond is unknown and is drawn arbitrarily here. c) Dichotomy of reactions of captodative-substituted radical centers in *cis*- and *trans*-selective processes. The assignment of the configuration of the bromo derivative is somewhat uncertain [135]. d) Known reactions of 1,3-oxazolidinones and -thiazolidinones via acyliminium ions that proceed with a strong preference for the *cis* product. e) Three Zimmerman–Traxler diagrams [291] A, B, and C for the interpretation of aldol additions of heterocyclic enolates to aldehydes. For a compilation of the topicities observed in additions of the five- and six-membered ring heterocyclic enolates discussed here to aldehydes, enones, enoates, and nitroolefins, see Table F in the appendix. For the definition of the “*cis* effect”, see the text and Schemes 30–32.

apparently small change in the structure of the reactant results in the reversal of the stereochemical course of the reaction. As has already been mentioned, the point most worthy of note is perhaps that these reactions so often occur with *cis* selectivity. In these cases, either the *cis* product is thermodynamically more stable than the *trans* isomer or, when the reaction proceeds under kinetic control, the trigonal enolate, radical, or acyliminium center of the reactant reacts preferentially from the side that features the substituent (usually a *t*Bu group) at the acetal center. In this fashion, the cyclization with concomitant acylation of a Schiff base derived from an amino acid or amide yields the *cis*-oxazolidines, -oxazolidinones, or -imidazolidinones either predominantly or exclusively (Scheme 29 a).<sup>[281, 282]</sup> The example shown in Scheme 29 b (top right) is the *cis* attack on a bicyclic enolate<sup>[283]</sup> leading to the thermodynamically more stable product (*cis* fusion of four and five-membered rings, with substituents in the *exo* position!). The *cis*-selective reaction of dioxolanone enolates with exocyclic double bonds<sup>[284]</sup> and the reversal of this preference on moving from alkylation to hydroxyalkylation of a tartrate derivative are particularly interesting.<sup>[92–94, 285]</sup> When a dioxanone enolate is replaced with a perhydropyrimidinone enolate, the poor *cis* selectivity is transformed into an excellent *trans* preference (66% vs. 97% *ds*,<sup>[141, 286]</sup> Scheme 29 b bottom). This increase in selectivity is typical of the differences observed in reactions of all O-substituted heterocycles relative to those of an N-heterocycle with an N-acyl exocyclic group (cf. the ester enolate of dioxolane and the *N*-acyloxazolidine and thiazolidine carboxylic acids<sup>[287]</sup>). The stereochemical course of radical reactions is also very dependent upon the heteroatoms in the ring. Such reactions occur with preferential *cis* attack at an *N*-acyl derivative and *trans* attack at a dioxolanone, and the result also appears to be dependent upon the reaction partner ( $R_3SnH$  vs. NBS, see Scheme 29 c<sup>[288–290]</sup>). Nucleophilic substitution next to the nitrogen atom of the *N*-acyloxazolidine and -thiazolidine (Scheme 29 d) occurring via acyliminium ions (with the assistance of a Lewis acid) virtually always provides the *cis*-substituted compound as the major product (see Section 5 and the references cited therein). Finally, examination of the six-membered ring chair model<sup>[291]</sup> for the Li-enolate aldol addition of *N*-acylimidazolidinones and -oxazolidinones shows a preference for the R group of RCHO to adopt an axial position, that is, *cis* to the heterocyclic ring (Scheme 23 b and **B** in Scheme 29 e; Table F<sup>[254]</sup>).

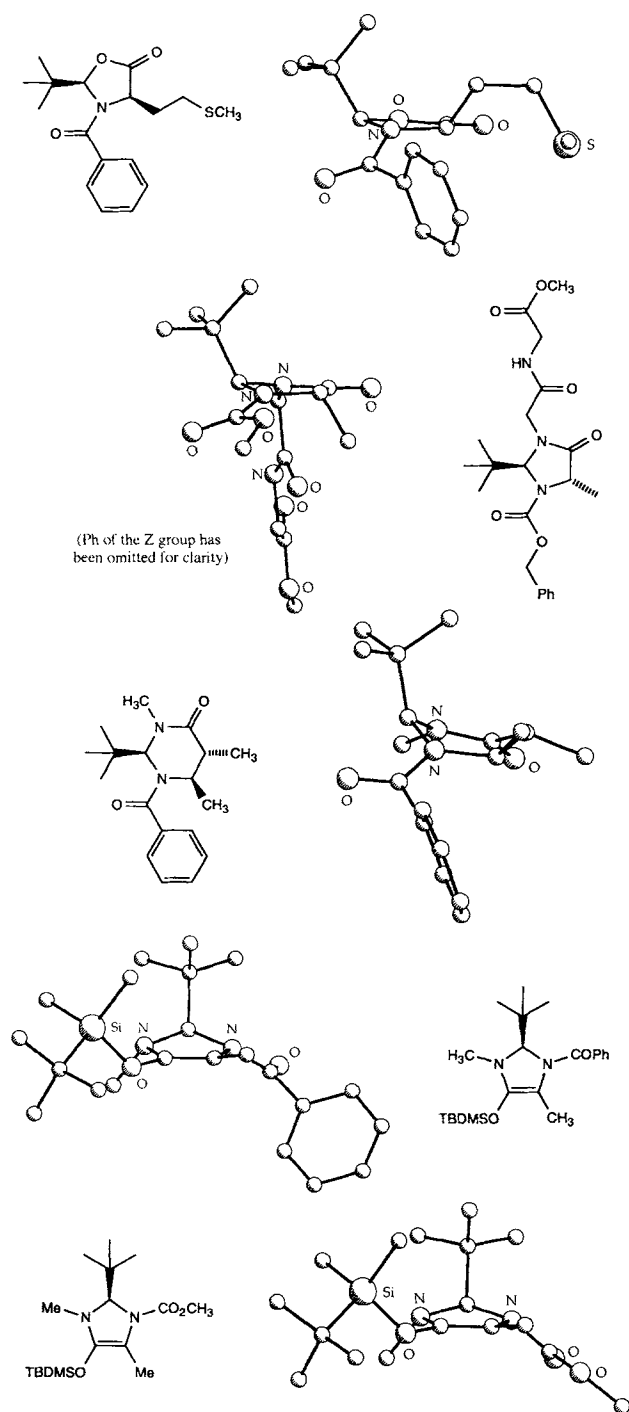
Closer examination of X-ray crystal structures (either those carried out by us to determine the configuration of our products<sup>[62, 143, 157, 229, 255, 292, 293]</sup> or by others, which were retrieved from the Cambridge Database) proved to be crucial in the interpretation of the observed *cis* effects. It is well known that five-membered rings (“natural” angle 108°) with trigonal,  $sp^2$  centers (“natural” angle 120°) are strained and that pyramidalization leads to a reduction in this strain.<sup>[294]</sup> However, the crystal structures made us realize the enormous effect of the 1,3-allyl ( $A^{1,3}$ ) strain<sup>[295–297]</sup> of amide and carbamate groups. The substituent at the acetal C atom of 1,3-dioxolanones, 1,3-dioxanones, 1,3-dioxinones, and even of 1,3-oxazolidinones and 1,3-imidazolidinones not having *N*-acyl substituents adopts an equatorial or quasi-equatorial position (**A**, **C**, **E** in Scheme 30). In contrast, in the *N*-acyl derivatives, these substituents are usu-



Scheme 30. A compilation of schematic diagrams of the typical structures of acylated (**B**, **D**) and nonacylated heterocycles (**A**, also when  $NH = O$ , **C** and **E**) such as dioxolanones, imidazolidinones, oxazolidinones, dioxanones, dioxinones, and hydroxypyrimidinones, which have been used in reactions employing the SRS principle (see also Scheme 29). Between 1991 and 1995 the Cambridge Structural Database listed 55 structures of such molecules (CSD codes given below), an additional 8 structures have been published in ref. [143], and a further 14 older structures are shown and discussed in ref. [62]. **F** is the most commonly found arrangement with a pyramidalized amide nitrogen (to minimize the angle strain) and with the neighboring centers pointing in the opposite direction so as to minimize the  $A^{1,3}$  strain. Six of the structures referred to belong to Type **A** (HEBSEM, KOYXIF, LERLEZ, VURBEP, VURBIT, YADSEB), 18 to Type **B** (HEVTIL, JILROL, JILRUR, JODMEU10, JOPWUG, JOPXER, LAFWEU, LAFWIY, LAXWEM, LAXXIR, PATCAO, PEFLOB, PEVWUI, PEXFED, PIWFIK, SOSDEJ, TAPSOZ, VOBYUG), 2 to Type **C** (HEJNAL, KOHKEK), 8 to Type **D** (JOPYUI, JOPZAP, JOPZET, JOPZIX, JOPZOD, SUCJEF, SUCJII, SUMNIX), 8 further Type **D** structures are described in [143], 16 belong to Type **E** (*sofa* conformers) (JOPYAO, JOPYES, JOPYIW, JOPYOC, LEDXAT, LEDXEX, LESJEY, LESJIC, LESJOI, LESJUO, PEKTII, SOSFIP, WEBXAC, WEBXEG, WEBXIK, WEBXUW) and 5 to Type **E'** (*boat* conformers) (PALFEN, PIPJAZ, PIPJED, PIPJIH, PIPJON). The majority of the structures were determined by the groups of A. L. J. Beckwith, S. G. Pyne, D. Seebach, and F. J. Urban; the literature citations not given here can be retrieved from the CSD files.

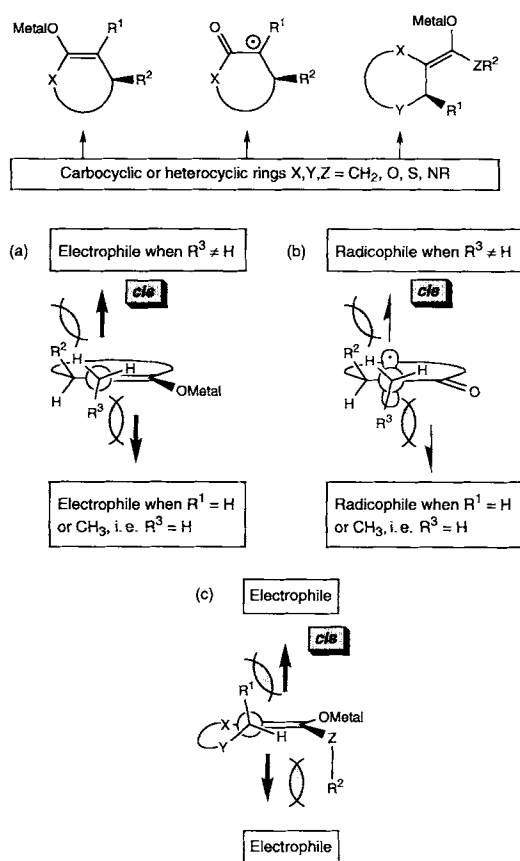
ally found in a quasi-axial position on five-membered rings and in fully axial positions on the hydroxypyrimidinones (see **B** and **D** in Scheme 30). The amide nitrogen in the five-membered ring is indeed considerably pyramidalized ( $\Delta \leq 0.43 \text{ \AA}$ ,<sup>[298]</sup> indicative of a nearly  $sp^3$  amine nitrogen). However, in the majority of cases, the amide group is hardly twisted at all. Obviously much less resonance energy is lost if the nitrogen of the amide group is pyramidalized rather than the  $R_2N-CO$  bond rotated.<sup>[299]</sup> The resulting substructures of the *N*-acyl heterocycles then appear, if viewed from the carbonyl C atom, like structure **F** in Scheme 30. If possible, the  $O=C-R$  unit adopts a position to a greater (five-membered ring) or lesser (six-membered ring) extent<sup>[300]</sup> below the plane formed by the C, N, C ring atoms; the substituents at the neighboring C atoms are above the plane. Some particularly impressive examples are shown in Scheme 31.<sup>[301]</sup>

This structural information explains the higher thermodynamic stability of the *cis*-substituted *N*-acyl five-membered ring heterocycles (Scheme 29 a) and also the many differences in the reactivity of heterocycles with or without exocyclic *N*-acyl groups (Scheme 29 b, c, e<sup>[302]</sup>). However, another type of  $A^{1,3}$  strain (Scheme 32) is responsible for the *cis* selectivity of several enolate and radical reactions (cf. Scheme 29 b, c). It is known that an exocyclic  $CH_2R$  group at an enolate double



Scheme 31. Typical crystal structures of derivatives of *N*-acylimidazoline [301], -imidazolidine [234], -oxazolidine [62], and -perhydropyrimidine [62,143]. The plane of the benzene ring of the *N*-benzoyl group in the structures shown here, and in almost all those of this type known, is practically perpendicular to the carbonyl plane. The degree of pyramidalization  $\Delta$  [298] at the methyl-substituted ring C atom of the methyl carbamate and of the benzamide silyl enol ether is 0.07 and 0.11 Å, respectively. In most of the structures the carbonyl oxygen of the *N*-acyl group is in a *cisoid* arrangement with the acetal center; exceptions are found in structures of compounds in which there is a bulky substituent on the  $\alpha$ -carbonyl carbon. For details of further structures of this type and the corresponding references, see Scheme 30.

bond can lead to a reversal of the topicity of attack at the double bond due to the "allylic" endocyclic substituent (Scheme 32a). This has been observed for both carbocyclic (cyclopentanones<sup>[30,31]</sup>) and heterocyclic enolates (lactones,<sup>[304]</sup> di-



Scheme 32. Reactions of enolates and  $\alpha$ -carbonyl radicals. When  $R^1$  is H or  $\text{CH}_3$ , in those systems with an endocyclic double bond, reaction occurs from below (*trans* to  $R^2$ ). When  $R^1 = \text{CH}_2\text{R}^3$ , the  $R^3$  group is positioned beneath the plane due to  $A^{1,3}$  strain and hence, the lower face is shielded to a greater extent than the top face is by  $R^2$  (see a) and b)). An analogous effect is likely to be responsible for the *cis* selectivity observed with certain ester enolates containing exocyclic double bonds (c). References are given in the text.

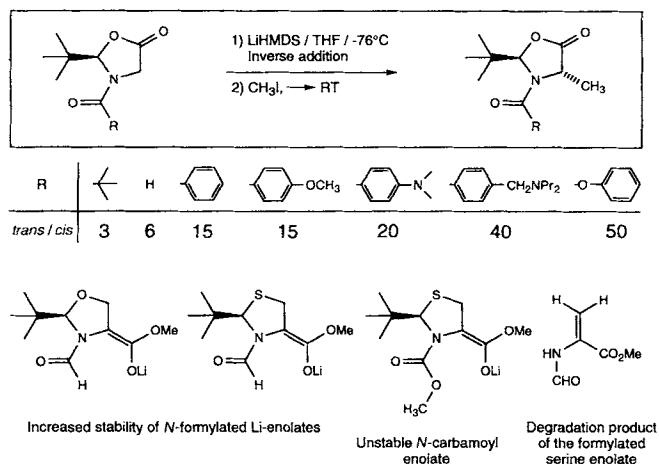
oxanones<sup>[37, 153, 280]</sup> with endocyclic double bonds. Equally, in a whole range of examples of reactions of carboxylic ester and thioester Li-enolates with carbocycles<sup>[98]</sup> and heterocycles<sup>[93–95, 102, 285]</sup> electrophilic attack at the exocyclic enolate double bond occurs *cis* to a substituent in the ring (Scheme 29b, 32<sup>[305, 306]</sup>). This can also be explained by some form of the  $A^{1,3}$  effect: the RO or RS group of the ester enolate shields the "lower face" of the enolate plane and the allylic substituent on the neighboring stereogenic center shields the "upper face". (Furthermore, in the case of the heterocyclic carboxylic ester enolates, a chelate effect might be involved.<sup>[306]</sup>) Whether or not attack occurs from the side *cis* to  $R^1$  at the trigonal center is dependent upon whether the transition state of the electrophilic attack at the enolate double bond is early or late and also upon the relative sizes of the  $R^1$  and  $R^2$  groups (Scheme 32c). The movement of the RZ group out of the plane of the ester enolate has been confirmed by X-ray crystal structure analysis,<sup>[209, 307–312]</sup> and the relationship between *cis* selectivity and size of the RO group has been noticed previously.<sup>[95]</sup>

Incidentally,  $A^{1,3}$  effects of this type in reactions of  $\alpha$ -carbonyl radicals, in which the radical center in the ring bears a  $\text{RCH}_2$  substituent and is adjacent to a stereogenic center in the ring (Scheme 32b<sup>[290]</sup>), were first noticed in 1977.<sup>[313]</sup>

The *cis* selectivity of reactions that proceed via acyliminium ions (Scheme 29 d) can be traced back to, amongst other things, the barrier to rotation of the RCO–N bond, which is much lower for cations than for amides (by roughly one-third), and hence the  $A^{1,3}$  effect no longer dominates the course of the reaction.<sup>[62, 183, 196]</sup>

#### 9.4. Protecting Groups Are Not Just Passive Spectators!

Numerous examples have confirmed one observation: a protecting group can have differing influences on the course of a reaction at a neighboring functional group—it is certainly not simply a spectator. For example, the diastereoselectivity of reactions of the Li-enolate of *N*-acyl-2-*tert*-butyl-1,3-oxazolidin-5-ones is extremely dependent upon the nature of the acyl group (Scheme 33<sup>[314]</sup>). It can be seen from the structures of enol



Scheme 33. The influence of “protecting” groups on the course of the reaction. Top: The diastereoselectivity of methylation of a range of *N*-protected 2-*tert*-butyl-1,3-oxazolidin-5-ones varies from 3:1 to 50:1. Bottom: The stability of enolates of 2-*tert*-butyl-1,3-oxazolidin-5-ones and -thiazolidin-5-ones is highly dependent on the nature of the *N*-acyl group. The reaction of the aldehyde  $\text{CH}_2\text{CH}=\text{CHCH}_2\text{CF}(\text{CH}_3)\text{CHO}$ , shown in Scheme 25, with a variety of Li-enolates of *N*-acylated 2-*tert*-butyl-1,3-oxazolidin-5-ones is a further example of the influence of *N*-acyl groups on enolate reactions of these types of heterocycles: Use of allyloxy-, benzyloxy-, and phenyloxycarbonyl-substituted oxazolidinones did not lead to the required products; the use of the trichloroethoxycarbonyl protecting group led to the first success. As in all the examples shown in this article, the geometry of the enolate double bond is not known and is drawn arbitrarily. For details about the *cisoid* arrangement of the carbonyl oxygen atom of the *N*-acyl group and the acetal center, see also the legend of Scheme 31; to date, the conformation of the *N*-formyl group has not been determined.

derivatives of such heterocycles (Scheme 31 bottom<sup>[315]</sup>) that the substituent at the carbonyl C atom of the acyl group could formally be in contact with the atoms and groups involved in the transition state of an  $\text{S}_{\text{N}}2$  reaction. This also applies to the acyl groups of the oxazolidinone and thiazolidinone carboxylic esters (Scheme 33 bottom): The *N*-formyl derivative is more stable than the carbamoyl analog possibly because the formyl-substituted enolate has less  $A^{1,3}$  strain than the carbamoyl derivative<sup>[316]</sup> and not only because the formyl group is more electron-withdrawing.

#### 10. Concluding Remarks

The principle of the self-regeneration of stereocenters has led not only to the increase in the synthetic potential of readily available, chiral synthetic building blocks such as naturally occurring amino acids, but also to the development of simple, synthetic, heterocyclic starting materials which are available by resolution of racemic mixtures. There is very little risk involved in predicting that the SRS principle will find many more applications and that the chiral acetals, which are now also commercially available in large quantities, will be employed more and more frequently in EPC synthesis.

*The enthusiastic work of many graduate students and postdoctoral co-workers over the last 15 years has led to the results of our group described in this article. D. S. expresses his deepest thanks to them all; their names are given in the list of references. The following people are due special thanks: Reto Naef<sup>[317]</sup> for his crucial contributions during the conception of the SRS principle and also Robert Fitzi,<sup>[318]</sup> Stefan Müller, Urs Gysel,<sup>[319]</sup> and Joachim Kinkel<sup>[320]</sup> for solving the problems related to the resolution of racemic mixtures of glycine acetals. We thank the following companies for their generous donations of chemicals: BASF AG (Ludwigshafen, Germany; pivalaldehyde), Degussa AG (Hanau, Germany; amino acids and Boc-BMI), Zeneca Bio Products (Billingham, UK; PHB and BIOPOL). We are very grateful to Sandoz Pharma AG (Basel, Switzerland) for their generous financial support of our research group over so many years. S. Sigrist and M. Graedel are thanked for their considerable help during the preparation of this manuscript. Finally, we also acknowledge Privatdozent Dr. Volker Gramlich, the organizer of the crystallography laboratory courses at ETH-Zürich, where so many of the crystal structures were solved; his work has had so much significance, in so many different ways, on the work from our laboratories described here.*

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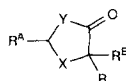
German version: *Angew. Chem.* **1996**, *108*, 2880–2921

Translated by Dr. Jennifer L. Matthews, Zürich (Switzerland)

#### Appendix

The following abbreviations are used in the tables: All =  $\text{H}_2\text{C}=\text{CHCH}_2$ ; Alloc =  $\text{H}_2\text{C}=\text{CHCH}_2\text{OCO}$ ; Bn =  $\text{PhCH}_2$ ; Boc = *t*BuOCO; Bz = PhCO; MOM =  $\text{CH}_3\text{OCH}_2$ ; TBS = TBDMS = *tert*-butyldimethylsilyl; TBDPS = *tert*-butyldiphenylsilyl; Z =  $\text{PhCH}_2\text{OCO}$ .

Table A. Examples of the  $\alpha$ -alkylation of a variety of amino-, hydroxy-, and sulfanylcarboxylic acids according to Scheme 5. In many cases the heterocyclic alkylation products were not hydrolyzed to give the corresponding  $\alpha$ -, $\alpha$ -disubstituted,  $\alpha$ -heterosubstituted carboxylic acids. Some examples of carboxylic acid derivatives prepared in this manner and some applications in natural product synthesis are shown in Scheme 7 and 8.



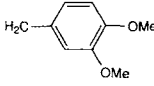

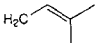
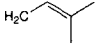
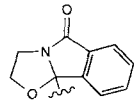
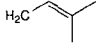
R	R <sup>A</sup>	X	Y	R <sup>E</sup>
<b>Alanine</b>				
Me	<i>t</i> Bu	NBz	NMe	Et [64], Bn [64],  [64], CH <sub>2</sub> (Boc-Indolyl) [120], CH(Me)CH <sub>2</sub> NO <sub>2</sub> [123]
Me	Ph	NBoc	NMe	<i>i</i> Pr [321]
Me	<i>t</i> Bu	NBz	O	Allyl [322], Ph [119], Bn [70], CH <sub>2</sub> (Boc-Indolyl) [120]
Me	Ph	NBz	O	Et [323], CH <sub>2</sub> CO <sub>2</sub> Et [113]
Me	Ph	NZ	O	H [324, 325], Bn [324, 325], CH <sub>2</sub> CO <sub>2</sub> <i>t</i> Bu [326], (CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> <i>t</i> Bu [326], (CH <sub>2</sub> ) <sub>4</sub> N(Boc) <sub>2</sub> [326]
Me	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	NZ	O	Bn [324, 325]
Me		NCO <i>t</i> Bu	O	Bn [327]
<b>Valine</b>				
<i>i</i> Pr	<i>t</i> Bu	NBz	NMe	D [64], Me [64], Et [64], Allyl [64]
<i>i</i> Pr	<i>t</i> Bu	NBz	O	Me [70], Bn [70]
<i>i</i> Pr	Ph	NBz	O	CH <sub>2</sub> CO <sub>2</sub> Et [113]
<i>i</i> Pr	<i>t</i> Bu	NAlloc	O	 [328]
<i>i</i> Pr	Ph	NZ	O	Me [329]
<b>Leucine</b>				
<i>i</i> Bu	<i>t</i> Bu	NAlloc	O	 [328]
<i>i</i> Bu	Ph	NZ	O	Et [329]
<b>Isoleucine</b>				
CH(Me)CH <sub>2</sub> Me	Ph	NZ	O	Me [329]
<b>Methionine</b>				
(CH <sub>2</sub> ) <sub>2</sub> SMe	<i>t</i> Bu	NBz	NMe	D [223], Me [64, 223], Et [64, 223], <i>i</i> Pr [223], CHMe(OH) [71]
(CH <sub>2</sub> ) <sub>2</sub> SMe	<i>t</i> Bu	NH	NMe	C(Me) <sub>2</sub> OBz [71], CHPhOBz [71]
(CH <sub>2</sub> ) <sub>2</sub> SMe	<i>t</i> Bu	NBz	O	Me [70, 72], CH <sub>2</sub> CN [330], CH <sub>2</sub> (Boc-Indolyl) [120], CHMe(OH) [71],  [330]
(CH <sub>2</sub> ) <sub>2</sub> SMe	Ph	NBz	O	CH <sub>2</sub> CO <sub>2</sub> Et [113]
<b>Phenylalanine</b>				
Bn	<i>t</i> Bu	NBz	O	Me [70], CHPh(OH) [70]
Bn	Ph	NBz	O	CH <sub>2</sub> CO <sub>2</sub> Et [113]
Bn	Ph	NZ	O	Me [324, 325], CH <sub>2</sub> COR (R = Cl, OH, OCHPh <sub>2</sub> ) [331], (CH <sub>2</sub> ) <sub>2</sub> OH [332], CH <sub>2</sub> COC(CO <sub>2</sub> Et)=PPh <sub>3</sub> [331]
Bn	2,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	NZ	O	D [324, 325], Me [324, 325]
Bn	<i>t</i> Bu	NAlloc	O	 [328]
<b>Aspartic acid</b>				
CH <sub>2</sub> CO <sub>2</sub> H	<i>t</i> Bu	NBz	NMe	D [114], Me [114], Bn [114]
<b>Glutamic acid</b>				
(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	<i>t</i> Bu	NBz	NMe	D [114], Me [114], Bn [114]
<b>Lysine</b>				
(CH <sub>2</sub> ) <sub>4</sub> NHZ	<i>t</i> Bu	NBz	NMe	Me [120], Bn [120], CHMe(OH) [120], CHPh(OH) [120]
(CH <sub>2</sub> ) <sub>4</sub> NHBoc	<i>t</i> Bu	NBz	O	Me [120]
(CH <sub>2</sub> ) <sub>4</sub> NHZ	Ph	NZ	O	<i>i</i> Pr [329]
<b>Ornithine</b>				
(CH <sub>2</sub> ) <sub>3</sub> NHZ	<i>t</i> Bu	NBz	NMe	Me [120]
(CH <sub>2</sub> ) <sub>3</sub> NHZ	Ph	NZ	O	Et [329]
<b>Vinylglycine</b>				
CH=CH <sub>2</sub>	<i>t</i> Bu	NBz	NMe	D [223], Me [223], Et [223], Allyl [223], Bn [223], CMe <sub>2</sub> (OH) [71], CHMe(OH) [71]



Table A. (continued)

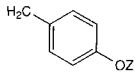
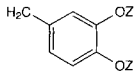
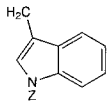
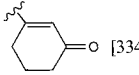

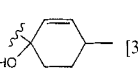
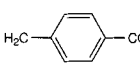
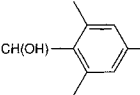

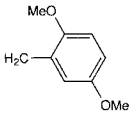
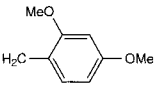
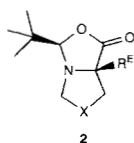
R	R <sup>A</sup>	X	Y	R <sup>E</sup>
<b>2-Aminoheptanoic acid</b>				
Bu	Ph	NBz	O	CH <sub>2</sub> NPhthaloyl [122]
<b>Tyrosine</b>				
	Ph	NZ	O	Me [329]
<b>DOPA</b>				
	Ph	NZ	O	Me [329]
<b>Tryptophan</b>				
	Ph	NZ	O	Et [329]
<b>Lactic acid</b>				
Me	<i>t</i> Bu	O	O	Et [43, 47], Pr [47], Bu [42, 47], Heptyl [47], Allyl [42, 43, 47, 126, 333], Bn [43, 47], CH <sub>2</sub> CBr=CH <sub>2</sub> [124], CH <sub>2</sub> CONMe <sub>2</sub> [47], (CH <sub>2</sub> ) <sub>3</sub> C(OMe) <sub>2</sub> Me [46], CMe <sub>2</sub> (OH) [43, 47], C(CH <sub>3</sub> ) <sub>4</sub> (OH) [43, 47], CPh <sub>2</sub> (OH) [43, 47], CPh(OH)Me [43, 47], CHMe(OH) [43, 47], CHEt(OH) [47], CH <i>t</i> Bu(OH) [43, 47], CH(OH)CH <sub>2</sub> =CHPh [47], CHPh(OH) [43, 47], (CH <sub>2</sub> ) <sub>2</sub> NO <sub>2</sub> [123], CH(Me)CH <sub>2</sub> NO <sub>2</sub> [123], CH(Et)CH <sub>2</sub> NO <sub>2</sub> [123], CH(CH <sub>2</sub> Br)CH <sub>2</sub> NO <sub>2</sub> [123], CH(Ph)CH <sub>2</sub> NO <sub>2</sub> [123],  [334],  [47],  [334],  [335],  [47]
<b>3-Chlorolactic acid</b>				
CH <sub>2</sub> Cl	<i>t</i> Bu	O	O	 (R = H, Me) [336]
<b>3-(2,5-Dimethoxy)phenyllactic acid</b>				
	<i>t</i> Bu	O	O	CH <sub>2</sub> COR (R = Cl, OH) [337]
<b>3,3,3-Trifluorolactic acid</b>				
CF <sub>3</sub>	<i>t</i> Bu	O	O	Me [250]
<b>2-Hydroxybutanoic acid</b>				
Et	<i>t</i> Bu	O	O	Allyl [128]
<b>2-Hydroxy-3-methylbutanoic acid</b>				
<i>i</i> Pr	<i>t</i> Bu	O	O	CHMe(OH) [125, 338]
<b>Malic acid</b>				
CH <sub>2</sub> CO <sub>2</sub> H	<i>t</i> Bu	O	O	Me [47], CD <sub>3</sub> [126], Allyl [47], CH(Me)CH <sub>2</sub> NO <sub>2</sub> [123], Bn [47],  [337]
<b>Mandelic acid</b>				
Ph	<i>t</i> Bu	O	O	D [339], Me [42], Pr [42, 43, 47], CH <sub>2</sub> Cl [336], Allyl [42], CH(Me)CH <sub>2</sub> NO <sub>2</sub> [123]
Ph	<i>i</i> Pr	O	O	Me [42]
Ph	Me	O	O	D [339]
Ph	Et	O	O	D [339]
Ph	Me	O	NMe	D [339]
Ph	Ph	O	NMe	D [339]
<b>3-Methylphenylglycolic acid</b>				
3-MePh	<i>t</i> Bu	O	O	CH <sub>2</sub> Cl [336]
<b>3-Phenylactic acid</b>				
Bn	<i>t</i> Bu	O	O	Me [47], Et [47], Pr [47], Allyl [47]

Table A. (continued)

R	R <sup>A</sup>	X	Y	R <sup>E</sup>
<b>Thiolactic acid</b> Me	<i>t</i> Bu	S	O	Et [121], Allyl [47, 121], Bn [121], CMe <sub>2</sub> (OH) [121], CHPh(OH) [121], CHMe(OH) [121], CMe(CH=CH <sub>2</sub> )(OH) [121], (CH <sub>2</sub> ) <sub>2</sub> COMe [121]
<b>4-Methyl-2-sulfanylpentanoic acid</b> <i>i</i> Bu	<i>t</i> Bu	S	O	Me [121], Bn [121]
<b>(3<i>S</i>)-3-Methyl-2-sulfanylpentanoic acid</b> CH(Me)CH <sub>2</sub> Me	<i>t</i> Bu	S	O	Me [121], Bn [121]
<b>Thiomandelic acid</b> Ph	<i>t</i> Bu	S	O	Me [121], Bn [121]
<b>3-Phenylthiolactic acid</b> Bn	<i>t</i> Bu	S	O	Me [121]

Table B. Examples of  $\alpha$ -alkylations of bicyclic derivatives of azetidine carboxylic acids, proline, hydroxyproline, and cysteine, shown in Scheme 6, to give products of type 2. These reactions proceed with retention of configuration.




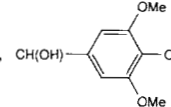
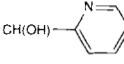
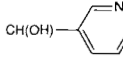
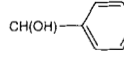

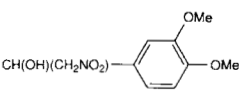
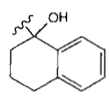
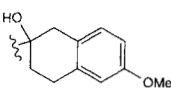
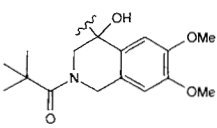
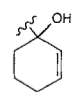
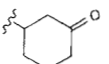
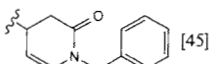






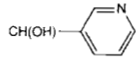
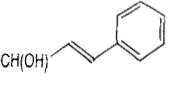
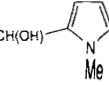
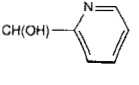
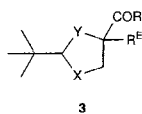
X	R <sup>t</sup>
<b>Azetidinecarboxylic acid</b> -	D [86], CHMe(OH) [86], CH(OH)-  [86], CH(OH)-  [86], CH(OH)-  [86], CH(OH)-  [86], CH(OH)-  [86], CH(OH)-  [86], CH(OH)-  [86]
<b>Proline</b> CH <sub>2</sub>	D [45], Me [45, 117, 118], Allyl [43, 45, 118, 127], Ph [45], PhS [45], Bn [45, 118], CH <sub>2</sub> NMe <sub>2</sub> [45], CH <sub>2</sub> CO <sub>2</sub> Me [45], CH <sub>2</sub> CONMe <sub>2</sub> [45], CHMe(OH) [45], CH <i>t</i> Bu(OH) [45], CMe <sub>2</sub> (OH) [45], CMe(OH)CH <sub>2</sub> CO <sub>2</sub> Me [45], Ac [45], Bz [45], CO <sub>2</sub> Me [45], H <sub>2</sub> C=CH-TMS [340], CH(OH)-  [45], CH(OH)(CH <sub>2</sub> NO <sub>2</sub> )-  [45],  [45],  [45],  [45],  [45],  [45],  [45]
<b>Hydroxyproline</b> CHOAc	D [87], Me [87], Allyl [87], Bn [87], CHMe(OH) [87], CH(OH)-  [87]
<b>Cysteine</b> S	CH(OH)-  [89], CH(OH)-  [89], CH(OH)-  [89], CH(OH)-  [89], CH(OH)-  [89], CH(OH)-  [89], CH(OH)-  [89], CH(OH)-  [89], CH(OH)-  [89]

Table C. Examples of the imidazolidine, oxazolidine, and thiazolidine derivatives **3**, depicted in Scheme 6d, which were obtained by alkylation of enolates having exocyclic double bonds (Scheme 6e, left). It should be noted that, in the case of cysteine, a satisfactory yield can only be obtained when the nitrogen atom in the ring is protected by a formyl group (in addition, see refs. [104–109], the discussion in ref. [111], Scheme 33 bottom).



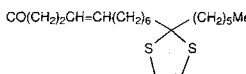
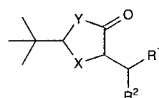
X	Y	R	R <sup>E</sup>
<b>Serine</b>			
O	NCHO	OMe	D [93], Me [93], Et [93], Allyl [93], Bn [93], CMe <sub>2</sub> (OH) [93], Bz [93], C <sub>9</sub> H <sub>19</sub> [330], C <sub>15</sub> H <sub>31</sub> [330], CH <sub>2</sub> CH=CH(CH <sub>2</sub> ) <sub>12</sub> Me [330], CO(CH <sub>2</sub> ) <sub>16</sub> Me [341],  [341]
O	NCHO	OBn	C <sub>9</sub> H <sub>19</sub> [330]
O	NBn	OMe	CH <i>i</i> Pr(OH) [129]
<b>Glyceric acid</b>			
O	O	S <i>t</i> Bu	D [93], Allyl [93], Bn [93], CMe <sub>2</sub> (OH) [93], CHMe(OH) [93], CHPh(OH) [93], CH(CH=CHPh)(OH) [93], CMePh(OH) [93]
<b>Cysteine</b>			
S	NCHO	OMe	Me [105–109], Et [106], Bn [106], Allyl [106], CH <sub>2</sub> CO <sub>2</sub> Me [106]
<b>2,3-Diaminopropanoic acid [342]</b>			
NMe	NBoc	OMe	D [99], Me [99], Et [99], <i>i</i> Pr [99], Bu [99], Allyl [99], Bn [99], SPh [99], SePh [99], OH [99], CHRCH <sub>2</sub> COCPh <sub>3</sub> (R = Me, Ph) [255]

Table D1. Products of Michael and radical additions to derivative **5**, which has an exocyclic double bond. The preparation of **5** is outlined in Scheme 9a,b; a few of these products are shown at the top of Scheme 10a. R<sup>2</sup> denotes the newly introduced substituent. Some selected examples of products of this type can also be found in Scheme 12.



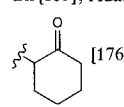
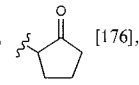
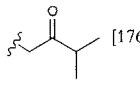
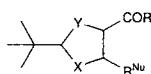
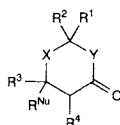
X	Y	R <sup>1</sup>	R <sup>2</sup>
NBoc	NMe	H	Me [253], Bu [253]
NBoc	NMe	Me	Me [253], Et [253], Bu [253], Ph [253]
NBoc	NMe	Me	Et [253], Bu [253], Ph [253]
NBoc	NMe	Pr	Bu [253]
NCOPh	O	H	Me [139, 172], Pr [172], <i>t</i> Bu [139, 172], CH <sub>2</sub> OMe [172], CH <sub>2</sub> CO <sub>2</sub> Me [172], C(Me) <sub>2</sub> NO <sub>2</sub> [343], (CF <sub>2</sub> ) <sub>3</sub> CF <sub>3</sub> [172], Bn [139], Adamantyl [172], Tetra- <i>O</i> -acetylglucosyl [172], <i>c</i> -C <sub>6</sub> H <sub>11</sub> [172],  [176],  [176],  [176]
NCOPh	NMe	H	<i>c</i> -C <sub>6</sub> H <sub>11</sub> [139]
NCOMe	O	H	<i>c</i> -C <sub>6</sub> H <sub>11</sub> [172]
NCOBn	O	H	<i>c</i> -C <sub>6</sub> H <sub>11</sub> [172]
NCO(1-Naphthyl)	O	H	<i>c</i> -C <sub>6</sub> H <sub>11</sub> [172]
NCOOMe	O	H	<i>c</i> -C <sub>6</sub> H <sub>11</sub> [172]
NCOOPh	O	H	<i>c</i> -C <sub>6</sub> H <sub>11</sub> [172]
NCOOBn	O	H	<i>c</i> -C <sub>6</sub> H <sub>11</sub> [172]
O	O	CO <sub>2</sub> Et	Me [344], Et [344], Bu [344], <i>t</i> Bu [344], <i>c</i> -C <sub>6</sub> H <sub>11</sub> [344]
O	O	H	Bn [136], (CH <sub>2</sub> ) <sub>2</sub> Ph [136], <i>c</i> -C <sub>6</sub> H <sub>11</sub> [136]

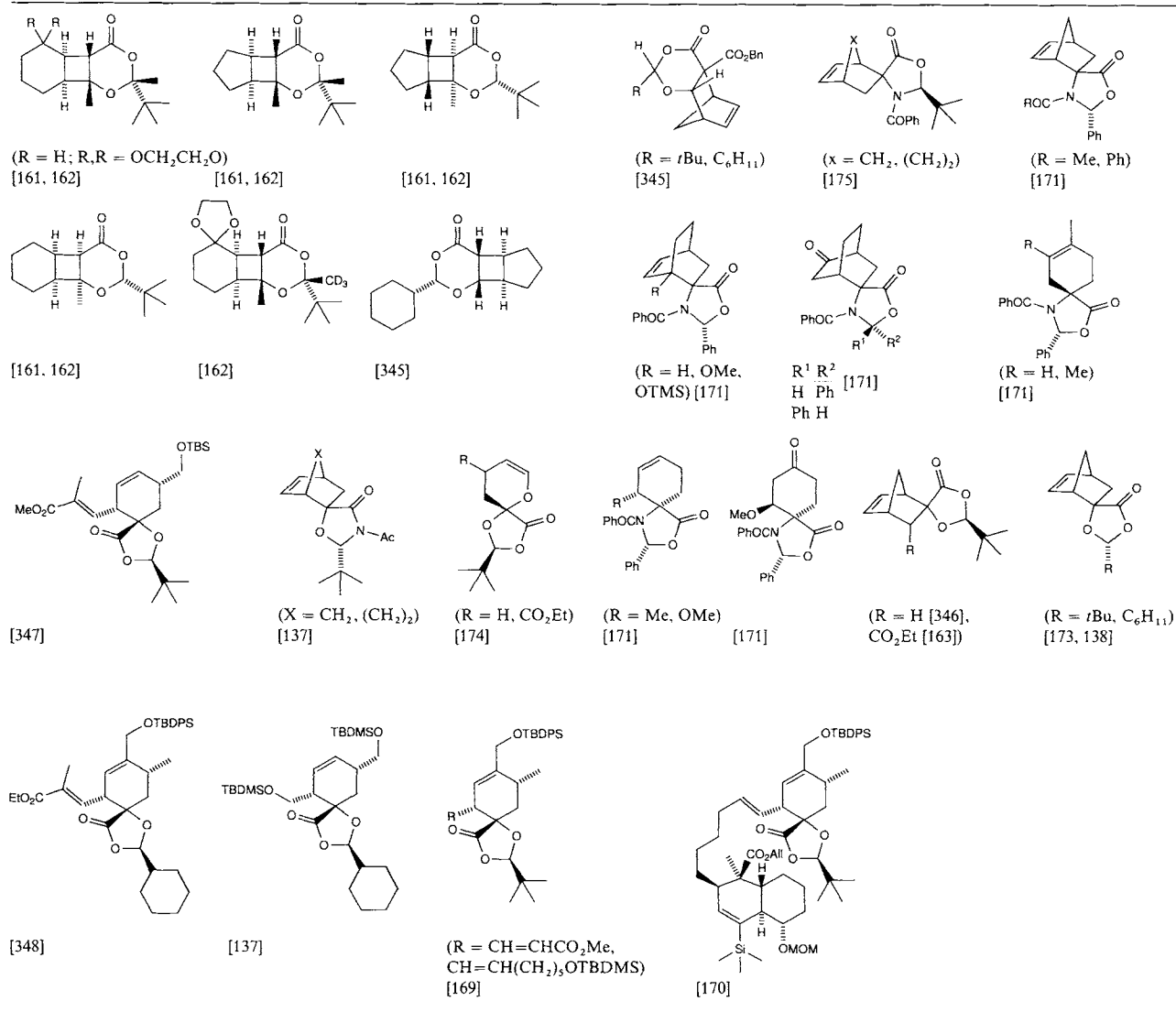
Table D2. Products of Michael addition to derivative **6**, which has an endocyclic double bond. The preparation of **6** is outlined in Scheme 9c; a few of these products are shown at the bottom of Scheme 10a. Some selected examples of products prepared in this manner can be found in Schemes 12 and 14a (see also Scheme 15).

X	Y	R	R <sup>Nu</sup>
NMe	NBoc	OMe	Bu [99]
NMe	NBoc	Ph	Ph [99]
O	NCO <sub>2</sub> Me	OMe	Bu [140]
S	NCO <sub>2</sub> Me	OMe	
S	NCO <sub>2</sub> Bn	OMe	Bu [104]

Table D3. Products of Michael addition to derivative **7**, which has an endocyclic double bond. The preparation of **7** is outlined in Scheme 9d; a few of these products are shown in Scheme 10b. Some examples of products shown here can be found in Schemes 12, 13, and 14b.

X	Y	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	R <sup>Nu</sup>
NAc	NMe	H	<i>t</i> Bu	H	H	Bu [147]
O	O	H	<i>t</i> Bu	CF <sub>3</sub>	H	Me [157], CD <sub>3</sub> [157], Et [157], Pr [157], <i>i</i> Pr [157], Bu [157], <i>t</i> Bu [157], CH <sub>2</sub> CH=CH <sub>2</sub> [157], Ph [157], Bn [157]
O	O	H	<i>t</i> Bu	Me	H	Me [152], CD <sub>3</sub> [152], Et [152], Pr [152], Bu [152], Oct [152], Ph [152], CH <sub>2</sub> CH=CH <sub>2</sub> [152]
O	O	H	<i>t</i> Bu	Me	Me	Me [153], Bu [153], Ph [153]
O	O	H	<i>t</i> Bu	Me	Et	Me [153], Bu [153], Ph [153]
O	O	H	<i>t</i> Bu	Me	Pr	Me [153], Bu [153]
O	O	H	<i>t</i> Bu	Me		Me [153]
O	O	H	<i>t</i> Bu	Et	H	Me [152]
O	O	H	<i>t</i> Bu	CH <sub>2</sub> OTBDMS	H	Bu [152]
O	O	H	<i>t</i> Bu		H	Me [179]
O	O	Me	<i>t</i> Bu	Me	H	Et [161, 162], Bu [161, 162]
O	O	H	Ph	H	H	Pr [244], Dec [244]
O	O	H	Ph	Me	H	Bu [244], Ph [244]

Table D4. Structural formulas of products of cycloaddition reactions (Diels–Alder reactions, [2 + 2] cycloadditions) of compounds 5–7 (Scheme 9). See also Schemes 10, 12, and 13.


 Table E. Some products obtained by the reaction of enolates of Boc-BMI, Z-BOX, and other similar heterocyclic acetals of type 11 (Schemes 21, 23, 25, and 33). In most cases, products with R<sup>1</sup> or R<sup>2</sup> ≠ H were prepared by carrying out a second alkylation of the monoalkylated product in situ, without isolation of the intermediate product (see Scheme 26 and text). A few of these compounds are also shown in Scheme 24.

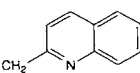
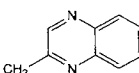
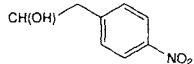



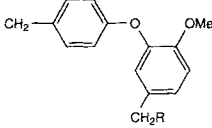
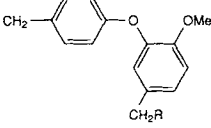
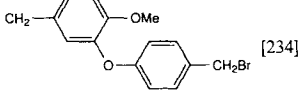
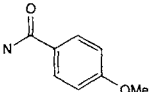
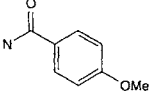
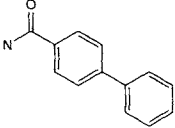
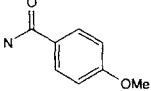
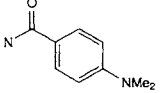
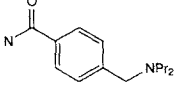
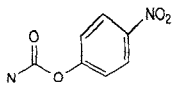
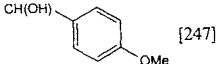
R <sup>A</sup>	X	Y	R <sup>1</sup>	R <sup>2</sup>
<i>t</i> Bu	NBoc	NMe	Allyl [240], Br [134], Bn [81], CH <sub>2</sub> CN [240], CH <sub>2</sub> CO <sub>2</sub> Me [81], CHMe(OH) [258], CHEt(OH) [258], CH(OH)(C <sub>2</sub> H <sub>5</sub> ) [258], CH(Me)Ph [240], CH(Me)CH <sub>2</sub> NO <sub>2</sub> [240], (CH <sub>2</sub> ) <sub>2</sub> Ph [240], CH <sub>2</sub> CH=CHMe [240], CH <sub>2</sub> C(CO <sub>2</sub> Me)=CH <sub>2</sub> [240], (CH <sub>2</sub> ) <sub>2</sub> Cl [240], (CH <sub>2</sub> ) <sub>4</sub> Cl [240], (CH <sub>2</sub> ) <sub>5</sub> Cl [81], (CH <sub>2</sub> ) <sub>2</sub> <sup>11</sup> CN [349], (CH <sub>2</sub> ) <sub>3</sub> <sup>11</sup> CN [349], (CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> <i>t</i> Bu [254], CH(Me)CH <sub>2</sub> CO <sub>2</sub> Me [254], CH(Me)CH <sub>2</sub> CO <sub>2</sub> Et [254], CHRCH <sub>2</sub> COCPh <sub>3</sub> (R = Me, Ph) [255], CH <sub>2</sub> -[cyclopropyl] [240],  [350],  [350],	H

Table E. (continued)

R <sup>A</sup>	X	Y	R <sup>1</sup>	R <sup>2</sup>
<i>t</i> Bu	NBoc	NMe		H
<i>t</i> Bu	NMe	NBoc	Me [99]	H
<i>i</i> Pr	NBoc	NMe		H

Table E. (continued)

R <sup>A</sup>	X	Y	R <sup>1</sup>	R <sup>2</sup>
<i>t</i> Bu [358]	NBz	NMe	Me [71, 224], <i>i</i> Pr [71, 224], Bu [71, 224], Allyl [359], (CH <sub>2</sub> ) <sub>2</sub> OH [240], (CH <sub>2</sub> ) <sub>3</sub> Br [360], (CH <sub>2</sub> ) <sub>3</sub> PO(OH) <sub>2</sub> [361], Bn [71, 224],  [362]	H
<i>t</i> Bu	NZ	NMe	Me [71], <i>i</i> Pr [240], CH <sub>2</sub> CO <sub>2</sub> Me [240], CH <sub>2</sub> CO <sub>2</sub> Et [240], CH <sub>2</sub> SiMe <sub>3</sub> [240], CHPh(OH) [71]	H
<i>t</i> Bu	NZ	NCH <sub>2</sub> CO <sub>2</sub> Et	Allyl [234],  [234], CH <sub>2</sub> -  [234],  [234],  (R = Br, OH, OTBDPS) [234]	H
<i>t</i> Bu	NZ	NCH <sub>2</sub> CO <sub>2</sub> Et	Me [230, 232], Et [230, 232]	H
<i>t</i> Bu	NZ	NCH(Me)CO <sub>2</sub> Me	Me [230, 232]	H
<i>t</i> Bu	NZ	NCH <sub>2</sub> CO-Gly-OMe	Me [234], Bn [234],  (R = Br, OH, OTBDPS) [234],  [234]	H
<i>t</i> Bu		NMe	Me [71]	H
<i>i</i> Pr	NBz	NMe	Me [71]	H
<i>i</i> Pr		NMe	Me [71]	H
<i>i</i> Pr		NMe	Me [71]	H
<i>t</i> Bu	NCHO	O	Me [82]	H
<i>t</i> Bu	NCO <i>t</i> Bu	O	Me [82]	H
<i>t</i> Bu	NBz	O	Me [82], Bu [82], Bn [82]	H
<i>t</i> Bu		O	Me [82]	H
<i>t</i> Bu		O	Me [82], Et [82], Allyl [82], Bn [82]	H
<i>t</i> Bu		O	Me [82], Et [82]	H
<i>t</i> Bu	NCO <sub>2</sub> Ph	O	Me [82], Allyl [82], Bn [82]	H
<i>t</i> Bu		O	Me [82]	H
Ph	NBoc	O	Me [247],  [247]	H

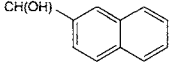
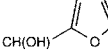
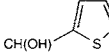
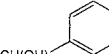
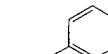
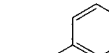
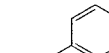

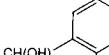
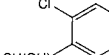
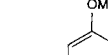
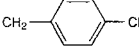
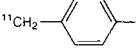
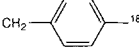
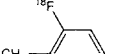
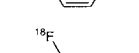
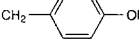
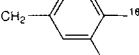
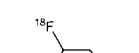
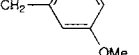
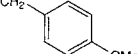

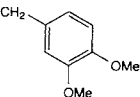

R <sup>^</sup>	X	Y	R <sup>1</sup>	R <sup>2</sup>
<i>t</i> Bu [363]	NZ	O	CH(OH)Et [246], CH(OH) <i>i</i> Pr [246], CH(OH)Ph [246],  [246], CH(OH)C <sub>10</sub> H <sub>21</sub> [246], CH(OH)C <sub>13</sub> H <sub>27</sub> [246],  [246],  [246],  [246],  [246],  [246],  [246],  [246],  [246],  [246],  [246]	H
<i>t</i> Bu	NBoc	NMe	Me [81], Et [81], CH <sub>2</sub> <i>i</i> Pr [81], Bn [81], CD <sub>2</sub> C <sub>6</sub> D <sub>5</sub> [81]	D
<i>t</i> Bu	NBoc	NMe	Me	 [351],  [259, 351],  [356],  [356],  [356],  [356],  [356],  [356],  [356]
<i>t</i> Bu	NBoc	NMe	Et	Allyl [240]
<i>t</i> Bu	NBoc	NMe	Et [81]	(CH <sub>2</sub> ) <sub>2</sub> Cl
<i>t</i> Bu	NBoc	NMe	Me [81], Et [81]	(CH <sub>2</sub> ) <sub>4</sub> Cl
<i>t</i> Bu	NBoc	NMe	Me [81]	(CH <sub>2</sub> ) <sub>5</sub> Cl
<i>t</i> Bu	NBoc	NMe	Me	Et [82],  [82]
<i>t</i> Bu	NBoc	NMe	Bn	<i>i</i> Pr [82],  [82]
<i>t</i> Bu	NBoc	NMe		Et [82], <i>i</i> Pr [82], Bn [82].
				 [82]



Table E. (continued)

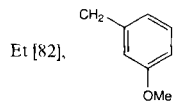
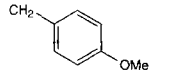
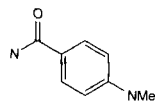
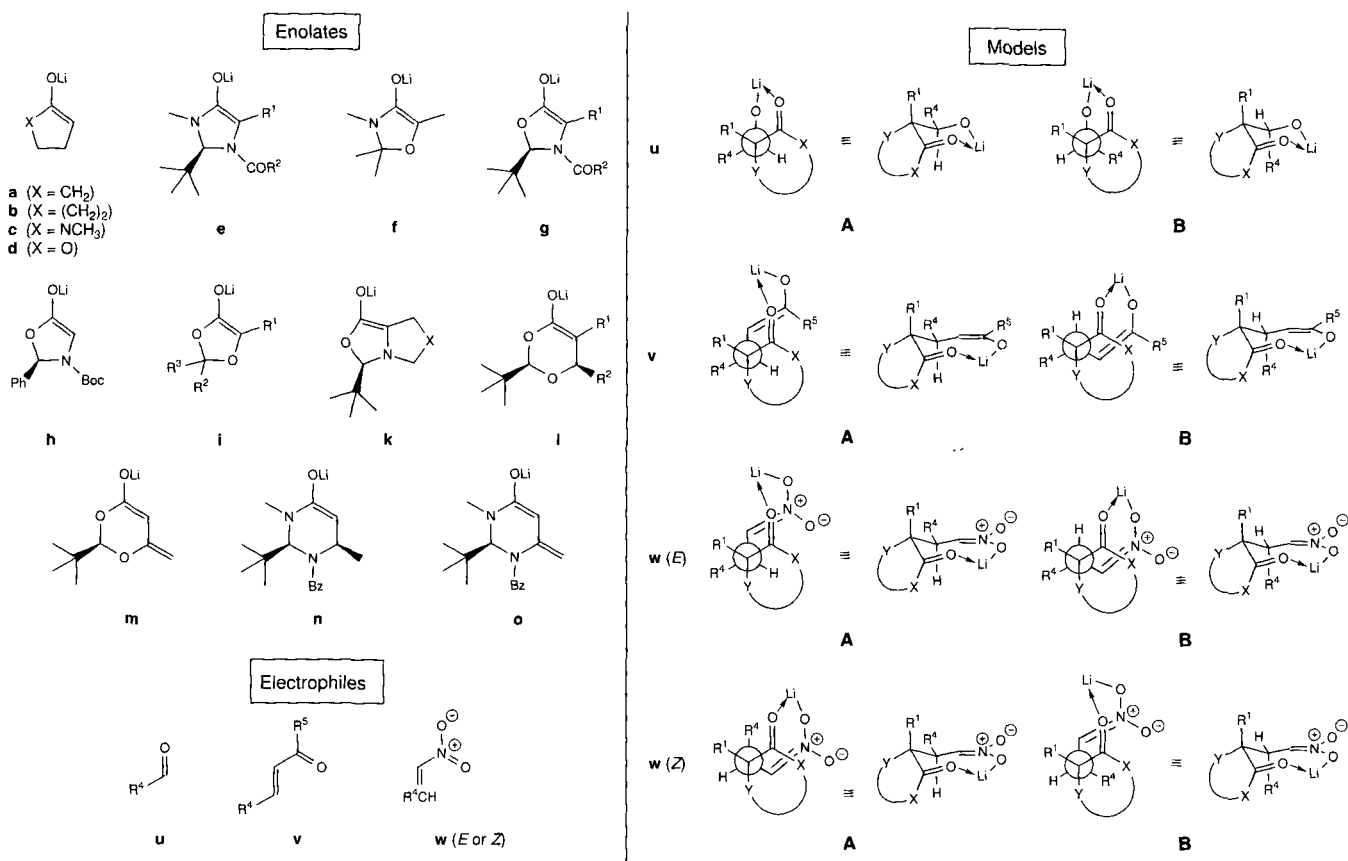
R <sup>A</sup>	X	Y	R <sup>1</sup>	
<i>t</i> Bu	NBz	O	Me	Et [82], 
<i>t</i> Bu	NBz	O	Bn	
<i>t</i> Bu		O	Me	Allyl [82]
<i>t</i> Bu	NCO <sub>2</sub> Ph	O	Me	Et [82], Bn [82], Allyl [82]

Table F. Stereochemical course of the aldol addition of cyclic enolates **a–o** to aldehydes **u**, and the Michael addition to  $\alpha,\beta$ -unsaturated carbonyl compounds **v** and nitroolefins **w** [364]. The primary adducts are presented as Newman projections and as Zimmerman–Traxler diagrams on the right side of the table. The substituent R<sup>4</sup> is always equatorial in case **A** and axial in case **B** for the adducts shown in the chair conformation (see the discussion in the text and Scheme 29e).



R <sup>1</sup>	Enolate R <sup>2</sup>	R <sup>3</sup>	X	Electrophile R <sup>4</sup>	R <sup>5</sup>	Config.	Model	Selectivity [a]	Ref.
<b>a</b>				<b>u</b>	Aryl		<b>A</b>	++	[22, 39, 366, 367]
<b>a</b>				<b>w</b>	Me	( <i>E</i> )	<b>A</b>	++	[368]
<b>a</b>				<b>w</b>	Me	( <i>Z</i> )	<b>B</b>	++	[368]
<b>b</b>				<b>u</b>	Aryl		<b>A</b>	+++	[22, 39, 366, 367]
<b>b</b>				<b>w</b>	Me	( <i>E</i> )	<b>A</b>	++	[368]
<b>b</b>				<b>w</b>	Me	( <i>Z</i> )	<b>B</b>	++	[368]

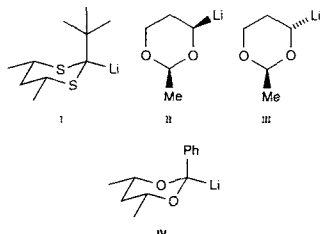
Table F. (continued)

	R <sup>1</sup>	Enolate R <sup>2</sup>	R <sup>3</sup>	X	Electrophile R <sup>4</sup>	R <sup>5</sup>	Config.	Model	Selectivity [a]	Ref.
c					v	Me		<b>B</b>	+ to + + +	[369]
c					v	Alkyl		<b>B</b>	+ +	[369]
d					u	Aryl		<b>A</b>	+	[370]
e	H	Ph			u	Alkyl		<b>B</b>	+ + +	[71]
e	H	Ph			u	Aryl		<b>B</b>	+ + +	[71]
e	(CH <sub>2</sub> ) <sub>2</sub> SMe	Ph			u	Alkyl		<b>B</b>	+ + +	[71]
e	(CH <sub>2</sub> ) <sub>2</sub> SMe	Ph			u	Aryl		<b>B</b>	+ + +	[71]
e	H	OrBu			u	Alkyl		<b>B</b>	+ to + + +	[134, 258]
e	H	OrBu			v	Alkyl	OAlkyl	<b>A</b>	+ +	[254]
e	H	OrBu			v	Alkyl, Aryl	OArlyl	<b>A</b>	+ + +	[254]
e	H	OrBu			w	Me	(E)	<b>B</b>	+ +	[240, 318]
f					u	Aryl		<b>A</b>	+	[302]
g	(CH <sub>2</sub> ) <sub>2</sub> SMe	Ph			u	Me		<b>B</b>	+ + +	[71]
g	H	OBn			u	Alkyl, Aryl		<b>B</b>	+ + +	[246]
h					u	Aryl		<b>B</b>	+ + +	[247]
i	Me	H	H		u	Alkyl, Aryl		<b>A</b>	+	[302]
i	Me	Me	Me		u	Alkyl, Aryl		<b>A</b>	+	[302]
i	Me	<i>t</i> Bu	H		u	Alkyl		<b>B</b>	+ to + +	[43, 47]
i	Me	<i>t</i> Bu	H		u	Aryl		<b>B</b>	+ to + + +	[43, 47]
i	Me	<i>t</i> Bu	H		w	Me	(E)	<b>A</b>	+ + +	[123]
i	Me	<i>t</i> Bu	H		w	Me	(E)	<b>A</b>	+	[123]
i	Ph	<i>t</i> Bu	H		w	Me	(E)	<b>A</b>	+ + +	[123]
i	CH <sub>2</sub> CO <sub>2</sub> Li	<i>t</i> Bu	H		w	Me	(E)	<b>A</b>	+ +	[123]
k				-	u	Me		<b>A</b>	+ + +	[45]
k				-	u	Aryl		<b>A</b>	+ +	[86]
k			CH <sub>2</sub>		u	Alkyl, Aryl		<b>A</b>	+ + +	[86]
k			S		u	Aryl		<b>A</b>	+ + +	[89]
l	H	Me			u	Alkyl		<b>A</b>	+ to + +	[178, 280]
l	H	Me			u	Aryl		<b>A</b>	+ +	[280]
l	H	CF <sub>3</sub>			u	Alkyl		<b>A</b>	+ + +	[293]
m					u	Alkyl		<b>A</b>	+ + +	[264, 265]
n					u	Alkyl, Aryl		<b>A</b>	+	[143]
o					u	Me		<b>B</b>	+	[143]
o					u	Aryl		<b>B</b>	+ + +	[143]

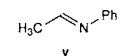
[a] +: < 60% ds; ++: 60–80% ds; +++: > 80% ds.

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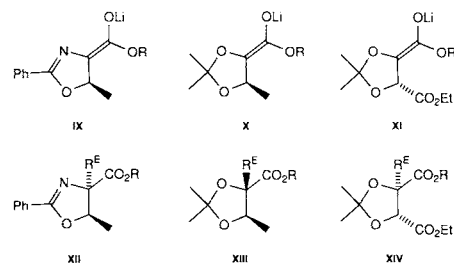
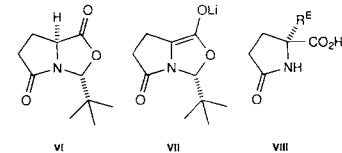


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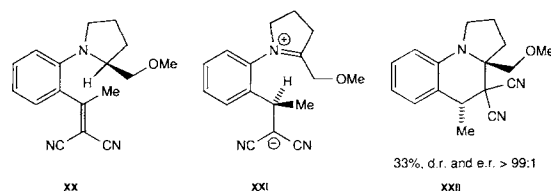
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- [221] If one considers the necessary steps, the chiral cyclic acetals shown in Schemes 10 and 16, which are derivatives of achiral carboxylic acids and are prepared by decarboxylation (aspartic acid  $\rightarrow$  dihydropyrimidinone; serine, threonine, cysteine  $\rightarrow$  imidazoline, oxazoline, thiazoline), are perhaps already results of overextending the SRS principle (laborious), despite their unique reactivity!
- [222] The glycine derivative shown in Scheme 21 (top right) may also be prepared from methionine by formation of the imidazolidinone, elimination via a vinyl-glycine derivative, oxidative cleavage, and finally decarboxylation [223].

[223] T. Weber, R. Aeschmann, T. Maetzke, D. Seebach, *Helv. Chim. Acta* **1986**, *69*, 1365–1377.

[224] D. Seebach, D. D. Miller, S. Müller, T. Weber, *Helv. Chim. Acta* **1985**, *68*, 949–952. In the overall process, amino acids prepared by alkylation of the imidazolidinone shown in Scheme 21 (top) are the result of the replacement of the serine CH<sub>2</sub>OH group by another substituent following the SRS principle.

[225] “Syntheses of Enantiomerically Pure Compounds (EPC-Syntheses).—Tartaric Acid, an Ideal Source of Chiral Building Blocks for Syntheses?”: D. Seebach, E. Hungerbühler in *Modern Synthetic Methods, Vol. 2* (Ed.: R. Scheffold), Salle + Sauerländer, Frankfurt/Aarau, **1980**, pp. 91–171.

[226] The separation of the product may also cause difficulties: for example, in Schöllkopf’s synthesis of amino acids via bislactim ethers derived from dike-topiperazines, the final step requires the separation of two amino acid esters (for a reference, see Scheme 22).

[227] a) “Stereoselective Aldol Condensations”: D. A. Evans, J. V. Nelson, T. R. Taber in *Topics in Stereochemistry, Vol. 13* (Eds.: N. L. Allinger, E. L. Eliel, S. H. Wilen), Wiley, New York, **1982**, pp. 1–115; b) “Stereoselective Alkylation Reactions of Chiral Metal Enolates”: D. A. Evans in *Asymmetric Synthesis, Vol. 3* (Ed.: J. D. Morrison), Academic Press, Orlando, **1984**, pp. 1–110; c) “The Aldol Addition Reaction”: C. H. Heathcock in *Asymmetric Synthesis, Vol. 3* (Ed.: J. D. Morrison), Academic Press, Orlando, **1984**, pp. 111–212; d) J. R. Gage, D. A. Evans in *Organic Syntheses, Vol. 68* (Ed.: J. D. White), Wiley, New York, **1990**, pp. 77–82; J. R. Gage, D. A. Evans in *Organic Syntheses, Vol. 68* (Ed.: J. D. White), Wiley, New York, **1990**, pp. 83–91; e) “Modern Enolate Chemistry: Regio- and Stereoselective Formation of Enolates and the Consequence of Enolate Configuration on Subsequent Reactions”: C. H. Heathcock in *Modern Synthetic Methods, Vol. 6* (Ed.: R. Scheffold), Verlag Helvetica Chimica Acta/VCH, Basel/Weinheim, **1992**, pp. 1–102; f) see also ref. [31]. New books that collate many examples of the auxiliary approach include: g) J. Seyden-Penne, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, Wiley, New York, **1995**; h) D. J. Ager, M. B. East, *Asymmetric Synthetic Methodology*, CRC Press, Boca Raton, **1996**.

[228] For articles dealing with the application of amino acid derivatives as auxiliaries in organic synthesis, see: “Construction of Chiral Molecules Using Amino Acids”: G. M. Coppola, H. F. Schuster in *Asymmetric Synthesis*, Wiley, New York, **1987**; “Synthesis and Use of Enantiomerically Pure *t*-Leucine”: A. S. Bommarius, M. Schwarm, K. Stingl, M. Kottenhahn, K. Huthmacher, K. Drauz, *Tetrahedron: Asymmetry* **1995**, *6*, 2851–2888; “Amino Acids and their Derivatives as Stoichiometric Auxiliaries in Asymmetric Synthesis”: A. Studer, *Synthesis* **1996**, 793–815.

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[247] J. N. Kinkel, U. Gysel, D. Blaser, D. Seebach, *Helv. Chim. Acta* **1991**, *74*, 1622–1635.

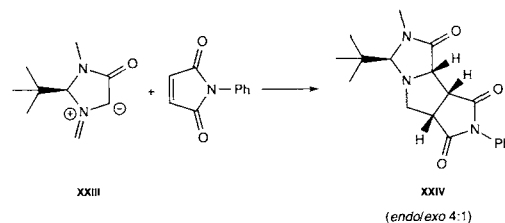
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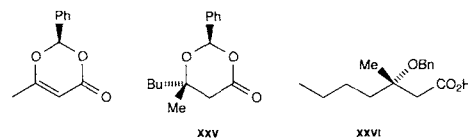
[250] A. R. Sting, Dissertation No. 11669, ETH, Zürich, **1996**; A. R. Sting, D. Seebach, unpublished results.

[251] Boc-BMI, Bz-BMI, and Z-BMI are commercially available in both enantiomeric forms from the following companies: Aldrich Chemical Company, Fluka Chemie AG, Interchim s. a. (France), E. Merck (Germany), Senn Chemicals AG (Switzerland), Wako Chemicals (USA).

[252] There are many examples in the literature of other applications of the chiral acetals shown at the bottom of Scheme 21. Two examples are briefly described here: 1) Formation of ylide **XXIII** by reaction of BMI with formaldehyde and subsequent treatment with, for example, *N*-phenylmalonic acid imide results in the tricyclic compound **XXIV**, which contains three new stereocenters (J.-F.



Peyronel, S. Grisoni, B. Carboni, T. Courgeon, R. Carrié, *Tetrahedron* **1994**, *50*, 189–198). 2) Michael addition to a methyl phenyl dioxinone ( $\rightarrow$  **XXV**) with subsequent hydrogenolysis of one of the benzylic C–O bonds results in the formation of O-benzyl-protected 3-hydroxy-3-methylheptanoic acid **XXVI** [244].



[253] D. Seebach, H. M. Bürger, C. P. Schickli, *Liebigs Ann. Chem.* **1991**, 669–684.

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[256] D. Seebach, A. Studer, E. Pfammatter, H. Widmer, *Helv. Chim. Acta* **1994**, *77*, 2035–2050.

[257] A. Studer, D. Seebach, *Heterocycles* **1995**, *40*, 357–378.

[258] S. Blank, D. Seebach, *Liebigs Ann. Chem.* **1993**, 889–896.

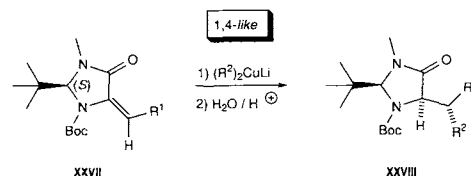
[259] M. J. Al-Darwish, C. Lemaire, G. Delfiore, D. Comar, *J. Labelled Compds. Radiopharm.* **1994**, *35*, 108–110.

[260] For example, see the discussion about “flustrates” in Section 2.2 of ref. [261].

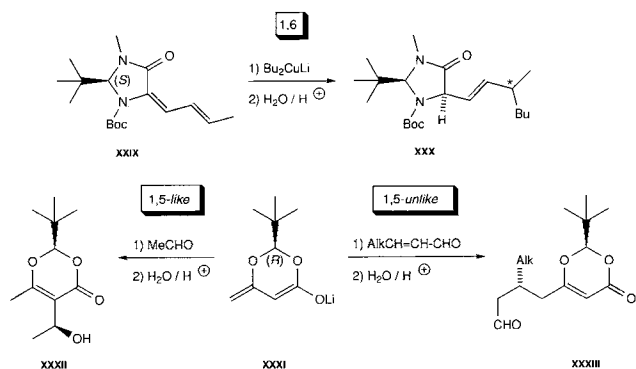
[261] D. Seebach, *Angew. Chem.* **1990**, *102*, 1363–1409; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1320–1367.

[262] Only the use of a special trick allows the formation of the free  $\alpha$ -branched amino acids that bear two bulky substituents [83]. Interestingly, drastic conditions are required for the hydrolysis of the 5,5-disubstituted *N*-benzoyl oxazolidinones with bulky substituents; the final step in which the benzoyl amide is cleaved requires: HOAc/conc. HCl (2/1), reflux [82], cf. ref. [83] and D. Obrecht, C. Spiegler, P. Schönholzer, K. Müller, H. Heimgartner, F. Stierli, *Helv. Chim. Acta* **1992**, *75*, 1666–1696; D. Obrecht, U. Bohdal, R. Ruffieux, K. Müller, *ibid.* **1994**, *77*, 1423–1429.

[263] For example, the addition of a cuprate to an alkylidene-Boc-BMI derivative is completely selective (rel. toxicity 1,4-*lk*) by NMR analysis, even though three bonds and three trigonal centers separate the inducing and newly formed stereogenic centers (**XXVII**  $\rightarrow$  **XXVIII**) [134,253]. It is even more



surprising that the reaction of the dienylidene **XXIX** with dibutylcuprate leads to a single product **XXX** (to date of unknown configuration), although five bonds separate the stereogenic acetal center and the site of substitution in the substrate (see ref. [253] and footnote [27] therein). Stereogenic centers positioned in a 1,5-fashion result from the 1,2- or 1,4-addition of the dienolate **XXXI** of 2-*tert*-butyl-6-methyl-1,3-dioxin-4-one, at the 5- and 1'-position, to an aliphatic aldehyde ( $\rightarrow$  **XXXII**) or enal ( $\rightarrow$  **XXXIII**), respectively [264,265].

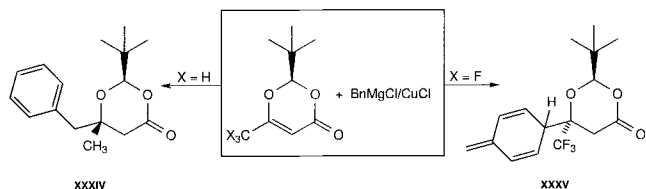


[264] D. Seebach, U. Misslitz, P. Uhlmann, *Angew. Chem.* **1989**, *101*, 484–485; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 472–473.

[265] D. Seebach, U. Misslitz, P. Uhlmann, *Chem. Ber.* **1991**, *124*, 1845–1852.

[266] For examples of 1,5-, 1,6-, and 1,7-induction see M. Nógrádi, *Stereoselective Synthesis—A Practical Approach*, 2nd ed., VCH, Weinheim, **1995**.

[267] Reactions of 4-methyl and 4-trifluoromethylidioxanones with Cu-doped benzyl Grignard reagents (to give **XXXIV** and **XXXV**, respectively) under identical conditions. In the first case, the standard *trans* addition (of the benzylic C atom) occurs, but the second example shows a *cis* addition (of the *para* C atom) with concomitant formation of the quinoid system [156, 157]. We have previously called F-containing reactants “flustrates” [261].



[268] As is evident from the discussion in ref. [29], it has been accepted for many years (work of Creger and Pfeffer) that deuterolysis of an enolate produced by the use of LDA is not a reliable method for determining the degree of enolate formation.

[269] For a review article dealing with the themes [Li-enolate·HNR<sub>2</sub>] and [Li-enolate·LiNR<sub>2</sub>], see refs. [21–23, 26–28, 48] and K. Rück, *Angew. Chem.* **1995**, *107*, 475–477; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 433–435.

[270] One further equivalent of Li-amide is produced, such that the desired product of the reaction with electrophiles is now at the mercy of this strong base!

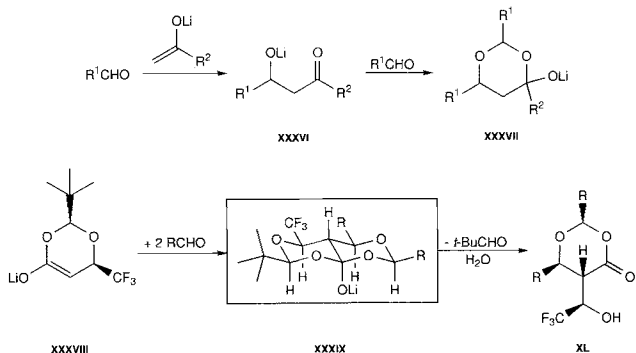
[271] The stereoelectronic barrier, already discussed in Section 3, which protects the corresponding enolate from facile  $\beta$ -elimination, is nowhere near as high when the leaving group is RS<sup>-</sup> in place of RO<sup>-</sup>. When the rules for cyclization (the reverse of this elimination) were initially proposed, Baldwin explicitly stated that these are only valid for cases in which no elements of the second or a higher period are involved (see also Scheme 6 and ref. [111a]).

[272] “The Synthetic Utility of  $\alpha$ -Amino-Alkoxides”: D. L. Comins, *Synlett* **1992**, 615–625.

[273] Y. Kai, P. Knochel, S. Kwiatkowski, J. D. Dunitz, J. F. M. Oth, D. Seebach, *Helv. Chim. Acta* **1982**, *65*, 137–161.

[274] P. E. O'Bannon, W. P. Dailey, *J. Am. Chem. Soc.* **1989**, *111*, 9244–9245.

[275] Such adducts of RXLi and carbonyl groups appear to be involved in other reactions of Li-enolates and possibly play a much larger role than previously thought [272]. They could, for example, be responsible for the 2:1 reactions of aldehydes with Li-enolates and also possibly for the known stabilization of Li-aldolates against elimination to give  $\alpha,\beta$ -unsaturated carbonyl compounds (see **XXXVI**  $\rightarrow$  **XXXVII** and **XXXVIII**  $\rightarrow$  **XXXIX**  $\rightarrow$  **XL** [293]).



[276] For the first attempts at explaining a few of the observed effects, see ref. [48].

[277] See ref. [227b].

[278] H. O. House, B. A. Tefertiller, H. D. Olmstead, *J. Org. Chem.* **1968**, *33*, 935–942.

[279] See footnotes [41–45] in ref. [23] and the general discussion in ref. [254].

[280] W. Amberg, D. Seebach, *Angew. Chem.* **1988**, *100*, 1786–1787; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1718–1719; *Chem. Ber.* **1990**, *123*, 2413–2428; *ibid.* **1990**, *123*, 2439–2444.

[281] See Section 3 and Schemes 5 and 6 for references to the literature.

[282] The alternative course of the cyclization reaction when transition metal acetalization catalysts are used has already been pointed out in Section 3 [57].

[283] See the bicyclic azetidine carboxylic acid, proline, thiaproline, hydroxyproline, and pyrroglutamic acid derivatives in Section 3, Schemes 6 and 28, Table C in the appendix and ref. [91].

[284] See Section 3 and ref. [92] for references to the literature.

[285] D. A. Evans, J. C. Barrow, J. L. Leighton, A. J. Robichaud, M. Sefkow, *J. Am. Chem. Soc.* **1994**, *116*, 12111–12112.

[286] J. Zimmermann, D. Seebach, T.-K. Ha, *Helv. Chim. Acta* **1988**, *71*, 1143–1155.

[287] For example, compare the benzylation of the dioxolane carboxylic *tert*-butylthioester (d.r. = 80:20, *cis* [93,102]) with that of the *N*-formyloxazolidinocarboxylic acid methyl ester (d.r. = 98.5:1.5, *trans* [93,100]) and also with the methylation of *N*-formylthiazolidinocarboxylic acid methyl ester (d.r. > 98:2, *trans* [106]). See the equations in the second line of Scheme 29b, Section 3, and Table B.

[288] See our work on NCS reactions [133, 134].

[289] Reactions at radical centers of the heterocycle with formation of C–C and C–H bonds have been studied by Beckwith et al. [135]. Furthermore, see the radical reactions of methylenedioxanones performed by B. Giese et al. (discussion and references in [290]).

[290] For a comprehensive review article, see D. P. Curran, N. A. Porter, B. Giese, *Stereochemistry of Radical Reactions—Concepts, Guidelines, and Synthetic Applications*, VCH, Weinheim, **1996**.

[291] H. E. Zimmerman, M. D. Traxler, *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.

[292] See ref. [178a].

[293] J.-M. Lapiere, M. Gautschi, G. Greiveldinger, D. Seebach, *Chem. Ber.* **1993**, *126*, 2739–2746.

[294] It was not to be expected that the larger stability of the 1,3-*cis*-substituted five-membered ring heterocycle would be due to the diequatorial arrangement of the substituents in an envelope conformation (the *cis/trans* energy difference of 1,3-dimethylcyclopentane is 0.2 kcal mol<sup>-1</sup>). See: J. Dale, *Stereochemie und Konformationsanalyse*, 1st ed., VCH, Weinheim, **1978**.

[295] F. Johnson, *Chem. Rev.* **1968**, *68*, 375–413.

[296] R. W. Hoffmann, *Chem. Rev.* **1989**, *89*, 1841–1860.

[297] J. L. Broeker, R. W. Hoffmann, K. N. Houk, *J. Am. Chem. Soc.* **1991**, *113*, 5006–5017.

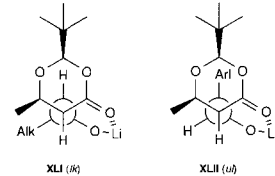
[298] Here, we use Dunitz's definition for pyramidalization (*d*) of trigonal centers: K. L. Brown, L. Damm, J. D. Dunitz, A. Eschenmoser, R. Hobi, C. Kratky, *Helv. Chim. Acta* **1978**, *61*, 3108–3135.

[299] The value of almost 20 kcal mol<sup>-1</sup> of the partial amide C=N bond corresponds to practically a third of that of the C=C bond.

[300] For example, see the data in Table 1 of both refs. [62] and [178a] and also Table 4 of ref. [143].

[301] D. Seebach, T. Maetzke, W. Petter, B. Klötzer, D. A. Plattner, *J. Am. Chem. Soc.* **1991**, *113*, 1781–1786.

[302] Hence, the reversal of topicity from a weakly *unlike* to a strongly *like* preference during the aldol addition reaction of a trigonal center of a dioxolanone, *N*-acyloxazolidinone, or *N*-acylimidazolidinone Li-enolate to an aldehyde might be attributed to the close proximity of R<sup>1</sup> and H (in comparison with R<sup>1</sup> and R<sup>2</sup>) (see structure **B** in Scheme 29e). See the general discussion in ref. [254] and the collection of data in Table F. Aldol additions of dioxolanones: ref. [47] and C. H. Heathcock, M. C. Pirrung, S. D. Young, J. P. Hagen, E. T. Jarvi, U. Badertscher, H.-P. Märki, S. H. Montgomery, *J. Am. Chem. Soc.* **1984**, *106*, 8161–8174; of oxazolidinones: [71, 246, 250]; of imidazolidinones: [71, 134, 258]. The higher proportion of *ul*-combination seen in the transition from aliphatic to aromatic aldehydes in the aldol addition of dioxanone-enolates [153, 178, 265, 293] may be due to a  $\pi$ - $\pi$  interaction (see **XLI** und **XLII**).



[303] A. J. Birch, G. S. R. Subba Rao, *Aust. J. Chem.* **1970**, *23*, 547–552.

[304] T. Takahashi, M. Nisar, K. Shimizu, J. Tsuji, *Tetrahedron Lett.* **1986**, *27*, 5103–5104; K. Tomioka, K. Yasuda, H. Kawasaki, K. Koga, *Tetrahedron Lett.* **1986**, *27*, 3247–3250; K. Tomioka, H. Kawasaki, K. Yasuda, K. Koga, *J. Am. Chem. Soc.* **1988**, *110*, 3597–3601.

[305] Following a suggestion of B. Trost during a discussion with R. W. Hoffmann, the rather unfortunate expression “contrasteric” has been used in the literature for this effect [95, 98].



