CRYSTAL STRUCTURES AND STEREOSELECTIVE REACTIONS OF ORGANIC LITHIUM DERIVATIVES

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Zürich, February 1985.

DR. DIETER SEEBACH

CHAPTER IV

CRYSTAL STRUCTURES AND STEREOSELECTIVE REACTIONS OF ORGANIC LITHIUM DERIVATIVES*

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A) Introduction - Puzzling Non-stoichiometric Effects

In reactions of polar organometallic reagents, there is a large number of published and unpublished examples of what I would like to call non-stoichiometric effects. My first personal experience with one of these effects dates back to the time I spent at Harvard, almost twenty years ago. I observed, that lithio-dithianes tend to give diadducts with carboxylic acid derivatives, even if slowly added to a large excess of an acid chloride, see equation (1) in Figure 1. A similar, more recent observation is the reluctance of phosphorous oxychloride to combine with tri-t-butyl-phenyllithium to give a mono-adduct, equation (2) [1a]. On the other hand, the tendency of allyllithium to add twice to the ester shown in equation (3) of Figure 1 can be largely suppressed by performing the reaction in the presence of excess lithium diethylamide, three equivalents of which being an optimum [1b]. Finally, the reaction-type selectivity (deprotonation vs. addition) is reversed in the reaction (4) when a 1:1 mixture of lithium acetylide and lithium bromide is used [2]. A speculation about a possible reason for the double addition of lithiodithianes to carboxylic acid derivatives is the statement reproduced in Figure 2. In this statement, the surprizing result of a chemical reaction is referred to the state of aggregation of one of the reagents [3]. The existence of dimeric species of 2-lithio-1.3-dithianes in solution, or their involvement as reactive species has yet to be proved rigorously [4]. The dimeric structure of crystalline 2-lithio-2-methyl dithiane is, however, established (see Figure 3) [5] [6].

Another field, in which non-stoichiometric effects with organolithium derivatives were observed, is the asymmetric addition to carbonyl compounds, as influenced by chiral complexing reagents, see Figure 4. Optimizations led to recipes, according to which only part of the stoichiometrically available organometallic compound is exploited, ca. a third with the axially chiral binaphthyl-substituted ethylene diamine [7],

*Based on an address presented before "The Robert A. Welch Foundation Conferences on Chemical Research XXVII. Stereospecificity in Chemistry and Biochemistry," which was held in Houston, Texas, November 7-9, 1983.

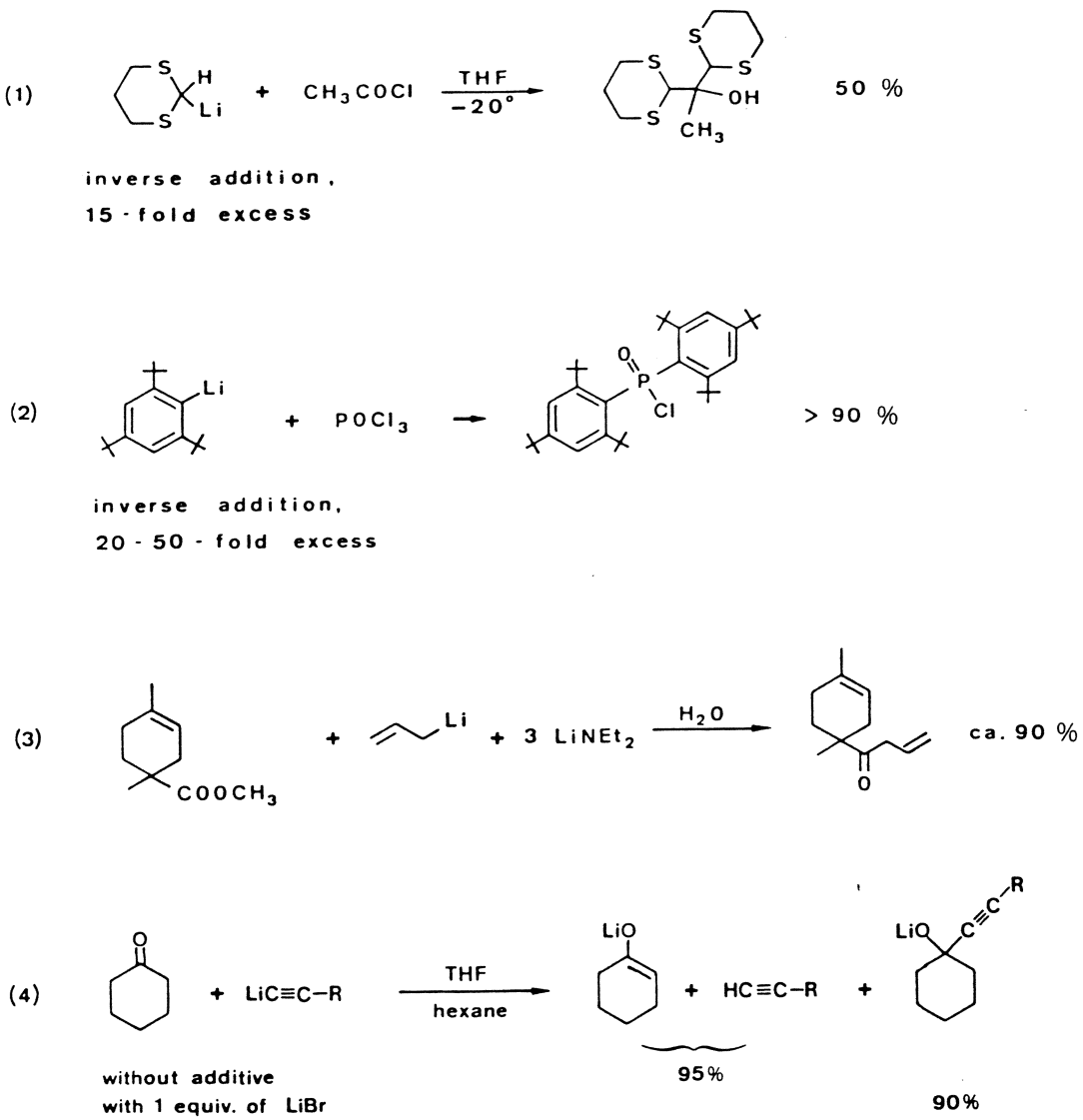
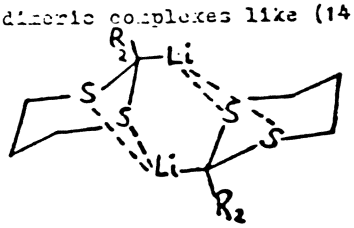


Figure 1

Four cases of non-stoichiometric effects in additions of organolithium compounds to acid derivatives.

7.) The tendency of the anions (2) to add twice to carbonylic acid derivatives is surprisingly high, even under the conditions given in item 2 This might stem from strong association of the organometallic compounds in dimeric complexes like (14)



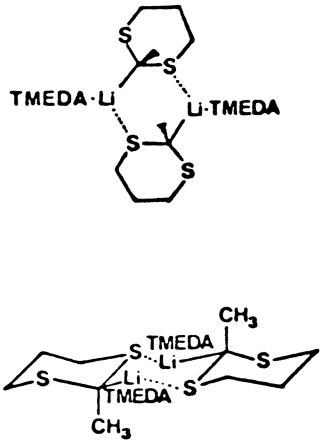
(14)

The reactions carried out with acid derivatives are listed together with details about the conditions in the experimental section (II, 7 and Table V pg.42,43 pg 62-

Research report of D.S. to Prof. E.J.Corey, December 1965

Figure 2

Early, speculative suggestion rationalizing the result of the reaction shown in equation (1) of Fig. 1.



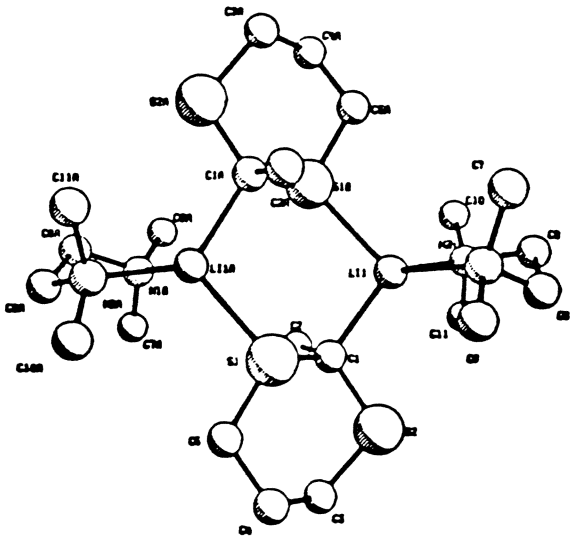
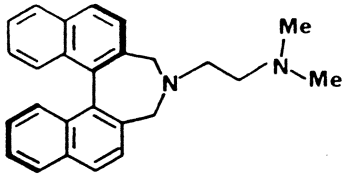


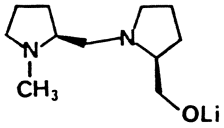
Figure 3

Dimeric crystal structure of 2-Lithio-2-methyl-1.3-dithiane·TMEDA. Formulae and PLUTO plot from x-ray structure determination [5][6].

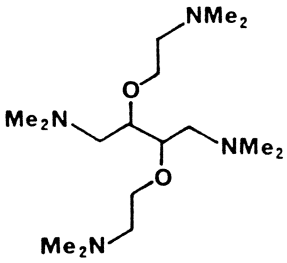
Ratios for best asymmetric induction

(5) 

: R–Li : Ar CHO ≈ 3 : 3 : 1

(6) 

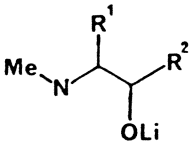
: R–Li : Ar-CHO = 4 : 2,7 : 1

(7) 

: BuLi : ϕCHO = 2 : 1 : 1

1st 20% 45% e.e.

5th 20% 17% e.e.

(8) 

: ϕ – CH=C(OLi)(OLi) : RCHO = 2 : 1 : 1

Figure 4

Examples of non-stoichiometric effects in enantioselective additions of organolithium compounds and of an Ivanov-reagent to aldehydes.

see (5), and with the proline derived 3.6-diaza-alkoxide, see (6) [8]. Also, enantioselectivity at the beginning and towards the end of the stoichiometric reaction of butyllithium with benzaldehyde under the influence of a tartaric acid-derived tetramine is very different [9], see (7), and two equivalents of chiral amino-alkoxides of the type shown in the last entry (8) of Figure 4 cause the highest asymmetric inductions in additions of the Ivanov-reagent from phenyl-acetic acid to aldehydes [10].

Some diastereoselective reactions of chiral, non-racemic enolates are also subject to non-stoichiometric effects; thus, a threefold excess of alkylating reagent is necessary to achieve reasonable yields of alkylation of Evans' valine-derived lithium enolate shown in equation (9) [11] [12]. It is also noteworthy that the relative topicity [13] of attack of the electrophile reverses upon switching from lithium to boron enolates and, at the same time, replacing alkyl halides by aldehydes as electrophiles [11], cf. equations (9) and (10) in Figure 5. Also, both, the β- and the α- alkylated products from the doubly deprotonated di-t-butyl N-formyl-aspartate shown in Figure 6 were found by us to be formed stereoselectively [14]. While the lk-selectivity of alkylation in the β- position is well precedented [15] [16] [17] [18], the ca. 80:20 enantioselectivity of branching in the amino-substituted position is striking. After an axial chirality of the "α-enolate" could be excluded, we have to assume that the chiral enolate from β- deprotonation has an asymmetric inducing effect upon the reaction of the achiral enolate from α- deprotonation!

For reactions of the aza-analogues of chiral lithium enolates, such as Meyer's oxazolines [19], Enders' prolinol derived hydrazines [20], or Schöllkopf's lactimethers of diketopiperazines [21] (see Figure 7, upper three formulae), the mechanistic presentations shown in the bottom line of Figure 7 have been forwarded. While an N-lithio-enamine was preferred in the first case, a lithium cation was proposed to be located above the plane of the anionic π- system, helping to guide in the attacking electrophile, in the two other cases. Such locations of lithium atoms above π- planes have been found in hydrocarbon derivatives such as benzyl- [22] and trityllithium [23], the dilithioderivative of hexatriene dianion [24] and other lithiated π- systems [25]. In enolate-type systems, the negative charge resides on the heteroatom, and that is where the lithium cation is expected to be located. The recent x-ray crystal structure determination [26] of a lithiated diketopiperazine derivative of alanine confirms this expectation, see Figure 8 and 9. What is more important is (i) the dimeric structure of the reagent; (ii) the fact that in the crystal of the racemic form studied, homo-chiral moieties form dimeric aggregates with each other; (iii) the non-equivalence of the two lithium atoms: one bears two THF-ligands, the other one is binding to the Et-O-heteroatoms and to a single THF molecule; (iv) the lithium atoms with their ligands impose a stronger differentiation between the Re- and the Si-face of the reacting trigonal center than does the asymmetric carbon atom bearing a methyl group and a hydrogen atom. Thus, again a non-stoichiometric effect might be at least partially responsible for the diastereoselective alkylation [21] of this species.

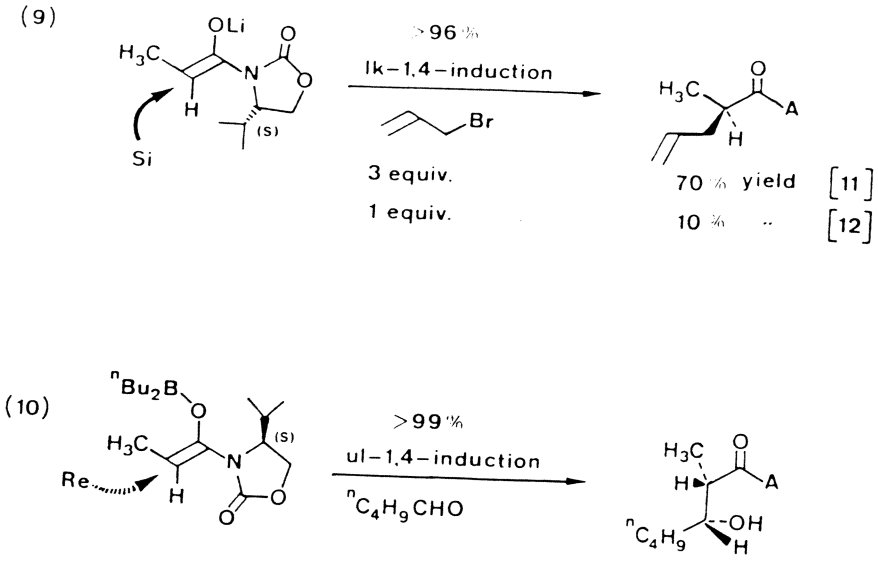


Figure 5

Comparison of yields of the 1:1- and 1:3-reaction of a chiral enolate with allyl bromide, and reversal of relative topicity upon metal and electrophile exchange in the reaction of the same enolate [11].

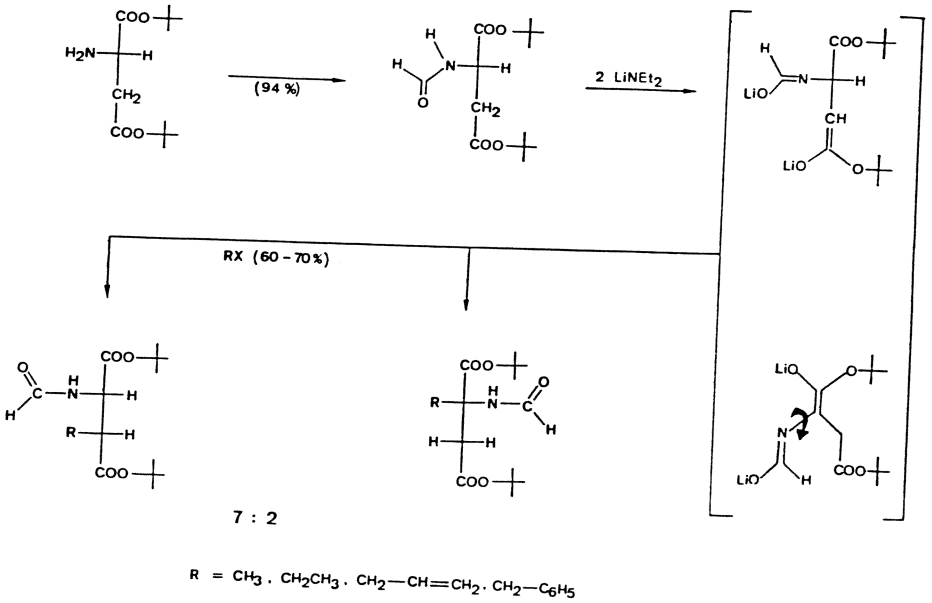


Figure 6

α- and β-Alkylation of di-t-butyl N-formyl-aspartate to give optically active products. The 3-alkylated products of u-configuration are formed in >95 % diastereomeric purity. The 2-alkylated α-amino-acid derivatives are isolated with ca. 60 % e.e. (ratio of enantiomers 80:20) [14].

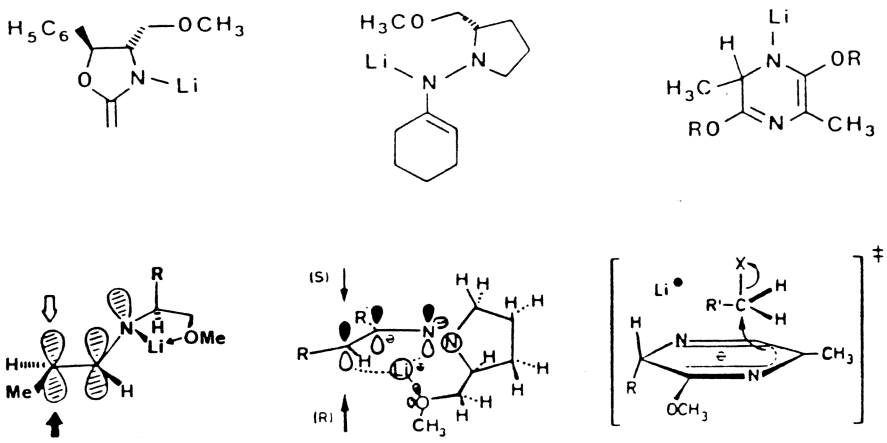


Figure 7

N-Analogues of lithium enolates derived from chiral oxazolines, hydrazones, and diketopiperazines, and the mechanistic pictures drawn to explain the observed stereochemical course of reaction. The presentations in the second line are taken from ref. [19][20][21].

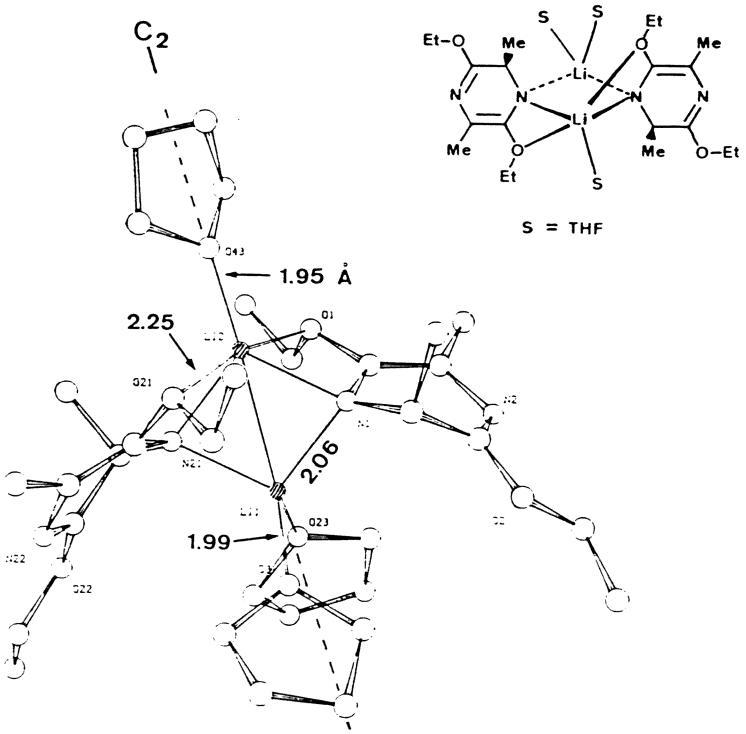
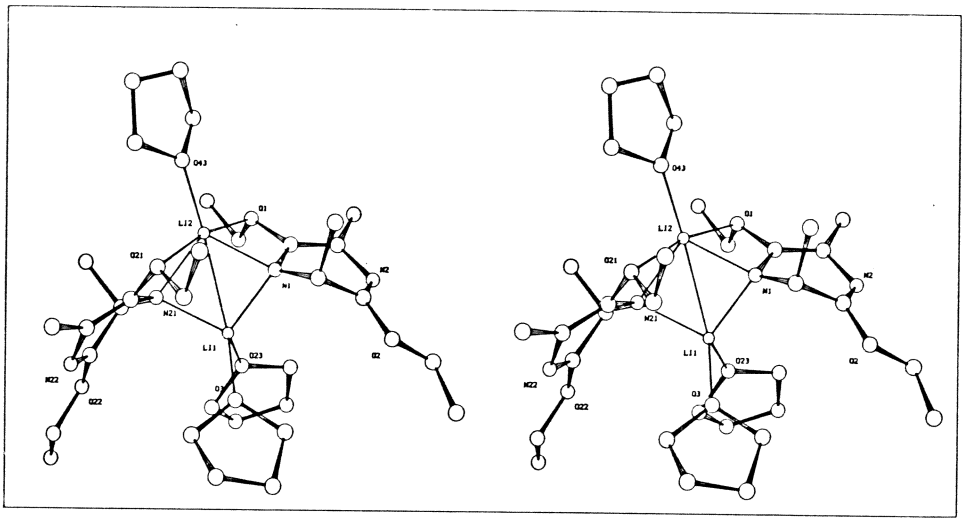


Figure 8

Crystal structure of the $[3.6\text{-diethoxy-1-lithio-2.5-dimethyl-1.2-dihydro-pyrazin}]_2 \cdot 3\text{-tetrahydrofuran}$ *complex. For a stereoview of the PLUTO representation see Fig. 9.*

Figure 9

Stereoview of the lithiated diketopiperazine derivative shown in Fig. 8. The structure was determined with a crystal of a racemic sample. The unit cell contains four dimers of two homochiral monomeric units each, two contain two R-, the other two



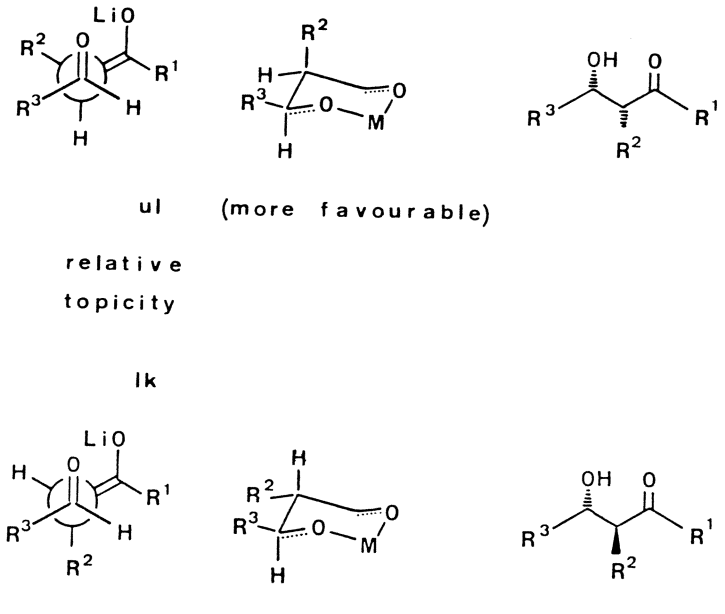
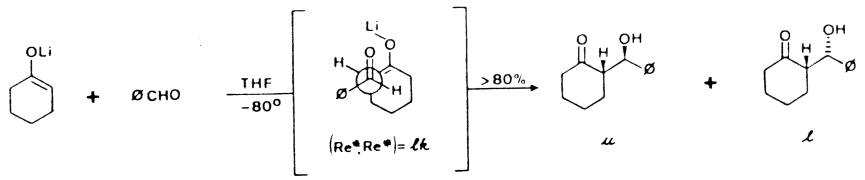


Figure 10

ul- and lk- addition of diastereomeric lithium enolates to aldehydes. The addition occurring with relative topicity ul is generally favored - although the R^2-group is in an axial position. For possible reasons see ref. [28] and [29].



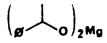
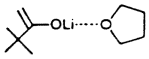
ADDITIVE	RATIO
— / $MgBr_2$	85 : 15 / 70 : 30
	92 : 8
	95 : 5
	63 : 37
	48 : 52
	26 : 74

Figure 11

Addition of cyclohexenolate to benzaldehyde in the presence magnesium bromide, of lithium alkoxides, of menthone lithium enolate, of di-t-butoxy-iron, and of the magnesium alkoxide of phenyl-ethanol. The reversal of relative topicity with the last mentioned additive is not compatible with current mechanistic views.



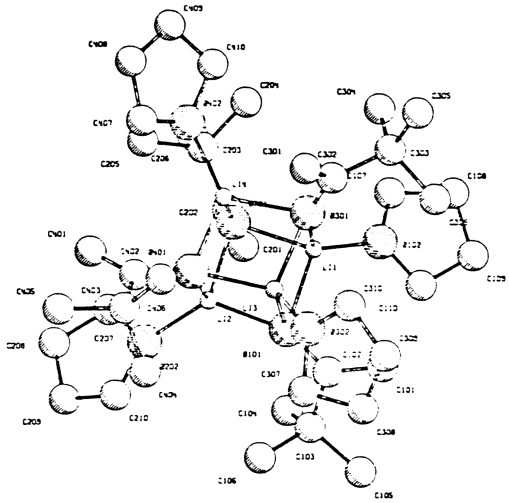


Figure 12

Tetrameric cubic crystal structure of lithium 3.3-dimethyl-1-buten-2--olat·THF)4 with tetracoordinated lithium and oxygen atoms. According to ref. [35].

Even the now generally accepted mechanism of the aldol addition of lithium enolates to aldehydes is subject to pronounced non-stoichiometric effects. According to Zimmerman [27] and Heathcock [28], cis/trans-isomeric enolates add to aldehydes with opposite relative topicity, see Figure 10. When applied to cyclohexanone enolate, of which only the E-configuration exists, see Figure 11, the mechanism predicts a lk-combination with benzaldehyde, with formation of the u-product [28]. This is indeed formed preferentially with lithium and with magnesium enolates. We have now found [30] that the stereochemical result can be strongly influenced by additives which do not participate in the stoichiometric reaction, see Figure 11: the 85:15 selectivity of the lithium enolate is increased to 95:5 in the presence of lithium alkoxides, and the 70:30 selectivity of the magnesium enolate is reversed by using the magnesium alkoxide of 1-phenyl-ethanol as an additive!

B) Crystal Structure Analyses of Lithium Enolates - Dimers and Tetramers

Puzzling effects such as those discussed in the previous chapter led us to start a program several years ago, aimed at the structure elucidation of organolithium reagents of preparative importance [31]. Previously, mainly alkyl and aryllithium compounds [3] [22] [23] [24] [25] and simple alkoxides had been investigated by x-ray analysis [32]. Thus, we prepared [31] [33] single crystals of sulfur substituted lithium derivatives and determined the structures of methyl- and phenyl-thiomethyllithium, of 2-lithio-2-methyl- and -2-phenyl-1.3-dithiane [5] [6] [34]. Simultaneously, we prepared crystals of lithium enolates, possibly the most important, single class of nucleophiles for C,C-bond formation in modern organic synthesis. The first two enolate structures which we were able to solve were the 1:1-complex of pinacolone lithium enolate with tetrahydrofuran (THF) and the corresponding cyclopentanone derivative, see Figure 12 and 13, and the discussion in references [35] and [36]. Both are cubic tetramers. The same tetrameric structures must be present in the crystals of numerous other lithium enolates which we have prepared and shown by quenching to contain an equivalent amount of solvent molecules [THF, dioxane, ether, hexamethyl phosphoric acid triamide (HMPT)]: for lithium to reach its preferred coordination number of four, a monomeric LiX with a monohapto anion must have three ligands from the solvent [34], a dimer two [6], and a tetramer one.

In order to gain information about the stereochemical course of the aldol addition, we also tried to co-crystallize LiX-compounds and carbonyl derivatives. This has led to the two structures shown in Figure 14 and 15 [31] [37]. In the acetone solvate of lithium bromide dimer the metal is formally bonded to an sp^2-hybridized oxygen. In acetone, higher aggregation to a tetramer or a polymer is obviously less favorable. More informative is the structure of the dienolate in Figure 15. It crystallized when we tried to prepare a pinacolone enolate solvated by DMPU, a cyclic urea which can replace the carcinogenic HMPT as cosolvent in many organometallic reactions [38] [39]. Obviously,

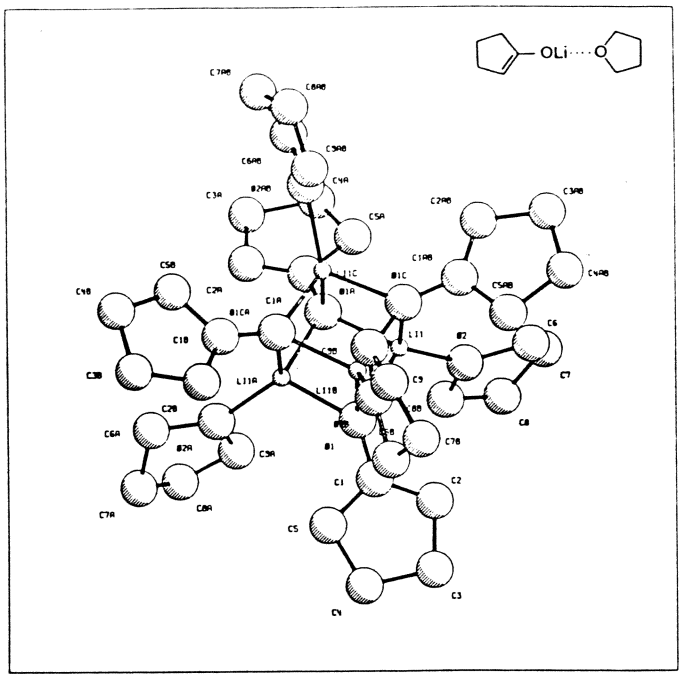


Figure 13

Cubic tetramer of (lithium cyclopentenolate·THF)$_4$; taken from ref. [35].

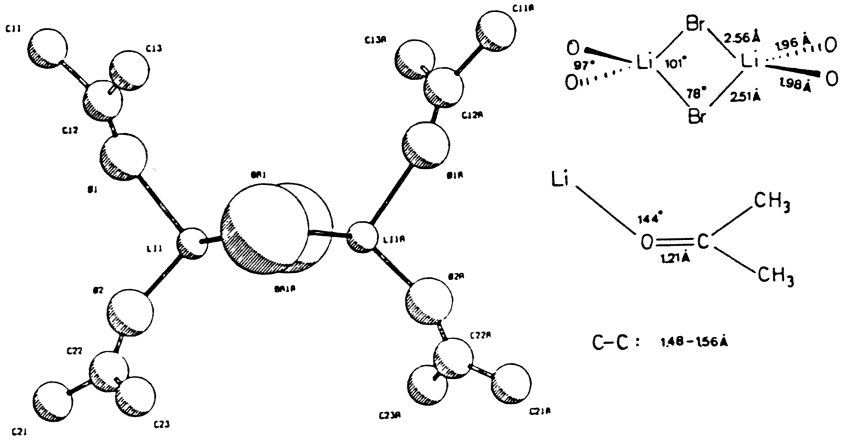
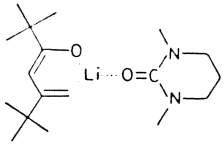
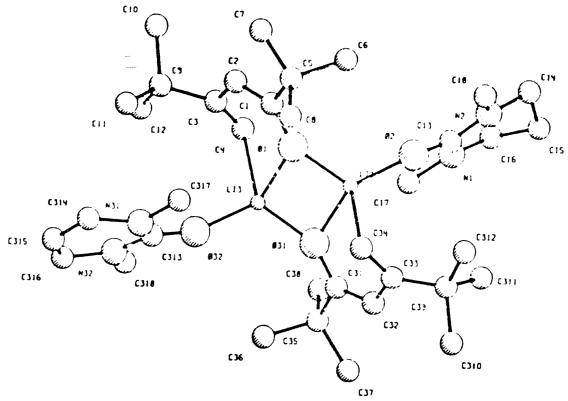


Figure 14

Crystal structure of [LiBr·(acetone)$_2$]$_2$. The two LiBr units form a rhombic dimer. The lithium atom and the C=O group are in a non-linear arrangement.





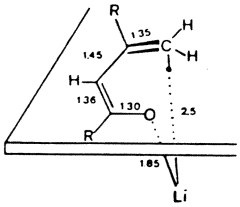
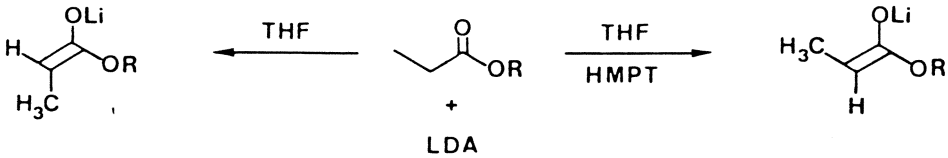


Figure 15

Crystal structure of lithium Z-2.2.6.6-tetramethyl-5-methylene-3-hepten-3--olate complexed with N.N'-dimethyl-propylene urea (DMPU). The fourth ligand on the lithium atoms of the dimeric structure is the terminal carbon atom of the dienolate.



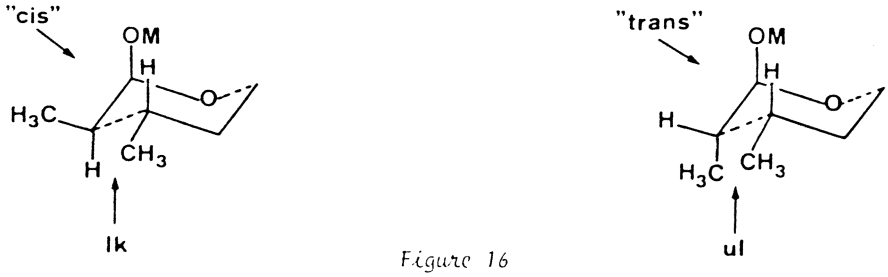


Figure 16

Ireland's [41] assignment of ester enolate configuration by Claisen rearrangement of enolates from crotyl propionates. The assignment is confirmed by the crystal structures shown in Fig. 17 - 21.

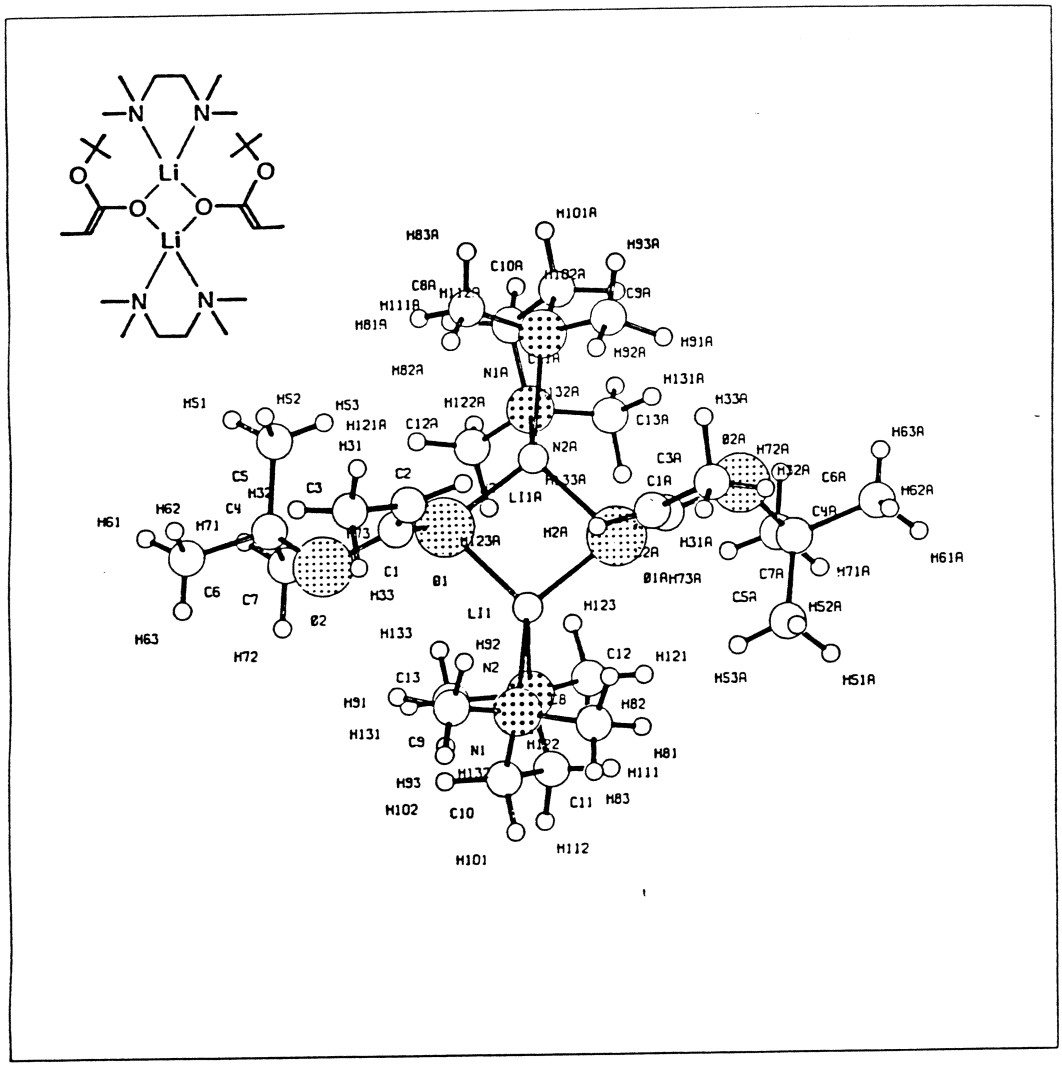


Figure 17

PLUTO plot of the crystal structure of [(lithium Z-1-t-butoxy-1-propenolate).TMEDA]$_2$, prepared by deprotonation of t-butyl propanoate with lithium diisopropylamide (LDA) in pure THF, with subsequent addition of TMEDA. The heteroatoms oxygen and nitrogen are labelled. The two enolate moieties point towards the viewer. See also Fig. 18 and 19.

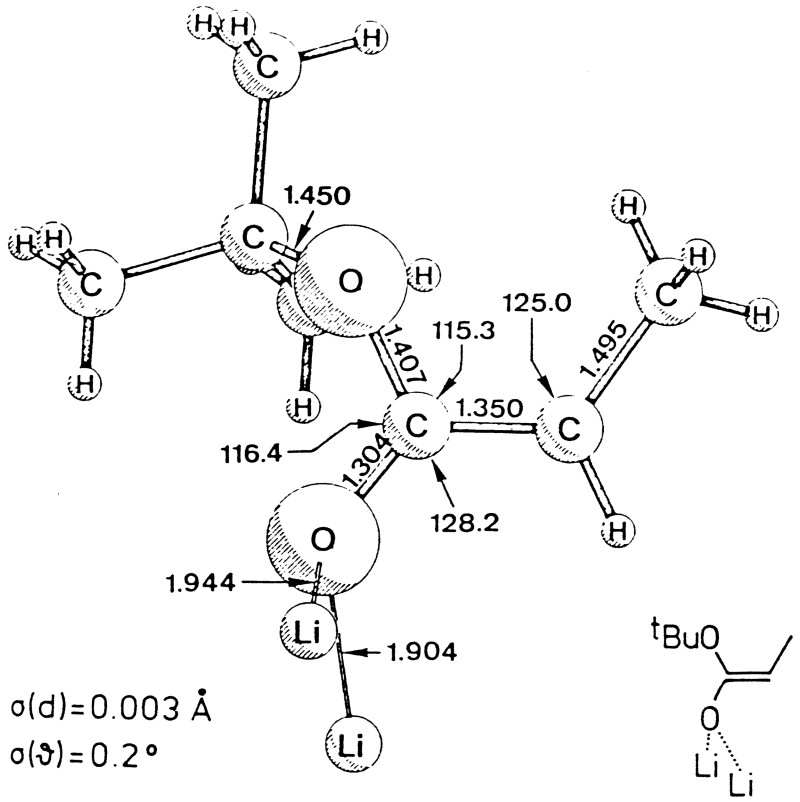


Figure 18

Representation of the enolate plane of the lithium Z-enolate of t-butyl propanoate (cf. Fig. 17 and 19). Bond angles and bond lengths obtained from the x-ray crystal structure analysis. Note the in-plane distortions of the sp^2-carbons, the drastically different C-O bond lengths and the position of the t-butyl group behind the plane (dihedral angle C=C-O-C 120°). Compare with Fig. 22.

Figure 19

Stereoview in ORTEP representation of the crystal structure of [(lithium Z-1-t-butoxy-1-propenolate)·TMEDA]$_2$. The crystals turn pale and cloudy above -30°C and melt at ca. 0°C. The data set was collected at 143 K. See also the accompanying Fig. 17 and 18.

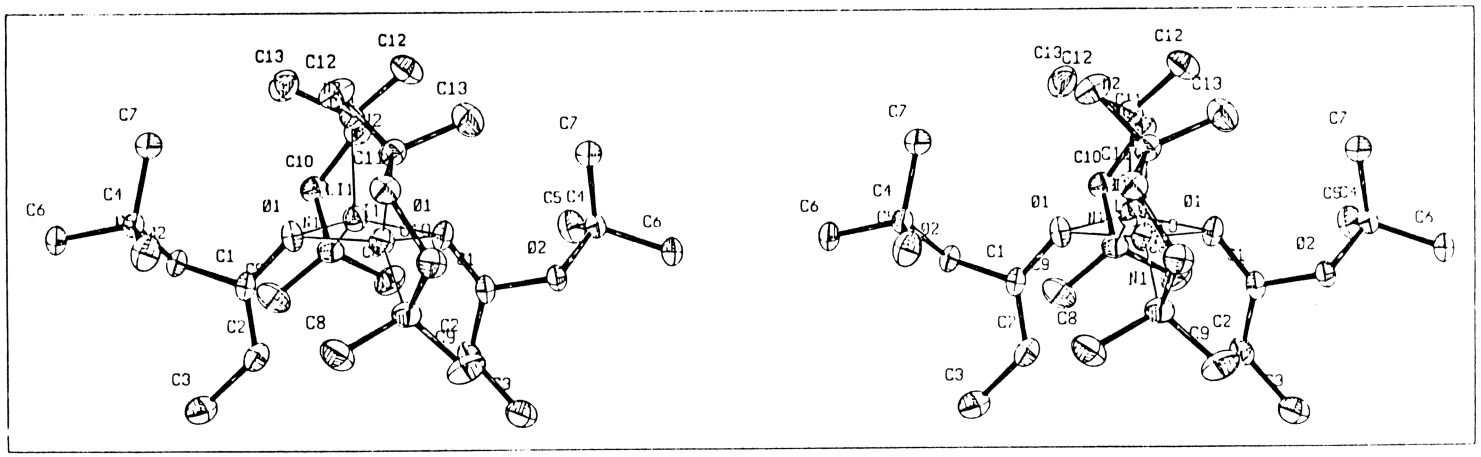
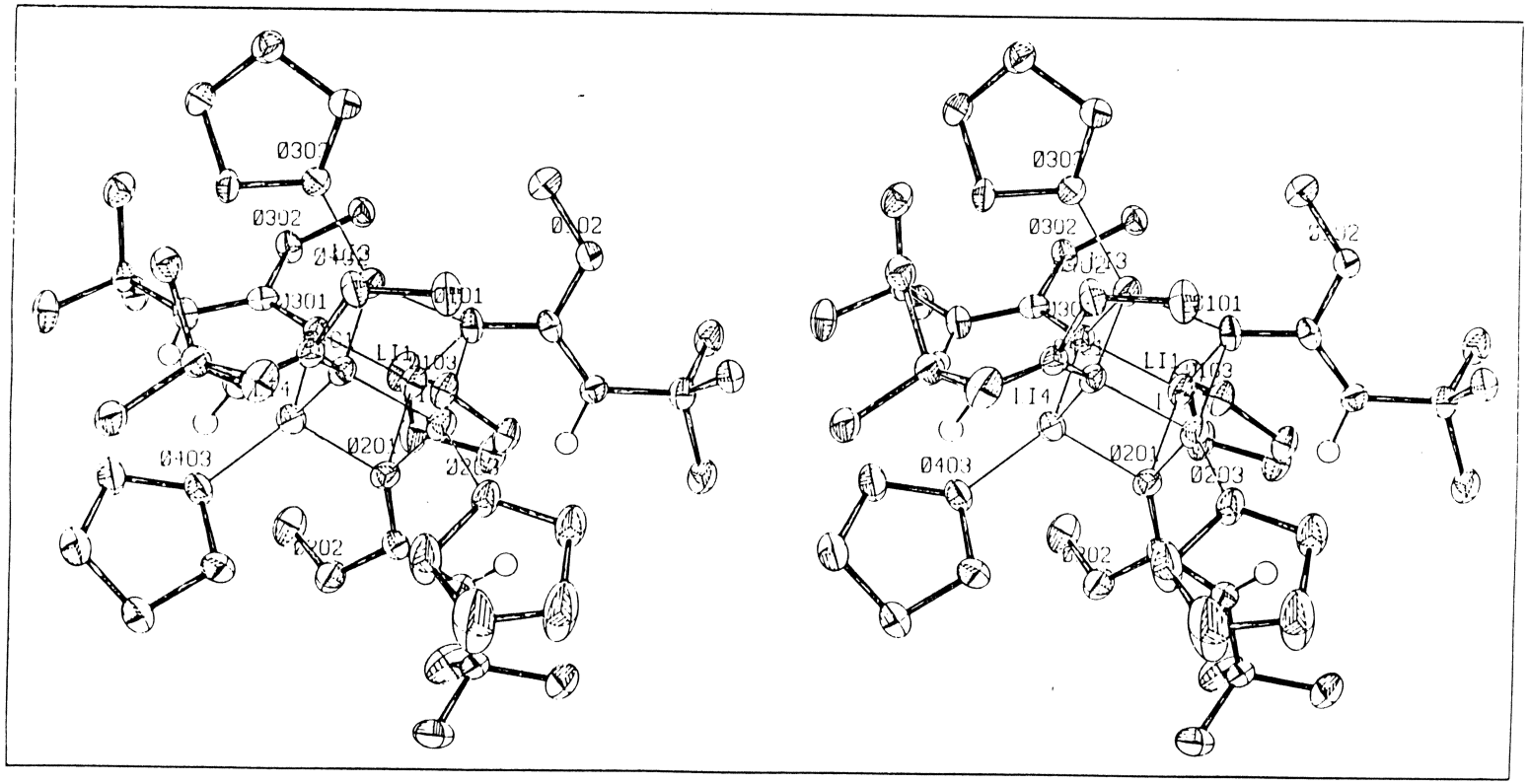


Figure 20

Stereoview in ORTEP representation of the crystal structure of [(lithium 1-methoxy--3.3-dimethyl-1-butenolate)·THF]$_4$. The data set was collected at 98 K. See also Fig. 21.



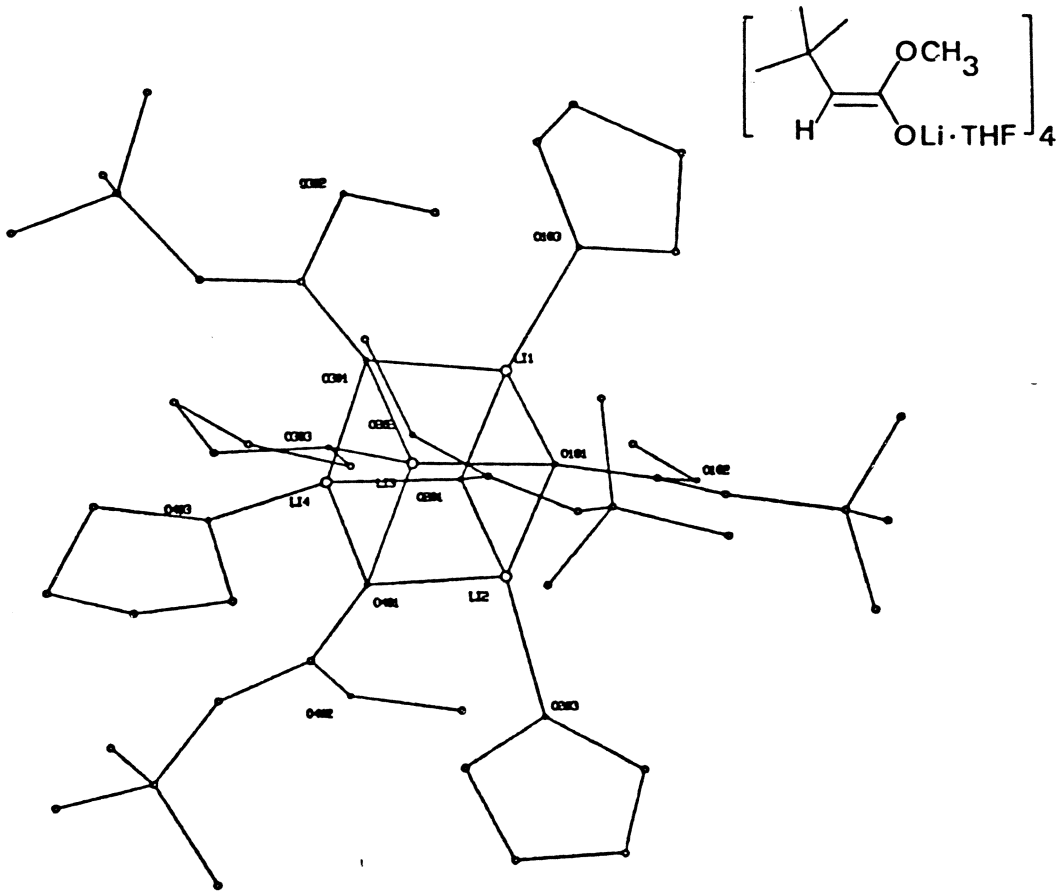


Figure 21

PLUTO plot (without hydrogen atoms) of the cubic tetrameric moiety in the crystal structure of [(lithium Z-1-methoxy-3.3-dimethyl-1--butenolate)·THF]4. See also Fig. 20.

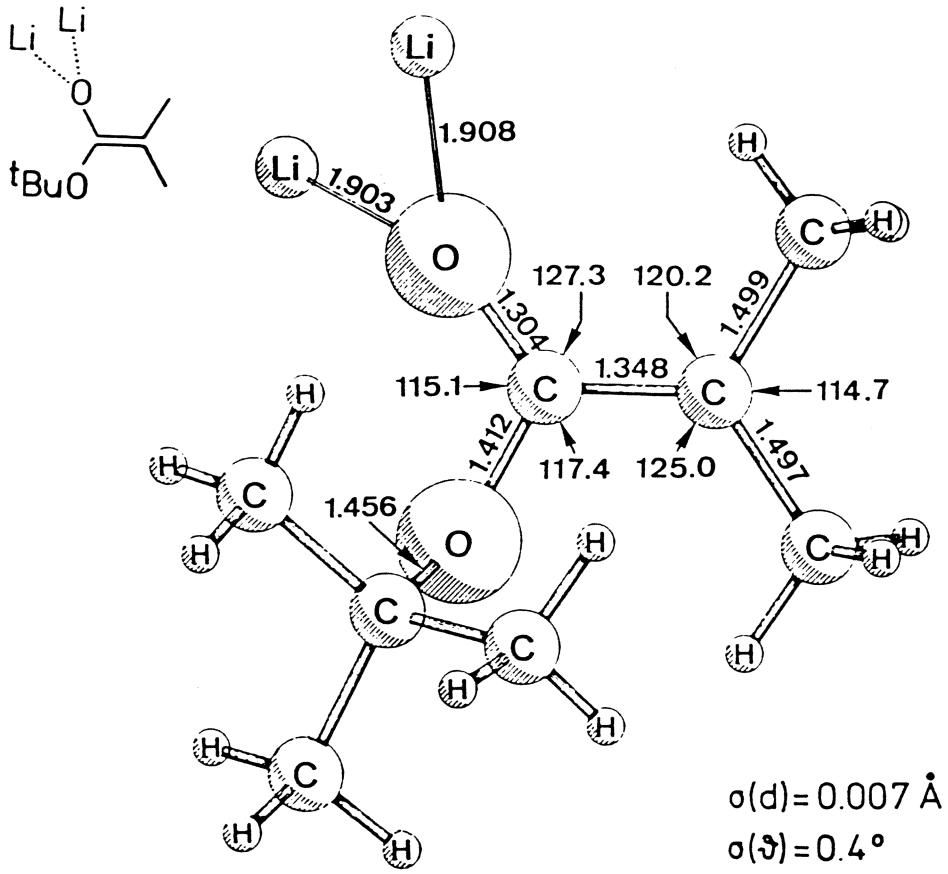
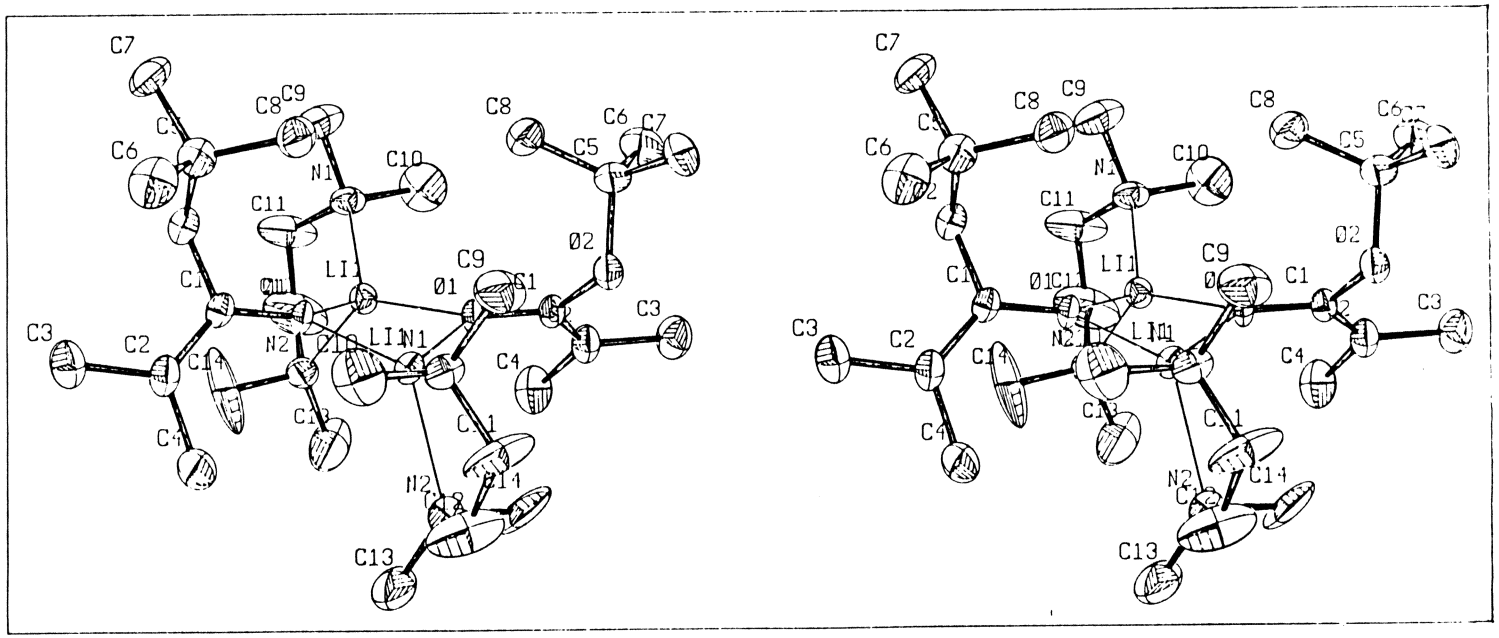


Figure 22

PLUTO plot of the enolate plane of [(lithium 1-t-butoxy-2-methyl-1--propenolate)·TMEDA]$_2$ (see also Fig. 23). The angles and bond lengths are taken from the x-ray crystal structure analysis. Note the dihedral angle C=C-O-C of 103°, the three different C,O bond lengths and the geometry of the olefinic carbon atoms. Compare with Fig. 18.

Figure 23

ORTEP stereoview of the dimeric moiety in the crystal structure of [(lithium 1-t-butoxy-2-methyl--propenolate) TMEDA]$_2$. The enolate was generated from the t-butyl ester of isobutyric acid. The data used for the crystal structure analysis were collected at 133 K. See also Fig. 22.



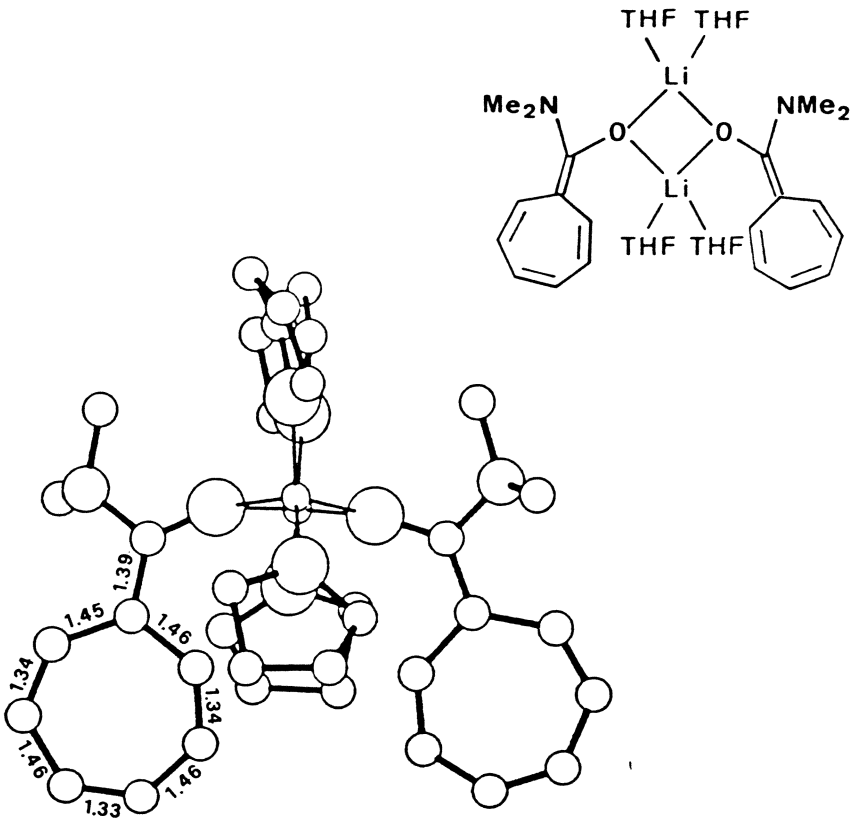


Figure 24

Dimeric unit of the x-ray crystal structure of the lithium enolate of 2.4.6-cycloheptatriene carboxylic acid N.N-dimethylamide. Note the cisoid arrangement of the two enolate moieties on the four membered ring containing two lithium and two oxygen atoms and the C_2-axis through the center of this ring. See also Fig. 25 and 26. The double bond/single bond alternation can be clearly recognized in the seven-membered ring on the left hand side.

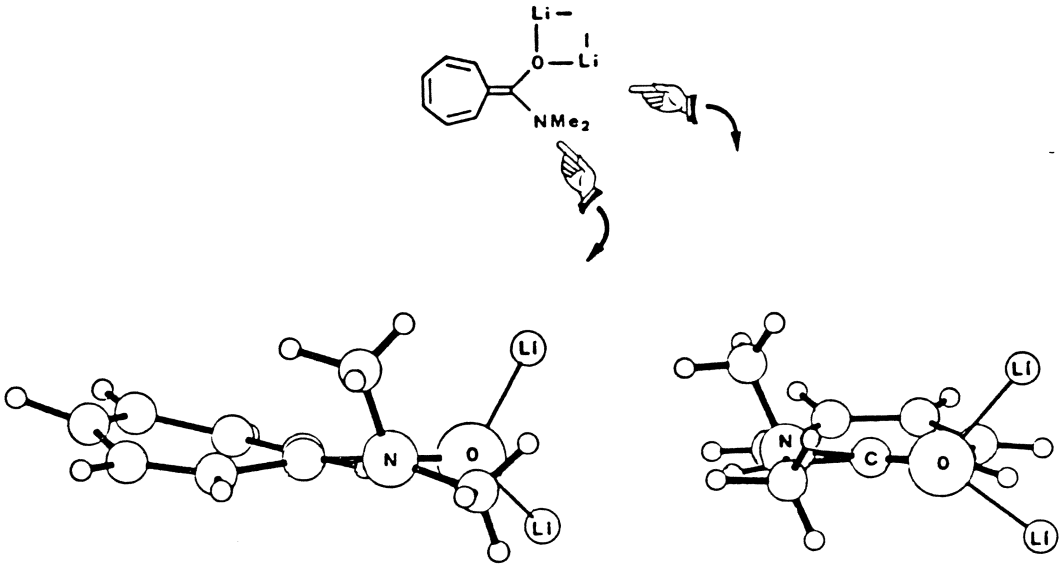
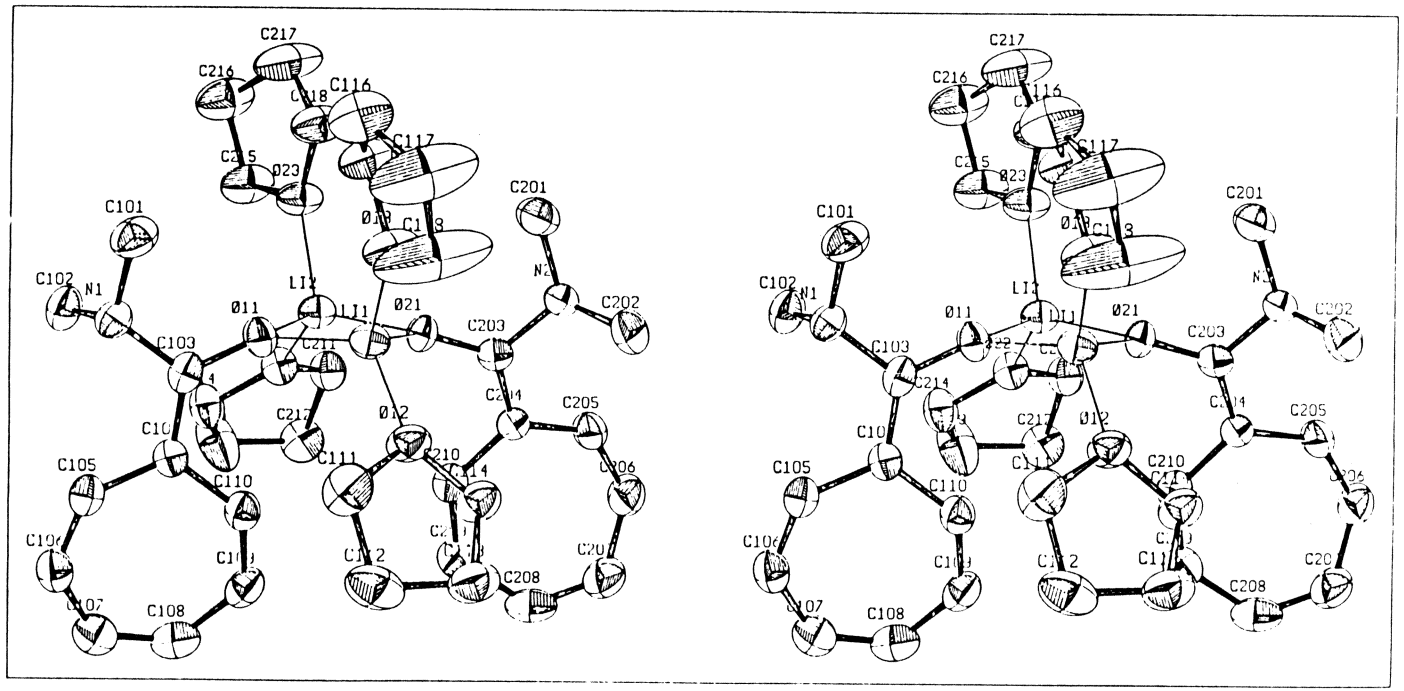


Figure 25

Two Newman projections in the structure of the amide enolate (see also Fig. 24 and 26) derived from cycloheptatriene carboxylic acid. Note the almost planar geometry of the seven-membered ring and the strongly pyramidalized nitrogen (pyramidalization [43] ca. 0.36 Å) with one of the methyl groups eclipsed with the C-OLi bond.

Figure 26

ORTEP stereoview from the crystal structure of $\{$[lithium-8-(N,N-dimethylamino)-heptafulven-8-olat] 2 THF$\}_2$. The data set was collected at 158 K.



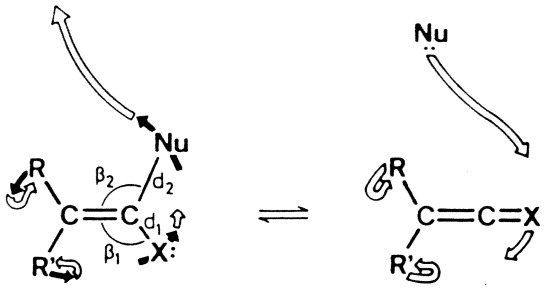
an aldol condensation between two pinacolone molecules took place, and the resulting α.β-unsaturated ketone was deprotonated to the di-(t-butyl)-substituted dienolate. The following features of the structure are remarkable: (i) In contrast to the simple lithium enolates (Figure 12 and 13) the dienolate crystallizes in a dimeric structure. (ii) Only one solvent molecule is present per lithium. (iii) The fourth ligand site of lithium is occupied by the terminal carbon atom of the dienolate π-system (Li, C bond length 2.5 Å vs. the normal ca. 2.25 Å). (iv) The Li-O=C bond angle is ca. 155°, the LiOCN dihedral angles in the two moieties are ca. 0° and ca. 40°. A detailed discussion will be given elsewhere [40].

Most recently, we have been able to grow suitable single crystals of the more labile ester enolates [30] [33] [37] and to determine their structures. This was an important task, since the configuration of E/Z-isomeric ester enolates has so far been deduced only indirectly by Ireland's enolate Claisen rearrangement, see Figure 16 [41]. The mode of preparation, the crystallization, the results of quenching with chlorosilanes, and the x-ray crystal structure analyses of the lithium enolates of t-butyl propionate [33] (Figure 17 - 19) and of the isomeric methyl 3.3-dimethyl-butanoate [30] [37] (Figure 20 and 21) fully confirm the original assignment. The structures of the lithium enolates of an α-branched carboxylic ester [33] (Figure 22 and 23) and of an N.N-dimethyl carboxamide [33] and [42] (Figure 24 -26) could also be determined. In three of the structures, the lithium enolates are dimeric, with tetramethylethylenediamine (TMEDA) or two THF ligands on each lithium, in the fourth, a cubic tetramer is present. The three dimers look like cubic tetramers cut in halves, with the enolate moieties on the same side of the central Li_2O_2 four-membered rings, and with C_2-axes running through the centers of the rings.

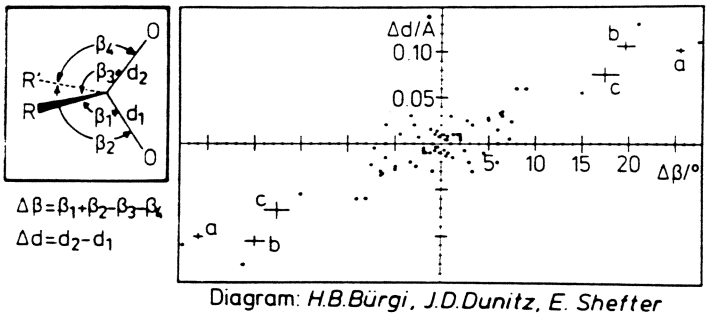
C) The Structural Features of Lithium Ester Enolates - A Trajectory of Nucleophilic Addition to Ketenes?

Although a detailed evaluation must be reserved for a forthcoming full paper [40], a few salient features of these structures, apart from the dimeric and tetrameric aggregation, will be briefly discussed.

Inspection of the structures of the three ester enolates reveals immediately that the methyl and t-butyl groups on oxygen do not lie in the olefinic plane, but are rotated away from the lithiated oxygens with dihedral angles C=C-O-R of 103 - 168°. In esters, the R-group on oxygen is held in a syn-coplanar position with respect to the carbonyl oxygen [44]. Similarly, while the nitrogen of carboxylic acid amides (and peptides !) is planar [45], the dimethylamino-group in the amide enolate is strongly pyramidalized, as in enamines [43] and in an N,O-acetal of a ketene [46a]. These changes in geometry could be described as arising from a change of hybridization of the heteroatom from sp^2 to sp^3.



−X	−O⁻	−OR''	−O⁻	−NR''₂	−NR''₂
−Nu	−OR''	−OR''	−NR''₂	−OR''	−Cl
[Ref.]	[40]	[46e]	[42]	[46a]	[46f]



$\Delta\beta = \beta_1 + \beta_2 - \beta_3 - \beta_4$
$\Delta d = d_2 - d_1$

	a	b	c
R	Me	Me	^{t}Bu
R'	H	Me	H
X	O⁻	O⁻	O⁻
Nu	O^{t}Bu	O^{t}Bu	OMe

$\Delta\beta = 2(\beta_1 - \beta_2)$
$\Delta d = d_2 - d_1$

Diagram: *H.B.Bürgi, J.D.Dunitz, E. Shefter*
Acta Cryst. B30, 1517 (1974)

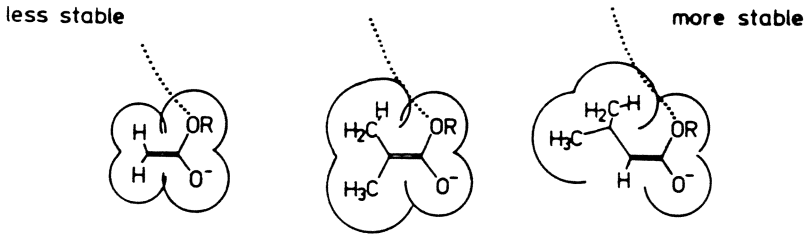


Figure 27

Explanation and consequences of the molecular geometries of the ester enolates, for a discussion see the accompanying text.

Another remarkable change in geometry of the groups attached to the C=C double bond of the enolates is the systematic deviation from the expected angles around the sp^2-hybridized carbons, see Figure 27. In the ester enolates, the C=C-OLi angle β_1 is larger than the C=C-OR angle β_2. At the same time, the C-OLi bond length d_1 is considerably smaller than the C-OR bond length d_2 (1.304 - 1.319 vs. 1.379 - 1.412 Å). These differences may be interpreted as representing the incipient stages of the elimination of the RO^--group with formation of a ketenic C=O bond [46b]. This interpretation follows along the line of similar observations on sp^3-centers, which were related to the Bürgi-Dunitz trajectory for addition of nucleophiles to carbonyl bonds or for the corresponding elimination from tetragonal carbons [46c] [46d], see center of Figure 27 and the reference cited therein. As is indicated by the black arrows in the top left formula of Figure 27, the displacement of the groups R and R' on the β- carbon follows the displacement of the groups on the oxygen-substituted carbon, as if to give way to the leaving group Nu on its suggested trajectory of elimination (see the non-solid arrows). Similar bond angle and bond length displacements have been observed in α- substituted enamines (see the table in the upper part of Figure 27). The degree of the discussed displacements in the ester enolates correlates with their relative stability, see bottom line of Figure 27.

D) Lithium Enolate Aggregates - Higher Organization with Characteristic Behaviour

The results described in the two previous chapters leave no doubt that lithium enolates crystallize as dimeric or tetrameric aggregates with characteristic structures. Most of the puzzling, non-stoichiometric effects mentioned in the first chapter above, would be compatible with a participation of these aggregates in the product determining steps. For a definitive proof of such a participation, it is necessary to show that the aggregates are also present in solution, and, furthermore, that they can react with electrophiles as entities of their own, rather than dissociating to monomers prior to reaction.

With lithium derivatives of hydrocarbons, kinetic measurements have revealed cases of both types [3]: (a) a broken kinetic order of 0.5, 0.25 or 0.17 indicates that a dimer, tetramer and hexamer, respectively, dissociates to give the product-forming monomeric species; (b) if the aggregate itself reacts, the kinetic equation is first order in RLi concentration - just as if the reagent were monomeric; a classical investigation about such a case is Bartlett's kinetic measurement of the ethylenation of secondary and tertiary alkyllithium derivatives [47]. The presence of aggregates of organolithium derivatives in solution was recently confirmed by ^{13}C-NMR spectroscopy with ^6Li- and ^{13}C-labelled samples [48], see for instance the spectra in Figure 28 [49].

NMR-relaxation time measurements and kinetic measurements of reactions with electrophiles by Jackman and his group [50] have shown that lithium enolates and phenolates are present in solution and can react as dimeric or tetrameric aggregates.

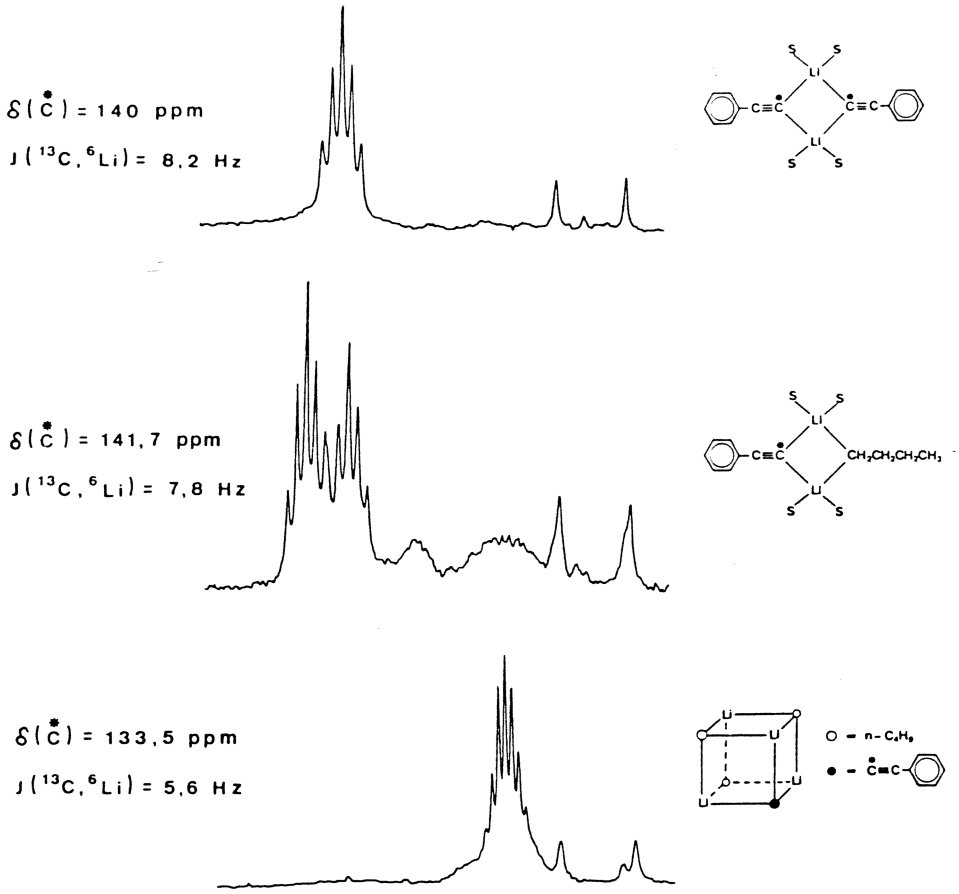
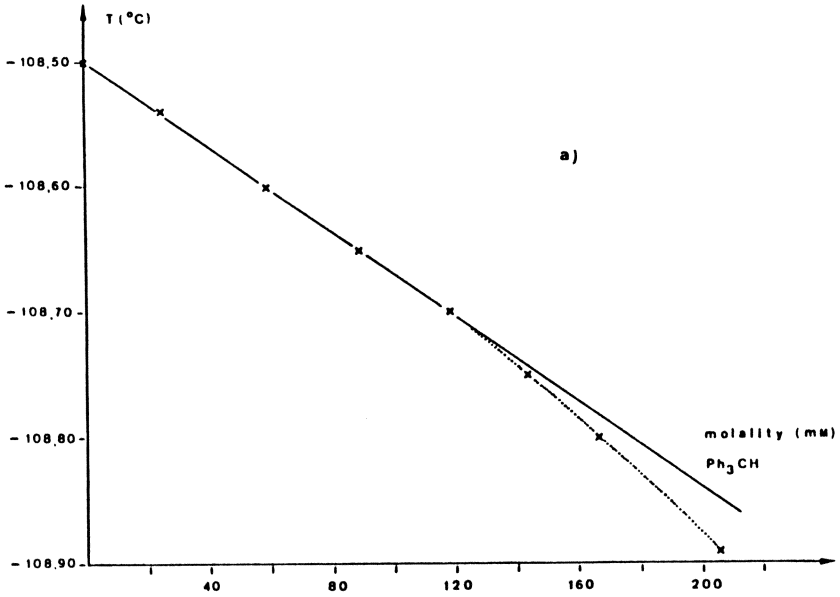


Figure 28

*^{13}C-NMR spectra of ^{13}C-labelled (*C) ^{6}Li-phenylacetylide (from ref. [49]) in THF solution at temperatures below -95°C. The quintuplet Li,C coupling proves the dimeric structure. Addition of [^{6}Li]-butyllithium leads to a mixed dimer with different chemical shift of the acetylenic carbon, and, with a large excess, to a tetramer, the structure of which is assigned from the septuplet coupling of the carbon signal by three ^{6}Li neighbors.*



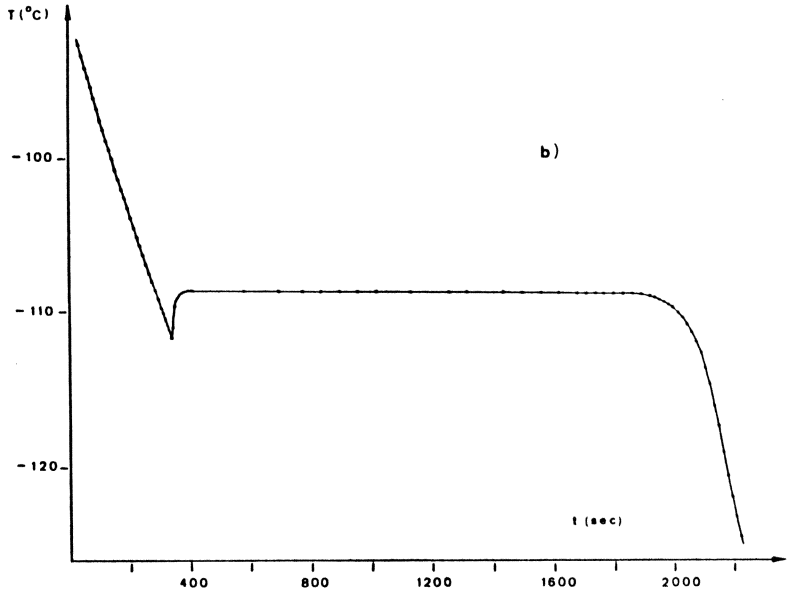
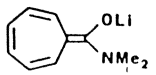
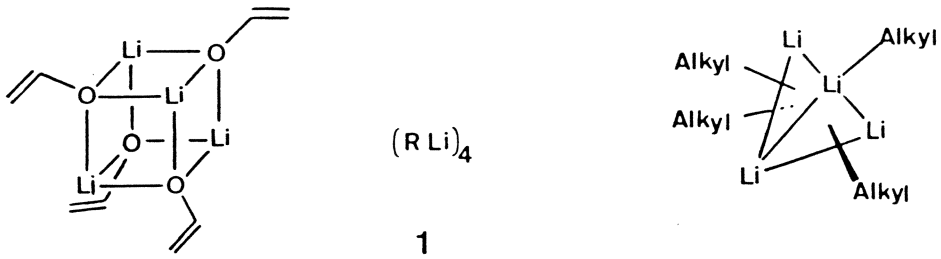


Figure 29

Molecular weight determination of organolithium compounds by cryoscopy in THF. - (a) Calibration curve with melting points of THF solutions of triphenylmethane. (b) Cryometric curve obtained with a 0.0973 - molal (calc.) THF solution of LDA (W. Bauer, unpubl. results, ETH Zürich, 1983).

example	$c_{calc.}$ (mM)	$c_{obs.}$ (mM)	degree of aggregation	% dimer
$(i\text{-}Pr)_2NLi$	97	59	1.64	65
	74	59	1.25	25



$(RLi)_4$

1

$$1 + R'CHO \longrightarrow [(RLi)_3(R'RCH-OLi)] \quad 2$$

$$2 + R'CHO \longrightarrow [(RLi)_2(R'RCH-OLi)_2] \quad 3$$

$$3 + R'CHO \longrightarrow [(RLi)(R'RCH-OLi)_3] \quad 4$$

$$4 + R'CHO \longrightarrow (R'RCH-OLi)_4$$

Figure 30

Four different reagents 1 - 4 can be involved in the course of reaction of a tetrameric aggregate 1 with an electrophile to give a tetrameric product aggregate.

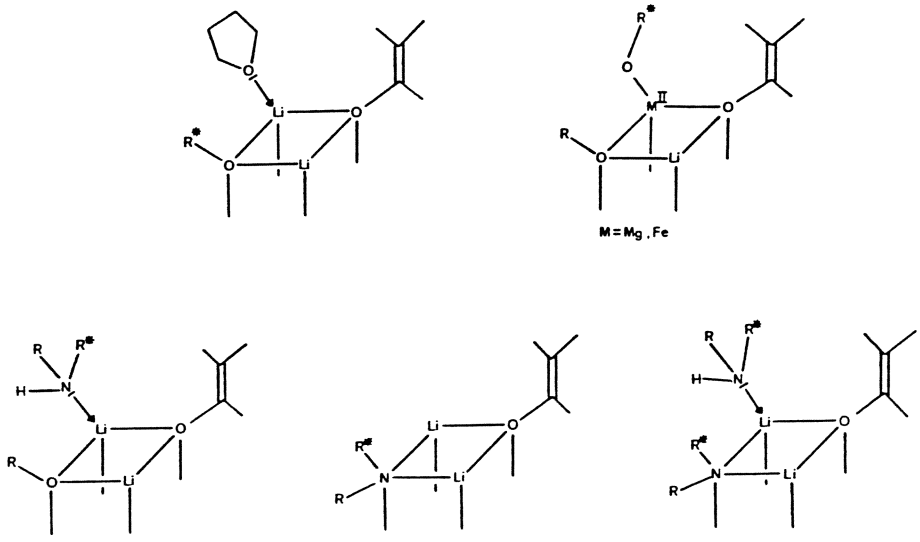


Figure 31

*Addition of chiral alkoxides R*OLi or amides R_2*NLi to achiral enolates should furnish mixed aggregates, the reacting lithium enolates of which should exhibit enantioselectivity in additions to 2 D-chiral trigonal centers.*

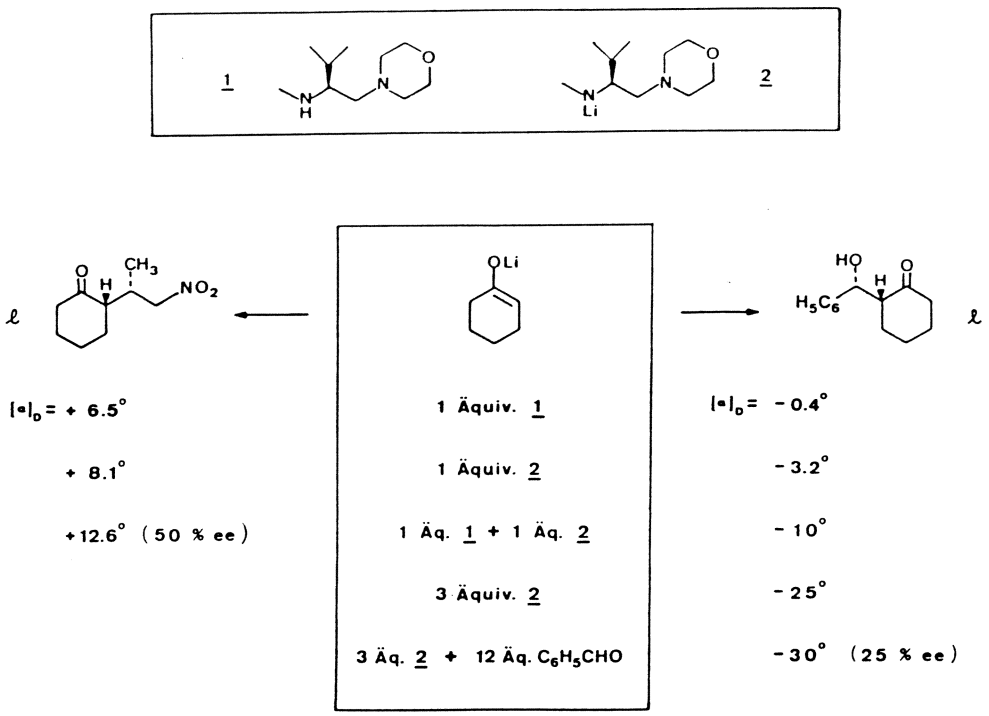


Figure 32

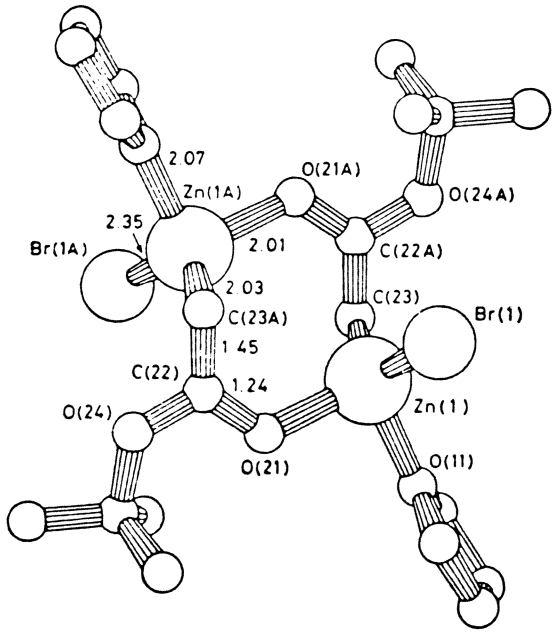
Asymmetric additions of lithium cyclohexenolate to benzaldehyde and to nitropropene under the influence of an added chiral lithium amide.

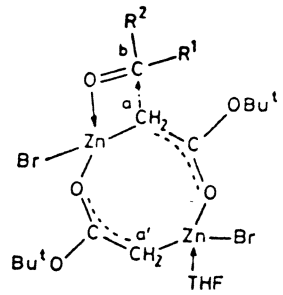
Alkoholat-Bündel („Aggregate") und ihre Rolle bei Alkin-bildenden Eliminierungsreaktionen[**]

Alcoholate Clusters ("Aggregates") and Their Role in Alkyne-Forming Elimination Reactions[**]

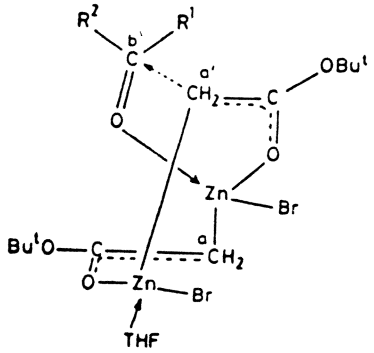
Figure 33

Clusters of potassium alkoxides [32] are shown by kinetic measurements to act as reagents in HCl elimination. Taken from ref. [53].





(A)



(B)

Figure 34

Crystal structure of the Reformatzky-reagent from t-butyl bromoacetate and possible involvement of the dimeric aggregate in carbonyl additions, taken from ref. [54].

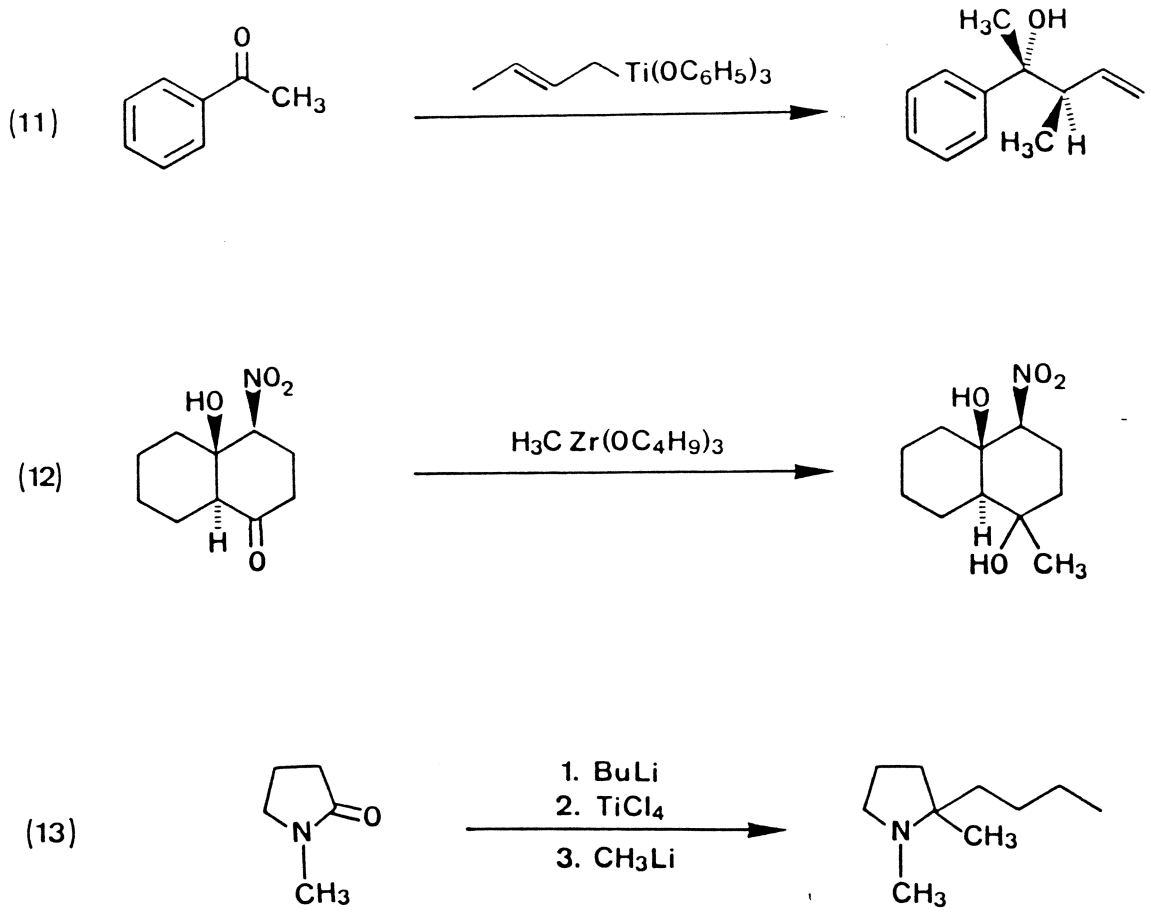


Figure 35

Three examples of selective additions of Ti- and Zr-reagents to carbonyl groups [55b][55c] and [55d]. These reagents do not seem to form aggregates as rate determining species.

On the other hand, our molecular weight determinations from freezing point depression of THF solutions (-108.50 to -108.60° C) have revealed that at low concentrations (0.07 M), the above mentioned lithium enolate of an amide which is dimeric in the crystal (Figure 24 - 26) is mainly monomeric in solution, see Figure 29.

We have recently used the most sensitive probe to prove that aggregates are the reacting species in aldol additions and in Michael-additions of lithium enolates: the asymmetric induction by chiral lithium alkoxides and amides upon the reaction of achiral lithium enolates. Such experiments are suggested by the stepwise change of the structure and of the nature of the groups gathered in aggregates in the course of a reaction, see Figure 30 and 31. As a chiral auxiliary we used the ethylenediamine derived from valine which is shown in Figure 32. When mixtures of lithium cyclohexenolate and the chiral lithium amide were quenched with benzaldehyde, the (-)-form of the l-aldol was formed preferentially, and, not surprizingly, the effect increased (by an order of magnitude) upon changing the ratio of amide to enolate from 1:1 to 3:1 [12]. Similar results were obtained in the addition to nitropropene; the nitroketone product was formed with up to 50 % enantiomeric excess [12] [51].

These experiments show, that the components of mixed aggregates delicately influence each other's reactivity. The message, I want to deliver, is that organometallic reagents are not just more or less reactive in a certain type of reaction, depending upon their degree of aggregation, but that aggregates can bring about types of conversions which the corresponding monomers can not possibly bring about. The very nature of aggregation conveys a characteristic quality to the reagent.

In Figure 33 and 34 two examples are quoted, in which reactions of derivatives of metals other than lithium are subject to similar effects as those found with lithium and magnesium compounds [52].

The recently introduced [55] organo-titanium and -zirconium reagents which exhibit spectacular selectivities in diastereoselective [Figure 35, equation (11)] and functional group selective [equations (12) and (13)] carbonyl additions do probably not form aggregates, but can be influenced by the addition of alkoxides with formation of ate-complexes [55d].

E) Chiral Enolates, the Pool of Chiral Building Blocks, and the Self-Reproduction of Chirality

There are three fundamentally different methods of preparing enantiomerically pure products (EPC-syntheses) [56]: A) the classical resolution (with recycling!), B) the stoichiometric or catalytic asymmetric synthesis, and C) the incorporation of natural products (pool of chiral building blocks). We have been propagating for years [56] the last mentioned approach as being the most economical one in many situations. Thus, starting materials such a polyhydroxybutyrate (see Figure 36), which is available in kg amounts, are hard to beat by products which have to be made by asymmetric synthesis,

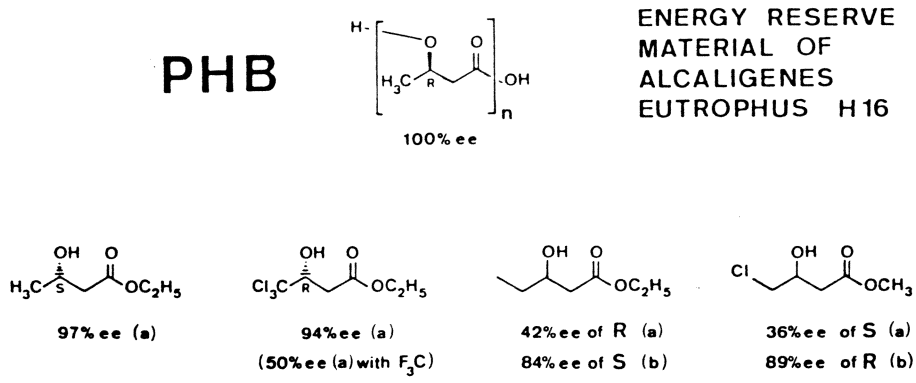


Figure 36

Readily available ß-hydroxy-carboxylic esters as starting materials for EPC-syntheses [56][57].

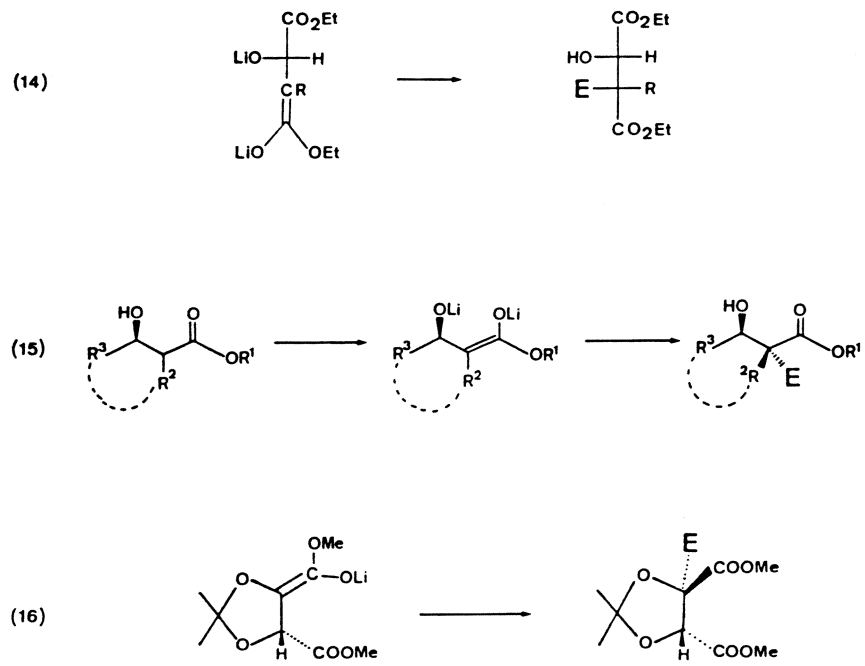


Figure 37

Alkylation of alkoxide-enolates from malic acid and other ß-hydroxy-carboxylic acid esters [58]. *Preparation of enantiomerically pure derivatives with quaternary centers through the enolate of tartaric ester acetonide* [56][59].

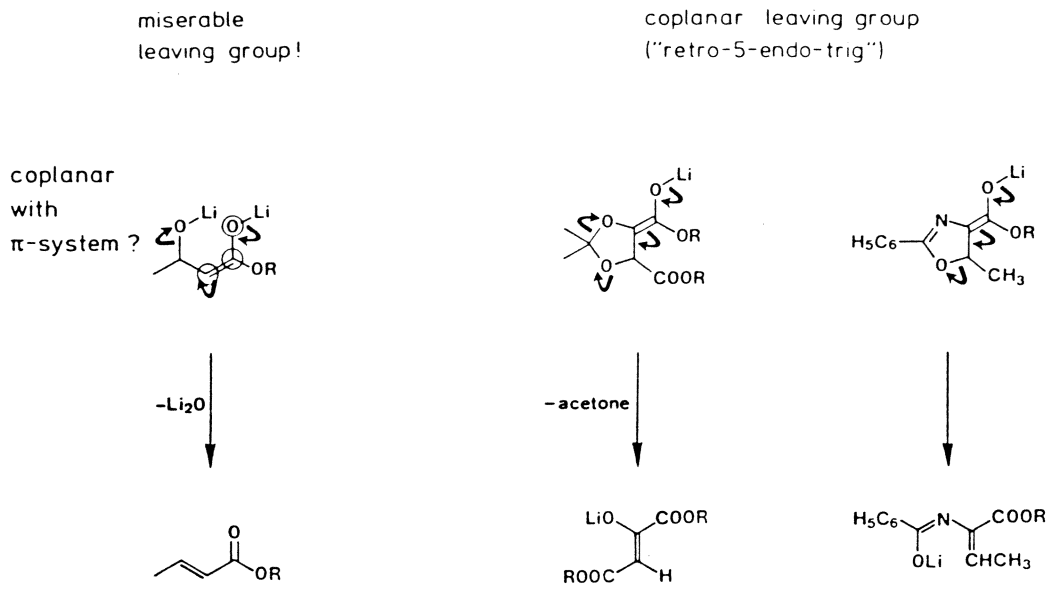


Figure 38

Prevented elimination from β-hydroxy-carboxylic acid-derived enolates.

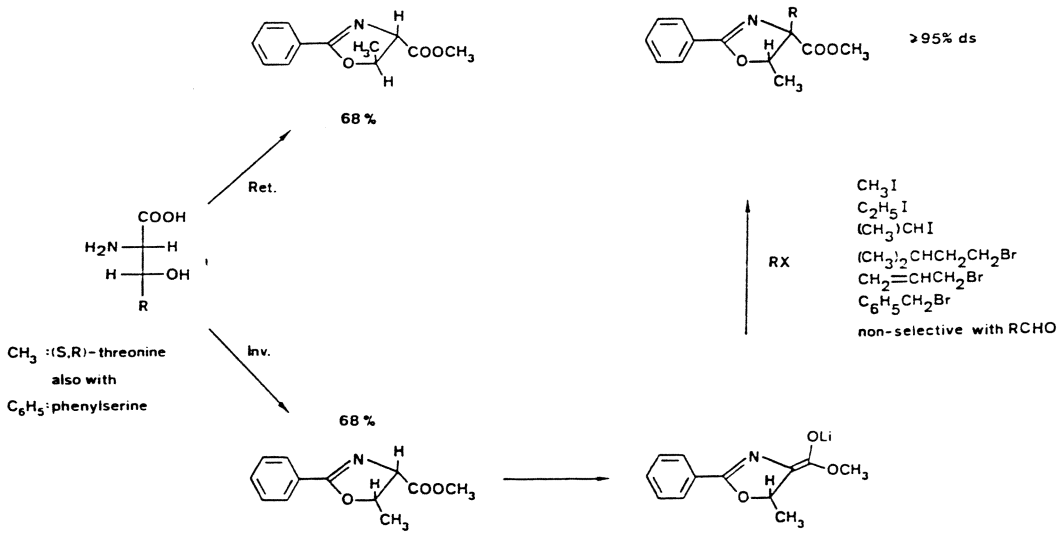


Figure 39

Threonine can be α-alkylated in both enantiomeric series: cyclization to the benzoic acid derivative is possible with retention or with inversion to give the diastereomeric oxazolines which in turn furnish enantiomeric enolates [60].

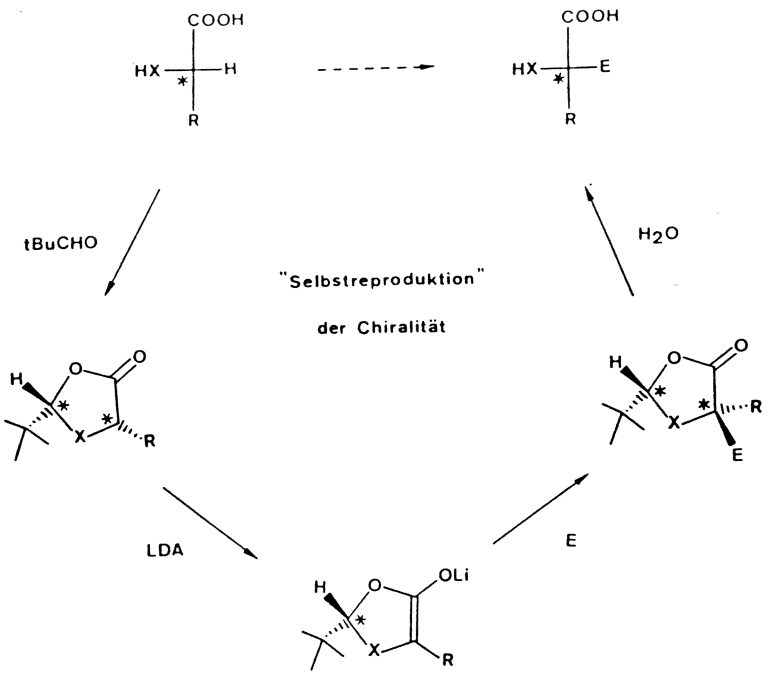


Figure 40

The principle of self-reproduction of chirality for α-alkylation of α-(XH)--substituted carboxylic acids. The case shown furnishes α-branched acids with retention of configuration in the electrophilic substitution of the hydrogen α to carbonyl and heteroatom.

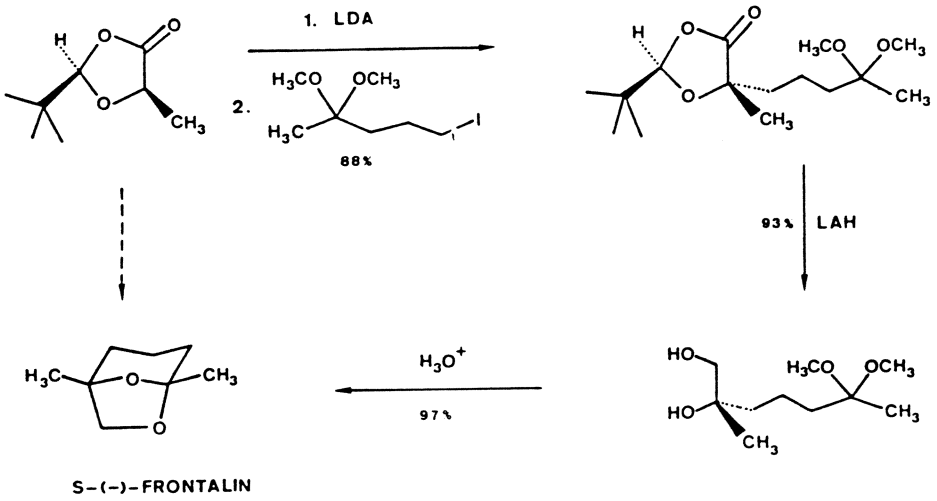


Figure 41

Frontaline synthesis by alkylation of the enolate derived from lactic acid with 4.4-dimethoxy-1-iodo-pentane (from commercial 5-chloro-2-pentanone). Only one diastereomeric alkylation product could be detected by NMR spectroscopy. Note the overall yield of almost 80 % [63].

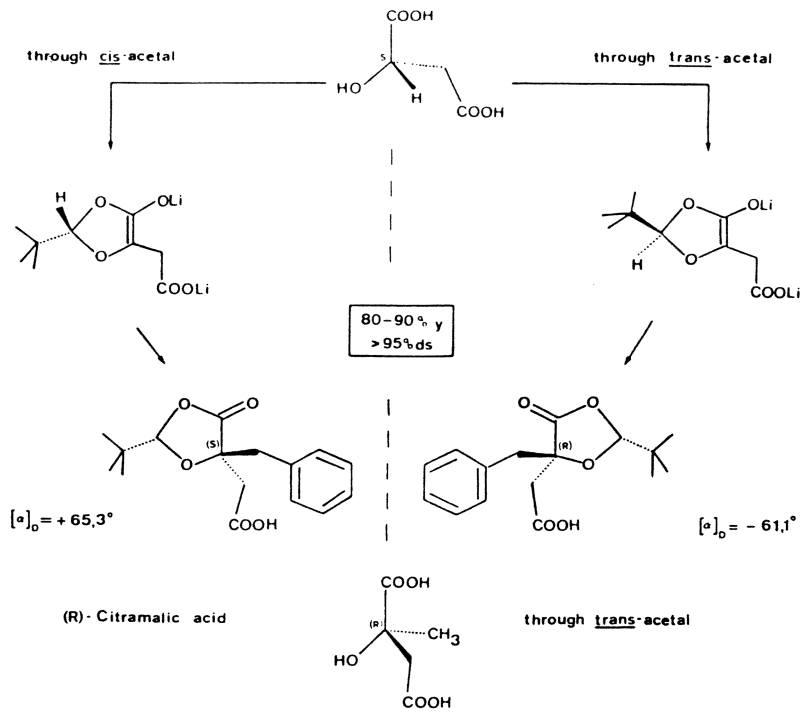


Figure 42

Preparation of acetals of both enantiomeric α-benzylated malic acids from the natural (S)-malic acid and correlation by methylation of malic acid to citramalic acid [64].

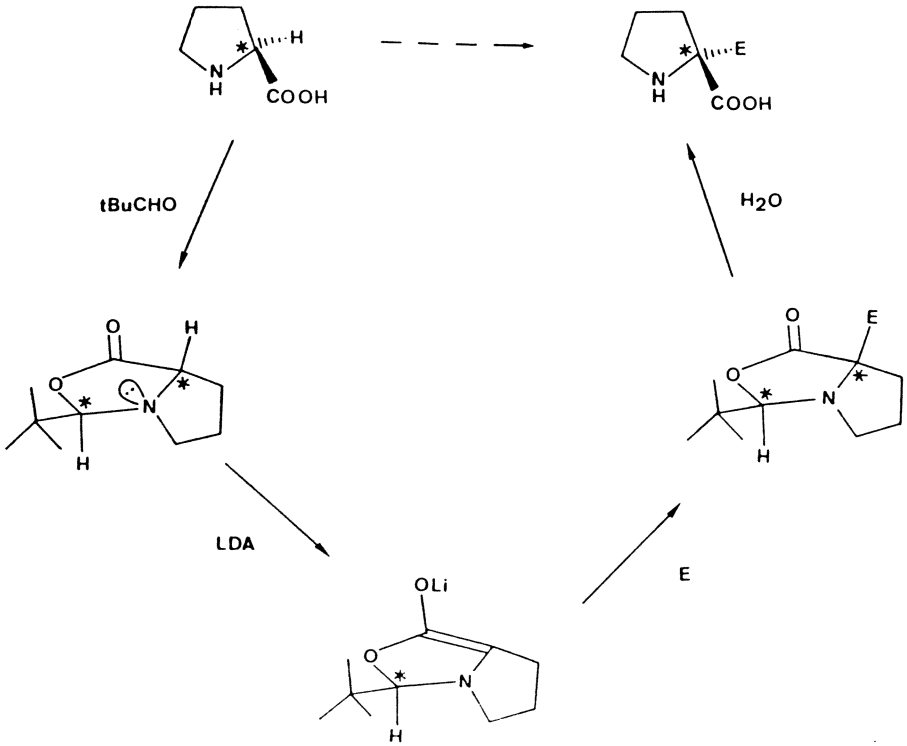


Figure 43

Alkylation of proline with self-reproduction of chirality, cf. Fig. 40.

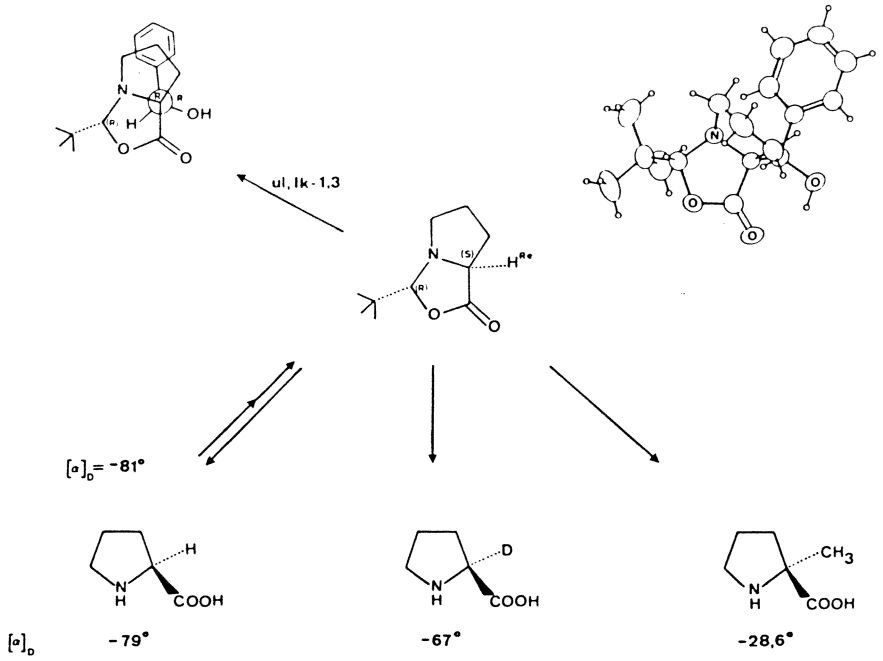


Figure 44

Configurational assignment of the products from the proline-derived bicyclic N,O-acetal.

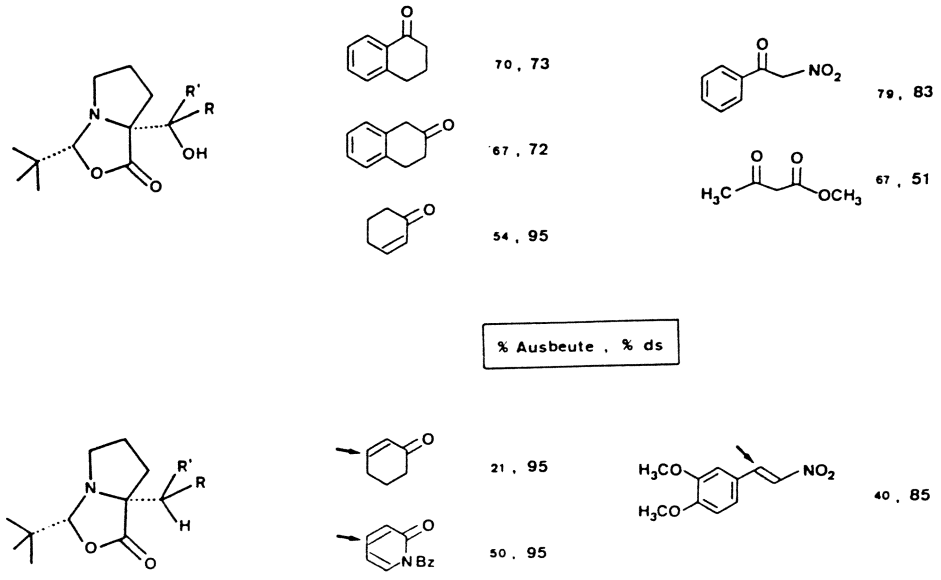


Figure 45

Chemical yields of addition (smaller numbers) and percentages of the main diastereomers formed (% ds, lager numbers) in reactions of the proline derived enolate (see Fig. 43) with readily enolized ketones, with enones, and with a nitroolefin. - In each case, only two of the four possible diastereomers are formed.

with recycling of the chiral auxiliary. Sometimes, nature's reagents will also act efficiently on unnatural substrates as demonstrated by the microbial reductions of acetoacetates to the hydroxyesters shown in Figure 36.

For further elaboration, such esters can be alkylated highly diastereoselectively through the alkoxide-enolates shown in equation (14) and (15) of Figure 37. Tartaric acid, which is at the same time an α- and β-hydroxyacid, can be branched through the enolate of its acetonide ester, see equation (16). In these cases, the β-leaving group, which is bonded to the only asymmetric carbon atom of the chiral enolate, does not eliminate - with loss of chirality - because it is as miserable a leaving group as an alkoxide and/or because it is located in the plane of the enolate double bond system, see Figure 38. We have used the same trick to also α-alkylate threonine, see the third example in Figure 38 and Figure 39 [60].

The number of available chiral building blocks has now been greatly increased by the development in our laboratory of a general method, by which α-hydroxy-, α-mercapto-, and α-aminoacids can be α-alkylated without racemization [61] [62] [63] [64] [65] and [66]. As shown in Figure 40, the trick is to prepare a privalaldehyde acetal of the α-heterosubstituted carboxylic acid diastereoselectively. In the second step of the sequence, this furnishes a chiral, non-racemic enolate, the reactions of which are strongly directed by the t-butyl group with "regeneration" of the second asymmetric carbon atom. The concluding step is the hydrolysis of the acetal to yield the desired product. Thus, chirality has reproduced itself on the α-carbon atom through the temporary, auxiliary center of chirality at the acetal carbon.

It turns out that the thermodynamically more stable isomers are always the cis-1.3-disubstituted heterocyclic five-membered rings, see the (-)-frontaline synthesis from R-lactic acid outlined in Figure 41 [63]. If both diastereomeric acetals are accessible from the same precursor, it is possible to generate either one of the two enantiomeric enolates, see the benzylation of malic acid in the 2-position, Figure 42 [64].

Of the common aminoacids, only proline could be subjected to the series of transformations outlined for the hydroxyacids, see Figure 43 [62]. It forms a single stereoisomeric bicyclic derivative with pivalaldehyde. The corresponding enolate combines with electrophiles in the cis-position with respect to the t-butyl-group - otherwise this bulky substituent would be pushed into the endo-position of the bicyclo[3.3.0]octane skeleton. The overall result is again a retention substitution, at the α-carbonyl center of proline, see Figure 44. The enolate of the proline derivative has most unusual properties (see Figure 45): (i) it adds diastereoselectively to aldehydes and even to unsymmetrical ketones with formation of products having three asymmetric carbon atoms; (ii) it undergoes Michael-additions to enones and ω-nitrostyrenes, and (iii) its nucleophilicity dominates so strongly over its basicity that it will even add to β-ketoesters and to α-nitroketones ! Another fascinating system is the thia-analogue

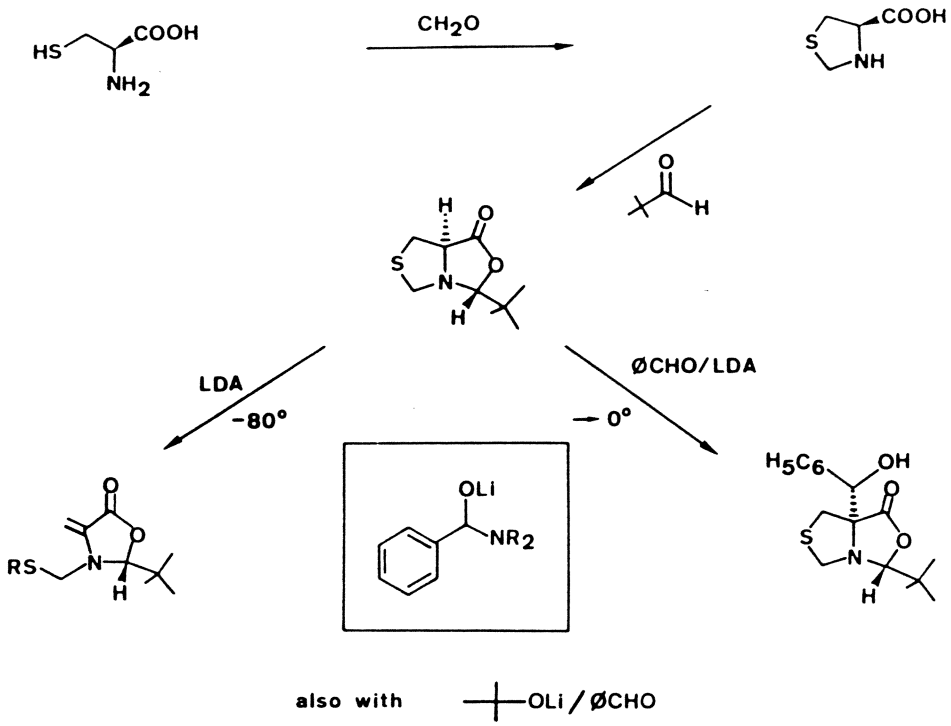


Figure 46

In situ hydroxybenzylation of a cysteine derivative [66], in analogy with the proline analogue (Cf. Fig. 43 and 44).

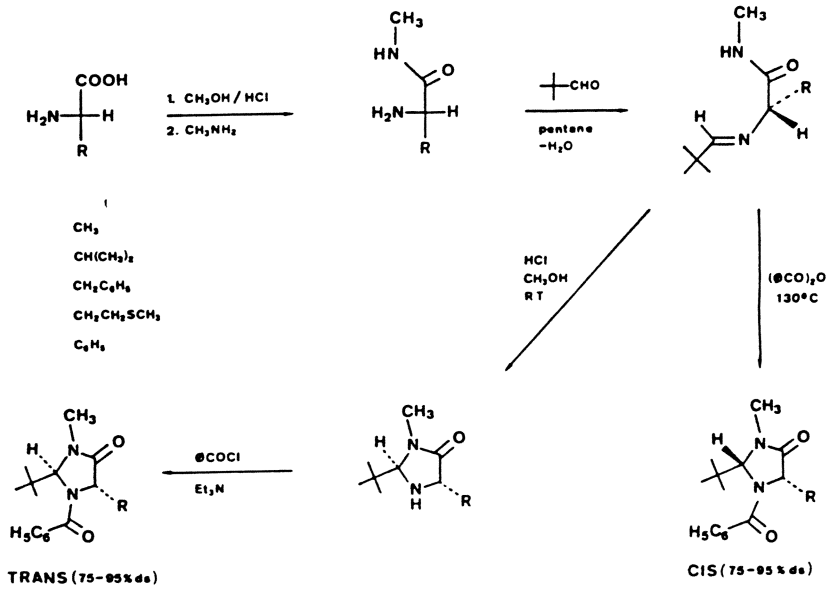


Figure 47

Preparation of diastereomeric 1-benzoyl-2-t-butyl-3-methyl-imidazolidin-4--ones from amino acids. The minor diastereomer and racemized material can be removed by crystallization, so that the cis- or the trans-isomer can be obtained in enantiomerically pure form [68].

AMINOACID	alanine	phenyl-alanine	valine	phenyl-glycine	methionine
R	CH_3	$CH_2C_6H_5$	$CH(CH_3)_2$	C_6H_5	$CH_2CH_2SCH_3$
cis	116 °C -214 (365nm)	193 °C -27	112 °C +22		93 °C +46.8
trans	175 °C +181 (365nm)				129 °C +59
				R^1: COC_6H_5 :	218 °C -89
				R^1: H :	111 °C -69.3

m.p.
$[\alpha]_D^{RT}$

Figure 48

List of some cis- and trans-1-benzoyl-2-t-butyl-3-methyl-imidazolidin-4-ones from aminoacids [68].

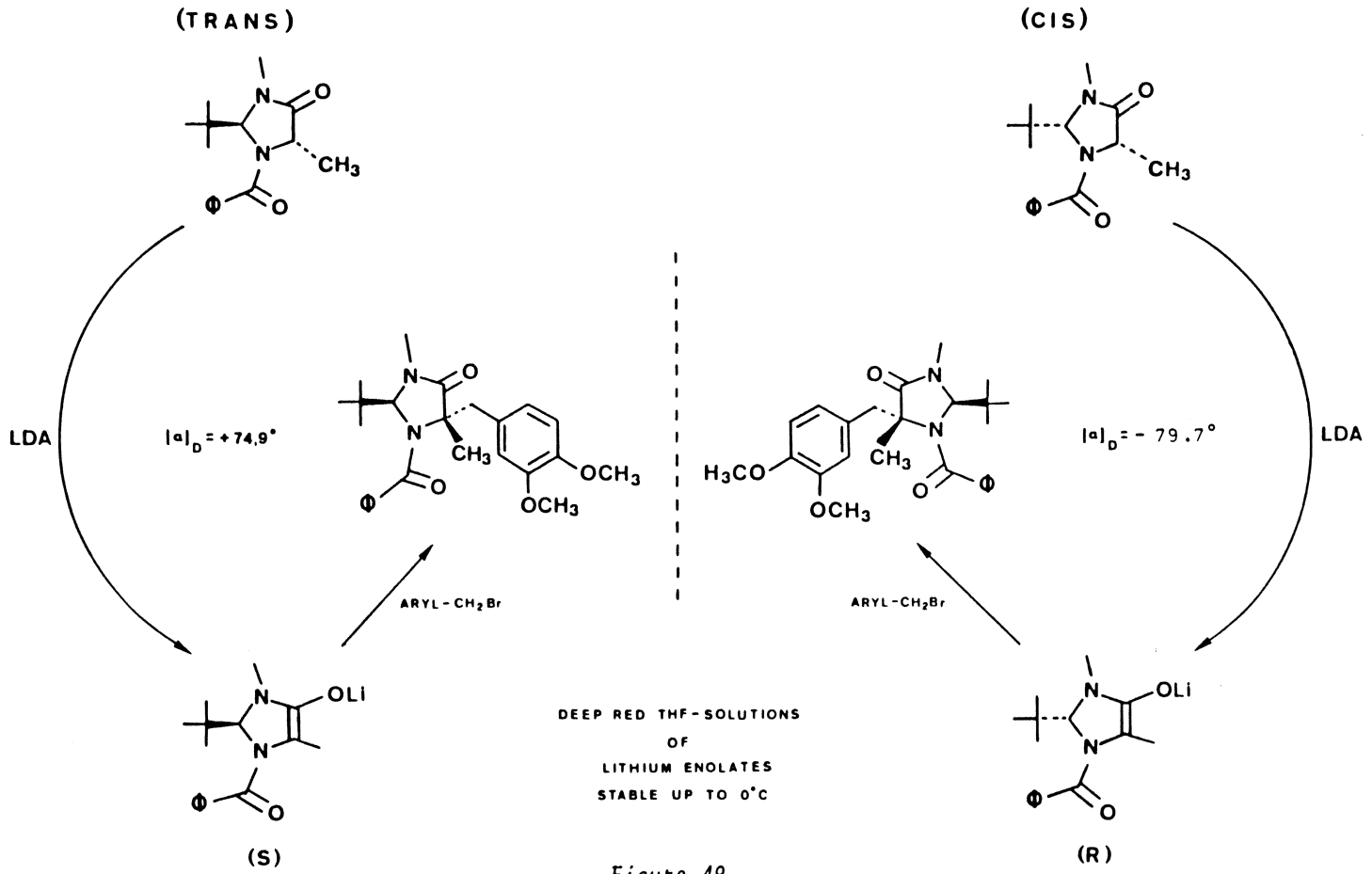


Figure 49

Preparation of a derivative of (S)- and (R)-α-methyl-Dopa from (S)-alanine through the intermediate (2R,5S)-cis- and (2S,5S)-trans-1-benzoyl-2-t-butyl-3.5-dimethyl-imidazolidin-4-ones.

of the proline derivative, see Figure 46 [66]. It is prepared from cystein, which is first condensed with formaldehyde and then with pivalaldehyde. As might have been expected, treatment with base and addition of alkylating reagents produces even at -80° C the product of elimination - with captodative [67] substitution of the double bond. If, however, the bicyclic cystein derivative is combined with the adducts of lithium diisopropyl amide and non-enolizable aldehydes and warmed up, hydroxy-alkylation products such as those shown on the right-hand bottom side of Figure 46 are isolated in good yields after aqueous workup [66].

All simple aminoacids, but also the four- and six-ring analogues of proline [62] could not be converted to pivalaldehyde derivatives suitable for self-reproduction of chirality. After a frustrating year of experimentation, we found, however, that we could prepare t-butyl-substituted imidazolidinones from the simple aminoacids and use them for alkylation with self-reproduction of chirality. As shown in Figure 47, the methyl esters of the aminoacids were first converted to N-methyl-amides which formed Schiff-bases with pivalaldehyde (pentane, azeotropic removal of water). The imines cyclized under two different sets of conditions, leading to either cis- or trans-imidazolidinones. The cis-1-benzoyl-derivatives were formed preferentially under thermodynamic conditions, i.e. by heating the imines at 130° C with benzoic acid anhydride. The trans-isomers were obtained as major products in two steps, by first cyclizing the imine in methanol under acid catalysis to the imidazolidinone unsubstituted in the 1-position, and then by treating the latter with benzoyl chloride/triethylamine. In both cases, the main isomers were present in the crude product mixtures to the extent of 75 - 95 %. Since all derivatives readily crystallize, and have melting points above 100° C, the enantiomerically and diastereomerically pure products could easily be prepared on large scale. For some examples and data see Figure 48 [68].

Deprotonation of the cis/trans-isomeric imidazolidinones produces the enantiomeric enolates (lithioxy-imidazolines). For examples see Figure 49 and 50. We find, that the alkylations of these enolates are so selective that we do not detect signals of a second diastereomer in the ^{1}H-NMR spectra of the crude products [68]. As demonstrated by the results described in Figure 49, both enantiomers of α-branched α- aminoacids are accessible from the same, single enantiomeric starting aminoacid, which may be available for the synthesis. The alkylations of the lithium enolates occur from the face opposite to the t-butyl-group, i.e. with relative topicity lk, see the products formulae in Figure 49. This was proved by ^{1}H-NMR nuclear Overhauser measurements (NOE).

Some examples of cleavages of the heterocyclic systems derived from proline, cysteine, threonine, valine, and methionine are given in the accompanying figures (Figure 51 - 53). The free α- alkylated aminoacids shown were isolated in high yields as nicely crystalline, colorless substances, after purification through an ion-exchange column.

YIELDS OF PURE DIASTEREOMERS FORMED WITH

RELATIVE TOPICITY Ik

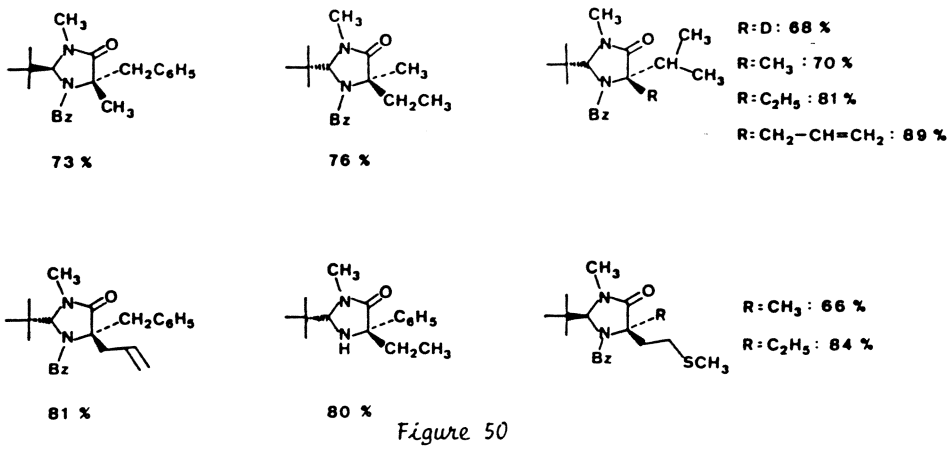


Figure 50

Products of alkylation of aminoacid-derived imidazolidinones. The yields refer to purified products. From top left to bottom right the following precursors were used (I = imidazolidine): trans-I from L-Ala, benzyl bromide; cis-I from L-Ala, iodoethane; cis-I from L-Val, DOAc, iodomethane, iodoethane, allyl bromide; cis-I from L-Phe, allyl bromide; trans-I from D-C-Ph·Gly, iodoethane; trans-I from L-Met, iodomethane, iodoethane.

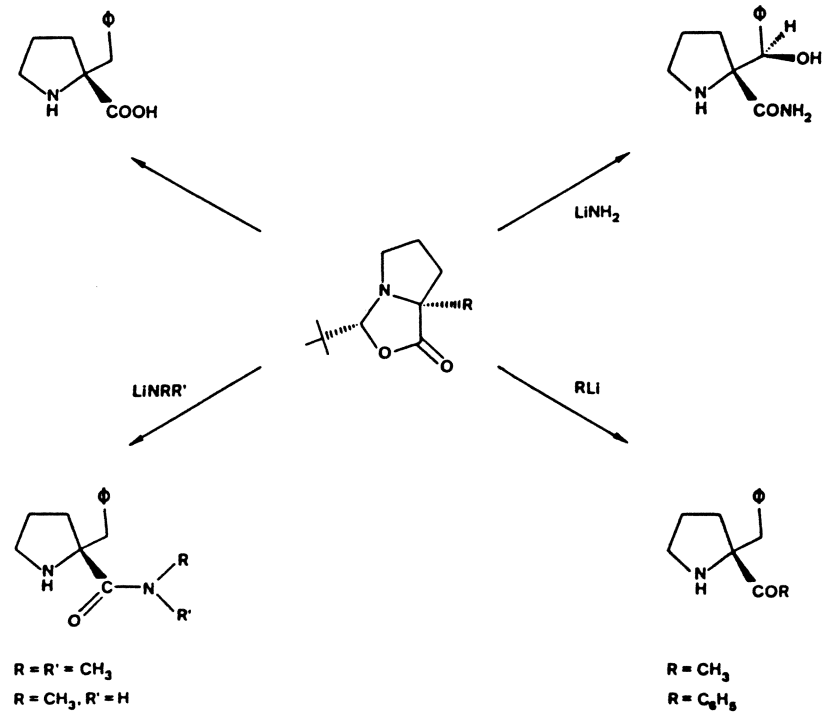


Figure 51

Cleavage of the α-benzylation and α-hydroxybenzylation products of the hetero-bicyclic derivative from proline [62]. See also Fig. 43 - 45.

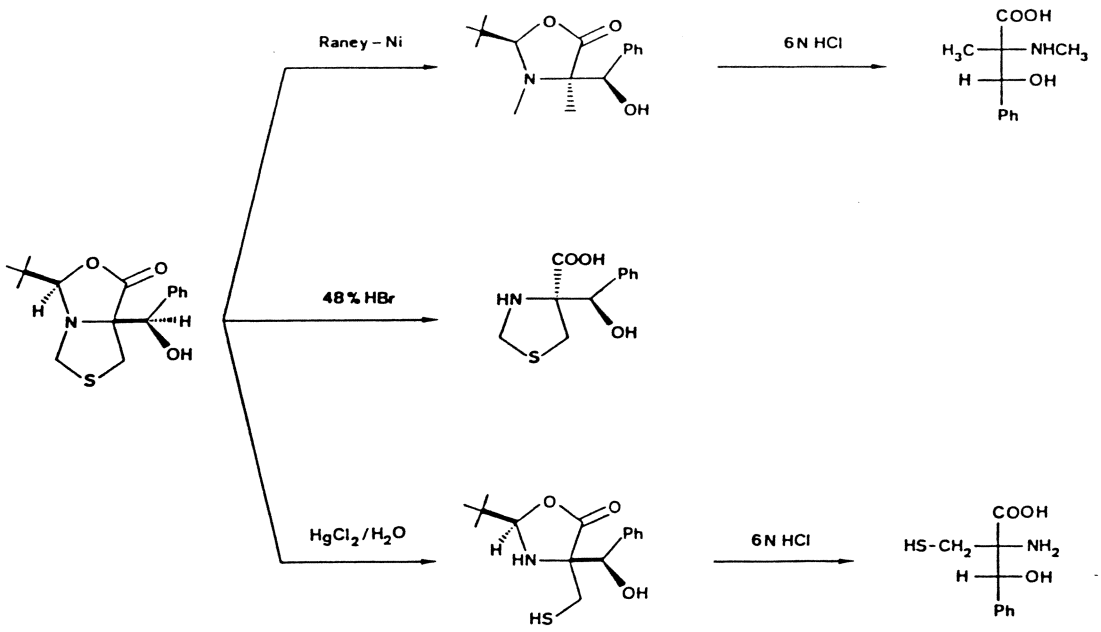


Figure 52

Reductive desulfurization and hydrolytic cleavages of the product derived from cysteine and benzaldehyde (see Fig. 46). Preparation of an α-methyl--phenylserine and of a hydroxybenzylated cysteine derivative [69].

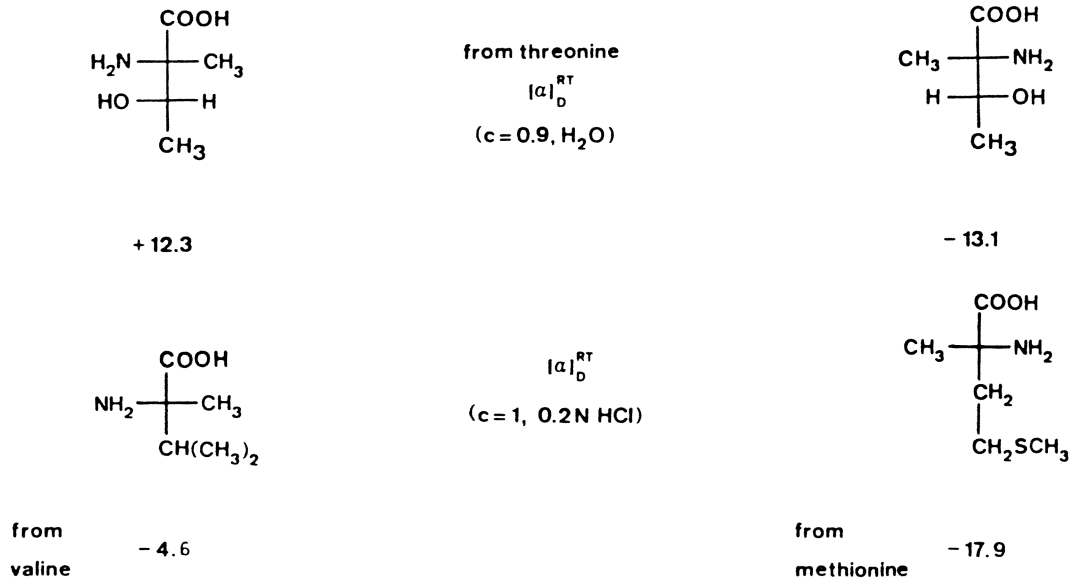


Figure 53

L- and D-α-Methyl-allothreonine from the oxazolines shown in Fig. 39 (hydrolysis with 6 N aqueous HCl, 10 h reflux). L-α-Methyl-valine and D-α-methyl--methionine from the imidazolidinones shown in Fig. 50 (hydrolysis by heating at 180°C for 4 h in 6 N aqueous HCl in a sealed tube) [69].

The present method of α-alkylation of aminoacids without racemization is superior to previous methods of preparing enantiomerically pure or enriched branched aminoacids. Unlike all other procedures, ours does not require an external chiral auxiliary. The more successful literature methods employ imines from chiral carbonyl compounds and aminoacids [70] [71], imidazolin-4-ones with a chiral substituent in the 3-position [72], or diketopiperazines from two different aminoacids [21] as intermediates for asymmetric induction. In our case, the aminoacid to be alkylated is itself the sole source of chirality. Furthermore, we can prepare either one of the two enantiomeric products of alkylation from one and the same enantiomeric form of the starting aminoacid.

The products which become available by this method should not only be of interest for their possible pharmacological activity but also as starting materials for EPC-syntheses of target molecules with quaternary carbon centers [73] and for new chiral auxiliaries with more rigid structures due to the presence of persubstituted carbon atoms.

Although we do not have structural information as yet, the practically exclusive formation of one diastereomeric alkylation product from our dioxolanone, oxazolidinone, and imidazolidinone lithium enolates may well result from an asymmetry of "higher order" as discussed in the first four sections of this article.

F) Acknowledgements

I gratefully appreciate the enthusiastic collaboration of many coworkers whose names are given in the list of references. René Amstutz and Thomas Laube did most of the structural work on lithium derivatives, and Reto Naef developed the methods for self-reproduction of chirality. Warm thanks go to my friend and colleague Jack D. Dunitz and his collaborators Bernd Schweizer and Paul Seiler for valuable discussions and for allowing us to use the x-ray instruments and the programs for structure elucidation. This manuscript would not have been finished in time without a special pressure group of collaborators, including Silvia Sigrist, Walter Bauer, Albert K. Beck, Jesper Hansen, and Thomas Laube.

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INTRODUCTION AND DISCUSSION

Dr. Gary H. Posner (Discussion Leader), **The Johns Hopkins University:** I'd like to start this morning's session by introducing the first speaker for today's event, Professor Dieter Seebach.

Dieter received his training under Professor Criegee in Karlsruhe, and his post-doctoral training under E. J. Corey at Harvard University. He began his professional career at the University of Karlsruhe, moved to Giessen some years later, and then received a call from the famous E.T.H. in Zurich, where he is now professor of chemistry.

Dieter is well known to us for many contributions in organometallic chemistry, starting perhaps with the work in conjunction with E. J. Corey on dithianes, acyl anion equivalents. He has also introduced to us the term umpolung, reactivity inversion, and many other concepts and contributions in organometallic chemistry.

I want to touch just briefly on one other aspect of Dieter's capabilities which deal with his ability in the laboratory, not only to develop ideas, but to handle chemicals.

When I was a first-year graduate student, I sent an analysis, carbon hydrogen analysis, off, and received the results, which were marginal. I went to my mentor at the time and showed him the results. He said "You know, if you want to learn good technique, you should have as a role model Dieter Seebach. In the last three or six months" — I forget which number — "he has submitted 100 samples for C and H analyses, and 98 of them came back perfect."

Since that time, I have been following Dieter as a role model, and it's a pleasure to introduce him now to you.

[The following discussion took place after Dr. Seebach's presentation.]

Dr. Posner: Discussion is available.

Dieter, I'd like to ask the first question, if I may. Very often, the isolation of lithium enolates is difficult. Could you comment a little bit about the operating procedures you used for the isolation of these compounds?

Dr. Seebach: There are methods described in the literature, for instance, by Professor Lipscomb (Harvard) and by Professor Bärninghausen (Karlsruhe), by which one can isolate air-sensitive compounds at very low temperatures in crystalline form. We find that our reagents are extremely sensitive. We have crystals which could not even be handled in the best dry box. So we developed a special apparatus to do it in. It's very, very tricky in some cases.

Dr. Posner: Yes. Thank you very much.

Dr. Craig S. Wilcox, The University of Texas at Austin: In determining the structures for crystals of lithium ester enolate anions of Z configuration you observed that the O-alkyl group twists out of the olefinic plane from 10 to 80 degrees.

Dr. Seebach: Well, the dihedral angle is between 100 and 160 degrees.

Dr. Wilcox: In other words, the O-alkyl group is rising out of the plane of the double bond?

Dr. Seebach: Yes.

Dr. Wilcox: I wonder: do you have enough information to observe a consistent relationship between the size of the O-alkyl group and the magnitude of that twist?

Dr. Seebach: Yes, we do, because we have methyl and tert.-butyl esters, and the dihedral angle is larger with the t-butyl than it is with the methyl groups.

Dr. Wilcox: It's interesting to try to separate the steric and electronic factors which may influence this excursion. As you are aware, in methyl vinyl ether the most stable conformer is planar. For the ester enolate anions, it may —

Dr. Seebach: Well, the easiest explanation is to assume that the oxygen which bears the R group has been rehybridized upon deprotonation of the ester, and similarly the nitrogen of the amide - from sp^2 to sp^3.

Dr. Wilcox: One other question. The steric factors in E isomers of ester enolate anions should differ significantly from the steric factors in Z ester enolate anions. I wonder if you have had success in crystallizing E ester enolate anions, and what the technical difficulties might be in such an experiment.

Dr. Seebach: We have crystallized them, but they crystallize with HMPT, the cosolvent necessary for their generation. It turns out that the crystals contain E lithium enolate plus HMPT in a one to one ratio, which indicates a tetrameric aggregate. We have data sets which could not be solved so far, and the experts say that this is because the amide groups of the HMPT are disordered.

Dr. Wilcox: Thank you.

Dr. Lee Latimer, Eastman Kodak Company: The addition of TMEDA or HMPA is a frequent way of working with the organolithiums. Have you had any success at crystallizing the reaction mixtures with t-butoxide or any of that type of activator to look at the change, whether you can observe if the oxygen is forced into the cubic or tetrameric structure?

Dr. Seebach: Yes, yes. We have such crystals. I mentioned that we tried to crystallize the components of a beginning aldol reaction, which is the enolate plus the ketone. We also tried to crystallize such components which would be present at the end of an aldol reaction, and that is lithium aldolate or alkoxide plus enolate.

We have crystals containing t-butoxide and enolates in one to one ratios, but we have no structures yet. All the structures are done with Professor Dunitz' equipment. The graduate students Rene Amstuts and Thomas Laube, who work in my group, use all the programs and facilities of the Dunitz' group. It is amazing how these young people learn to handle the programs, and get a structure within a few days.

Dr. Latimer: The tetrameric structures of the organolithium themselves, rather than just the enolates —

Dr. Seebach: Yes.

Dr. Latimer: A very different reactivity is observed with the t-butoxide activation. Frequently a more basic reactivity rather than the nucleophilic reactions which are observed more with the amine complexation. Would you care to comment on what your results indicate about why that takes place?

Dr. Seebach: Schlosser recommends to use mixtures of butyl lithium and potassium t-butoxide, for instance, for generating better bases, and I think I cannot say anything about the origin of the effect.

Inspite of R factors of 3 to 4 percent in our structure determinations, we are so far not successful in determining the electron densities, which may tell us about your question.

You have to realize that these are very difficult structures. They all contain several aggregates in the unit cell, for instance up to eight tetramers. Therefore, the x-ray structure determination gets close to that of small peptides in complexity.

Dr. Edward Grabowski, Merck & Company: Have you been able to do anything with chiral alkylations of serine? You have solved the cysteine problem. Have you been able to do anything with serine itself?

Dr. Seebach: Yes, we have.

Dr. Grabowski: Can you report anything?

Dr. Seebach: It will soon be published. We can alkylate serine in a similar fashion as the other aminoacids. What we are especially interested in, is to clip off the CH_2OH carbon atom of serine to get a heterocycle, which would give normal, non-branched amino acids upon alkylation. Therefore, we investigated the serine case extensively.

Dr. Grabowski: When will this be published?

Dr. Seebach: I hope, soon. I publish a lot, but there's a limit to how many papers I can write.

Dr. Grabowski: Thank you.

Dr. Seebach: You can contact me directly and ask for details.

Dr. Robert D. Sindelar, The University of Mississippi: You had commented on the synthetic utility of microbial reductions of β-keto-esters by a thermoanaerobium species; does that have to be done under the more difficult anaerobic conditions?

Dr. Seebach: Yes, it is done under anaerobic conditions. This work is the result of a collaboration with the group of Professor Fiechter of the Biotechnology Laboratory of E.T.H. They have grown thermoanaerobium Brockii microorganisms in a small bio-reactor with three liters working volume to which were added β-ketoesters in amounts of up to 0.2 moles at a time. We could use the same culture many times.

Dr. Sindelar: Do you know, is there an aerobic microorganism that would do the same thing?

Dr. Seebach: Yeast ! Charles Sih and his group in Madison has just shown that 4-chloro-3-keto-butyrate can be reduced with high enantioselectivity using fermenting yeast, if the octyl ester is employed. We reduced methyl 4-chloro-3-keto-butyrate with the thermophilic bacteria to get the same enantiomeric alcohol, also in >90% e.e..

Dr. David A. Evans (Speaker), **Harvard University:** Dieter, I was very surprised, actually, to see your lithium acetone complex being nonlinear.

Dr. Seebach: Why were you surprised?

Dr. Evans: Well, I've been very interested in this point myself, and with regard to metal, carbonyl complexation, I guess we're both aware of the theory that's been done for both lithium and magnesium carbonyl complexation. In addition, the Goddard group at Cal Tech has examined the formaldehyde-aluminum chloride complex theoretically.

Dr. Seebach: Yes. I know.

Dr. Evans: The Goddard study indicated that there's basically a very flat potential surface for metal positioning in the sigma plane.

You have a very nice example of a nonlinear metal carbonyl complex. Do you have any additional cases?

Dr. Seebach: Not only acetone, but also the urea DMPU is coordinating with lithium in a non-linear geometry, although the urea would have "more reason" to coordinate linearly because of the two methyl groups in the alpha positions. So I think your theory is not good enough in this case.

Dr. Posner: No further questions?

We'll thank Dieter very much for a beautiful presentation. We'll have a fifteen-minute break, and come back about ten to 11:00.