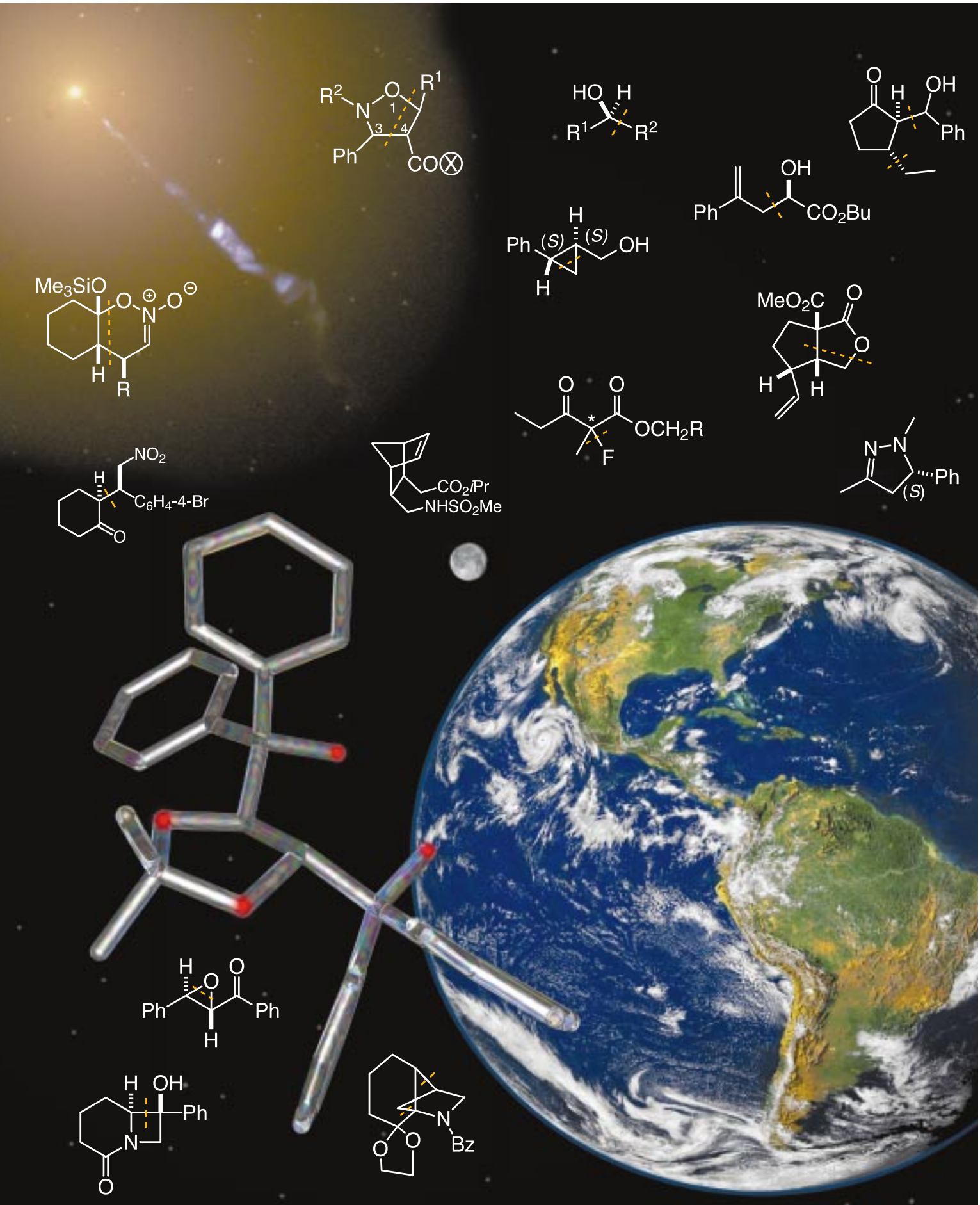


The picture of the Earth was provided by NASA (rsd.gsfc.nasa.gov/rsd).
The top left section of the picture was photographed by the Hubble telescope (oposite.stsci.edu/pubinfo/PR/2000/20/pr-photos.html).

ANGEWANDTE CHEMIE

TADDOLs, Their Derivatives, and TADDOL Analogues: Versatile Chiral Auxiliaries

Dieter Seebach,* Albert K. Beck, and Alexander Heckel

TADDOLs, which contain two adjacent diarylhydroxymethyl groups in a *trans* relationship on a 1,3-dioxolane ring, can be prepared from acetals or ketals of tartrate esters by reaction of the latter with aromatic Grignard reagents. They are extraordinarily versatile chiral auxiliaries. Here, a historical review of the subject is followed by discussion of the preparation of TADDOLs and analogous systems, including TADDOLs with N-, P-, O-, and S-heteroatom ligands appropriate for metals. Crystal structure analysis reveals that the heteroatoms on the diarylmethyl groups are almost always in close proximity to each other, joined together by H-bonds, and predisposed to form chelate complexes in which the metallic centers reside in propeller-like chiral environments. Applications of TADDOL derivatives in enantioselective synthesis extend from utilization as stoichiometric chiral reagents or in Lewis acid mediated reactions, to roles in catalytic hydrogenation and stereoregular metathesis polymerization. Derivatives and complexes based on the following metals have so far been investigated: Li, B, Mg, Al, Si, Cu, Zn, Ce, Ti, Zr, Mo, Rh, Ir, Pd, Pt. The number of stereoselective reactions already accomplished with TADDOLs is correspondingly large. It is also easy to prepare TADDOL derivatives that are readily polymerizable and graftable, and to transform them into immobilized solid-phase catalysts. The result is catalysts, simply or dendritically immobilized in polystyrene or on silica gel and characterized by unexpected stability even after multiple use in titanium TADDOLate mediated reactions. TADDOLs show further unusual characteristics that make them useful for applications in material science and supramolecular chemistry: they are the most effective doping agents known for phase transformations of achiral (nematic) into chiral (cholesteric) liquid crystals. The TADDOL OH group that is not involved in intramolecular H-bonding shows a strong tendency to associate intermolecularly with H-bond acceptors. In the process of crystallization this leads, enantioselectively, to the formation of inclusion compounds that lend themselves to the separation of racemic mixtures not otherwise suited to the classical method of crystallization through diastereomeric salts. The high melting points of TADDOLs even make possible the resolution of racemates by distillation! Host–guest compounds formed between TADDOLs and achiral partners can serve as platforms for enantioselective photoreactions. It seems safe to predict that many more applications will be discovered for the TADDOLs and their derivatives.

Keywords: asymmetric catalysis · asymmetric synthesis · enantiomer separation · TADDOL

1. Introduction and Historical Background

Degradation of carboxylic acids to their next lower homologues was employed for purposes of structure determination based on chemical correlation early in the twentieth century. One strategy took advantage of the Barbier–Wieland reaction sequence: transformation of an ester into a tertiary alcohol (a "benzhydrol" or "diphenylcarbinol"), which was dehydrated and then subjected to oxidative C–C bond cleavage to produce a new carboxylic acid containing one less carbon atom in the chain (Figure 1a).[1] In the 1930s, attention was directed toward the study of reaction mechanisms, and Georg Wittig took advantage of the reaction of cyclohexanedicarboxylic acid esters (*cis*, *rac-trans*, and (+)-*trans*!) with phenylmagnesium bromide as a route to ethers of tertiary alcohols for investigation of the cleavage—today we would describe it as fragmenting—of ethers with potassium (Figure 1b).[2] Decades later, derivatives of the same type appeared yet again (indeed, twice!): On one hand in the context of a novel route to their synthesis[4] (Figure 1d), and on the other with respect to the question of whether the

[*] Prof. Dr. D. Seebach, A. K. Beck, Dipl.-Chem. A. Heckel
Laboratory for Organic Chemistry
Eidgenössische Technische Hochschule
ETH Zentrum, Universitätstrasse 16
8092 Zürich (Switzerland)
Fax: (+41) 1-632-1144
E-mail: seebach@org.chem.ethz.ch

Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

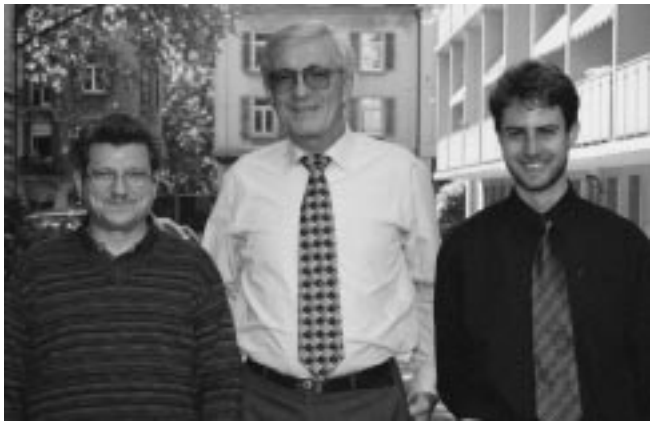
  1433-7851/01/4001-0093 $ 17.50+.50/0

presence of a four-membered ring in the 2,3-position might lead to an isolable "optically active" (helical chiral) 1,1,4,4-tetraphenylbutadiene (Figure 1 c).[3, 5]

Toward the end of the twentieth century, the preparation of enantiomerically pure[6] compounds (EPCs[7–12]) was recognized to be one of the most important goals in the methodology of organic synthesis, and—in fulfillment of a prediction offered in 1990[11]—chemists now are already well on the way toward having at their disposal (catalytic) enantioselective variants of all the standard synthetic methods, permitting the preparation of chiral products from achiral precursors or intermediates.[13–20] With respect to this goal as well, the reaction of aryl Grignard reagents with (enantiomerically pure!) esters, mainly ones derived from natural products, has played a key role. The first systematic application involved the compound TADDOL,[21–24] derived from tartaric acid (Scheme 1).

Relative to classical Li and Mg derivatives, organotitanium derivatives react with similar functionalities (for example, aldehydes/ketones/esters), but with much more selectivity with respect to diastereotopic groups and faces present in the substrate molecules.[25–31] It was thus obvious that enantioselective titanium derivatives would be worth seeking. One of the first chiral ligands we utilized successfully in this context was the TADDOLate shown in Scheme 1.

TADDOLs and analogous compounds, as well as various derivatives in which one or both of the OH groups is derivatized or replaced by another functional group, have since 1982[23] been found to be so useful that one can now speak in a formal sense of a "TADDOL auxiliary system". We wish to emphasize that the term "chiral auxiliary" should here be understood in the broadest possible sense, that is, as a way of describing a compound or a class or family[33] of compounds with the aid of which it becomes possible to "introduce



A. K. Beck D. Seebach A. Heckel

Dieter Seebach was born in Karlsruhe (Germany) in 1937. He studied chemistry at the University of Karlsruhe, where he completed doctoral work on small rings and peroxides under the supervision of R. Criegee (1964). After a nearly two-year sojourn at Harvard University as postdoctoral fellow (working with E. J. Corey) and lecturer, he returned to Karlsruhe and qualified for habilitation in 1969 with a paper based on sulfur- and selenium-stabilized carbanion and carbene derivatives. He was appointed to professorial positions first at the Justus Liebig University in Giessen in 1971 and subsequently (in 1977) at the Eidgenössische Technische Hochschule (ETH) in Zürich. His current research activity relates primarily to the development of new synthetic methods, preparation and secondary structural investigations of β-peptides, synthesis and applications of oligomers of (R)-3-hydroxybutyric acid (HB) and of the biopolymer PHB, the synthesis of chiral dendrimers, and applications of chiral titanates to organic synthesis. Dieter Seebach has been a visiting professor at numerous prestigious universities, and is a member of the Deutschen Akademie der Naturforscher Leopoldina and the Swiss Academy of Technical Sciences (SATW) as well as a corresponding member of the Akademie der Wissenschaften und Literatur in Mainz. He has been awarded an honorary doctorate by the University of Montpellier.

Albert Karl Beck was born in 1947 in Karlsruhe (Germany), and after completing secondary school he undertook a chemistry technician's apprenticeship at the Institute for Organic Chemistry of the University of Karlsruhe from 1963 to 1966. Following 18 months of military service he joined the Seebach research group in 1968. Between 1969 and 1972 he continued his education, obtaining official certification as a chemical technician at the Fachschule für Chemotechnik in Karlsruhe. In 1971 he followed D. Seebach to the Institute for Organic Chemistry at the University of Giessen, and in 1974 he engaged in a six-month research visit to the California Institute of Technology in Pasadena. Albert K. Beck has been an active part of the Laboratory for Organic Chemistry at the ETH in Zürich since the time of Seebach's arrival there. During his long association with the Seebach research group he has participated in essentially all of the group's research themes, as evidenced by his coauthorship of more than 70 publications. In recent years he has been occupied primarily with the chemistry of TADDOLs and TADDOL derivatives.

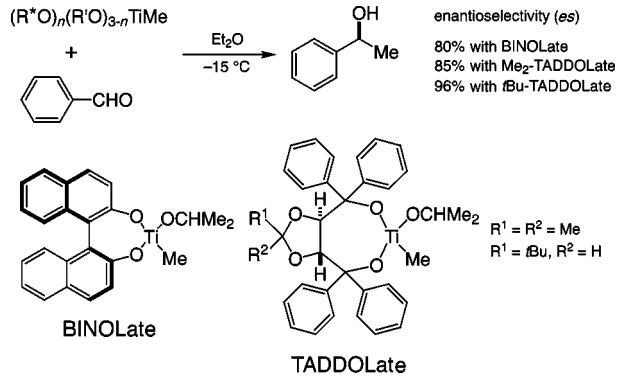
Alexander Heckel was born in 1972 in Lindau on Lake Constance (Germany). He studied chemistry from 1992 to 1997 at the University of Constance with the aid of a Hundhammer Fellowship, and he graduated with honors. His diploma thesis dealt with oligosaccharide solid-phase synthesis, work carried out under the direction of R. R. Schmidt. He subsequently moved to the ETH in Zürich, where he is currently completing doctoral work in the area of heterogeneous enantioselective catalysis under D. Seebach. In his free time he does volunteer work as a paramedic with the Red Cross.

Figure 1. The reaction of carboxylic acid esters with phenyl Grignard reagents at various junctures in the history of organic chemistry. a) The Barbier-Wieland method for degrading carboxylic acids.[1] b) Wittig's investigation of ether cleavage with the breaking of C–C bonds.[2] c) The search for a helical π system.[3] d) An original synthetic pathway for preparing a diarylmethanol derivative.[4]

chirality". Such a material should be capable of creating a "chiral environment" not only around a specific reaction center, but also—through supramolecular interactions—in solution, within a liquid crystalline system, or in the solid state.

2. Preparation of TADDOLs and Their Analogues

If one chooses not to start from the commercially available acetonide of a tartrate,[34] a 2,2-dimethyl-1,3-dioxolane derivative, then alternative precursors to TADDOLs **1** are most readily obtained by treatment of dimethyl or diethyl tartrate with the appropriate aldehyde or ketone under acid catalysis and with azeotropic removal of water. The products are then reacted with aryl Grignard reagents. A related and often more effective method is acid-catalyzed transacetalization, in which dimethyl tartrate is treated with the dimethyl acetal or ketal of some aldehyde or ketone with concurrent removal of the resulting methanol. Rather than resorting to distillation, one can also remove the byproduct methanol or water by treatment with an equimolar amount of $BF_3 \cdot OEt_2$; for literature references, see Scheme 2.

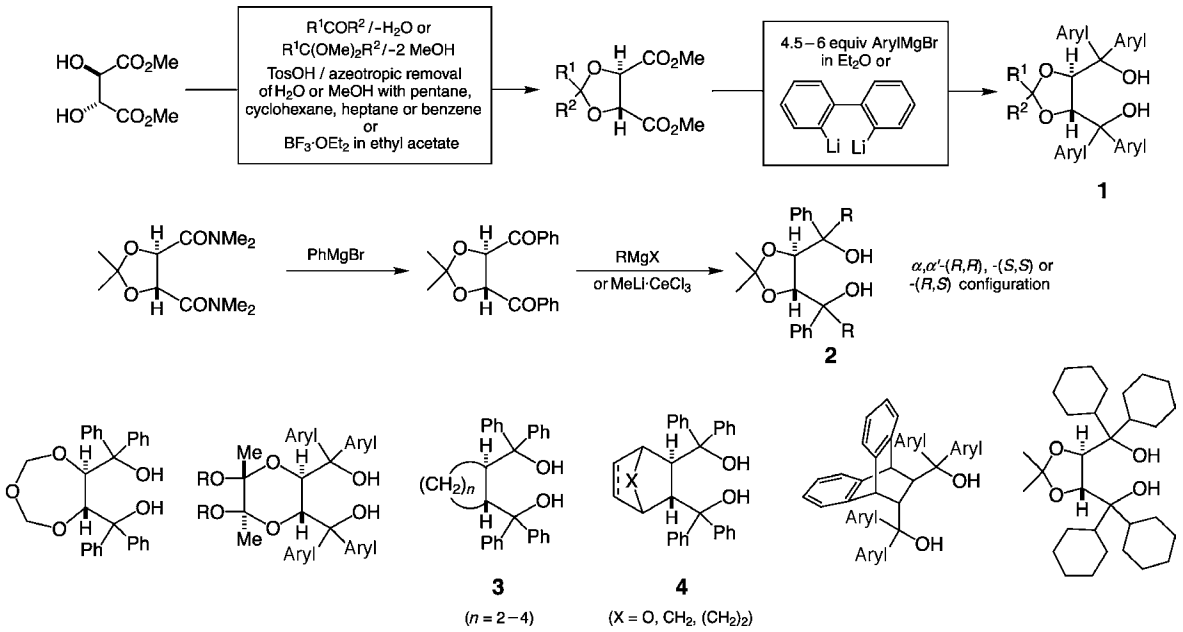


Scheme 1. The first use of TADDOLates (derived from tartrate esters and phenyl Grignard reagents) for enantioselective nucleophilic addition to aldehydes. Apart from BINOL and TADDOL, numerous other chiral alcohols and diols have also been tested, but with only modest success.[25–27, 32]

The most frequently utilized TADDOLs, **1a**–**p**, are presented in Table 1. Given the number of aldehydes, ketones, and aromatic halides available for incorporation, it should come as no surprise that several hundred different TADDOLs and TADDOL analogues have already been described.[61] (See the Supporting Information for a list which is, to the best of our knowledge, complete and represents the state of the literature at the beginning of 2000). All the substances described are nonvolatile solids, with most showing a strong tendency to crystallize. They are also characterized by high optical rotation values (in most cases compounds prepared from (*R*,*R*)-tartaric acid are levorotatory in aprotic solvents;[36, 68] see also Section 5 and Figure 9), and they behave like nonpolar materials in terms of solubility and chromatographic R_f values. Even though TADDOLs with two methyl groups in the 2-position of the dioxolane ring are acetonides, they are extraordinarily stable, and they survive acidic workup with no problems whatsoever. The thermal stability of these "benzhydrol" derivatives is also high; the compounds melt without decomposition at temperatures between approximately 180 and 220 °C.

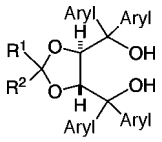
3. Derivatization and Substitution of the OH Groups in TADDOLs

The OH groups in TADDOLs are subject to the usual chemical reactions: ether formation, esterification, silylation (with $ClSiR_3$ or Cl_2SiR_2), and treatment with $ClPR_2$, Cl_2PR,



Scheme 2. Preparation of TADDOLs and analogous 1,4-diols from cyclic carboxylic acid esters (only one enantiomer is shown in each case). Detailed standard conditions for acetalization/ketalization,[35] for the reaction with phenylmagnesium bromide, and for isolation and purification of the TADDOLs **1** have been published.[35–37] New TADDOLs introduced for the first time in this review were prepared similarly[38–43] (see also the literature references in Table 1). Derivatives **2** containing various groups on the methanol units (which thereby become stereocenters) are accessible via the diketones shown in the middle.[44, 45] The trioxacycloheptane derivative shown at the lower left resulted from an "accident" encountered during the preparation of TADDOL **1** with $R^1 = R^2 = H$ and Aryl = C_6H_5. The 1,4-dioxandimethanols (TARTROLs) are derived from tartrate esters, butan-2,3-dione, methanol or ethanol, and ArylMgX.[46–49] Of the carbocyclic analogues **3** ($n = 2$,[44] 3,[44] and 4,[2, 44]), the one most commonly prepared is that derived from the *trans*-cyclohexane dicarboxylic acid. Bicyclic derivatives **4** (X = O,[44] CH_2,[44, 50], $(CH_2)_2$[44, 51]), the dibenzobicyclo[2.2.2]octadiene derivative,[51–59] and the tetracyclohexyl analogue (prepared by hydrogenation of **1a**[60]) would so far be classed among the more exotic of the chiral complexing agents. Tos = toluene-4-sulfonyl.

Table 1. The most frequently utilized TADDOLs **1a**–**p**.[a]

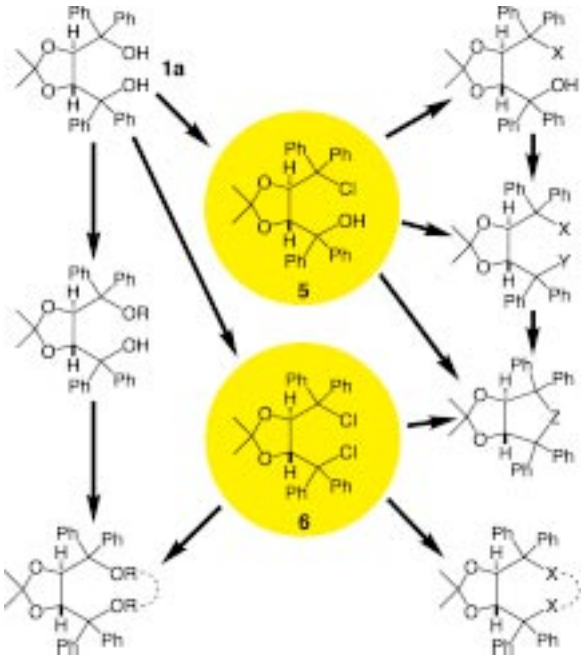


R^1	R^2	Aryl	**1**	Ref.
Me	Me	Ph	**a**	[35, 36]
Me	Ph	Ph	**b**	[44, 64]
$(CH_2)_4$		Ph	**c**	[65]
$(CH_2)_5$		Ph	**d**	[35, 36]
Me	Me	1-Nph	**e**	[36]
Me	Me	2-Nph	**f**	[36]
Ph	Ph	Ph	**g**	[66–68]
Ph	H	Ph	**h**	[35]
*t*Bu	H	Ph	**i**	[35, 36]
Me	Me	3,5-$Me_2C_6H_3$	**j**	[37]
Et	Et	Ph	**k**	[69]
Et	Et	3,5-$Me_2C_6H_3$	**l**	[37, 69]
Me	Me	4-HOC_6H_4	**m**	[63]
H	H	4-$(Me_2N)C_6H_4$	**n**	[70]
4-$(HOCH_2)C_6H_4$	H	Ph	**o**	[71]
4-$(CH_2{=}CH)C_6H_4$	H	Ph	**p**	[71]

[a] Literature references in each case contain information about preparation and characterization of the compounds. Commercially available materials include **1a**, **1b**, **1e**, **1f**, and **1i**.[62] Hexol **1m** is used for preparation of dendritic TADDOLs.[63] Compound **1n** is stable even to strong aqueous acid, and can therefore be extracted out of organic solutions. The TADDOLs **1o** and **1p** are used for the preparation of copolymers with styrene and for immobilization (See Section 9).

Cl_3P, or Cl_2SO, in the course of which bicyclic compounds may be produced (Scheme 3). In particular, experience with the hexahydroxy derivative **1m** has shown that *one* OH group in the two diarylmethanol units is significantly more acidic than the other,[63] consistent with the presence of an intramolecular hydrogen bond.

Key intermediates in the substitution process are the monochloride **5** and dichloride **6**. The former is obtained selectively[72] by treatment with CCl_4/PPh_3 (Appel reaction[73]), whereas the latter forms with $SOCl_2$.[74, 75] Both compounds (and especially the analogous bromine and naphthyl derivatives!) are highly reactive, and readily undergo solvolysis (even on silica gel!), for which reason purification, especially on a large scale, should be effected by crystallization. Reactions with nucleophiles such as alcohols, phenols, ammonia and amines, anilines, azide, phosphites, phosphinites, thiols, thiocyanate, and thiourea lead to products of the types indicated in Scheme 3. Simply to demonstrate the versatility of structures accessible in this way we have assembled in Figure 2 what amounts to a collage—complete with literature references—of compounds derived from TADDOL **1a** (see also the Supporting Information). These compounds are available for use as chiral ligands with metallic centers, as auxiliaries, and as reagents for EPC syntheses. We delayed venturing into substitution reactions with TADDOLs for a long time: one would anticipate that such transformations should inevitably take place through S_N1 mechanisms (that is, via carbocations), and we were con-



Scheme 3. Overview of routes leading from the original (*R*,*R*)-TADDOL to various derivatives and substitution products. The OH groups of TADDOL are ultimately replaced—by way of mono- and dichlorides **5** and **6**—with carbon substituents (using *N*-methylaniline or diphenylamine), NH_2, NHR, NR_2, $P(O)R_2$, $PO(OR)_2$, O-Alkyl, O-Aryl, OOH, SH, or SR (see Figure 2 for examples). The bold arrows represent reaction pathways, which are not always single reaction steps.

cerned that we would therefore also encounter eliminations, fragmentations, and rearrangements. The high yields actually achieved show that our fears were in fact unfounded. On the other hand, if one starts not with TADDOL **1a**, which contains unsubstituted benzene rings, but rather with the tetra(4-methoxy) analogue, problems of this nature can indeed arise[68] (Scheme 4, top). We have also observed that interesting reductive eliminations and fragmentations accompany attempts to introduce PR_2 groups by substitution with HPR_2 and $LiPR_2$[89] (Scheme 4, bottom).

In summary, it should be noted that TADDOLs and their analogues are extraordinarily easy to prepare, and that it is possible to carry out "combinatorial" optimization for a particular application. The commercially available building blocks alone—namely, chiral cyclic 1,2-*trans*-dicarboxylic acid esters or tartrate esters, aldehydes or ketones, aryl halides, and heteroaromatic halides in combination with C, N, P, O, and S nucleophiles—provide the potential for innumerable possibilities with respect to structural variation (Figure 3). At the diarylmethanol center (dialkyl analogues do not work well as ligands; see also Schemes 26 and 27), steric hindrance can be increased through the series phenyl, 2-tolyl, 1-naphthyl, and 9-phenanthryl, continuing all the way to fluorenylides. At the ketal/acetal center it is possible to go from two hydrogen atoms, two methyl or ethyl groups, five- and six-membered rings, or two phenyl groups again as far as fluorenylides, or, dispensing with C_2 symmetry, to combinations like Ph/Me,

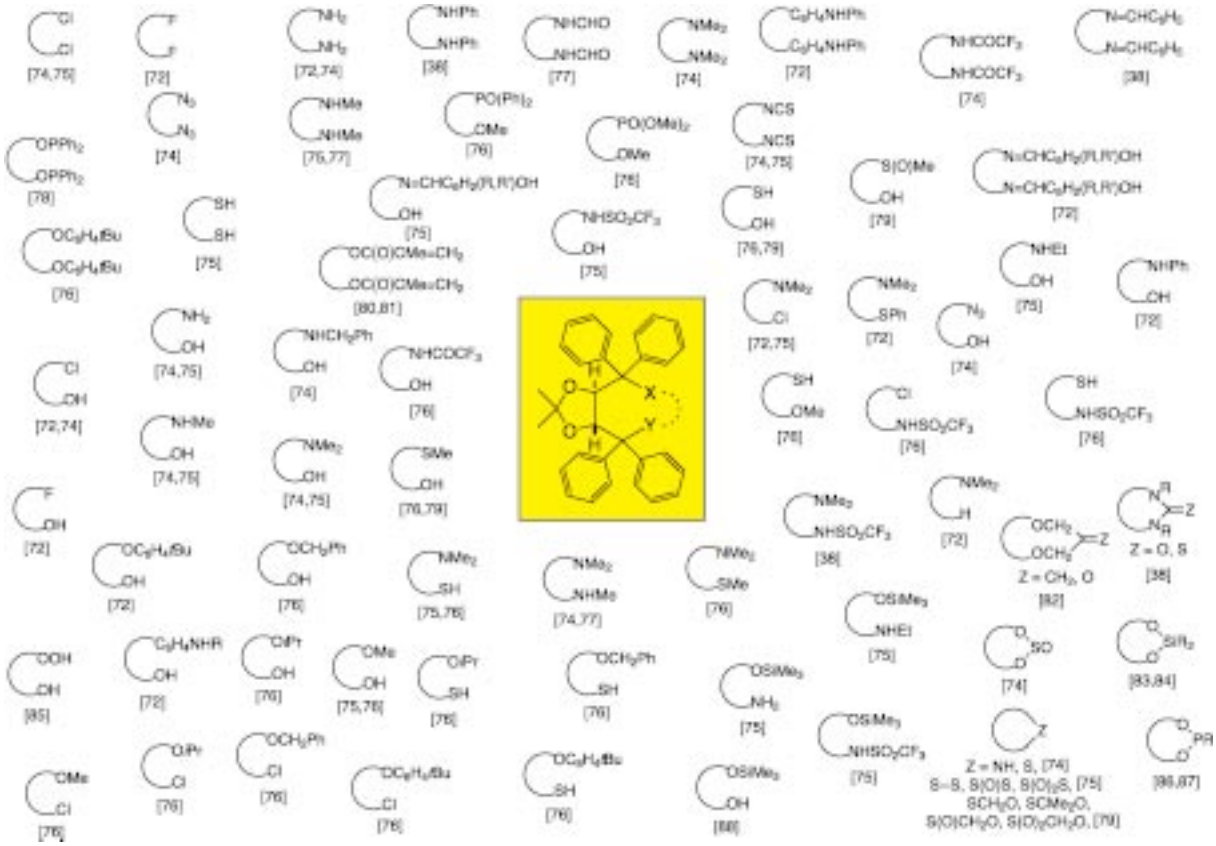
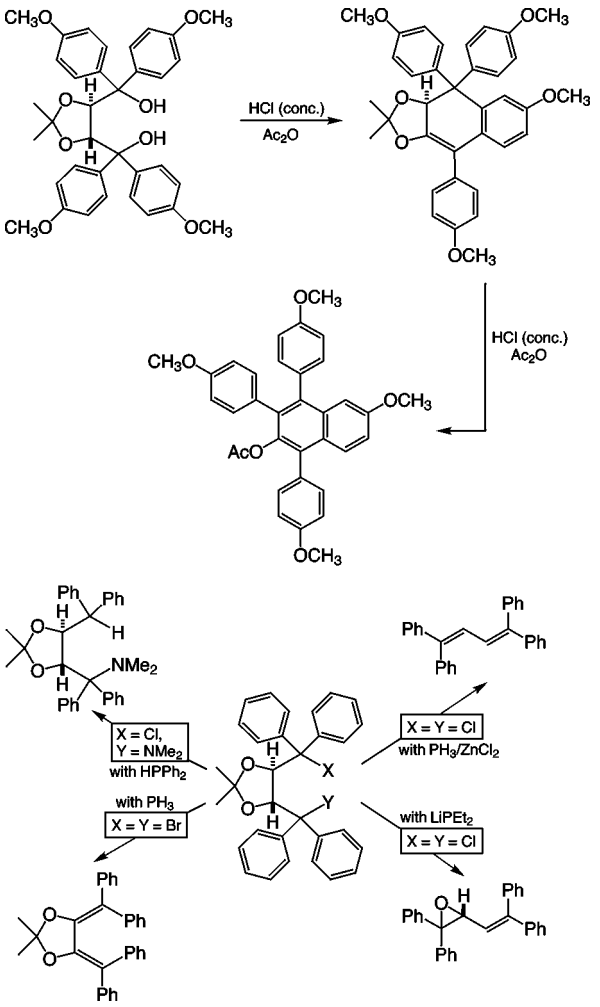


Figure 2. Schematic representation of C_2-symmetrical dioxolanes and bicyclic, as well as unsymmetrical derivatives, that have to date been prepared from TADDOL **1a**. The literature citations refer to papers containing typical experimental procedures. Applications are discussed in subsequent sections. Substitution of the OH groups is also possible with the hexaphenyl derivative **1g**, which has been transformed into OH/Cl, OH/NMe_2, and OH/SH derivatives, and with the 2-naphthyl derivative **1f**, which so far has been converted into unsymmetrical compounds containing OH/Cl, OH/OMe, OMe/Cl, and OMe/SH.[76]



Scheme 4. Dehydration, intramolecular Friedel-Crafts reaction, and reductive elimination in TADDOLs. Top: Bis(4-methoxyphenyl)methyl carbocations are produced upon treatment of the 2,2-dimethyltetraanisyl derivative with HCl/Ac_2O.[68] These cations can deprotonate and can effect electrophilic attack on neighboring methoxyphenyl groups. The final product has an achiral 1,2,4-trianisylnaphthalene skeleton. Analogous reactions occur also with the TADDOL that is unsubstituted in the 2-position of the dioxolane ring, as well as with the 2-methoxyphenyl isomers. Bottom: Phosphanes and phosphides cause reduction and/or elimination of chlorides and bromides derived from TADDOL; starting from the chloroamine, the monoamine forms in a yield of approximately 50%,[72] the bis(diphenylmethylene)dioxanone in about 15%, the tetraphenylbutadiene in up to 80%, and the corresponding epoxide in about 85% yield.[89] Cl/P substitution is successful with TADDOL derivatives only by way of the Michaelis–Arbuzov reaction.[76] Ac = acetyl.

Ph/H, 1-naphthyl/H, or *t*Bu/H (see also Table 1 and the Supporting Information). In place of a dioxolane ring, carbocyclic or bicyclic systems can also be used to carry the diarylmethanol groups (Scheme 2). The heteroatoms in the diarylmethyl groups can be varied from oxygen (for oxophilic, polar metallic centers) through nitrogen, phosphorus, and sulfur (for centers involving the late transition metals), and from uncharged to anionic groups (with C_2 symmetry or unsymmetrical). Observed pK_a values range from approximately 35 (for N*H*alkyl), through 28 (for N*H*aryl), 17 (for O*H* and N*H*COR), and 10 (for S*H*, N*H*COCF$_3$, or N*H*R$_2^+$), down to as low as 6 (for N*H*SO$_2$CF$_3$).[90] After many attempts[91, 92] we finally succeeded[76] in introducing PR_2 groups directly at the diarylmethyl carbon atom (although preparation of a tetraphenyl DIOP derivative[93] has still not been accomplished).

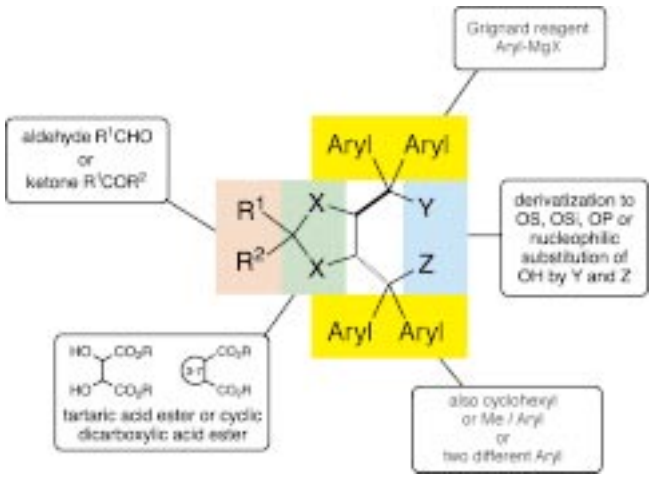


Figure 3. Components for the preparation of TADDOLs and their analogues. For concrete examples, see Schemes 2 and 3, as well as Figure 2, Table 1, and the Supporting Information.

4. Structures of TADDOLs

The great diversity of readily accessible TADDOLs has generated a wealth of structural information, thanks to the great tendency of these compounds to crystallize. We are aware of roughly 120 crystal structures of compounds of the type shown in Figure 3, 92 of which have been incorporated into the Cambridge Structural Database (CSD; see the Supporting Information). Even though far fewer structural studies have been carried out in solution[45, 94, 95] (see also Sections 5 and 10), and even though there have been relatively few theoretical computations of TADDOL structures,[44, 96] the large number of available crystal structures permits one to draw statistically relevant conclusions[97] about the preferred conformation of TADDOLs and their analogues. Single crystals are best obtained by crystallization from solvents with hydrogen bond accepting characteristics, or at least in the presence of compounds of this type, since this permits the formation of TADDOL inclusion compounds (referred to variously as solvates, clathrates, or "host–guest" compounds[98]). In the vast majority of cases the TADDOL units are present in conformations with near-C_2 symmetry, which feature perfect staggering about the exocyclic C–C bonds and staggering about the endocyclic C–C bonds that is as near ideal as possible for a dioxolane ring. The TADDOLs also display an antiperiplanar (*ap*) arrangement of endo- and exocyclic C–O bonds, and quasi-axial and quasi-equatorial placement, respectively, of the two members constituting each pair of aryl groups, where in the former case an "edge-on" conformation is preferred and in the latter a "face-on" conformation is preferred when the molecule is observed along the C_2 axis (see the overlay of 35 crystal structures of compounds of type **1** (where $R^1 = R^2 = Me$ or $R^1–R^2 = (CH_2)_4$, $(CH_2)_5$; Aryl = Ph) in Figure 4). An intramolecular

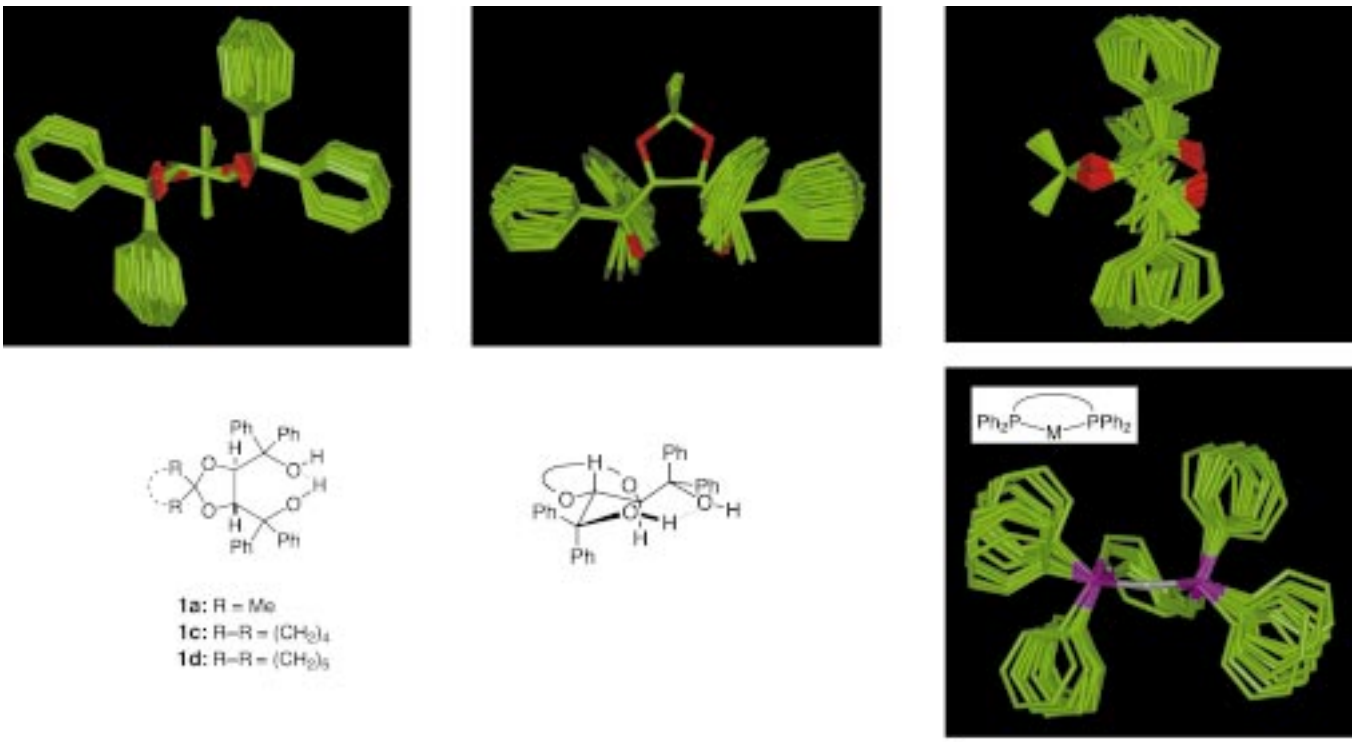


Figure 4. Overlays[99] of TADDOL structures determined from a total of 35 crystal structure analyses, shown in projection along the C_2 axes of the molecules (left) and in two directions perpendicular to that axis (middle and right). Only structures based on one of the three TADDOLs **1a** (19 examples), **1c** (8 examples), and **1d** have been included (cyclopentane and cyclohexane rings in **1c**/**1d** have been omitted for clarity). Thirteen additional structures with R = Me, but other aryl groups (see formula bottom left), could have been incorporated without producing any change in the overall picture. For the corresponding CSD Refcodes, see the Supporting Information. Positions of hydrogen atoms in the OH groups are specified in several of these crystal structures (see picture, bottom center). The similarity between the propeller-like structures of the TADDOLs and the bis(diphenylphosphanyl)metal complexes is apparent through a comparison of representations at the top left and the bottom right. CSD Refcodes for the 15 phosphorus complexes shown in the overlay at the bottom right: ALANPD, BAVSAS, BNAPRH, BUTWES, CEJJEG, CUNKUR, CUYYAW, FUXSUM, JIPCAM, JUBVUX, JUBWAE, JUBWEI, LEGZOM, SACHIN, VIXZOR.[100] The principal difference in the two situations is of course the fact that phenyl groups in the diphosphanes are located *on* the complexing heteroatom, whereas in the TADDOLs they are *adjacent* to it.

hydrogen bond forms between the OH groups, so that one OH proton remains available for intermolecular hydrogen bonding. The dioxolane ring and the seven-membered ring that results from hydrogen bonding are disposed in a *trans*-fused bicyclo[5.3.0]decane-like arrangement, whereby the bridging hydrogen atom falls nearly along the C_2 axis—that is, at the very place where a chelate-bonded metal ion would be situated in a seven-membered ring chelate (see below). The similarity between this system and a bis(diphenylphosphanyl) metal complex is quite striking.[101]

The first set of overlays in Figure 5 shows that substitution products bearing XH/Y rather than OH/OH groups on the diphenylmethyl substituents of the dioxolane rings also assume the same conformation, although in some cases the hydrogen bonds are much weaker. The dimethyl ether of TADDOL **1a** has an identical framework as well,[102] which shows that the hydrogen bond (where the donor is always the more acidic XH group!) at most contributes to the stability of the propeller-like form of the TADDOLs, with two axial and two equatorial groups. Apparently the preferred arrangement is one with the heteroatoms in close proximity, hence the observed predisposition to ring formation and chelation, driven by the two geminal aryl groups (compare with the influence of geminal methyl groups on rates of ring-closure reactions, the Thorpe–Ingold effect[103, 104]). It is thus no wonder that bicyclic TADDOL derivatives in which the heteroatoms at the diphenylmethyl groups participate in six- or seven-membered rings (overlay in the center of Figure 5) show precisely the same orientation of the aryl groups as titanium TADDOLates (Figure 5, right), and that they conform almost exactly with the structures of the TADDOL precursors. Structures of analogues in which other heterocyclic,[36] carbocyclic (for example, cyclobutane[44]), or carbobicyclic[98] ring systems replace the dioxolane ring fall nicely into place as well, as do systems in which all or some of the aryl groups are replaced by cyclohexyl[37, 60] or methyl[44] groups.

Of further interest are the structures of TADDOLs whose two substituents are smaller (such as H) or larger (such as Ph in **1g**) than methyl groups, or which have two different substituents at the 2-position of the dioxolane ring (as for example in **1b**, **1h**, **1i**). The overlay for these cases is shown on the left in Figure 6. The corresponding titanium TADDOLates often promote higher enantioselectivities when acting as chiral Lewis acids. The overlay clearly shows that substitution at the acetal/ketal center influences the conformation about the C–aryl bond, where the ligand sphere of a metal ion resting between the oxygen atoms may be subtly transformed! The structure of the palladium bis(diphenylphosphinite) complex[78] shown in the middle of Figure 6 is

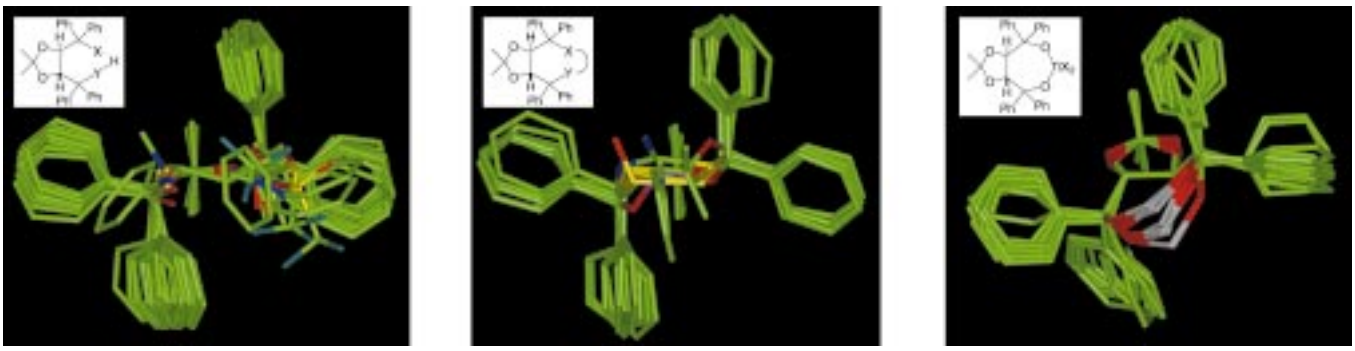


Figure 5. Overlay[99] of the results of crystal structure determinations for 16 substitution products (left), 7 cyclic derivatives (center), and 11 titanates (right) of TADDOL **1a**. In most cases, structures containing the heterosubstituents NR_2, OR, and SR have not previously been published, and are taken from an ETH doctoral dissertation;[76] the groups X/YH are NH_2/NH_2, NHMe/NHMe, NHPh/NHPh, $NH_2/NHSOCF_3$, NHPh/OH, NMe_2/OH, N=CHNMe_2/OH, OMe/OH, O*i*Pr/OH, OBn/OH, $OCOCF_3$/OH, OH/OOH, SH/$NHSO_2CF_3$, SMe/OH, OMe/SH, SH/SH (in the structure of the NMe_2/OH derivative phenyl groups at the 2-position of the dioxolane ring have been omitted for the sake of clarity). The bicyclic systems shown in the center contain in addition to the dioxolane ring a 6- or 7-membered heterocyclic ring: the groups X–Y are C(SH)–O, O–P(NMe_2)–O, O–PPh–O, O–CMe_2–S, S–S, S–C(NH_2)=N, S(O)–S. On the right is an overlay of titanium TADDOLate structures representing a wide variety of groups X on titanium (CSD Refcodes: JUCHIY, JUPWAS, POPROB, VUDGAC, YUGJAL), wherein TADDOL units present independently in the unit cell have been incorporated separately into the overlay (residual substituents on titanium are not shown); in the case of the spirotitanate (JUPWAS), *both* titanium TADDOLate units are included. It is worth noting the small deviations in O–Ti–O angles and Ti–O distances in the chelate ring despite the fact that some of the titanium coordination is tetrahedral and some octahedral. Average values for tetrahedral coordination geometry are 103° and 1.78 Å for JUPWAS, 99° and 1.81 Å for POPROB, and 98° and 1.79 Å for VUDGAC; for octahedral coordination geometry the corresponding values are 97° and 1.78 Å for YUGJAL and 99° and 1.78 Å for JUCHIY. Apparently here, too, the TADDOL dictates the outcome! CSD Refcodes for the published compounds are available from the Supporting Information, where reference is also made to unpublished structures. All the structures shown could also have been included in the overlay of Figure 4 without significantly altering the overall picture! For another representation of the titanium TADDOLate complexes, see Figure 17.

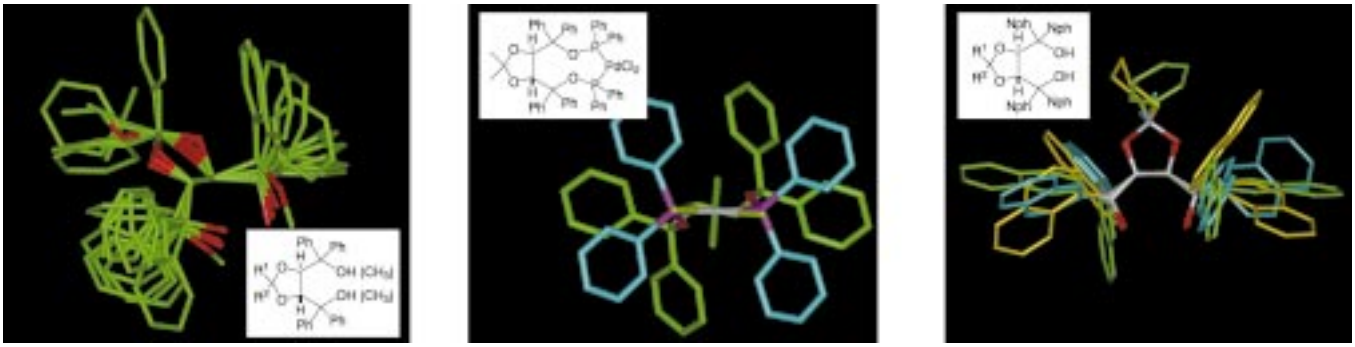


Figure 6. Crystal structures of TADDOLs with substituents other than methyl at the 2-position of the dioxolane ring (left; CSD Refcodes: JUPVIZ, JUPVOF, POPJOT, ROLWIY, YONVIG), of a palladium complex of TADDOL-bis(diphenylphosphinite) (center, ZOCJUW), and of TADDOLs with Aryl = naphthyl (Nph; right).[99] The structures of the naphthyl derivatives correspond to the compounds with $R^1 = R^2 = CH_3$, Aryl = β-naphthyl (**1f**, YONVAY, light blue), R^1–$R^2 = (CH_2)_5$, Aryl = α-naphthyl (YONVEC, yellow), and R^1 = Me, R^2 = Ph, Aryl = β-naphthyl[105] (green).

also informative: the eight phenyl groups orient themselves in a consistently staggered way about the nine-membered chelate ring such that a chiral ligand sphere develops around the metal, far removed from the stereogenic centers on the dioxolane ring! Finally, the three known TADDOL structures with naphthyl groups on the diarylmethanol substituents are shown in the form of an overlay on the right in Figure 6. A significant difference is apparent between the 2-naphthyl (phenyl-like) and 1-naphthyl derivatives; in the latter the annellated benzene ring extends forward in the quasi-equatorial position, but back in the quasi-axial position; it is thus not surprising that the stereochemical course of a reaction can reverse itself when carried out successively with the two isomeric naphthyl derivatives,[37] that 1-naphthyl derivatives show broad NMR signals at room temperature (slow rotation about the C–aryl bond), or that titanium TADDOLates bearing four 1-naphthyl groups often show a complete absence of catalytic activity[102] (too much steric hindrance).

Exceptions: are there any?[106, 107] There of course exist TADDOL derivatives in which the heteroatoms at the diarylmethyl groups do *not* lie in close proximity, and as the "black sheep" in their families they are of special interest. Indeed, they can convey important lessons! We first discovered such a system when we examined the crystal structure of the diazide:[75] one N_3 group extends forward in the usual way (*ap* conformation O-C-C-N_3), whereas the second hovers over the dioxolane ring in a *gauche* or (+)-synclinal (*sc*) arrangement of N_3 and O, which is favored due to stereoelectronic effects.[108–110] Similar structures characterize the chloramine and the dichloride (see the overlay in Figure 7a1), whereas in the fluoroalcohol both heteroatoms rest above the dioxolane ring (Figure 7a2). In all four structures, either one heteroatom and a benzene ring or two superimposed benzene rings in

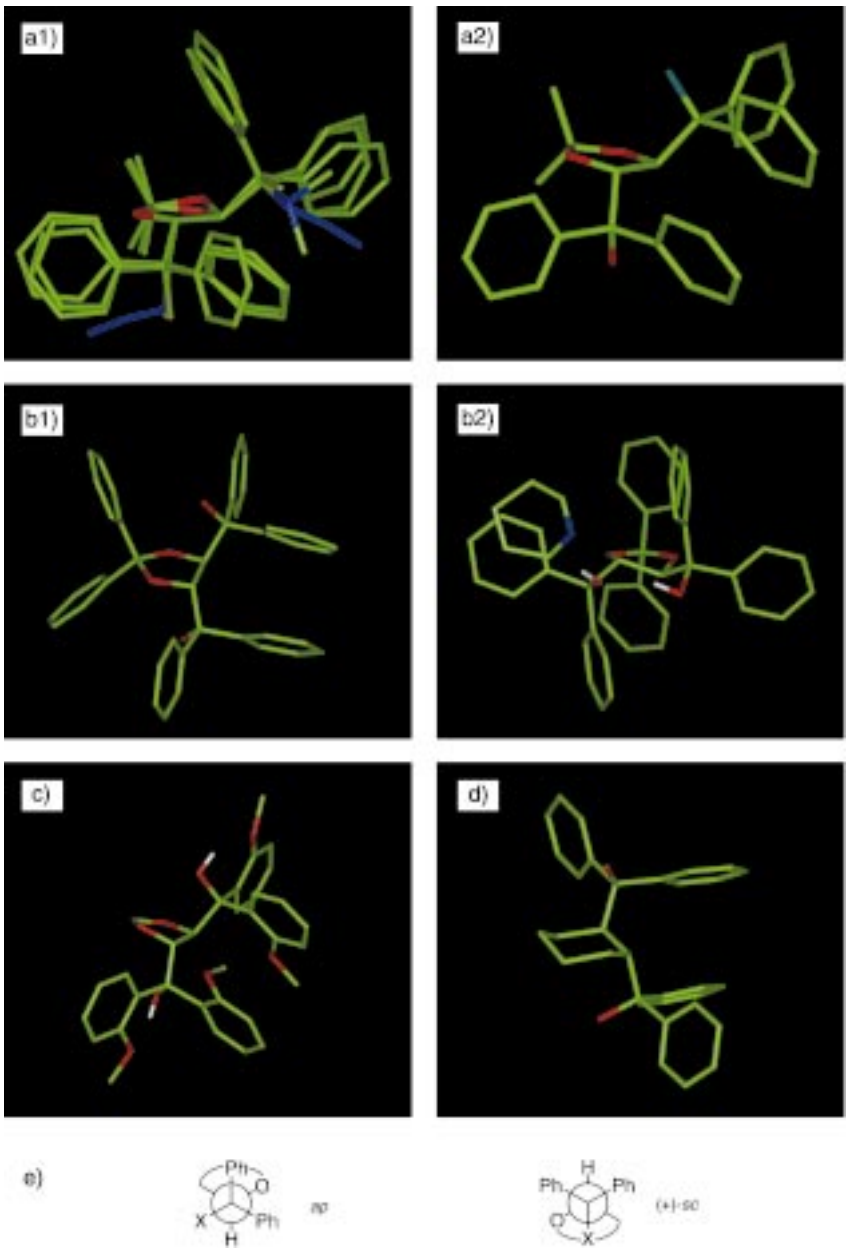


Figure 7. Exceptions to the rule: Crystal structures of TADDOL derivatives and analogues in which heterosubstituents on the diarylmethyl groups are *not* mutually close. a1) The diazide[75] (CSD Refcode: NIBZIH), the dichloride **6**[75] (NICBUW), and the chloroamine[76] all have one heteroatom above the dioxolane ring whereas the second one extends forward. a2) In the structure of the fluoroalcohol[72] (HOLYAI), both heteroatoms extend to the rear. b1) The hexaphenyl derivative **1g** without inclusion[67] (anomalous, VUSLEA) and b2) with inclusion[68] (normal, POPJOT). c) A tetrakis(2-methoxyphenyl) derivative (POPJIN).[68] d) The cyclohexane analogue of TADDOL, which is present with[44] (YIHJOO) and without[44] (YIHJUU) inclusion in the conformation shown here, with large axial substituents on the six-membered chair ring. As in the case of hexaphenyl derivative **1g**, a *single* structure was found for the dibenzobicyclo[2.2.2]octadiene-8,9-bis(diarylmethanols), in which the OH groups together build an intramolecular hydrogen bond (TAXKOS). In most cases, however, (REQXAM, REQXEQ, REQXIU, TAXKUY, TAXLAF) they are rotated away from each other, whereby two aryl groups come to lie parallel and directly above each other (similar to (a2), (b1), (c), and (d), essentially at the van der Waals distance of 3.3–3.5 Å). In (e) the conformation found about the exocyclic C–C bonds in most TADDOL derivatives is illustrated: the antiperiplanar (*ap*) conformation, and, for comparison, the stereoelectronically stabilized synclinal (*sc*) conformation.

van der Waals contact extend forward. It is difficult to say whether the unusual conformation is ultimately a consequence of the absence of a hydrogen bond,[111] repulsion of the dipoles, or π interaction between the heteroatom and an aromatic ring. An instructive system is the hexaphenyl derivative **1g**, which in the absence of any guest molecule in the crystal relegates the OH groups "to the back", with a hydrogen bond to the benzene rings at the ketal center, whereas when it is crystallized in the presence of piperidine an inclusion compound forms instead, with the familiar TADDOL geometry (Figures 7b1 and 7b2). In the TADDOL with no substituents at the 2-position of the dioxolane ring and four 2-methoxyphenyl groups, the OH groups prefer to form a hydrogen bond with an oxygen atom in the *ortho* position rather than with each other, thereby assuming positions above the dioxolane ring (Figure 7c). Finally, special mention should be made here of one other, at first glance unusual, cyclohexane derivative (Figure 7d), the carbocyclic TADDOL analogue in which the large diphenylmethanol groups are *ap* to each other in *axial* positions on a six-membered chair ring (with the OH groups above!).

As both hexaphenyl-TADDOL **1g** and the cyclohexane derivative readily form titanium complexes—which, for example, catalyze nucleophilic addition to aldehydes[112] as well as Diels-Alder reactions[113] in the usual way—one must conclude that both diolates function as chelate ligands, and that in this case a rule of thumb that is familiar to inorganic and complex chemists applies: it is not possible to predict the structure of a ligand in a metal complex from that of the ligand alone.

In general, it should be noted again that the TADDOL structures discussed here also serve as valuable models for the corresponding metal complexes, and that the (nearly) universal property of a roughly C_2-symmetric, propeller-like arrangement for the four phenyl groups provides a solid basis for mechanistic discussions (see Section 10).

As a result of their structures, TADDOLs and related compounds are well suited to a) formation of clathrates (no specific interactions with the guest molecules, which serve mainly as fillers), b) formation of inclusion compounds (hydrogen bonds to the guest molecule), c) formation of hydrogen-bond donor–acceptor complexes in solution, d) induction of cholesteric phases (the rigid, chiral propellers initiate orientation of the molecules in a liquid-

crystalline medium), e) chelate (bidentate) complexation with metallic centers (the conformation with neighboring heteroatoms is preorganized; no entropic disadvantage exists with respect to the binding of neutral, monoanionic, or dianionic ligands), and f) functioning as chiral reagents.

5. TADDOLs as Chiral Doping Agents in Liquid Crystals

A considerable demand has developed in recent years for cholesteric liquid crystals.[114, 115] One attractive approach to their preparation is the doping of achiral (nematic) phases with chiral additives.[116] As in the case of catalysis, it is important that one employ as little doping agent as possible consistent with achieving the desired degree of helicity (step-height of the pitch of the induced helix, reported in μm). The standard measure for this characteristic is called the helical twisting power (HTP, expressed in μm^{-1}, Figure 8).[117] Before the first TADDOLs were tested as doping agents, HTP values of 100 μm^{-1} were regarded as high,[119] but experiments based on our stock of TADDOLs quickly resulted in derivatives with HTP values of 300–400 μm^{-1}.[83] A record of 534 μm^{-1} was achieved with a fluorenylidene derivative containing two tetrakis(2-naphthylmethanol) substituents[118, 120] (Figure 8). The theory underlying the HTP effect is complicated, and it is still not certain whether TADDOL conformation is the only important factor, or if a change in the orientation of the principal axes of the ordering tensor towards the skeleton of the molecule within the liquid crystal might also play a role (note the substantial HTP decrease from 250 to 150 μm^{-1} at 24 °C when the 2-naphthyl-TADDOL **1f** is "protected" as a cyclic $OSiMe_2O$ derivative; Figure 8, bottom right). Commercial utilization of TADDOLs as chiral doping agents appears feasible.[122, 123]

The inductive effect of TADDOLs in liquid crystals can also be used to learn more about TADDOL conformation(s) in the noncrystalline phase with the aid of NMR and CD spectroscopic methods. It is a striking observation that the sign of the HTP (+ for a helix wound to the right, − for one to the left) can be reversed by changing the substituents in the 2-, 4-, and 5-positions on the dioxolane ring[83] (as can the optical rotation[68] and the stereochemical course of metal TADDOLate catalyzed reactions[37]). Numerous structure- and solvent-dependent UV and CD spectra of TADDOLs have been recorded. Particularly in the region of exciton transitions we have observed not only well-structured curves of the degree of anisotropy (UV spectra) but also major changes in the couplets of the CD spectra (Figure 9), as in the transition from 2,2-dimethyldioxolanes to the corresponding mono- and unsubstituted derivatives (no changes are made in the aryl groups of the diarylmethanol units).[120] This argues for a change in conformation about the C–aryl bond. Detailed conclusions should result[125] from the investigation of a number of deuterated TADDOLs.[34] TADDOLs may well prove to be the key to understanding the relationship between the structure of a doping agent and the magnitude and sign of an observed HTP effect.

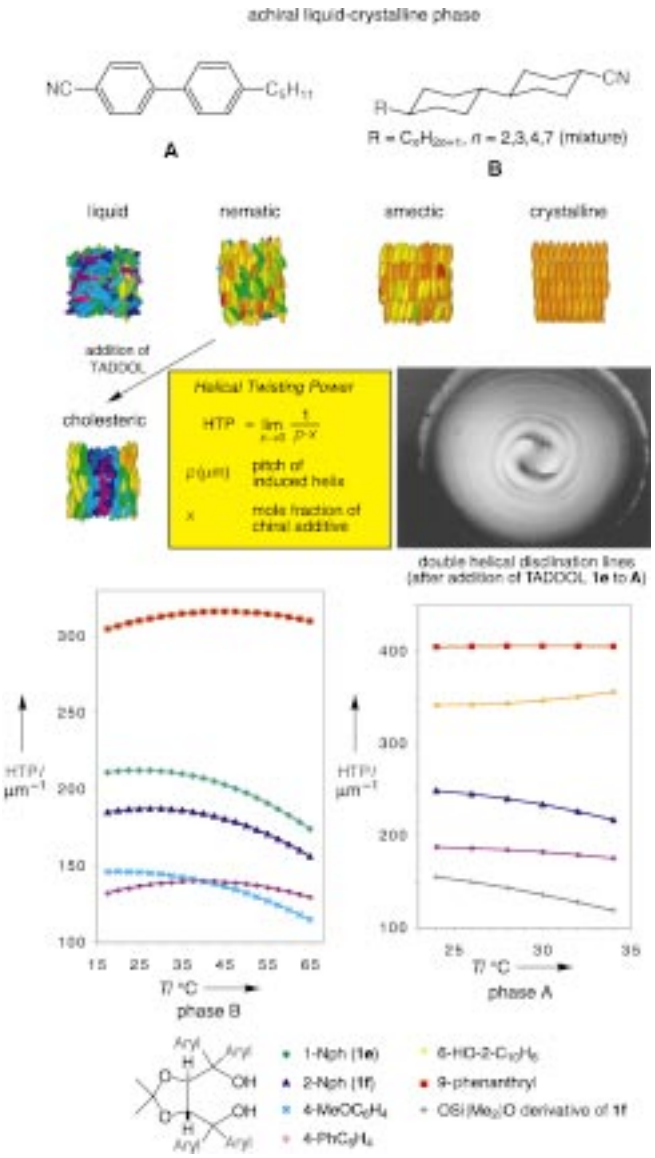


Figure 8. Induction of cholesteric phases by TADDOL addition to achiral, liquid-crystalline compounds in the nematic phase: **A** (K 15, Merck, UK) and **B** (ZLI-1695, Merck, Darmstadt, Germany).[83, 118] The measure of the effect is the so-called helical twisting power (HTP). The step height is determined microscopically (see disclination lines). The cyanobiphenyl material is characterized by a nearly temperature-independent effect. The highest HTP value so far observed (534 μm^{-1}) was achieved with **A** and a TADDOL which contained a 9-fluorenylidene group in the 2-position of the dioxolane ring and which had four 2-naphthyl groups on the diarylmethanol substituents.[118]

6. TADDOLs in the Analysis of Enantiomers[126]

TADDOLs are chiral hydrogen-bond donors that contain aryl groups in the immediate vicinity of the donor OH groups. As a consequence, hydrogen-bond acceptors that dock on these OH groups enter the shielding or deshielding regions (caused by ring-current effects) of nearby aromatic rings; this raises the possibility that diastereomeric hydrogen-bonding complexes could become distinguishable by NMR spectroscopy. Apart from signals in the aromatic region, C_2-symmetric TADDOLs show only two singlets in their NMR spectra

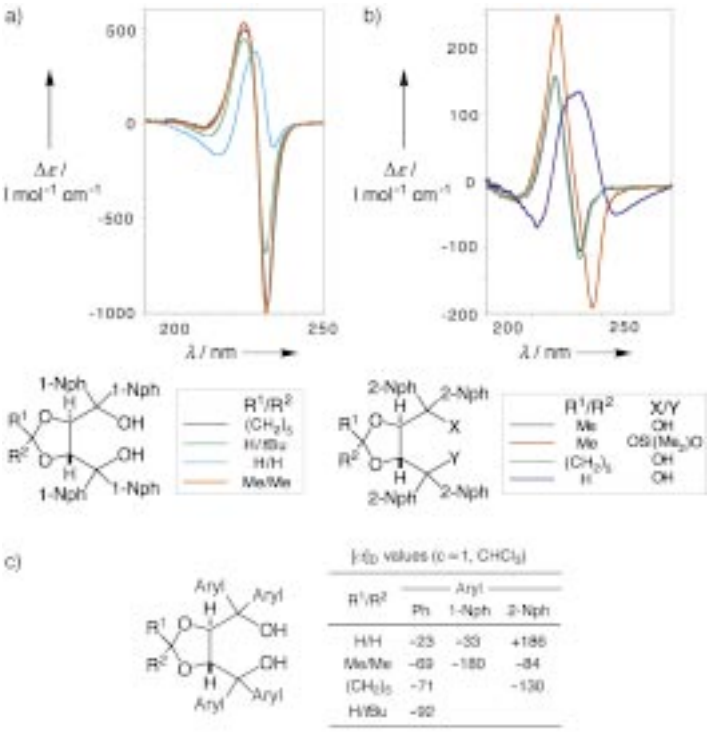
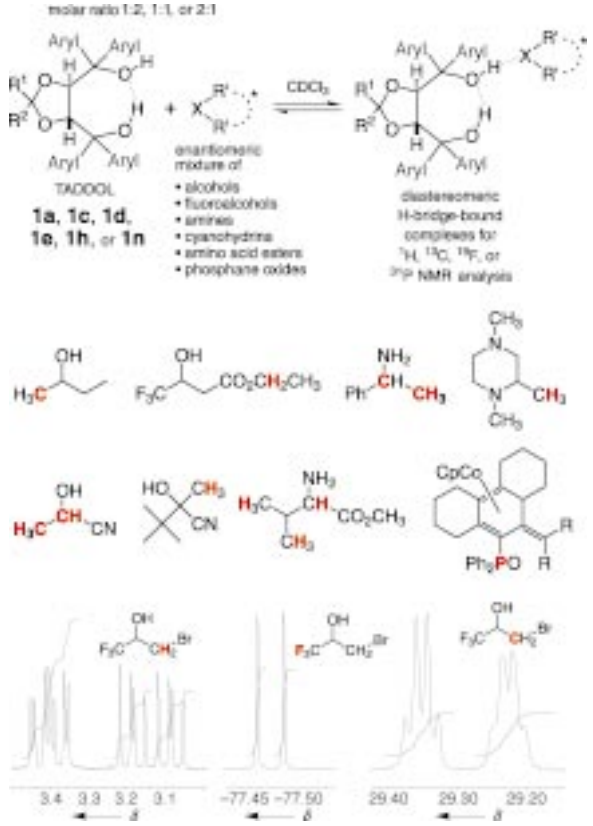


Figure 9. Exciton regions of the circular dichroism spectra (in acetonitrile) of TADDOLs with 1- and 2-naphthyl groups and various substitution patterns at the acetal/ketal center in the 2-position of the dioxolane ring,[120, 124] as well as $[\alpha]_D$ values for a few TADDOLs in $CHCl_3$. a) CD Spectra of 1-naphthyl derivatives. b) CD Spectra of 2-naphthyl derivatives. c) Comparisons of rotational values for a selection of TADDOLs. The significant changes observed in the transition from H/H to H/*t*Bu or to Me/Me (intensity and wavelength of the extremes, additional Cotton effects) argue for changes in conformation about the C–aryl bond. Differences are even apparent at the Na_D line. Various substituents in the 2-position of the dioxolane ring also have an influence on stereoselectivities of metal TADDOLate mediated reactions (Section 8) and on X-ray structures of TADDOLs (see Figure 6, left).



Scheme 5. TADDOLs as chiral shift reagents in NMR spectroscopy for determining the enantiomer purity of alcohols, fluorine compounds, amines, cyanohydrins, esters of amino acids,[70, 127] and phosphine oxides.[128] Magnetic nuclei whose NMR signals are split in an enantiomer-specific way are printed in red. The lower part of the scheme shows a ^{1}H NMR spectrum (each enantiomer leads to 2 dd signals for the protons marked in red in the formula), a ^{1}H-decoupled ^{19}F NMR spectrum, and an "inverse gated" ^{13}C NMR spectrum of a 2:1 mixture of TADDOL **1a** and the racemate of the illustrated fluorinated bromohydrin. Cp = cyclopentadienyl.

(for example, due to CH_3 groups and CH protons at the 4- and 5-positions on the dioxolane ring in **1a**). Broad *windows* are thus open for viewing the ^{1}H and ^{13}C signals of substrate molecules (^{19}F and ^{31}P spectra are of course *completely* free of interference!). In contrast to spectra resulting from the use of lanthanide shift reagents, signals in this case are not subject to line-broadening effects. Examples of this particular application are provided in Scheme 5. By recording a large number of spectra of similar compounds with known absolute configurations (amines, esters of amino acids, cyanohydrins) it is possible on the basis of analogies to assign absolute configurations.[127]

At a somewhat higher level of sophistication, the absolute configuration of a compound can be established with virtually absolute certainty by X-ray structural analysis of a corresponding inclusion compound with an (*R*,*R*)- or (*S*,*S*)-TADDOL (see Section 7.1.).

7. Inclusion Compounds Based on TADDOLs

As previously noted, TADDOLs crystallize especially well in the presence of hydrogen-bond acceptors, with which they also form inclusion compounds. If a TADDOL is crystallized in the absence of such an additive, the "free valence" still associated with one of the OH protons is, in principle, available for additional intra- or intermolecular interactions within the crystal. However, many enantiomerically pure TADDOLs crystallized without additives do not engage in intermolecular H···O interactions in the solid state. In special cases additional intramolecular hydrogen bonds develop (CSD Refcodes: POPJIN, VUSLEA; see Figure 7). In one case, dimer formation becomes possible through crystallographic symmetry (KOGJAR); the special situation in which a hydrogen-bonded TADDOL dimer constitutes the asymmetric unit also arises only once (SEWVUL). This is in sharp contrast to the solid-state structures of *meso*- or *rac*-TADDOLs (SEWWEW, SEWWAS, NIYTIY, NIYTUK), all of which crystallize in centrosymmetric space groups (with, in each case, a single molecule per asymmetric unit) and form dimers through crystallographic symmetry.[129]

For purposes of purification through recrystallization, and also for preparation of crystals suitable for single-crystal analysis, it is advantageous to introduce specific hydrogen-bond acceptors. Toda, a specialist in the field of solid-state organic chemistry who has also investigated other chiral

compounds as potential *host structures* for specific inclusions,[130] recognized[131] at an early stage the value of TADDOLs in this context (roughly 75 Toda papers in which TADDOLs play a role have appeared over the course of time). TADDOL hydrogen-bond donors crystallize readily—and preferentially with hydrogen-bond acceptors—and they can be exploited for the resolution of racemates as well as for promoting enantioselective solid-state reactions.

7.1. Use of TADDOLs in the Separation of Enantiomeric Hydrogen-Bond Acceptors

The separation of enantiomers, that is, resolution of racemates still represents the most frequently followed approach to commercial preparation of enantiomerically pure compounds. The classic technique for separating racemic acids (bases) involves crystallizing the diastereomeric salts that form with chiral bases (acids), where the ultimate source of chirality is always some natural product. More recently, chromatographic procedures have assumed a role in the synthesis of chiral pharmaceuticals, even on the multiton scale ("simulated moving bed" (SMB) chromatography), with amino acids or carbohydrates serving as the chiral components in stationary phases.[132] Another promising route takes advantage of differential crystallization of TADDOL inclusion compounds, especially in situations where the incorporated partners cannot be classified as bases in the usual sense. Not only enantiomers, but also diastereomers and even compounds differing in constitution, lend themselves to separation by way of TADDOL inclusion compounds.[66, 133]

The procedure for separating enantiomers in this way is, in principle, quite simple.[70, 134, 135] For example, one can begin by generating a solution consisting of two equivalents of a racemic compound and one equivalent of a TADDOL dissolved in an "inert" solvent such as toluene or hexane. Crystallization is then allowed to proceed. The resulting crystalline product is heated under vacuum, and the incorporated enantiomer is removed by evaporation. Yields often approach the theoretical limit of 50%, with enantiomer purities greater than 99%. X-ray structures of two inclusion compounds—(*S*)-3,4,4,5-tetramethylcyclohexenone in TADDOL **1a**[135] and (*S*)-1,3-dimethyl-5-phenyl-4,5-dihydropyrazoline in a TADDOL derivative containing *ortho*-tolyl groups—prepared in this way are presented in Figure 10.[134]

Instead of allowing the inclusion compound to crystallize from homogeneous solution, one can also—often with greater success—add a stirred suspension of the TADDOL host in hexane or water to a racemic mixture of the material to be resolved. The mixture is later filtered, after which the enantiomerically pure guest is removed under vacuum.

The method of racemate resolution through formation of inclusion compounds is an extraordinarily versatile one, as will be apparent from the limited set of examples collected in Scheme 6. All the compounds shown have been obtained in this way with enantiomer purities (*ep*)[137] exceeding 98%. The

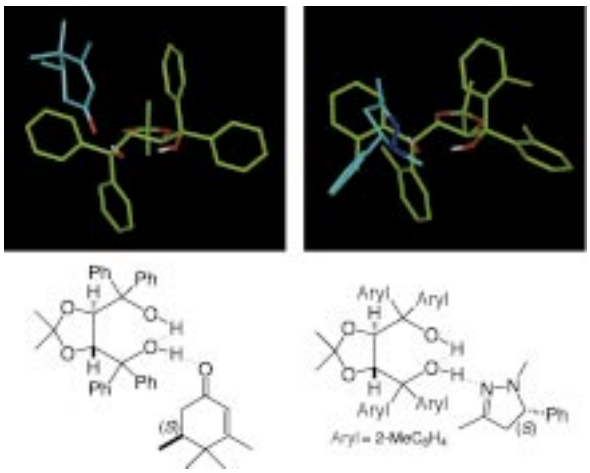


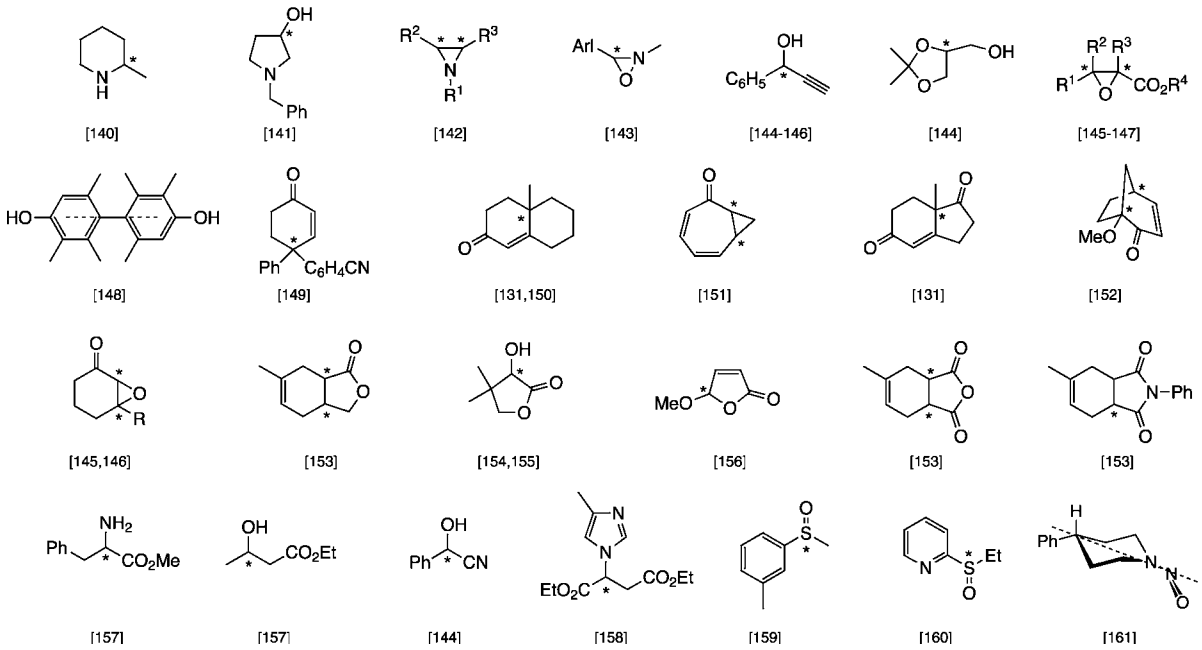
Figure 10. Two inclusion compounds involving TADDOLs prepared with racemate resolution of the guest molecules, and determination of the absolute configurations (by X-ray structure analysis) of the guest molecules (a cyclohexenone (CSD Refcode: RAZSUG), left, and a pyrazoline derivative (ZADMAS), right). The *rac*-cyclohexenone,[135] as a "neutral" compound, would not have been subject to "classical" resolution through diastereomeric salts; the *rac*-pyrazoline[134] had previously been separated by chromatography on a triacetylcellulose column.[136]

cited literature describes many additional examples. Thus, separations have been accomplished with enantiomer mixtures of nitrogen- (amines, nitrosamines, *N*-heterocycles), oxygen- (alcohols, phenols, ethers, ketones, esters, lactones, anhydrides), and sulfur-containing compounds (sulfoxides), as well as such multifunctional materials as esters of hydroxy or amino acids, cyanohydrins, alkoxylactones, and oxaziridines.

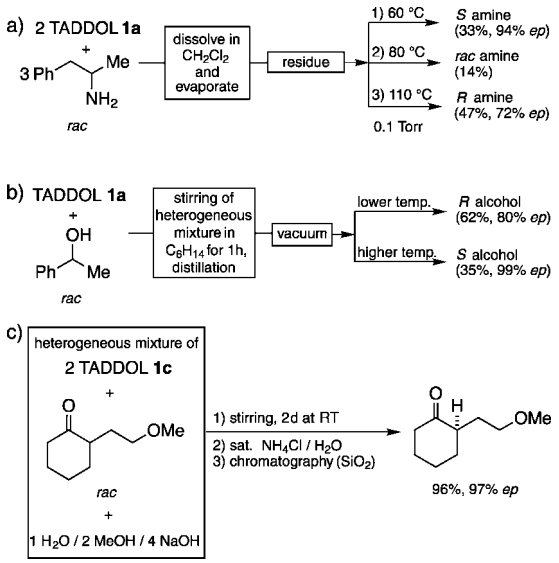
Inclusion compounds with TADDOLs have also made possible the distillatory separation of racemates.[162, 163] Two examples are shown in Schemes 7a and b. The nonincluded enantiomer is first distilled off at low temperature, followed by the included isomer at higher temperature under vacuum. The TADDOL itself—perhaps after recrystallization—can then be employed in a new process cycle.

Finally, so-called dynamic racemate resolution (previously known also as "asymmetric transformation of the second kind"[167]) has been accomplished with *rac*-2-allyl-, -2-benzyl-, and -2-methoxyethylcyclohexanones. In this application the two isomers are subjected to equilibration under basic conditions, but only one of them is captured within a TADDOL inclusion compound. Thus, a single 2-substituted cyclohexanone can ultimately be isolated with an enantiomer purity greater than 90% (Scheme 7c).[165]

This technique using TADDOLs for separation of enantiomers of "neutral" compounds (also feasible in the variant referred to as the "Dutch family" procedure[33]) is a welcome enhancement to what is still a very attractive approach to preparing enantiomerically pure compounds. Crystallization, both small- and large-scale (today often touted in conjunction with the fashionable label "molecular recognition"[168]) is perhaps the most esthetically pleasing purification method known to chemistry. Nevertheless, the new distillatory version of racemate resolution, also accomplished with the aid of TADDOLs,[169] might find broad application as well.



Scheme 6. Compounds whose racemates have been successfully resolved by crystallization in the form of inclusion compounds with TADDOLs. Enantiomer purities > 98% were achieved for all compounds shown (often after only a single crystallization). The TADDOLs utilized were **1a** (the parent molecule), **1c** and **1d** (based on 2,2-tetra- and -pentamethylenedioxolane), **1b** (the acetophenone derivative), **1h** (a TADDOL with five phenyl groups), and a derivative of **1a** bearing four *ortho*-tolyl groups. The inclusion compounds displayed host:guest ratios of 1:1, 2:1, or (less frequently) 1:2; separation was often accomplished by distillation of the low molecular weight inclusion compound (see also Scheme 7a). During the isolation of products (for example, by kugelrohr distillation) from reaction mixtures into which TADDOL derivatives have been introduced as reagents, mediators, or catalysts it is important that this volatility be borne in mind, because in the process the system might become enriched or depleted with respect to one enantiomer, thereby altering the apparent enantioselectivity of the corresponding reaction (see also Scheme 7). Intentional enrichment in terms of the enantiomer formed in excess is also possible in the workup of such a reaction.[138, 139]



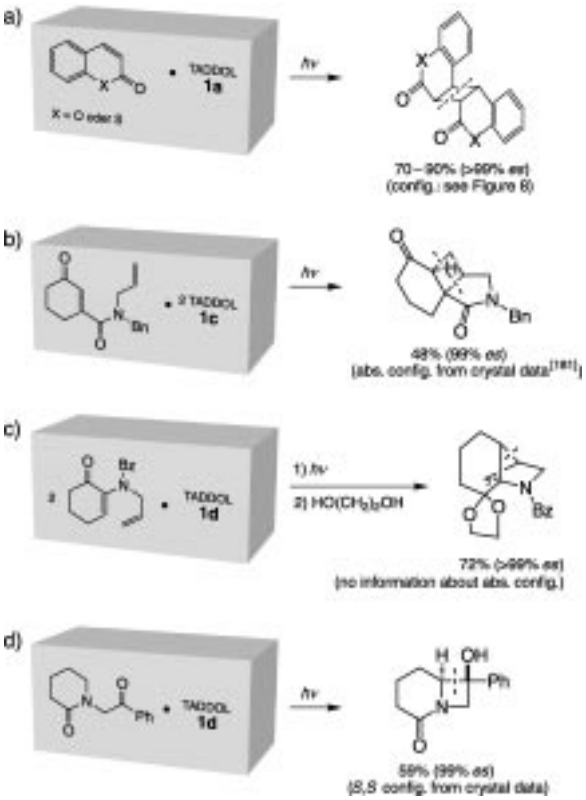
Scheme 7. a), b) Two distillatory resolutions[162] of racemates with the aid of TADDOL **1a**,[145, 146, 164] and c) quantitative enantioselective inclusion of (*R*)-2-methoxyethylcyclohexanone in TADDOL **1c** from a heterogeneous reaction mixture consisting of MeOH, H_2O, NaOH, *rac*-ketone, and TADDOL; here the enantiomeric ketones rapidly equilibrate with each other.[165] Caution: Either type of racemate resolution can, if it happens to occur during workup and isolation of products, alter the apparent results of an enantioselective reaction (in either a positive or a negative sense!); see also the legend to Scheme 6. This is an appropriate place to remind the reader that chromatographic purification of nonracemic mixtures of enantiomers (and of mixtures of *any type* of nonracemic compounds, including TADDOL-containing crude products from enantioselective reactions) can lead to enrichment or depletion of enantiomers in specific fractions![166]

7.2. Enantioselective Photoreactions in TADDOL Inclusion Compounds

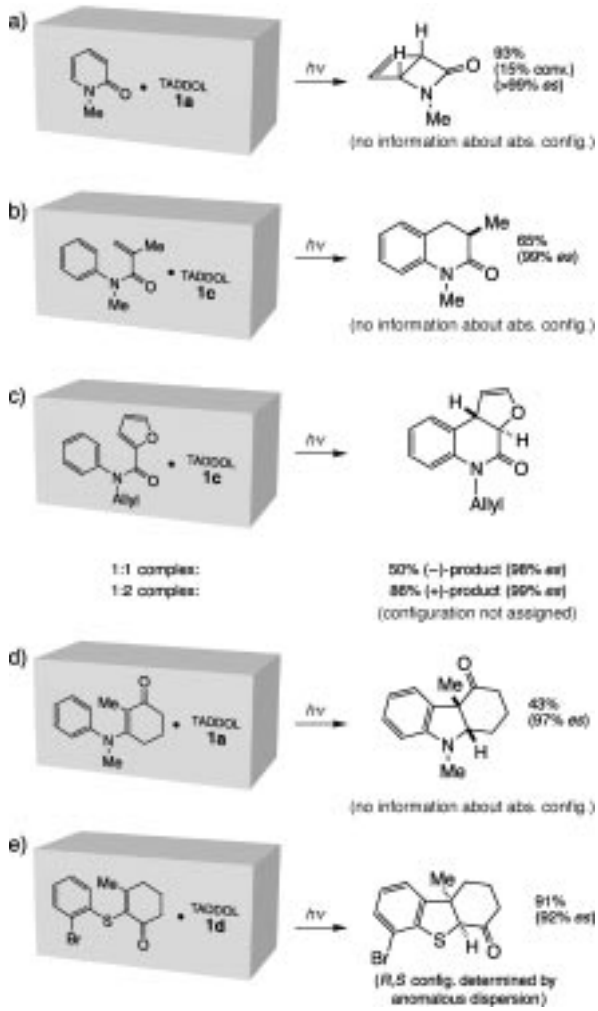
Once it had been recognized that TADDOLs, upon crystallization, form chiral structures with inclusion cavities capable of distinguishing between enantiomers (which might be regarded as "hotels offering chiral accommodations"), it was a natural step for a solid-state chemist like Toda to attempt to trap achiral molecules in the chiral cavities and thereby carry out (enantioselective) chemical reactions.[170, 171] Although regioselective[172] and diastereoselective[173, 174] transformations have also been observed in TADDOL host–guest compounds, we limit our discussion here to enantioselective transformations, especially photochemical reactions.

The studies in question were directed toward investigation of inter- and intramolecular [2+2] photocycloadditions,[175] Norrish type II reactions,[175] and electrocyclic photoreactions of the Ninomiya type[176, 177] (Schemes 8 and 9).

Since the pioneering efforts at the Weizmann Institute,[191] in which it was demonstrated that enantiomorphic crystals of achiral unsaturated compounds produce chiral, nonracemic cyclobutane derivatives upon irradiation, [2+2] photocycloaddition[107] has assumed a central role in solid-state and crystal chemistry. It is therefore no accident that this reaction has also been intensively investigated in the context of TADDOL inclusion compounds (see the three examples in Scheme 8). All the cyclizations proceed from achiral starting materials that have been incorporated into TADDOL host



Scheme 8. Enantiomerically pure four-membered ring compounds prepared from TADDOL inclusion compounds by photochemical inter- and intramolecular [2+2] cycloadditions and a Norrish type II reaction. a) For the *anti*-head-head dimerization of the coumarins,[178] see also Figure 11. b) This cyclobutane with annellated rings can be prepared with the aid of TADDOL **1c** by photolysis of a crystalline inclusion compound or by trituration of the oily amide mixture with **1c** in a mortar.[179–181] c) A bridged and annellated tricyclic system containing a four-membered ring is obtained from a 2:1 inclusion compound.[182] d) An enantioselective Norrish type II reaction in a TADDOL-host lattice.[183, 184] Photoreactions were carried out with a high-pressure mercury lamp (Pyrex filter). Bn = benzyl, Bz = benzoyl.



Scheme 9. Enantioselective photochemical cyclizations in TADDOL inclusion compounds. In addition to an electrocyclic valence isomerization to a cyclobutene derivative (a),[185] there occurs in this case a photoreaction in which a six-electron π system formally undergoes an electrocyclic reaction followed by a 1,3-sigmatropic hydrogen shift (Ninomiya cyclization). [176, 177] Anilides of carboxylic acids are introduced in (b) and (c),[186–188] as is an enamine of 2-methylcyclohexan-1,3-dione (a vinylogous anilide) in (d),[189] and a 2-arylthiocyclohexenone (a derivative of 3,5,5-trimethylcyclohexan-1,2-dione) in (e).[190] In the photoreaction illustrated in (c), a levorotatory product is obtained by irradiation of a 1:1 inclusion compound with TADDOL **1c**, whereas a dextrorotatory product forms from a 1:2 inclusion compound. All reactions were carried out with a high-pressure mercury lamp (Pyrex filter).

lattices, and they produce essentially enantiomerically pure products. The most spectacular example is certainly the coumarin dimerization, in which a single-crystal to single-crystal reaction has been accomplished. In the inclusion complex consisting of TADDOL **1a** and coumarin there exists a pair of coumarin molecules oriented in an *anti*-head-head orientation to each other, held in place by two TADDOLs through appropriate hydrogen bonds (Figure 11, red structure). Under irradiation the crystal remains intact, but it is nevertheless transformed ultimately into a single crystal of the cyclobutane-TADDOL inclusion compound (light blue structure in the overlay of Figure 11). The classic[5] photochemical valence isomerization converting pyridone into azabicyclo[2.2.0]hexene leads to an enantiomerically pure product when carried out in an inclusion compound with TADDOL **1a** (see Scheme 9a). The other four reactions presented in this particular scheme are also examples of photoisomerizations taking place within the chiral host lattice. The products obtained are five- (d, e) and six-membered (b, c) heterocyclic ring systems, enantiomerically pure or at least generated through processes that occur with high enantioselectivity. Especially noteworthy is formation in the case of the furan derivative of enantiomeric products, depending upon whether a 1:1 or a 2:1 complex is irradiated (Scheme 9c). TADDOLs with four phenyl groups appear especially well-suited to solid-phase photoreactions. (For additional examples see the review article by the Toda group.[170])

Other solid-state reactions with TADDOLs have so far proven less successful, at least with respect to enantioselectivity. Investigations have been conducted on borane reductions of unsymmetrical ketones,[65] Baeyer–Villiger oxidations,[192] ether formations,[193] Wittig olefinations,[194] Michael additions of thiols to enones,[195] and cyclopropanations of α,β-unsaturated carbonyl compounds with sulfoxonium ylides.[196] In every case, the reagents and TADDOL were mixed,

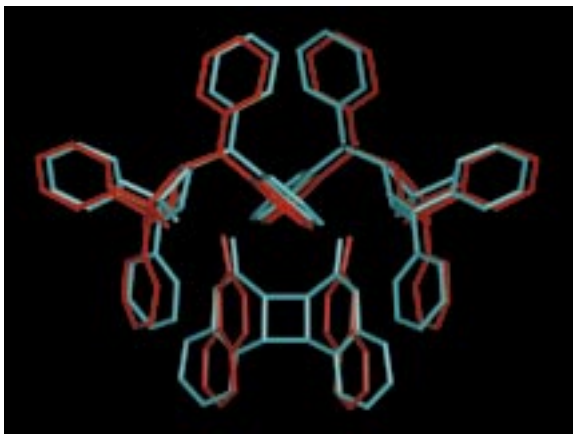


Figure 11. Overlay of structures of starting material and product for the photodimerization of coumarin in an inclusion compound with TADDOL **1a**. This is an unusual case of a single-crystal to single-crystal reaction.[178] The structure of a 1:1 host–guest crystal of coumarin with **1a** is shown in red. The crystal was irradiated to the point of complete photodimerization. It remained intact, and X-ray analysis showed the resulting structure to be that of a 1:2 *anti*-head-head dimer inclusion complex with **1a** (shown in light blue).

triturated, and left to stand for a period of time prior to workup. New attempts will undoubtedly be made with the TADDOL substitution products and derivatives described in Section 3, and at least some of the cited reactions will surely evolve to the point of generating product with the crucial level of at least 90% enantiomer purity.

8. TADDOL Derivatives as Reagents, and also as Ligands in Metal Complexes for Enantioselective Transformations

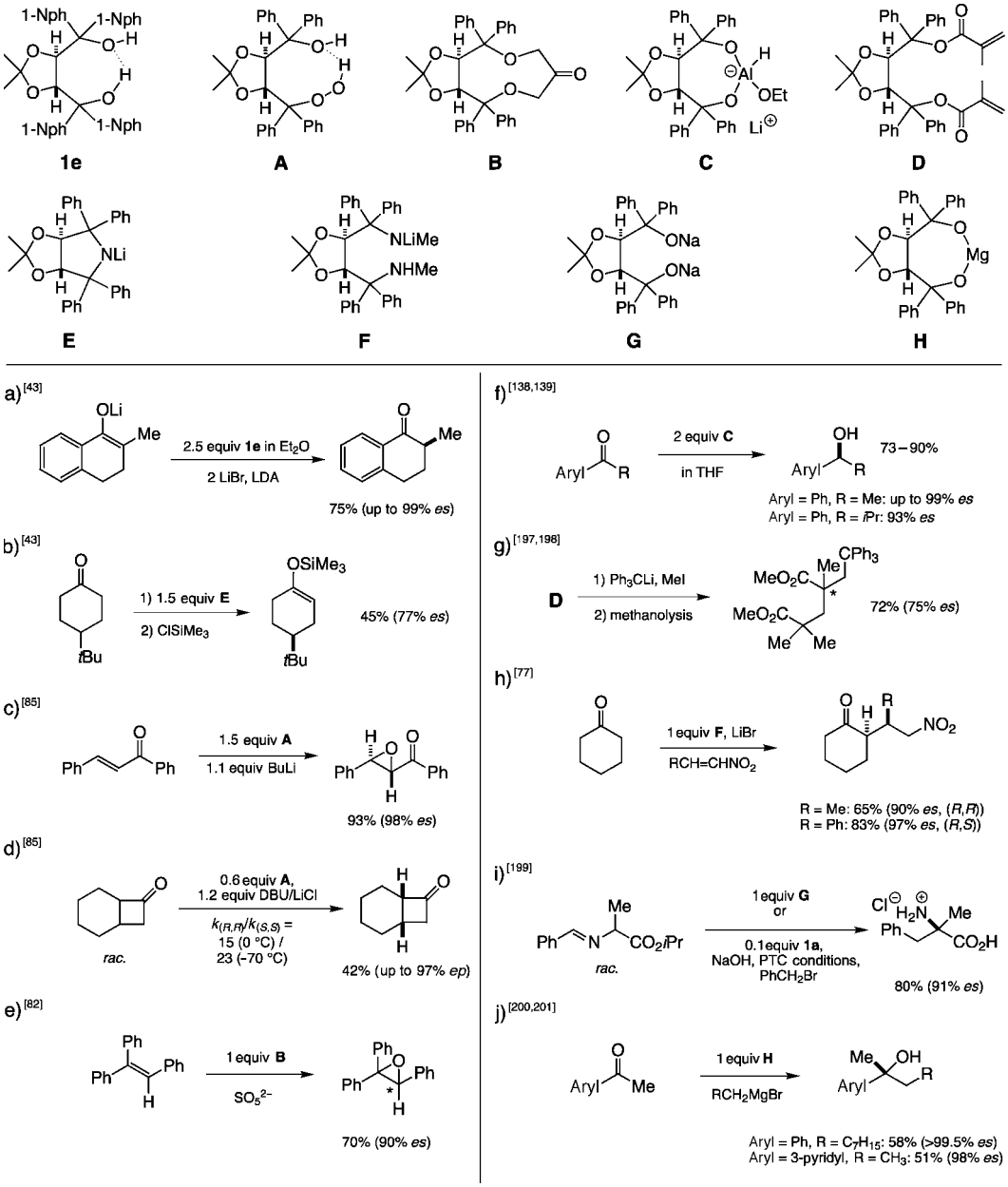
The strong tendency (documented in Section 7) of TADDOLs to cocrystallize with hydrogen-bond acceptors, which thereby become fixed within a chiral environment, establishes the TADDOLs as novel tools valuable in the separation of enantiomers ("chiral sorting machines") and the promotion of enantioselective solid-state reactions ("chiral vices"). The interactions responsible for these effects are of course also present in solutions based on suitably selected solvents (see the discussion of NMR shifts in Section 6). More important, however, has been the discovery through structural studies (Sections 4 and 7) that TADDOL derivatives are predisposed structurally to complex with metallic centers, in that heteroatoms in the diarylmethyl units position themselves—with few exceptions—in close proximity to each other, conformationally fixed to act as chelating ligands with well-defined geometry. This opens the way to the most valuable application of TADDOL systems to date from the standpoint of the synthetic organic chemist: enantioselective synthesis. After all, resolution of a racemate can scarcely be regarded as a chemical reaction, and solid-phase photosynthesis represents a very special case, one not necessarily adaptable to the large-scale commercial preparation of enantiomerically pure compounds. Moreover, TADDOL derivatives might also have a future as chiral reagents on a stoichiometric basis. In the sections that follow we first examine applications involving the chemistry of derivatives of main-group metals (Li, Na, Mg, Al) and stoichiometric transformations (Section 8.1), then the most intensively investigated titanium TADDOLate mediated reactions (Section 8.2), and finally use of TADDOLs as ligands on other transition-metal centers (Section 8.3). In the course of this account it will become clear that TADDOL derivatives can also function as "chiral tools" for assisting in chemical transformations (acting at least figuratively as chiral tweezers, tongs, hammers, chisels, files, and screwdrivers in the accomplishment of molecular processes). In many cases record-breaking results have been achieved, although some of the examples could more accurately be described as promising beginnings.

8.1. Chiral Acids, Bases, Oxidizing/Reducing Agents, and Additives Based on TADDOLs and TADDAMINes

Selected examples of the reactions of interest here are presented in Scheme 10. We begin by showing how the acidity of a TADDOL can be exploited for enantioselective protonation of an achiral enolate, as in the transformation of a *rac*-ketone into its enantiomerically pure form (Scheme 10a).[202, 203] Initial experiments have shown that the lithium amides **E** and **F** of TADDAMINes (prepared from TADDOLs by OH/NR_2 substitution; see Section 3) are capable of preferentially deprotonating one of the enantiotopic CH_2 groups of 4-*tert*-butylcyclohexanone (Scheme 10b; see the work of Koga,[204] and Cox and Simpkins[205]), or causing the achiral lithium enolate of cyclohexanone to add with high enantioselectivity to a nitroolefin (Scheme 10h; see results reported by Koga and co-workers[204, 206] and reviews of the structure and reactivity of lithium enolates[207, 208]).

The remarkably stable hydroperoxide TADOOH (**A** in Scheme 10) can be deprotonated with BuLi (stoichiometrically) or DBU/LiCl (catalytically) and utilized for the epoxidation of unsaturated phenylketones. TADOOH reacts with cyclobutanones under Baeyer–Villiger oxidation conditions in such a way as to effect enantiomer differentiation, especially at low temperature (Scheme 10c, d[209, 210]). A ketone derived from dihydroxyacetone and TADDOL **B** has been used as a catalyst (which forms a dioxirane) for enantioselective epoxidations with Caro's acid (H_2SO_5, Oxone;[211] Scheme 10e).

Reduction of arylketones can be accomplished with high enantioselectivity using **C**, a lithium aluminum hydride derivative of TADDOL (Scheme 10f). Superb catalytic variants on this reaction are now available as well, for example, the Corey–Itsuno reduction.[212] A useful feature of the method illustrated here is the fact that in many cases the enantiomer purity of the product can be raised to $>99\%$ during workup by taking advantage of the "enantioselective affinity" of the TADDOL for hydrogen-bond donors. Thus, a crude-product residue is digested with hexane, causing the underrepresented enantiomer to pass preferentially into solution, with the principal enantiomer being retained by the TADDOL.



Scheme 10. Use of TADDOL **1e** and the derivatives **A**–**H** as reagents (a–d, f–h), as stoichiometric additives (e, h–j), and/or as catalysts (i) in enantioselective protonations (a)/deprotonations (b), oxidations (c–e), reductions (f), and C–C bond formations (g–j). Most of the cited references provide additional examples. The configurations of the chiral centers which are marked with a star in the products have not been defined. 1-Nph = 1-naphthyl, LDA = lithium diisopropylamide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, PTC = phase-transfer catalysis.

In the enantioselective C–C bond-forming reactions shown in Scheme 10 a TADDOL serves (in the formation of glutaric acid esters) as the covalently bonded *RO fragment of a starting diester (**D**, Scheme 10g); in the synthesis of α-branched amino acids, sodium TADDOLate **G** appears to function as a phase-transfer catalyst (Scheme 10i); and in Grignard additions to aromatic, heteroaromatic, and α,β-unsaturated ketones a magnesium TADDOLate **H** (Scheme 10j), introduced in stoichiometric amounts, behaves as a chiral Lewis acid and is responsible for record-breaking selectivity, only one enantiomer of the product being detectable by gas chromatography.

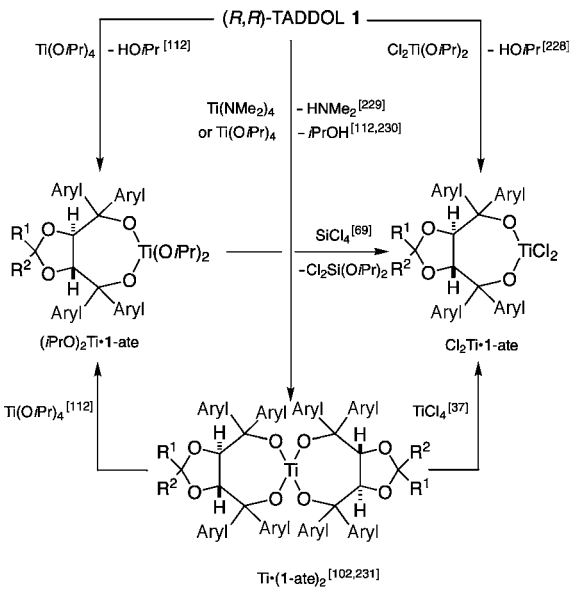
The new nitrogen- and sulfur-containing TADDOL derivatives (Figure 2 and Scheme 5 left and center) should prove especially well suited to a host of other stoichiometric applications. It should not be forgotten, however, that this involves manipulation of large amounts of the auxiliary (molecular mass of **1a**: 466 Da), and in this context attention should be directed toward Section 9, which deals with polymeric and solid state bound TADDOLs.

8.2. Titanium TADDOLates in Enantioselective Synthesis

Apart from resolution of racemates and solid-state reactions, the principal field of application to date for TADDOLs has been enantioselective syntheses mediated by titanium

TADDOLates. Two types of reaction must here be distinguished: a) nucleophilic additions to aldehydes, ketones, α,β-unsaturated carbonyl compounds, esters, anhydrides, and nitroolefins, along with reactions of nucleophiles with halogenating or oxidizing agents, in which the actual nucleophile may be an Nu–TiX · TADDOLate;[213] and b) Lewis acid catalyzed transformations in which the electrophile is activated by an X_2Ti-TADDOLate (for example, sulfoxidations, epoxidations, Baeyer–Villiger oxidations, cyclopropanations, and [2+2], [3+2], or [4+2] cycloadditions). With X_2Ti-TADDOLates, the donor strength or anion stability of the X groups, and thus the Lewis acidity of the titanate,[214, 215] can be varied from amide (NR_2) through cyclopentadienide, alkoxide, phenoxide, sulfonate, bromide, and chloride all the way to fluoride.[216] As in the case of classic Lewis acid dependent reactions (such as Friedel–Crafts acylation), a stoichiometric amount of the Lewis acid is often required[217–226] because this may bind more firmly with the product than with the starting electrophile one wishes to activate.

A few observations regarding the preparation of titanium TADDOLates are in order (Scheme 11) before we discuss these two types of reaction in detail in the sections that follow.



Br_2Ti•**1**-ate	(from **1** and $Br_2Ti(OiPr)_2$) [232]
$(TolSO_2O)_2$Ti•**1**-ate	(from Cl_2Ti•**1**-ate and 2 AgOTos) [233]
(CF_3SO_2O)Ti•**1**-ate	(from Cl_2Ti•**1**-ate and 2 AgOTf) [233]
(ClO_4)ClTi•**1**-ate	(from Cl_2Ti•**1**-ate and 1 $AgClO_4$) [37]
$(ClO_4)_2$Ti•**1**-ate	(from Cl_2Ti•**1**-ate and 2 $AgClO_4$) [37]
CpClTi•**1**-ate	(from **1**, $CpTiCl_3$ and 2 Et_3N) [234]
$(NC)_2$Ti•**1**-ate	(from Cl_2Ti•**1**-ate and 3 Me_3SiCN) [235]
BINOLate•Ti•**1**-ate	(from $(iPrO)_2$Ti•**1**-ate and BINOL) [236]

Scheme 11. Preparation and in situ generation of titanium TADDOLates by ligand exchange. The spirotitanate of **1a** is a stable material that can be stored, is useful for the preparation of pure TADDOLates of the type X_2Ti · **1a**-ate by "symproportionation", and often functions itself as a catalyst. In particular, Cl_2Ti-TADDOLates are frequently used in the presence of *i*PrOH, so Brønsted catalysis (HCl!) may play a role in the transformations.[203, 227] The cited references include typical procedures, or at least data for synthesis or preparation of the corresponding titanates. Tf = trifluoromethanesulfonyl, BINOL = 2,2′-dihydroxy-1,1′-binaphthyl.

Numerous recipes have been proposed by various authors according to which the complexes of interest can be obtained and introduced into reactions. In most cases, a TADDOL is treated with $Ti(OiPr)_4$ or $Cl_2Ti(OiPr)_2$ in toluene, CH_2Cl_2, or some other aprotic solvent. With the former titanium reagent, 2-propanol is then removed under vacuum, along with the solvent. In the latter case only one equivalent of alcohol can be removed in this way;[228] that means, what remains behind is a complex of the type Cl_2Ti · **1**-ate · *i*PrOH. Often there is simply introduced a solution containing both TADDOL and $Cl_2Ti(OiPr)_2$, so that various titanium TADDOLates, together with *i*PrOH and HCl, may all be present and in equilibrium. The addition of molecular sieves has also been recommended, which might bind traces of water but certainly not *i*PrOH. If one employs a C_1-symmetric TADDOL with two different R groups in the 2-position of the dioxolane ring, the catalytically active mixture may contain *cis*/*trans*-isomeric complexes as well (for example, the XYTi · **1b**-ates). On the other hand, uniform X_2Ti-TADDOLates can be obtained by 1:1 reaction of a spirotitanate Ti · (**1**-ate)$_2$ with TiX_4. The spiro compound is best prepared by reacting $Ti(NMe_2)_4$ with TADDOL in a ratio of 1:2 and removing the resulting dimethylamine under vacuum. The parent compound Ti · (**1a**-ate)$_2$ is a crystalline solid sufficiently stable in air to be suitable for storage. The required quantity can therefore be introduced into a reaction simply by weighing the reagent in the open air. Another trick for preparing a pure Cl_2Ti-TADDOLate is treatment of the corresponding $(iPrO)_2$ derivative with $SiCl_4$, with removal of $Cl_2Si(OiPr)_2$ under vacuum. The reader is referred to the literature for experimental details, which can often prove decisive with respect to reproducibility of the reactions presented in the schemes below and, thus, to achieving the reported results. Attention is also directed to review articles dealing with chiral titanates.[27, 218, 226, 237–240]

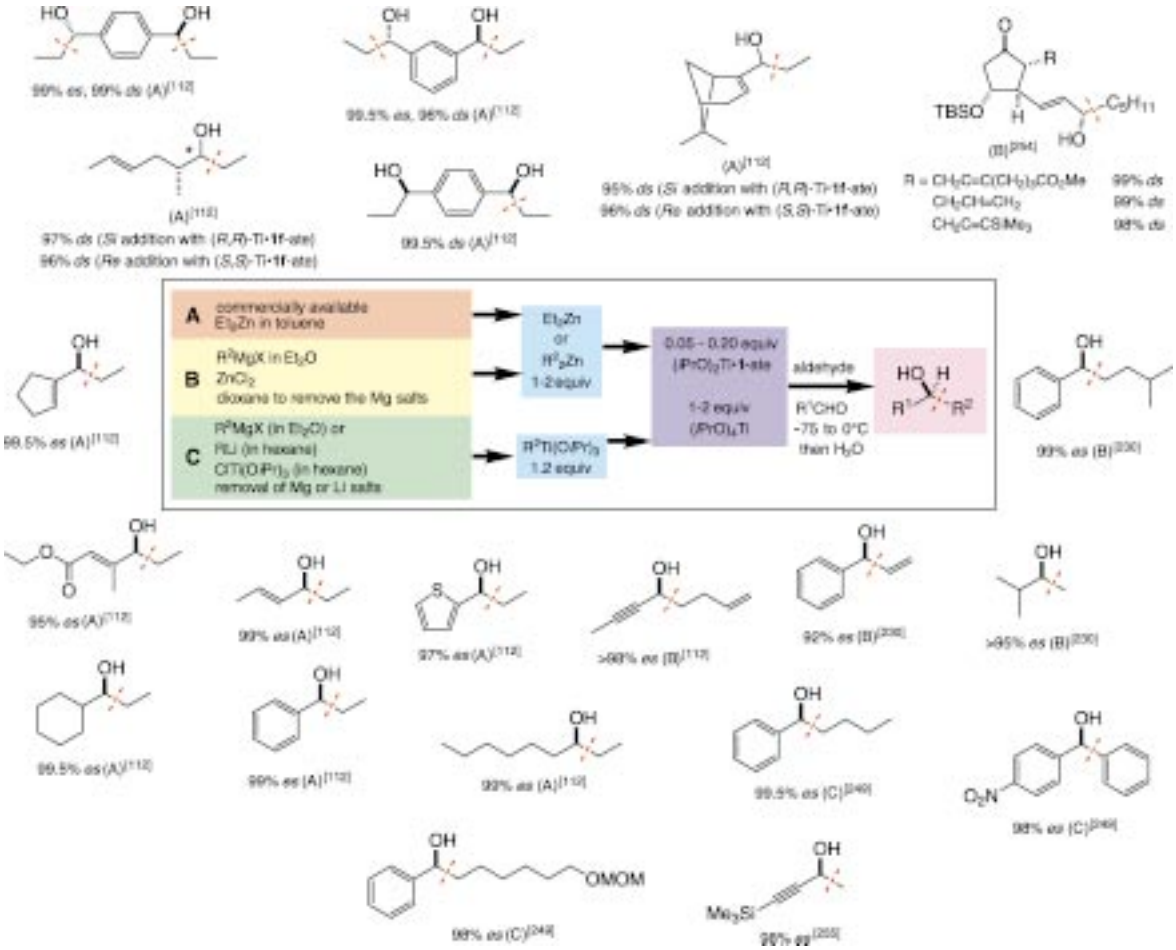
8.2.1. Nucleophilic Additions in the Presence of Titanium TADDOLates, and Reactions of Nucleophilic TADDOLato-Titanium Derivatives

Once early TADDOL experiments had revealed that "Grignard additions" to aldehydes can be rendered enantioselective by exchanging XMg (or Li) in the organometallic compound for $(R^*O)_3$Ti, it was of course tempting to seek a catalytic variant of the process. Since the usual polar metal derivatives are much too reactive to profit at ordinary reaction temperatures from the availability of a catalyst, there appeared to be merit in following the trail backward from Grignard to Frankland. Over 150 years ago the latter stumbled across the gateway to organometallic chemistry with the preparation of alkylzinc compounds,[241] and these react only poorly with aldehydes, even at room temperature. Noyori et al. has in recent years demonstrated that chiral amino alcohols can function as (basic!) catalysts for a highly enantioselective addition of diethylzinc to aldehydes,[242] and Ohno and co-workers discovered further that a mixture of achiral $Ti(OiPr)_4$ with the bistriflamide of (*R*,*R*)-1,2-cyclohexanediamine (in a ratio up to 5000:1) is capable of effecting superb (Lewis acidic!) enantioselective catalysis of this reaction.[243–245] Unfortunately, however, very few organozinc

derivatives are commercially available,[246] and the prospect of preparing a pure organozinc compound as needed has never been a pleasant one.[243, 247]

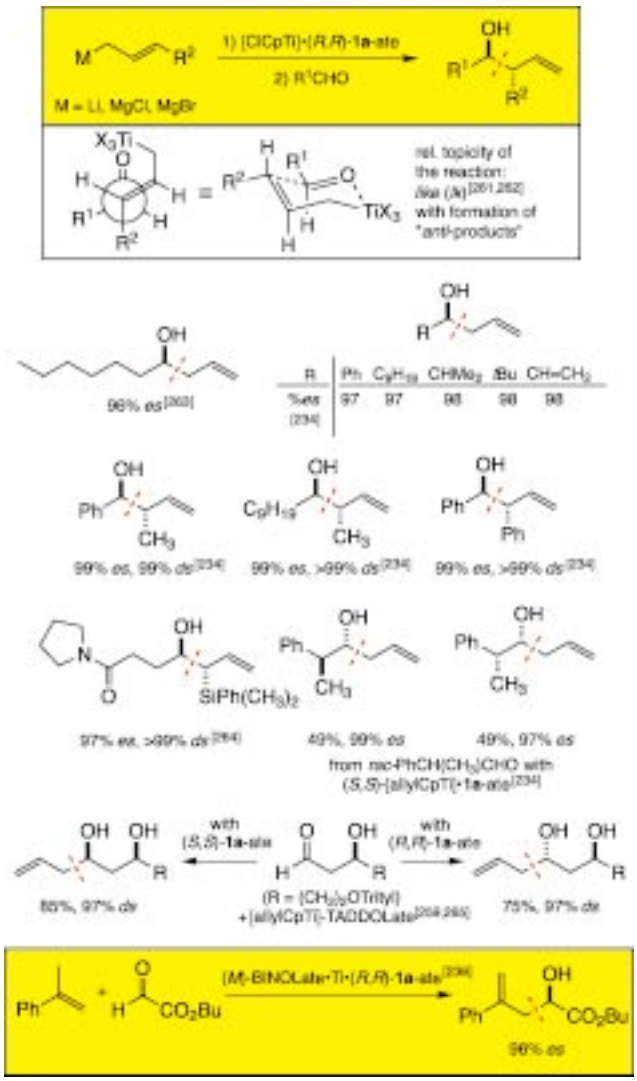
In our research group we discovered[231] that 0.05 – 0.20 equivalents of $(i\mathrm{PrO})_2\mathrm{Ti}\cdot\mathbf{1}$-ate also catalyzes the highly enantioselective addition of diethylzinc to aldehydes, but only in the presence of excess $(i\mathrm{PrO})_4\mathrm{Ti}$. We also developed a simple procedure for in situ preparation of other organozinc compounds, starting from lithium or XMg precursors.[230, 248] The organometallic titanates $\mathrm{RTi}(\mathrm{O}i\mathrm{Pr})_3$, which are accessible by the same route, also add to aldehydes with high enantioselectivity in the presence of titanium TADDOLate (and with better stoichiometric utilization, relative to $\mathrm{R_2Zn}$, of the group R that is to be introduced!).[249] This observation is especially noteworthy because such organotitanates react with aldehydes at temperatures as low as $-60\,^{\circ}\mathrm{C}$, albeit not enantioselectively.[27] (With respect to mechanistic studies, see Section 10.) The titanium TADDOLate catalyzed addition of carbon nucleophiles to aldehydes has proven to be the most widely applicable and most highly enantioselective variant of this type of reaction, serving to some extent as a standard for comparison purposes[250] (see Scheme 12). Often, but not always, the TADDOL bearing 2-naphthyl groups leads to record values.[112, 230, 251] Substituents on the phenyl groups—through to 4-dimethylamino groups—have almost no effect on selectivity.[102, 252] Carbocyclic and carbobicyclic TADDOL analogues also lead to no better results,[44, 50, 51] and titanates other than isopropyltitanates are less well suited to the purpose.[253] The method is applicable to all types of aldehydes so long as they contain no other functional groups capable of forming chelates with metals. In the case of chiral aldehydes the (diastereoselective) course of the reaction is dictated by the nature of the titanium TADDOLate. The structure of the nucleophile can also be varied within wide limits, again so long as there are no heteroatoms present capable of forming five- or six-membered cyclic chelates.

Tests have been conducted as well with 1:1-ate complexes composed of a titanium TADDOLate and RLi or

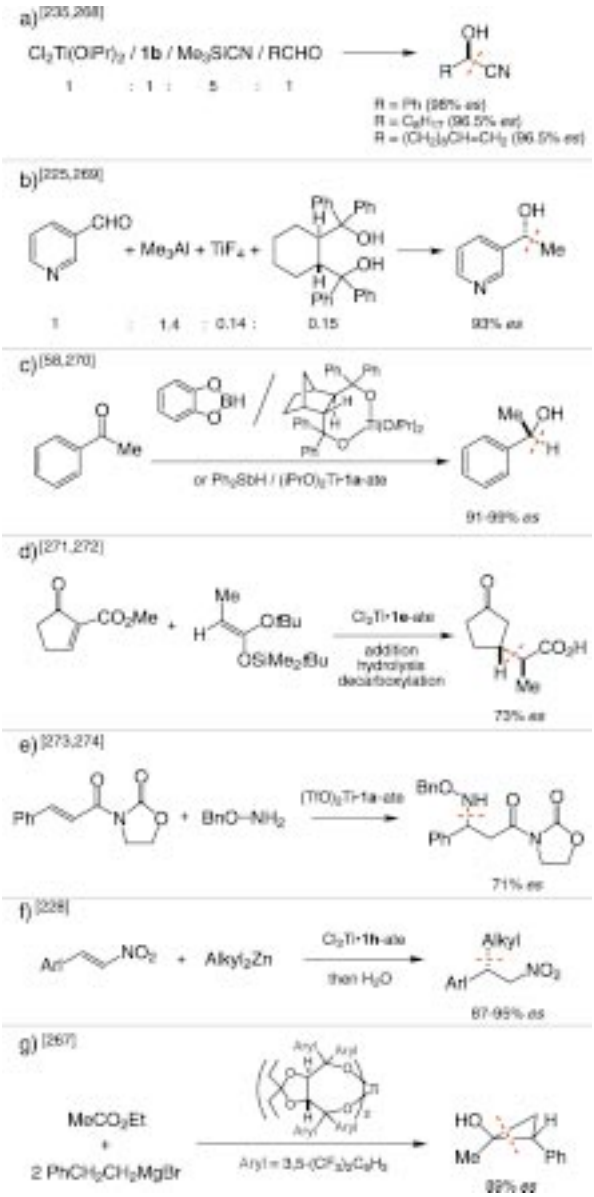


Scheme 12. Nucleophilic additions of organometallic compounds R–M to aldehydes in the presence of substoichiometric amounts of $(i\mathrm{PrO})_2$Ti-TADDOLates, or with in situ preparation (methods B and C) of salt-free solutions of $\mathrm{R_2Zn}$[246] and $\mathrm{RTi}(\mathrm{O}i\mathrm{Pr})_3$ from Grignard reagents or lithium compounds in diethyl ether, THF, hexane, or toluene. Newly formed C–C bonds are indicated by dotted lines. Addition occurs from the *Si* side of the aldehyde carbonyl group when (*R*,*R*)-TADDOL is used as the auxiliary, and from the *Re* side with (*S*,*S*) material (relative topicity *unlike* (*ul*)). In most of the examples shown here, TADDOL **1f** (with β-naphthyl groups) is utilized. The reported high selectivities are achieved only in the presence of excess $\mathrm{Ti}(\mathrm{O}i\mathrm{Pr})_4$. It is not necessary that there be two different types of metallic species ($\mathrm{Ti^{IV}/Zn^{II}}$) present in the reaction mixture (in method C only titanates!). Functional groups in the reactants are tolerated so long as they cannot form 5- or 6-membered cyclic chelates with metals. With chiral aldehydes the stereochemical course of the reaction is determined by the titanium TADDOLate ("reagent control"). Note that the C–C bond forming reaction permits enantioselective preparation of secondary alcohols RCH(OH)R′ with very similar R groups (alkyl/alkyl′ or aryl/aryl′), a result that cannot be achieved by reduction of the corresponding ketones or hydroboration of olefins. TBS = *tert*-butyldimethylsilyl, MOM = methoxymethyl.

RMgX,[231, 256] but these have rarely shown enantioselectivities exceeding 90%. The addition of allylic nucleophiles is most successful, on a stoichiometric basis, with Duthaler's CpTi-TADDOLate complexes or, catalytically, through an ene reaction with an activated aldehyde (Scheme 13). Examples of other nucleophilic additions, including reductions of ketones, are collected in Scheme 14; reactions of TADDOLato-titanium enolates are shown in Scheme 15.

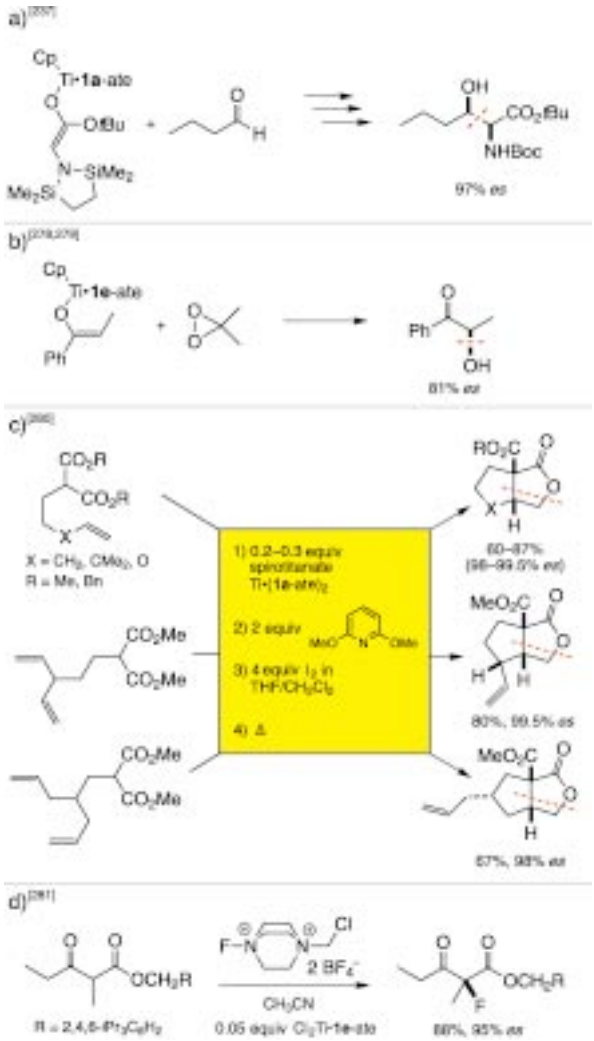


Scheme 13. Enantioselective transfer of allyl groups to aldehydes (with the formation of one or two new stereocenters) with allylcyclopentadienyltitanium TADDOLates[237] or by a Lewis acid catalyzed ene reaction.[236] Lower enantioselectivities are obtained with simple allyl derivatives of zinc or through ate complexes.[231, 257] [$CpTiCl_3$] used to prepare the Duthaler reagent can be regenerated (to some extent recovered) at the conclusion of the reaction. Substituted allyl groups ($R^2 \neq H$) are preferentially transferred with relative topicity *lk*, which is true as well of nonchiral allyltitanates[258] (*ul* in the case of the silyl derivative illustrated because of a reversal in the CIP priority sequence). It is worth noting that the diastereoselective addition of allyl-Cp-titanate to the *unprotected* 3-hydroxyaldehyde is "dictated" by the TADDOLate.[259] The ene reaction generally gives higher selectivities with titanium BINOLates than with titanium TADDOLates.[236, 260] The Lewis acid employed in the example shown is a spirotitanate with the two bidentate ligands BINOLate *and* TADDOLate (a sort of "marriage" of two systems!). Trityl = triphenylmethyl.



Scheme 14. Enantioselective 1,2- and 1,4-additions to carbonyl compounds and nitrostyrenes, mediated by titanium TADDOLates. a) Cyanohydrin reactions, which—depending on the type of aldehyde (aliphatic/aromatic) and the technique for preparing the reagent (with/without warming; with/without addition of molecular sieves)—result in varying yields and stereoselectivities. Under optimal conditions, alkyl-CH(OH)CN *and* aryl-CH(OH)CN are obtained in 80–90% yield with >97% *es*. b) Titanium fluoride catalyzed addition of Me_3Al to an aldehyde in the presence of the cyclohexane analogue of TADDOL. c) Ketone reduction with catecholborane or a stibane (radical mechanism?) occurs enantioselectively with addition of $(iPrO)_2Ti \cdot$ TADDOLate or the norbornane analogue; see also the hydrosilylations in Figure 12. d)–f) Michael additions do not show high enantioselectivities; in the case of addition of an alkylzinc compound to a nitrostyrene (f), the enantiomer purity can be increased by crystallization at the stage of the reduction product Aryl–$CHRCH_2NH_2$. g) The formation of cyclopropanols from esters and Grignard reagents with β-hydrogen atoms[266] in the presence of titanates can best be directed enantioselectively using the TADDOLate that bears four 3,5-bis(trifluoromethyl)phenyl groups (for a mechanistic suggestion, see ref. [267]).

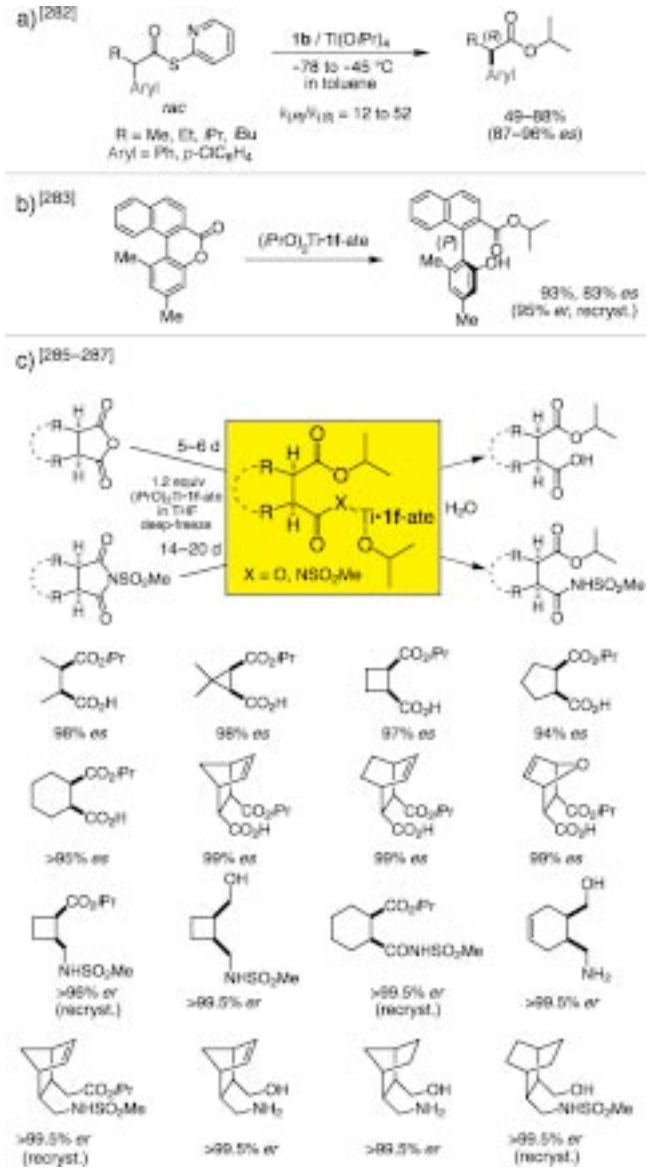
The system $(iPrO)_2$Ti-TADDOLate can also be used for transesterifications that involve differentiation between enantiomers,[282] for ring openings of lactones[283] and azlactones,[284] and for the enantioselective opening of *meso* five-



Scheme 15. Reactions of TADDOLato-titanium enolates with electrophiles. a) CpTi-enolates with TADDOLate ligands generally add to aldehydes with poorer selectivity than do the corresponding allyltitanates (Scheme 13), although the example shown here is an exception;[275, 276] in most cases, carbohydrate derivatives (diacetoneglucose, DAGO) are more effective. b) Hydroxylation with dioxirane also occurs with disappointing selectivity. c) The highly enantioselective cyclizations of ω-pentenyl malonic esters described by Taguchi et al.[277] are a result of intramolecular alkylation of TADDOLato-titanium malonic ester enolate complexes by iodonium ions, followed by lactone formation. d) An acetoacetic ester enolate is enantioselectively fluorinated under the influence of a $Cl_2Ti\cdot$ TADDOLate. Boc = *tert*-butoxycarbonyl.

membered cyclic anhydrides[285, 286] and *meso*-*N*-sulfonylimides.[287] In particular, opening of an anhydride to a half ester displaying a high degree of enantiomer purity has been shown to be a generally applicable process, and should represent a real alternative to enzymatic saponification or the esterification[288] of a dicarboxylic acid derivative, or other reactions that lead to half esters.[289] For information regarding the conduct of such reactions and a few examples, see Scheme 16.

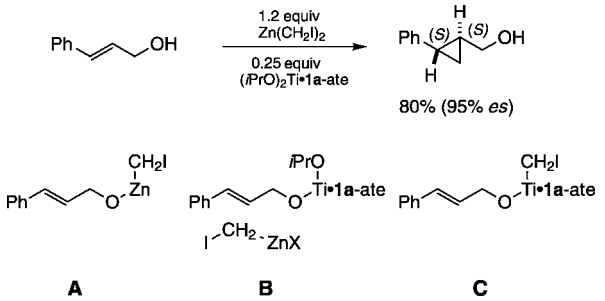
The applications illustrated with respect to titanium TADDOLates, especially nucleophilic addition, provide evidence of the versatility of this auxiliary for the enantioselective preparation of synthetic starting materials, but also for



Scheme 16. Enantioselective formation of isopropyl esters by *i*PrO transfer from $(i\mathrm{PrO})_2\mathrm{Ti}\cdot$TADDOLates. a) The illustrated racemic "active esters" of pyridinethiol are transformed (with kinetic resolution through in situ recycling) into 2-arylalkanoic acid isopropyl esters. b) Phenolic lactones can also be opened with "dynamic" racemate resolution to axial chiral biphenyl esters. c) The anhydrides of *meso*-succinic acid derivatives and the corresponding *N*-sulfonylsuccinimides are opened with diisopropoxytitanium TADDOLates containing 2-naphthyl groups to give half esters or sulfonylamido esters. The observed selectivity is largely independent of structure, and lies in the range 95 – 99 % *es* with anhydrides and 85 – 95 % *es* with imides, where the amido esters can be readily enriched further by recrystallization (hence the data in % *er* rather than % *es*!). Separation of the products from TADDOL after hydrolysis is accomplished by extraction of the carboxylic acid or *N*-acylsulfonamide into aqueous base. The half esters are readily transformed into γ-lactones, and hydroxysulfonamides or 4-aminoalcohols are accessible by reduction of the amidoesters (see the examples in the bottom two rows of formulae in (c)). Transformation of *meso* starting materials into chiral products by differentiation of enantiotopic groups (in the present case, with the "normal" CIP priority sequence, it is the *Re* carbonyl groups that are attacked by isopropoxide) is also referred to as "desymmetrization" (starting material with C_s symmetry is transformed into a C_1-symmetrical product); an excellent review article on this subject has recently been published,[290] which offers the opportunity to compare the titanium TADDOLate method of preparing half esters and their derivatives with other procedures.

carrying out diastereoselective transformations with complex synthetic intermediates. In most cases it has not been established whether—and in which of the various reactions discussed—the nucleophile is transferred directly from an Nu−TiX · TADDOLate species to the electrophilic center, or if the titanium TADDOLate behaves as a chiral Lewis acid in activating the electrophile, after which a nonchiral nucleophile carries out the actual attack (see Section 8.2.2). In fact, accomplishing such a distinction would entail complex kinetic and spectroscopic studies.

Another interesting example is provided by enantioselective Simmons – Smith cyclopropanation in the presence of 0.25 equivalents of $(i\mathrm{PrO})_2\mathrm{Ti}\cdot$ **1a**-ate, an achievement that cannot be assigned unambiguously to any of the reaction categories discussed in Sections 8.2.1 and 8.2.2[291, 292] (Scheme 17).



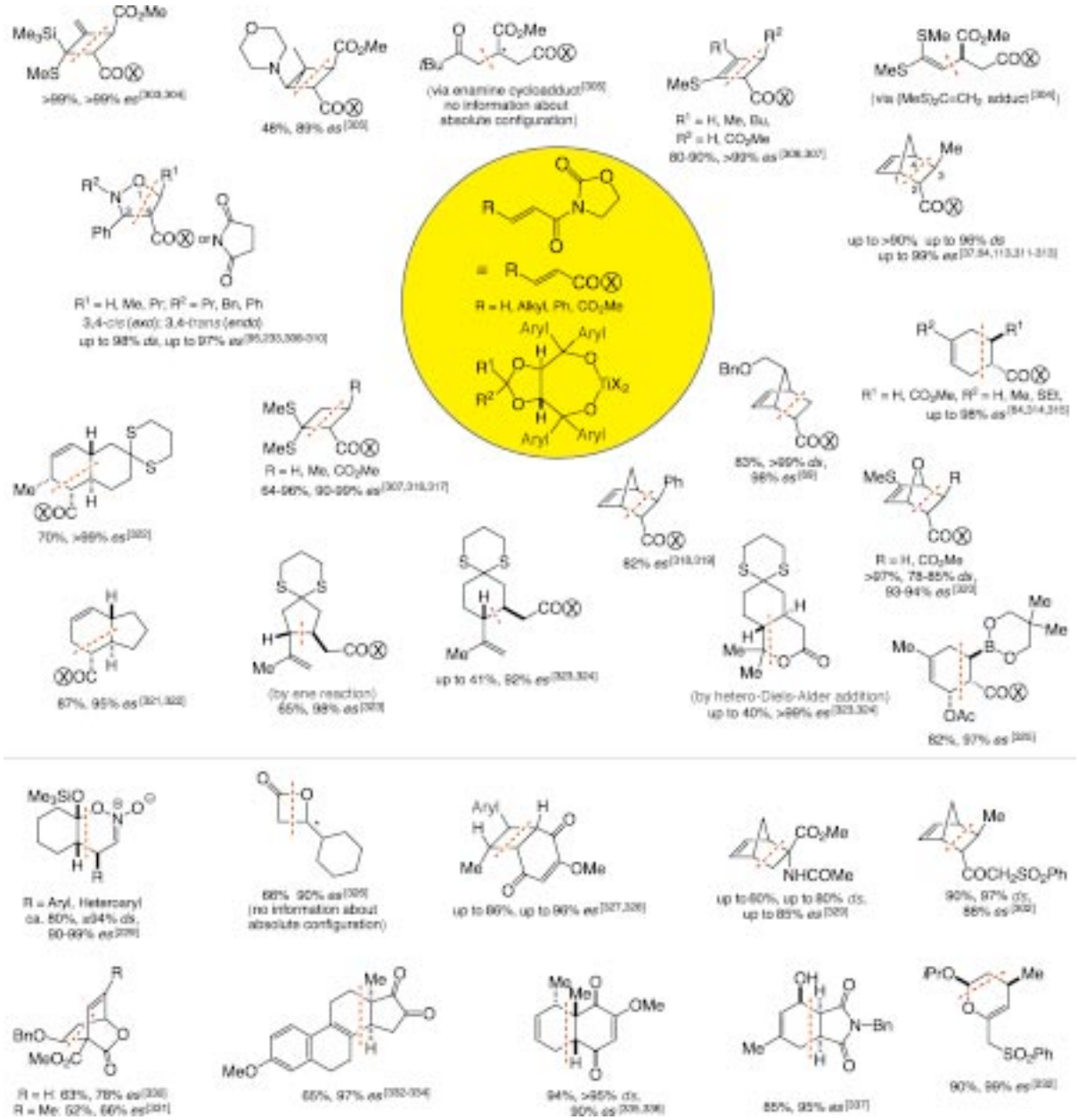
Scheme 17. An enantioselective Simmons – Smith reaction in the presence of a diisopropoxytitanium TADDOLate.[291] The diastereoselectivity of Simmons – Smith cyclopropanation is usually explained in terms of the formation of a zinc alkoxide and subsequent intramolecular carbene transfer (see **A**). In the presence of titanates it could be—considering two of the many possibilities—that carbene adds to the double bond of a chiral titanium alkoxide (**B**), or else a titanium analogue of Simmons – Smith intermediate (**C**) might form. In case **B** the titanium TADDOLate would "only" provide for the trigonal centers of the allyl alcohol to have diastereotopic faces (for attack of an achiral electrophile), whereas in case **C** the titanium center could be the donor of the electrophilic carbene. Based on the current state of understanding it is not possible to classify this reaction based on reactivity criteria (Sections 8.2.1 and 8.2.2). For a lucid discussion of enantioselective Simmons – Smith reactions, including other chiral auxiliaries and a suggested mechanism, see ref. [293, 294].

8.2.2. Enantioselective Cycloadditions[295] with X_2Ti-TADDOLate Lewis Acids

Cycloadditions play a key role in organic synthesis, especially since they result in simultaneous formation of two new bonds and proceed according to a set of rules—first formulated empirically, and later explained, by Woodward and Hoffmann[107]—to generate stereoselectively as many as four new stereo centers.[295] The [4+2]-cycloaddition process (which covers "homo" and "hetero" Diels – Alder reactions) can justifiably be called one of the most valuable "work horses" in the entire synthetic repertoire. The second most important of the broadly applicable cycloaddition processes is probably 1,3-dipolar or [3+2] cycloaddition. Less synthetic attention has been directed toward [2+2] cycloaddition, although the resulting four-membered rings—like cyclopropanes and epoxides—are easily opened as a consequence of ring strain, and can thus serve as welcome precursors to various open-chain targets.[296] There exists therefore considerable interest in cycloaddition reactions that occur in an enantioselective way starting from achiral reactants, and many possibilities can of course be envisioned. The use of TADDOLs as auxiliaries in such transformations is the subject of the discussion that follows, which is organized on the basis of increasing ring size. Comparisons with other methods have appeared in comprehensive review articles by qualified authors dealing with enantioselective Diels – Alder[297–299] and [3+2]-cycloaddition reactions.[226]

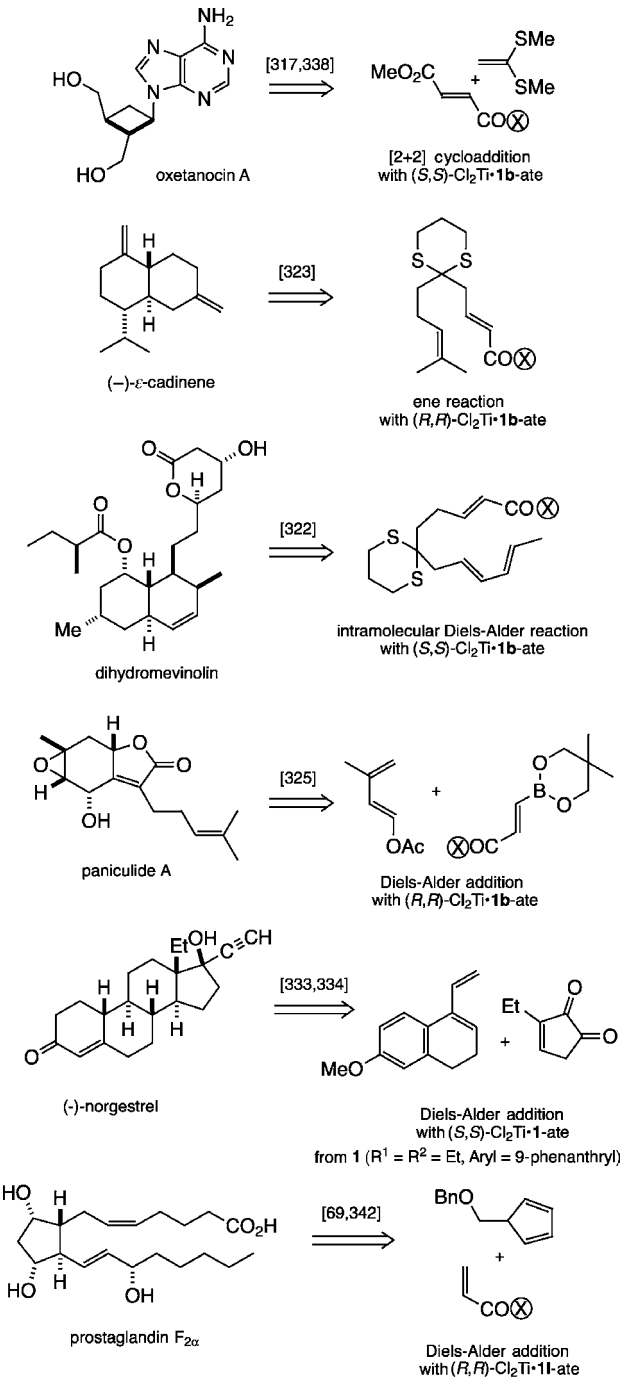
Earlier attempts were made to employ titanium TADDOLates as Lewis acids for cycloaddition reactions,[300] but Narasaka deserves the credit for having recognized that 3-enoyl-1,3-oxazolidin-2-ones[301] are the ideal C_2 components for reactions of this type[218] (Scheme 18, top). In a series of publications and patent applications, Narasaka's group has reported catalytic variants demonstrating the breadth of applicability and utility of this method in the synthesis of natural products and pharmacological agents,[338] all the reactions being carried out and optimized exclusively with the unsymmetrical TADDOL **1b** (with Me/Ph at the 2-position of the dioxolane ring). This is not to say that equally satisfactory results could not be achieved on a large scale with the more readily accessible and more easily purified C_2-symmetric TADDOLs. Indeed, careful optimization[37] in the case of the Diels – Alder reaction between cyclopentadiene and crotonoyloxazolidinone has verified that, within the limits of error, the same enantioselectivity can be accomplished with TADDOL derivative **1f** bearing 2-naphthyl groups.[339] It should be noted in this context, however, that the reaction conditions, the solvent employed, and especially the method of preparing the catalyst can all exert a major influence on the stereochemical course of such reactions, even to the point of reversing the observed results (see Scheme 11, and the introduction to Section 8.2).

Acyloxazolidinones of fumaric, acrylic, and crotonic acid are all subject to coupling under Lewis acid catalysis with ketenethioacetals, methylthioallenes or -acetylenes, and enamines to generate four-membered ring systems. The resulting amino and bis(methylthio)cyclobutane carboxylic acid esters can easily be cleaved to open-chain compounds that still contain a stereocenter. The corresponding addition to nitrones also depends upon Lewis acid catalysis, and investigations by Jørgensen have shown that it is subject to enantioselective control through the use of titanium TADDOLates.[340, 341] The most extensive efforts have been dedicated to Diels – Alder reactions of enoyloxazolidinones, again involving the addition of crotonoic acid derivatives to cyclopentadiene, which under appropriate conditions leads almost quantitatively to a single stereoisomer (2*R*,3*R* with (*R*,*R*)-TADDOLs). Narasaka and co-workers have also carried out intramolecular variants of the reaction of enoyloxazolidinone units with diene (Diels – Alder reaction) and ene groups (ene reaction, hetero-Diels – Alder addition), in which up to four new stereocenters are formed in bi- and tricyclic products with >99% enantioselectivity (Scheme 18, middle). Cycloadditions involving other α,β-unsaturated carbonyl compounds (quinones, ene-1,2-diones, phenylsulfonylmethyl enones, maleimides, amidoacrylates, pyrones) and nitrostyrenes have also been accomplished



Scheme 18. Products from cycloadditions of enoyloxazolidinones (top) and other electrophiles (bottom) to electron-rich π systems (enol ethers, thioenol ethers, ketene thioacetals, enamines, styrenes, dienes, nitrones), as well as from ene reactions carried out in the presence of $X_2Ti \cdot$TADDOLates. The enantiomers shown arise by use of (*R*,*R*)-TADDOLs (Caution: Use of TADDOLs with 1-naphthyl groups can cause the stereochemical course of the reaction to be reversed[37, 302]). Following the lead of Narasaka, in many cases the only tests so far carried out have been with TADDOL **1b** ($R^1 = Ph$, $R^2 = Me$, an acetophenone ketal). Ordinarily the Lewis acid ($Cl_2Ti(OiPr)_2$ + TADDOL), introduced at a level of 10–20 mol %, is used in situ without evaporative removal of volatile components and with or without addition of molecular sieves, which means that *i*PrOH is present in the reaction medium, and perhaps also HCl. The illustrated Diels–Alder product from $PhSO_2CH_2CO$-CH=CHMe and cyclopentadiene is formed with $Br_2Ti \cdot$**1j**-ate containing 3,5-dimethylphenyl groups; using $Br_2Ti \cdot$**1a**-ate the enantiomeric product is obtained, but with very poor selectivity.[302] For the preparation of $X_2Ti \cdot$TADDOLates where $X \neq Cl$, see Scheme 11. TADDOL auxiliaries are usually quite easy to separate from products because of the great tendency of the former to crystallize, and also due to their chromatographic behavior. A rule of thumb worth noting is that (with a \(normal\) CIP priority sequence) the nucleophile adds from the *Re* side at the trigonal α-carbonyl carbon atom (see the dotted lines in the formulae for an indication of newly formed bonds, as well as the mechanistic observations in Section 10). Some of the compounds shown—especially those from Narasaka et al.—were introduced as chiral starting materials into natural product syntheses (see Scheme 19).

with Cl_2Ti-TADDOLate catalysis, and lead in many cases to essentially enantiomerically pure products (Scheme 18, bottom). Examples of further conversion of multigram quantities of compounds prepared in this way into more complex systems are presented in Scheme 19, where the proper chiral form of the TADDOL must be selected depending on the desired configuration of the product. In the vast majority of reactions leading to the products shown in Schemes 18 and 19, the Lewis acids are prepared in 5–20 mol % quantities by mixing $TiCl_4$ and $Ti(OiPr)_4$ (which form $Cl_2Ti(OiPr)_2$) with a TADDOL in situ, although sometimes as much as a twofold stoichiometric excess of the catalyst is introduced



Scheme 19. Natural products and active substances from cycloadducts, and from the product of an ene reaction with enoyloxazolidinones and with a cyclopentenedione (⊗ = 1,3-oxazolidin-2-on-3-yl, see Scheme 18). The products initially formed (or their enantiomers) in the presence of (*R*,*R*)- or (*S*,*S*)-Cl_2Ti-TADDOLate are shown in Scheme 18. The main synthetic effort commences *after* the enantioselective step, and itself consists of numerous steps (see the comments in ref. [17]).

(200 mol %). In the case of [4+2] cycloaddition of silylenol ethers to nitrostyrenes, equally satisfactory results (if not greater selectivity) were observed when, in place of excess Cl_2Ti-TADDOLate, a mixture was instead added containing (achiral!) $Cl_2Ti(OiPr)_2$[229] (see Section 10).

Titanium TADDOLates have also been tested in conjunction with Sharpless oxidation, sulfoxidations,[343] and Baeyer–Villiger oxidations[210, 344] involving *t*BuOOH, as well as in ring-opening reactions of *meso*-epoxides to chlorohydrins.[345] In most cases to date, however, the observed enantioselectivity has not been acceptable, or the processes have been found to be highly structure dependent.

The reactions discussed in this section employing titanium TADDOLates as chiral auxiliaries (reagents, mediators, substoichiometric additives, catalysts) are unquestionably of considerable synthetic value, applicable to such fundamental transformations as nucleophilic addition to carbonyl compounds and their analogues and to cycloadditions. High enantioselectivity can be anticipated, and the procedures can be optimized by simple adjustment of the structure of the TADDOL.

8.3. Use of Complexes of TADDOL Derivates with Other Metallic Centers for Enantioselective Transformations

Once TADDOLates had been successfully implemented as ligands for use with the strongly polar, oxophilic metal titanium, the question naturally arose whether derivatives might also be prepared with an affinity for the late transition metals. The simplest route would clearly be the coupling of PR_2 groups with the TADDOL oxygens to give cyclic (**A**, **B** in Figure 12) or diphosphorus esters (**C**). It is therefore not surprising that derivatives of these types appear most frequently in the literature, employed as ligands with the metals Rh, Pd, Ir, and Cu. Rhodium complexes have been utilized for hydrosilylation of ketones with enantioselectivities as high as 98 %. Other illustrations of the principle include palladium complexes applied to allylation (up to 98 % *es*), an iridium complex used for the enantioselective catalytic hydrogenation of styrenes (up to 95 % *es*), and copper complexes of the phosphoramidites **Aa** and **Ab** that effect conjugate Et_2Zn additions to enones (Figure 12, bottom left) and the stereoselective ring opening of epoxides and aziridines by organometallic nucleophiles (Scheme 20, middle). With respect to the many TADDOL derivatives shown schematically in Scheme 5 in which one or both of the OH groups have been replaced by nitrogen, phosphorus, or sulfur substituents, few applications have so far been reported.

One would expect that the sulfur-containing compounds should be of interest, for example, with respect to nickel, silver, or copper. The monothiolato-Cu complexes **D** in fact do catalyze enantioselective 1,4-addition of Grignard reagents to enones (Figure 12). Molybdenum complexes **E** and **F** have been prepared from TADDOLs and a TADAMINe, where the former show outstanding characteristics as catalysts for ring-opening metathesis polymerization (ROMP), and the latter induces modest selectivity in reactions of benzaldehyde and styrene oxide with Me_3SiCN.

Higher valency, or more highly charged, metallic centers such as those of the lanthanides, when chelated with BINOLs, are extraordinarily successful at promoting enantioselective reactions,[358–361] but they require ligand atoms that are more electronegative ("more strongly charged" and less vulnerable to water and protic solvents) than those available in TADDOL. It is thus not surprising that there have to date been far

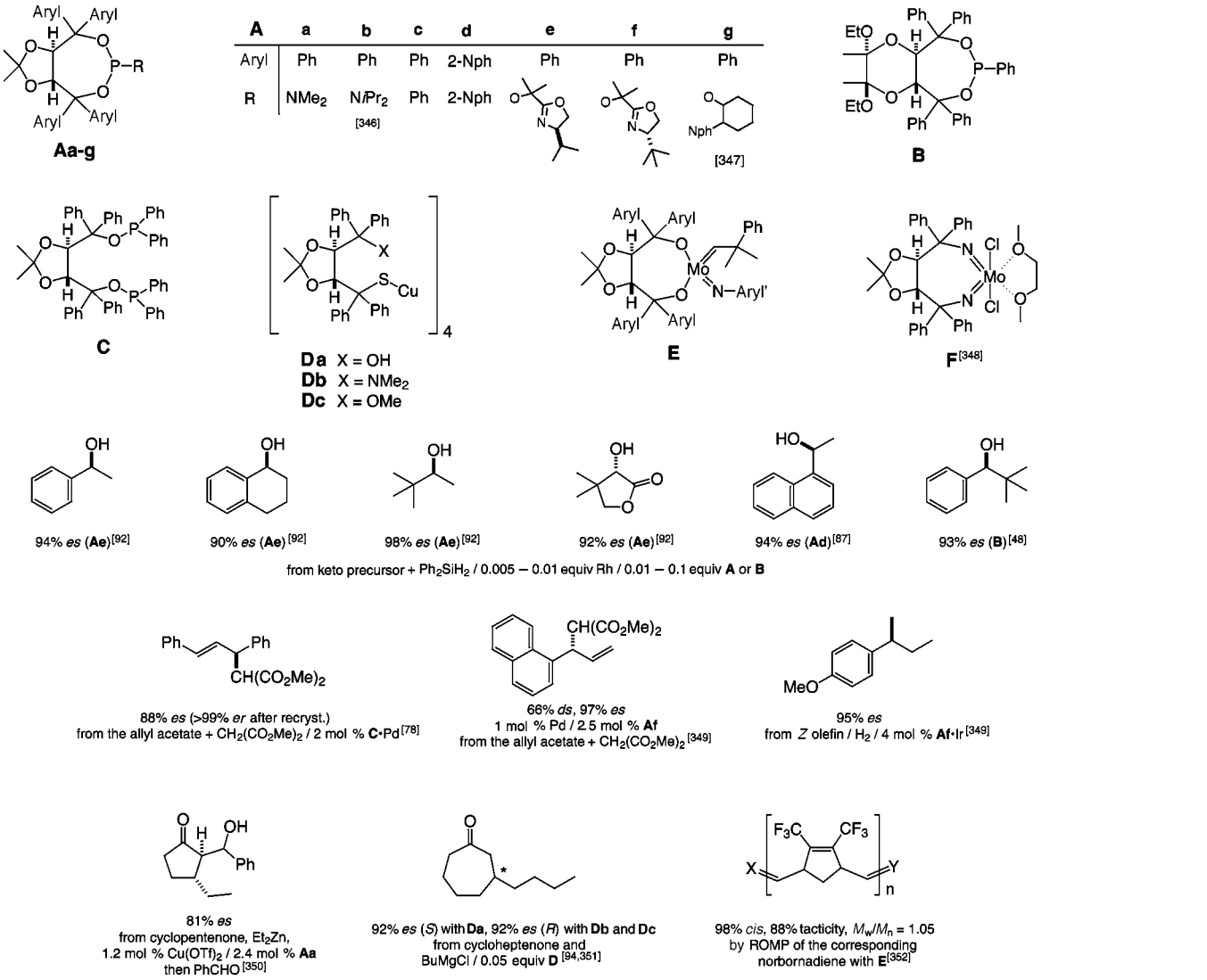


Figure 12. Phosphorus and sulfur derivatives of TADDOLs and a 1,4-dioxane analogue, copper and molybdenum complexes, as well as the products of addition reactions prepared stereoselectively with the aid of these auxiliaries. Using Cl_3P, Cl_2PR, or $ClPR_2$ and TADDOLs, what ultimately results is bicyclic or monocyclic phosphorus derivatives **A** – **C**, which may contain additional chelating units, such as oxazolinyl or 2-arylcyclohexanolate groups (**Ae** – **Ag**). Copper complex **D** and molybdenum(VI) complexes **E** and **F** are derived from TADDOL. Rhodium, palladium, iridium, and copper complexes have been utilized for hydrosilylations, allylations, hydrogenations, Michael additions, and stereoregular polymerization (see the products in the lower part of the Figure). Enantioselectivities as high as 98% have been achieved with, in some cases, very small amounts of catalyst (as little as 0.005 of an equivalent of the metal and 0.05 of an equivalent of the chiral ligands). X-ray structures of ligands and complexes of the types shown here are illustrated in Figure 13. Two examples of copper-catalyzed nucleophilic substitution (S_N2 and S_N') conducted by employing TADDOL-phosphorus derivatives are shown in the middle of Scheme 20.

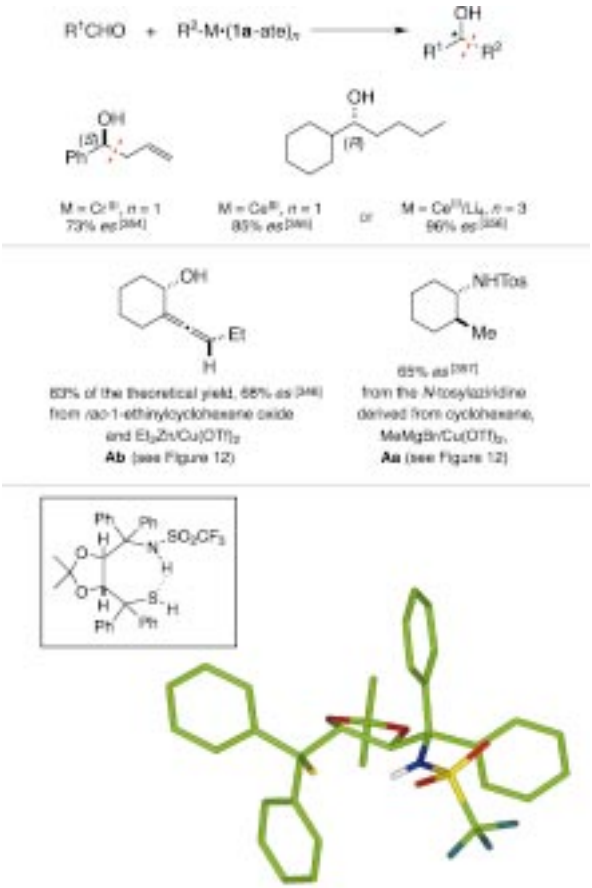
less applications of TADDOLs in this area, and the few observed have been only marginally successful (see the Cr^{III} and Ce^{III} reagents in Scheme 20, top). The large pK_a difference of roughly seven orders of magnitude between the phenolic BINOL and the alcoholic TADDOL sets limits we hope to overcome with compounds like the sulfanyltriflamide shown at the bottom of Scheme 20 (pK_a (AlkSH) approximately 10; pK_a ($NHSO_2CF_3$) approximately 6].

Numerous crystal structures have been determined for ligands derived from TADDOL and the corresponding metal complexes (Figure 5, right, and Figure 13). These will ultimately help to make the stereochemical outcomes of reactions catalyzed by such complexes more understandable (see also the mechanistic models for titanium TADDOLate mediated transformations in Section 10).

9. Macromolecular, Polymeric, and Silica Gel Bound TADDOLs

The facile separation of TADDOLs from reaction products has already been noted several times. Two particularly convenient workup procedures stem from the applications sketched in Scheme 21. Nevertheless, we thought it desirable to try to modify TADDOLs in such a way that products derived from their use could be isolated by a phase-separation protocol. In principle, four possibilities exist for modifying chiral ligands to this end, two of which permit the use of homogeneous reaction conditions whereas the other two entail heterogenic conditions.

a) The ligand can be incorporated into a macromolecule with a molecular mass high enough to permit membrane



Scheme 20. Nucleophilic additions (top) and substitutions (middle) by way of organometallic compounds of Cr^{III}, Ce^{III},[353] Zn^{II}, Cu^{II}, and Mg^{II}, which proceed enantioselectively in the presence of TADDOL derivatives. Below: An acidic TADDOL derivative in which the OH groups have been replaced by SH and $NHSO_2CF_3$, which should be suited to complexation with lanthanides.[76] From the X-ray structure of the sulfonamide it is apparent that the more acidic NH group functions as a hydrogen-bond donor, with HS as acceptor. The structure of the triflamide is also present in the overlay of Figure 5 (left).

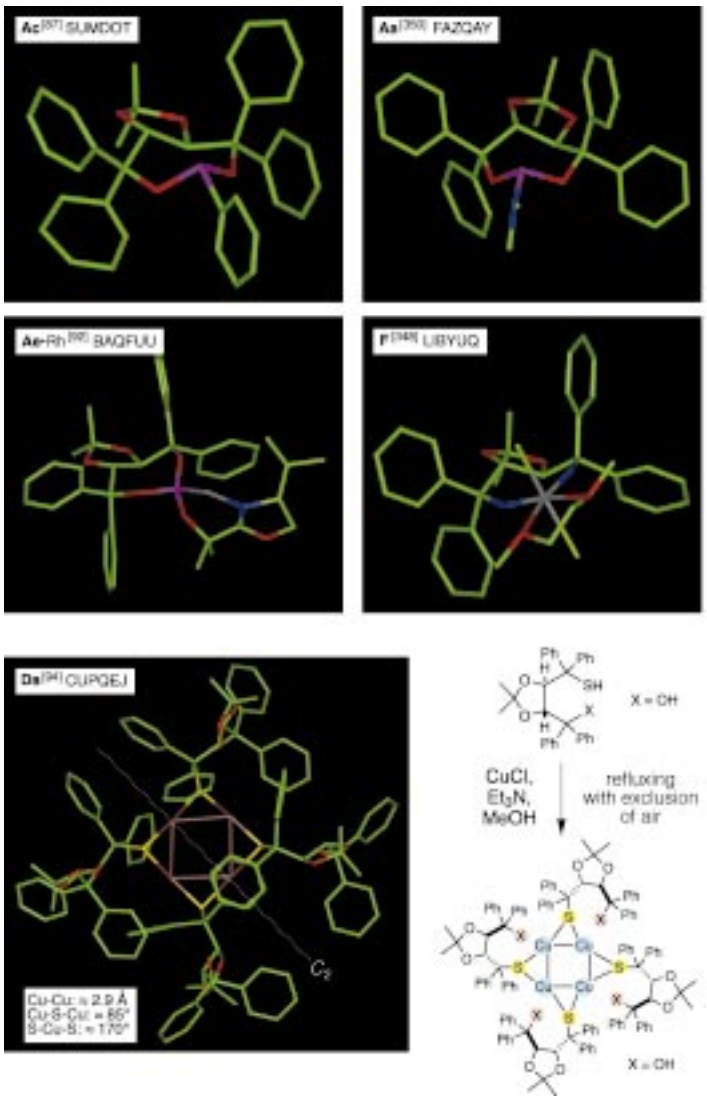
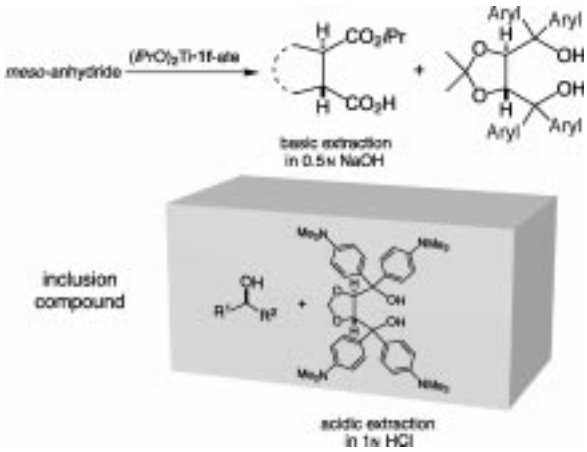


Figure 13. Crystal structures of two TADDOL-phosphorus derivatives and three metal complexes (Rh, Mo, Cu) with ligands derived from (*R*,*R*)-TADDOL. (For **A**, **F**, and **D**, see Figure 12). In addition to literature citations, Refcodes for the Cambridge Databank are also provided for these structures. In the case of the rhodium complex, the cod ligand has been omitted for the sake of clarity. The enclosed toluene molecule is not shown in this representation of the molybdenum complex. One sees in all cases the familiar geometrical arrangement of quasi-axial (upper right/lower left) and quasi-equatorial phenyl groups. The tetrameric copper complex with C_2 symmetry shown at the bottom is so stable that it persists even in solution and in the gaseous state (ESI-MS experiment). The sulfanylhydroxy derivative is bound in monodentate fashion. The complexes **Db** ($X = NMe_2$) and **Dc** ($X = OMe$) with Cu^I[94] and the corresponding Ag complexes are also present in tetrameric form.[76] The structures of **Aa** and **Ac** are included in the overlay of Figure 5 (center). The crystal structure of the $PdCl_2$ complex of the diphosphinite of TADDOL (formula **C** in Figure 12) is shown in the center of Figure 6. cod = cycloocta-1,5-diene.

filtration, a method[362] that has been shown to be particularly valuable in the case of enzymatic transformations.[288] In order to ensure that the catalyst does not pass through pores in the membrane, the carrier should not be one based on a linear macromolecule or polymer, but should rather display a globular profile, rather like an enzyme. For this reason we prepared TADDOL derivatives[63, 71] with the formulae shown in Figure 14, which, in a way, could be regarded as by-products of our work in the field of chiral dendrimers.[363]

b) The ligand can be bonded to a polymer that is soluble under the reaction conditions but will precipitate with a change in solvent (polyethylene glycol[364]). To our knowledge, this approach has not yet been attempted with TADDOLs.

c) An appropriate derivative of the ligand can be subjected to grafting by reaction with a suitable polymer. The desired covalent attachment is usually accomplished with an insoluble, cross-linked, chloromethylated polystyrene (Merrifield resin[365]), one which is subject to swelling. TADDOL derivatives for this purpose are readily accessible synthetically (Scheme 22), for example bearing *para*-hydroxymethylphenyl groups at the 2-position of the dioxolane ring.[71] Alternatively, TADDOL units can be synthesized directly on a polymer by first introducing aromatic aldehyde functions into phenyl groups of the resin, transforming these into acetals with tartrate esters, and subsequently treating with ArylMgX[366–368] (see the general TADDOL synthesis shown in Scheme 2). In place of a chloromethylated polystyrene or a copolymer with polyethylene (SMOP),[369] it is also possible to employ an inorganic carrier material for grafting purposes, the use of



Scheme 21. Two examples of especially facile separation and isolation of products from enantioselective reactions and TADDOL auxiliaries by aqueous alkaline or acidic extraction and phase separation.[70, 102, 286] The formaldehyde acetal (no substituents in the 2-position of the dioxolane ring) was selected to assure maximum possible acid stability for the tetraamino-TADDOL. For examples of stereoselective ring openings in the case of five-membered ring anhydrides mediated by TADDOL-titanate, see Scheme 16.

which does not depend upon swelling capacity in specific solvents. To this end, porous silica-gel preparations ("controlled-pore glass", CPG) with surface areas up to 350 $m^2 g^{-1}$ and pore diameters of 200 Å were first loaded with $(CH_2)_3SH$, onto which TADDOLs were then grafted.[39, 370]

d) Finally, the ligand to be immobilized can be prepared in such a way that it contains one or more styryl substituents, permitting it to be subjected to cross-linking polymerization with styrene itself (to form a "homemade polymer"). This approach can also be exploited for the preparation of porous silica gel with ligands already built in, by way of the sol–gel process.[373] At first glance, this procedure might appear to be the most risky, because the ligands in such a polymer could become so deeply embedded in the matrix that they would no longer be accessible for complexation, or to provide catalytic activity. On the other hand, it is known that polymers containing tailor-made cavities can be prepared in a similar fashion ("molecular imprinting"[374]). For example, if one equips a carbohydrate unit with some polymerizable functionality by way of a labile bond, permits cross-linking polymerization to occur, and then removes the carbohydrate "template", what results is a material with a specific affinity for the sugar derivative originally employed.

Three styryl-substituted TADDOLs we have prepared for polymerization purposes are shown in Scheme 22. The dendritic derivative with eight peripheral styryl groups is a novelty in two respects; quite apart from its TADDOL nucleus, it was the first dendritic cross-linking agent ever prepared for styrene, and this also represents the first occasion on which a chiral ligand—and thus an enantioselective catalytic agent (see below)—had been incorporated dendritically into a polymer.[371, 376] The cross-linking suspension–copolymerization of styryl-TADDOLs with styrene under standard conditions[375] resulted in nicely formed spheres that displayed good swelling capacity and a remarkable set of properties[71, 371, 372] (Figure 15).

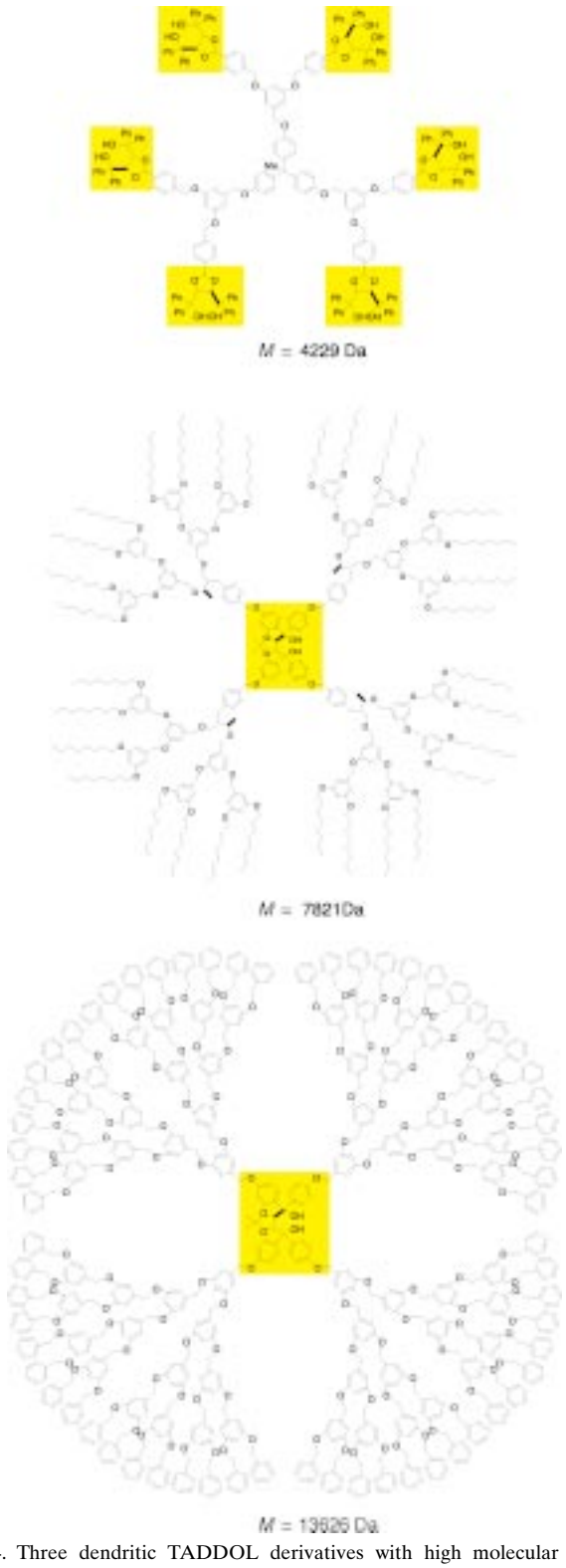
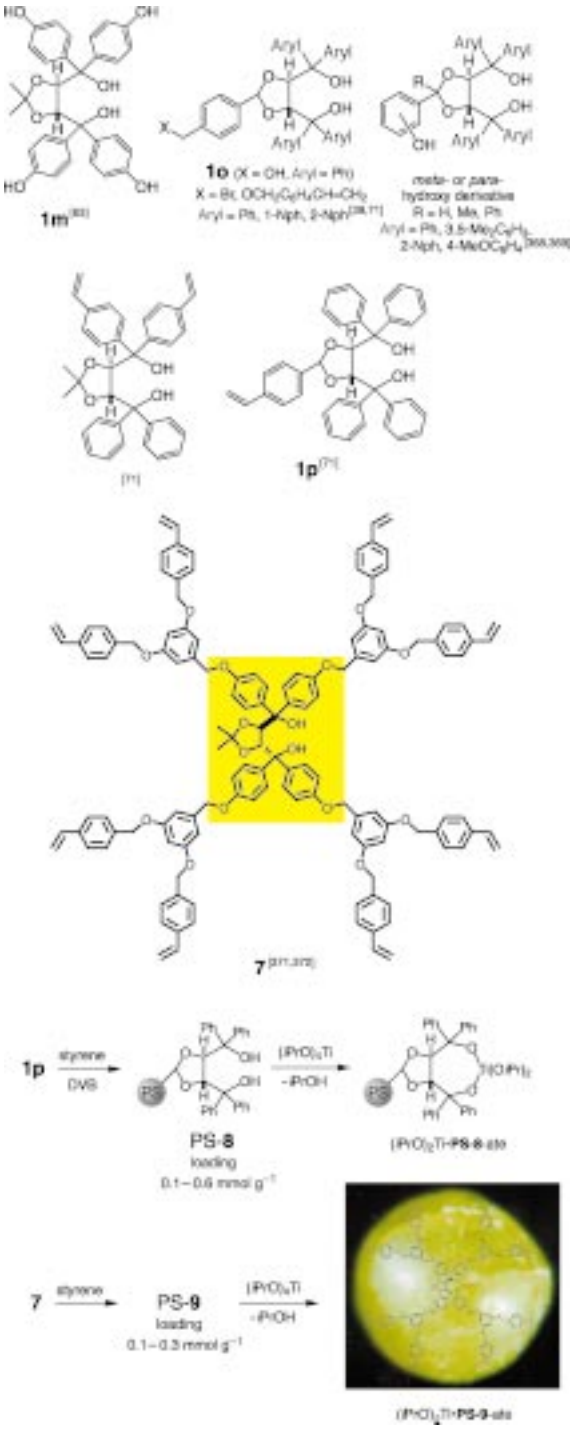


Figure 14. Three dendritic TADDOL derivatives with high molecular mass, prepared for use in the form of titanium complexes in membrane reactors.[63, 71, 363]

Charging of the TADDOL-containing polymers with titanates was accomplished just as in the case of simple, soluble TADDOLs (see, for example, the information provided at the bottom of Scheme 22 for derivatives prepared by copolymerization). Based on elemental analysis, and espe-



Scheme 22. TADDOLs for the preparation of macromolecular titanates (see Figure 14) and polymer-bound titanates in polystyrene (PS). Top: The building blocks. Information regarding synthesis of the compounds can be obtained from the references cited. Hexol **1m** is prepared by the standard reaction (Scheme 2) with TBS protective groups; during transformation of **1m** into ethers with benzylic bromides (for example, to compound **7**), pentabenzylated products invariably form, which is an indication of the relatively high acidity of one OH group in the TADDOL nucleus.[63] The benzylic bromides, alcohols (type **1o**), and phenols shown were used for grafting to Merrifield resins and suitably prepared SiO_2. Compound **1p** is undoubtedly the simplest derivative available for polymeric incorporation into PS. Poor results were obtained for the PS prepared from geminal distyryl substituted TADDOL.[71] Bottom: Polymer-bound TADDOLs PS-**8** and PS-**9** obtained by suspension polymerization and subsequent charging with titanate to give the chiral Lewis acids $(i\text{PrO})_2\text{Ti}\cdot$PS-**8**-ate and $(i\text{PrO})_2\text{Ti}\cdot$PS-**9**-ate.

Figure 15. Polystyrene spheres (250–400 μm ∅) into which TADDOLs have been polymerized, and reaction vessels for multiple applications. a) Beads containing dendritic cross-coupled TADDOL (PS-**9**), which change from blue to yellow upon loading with titanate (interaction of the Lewis acid with phenol and resorcinol ether groups of the dendrimer branches?). b) Transparent beads of the monostyryl-TADDOL copolymer $(i\text{PrO})_2\text{Ti}\cdot$PS-**8**-ate before (left) and after (right) 20-fold utilization in the test reaction ($Et_2Zn + PhCHO$). c) As a result of high swelling capacity and low loading (0.1 mmol g^{-1}), the entire reaction volume is occupied by PS-**9** spheres (before (left) and after (right) loading with titanate). Reactions with this polymer-bound catalyst are diffusion controlled; that is, they proceed equally rapidly with and without stirring. d), e) Reaction vessel (inner diameter 6.5 cm, volume approximately 250 mL) for multiple use in the addition of organometallic nucleophiles to aldehydes. The PS-**8** spheres (charge 0.6 mmol per gram of TADDOL) are sewn into a pad made of polypropylene and "immobilized" between two perforated glass plates so that they do not rub against each other during stirring (this avoids abrasion!). After loading with titanate, execution of a reaction, and syphoning off of both reaction and wash solutions, another batch can be subjected to the reaction (see Scheme 23).[377]

cially as established by catalytic activity, 80–90% of the TADDOL units in the polymer were titanated, and the resulting Lewis acidic centers are clearly accessible to reactants.

Before discussing applications of the immobilized titanium TADDOLates, a few comments are in order regarding solid-phase synthesis, a process that has recently received increased attention due to the interest in combinatorial methodologies. Advantages provided by immobilized catalysts and reagents include not only the ease of separation from products already noted (which also applies to toxic components!) and spatial separation of reactive systems (the "wolf and lamb" principle of Patchornik[378]), but also the applicability of large excesses of reagents and reaction partners, especially through the repeated use of catalysts or reagents. If, in order to avoid chromatographic separation of an auxiliary, the reagent or catalyst of interest needed to be modified prior to bonding to a solid phase, and if it were then to be discarded after a single

use, one might with justice inquire whether the required effort would really be worthwhile. Indeed, from this perspective many of the solid-phase bound reagents currently "marketed" could legitimately be castigated as "consumer frauds". On the other hand, consider the case of an immobilized Lewis acid that, for chemical reasons, must necessarily be employed at the relatively high level of 5–20 mol%. A 20-fold reutilization would increase the "molar efficiency" factor to 0.25–1%. It is for this reason that we have established as an important criterion for the utility of our immobilized TADDOL Lewis acids that they always be reusable or regenerable (that is, that they display durability). It is hardly necessary to add that the only applications worth considering are ones for which, in homogeneous solution, there are no nonlinear effects (NLE) attributable to the involvement of more than one catalyst molecule in the rate-determining step.[379] This is a condition fulfilled by the titanium TADDOLate catalyzed addition of R_2Zn to aldehydes[380] (Scheme 12) and the [3+2] cycloaddition of nitrones,[71] but not by the Diels–Alder reaction of enoyloxazolidinones.[71, 113, 381] Finally, ease of utilization requires that the particles of an immobilized catalyst not be too small, for which reason our conditions for suspension polymerization have been so adjusted that spheres with a diameter of approximately 400 μm are preferentially formed. These can easily be confined, but they are also readily removed from a reaction solution simply by filtering or decanting, or by removing the supernatant solution with fine needles (Figure 15).

As a test reaction we selected the addition of Et_2Zn to PhCHO in toluene, catalyzed by $(i\mathrm{PrO})_2$Ti-TADDOLate/$(i\mathrm{PrO})_4$Ti. It was observed that TADDOLate incorporated into polystyrene in dendritic form possessed unique properties: at the low charge level of 0.1 mmol g^{-1} it produced, within the limits of error, a constant enantioselectivity of 98% under 20-fold reutilization. What prevented us from repeating the process even more times was not fatigue on the part of the catalyst, but rather fatigue displayed by the chemist (Figure 16a)! We also established that catalyst obtained from dendritically modified octastyryl-TADDOL shows, after being used 20 times, no decrease whatsoever in swelling capacity (Figure 16b/c). Finally, copolymers obtained from ordinary styryl-TADDOL **1p** led, as expected, to somewhat decreased reaction rates relative to the corresponding monomer TADDOL **1p** introduced in homogeneous solution (Figure 16b). However, we were astonished to discover that dendritic monomer **7** was associated with a lower reaction rate than the corresponding polymer (Figure 16c), although both dendritic derivatives produced slower reactions than nondendritic systems.

Using the reaction vessels illustrated in Figures 15d, e we conducted a total of 18 Et_2Zn additions to 5 different aldehydes, repeatedly employing the same packet filled with TADDOLate-charged (0.6 mmol g^{-1}) spheres. Enantioselectivities always exceeded 90%, and we observed essentially no cross-contamination of the isolated alcohols provided the particles were thoroughly washed before each use with toluene containing $(i\mathrm{PrO})_4$Ti (Scheme 23). The β-naphthyl analogue of $(i\mathrm{PrO})_2$Ti·PS-**8**-ate led to higher enantioselectivity, just as had been observed under homogeneous conditions.[377]

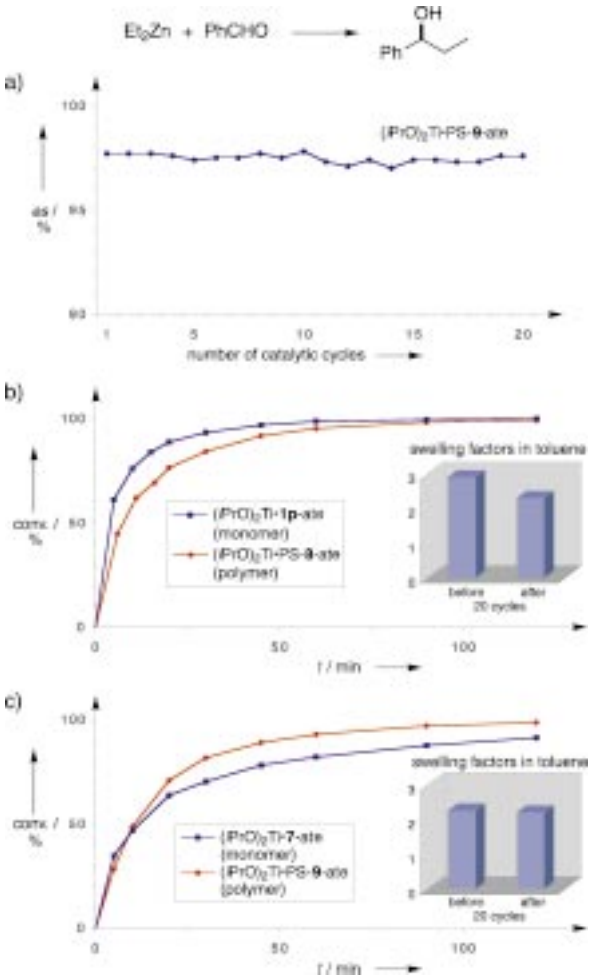
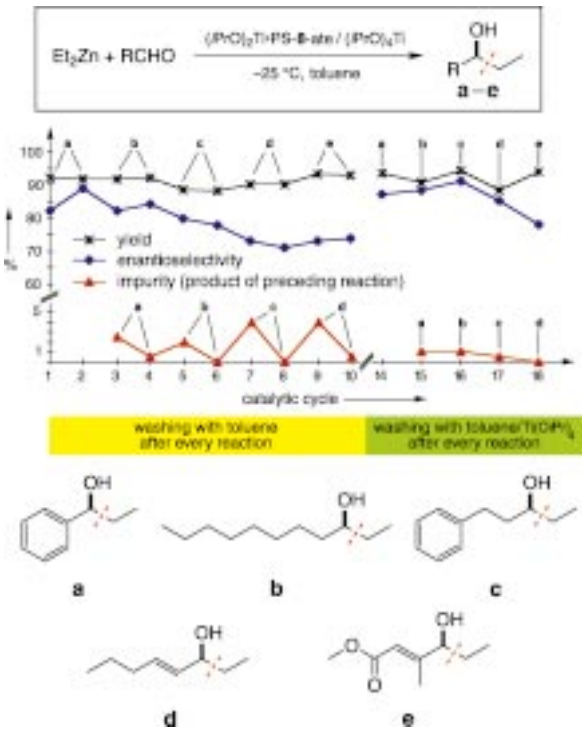
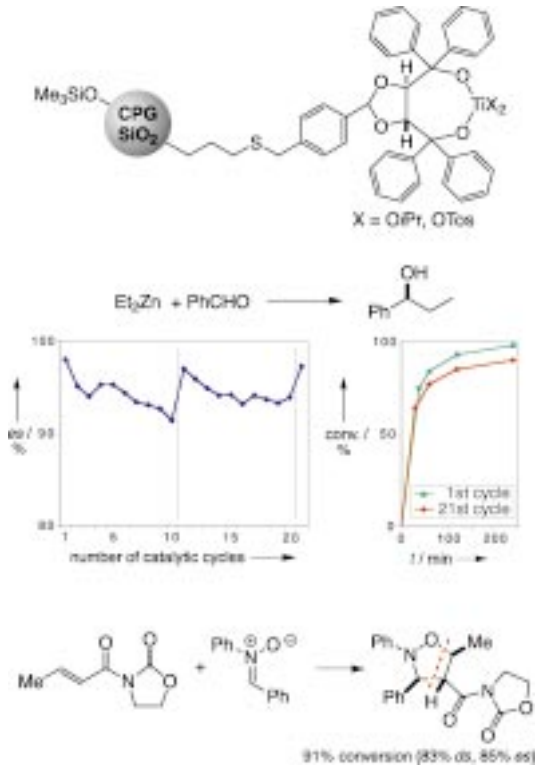


Figure 16. Reaction rates and enantioselectivities for Et_2Zn addition to benzaldehyde with the polymer-bound titanium TADDOLates $(i\mathrm{PrO})_2$Ti·PS-**8**-ate and $(i\mathrm{PrO})_2$Ti·PS-**9**-ate as well as $(i\mathrm{PrO})_4$Ti in toluene at −20 °C.[42, 372] a) Repeated utilization with essentially constant enantioselectivity of the titanium TADDOLate $(i\mathrm{PrO})_2$Ti·PS-**9**-ate (20 mol%) incorporated dendritically into polystyrene (0.1 mmol g^{-1} loading). b) Comparison of rates of addition with monomeric Ti-**1p**-ate and the corresponding polymer $(i\mathrm{PrO})_2$Ti·PS-**8**-ate (the monomer reaction is faster). c) Comparison of rates of addition with monomeric and polymeric dendritic titanium TADDOLate (the polymer reaction is faster!). The swelling capacity of the polymer containing "normal" titanium TADDOLate had decreased after 20 applications, but that containing dendritic TADDOLate had not.

Preliminary investigations with a TADDOL grafted onto silica gel (CPG) are equally promising. Enantioselectivities achieved in the test reaction (Et_2Zn+PhCHO) have been as high as 98%, the observed loading of the CPG with TADDOL is high as well (0.3 mmol g^{-1}), the material can be washed with HCl—and thus reactivated—without loss of hydrophobicity, we have found no evidence of "fatigue" (in contrast to the simple polystyrene-bound TADDOLates where swelling capacity diminishes), and after 20-fold reuse the reaction rate appears to decline only by an insignificant extent (Scheme 24). The yields and selectivities under homogeneous reaction conditions for the addition of diphenylnitrone to crotonoyloxazolidinone were, within the limits of error, also reproduced using ditosylatotitanium TADDOLate on CPG.[370]



Scheme 23. Addition of Et_2Zn to various aldehydes, with formation of the alcohols **a**–**e** (11-mmol batches with the same pouch full of spheres at −25 °C in toluene) in the presence of $(iPrO)_2Ti \cdot$ PS-**8**-ate, with the reaction vessel shown in Figure 15.[377] Polymer loading: 0.6 mmol g^{-1}, 20 mol % titanate, and 120 mol % $(iPrO)_4Ti$. If, in the case of successive reactions with different aldehydes, no cleansing measures are taken other than washing with toluene, the isolated alcohol always contains a few percent of the previously prepared alcohol; after washing with $(iPrO)_4Ti$ prior to carrying out a subsequent reaction, contamination is reduced to less than 1 %.



Scheme 24. Titanium TADDOLate immobilized on porous silica gel (CPG from the firm Grace), and two applications in catalysis.[370] CPG has the advantage over PS that it is chemically inert, stable to both temperature and pressure, and not subject to swelling in applicable solvents. The particles employed have a diameter of 35–70 μm (charge: approximately 0.3 mmol g^{-1}, pore size: 200 Å, surface area: 280–350 m^2 g^{-1}), and OH groups not used in grafting are made hydrophobic by trimethylsilylation. Addition of Et_2Zn is carried out in the usual way with the $(iPrO)_2$ derivative (20 mol % titanium TADDOLate, −20 °C, toluene), and 1,3-dipolar cycloaddition is accomplished with the ditosylated derivative (50 mol % titanium TADDOLate, RT, toluene). After ten additions of Et_2Zn + PhCHO (by which point the enantioselectivity has fallen from 98 % to 93 %), the material can be washed with aqueous HCl/acetone and then with H_2O/acetone, dried, and again titanated, a process that readily restores the initial enantioselectivity. In view of the observed *es* values and reaction rates, there appears to be no basis for assuming that CPG-bound catalyst cannot be used for considerably more than 20 reactions.

The immobilization of TADDOLs in and on polystyrene and porous silica gel increases, through repeated use, the efficiency with which titanium TADDOLates function as chiral Lewis acids. Moreover, our work in this area has brought to light an interesting "dendrimer effect" on the swelling capacity of polystyrene into which chiral ligands have been incorporated. Corresponding experiments with other popular complexing agents, such as BINOL and SALEN, have similarly led to solid-phase bound catalysts with outstanding characteristics.[382–387]

10. Mechanistic Observations Concerning Enantioselective Lewis Acid Catalysis with Titanates

Mechanistic studies of reactions catalyzed by organometallic species are notoriously difficult to conduct because, in an extreme case, the true catalytic species may be present at such low concentration that it is virtually impossible by any available method to detect it in the presence of the chief components. A classic example of a successful mechanistic analysis is provided by Halpern's work[388a] on the enantioselective hydrogenation of aminocinnamic acid derivatives catalyzed by rhodium diphosphine complexes. On the other hand, mechanisms for Sharpless epoxidation of allylic alcohols with *t*BuOOH in the presence of titanate and tartrate ester[388b] or addition of Et_2Zn to aldehydes in the presence of chiral aminoalcohols[242] still cannot be regarded as completely elucidated. The situation is no different in the present case of Lewis acid catalysis of nucleophilic additions and cycloadditions by chiral titanates. Particularly the first of these *requires* "dilution" with a large excess of achiral titanate $(iPrO)_4Ti$, even though the amount of chiral complex introduced is seldom less than 0.05 molar equivalents, and often stoichiometric quantities are added. In the case of alkylzinc addition to aldehydes, bimetallic mechanisms must be considered, and, as already noted, for cycloaddition to α,β-unsaturated carbonyl compounds a cocktail composed of a TADDOL, $TiCl_n(OiPr)_{4-n}$, *i*PrOH, HCl, and molecular sieves is introduced as the catalyst. The Diels–Alder reaction is characterized by a nonlinear relationship between the enantiomer purity of the TADDOL and that of the product (for example, in the

reaction of enoyloxazolidinone with cyclopentadiene). Finally, the reaction site—the ligand sphere of titanium in the product-forming, enantioselective catalytic step—is far from well-defined, apart from the fact that a TADDOLate ligand must certainly be involved. The titanium might engage in trigonal, tetrahedral, trigonal-bipyramidal, or octahedral coordination, it could bear a positive or negative formal charge (in the form of an onium or ate complex), and the site might function in a bimetallic way, either with a second identical metal atom (Ti-X-Ti) or with some other metal (Ti-X-Zn). NMR spectroscopy has led to the identification of concrete titanium TADDOLate complexes present in solution, as demonstrated especially in the work of DiMare and Jørgensen, but the conclusions remain controversial,[37, 44, 45, 69, 102, 310, 328, 389, 390] and this is not the place to delve into the matter in detail. Based on numerous X-ray structural analyses (Figures 4–6, 10, 13), one thing seems certain: TADDOL has a strong tendency to form chelates, and in every discussion it has been assumed to be present as a bidentate ligand. In the two sections that follow we wish to present a) possible reasons for ligand acceleration[388b] of titanate catalysis through the agency of TADDOLates and other chiral complex-forming agents, and b) models and a rule describing the stereochemical course of reaction (where we deliberately avoid use of the word *mechanism*). In the process we hope to make a useful comparison of titanium TADDOLates with the titanium BINOLates and titanium CYDISates,[386] which in general behave similarly[391–395] (see also the structures in Figure 17).

As noted, nucleophilic additions to aldehydes—apart from allylations with CpTi-TADDOLate (Scheme 13)—proceed with maximum enantioselectivity only if excess $(i\mathrm{PrO})_4\mathrm{Ti}$ is added along with titanium TADDOLate[380] (also true for use of BINOLate[392, 393] and CYDISate;[243, 245, 247] see the examples in Scheme 25). This means on one hand that the corresponding chiral titanates are much more active as catalysts than achiral titanate (factors of over 1000:1 have been estimated), but also that the chiral systems require the presence of the latter for optimum activity. Ligand acceleration[388b] in the case of titanium TADDOLates has been interpreted as due to steric hindrance and therefore a rapid dynamic for the exchange of starting material/product ligands (a high "in/out" rate). "Steric pressure" from the four aryl groups leads to formation of coordinatively unsaturated or even charged species (Scheme 26a).[44, 71, 102] When 1-naphthyl groups are present on the TADDOL, however, activity nearly disappears (too much hindrance), and the diol bearing methyl instead of aryl groups (and thus providing too little steric hindrance) gives product that is a racemic mixture (Scheme 26b). The function of excess $(i\mathrm{PrO})_4\mathrm{Ti}$ has been interpreted in two ways: removal of product alkoxide R*O from the titanium TADDOLate (a sort of "clean-up effect", Scheme 26c)[102] and/or displacement of a charged ligand from the bulky, complexed, TADDOL-bearing titanium to the simple titanate, with formation of a chiral Lewis acid center that is cationic (Scheme 26a).[71]

In the case of CYDISate it has also recently been shown[387] that extremely bulky substituents (SO_2mesityl instead of SO_2tolyl, SO_2alkyl, or SO_2CF_3 on the N atom) cause the complete collapse of enantioselective catalysis. However, the enormous ligand acceleration observed with titanium CYDISates is almost certainly not primarily a result of dynamic enhancement from steric hindrance at the titanium center, but rather of increased Lewis acidity resulting from the high electronegativity of the RSO_2N^- ligands (pK_a of $PhSO_2NH_2$ is

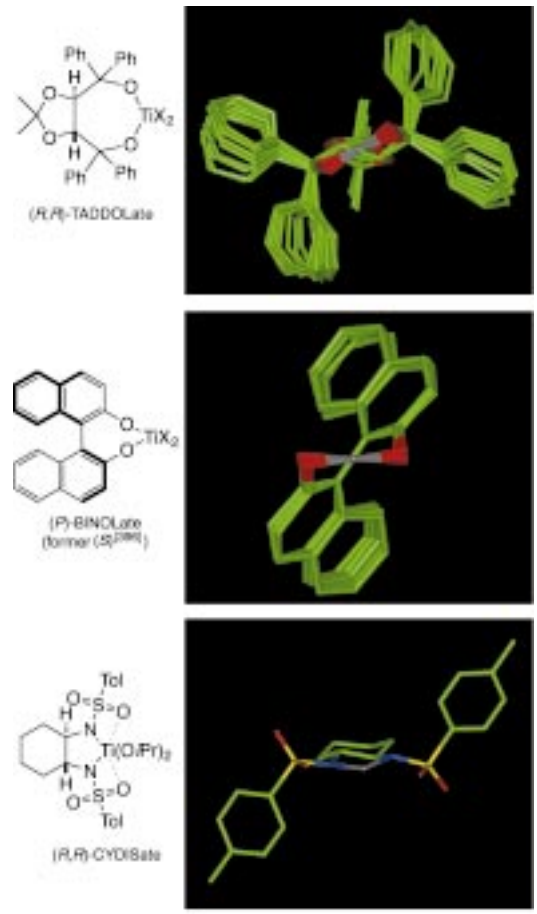
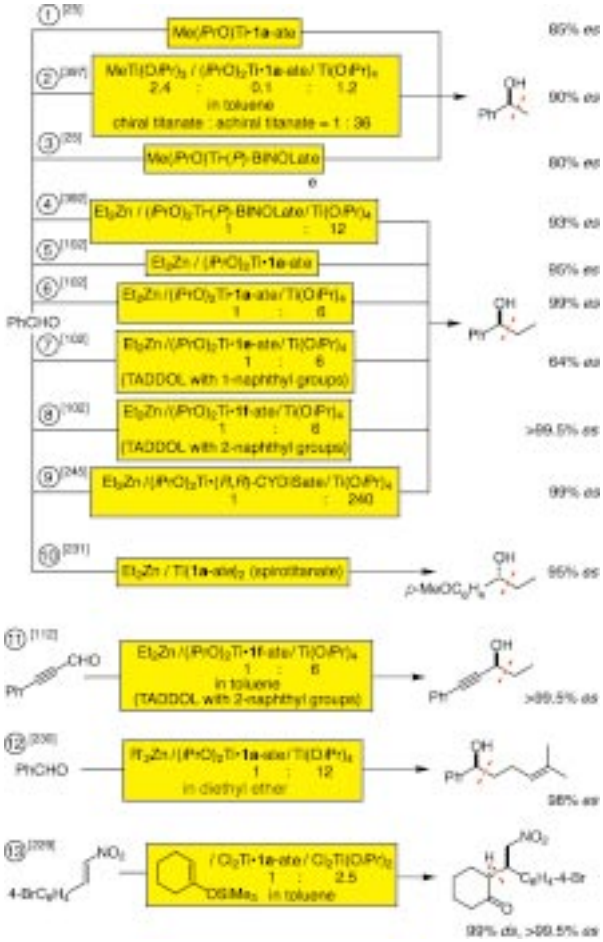
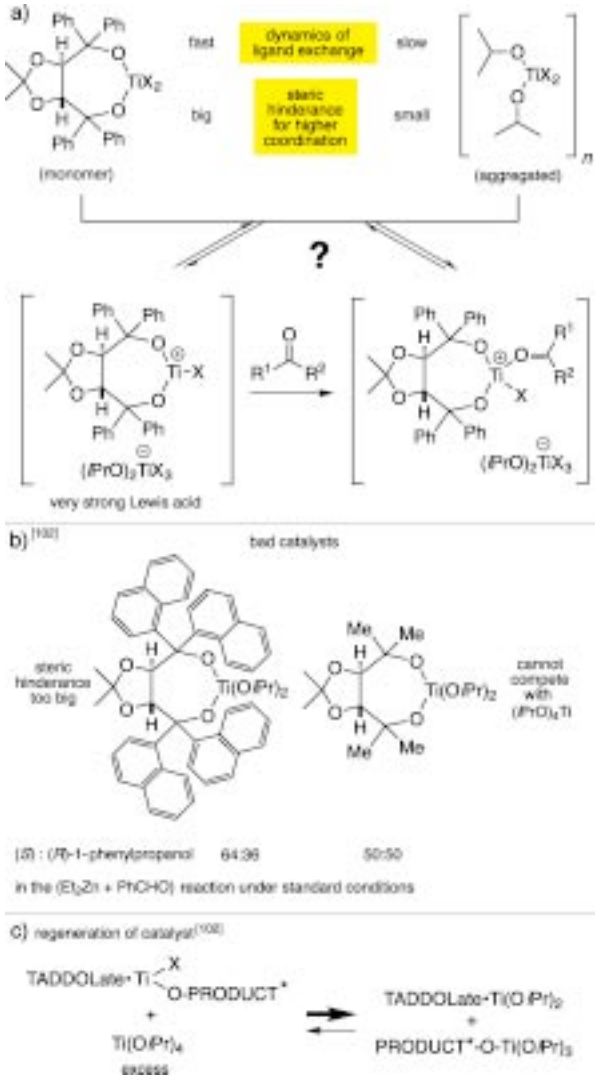


Figure 17. Formulae and crystal structures of (*R*,*R*)-titanium-TADDOLates, (*P*)-titanium-BINOLates, and a titanate with bis(tosylamidocyclohexane) ligands ((*R*,*R*)-cyclohexan-1,2-diaminedisulfonamide, CYDIS). The remaining ligands on the titanium have been omitted from the drawings. For another view of an overlay of the 11 titanium TADDOLate structures, see also Figure 5 (right). In contrast to the previous representation, C(4) and C(5) of the dioxolane ring and the titanium atom have been chosen as the fixed points in the overlay (see also Figure 4, bottom right). The eight overlayed titanium BINOLates (see ref. [37]) are registered in the Cambridge Databank under Refcodes BEYKUL, HELZIH, KOXGIN, KOXGOT, RIYDIM, VOZXAY, VOZXEN, and ZEHWOY. For purposes of clarity, substituents on the BINOL have again been omitted. When necessary, structures were recast in mirror-image form prior to overlaying. The bis(sulfonamido)diisopropyl titanate has been formulated with sixfold-coordinated titanium;[387] for the crystal structure of a zinc CYDISate, see ref. [294]. Note the similarity of the nearly or precisely C_2-symmetric structures (one is tempted to speak in terms of Lord Kelvin's definition[10] of homochirality): In all three cases more steric hindrance is present "upper right and lower left" than "upper left and lower right". During titanate-catalyzed nucleophilic addition to aldehydes, reaction with the three types of catalyst occurs from the *Si* face of the trigonal center. The relationship between the species extends considerably farther: Other reactions with (*R*,*R*)-TADDOL and (*P*)-BINOL derivatives also occur in the same stereochemical sense; even the HTP effect in liquid crystals (Section 5 and Figure 8) has the same sign with both (*R*,*R*)-TADDOL and (*P*)-BINOL!



Scheme 25. Enantioselective additions to aldehydes and a nitroolefin under the influence of a mixture of chiral and achiral titanates. In the absence of the achiral titanate (①, ③, ⑤) the enantioselectivity is lower than in the presence of as much as a 36-fold excess of achiral material (②, ④, ⑥–⑨, ⑪–⑬)! This applies not only to titanium TADDOLates with phenyl and 2-napthyl groups, but also to titanium BINOLate (④) and the cyclohexandiamine derivative (CYDIS, see also Figure 17; ⑨). The reaction is slow with the TADDOLate bearing 1-naphthyl groups (just as it is with $(i\mathrm{PrO})_4\mathrm{Ti}$ alone!), and it is not selective (⑦), whereas the TADDOLate with 2-naphthyl groups generally gives the best *es* values (see Scheme 12). With spirotitanate Ti(**1a**-ate)$_2$ the product is the (*R*)-1-phenylpropanol, not the *S* compound (entry 10); high enantioselectivity is observed only when a 2:1 excess is employed (99 % *es*). Also in the case of a [4+2] cycloaddition (formally a Michael addition after hydrolysis; see Schemes 10 and 18) of nitrostyrenes to silyl enol ethers the best enantioselectivities are achieved after "dilution" of the chiral Lewis acid with achiral material (⑬). Note that there is no need for zinc compounds to be present during the addition to aldehydes; see the pure $\mathrm{RTiX_3}$ systems (①–③). The example of the titanium TADDOLate demonstrates that, under standard conditions ($\mathrm{Et_2Zn}$, PhCHO, toluene, $-25\,^{\circ}\mathrm{C}$, 0.2 equiv Ti·**1**-ate, 1.2 equiv $(i\mathrm{PrO})_4\mathrm{Ti}$), there is a linear correlation between the enantioselectivity of TADDOL and that of the product.[71, 380]

approximately 10, that of $\mathrm{CF_3SO_2NH_2}$ is approximately 6). With titanium BINOLate, which generally affords less selectivity in alkylzinc addition to aldehydes relative to CYDISate and TADDOLate (see also Scheme 1), the presence of excess $(i\mathrm{PrO})_4\mathrm{Ti}$ also leads to better results than those achieved in the absence of achiral Lewis acid.[392–394] The ligand acceleration here may be due to the combination of a steric effect *and* the increased Lewis acidity (pK_a of arylOH is approximately 10).



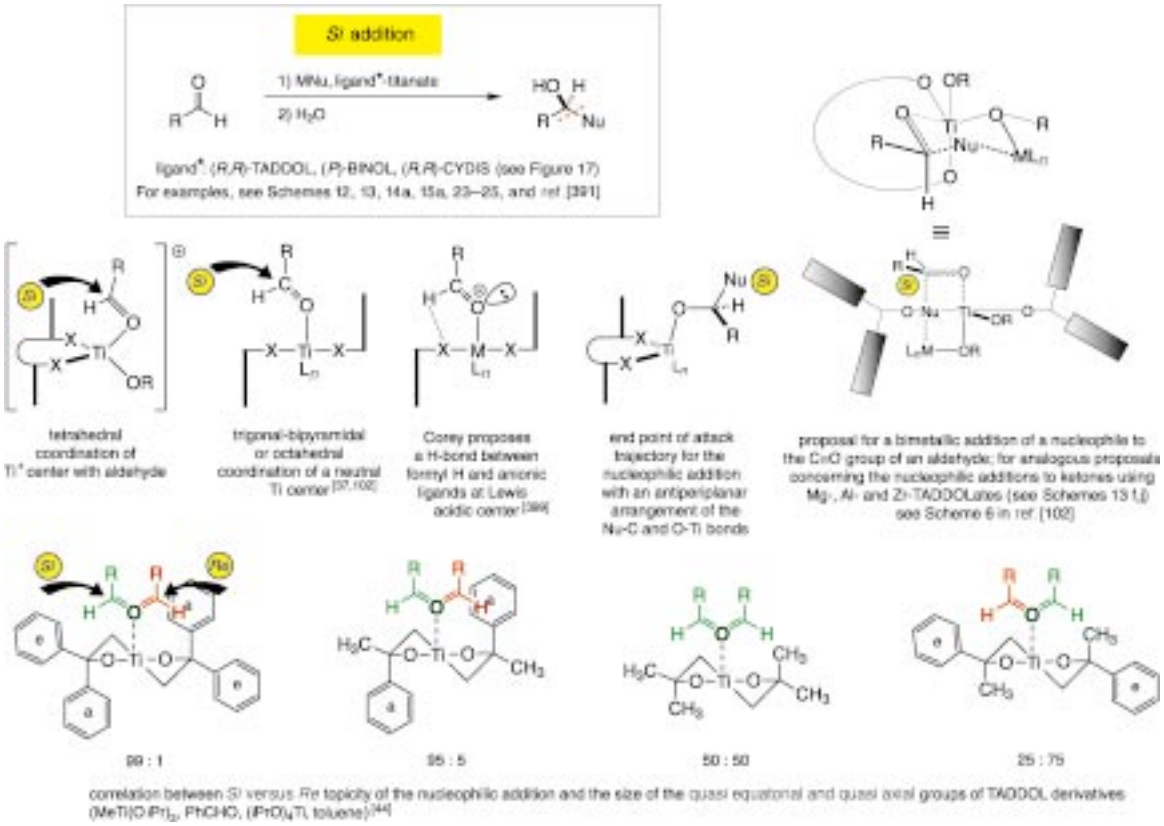
Scheme 26. Interpretation of ligand acceleration in titanium TADDOLates, and the role of excess $(i\mathrm{PrO})_4\mathrm{Ti}$ in the addition of organometallic compounds to aldehydes (see also Schemes 12, 25). a) The bulky TADDOLate ligand hinders increased coordination at titanium and leads to a high rate of exchange; for this reason, titanium TADDOLate is a much more active Lewis acid than the simple titanate. Perhaps the ligand-exchange process is even dissociative, whereby the achiral titanate could serve as a receptor for the cleaved ligand (X = OR or halogen), although there is as yet no experimental evidence for the ion pair shown. If a second titanium TADDOLate functioned as an anion acceptor, nonlinear effects could result (as, for example, in the Diels–Alder addition of enoyloxazolidinones). b) Excessive steric hindrance with the 1-naphthyl derivative $(i\mathrm{PrO})_2\mathrm{Ti}\cdot$**1e**-ate, on the other hand, reduces the catalytic activity in the dialkylzinc addition. The $\mathrm{Me_4}$ analogue of TADDOL **1a** gives a miserable catalyst, producing racemic product; the titanium center is here much less sterically hindered. c) Excess $(i\mathrm{PrO})_4\mathrm{Ti}$ leads to regeneration of the "best" catalyst $(i\mathrm{PrO})_2\mathrm{Ti}\cdot$**1**-ate, whereby product alkoxide is trapped (the "purging effect"); it has been shown that the TADDOLate $(\mathrm{RO})_2\mathrm{Ti}\cdot$**1a**-ate with (*S*)-1-phenylpropoxy in place of *i*PrO groups leads to poorer enantioselectivity. With use of excess spirotitanate (see entry 10 in Scheme 25), which causes the stereochemical course of the reaction to reverse, it may be that the latter functions in the role of "purgative".

More difficult to interpret than ligand acceleration is the stereochemical course of reactions induced by the three similar chiral ligands (*P*)-BINOLate, (*R*,*R*)-TADDOLate, and (*R*,*R*)-CYDISate (Figure 17). Account must of course be taken of all the experimental data before any interpretation is

proposed, and the data in this case are very numerous—it is truly astonishing how the wildest mechanistic speculations are sometimes committed to paper on the basis of a single example!

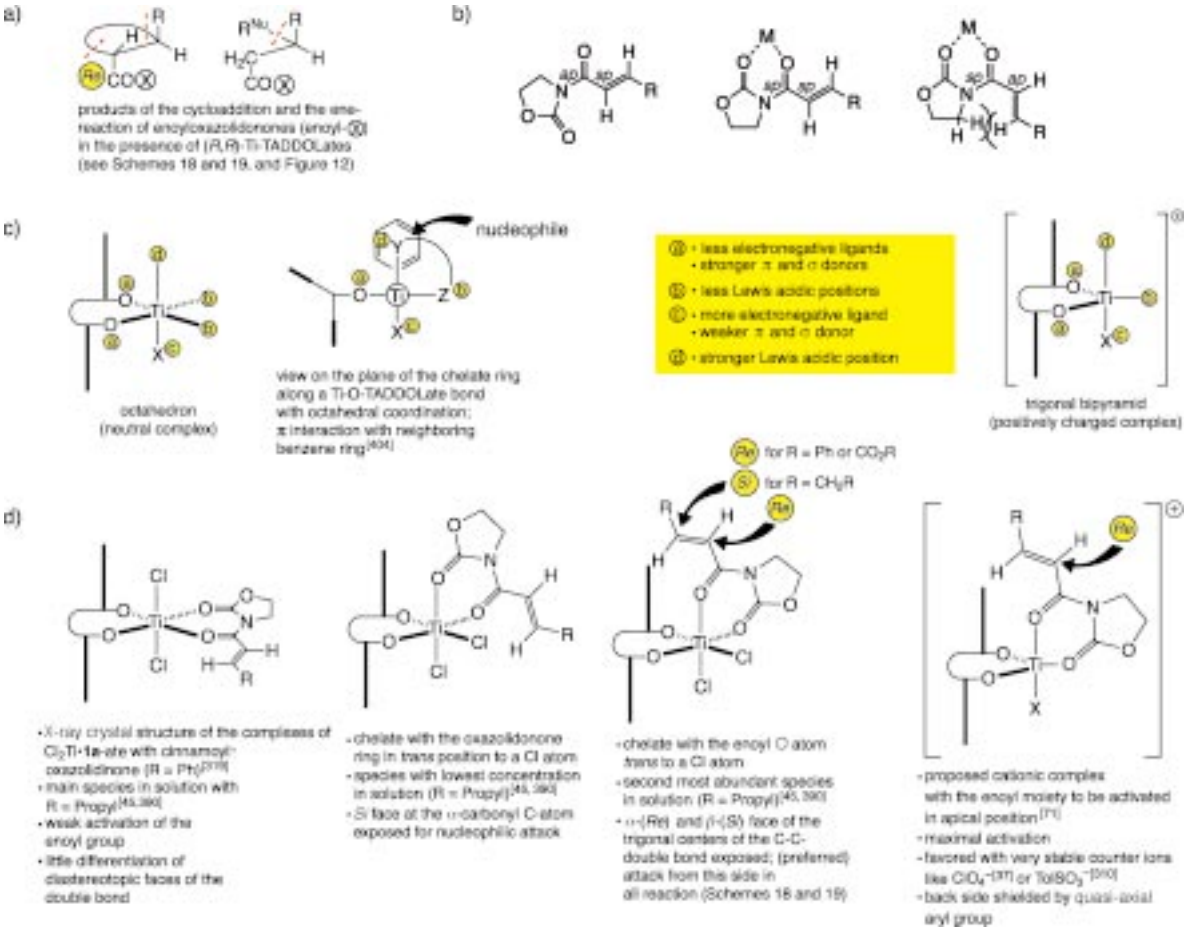
The situation appears to be as follows for addition to "simple" carbonyl compounds RCHO (in the absence of chelating effects due to another heteroatom!): in the presence of titanates bearing one of these three ligands, a nucleophile adds consistently from the *Si*-face of the trigonal carbonyl center. If one assumes—as seems apparent from Figures 4–6, 10, 13, and 17—that "above" the TADDOLate chelate ring in these complexes there is more space to the left than to the right (for symmetry reasons, the opposite is true "below"),[398] then an aldehyde in the *E* configuration (as illustrated in Scheme 27) could bind most readily to the Lewis acid center directed away from the quasi-axial group adjacent to the complexing heteroatom. If one further assumes that a nucleophile can approach only from the front and not from the rear (that is, from above the dioxolane ring in TADDOLates), then it is the *Si* face of the trigonal center that is open to nucleophilic attack. Whether this occurs in an intramolecular ("wandering" of an R^{Nu} group from titanium to the carbonyl carbon atom) or an intermolecular way (via some bimetallic complex) is unknown. It is also not possible at this point to say how the titanium center is coordinated in the transition state for nucleophilic addition, or if in fact a cationic complex is present (see the contribution to the discussion in the upper part of Scheme 27). The mechanistic model shown, which is undoubtedly highly simplified, is consistent with numerous tests of the TADDOL system involving structural variations. Thus, both the stepwise substitution of phenyl groups by methyl groups in the equatorial and axial positions, and also the transition to the tetrabenzyl analogue, result in the expected loss of selectivity[44] (Scheme 27, bottom). Simple model considerations also support the notion that coordination of an aldehyde with an *E* configuration—in the representation selected here—is most favorable to the left or outward relative to coordination to the right or inward.

The titanium TADDOLate mediated transformations that have been investigated most thoroughly from a mechanistic standpoint (including molecular model calculations) are certainly the Diels–Alder reaction and the [3+2] cycloaddition of enoyloxazolidinones. The fact is that *all* nucleophilic additions—including the ene reaction—to the double



Scheme 27. Models for the stereochemical course of nucleophilic addition to aldehydes in the presence of titanium TADDOLates (or BINOLates or CYDISates). The two bold lines at the top represent the quasi axial phenyl groups of the TADDOL (or the benzene ring of the BINOL or SO_2R substituents on CYDIS). As the R–metal additions proceed with very high selectivity, irrespective of the nature of substituents on the formyl carbon atom (saturated, unsaturated, acetylenic, aromatic), even when we go to *p*-dimethylamino groups on the TADDOL, or when we compare between SO_2CF_3 and $SO_2C_6H_5$ on CYDIS, there is no basis for an assumption that π interactions might play an important role. In a bimetallic mechanism (for which there is neither supporting nor contradictory evidence), two identical (Ti) or two different (Ti/Zn) metallic centers might be involved. The tetrahedral complex shown, with positively charged Ti (see Scheme 26), represents a purely speculative contribution to the discussion of a pathway leading to the observed product, comparable to the suggestions made in Scheme 28 and Figure 18 for titanium TADDOLate/electrophile complexes. The Lewis acid/Lewis base complexes shown in the bottom row of formulae are intended to help rationalize the observed differences in selectivity of the various 2,2-dimethyldioxolanes with different groups on the exocyclic methanolate carbon atom (like the Me_4 analogue, the tetrabenzyl analogue of the TADDOL—a tetrakis-homoTADDOL!—is a miserable ligand, as shown by the (Et_2Zn + PhCHO) reaction: *Si*/*Re* = 54:46[44]).

bond of these α,β-unsaturated carbonyl compounds (with retention of the *trans* configuration) mediated by (*R*,*R*)-titanium-TADDOLates occur from the *Re* face at the trigonal center adjacent to the carbonyl group! (In the cases investigated, this applies also to (*P*)-Ti-BINOLates.)[399] Discussion regarding a stereochemical course for this reaction that leads to the observed result is summarized in Scheme 28. Despite the overwhelming number of known examples, no generally accepted common reaction mechanism has yet been elucidated. Certainly a decisive factor is product-forming complexation of the enoyloxazolidinone with a titanium TADDOLate (and it is to this that we limit the present discussion). Based on an X-ray structural analysis of the complex of $Cl_2Ti \cdot$ **1a**-ate with cinnamoyloxazolidinone, an octahedron is present with *trans*-disposed chlorine atoms and a coplanar arrangement for the two TADDOLates and the two carbonyl oxygens.[319] NMR spectroscopy of solutions of corresponding complexes reveals in addition to this geometry another form with a carbonyl oxygen *trans* to Cl.[45, 390] Moreover, there is evidence of π interaction between neighboring enoyl and aryl groups.[45, 404] The sizes and polarities of polar groups (Cl, OSO_2Tol, ClO_4) on titanium can play a decisive role;[37, 233] moving to a 1-naphthyl group on the TADDOLate can result in a reversal in the reaction's stereochemical course.[37] Despite identical topicity in the addition, different titanium TADDOLate/enoyl complexes must be assumed to be the key to determining the nature of products from various types of reactions.[405] Finally, it has been observed that one of the Diels–Alder additions (crotonyloxazolidinone + cyclopentadiene) shows a nonlinear effect,[71] but a related [3+2] cycloaddition (crotonyloxazolidinone + diphenylnitrone) does not.[71] In most cases such "details" (!) have not even been



Scheme 28. Models for the stereochemical course of cycloadditions and ene reactions of enoyloxazolidinones RCH=CH-CO ⊗. a) Configuration of the product formed with (*R*,*R*)-titanium-TADDOLate (see also (*P*)-titanium-BINOLate Lewis acids[399]). b) Preferred conformation, as observed in numerous X-ray structures,[400] for 3-acyloxazolidinones with synperiplanar (*sp*)/antiperiplanar (*ap*) conformations of CO–N and CO–CH bonds, respectively, as well as *sp*/*sp* arrangements in metal complexes[401, 402] and destabilized *ap*/*sp* geometry due to 1,5-repulsion (Newman or $A^{1,3}$ strain[403]). c) Positions and Lewis acidities at octahedrally and trigonal-bipyramidally coordinated titanium TADDOLates; chelating complex formation with the O=C–C=C group Y (π stacking[302, 404]) that is to be activated and the chelating ligand Z. d) Three different types of complexing for enoyloxazolidinones at Cl_2Ti-**1**-ate with an octahedral ligand sphere around Ti (theoretical TADDOLate angle O-Ti-O, ca. 90°) and a possible cationic complex (theoretical O-Ti-O angle, ca. 120°; see however the experimental values in the legend to Figure 5); for the—experimentally observed—α-(*Re*)/β-(*Si*) approach of the nucleophilic partner, the complexes shown at the right appear probable. Corresponding structures have been demonstrated, modeled, or discussed as well for Cl(*i*PrO)Ti-TADDOLate/enoyloxazolidinone[95] and /crotonoylsuccinimide complexes.[310] In studies that have unfortunately not yet been published,[390] Sarko and DiMare demonstrated with low-temperature NMR spectroscopic studies, by trapping experiments with isobenzofuran, that the most stable complex (on the far left in (d), R = Bu) disappears more slowly than the isomeric complex present in smaller amount. It was pointed out in the legend to Scheme 26 that a cationic complex (with $X_3Ti \cdot$ **1**-ate$^-$ as counterion) could be responsible for nonlinear effects. For analogous complexes with other electrophiles, see also the arrangement illustrated in Figure 18.

investigated. We therefore propose a pragmatic, simple model, but one consistent with all the experimental results (Scheme 28): the electrophilic enoyl group that is to be activated sits in the reactive complex *trans* to the most polar ligand available on titanium (for example, chloride), and the chelating oxazolidinone carbonyl oxygen atom is *trans* to a TADDOLate oxide oxygen atom—so arranged that the nucleophile attacks from the side on which the TADDOLate bears an equatorial aryl group, which would be possible in either a neutral octahedral complex or in a trigonal-bipyramidal one bearing a positive charge.[37, 71, 102] Figure 18 illustrates the arrangement based on this principle that corresponds to the observed reaction of titanium TADDOLate and activated electrophile for a series of other transformations. Additional investigations, especially kinetic studies, will be required to confirm the overall applicability of our simple proposal.

11. Additional Diarylmethanols, and a Comparison with Other Chiral Auxiliary Systems

With additional diarylmethanols there is, to begin with, the "inverted" tetraphenylthreitol derivative in which hydroxy

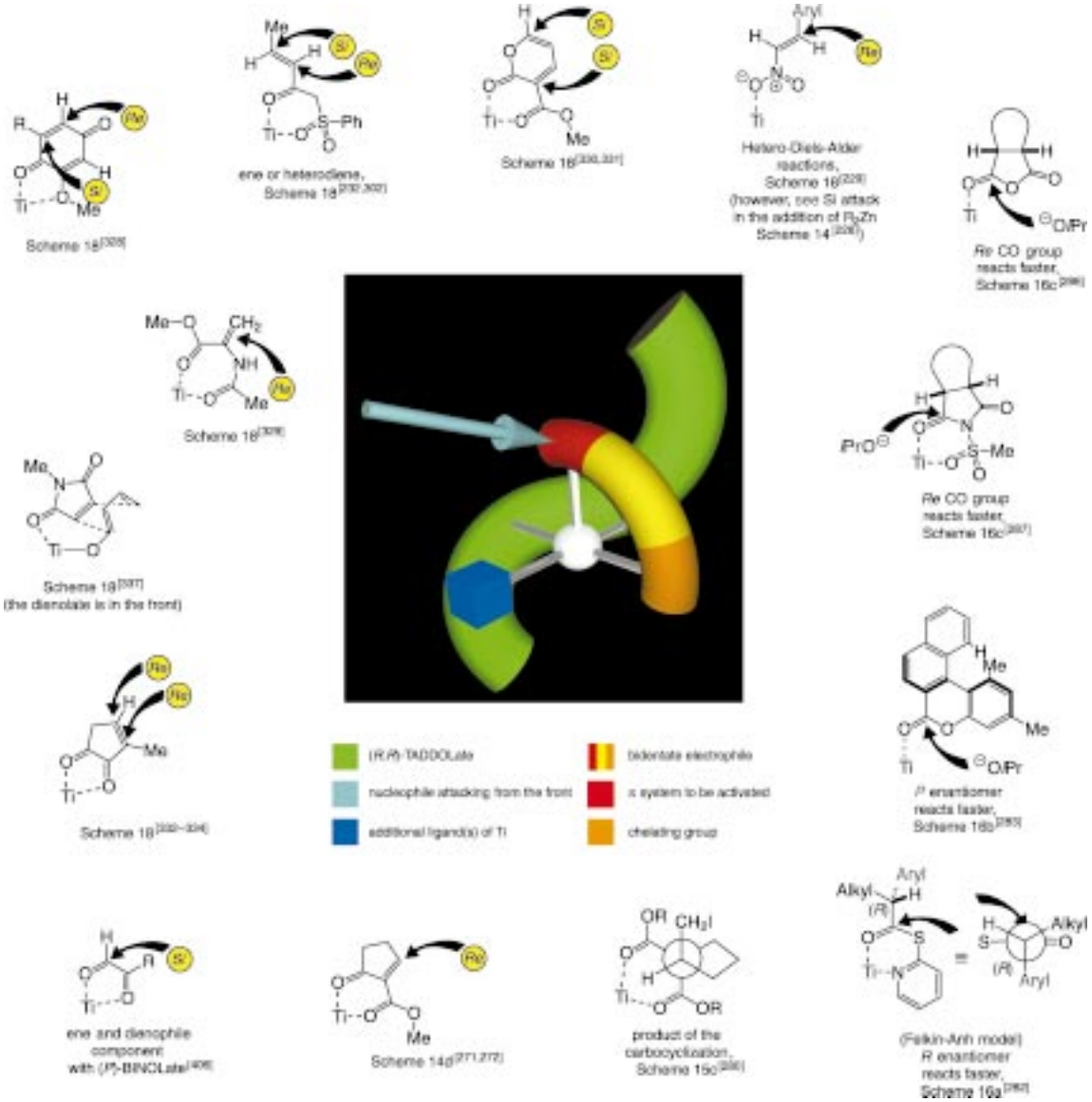
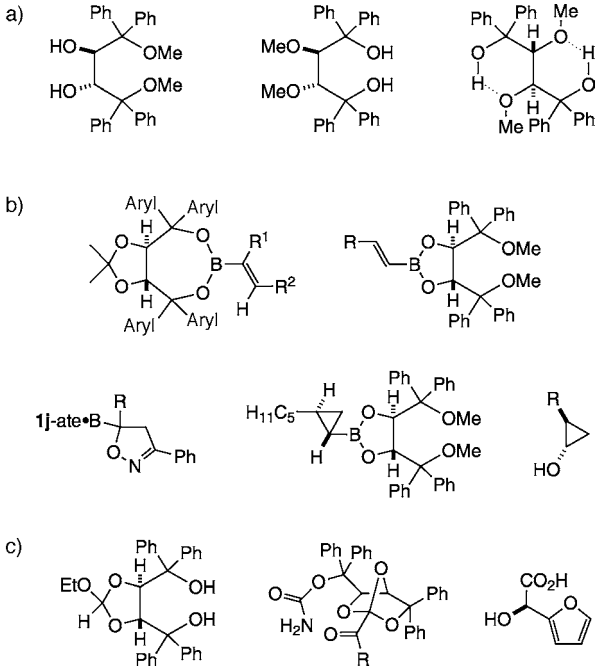


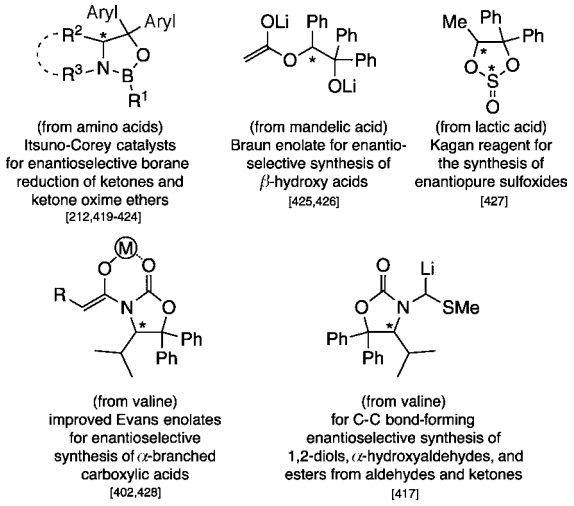
Figure 18. Schematic representation of the stereochemical course of (*R*,*R*)-titanium-TADDOLate mediated reactions with electrophiles other than enoyloxazolidinones (see Scheme 28). The electrophilic substrates have been so placed in the plane of the drawing that the nucleophile attacks from the side of the viewer (that is, from the front), an exception being the electrophilic attack during carbocyclization. Even in cases in which certain authors have complicated our task by putting labels like (+)-TADDOL under a structure for (−)-(*R*,*R*)-**1a**, we have here—to the best of our ability and conscience—summarized the reported stereochemical courses of Diels–Alder and hetero-Diels–Alder reactions, [2+2] cycloadditions, ene reactions (with (*P*)-BINOLate in place of (*R*,*R*)-TADDOLate), Michael additions, and enantioselective or enantiomer-differentiating *i*PrO transfers to activated carboxylic acid derivatives. In most cases the π system to be activated becomes directed "upward", and the additional chelating group present extends to the "right" (no chelation with nitroolefins, anhydrides, and phenolic lactones?). There is thus a resemblance to the stereochemical course of the reactions of enoyloxazolidinones shown in Scheme 28, an observation (irrespective of mechanistic accuracy) that can be regarded as a rule (see the artistic rendering with octahedrally coordinated titanium in the center of the figure).

groups at the 1- and 4-positions are protected, while those in the 2- and 3-positions are not. Five-membered metallic alkoxides can form with vicinal diols of this type, as for example the alkenyl boronic acid esters shown in Scheme 29. These lead to cyclopropanols after reaction with diazomethane and subsequent oxidation. A threitol derivatized in the opposite way has also been synthesized, with free OH groups in the 1- and 4-positions, but this proved to be a poor host for inclusion compounds. Finally, there exist esters[414] and orthoesters[410, 415] derived from the completely unprotected tetraphenylthreitol, in which the tetrol can function as a covalently bound chiral auxiliary[410] (see Scheme 29, bottom).



Scheme 29. Tetraphenylthreitol derivatives[21] that have been "protected" at the OH groups in the 1- and 4-[407] or the 2- and 3-positions[408] by conversion into ethers (a), an application of the compounds (b), and of corresponding orthoester derivatives (c).[409, 410] a) 2,3-Dimethoxy-1,4-diol is a poor host compound for the formation of inclusion compounds, probably because both OH groups are "saturated" by intramolecular hydrogen bonds, and thus not available for binding with guests.[408] b) Cyclic alkeneboronic acid esters,[411–413] readily accessible through hydroboration of acetylenes, react with phenylnitrile oxides to give 1,3-dipolar cycloadducts (*dr* up to 8:1[413]) and with diazomethane to give borylcyclopropanes (*dr* up to 13:1[411, 412]). The latter can be used to prepare enantiomerically enriched cyclopropanols (with R = C_4H_9, tC_4H_9, C_5H_{11}, and C_6H_5). Better results were achieved with the dimethoxy derivative than with the TADDOL ester! c) The orthoesters of 2-ketocarboxylic acids can be reduced with high diastereoselectivity to 2-hydroxycarboxylic acid derivatives using selectride (right).[410]

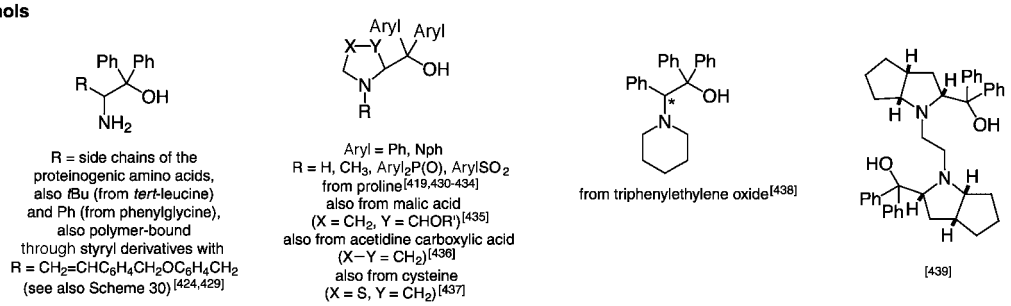
As previously discussed (Sections 4 and 10), the introduction of two geminal diaryl groups on a C–C or C–X single bond ($Aryl_2C$–C, $Aryl_2C$–X, $Aryl_2X$–C) in some molecule leads mainly to the following consequences: a) the aryl groups produce a conformational fixation that formally facilitates cyclization and, on the other hand, hinders ring opening; b) two identical geminal aryl groups in a chiral molecule (quasi equatorial and quasi axial to the rings) are diastereotopic, and thus lead to more pronounced distinctions between diastereomeric transition states in comparing $CH^{Re}H^{Si}$ with $CMe^{Re}Me^{Si}$ and $CAryl^{Re}Aryl^{Si}$; c) $Aryl_2C$ can function as a sterically effective protecting group for otherwise unprotected functionalities;[416, 417] d) on the other hand, the presence of $Aryl_2C$ or $Aryl_2X$ units can sometimes cause neighboring metallic centers to dispense with a ligand (that is, become coordinatively unsaturated), thereby leading to increased rates of ligand exchange;[418] alternatively, aggregate formation involving the participation of this metallic center may be suppressed; e) finally, experience has shown that geminal diaryl groups confer a greatly enhanced tendency toward crystallization, as well as increased melting points, relative to CH_2 and CMe_2 analogues (easier purification of intermediates and recovery of auxiliaries!).[416] It is therefore no surprise that the use of diarylmethanol derivatives in (stereoselective) organic synthesis has proven valuable, as illustrated by the examples in Scheme 30 and Figure 19. Apart from TADDOL, the diarylmethanol derivative most frequently encountered is the aminoalcohol derived from proline and phenyl Grignard reagent (Itsuno–Corey catalyst[451]).



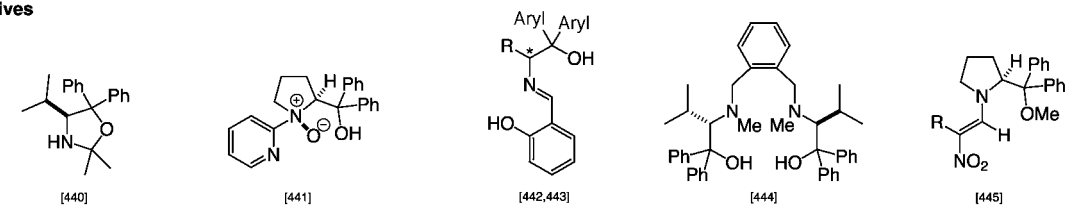
Scheme 30. A catalyst and four reagents derived from diarylmethanols for carrying out standard syntheses with enantioselectivity. For literature references and additional examples, see also Figure 19. In all cases, the two geminal aryl groups not only exert a steric effect on the course of the reaction; they also have a decisive effect in the formation and stabilization of cyclic reagents, intermediates, and complexes (see the discussion regarding the TADDOLs).

A question with wider ramifications than that directed simply toward alternative diarylmethanols is of course the search for other generally applicable auxiliary systems for the "introduction of chirality" (recall the definition specified in the Introduction). We hope we have succeeded here in showing TADDOL to be one such system, or at least that experience to date provides ample reason for dreaming that this might someday be the case. If we survey in a cursory way all the currently available—nonbiochemical—methods for EPC syntheses (Figure 20) and take note of which chiral scaffolds repeatedly turn up in reagent and ligand structures, we quickly discover that there are actually only very few indeed: vicinal aminoalcohols (from amino acids and cinchona alkaloids) and diols (primarily from tartaric acid), both

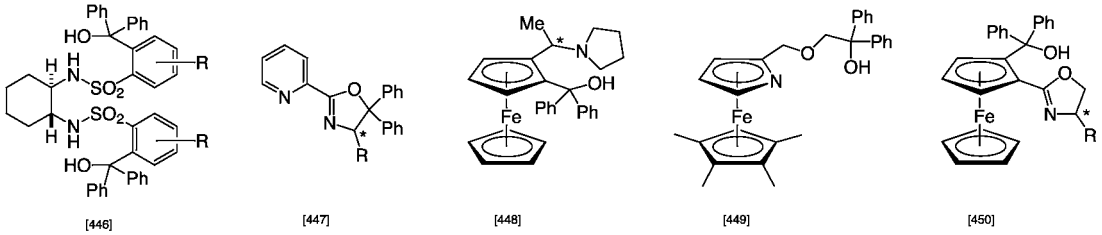
Amino Alcohols



Derivatives



"Combined" Ligands (see Figure 20)



Reactions That Can Be Made Enantioselective With These Ligands:

BH_3 reduction of ketones and oxime ethers [424,429-433,436,437,441]
R_2Zn addition to aldehydes (majority of examples) [435,439,440,446,448-450]
hydrosilylations [447]
substituting Michael additions to nitro olefins [445]
cyclopropanations [442,443]
Reformatsky reactions [434,444]

Figure 19. Chiral aminoalcohols and derivatives containing a diarylmethanol unit, together with types of standard reactions that can be carried out enantioselectively with these compounds (see also Scheme 30). It is worth noting that in the numerous applications reported so far for addition of Et_2Zn to aldehydes there is no case that offers broader applicability and generally higher enantioselectivity than has been demonstrated with titanium TADDOLates and titanium CYDISates!

derived ultimately from natural products, together with binaphthyls (occasionally biphenyls), vicinal diamines, and metallocenes, accessible by resolution of racemates or enantioselective synthesis. Much less frequently encountered—and then usually in special applications—are derivatives of terpenes or carbohydrates.

The path toward the goal[11] of developing standard enantioselective approaches—or, even better, catalytic enantioselective approaches—to all types of chiral products from all types of achiral starting materials will undoubtedly follow an evolutionary course, and in the end only a very few "systems" will remain.[467]

We wish to express our special gratitude to Dr. Engelbert Zass for the electronic literature search[467a] that was of such great value to us in preparing this article, to Dr. Dietmar Plattner for his searches in the CSD database and assistance in the discussion of crystal structures, and to Silvia Sigrist for invaluable help in preparing the manuscript. In addition, we wish to thank Felix Bangerter and Dr. Andreas Böhm for recording the NMR spectra shown in Scheme 5, Dr. Masao Aoki, Dr. Tobias Hintermann, Arkadius Pichota, Holger Sellner, and Daniel Weibel for their considerable assistance in proofreading, and all the many co-workers in the Seebach group who have been involved over the years in the TADDOL project, and whose names appear in the various literature citations. Finally, we are appreciative of generous support from Novartis Pharma AG and the Swiss National Science Foundation (SNF).

Received: May 18, 2000 [A 413]

[1] H. Krauch, W. Kunz, *Reaktionen der organischen Chemie. Ein Beitrag zur Terminologie der organischen Chemie*, 5th ed., Hüthig, Heidelberg, **1976**.
[2] G. Wittig, G. Waltnitzki, *Ber. Dtsch. Chem. Ges. A* **1934**, *67*, 667 – 675.

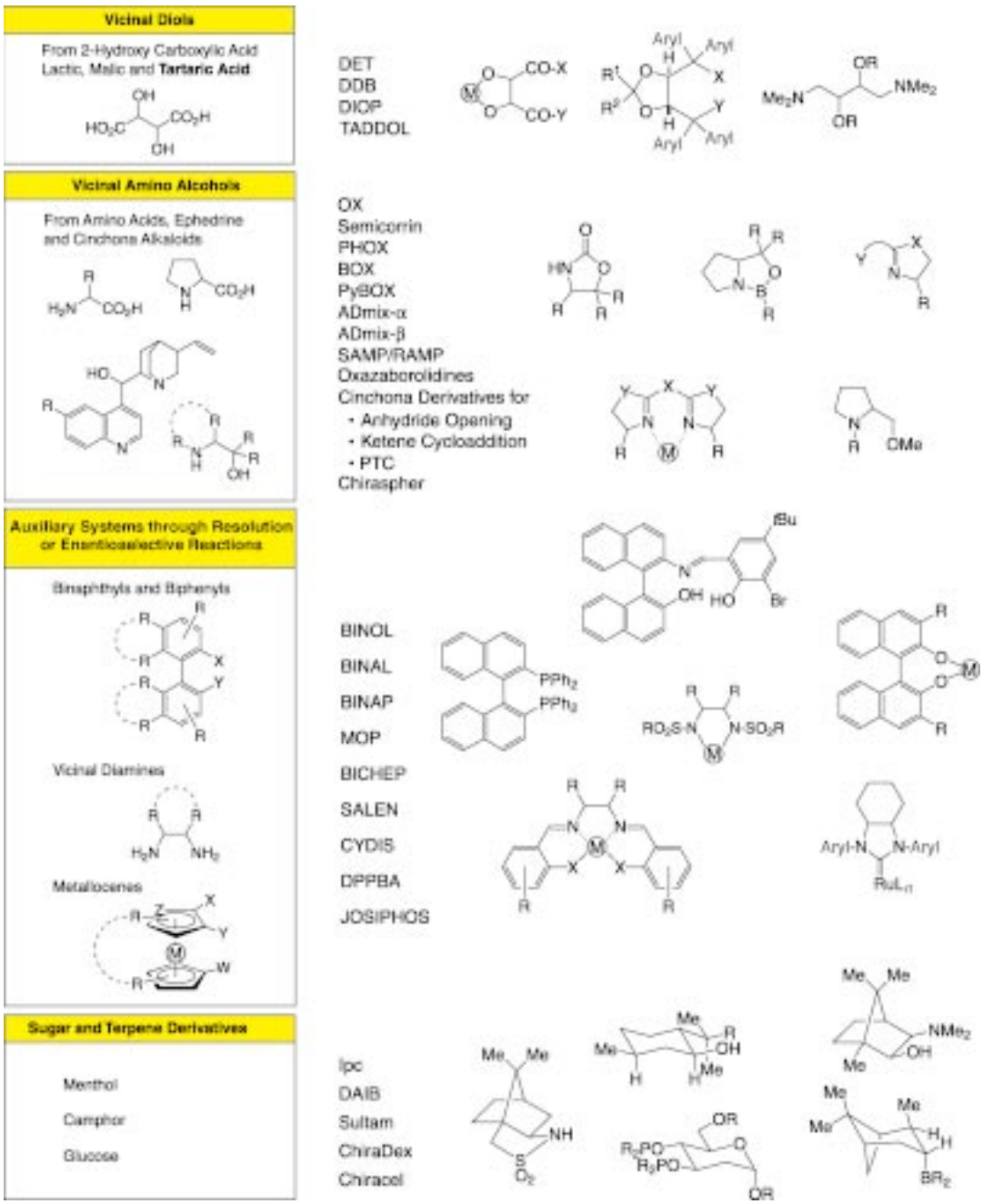


Figure 20. Leafing through reference works,[452] books,[453] and review articles[454] on stereoselective syntheses, the preparation of enantiomerically pure compounds, and chiral catalysts, one repeatedly encounters the same chiral skeletons.[452–465] Such skeletons find use not only in complexing agents for catalysts or catalyst precursors, but also as parts of reagents (including those bonded to a solid phase) introduced in stoichiometric quantities for resolution of racemates in chromatography, in analytical applications, and (as components) in materials. Were we to characterize such skeletons as "broadly applicable chiral auxiliaries", then the category would be limited to three members: substances derived from tartaric acid (including the TADDOLs), compounds accessible through amino acids, and binaphthyl derivatives. Here we present stylized and concrete formulae and abbreviations for selected compounds that belong to these auxiliary systems. For details see the extensive secondary literature cited above. A price comparison is also of interest.[466] It will be intriguing to see which systems prove to be most successful in the next few years, especially with respect to industrial applications.

[3] K. B. Alberman, R. N. Haszeldine, F. B. Kipping, *J. Chem. Soc.* **1952**, 3284 – 3288; see also: G. W. Griffin, R. B. Hager, D. F. Veber, *J. Am. Chem. Soc.* **1962**, *84*, 1008 – 1011.

[4] B. Teichmann, *Acta Chem. Acad. Sci. Hung.* **1965**, *46*, 241 – 246.

[5] See the exhaustive treatment of the chemistry of four-membered ring compounds in: D. Seebach, *Methoden der Org. Chem. (Houben-Weyl) Vol. IV/4*, **1971**, pp. 1 – 444; *Methods Org. Chem. (Houben-Weyl) Vol. E 17e/f*, **1997**.

[6] "Enantiomerically pure" or "enantiopure" compounds are ones in which the amount of enantiomer "impurity" is below the limit of detectability of the analytical method employed (GC, HPLC, NMR spectroscopy).

[7] For definitions and applications of these concepts, see ref. [8 – 11].

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

[9] "EPC Syntheses with C,C Bond Formation via Acetals and Enamines": D. Seebach, R. Imwinkelried, T. Weber in *Modern*

Synthetic Methods, *Vol. 4* (Ed.: R. Scheffold), Springer, Berlin, **1986**, pp. 125 – 259.

[10] "Nomenclature and Vocabulary of Organic Stereochemistry": G. Helmchen, *Methods Org. Chem. (Houben-Weyl) Vol. E21a*, **1995**, pp. 1 – 74.

[11] "Organic Synthesis—Where now?": D. Seebach, *Angew. Chem.* **1990**, *102*, 1363 – 1409; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1320 – 1367.

[12] "Basic Principles of EPC Synthesis": J. Mulzer, *Methods Org. Chem. (Houben-Weyl) Vol. E 21a*, **1995**, pp. 75 – 146.

[13] A book by Morrison and Mosher[14] that contained "all the asymmetric organic reactions" known up to 1971 consisted of 465 pages. The five-volume work on "asymmetric synthesis"[15] published by Morrison between 1983 and 1985 has 1828 pages, and treatment of the subject "stereoselective synthesis" in Houben-Weyl[16] (1996) required ten volumes with a total of 6989 pages.

[14] J. D. Morrison, H. S. Mosher, *Asymmetric Organic Reactions*, Prentice-Hall, Englewood Cliffs, NJ, **1971**.

[15] J. D. Morrison, *Asymmetric Synthesis*, *Vol. 1 – 5*, Academic Press, New York, **1983 – 1985**.

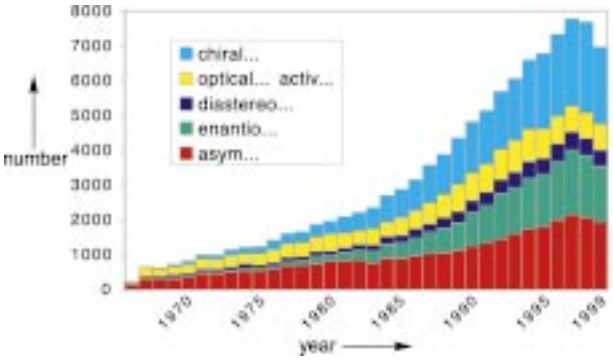
[16] "Stereoselective Synthesis": *Methods Org. Chem. (Houben-Weyl) Vol. E 21a – f*, **1995**.

[17] Today there is in fact the risk of overemphasizing enantioselective syntheses and the synthesis of enantiomerically pure compounds (EPC) in organic chemistry in general: The chemist interested in synthesizing complex molecules[18] must be concerned primarily with reactivity, differentiation of similar structural groups, protection/deprotection, and regio- and diastereoselectivity; the transformation (called "chirogenic" by Eschenmoser[19]) from achiral or racemic material to chiral, nonracemic educts, intermediates, or products represents only *a single step* in a multistep synthesis! The most straightforward and commonly employed approach to enantiomerically pure products entails incorporating into the structure of some naturally occurring substance (such as lactic, malic, tartaric, or mandelic acid, or one of the amino acids): "Enantiomerenreine Naturstoffe und Pharmaka aus billigen Vorläufern (Chiral Pool)—Zur Frage nach der chiral ökonomischen und ökologischen Totalsynthese": D. Seebach, H.-O. Kalinowski, *Nachr. Chem. Techn.* **1976**, 24, 415 – 418; "Beyond Nature's Chiral Pool: Enantioselective Catalysis in Industry": W. A. Nugent, T. V. RajanBabu, M. J. Burk, *Science*, **1993**, *259*, 479 – 483; Jacobsen has lectured on the topic "Expanding the Chiral Pool"; see, for example: H. Lebel, E. N. Jacobsen, *Tetrahedron Lett.* **1999**, *40*, 7303 – 7306.

[18] "The Art and Science of Total Synthesis at the Dawn of the Twenty-First Century": K. C. Nicolaou, D. Vourloumis, N. Winssinger, P. S. Baran, *Angew. Chem.* **2000**, *112*, 46 – 126; *Angew. Chem. Int. Ed.* **2000**, *39*, 44 – 122.

[19] S. Drenkard, J. Ferris, A. Eschenmoser, *Helv. Chim. Acta* **1990**, *73*, 1373 – 1390.

[20] The following bar graph shows the increase since 1966 in the number of papers whose titles include the words or word fragments "asym", "enantio", "diastereo", "optical activ", or "chiral" (CAS search, February 2000).



[21] Abbreviation of the systematic name $\alpha,\alpha,\alpha',\alpha'$-**t**etra**a**ryl-2,2-dimethyl-1,3-**di**oxolan-4,5-**di**methan**o**l. These compounds are frequently described as acetals or ketals of 1,1,4,4-tetraarylthreitol, a type of compound that Frankland prepared from diethyl tartrate and PhMgBr as early as 1904.[22]

[22] P. F. Frankland, D. F. Twiss, *J. Chem. Soc.* **1904**, 1666 – 1667.

[23] The "progenitor TADDOL" from the acetonide of dimethyl tartrate and PhMgBr was first synthesized by A. K. Beck (ETH Zürich, November 1982).

[24] To date, only brief review articles and two book chapters have appeared concerning TADDOLs: "2,2-Dimethyl-$\alpha,\alpha,\alpha',\alpha'$-tetraphenyl-1,3-dioxolane-4,5-dimethanolatotitanium Diisopropoxide": R. Dahinden, A. K. Beck, D. Seebach in *Encyclopedia of Reagents for Organic Synthesis*, *Vol. 3* (Ed.: L. A. Paquette), Wiley, Chichester, **1995**, pp. 2167 – 2170; "The 'Magic' Diarylhydroxymethyl Group": M. Braun, *Angew. Chem.* **1996**, *108*, 565 – 568; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 519 – 522; "Catalytic Enantioselective Reactions from Research to Application. Diarylmethanol-Containing Auxiliaries as a Study Case": D. Seebach, A. K. Beck, *Chimia* **1997**, *51*, 293 – 297; "TADDOLs, Their Complexes, and Related Compounds": J. Gawronski, K. Gawronska, *Tartaric and Malic Acids in Synthesis*, Wiley, New York, **1999**, Chap. 12, pp. 233 – 281; "TADDOLs—from Enantioselective Catalysis to Dendritic Cross Linkers to Cholesteric Liquid Crystals": D. Seebach, *Chimia* **2000**, *54*, 60 – 62; "TADDOL and its Derivatives—Our Dream of Universal Chiral Auxiliaries": D. Seebach, A. K. Beck, A. Heckel, *Essays in contemporary Chemistry. From molecular structures towards biology* (Eds.: G. Quinker, V. Kisakürek), VHCA, Basel, **2001**, in press.

[25] "Some Recent Advances in the Use of Titanium Reagents for Organic Synthesis": D. Seebach, A. K. Beck, M. Schiess, L. Widler, A. Wonnacott, *Pure Appl. Chem.* **1983**, *55*, 1807 – 1822.

[26] "Organometallic Compounds of Titanium and Zirconium as Selective Nucleophilic Reagents in Organic Synthesis": B. Weidmann, D. Seebach, *Angew. Chem.* **1983**, *95*, 12 – 26; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 31 – 45.

[27] "Titanium and Zirconium Derivatives in Organic Synthesis": D. Seebach, B. Weidmann, L. Widler in *Modern Synthetic Methods*, *Vol. 3* (Ed.: R. Scheffold), Salle+Sauerländer, Aarau, **1983**, pp. 217 – 353.

[28] "Anwendungen niedervalenter Titan-Reagentien in der Organischen Synthese": C. Betschart, D. Seebach, *Chimia* **1989**, *43*, 39 – 49.

[29] "Methods of Reactivity Umpolung": D. Seebach, *Angew. Chem.* **1979**, *91*, 259 – 278; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239 – 258.

[30] For reviews of independent efforts in this field, see: M. T. Reetz, *Organotitanium Reagents in Organic Synthesis*, Springer, Berlin, **1986**; "Chelation or Non-Chelation Control in Addition Reactions of Chiral α- and β-Alkoxy Carbonyl Compounds": M. T. Reetz, *Angew. Chem.* **1984**, *96*, 542 – 555; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556 – 569.

[31] "Organotitanium Reagents in Organic Chemistry": *Tetrahedron* **1992**, *48*, 5557 – 5754 (Tetrahedron Symposia-in-Print Number 47; Ed.: M. T. Reetz).

[32] B. Weidmann, L. Widler, A. G. Olivero, C. D. Maycock, D. Seebach, *Helv. Chim. Acta* **1981**, *64*, 357 – 361.

[33] T. Vries, H. Wynberg, E. van Echten, J. Koek, W. ten Hoeve, R. M. Kellogg, Q. B. Broxterman, A. Minnaard, B. Kaptein, S. van der Sluis, L. Hulshof, J. Kooistra, *Angew. Chem.* **1998**, *110*, 2491 – 2496; *Angew. Chem. Int. Ed.* **1998**, *37*, 2349 – 2354.

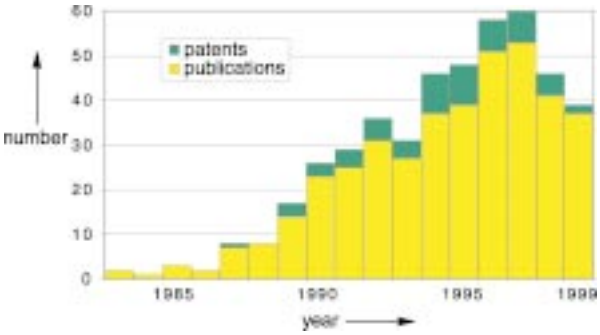
[34] Acetonides of the (*R*,*R*)- and (*S*,*S*)-tartaric acid dimethyl and diethylesters are commercially available from Acros, Aldrich, Fluka, Merck, and TCI (Japan). Starting from tartaric acid and 2,2-dimethoxypropane, the most convenient and "cheapest" method of preparing the dimethyl ester acetonide is described in: M. Carmack, C. J. Kelley, *J. Org. Chem.* **1968**, *33*, 2171 – 2173; D. Seebach, H.-O. Kalinowski, B. Bastani, G. Crass, H. Daum, H. Dörr, N. P. DuPreez, V. Ehrig, W. Langer, C. Nüssler, H.-A. Oei, M. Schmidt, *Helv. Chim. Acta* **1977**, *60*, 301 – 325.

[35] D. Seebach, A. K. Beck, R. Imwinkelried, S. Roggo, A. Wonnacott, *Helv. Chim. Acta* **1987**, *70*, 954 – 974.

[36] A. K. Beck, B. Bastani, D. A. Plattner, W. Petter, D. Seebach, H. Braunschweiger, P. Gysi, L. La Vecchia, *Chimia* **1991**, *45*, 238 – 244; A. K. Beck, P. Gysi, L. La Vecchia, D. Seebach, *Org. Synth.* **1999**, *76*, 12 – 22.

[37] D. Seebach, R. Dahinden, R. E. Marti, A. K. Beck, D. A. Plattner, F. N. M. Kühnle, *J. Org. Chem.* **1995**, *60*, 1788 – 1799.

[38] A. K. Beck, C. Müller, V. Doughty, H. U. Bichsel, P. Monnard, C. Tacheci, T. Styner, unpublished experiments, ETH Zürich, **1996**–**2000**.
[39] A. Heckel, L. Gehrer, P. Manini, unpublished experiments, ETH Zürich, **1998**–**2000**.
[40] T. Litz, unpublished experiments, ETH Zürich, **1996**–**1997**.
[41] R. Marti, unpublished experiments, ETH Zürich, **1995**–**1996**.
[42] H. Sellner, unpublished experiments, ETH Zürich, **1998**–**2000**.
[43] A. Cuenca, M. Medio-Simón, G. Asensio Aguilar, D. Weibel, A. K. Beck, D. Seebach, *Helv. Chim. Acta*, submitted.
[44] Y. N. Ito, X. Ariza, A. K. Beck, A. Bohác, C. Ganter, R. E. Gawley, F. N. M. Kühnle, J. Tuleja, Y. M. Wang, D. Seebach, *Helv. Chim. Acta* **1994**, *77*, 2071–2110.
[45] C. Haase, C. R. Sarko, M. DiMare, *J. Org. Chem.* **1995**, *60*, 1777–1787.
[46] U. Berens, D. Leckel, S. C. Oepen, *J. Org. Chem.* **1995**, *60*, 8204–8208.
[47] D. Haag, H. D. Scharf, *J. Org. Chem.* **1996**, *61*, 6127–6135.
[48] D. Haag, J. Runsink, H. D. Scharf, *Organometallics* **1998**, *17*, 398–409.
[49] V. K. Aggarwal, A. Mereu, G. J. Tarver, R. McCague, *J. Org. Chem.* **1998**, *63*, 7183–7189.
[50] C. Dreisbach, U. Kragl, C. Wandrey, *Synthesis* **1994**, 911–912.
[51] H. Waldmann, M. Weigerding, C. Dreisbach, C. Wandrey, *Helv. Chim. Acta* **1994**, *77*, 2111–2116.
[52] E. Weber, T. Hens, O. Gallardo, I. Csöregh, *J. Chem. Soc. Perkin Trans. 2* **1996**, 737–745.
[53] I. Csöregh, E. Weber, T. Hens, M. Czugler, *J. Chem. Soc. Perkin Trans. 2* **1996**, 2733–2739.
[54] J. Reinbold, K. Cammann, E. Weber, T. Hens, C. Reutel, *J. Prakt. Chem.* **1999**, *341*, 252–263.
[55] I. Csöregh, E. Weber, *Mol. Recognit. Inclusion Phenom.* **1998**, 301–304.
[56] H. Brunner, W. Zettlmeier, *Bull. Soc. Chim. Belg.* **1991**, *100*, 247–257.
[57] R. O. Duthaler, A. Hafner, P. L. Alsters, G. Bold, G. Rihs, P. Rothe-Streit, B. Wyss, *Inorg. Chim. Acta* **1994**, *222*, 95–113.
[58] G. Giffels, C. Dreisbach, U. Kragl, M. Weigerding, H. Waldmann, C. Wandrey, *Angew. Chem.* **1995**, *107*, 2165–2166; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2005–2006.
[59] N. M. Maier, G. Uray, *J. Chromatogr. A* **1996**, *732*, 215–230.
[60] R. O. Duthaler, P. M. Rothe, Central Research Ciba Geigy, Basel, **1990**–**1994**; P. M. Rothe, inaugural dissertation, Universität Basel, **1994**.
[61] The number of publications each year with references to TADDOLs can be determined from the bar graph below (based on a CAS search conducted in Feburary, 2000).



[62] According to the Available Chemicals Directory (ACD-3D under MDL ISIS Update 99.1), current suppliers are as follows: Acros, Aldrich, Fluka, Merck, Sigma, and TCI (Japan).
[63] P. B. Rheiner, D. Seebach, *Chem. Eur. J.* **1999**, *5*, 3221–3236.
[64] K. Narasaka, N. Iwasawa, M. Inoue, T. Yamada, M. Nakashima, J. Sugimori, *J. Am. Chem. Soc.* **1989**, *111*, 5340–5345.
[65] F. Toda, K. Mori, *J. Chem. Soc. Chem. Commun.* **1989**, 1245–1246.
[66] E. Weber, N. Dörpinghaus, I. Goldberg, *J. Chem. Soc. Chem. Commun.* **1988**, 1566–1568.
[67] J. Irurre, C. Alonso-Alija, J. F. Piniella, A. Alvarez-Larena, *Tetrahedron: Asymmetry* **1992**, *3*, 1591–1596.
[68] D. Seebach, P. B. Rheiner, A. K. Beck, F. N. M. Kühnle, B. Jaun, *Pol. J. Chem.* **1994**, *68*, 2397–2413.
[69] E. J. Corey, Y. Matsumura, *Tetrahedron Lett.* **1991**, *32*, 6289–6292.
[70] C. von dem Bussche-Hünnefeld, A. K. Beck, U. Lengweiler, D. Seebach, *Helv. Chim. Acta* **1992**, *75*, 438–441.
[71] D. Seebach, R. E. Marti, T. Hintermann, *Helv. Chim. Acta* **1996**, *79*, 1710–1740.
[72] D. Seebach, A. Pichota, A. K. Beck, A. B. Pinkerton, T. Litz, J. Karjalainen, V. Gramlich, *Org. Lett.* **1999**, *1*, 55–58.
[73] R. Appel, *Angew. Chem.* **1975**, *87*, 863–874; *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 801–811.
[74] D. Seebach, M. Hayakawa, J. Sakaki, W. B. Schweizer, *Tetrahedron* **1993**, *49*, 1711–1724.
[75] D. Seebach, A. K. Beck, M. Hayakawa, G. Jaeschke, F. N. M. Kühnle, I. Nägeli, A. B. Pinkerton, P. B. Rheiner, R. O. Duthaler, P. M. Rothe, W. Weigand, R. Wünsch, S. Dick, R. Nesper, M. Wörle, V. Gramlich, *Bull. Soc. Chim. Fr.* **1997**, *134*, 315–331.
[76] A. Pichota, unpublished experiments, ETH Zürich, **1998**–**2000**.
[77] "Enantioselective Aldol and Michael Additions of Achiral Enolates in the Presence of Chiral Lithium Amides and Amines": E. Juaristi, A. K. Beck, J. Hansen, T. Matt, T. Mukhopadhyay, M. Simson, D. Seebach, *Synthesis* **1993**, 1271–1290.
[78] D. Seebach, E. Devaquet, A. Ernst, M. Hayakawa, F. N. M. Kühnle, W. B. Schweizer, B. Weber, *Helv. Chim. Acta* **1995**, *78*, 1636–1650.
[79] O. De Lucchi, P. Maglioli, G. Delogu, G. Valle, *Synlett* **1991**, 841–844.
[80] S. Zheng, D. Y. Sogah, *Tetrahedron* **1997**, *53*, 15469–15485.
[81] "Diastereoselektive Polymerisation von TADDOL-dimethacrylat": C. Hanf, Inaugural Dissertation, Heinrich-Heine-Universität, Düsseldorf, **1999**.
[82] W. Adam, C.-G. Zhao, *Tetrahedron: Asymmetry* **1997**, *8*, 3995–3998.
[83] H.-G. Kuball, B. Weiss, A. K. Beck, D. Seebach, *Helv. Chim. Acta* **1997**, *80*, 2507–2514.
[84] J. Madsen, R. P. Clausen, R. G. Hazell, H. J. Jacobsen, M. Bols, C. C. Perry, *Acta Chem. Scand.* **1998**, *52*, 1165–1170.
[85] M. Aoki, unpublished experiments, ETH Zürich, **1999**–**2000**.
[86] A. Alexakis, J. Vastra, J. Burton, C. Benhaim, P. Mangeney, *Tetrahedron Lett.* **1998**, *39*, 7869–7872.
[87] J. Sakaki, W. B. Schweizer, D. Seebach, *Helv. Chim. Acta* **1993**, *76*, 2654–2665.
[88] A. Hafner, G. Rihs, R. O. Duthaler, unpublished results, Novartis Pharma AG, Basel.
[89] R. Wünsch, unpublished experiments, ETH Zürich, **1996**–**1997**.
[90] "Equilibrium Acidities in Dimethyl Sulfoxide Solution": F. G. Bordwell, *Acc. Chem. Res.* **1988**, *21*, 456–463.
[91] A list of unsuccessful experiments[89] is provided in footnote (2) of ref. [92].
[92] D. K. Heldmann, D. Seebach, *Helv. Chim. Acta* **1999**, *82*, 1096–1110.
[93] H. B. Kagan, T.-P. Dang, *J. Am. Chem. Soc.* **1972**, *94*, 6429–6433; "Asymmetric Catalysis in Organic Synthesis with Industrial Perspectives": H. B. Kagan, *Bull. Soc. Chim. Fr.* **1988**, 846–853.
[94] A. Pichota, P. S. Pregosin, M. Valentini, M. Wörle, D. Seebach, *Angew. Chem.* **2000**, *112*, 157–160; *Angew. Chem. Int. Ed.* **2000**, *39*, 153–156.
[95] K. V. Gothelf, K. A. Jørgensen, *J. Chem. Soc. Perkin Trans. 2* **1997**, 111–115.
[96] A. K. Beck, M. Dobler, D. A. Plattner, *Helv. Chim. Acta* **1997**, *80*, 2073–2083.
[97] For the principle of structure–reactivity correlation, see: D. Dunitz, *X-Ray Analysis and The Structure of Organic Molecules*, Cornell University Press, Ithaca, **1979**, 2nd corrected ed., VHCA, Basel, **1995**; H. B. Bürgi, J. D. Dunitz, *Structure Correlation*, *Vol. 2*, VCH, Weinheim, **1994**.
[98] "Shape and Symmetry in the Design of New Hosts": E. Weber in *Comprehensive Supramolecular Chemistry*, *Vol. 6* (Eds.: J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle), Elsevier Science, Oxford, **1996**, pp. 535–592.
[99] The three carbon atoms of the appropriate dioxolane rings served as fixed points for the overlays, and the structures of (*S*,*S*)-TADDOL derivatives were introduced as their mirror images. Inclusions that may have been present in the structures have been omitted.

[100] In this case the two phosphorus atoms and the metal center served as fixed points for the overlays. Substituents that may have been present on the chelate rings have been omitted for clarity. Mirror-image structures were used where required.
[101] See Figure 1 in "Asymmetric Hydrogenations": R. Noyori in *Organic Synthesis in Japan. Past, Present and Future* (Ed.: R. Noyori), Society of Synthetic Organic Chemistry, Japan, **1992**, pp. 301 – 307.
[102] D. Seebach, D. A. Plattner, A. K. Beck, Y. M. Wang, D. Hunziker, W. Petter, *Helv. Chim. Acta* **1992**, *75*, 2171 – 2209, and references therein.
[103] R. M. Beesly, C. K. Ingold, J. F. Thorpe, *J. Chem. Soc.* **1915**, *107*, 1080 – 1106.
[104] M. E. Jung, J. Gervay, *J. Am. Chem. Soc.* **1991**, *113*, 224 – 232.
[105] F. N. M. Kühnle, unpublished experiments, ETH Zürich, **1993 – 1996**; F. N. M. Kühnle, Dissertation No. 11782, ETH Zürich, **1996**.
[106] Adapted from the title of Section 12 in the Woodward – Hoffman review of pericyclic reactions: ref. [107].
[107] "The Conservation of Orbital Symmetry": R. B. Woodward, R. Hoffmann, *Angew. Chem.* **1969**, *81*, 797 – 869; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 781 – 853.
[108] P. Deslongchamps, *Stereoelectronic Effects in Organic Chemistry*, Pergamon, Oxford, **1983**.
[109] A. J. Kirby, *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*, Springer, Berlin, **1983**.
[110] E. Juaristi, G. Cuevas, *The Anomeric Effect*, CRC Press, Boca Raton, FL, **1995**.
[111] The conformation of the OH/F compound is another example of the lack of formation of a hydrogen bond between OH and F in organic compounds. For a systematic investigation of this phenomenon, which is contrary to common expectations, see: J. D. Dunitz, R. Taylor, *Chem. Eur. J.* **1997**, *3*, 89 – 98.
[112] D. Seebach, A. K. Beck, B. Schmidt, Y. M. Wang, *Tetrahedron* **1994**, *50*, 4363 – 4384.
[113] J. Irurre, C. Alonso-Alija, A. Fernandez-Serrat, *Afinidad* **1994**, *51*, 413 – 418.
[114] "Synthesis and Application of Chiral Liquid Crystals", D. Pauluth, A. E. F. Wächtler in *Chirality in Industry II* (Eds.: A. N. Collins, G. N. Sheldrake, J. Crosby), Wiley, Chichester, **1997**, pp. 263 – 286.
[115] "Polishing LCDs": M. Freemantle, *Chem. Eng. News* **1996**, *74*(51), 33 – 37.
[116] "From Chiral Molecules to Chiral Phases: Comments on the Chirality of Liquid Crystalline Phases": H.-G. Kuball, *Newsl. Int. Liq. Cryst. Soc.* **1999**, *9*, 1 – 7.
[117] "Liquid Crystals: A Tool for Studies in Chirality": G. Solladié, R. G. Zimmermann, *Angew. Chem.* **1984**, *96*, 335 – 349; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 348 – 362.
[118] H.-G. Kuball, B. Weiß, I. Kiesewalter, E. Dorr, A. K. Beck, D. Seebach, previously unpublished experiments, Universität Kaiserslautern and ETH Zürich, **1998 – 2000**.
[119] G. Heppke, D. Lötzsch, F. Oestreicher, *Z. Naturforsch.* **1986**, *41*, 1214 – 1218.
[120] B. Weiß, PhD Dissertation No. D 386, Universität Kaiserslautern, **1999**.
[121] L. Feltre, A. Ferrarini, F. Pacchiele, P. L. Nordio, *Mol. Cryst. Liq. Cryst.* **1996**, *290*, 109 – 118; A. Ferrarini, G. J. Moro, P. L. Nordio, *Mol. Phys.* **1996**, *87*, 485 – 499; A. Ferrarini, G. J. Moro, P. L. Nordio, *Phys. Rev. E* **1996**, *53*, 681 – 688; P. J. Camp, *Mol. Phys.* **1997**, *91*, 381 – 384; A. B. Harris, R. D. Kamien, T. C. Lubensky, *Phys. Rev. Lett.* **1997**, *78*, 1476 – 1479; H.-G. Kuball, H. Brüning, *Chirality* **1997**, *9*, 407 – 423; H.-G. Kuball, T. Höfer in *Chirality in Liquid Crystals*, Springer-Verlag, Berlin, **2001**, in print; H.-G. Kuball, T. Müller, H. Brüning. A. Schönhofer, *Mol. Cryst. Liq. Cryst.* **1995**, *261*, 205 – 216; H.-G. Kuball, H. Brüning. T. Müller, O. Türk, A. Schönhofer, *J. Mater. Chem.* **1995**, *5*, 2167 – 2174.
[122] F. Meyer, K. Siemensmeyer, H. G. Kuball, B. Weiß, D. Seebach (BASF AG) DE 196 11 101.3, **1997** [*Chem. Abstr.* **1997**, *127*, 301547s].
[123] The firm MLS GmbH (Leuna, Germany) is currently in the process of developing a commercial product. (Private communication from Prof. F. Kuschel.)
[124] For synthesis of the TADDOLs, see the references in Table 1 and the Supporting Information.
[125] ^{2}H-NMR spectra of specific and fully D-labeled TADDOLs should permit determination of the degree of order as well as the principal axes of the ordering tensors; I. Kiesewalter, PhD Dissertation, Universität Kaiserslautern, **1999**.
[126] A report recently appeared concerning a completely different type of analytical application in sensor technology (detection of organic solvent vapors) for the previously mentioned[52] TADDOL analogue with a bicyclo[2.2.2]octadiene skeleton.[54] In this case chirality plays no role whatsoever—at least, not yet.
[127] K. Tanaka, M. Ootani, F. Toda, *Tetrahedron: Asymmetry* **1992**, *3*, 709 – 712; T. Schrader, *Angew. Chem.* **1995**, *107*, 1001 – 1002; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 917 – 919.
[128] M. Malacria, C. Aubert, F. Slowinsky, O. Buisine, personal communication.
[129] This behavior provides an attractive verification of the principles established by Kitaigorodsky for the development of crystal packings: A. I. Kitaigorodsky, *Molecular Crystals and Molecules*, Academic Press, New York, **1973**.
[130] "Molecular Recognition": F. Toda, *Bioorg. Chem.* **1991**, *19*, 157 – 168.
[131] F. Toda, K. Tanaka, *Tetrahedron Lett.* **1988**, *29*, 551 – 554.
[132] "Simulierte Gegenstromchromatographie—eine effiziente Technik zur Herstellung optisch aktiver Verbindungen im industriellen Maßstab": M. Schulte, J. N. Kinkel, R.-M. Nicoud, F. Charton, *Chem. Ing. Tech.* **1996**, *68*, 670 – 683.
[133] Concurrent with the report by Toda et al.[131] of the first separation of enantiomers with TADDOL, Weber et al. described a separation of primary and secondary amines with **1a**, whereby the secondary amines were preferentially included; see ref. [66].
[134] F. Toda, K. Tanaka, L. Infantes, C. Foces-Foces, R. M. Claramunt, J. Elguero, *J. Chem. Soc. Chem. Commun.* **1995**, 1453 – 1454.
[135] Y. Takemoto, S. Kuraoka, N. Hamaue, K. Aoe, H. Hiramatsu, C. Iwata, *Tetrahedron* **1996**, *52*, 14177 – 14188.
[136] J.-L. Aubagnac, P. Bouchet, J. Elguero, R. Jacquier, C. Marzin, *J. Chim. Phys.* **1967**, *64*, 1649 – 1655.
[137] As dedicated opponents of the use of % *ee* data with respect to enantiomer purity, a characteristic now always determined by chromatography or NMR spectroscopy, we have in this article employed exclusively the terms "enantiomer purity" (*ep* [%]), "enantioselectivity" (*es* [%]), or "enantiomer ratio" (*er*); that is to say, we report the fraction of major enantiomer present or produced in a reaction.
[138] "Tartrate-Derived Ligands for the Enantioselective $LiAlH_4$ Reduction of Ketones—A Comparison of TADDOLates and BINOLates": A. K. Beck, R. Dahinden, F. N. M. Kühnle, *ACS Symp. Ser.* **1996**, *641*, 52 – 69.
[139] D. Seebach, A. K. Beck, R. Dahinden, M. Hoffmann, F. N. M. Kühnle, *Croat. Chem. Acta* **1996**, *69*, 459 – 484.
[140] F. Toda, K. Tanaka, M. Ootani, A. Hayashi, I. Miyahara, K. Hirotsu, *J. Chem. Soc. Chem. Commun.* **1993**, 1413 – 1415.
[141] K. Nishikawa, H. Tsukada, S. Abe, M. Kishimoto, N. Yasuoka, *Chirality* **1999**, *11*, 166 – 171.
[142] K. Mori, F. Toda, *Tetrahedron: Asymmetry* **1990**, *1*, 281 – 282.
[143] F. Toda, M. Ochi, *Enantiomer* **1996**, *1*, 85 – 88.
[144] F. Toda, S. Matsuda, K. Tanaka, *Tetrahedron: Asymmetry* **1991**, *2*, 983 – 986.
[145] F. Toda, Y. Tohi, *J. Chem. Soc. Chem. Commun.* **1993**, 1238 – 1240.
[146] F. Toda, *Mol. Cryst. Liq. Cryst. Sci. Technol. Sect. A* **1994**, *248*, 561 – 567.
[147] F. Toda, H. Takumi, K. Tanaka, *Tetrahedron: Asymmetry* **1995**, *6*, 1059 – 1062.
[148] K. Tanaka, A. Moriyama, F. Toda, *J. Chem. Soc. Perkin Trans. 1* **1996**, 603 – 604.
[149] H. E. Zimmerman, I. V. Alabugin, V. N. Smolenskaya, *Tetrahedron* **2000**, *56*, 6821 – 6831.
[150] L. R. Nassimbeni, M. L. Niven, K. Tanaka, F. Toda, *J. Crystallogr. Spectrosc. Res.* **1991**, *21*, 451 – 457.
[151] N. Morita, M. Kurita, S. Ito, T. Asao, C. Kabuto, M. Ueno, T. Sato, H. Sotokawa, M. Watanabe, A. Tajiri, *Enantiomer* **1998**, *3*, 453 – 461.
[152] F. Toda, K. Tanaka, D. Marks, I. Goldberg, *J. Org. Chem.* **1991**, *56*, 7332 – 7335.
[153] F. Toda, H. Miyamoto, H. Ohta, *J. Chem. Soc. Perkin Trans. 1* **1994**, 1601 – 1604.
[154] F. Toda, A. Sato, K. Tanaka, T. C. W. Mak, *Chem. Lett.* **1989**, 873 – 876.

[155] G. Kaupp, J. Schmeyers, F. Toda, H. Takumi, H. Koshima, *J. Phys. Org. Chem.* **1996**, *9*, 795 – 800.
[156] F. Toda, K. Tanaka, C. W. Leung, A. Meetsma, B. L. Feringa, *J. Chem. Soc. Chem. Commun.* **1994**, 2371 – 2372.
[157] F. Toda, A. Sato, L. R. Nassimbeni, M. L. Niven, *J. Chem. Soc. Perkin Trans. 2* **1991**, 1971 – 1975.
[158] P. Zaderenko, P. López, P. Ballesteros, H. Takumi, F. Toda, *Tetrahedron: Asymmetry* **1995**, *6*, 381 – 384.
[159] F. Toda, K. Tanaka, T. Okada, *J. Chem. Soc. Chem. Commun.* **1995**, 639 – 640.
[160] J. Zhu, Y. Qin, Z. He, F.-M. Fu, Z.-Y. Zhou, J.-G. Deng, Y.-Z. Jiang, T.-Y. Chau, *Tetrahedron: Asymmetry* **1997**, *8*, 2505 – 2508.
[161] T. Olszewska, M. J. Milewska, M. Gdaniec, T. Polonski, *J. Chem. Soc. Chem. Commun.* **1999**, 1385 – 1386.
[162] "Resolution of Racemates by Distillation with Inclusion Compounds": G. Kaupp, *Angew. Chem.* **1994**, *106*, 768 – 770; *Angew. Chem. Int. Ed. Engl.* **1994**, *106*, 728 – 729.
[163] F. Toda, H. Takumi, *Enantiomer* **1996**, *1*, 29 – 33.
[164] M. Ács, A. Mravik, E. Fogassy, Z. Böcskei, *Chirality* **1994**, *6*, 314 – 320.
[165] T. Tsunoda, H. Kaku, M. Nagaku, E. Okuyama, *Tetrahedron Lett.* **1997**, *38*, 7759 – 7760.
[166] W.-L. Tsai, K. Hermann, E. Hug, B. Rohde, A. S. Dreiding, *Helv. Chim. Acta* **1985**, *68*, 2238 – 2243.
[167] W. Bähr, H. Theobald, *Organische Stereochemie*, Springer, Berlin, **1973**, and references therein.
[168] For an imaginative satire on this theme, see: J. D. Dunitz, *Chem. Eur. J.* **1998**, *4*, 745 – 746.
[169] Other chiral host compounds have also been utilized by the Toda group (e.g. 1,6-diphenyl-1,6-bis(2-chlorophenyl)-2,4-hexadien-1,6-diol),[130] but they are less accessible than the TADDOLs!
[170] "Solid State Organic Reactions": F. Toda, *Synlett* **1993**, 303 – 312.
[171] "Solvent-Free Organic Synthesis": K. Tanaka, F. Toda, *Chem. Rev.* **2000**, *100*, 1025 – 1074.
[172] Thus, H. Zimmerman et al. of the University of Wisconsin, Madison, WI, observed that, within TADDOL inclusion compounds (relative to solution), the migration tendency of various aryl groups in the photorearrangement of 4,4-diaryl-2-cyclohexenones into 5,6-diarylbicyclo[3.1.0]hexan-2-ones can undergo reversal: a host-specific aryl migration.[149]
[173] Toda et al. have shown, for example, that when the inclusion compound formed between **1a** and (*R*)-6-methylbicyclo[4.4.0]-dec-1-en-3,7-dione (the Wieland-Miescher ketone) is triturated with $NaBH_4$ in an agate mortar and the mixture is subsequently allowed to stand at RT for three days with exclusion of moisture, reduction of the 7-keto group occurs with > 99 % diastereo- and regioselectivity to give the (6*R*,7*R*)-hydroxyketone (yield 95 %); see ref. [174].
[174] F. Toda, K. Kiyoshige, M. Yagi, *Angew. Chem.* **1989**, 101, 329 – 330; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 320 – 321.
[175] For a review, see the corresponding chapter in the Houben-Weyl volume which deals with four-membered ring compounds.[5]
[176] "Application of Enamide Photocyclisation to the Synthesis of Natural Products": I. Ninomiya, *Heterocycles* **1974**, *2*, 105 – 123.
[177] I. Ninomiya, T. Naito, *Photochemical Synthesis*, *Best Synthetic Methods* (Eds.: A. R. Katritzky, O. Meth-Cohn, C. U. Rees), Academic Press, London, **1989**.
[178] K. Tanaka, F. Toda, E. Mochizuki, N. Yasui, Y. Kai, I. Miyahara, K. Hirotsu, *Angew. Chem.* **1999**, *111*, 3733 – 3736; *Angew. Chem. Int. Ed.* **1999**, *38*, 3523 – 3525.
[179] F. Toda, H. Miyamoto, *Chem. Lett.* **1995**, 809 – 810.
[180] H. Miyamoto, S. Kikuchi, Y. Oki, M. Inoue, K. Kanemoto, F. Toda, *Mol. Cryst. Liq. Cryst. Sci. Technol. Sect. A* **1996**, *277*, 433 – 438.
[181] S. Akutsu, I. Miyahara, K. Hirotsu, H. Miyamoto, N. Maruyama, S. Kikuchi, F. Toda, *Mol. Cryst. Liq. Cryst. Sci. Technol. Sect. A* **1996**, *277*, 87 – 93.
[182] F. Toda, H. Miyamoto, K. Takeda, R. Matsugawa, N. Maruyama, *J. Org. Chem.* **1993**, *58*, 6208 – 6211.
[183] F. Toda, K. Tanaka, O. Kakinoki, T. Kawakami, *J. Org. Chem.* **1993**, *58*, 3783 – 3784.
[184] D. Hashizume, Y. Ohashi, K. Tanaka, F. Toda, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2383 – 2387.
[185] F. Toda, K. Tanaka, *Tetrahedron Lett.* **1988**, *29*, 4299 – 4302.
[186] K. Tanaka, O. Kakinoki, F. Toda, *J. Chem. Soc. Chem. Commun.* **1992**, 1053 – 1054.
[187] F. Toda, H. Miyamoto, K. Kanemoto, *J. Org. Chem.* **1996**, *61*, 6490 – 6491.
[188] F. Toda, H. Miyamoto, K. Kanemoto, K. Tanaka, Y. Takahashi, Y. Takenaka, *J. Org. Chem.* **1999**, *64*, 2096 – 2102.
[189] F. Toda, H. Miyamoto, T. Tamashima, M. Kondo, Y. Ohashi, *J. Org. Chem.* **1999**, *64*, 2690 – 2693.
[190] F. Toda, H. Miyamoto, S. Kikuchi, R. Kuroda, F. Nagami, *J. Am. Chem. Soc.* **1996**, *118*, 11315 – 11316.
[191] "Growth and Dissolution of Organic Crystals with 'Tailor-Made' Inhibitors—Implications in Stereochemistry and Materials Science": L. Addadi, Z. Berkovitch-Yellin, I. Weissbuch, J. van Mil, L. J. W. Shimon, M. Lahav, L. Leiserowitz, *Angew. Chem.* **1985**, *97*, 476 – 496; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 466 – 485.
[192] F. Toda, K. Mori, Y. Matsuura, H. Akai, *J. Chem. Soc. Chem. Commun.* **1990**, 1591 – 1593.
[193] F. Toda, K. Okuda, *J. Chem. Soc. Chem. Commun.* **1991**, 1212 – 1214.
[194] F. Toda, H. Akai, *J. Org. Chem.* **1990**, *55*, 3446 – 3447.
[195] F. Toda, K. Tanaka, J. Sato, *Tetrahedron: Asymmetry* **1993**, *4*, 1771 – 1774.
[196] F. Toda, N. Imai, *J. Chem. Soc. Perkin Trans. 1* **1994**, 2673 – 2674.
[197] See: G. Wulff, A. Matussek, C. Hanf, S. Gladow, C. Lehmann, R. Goddard, *Angew. Chem.* **2000**, *112*, 2364 – 2366; *Angew. Chem. Int. Ed.* **2000**, *39*, 2275 – 2277; ref. [81]; A. Matussek, inaugural dissertation, Heinrich-Heine-Universität, Düsseldorf, **1999**; G. Wulff, U. Zweering, S. Gladow, *Polym. Prepr. Am. Chem. Soc. Div. Polym. Chem.* **1996**, *37*, 448 – 449; G. Wulff, S. Gladow, B. Kühneweg, S. Krieger, *Macromol. Symp.* **1996**, *101*, 355 – 362; see also ref. [198, 470].
[198] T. Nakano, Y. Okamoto, D. Y. Sogah, S. Zheng, *Macromolecules* **1995**, *28*, 8705 – 8706.
[199] Y. N. Belokon, K. A. Kochetkov, T. D. Churkina, N. S. Ikonnikov, A. A. Chesnokov, O. V. Larionov, V. S. Parmár, R. Kumar, H. B. Kagan, *Tetrahedron: Asymmetry* **1998**, *9*, 851 – 857.
[200] B. Weber, D. Seebach, *Angew. Chem.* **1992**, *104*, 96 – 97; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 84 – 86.
[201] B. Weber, D. Seebach, *Tetrahedron* **1994**, *50*, 6117 – 6128.
[202] … also frequently referred to as "deracemization"; see the review articles: "Asymmetric Protonations": L. Duhamel, P. Duhamel, J.-C. Launay, J.-C. Plaquevent, *Bull. Soc. Chim. Fr.* **1984**, II, 421 – 430; "Formation of C–H Bonds": S. Hünig, *Methods of Org. Chem. (Houben-Weyl) Vol. E 21/7*, **1996**, pp. 3851 – 3911.
[203] "Asymmetric Protonations of Enol Derivatives": A. Yanagisawa, K. Ishihara, H. Yamamoto, *Synlett* **1997**, 411 – 420.
[204] "Asymmetric Synthesis Mediated by Chiral Ligands": K. Koga, *Pure Appl. Chem.* **1994**, *66*, 1487 – 1492.
[205] "Asymmetric Synthesis Using Homochiral Lithium Amide Bases": P. J. Cox, N. S. Simpkins, *Tetrahedron: Asymmetry* **1991**, *2*, 1 – 26.
[206] M. Murakata, T. Yasukata, T. Aoki, M. Nakajima, K. Koga, *Tetrahedron* **1998**, *54*, 2449 – 2458.
[207] "Crystal Structures and Stereoselective Reactions of Organic Lithium Derivatives": D. Seebach in *Proceedings of The Robert A. Welch Foundation Conferences on Chemical Research. XXVII. Stereospecificity in Chemistry and Biochemistry* (Houston, Texas) **1984**, pp. 93 – 145; "Structure and Reactivity of Lithium Enolates. From Pinacolone to Selective *C*-Alkylations of Peptides. Difficulties and Opportunities Afforded by Complex Structures": D. Seebach, *Angew. Chem.* **1988**, *100*, 1685 – 1715; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1624 – 1654.
[208] "The Structure of Lithium Compounds of Sulfones, Sulfoximides, Sulfoxides, Thioethers and 1,3-Dithianes, Nitriles, Nitro Compounds and Hydrazones": G. Boche, *Angew. Chem.* **1989**, *101*, 286 – 306; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 277 – 297; "Carbanions of Alkali and Alkaline Earth Cations: Synthesis and Structural Characterization": P. G. Williard in *Comprehensive Organic Synthesis*, *Vol. 1* (Eds.: B. M. Trost, I. Fleming, S. L. Schreiber), Pergamon, Oxford, **1991**, pp. 1 – 47; "Recent Results in NMR Spectroscopy of Organolithium Compounds": W. Bauer, P. von R. Schleyer in *Advances in Carbanion Chemistry*, *Vol. 1* (Ed.: V. Snieckus), Jai, Greenwich, CT, **1992**, pp. 89 – 175; "Solution Structures of Lithium Dialkylamides and Related N-Lithiated Species:

Results from ^{6}Li-^{15}N Double Labeling Experiments": D. B. Collum, *Acc. Chem. Res.* **1993**, *26*, 227 – 234.
[209] For cyclic peroxides derived from TADDOL cycloalkane analogues, see: T. Tamai, K. Mizuno, I. Hashida, Y. Otsuji, *Tetrahedron Lett.* **1993**, *34*, 2641 – 2644; K. Mizuno, T. Tamai, I. Hashida, Y. Otsuji, Y. Kuriyama, K. Tokumaru, *J. Org. Chem.* **1994**, *59*, 7329 – 7334.
[210] Recent reviews: "Transition Metal Catalysis in the Baeyer – Villiger Oxiation of Ketones": G. Strukul, *Angew. Chem.* **1998**, *110*, 1256 – 1267; *Angew. Chem. Int. Ed.* **1998**, *37*, 1198 – 1209; "100 Years of Baeyer – Villiger Oxidations": M. Renz, B. Meunier, *Eur. J. Org. Chem.* **1999**, 737 – 750.
[211] "The Development of Chiral, Nonracemic Dioxiranes for the Catalytic, Enantioselective Epoxidation of Alkenes": S. E. Denmark, Z. Wu, *Synlett* **1999**, 847 – 859.
[212] "Reduction of Carbonyl Compounds with Chiral Oxazaborolidine Catalysts: A New Paradigm for Enantioselective Catalysis and a Powerful New Synthetic Method": E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092 – 2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 1986 – 2012.
[213] "Lewis Acid Promoted Addition Reactions of Organometallic Compounds": M. Yamaguchi in *Comprehensive Organic Synthesis*, *Vol. 1* (Eds.: B. M. Trost, I. Fleming, S. L. Schreiber), Pergamon, Oxford, **1991**, pp. 325 – 353.
[214] V. Gutmann, *The Donor – Acceptor Approach to Molecular Interactions*, Plenum, New York, **1978**.
[215] W. B. Jensen, *The Lewis Acid-Base Concepts: An Overview*, Wiley, New York, **1980**.
[216] Approximate values for mean Ti–X bond energies: Ti–C 50, Ti–N 80, Ti–Cl 100, Ti–O 110 kcal mol^{-1} (from M. F. Lappert, D. S. Patil, J. B. Pedley, *J. Chem. Soc. Chem. Commun.* **1975**, 830 – 831).
[217] For recent reviews of Lewis acids and bifunctional catalysis (by mixtures of Lewis acids and bases), see ref. [25 – 27, 30, 213, 218 – 225].
[218] "Chiral Lewis Acids in Catalytic Asymmetric Reactions": K. Narasaka, *Synthesis* **1991**, 1 – 11.
[219] M. Santelli, J.-M. Pons, *Lewis Acids and Selectivity in Organic Synthesis*, CRC, Boca Raton, FL, **1996**.
[220] "Some Effects of Lithium Salts, of Strong Bases, and of the Cosolvent DMPU in Peptide Chemistry, and Elsewhere": D. Seebach, A. K. Beck, A. Studer in *Modern Synthetic Methods*, *Vol. 7* (Eds.: B. Ernst, C. Leumann), VHCA, Basel, **1995**, pp. 1 – 178.
[221] "Asymmetric Reactions with Chiral Lewis Acid Catalysts": K. Maruoka, H. Yamamoto in *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), VCH, New York, **1993**, pp. 413 – 440.
[222] "Designer Lewis Acids for Selective Organic Synthesis": H. Yamamoto, A. Yanagisawa, K. Ishihara, S. Saito, *Pure Appl. Chem*. **1998**, *70*, 1507 – 1512.
[223] "Studies on Enantioselective Synthesis": E. J. Corey in *Chiral Separations* (Ed.: S. Ahuja), ACS, Washington, DC, **1997**, pp. 37 – 58.
[224] "On the Conformation and Structure of Organometal Complexes in the Solid State: Two Studies Relevant to Chemical Synthesis": S. Shambayati, W. E. Crowe, S. L. Schreiber, *Angew. Chem.* **1990**, *102*, 273 – 290; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 256 – 272; "Lewis Acid Carbonyl Complexation": S. Shambayati, S. L. Schreiber in *Comprehensive Organic Synthesis*, *Vol. 1* (Eds.: B. M. Trost, I. Fleming, S. L. Schreiber), Pergamon, Oxford, **1991**, pp. 283 – 324.
[225] "Transition Metal Fluoride Complexes in Asymmetric Catalysis": B. L. Pagenkopf, E. M. Carreira, *Chem. Eur. J.* **1999**, *5*, 3437 – 3442.
[226] "Asymmetric 1,3-Dipolar Cycloaddition Reactions": K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863 – 909.
[227] K. Ishihara, M. Kaneeda, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 11179 – 11180.
[228] H. Schäfer, D. Seebach, *Tetrahedron* **1995**, *51*, 2305 – 2324.
[229] D. Seebach, I. M. Lyapkalo, R. Dahinden, *Helv. Chim. Acta* **1999**, *82*, 1829 – 1842.
[230] J. L. von dem Bussche-Hünnefeld, D. Seebach, *Tetrahedron* **1992**, *48*, 5719 – 5730; L. Behrendt, D. Seebach in *Synthetic Methods of Organometallic and Inorganic Chemistry*, *Vol. 1* (Eds.: W. A. Herrmann, A. Salzer), Thieme, Stuttgart, **1996**, pp. 103 – 104.
[231] B. Schmidt, D. Seebach, *Angew. Chem.* **1991**, *103*, 100 – 101; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 99 – 101.
[232] E. Wada, H. Yasuoka, S. Kanemasa, *Chem. Lett.* **1994**, 1637 – 1640.
[233] K. V. Gothelf, I. Thomsen, K. A. Jørgensen, *J. Am. Chem. Soc.* **1996**, *118*, 59 – 64.
[234] A. Hafner, R. O. Duthaler, R. Marti, G. Rihs, P. Rothe-Streit, F. Schwarzenbach, *J. Am. Chem. Soc.* **1992**, *114*, 2321 – 2336.
[235] H. Minamikawa, S. Hayakawa, T. Yamada, N. Iwasawa, K. Narasaka, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 4379 – 4383.
[236] K. Mikami, S. Matsukawa, T. Volk, M. Terada, *Angew. Chem.* **1997**, *109*, 2936 – 2939; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2768 – 2771.
[237] "Chiral Titanium Complexes for Enantioselective Addition of Nucleophiles to Carbonyl Groups": R. O. Duthaler, A. Hafner, *Chem. Rev.* **1992**, *92*, 807 – 832.
[238] "Asymmetric Ene Reactions in Organic Synthesis": K. Mikami, M. Shimizu, *Chem. Rev.* **1992**, *92*, 1021 – 1050.
[239] "Asymmetric Reactions Promoted by Titanium Reagents": K. Narasaka, N. Iwasawa in *Organic Synthesis: Theory and Applications*, *Vol. 2* (Ed.: T. Hudlicky), JAI, London, **1993**, pp. 93 – 112.
[240] D. J. Ramón, M. Yus, *Rec. Res. Dev. Org. Chem.* **1998**, *2*, 489 – 523.
[241] E. Frankland, *Justus Liebigs Ann. Chem.* **1849**, *71*, 171 – 213; E. Frankland, *Justus Liebigs Ann. Chem.* **1849**, *71*, 213 – 215; E. Frankland, *Justus Liebigs Ann. Chem.* **1853**, *85*, 329 – 373.
[242] "Enantioselective Addition of Organometallic Reagents to Carbonyl Compounds: Chirality Transfer, Multiplication, and Amplification": R. Noyori, M. Kitamura, *Angew. Chem.* **1991**, *103*, 34 – 55; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49 – 69; M. Kitamura, S. Suga, H. Oka, R. Noyori, *J. Am. Chem. Soc.* **1998**, *120*, 9800 – 9809.
[243] "Preparation and Reactions of Polyfunctional Organozinc Reagents in Organic Synthesis": P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117 – 2188.
[244] "*trans*-1,2-Diaminocyclohexane Derivatives as Chiral Reagents, Scaffolds, and Ligands for Catalysis: Applications in Asymmetric Synthesis and Molecular Recognition": Y. L. Bennani, S. Hanessian, *Chem. Rev.* **1997**, *97*, 3161 – 3195.
[245] M. Yoshioka, T. Kawakita, M. Ohno, *Tetrahedron Lett.* **1989**, *30*, 1657 – 1660; T. Hayashi, K. Tomioka, O. Yonemitsu, *Asymmetric Synthesis*, Kodansha, Tokyo, Gordon and Breach, Amsterdam, **1998**, p. 79.
[246] According to the Available Chemicals Directory (ACD-3D under MDL ISIS Update 99.1), the following organozinc compounds are commercially available: Me_2Zn, Et_2Zn, Bu_2Zn, $i Bu_2Zn$, Ph_2Zn (Acros, Aldrich, Fluka, Pfaltz-Bauer, Strem).
[247] "Zinc and Cadmium": P. Knochel in *Comprehensive Organometallic Chemistry II, Vol. 11* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson, A. McKillop), Elsevier, Oxford, **1995**, pp. 159 – 190; E. Erdik, *Organozinc Reagents in Organic Synthesis*, CRC, Boca Raton, FL, **1996**; P. Knochel, P. Jones, *Organozinc Reagents*, Oxford University Press, New York, **1999**.
[248] D. Seebach, L. Behrendt, D. Felix, *Angew. Chem.* **1991**, *103*, 991 – 992; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1008 – 1009.
[249] B. Weber, D. Seebach, *Tetrahedron* **1994**, *50*, 7473 – 7484.
[250] Even in an unfair comparison (only our short communications were taken into account; the work of Ohno and Knochel was ignored completely), the titanium TADDOLates are listed among the three best catalysts for the (Et_2Zn + RCHO) addition: L. Solà, K. S. Reddy, A. Vidal-Ferran, A. Moyano, M. A. Pericàs, A. Riera, A. Alvarez-Larena, J. F. Piniella, *J. Org. Chem.* **1998**, *63*, 7078 – 7082.
[251] Replacement of the methyl groups in **1f** by H/H, Ph/Ph, and 9-fluorenylidene leads to no change in selectivity for the test reaction Et_2Zn + PhCHO (all = 99 % *es*).[38]
[252] H. Brunner, E. L. Zang, *Z. Naturforsch. B* **1993**, *48*, 1723 – 1726.
[253] See footnote (19) in ref. [102].
[254] T. Sato, H. Shima, J. Otera, *J. Org. Chem.* **1995**, *60*, 3936 – 3937.
[255] N. Oguni, N. Satoh, H. Fujii, *Synlett* **1995**, 1043 – 1044.
[256] H. Takahashi, A. Kawabata, H. Niwa, K. Higashiyama, *Chem. Pharm. Bull.* **1988**, *36*, 803 – 806.
[257] B. C. Hong, J. H. Hong, Y. C. Tsai, *Angew. Chem.* **1998**, *110*, 482 – 484; *Angew. Chem. Int. Ed.* **1998**, *37*, 468 – 470.
[258] D. Seebach, R. Dahinden, R. E. Marti, A. K. Beck, D. A. Plattner, F. N. M. Kühnle, *J. Org. Chem.* **1995**, *60*, 1788 – 1799; Correction: *J. Org. Chem.* **1995**, *60*, 5364.
[259] S. BouzBouz, J. Cossy, *Org. Lett.* **2000**, *2*, 501 – 504.
[260] K. Mikami, M. Terada, T. Nakai, *J. Am. Chem. Soc.* **1990**, *112*, 3949 – 3954.

[261] D. Seebach, L. Widler, *Helv. Chim. Acta* **1982**, *65*, 1972 – 1981.
[262] "The Unambiguous Specification of the Steric Course of Asymmetric Synthesis": D. Seebach, V. Prelog, *Angew. Chem.* **1982**, *94*, 696 – 702; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 654 – 660.
[263] A. Fürstner, K. Langemann, *J. Am. Chem. Soc.* **1997**, *119*, 9130 – 9136.
[264] J. M. Adam, L. Ghosez, K. N. Houk, *Angew. Chem.* **1999**, *111*, 2897 – 2899; *Angew. Chem. Int. Ed.* **1999**, *38*, 2728 – 2730.
[265] "Custom Chemicals": S. C. Stinson, *Chem. Eng. News* **2000**, *78*(7), 91 – 117.
[266] O. G. Kulinkovich, S. V. Sviridiv, D. A. Vasilevsky, T. S. Prityckaja, *Zh. Org. Khim.* **1989**, *25*, 2244 – 2245; O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevski, *Synthesis* **1991**, 234.
[267] E. J. Corey, S. A. Rao, M. C. Noe, *J. Am. Chem. Soc.* **1994**, *116*, 9345 – 9346.
[268] K. Narasaka, T. Yamada, H. Minamikawa, *Chem. Lett.* **1987**, 2073 – 2076.
[269] B. L. Pagenkopf, E. M. Carreira, *Tetrahedron Lett.* **1998**, *39*, 9593 – 9596.
[270] H. J. Breunig, J. Probst, *J. Organomet. Chem.* **1998**, *571*, 297 – 303.
[271] A. Bernardi, K. Karamfilova, G. Boschin, C. Scolastico, *Tetrahedron Lett.* **1995**, *36*, 1363 – 1364.
[272] A. Bernardi, K. Karamfilova, S. Sanguinetti, C. Scolastico, *Tetrahedron* **1997**, *53*, 13009 – 13026.
[273] L. Falborg, K. A. Jørgensen, *J. Chem. Soc. Perkin Trans. 1* **1996**, 2823 – 2826.
[274] Somewhat greater selectivity in the formation of β-aminocarbonyl compounds is observed with an aluminum TADDOLate: T. Ishikawa, K. Nagai, T. Kudoh, S. Saito, *Synlett* **1998**, 1291 – 1293.
[275] The absolute configuration of the 2-amino-3-hydroxy carboxylic acid ester shown in Equation (A) is presented incorrectly in the cited paper;[237] in another publication[276] it is correctly portrayed as 2*S*,3*R* (Information based on communication with the corresponding author).
[276] "Asymmetric C–C-Bond Formation with Titanium Carbohydrate Complexes": R. O. Duthaler, A. Hafner, M. Riediker, *Pure Appl. Chem.* **1990**, *62*, 631 – 642.
[277] "Iodocarbocyclization Reaction": T. Taguchi, O. Kitagawa, T. Inoue, *Bull. Soc. Chem. Jpn.* **1995**, 770 – 779.
[278] W. Adam, F. Prechtl, *Chem. Ber.* **1994**, *127*, 667 – 671.
[279] W. Adam, H. G. Brünker, D. Golsch, P. Klug, J. Lin, C. M. Mitschell, F. Prechtl, M. Prein, M. Renz, M. Richter, C. R. Saha-Möller, R. Schuhmann, M. Shimizu, A. Smerz, U. Hoch, P. Schreier in *Stereoselective Reaction of Metal-Activated Molecules* (Eds.: H. Werner, J. Sundermeyer), Vieweg, Braunschweig, **1995**, pp. 39 – 44.
[280] "Iodocarbocyclization and Iodoaminocyclization Reactions Mediated by a Metallic Ragent": O. Kitagawa, T. Taguchi, *Synlett* **1999**, 1191 – 1199.
[281] L. Hintermann, A. Togni, *Angew. Chem.* **2000**, *112*, 4530 – 4533; *Angew. Chem. Int. Ed.* **2000**, *39*, 4359 – 4362.
[282] K. Narasaka, F. Kanai, M. Okudo, N. Miyoshi, *Chem. Lett.* **1989**, 1187 – 1190.
[283] D. Seebach, G. Jaeschke, K. Gottwald, K. Matsuda, R. Formisano, D. A. Chaplin, M. Breuning, G. Bringmann, *Tetrahedron* **1997**, *53*, 7539 – 7556.
[284] K. Gottwald, D. Seebach, *Tetrahedron* **1999**, *55*, 723 – 738.
[285] D. Seebach, G. Jaeschke, Y. M. Wang, *Angew. Chem.* **1995**, *107*, 2605 – 2606; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2395 – 2396.
[286] G. Jaeschke, D. Seebach, *J. Org. Chem.* **1998**, *63*, 1190 – 1197.
[287] D. J. Ramón, G. Guillena, D. Seebach, *Helv. Chim. Acta* **1996**, *79*, 875 – 894.
[288] K. Drauz, H. Waldmann, *Enzyme Catalysis in Organic Synthesis*, VCH, Weinheim, **1995**.
[289] The use of catalytic amounts of cinchona alkaloids for this ring opening, as recently reported by Bolm et al., could be regarded as confirmation of the maxim that "better is the enemy of good": C. Bolm, A. Gerlach, C. L. Dinter, *Synlett* **1999**, 195 – 196.
[290] "Enantioselective Desymmetrisation": M. C. Willis, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1765 – 1784.
[291] A. B. Charette, C. Brochu, *J. Am. Chem. Soc.* **1995**, *117*, 11367 – 11368.
[292] No matter which mechanism one formulates, the other titanium TADDOLate mediated formation of a cyclopropane (Scheme 17g) fails to fit into either of the Sections 8.2.1 and 8.2.2; it has been included among nucleophilic additions to C=O because development of the OH-substituted stereocenter in the cyclopropanol has been formulated as an (intramolecular) nucleophilic addition.[267]
[293] S. E. Denmark, S. P. O'Connor, *J. Org. Chem.* **1997**, *62*, 584 – 594.
[294] S. E. Denmark, S. P. O'Connor, S. R. Wilson, *Angew. Chem.* **1998**, *110*, 1162 – 1165; *Angew. Chem. Int. Ed.* **1998**, *37*, 1149 – 1151.
[295] Lewis acid catalyzed [2+2], [3+2], and [4+2] cycloadditions in particular need not be pericyclic reactions, that is, with simultaneous formation and breaking of the relevant bonds; they frequently proceed instead by way of dipolar intermediates. The term "cycloaddition" is used here strictly phenomenologically with respect to the corresponding reactions.
[296] In this way, suitably substituted cyclobutanones can be opened to carboxylic acid derivatives by nucleophilic attack or, under very mild conditions, by Baeyer – Villiger or Beckmann reactions to derivatives of γ-hydroxy or γ-amino acids.[5]
[297] "Catalytic Asymmetric Diels – Alder Reactions": H. B. Kagan, O. Riant, *Chem. Rev.* **1992**, *92*, 1007 – 1019.
[298] "Chiral Lewis Acid Catalysts in Diels – Alder Cycloadditions: Mechanistic Aspects and Synthetic Applications of Recent Systems": L. C. Dias, *J. Braz. Chem. Soc.* **1997**, *8*, 289 – 332.
[299] "Studies on Enantioselective Synthesis": E. J. Corey in *Chiral Separations: Applications and Technology* (Ed.: A. Satinder), ACS Publications, Washington, **1997**, pp. 37 – 58.
[300] R. Imwinkelried, PhD Thesis No. 8142, ETH Zürich, **1986**.
[301] We wish to emphasize at this point that, although (chiral) acyloxazolidinone first became popular especially through the work of Evans and his group, it was Mukaiyama who initially took synthetic methodological advantage of the chelating properties of such systems (through the example of the analogous *N*-acylthiazolidinethiones): T. Mukaiyama, *Challenges in Synthetic Organic Chemistry*, Clarendon, Oxford, **1990**.
[302] E. Wada, W. Pei, S. Kanemasa, *Chem. Lett.* **1994**, 2345 – 2348.
[303] Y. Hayashi, S. Niihata, K. Narasaka, *Chem. Lett.* **1990**, 2091 – 2094.
[304] K. Narasaka, K. Hayashi, Y. Hayashi, *Tetrahedron* **1994**, *50*, 4529 – 4542.
[305] Y. Hayashi, K. Otaka, N. Saito, K. Narasaka, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2122 – 2127.
[306] Y. Hayashi, K. Narasaka, *Chem. Lett.* **1990**, 1295 – 1298.
[307] K. Narasaka, Y. Hayashi, H. Shimadzu, S. Niihata, *J. Am. Chem. Soc.* **1992**, *114*, 8869 – 8885.
[308] K. V. Gothelf, K. A. Jørgensen, *J. Org. Chem.* **1994**, *59*, 5687 – 5691.
[309] K. B. Jensen, K. V. Gothelf, K. A. Jørgensen, *Helv. Chim. Acta* **1997**, *80*, 2039 – 2046.
[310] K. B. Jensen, K. V. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **1997**, *62*, 2471 – 2477.
[311] K. Narasaka, M. Inoue, N. Okada, *Chem. Lett.* **1986**, 1109 – 1112.
[312] K. Narasaka, M. Inoue, T. Yamada, *Chem. Lett.* **1986**, 1967 – 1968.
[313] J. Irurre, X. Tomás, C. Alonso-Alija, M. D. Carnicero, *Afinidad* **1993**, *50*, 361 – 365.
[314] K. Narasaka, M. Inoue, T. Yamada, J. Sugimori, N. Iwasawa, *Chem. Lett.* **1987**, 2409 – 2412.
[315] K. Narasaka, H. Tanaka, F. Kanai, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 387 – 391.
[316] Y. Hayashi, K. Narasaka, *Chem. Lett.* **1989**, 793 – 796.
[317] Y. Ichikawa, A. Narita, A. Shiozawa, Y. Hayashi, K. Narasaka, *J. Chem. Soc. Chem. Commun.* **1989**, 1919 – 1921.
[318] K. V. Gothelf, K. A. Jørgensen, *J. Org. Chem.* **1995**, *60*, 6847 – 6851.
[319] K. V. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Am. Chem. Soc.* **1995**, *117*, 4435 – 4436.
[320] I. Yamamoto, K. Narasaka, *Chem. Lett.* **1995**, 1129 – 1130.
[321] N. Iwasawa, J. Sugimori, Y. Kawase, K. Narasaka, *Chem. Lett.* **1989**, 1947 – 1950.
[322] K. Narasaka, M. Saitou, N. Iwasawa, *Tetrahedron: Asymmetry* **1991**, *2*, 1305 – 1318.
[323] K. Narasaka, Y. Hayashi, S. Shimada, J. Yamada, *Isr. J. Chem.* **1991**, *31*, 261 – 271.
[324] K. Narasaka, Y. Hayashi, S. Shimada, *Chem. Lett.* **1988**, 1609 – 1612.
[325] I. Yamamoto, K. Narasaka, *Bull. Chem. Soc. Jpn.* **1994**, *67*, 3327 – 3333.

[326] H. W. Yang, D. Romo, *Tetrahedron Lett.* **1998**, *39*, 2877 – 2880; H. W. Yang, D. Romo, *Tetrahedron* **1999**, *55*, 6403 – 6434; H. W. Yang, D. Romo, *Tetrahedron* **1999**, *55*, 9347.
[327] T. A. Engler, M. A. Letavic, J. P. Reddy, *J. Am. Chem. Soc.* **1991**, *113*, 5068 – 5070.
[328] T. A. Engler, M. A. Letavic, R. Iyengar, K. O. LaTessa, J. P. Reddy, *J. Org. Chem.* **1999**, *64*, 2391 – 2405.
[329] C. Cativiela, P. López, J. A. Mayoral, *Tetrahedron: Asymmetry* **1991**, *2*, 1295 – 1304.
[330] G. H. Posner, J. C. Carry, J. K. Lee, D. S. Bull, H. Dai, *Tetrahedron Lett.* **1994**, *35*, 1321 – 1324.
[331] H. Kusama, T. Mori, I. Mitani, H. Kashima, I. Kuwajima, *Tetrahedron Lett.* **1997**, *38*, 4129 – 4132.
[332] G. Quinkert, M. Del Grosso, A. Bucher, M. Bauch, W. Döring, J. W. Bats, G. Dürner, *Tetrahedron Lett.* **1992**, *33*, 3617 – 3620.
[333] "Progress in the Diels/Alder Reaction Means Progress in Steroid Synthesis": G. Quinkert, M. Del Grosso in *Stereoselective Synthesis* (Eds.: E. Ottow, K. Schöllkopf, B. G. Schulz), Springer, Berlin, **1993**, pp. 109 – 134.
[334] G. Quinkert, M. Del Grosso, A. Döring, W. Döring, R. I. Schenkel, M. Bauch, G. T. Dambacher, J. W. Bats, G. Zimmermann, G. Dürner, *Helv. Chim. Acta* **1995**, *78*, 1345 – 1391.
[335] T. A. Engler, M. A. Letavic, F. Takusagawa, *Tetrahedron Lett.* **1992**, *33*, 6731 – 6734.
[336] T. A. Engler, M. A. Letavic, K. O. Lynch, Jr., F. Takusagawa, *J. Org. Chem.* **1994**, *59*, 1179 – 1183.
[337] H. Bienaymé, *Angew. Chem.* **1997**, *109*, 2785 – 2788; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2670 – 2673.
[338] "Lobucavir": C. Ireland, P. A. Leeson, J. Castaner, *Drugs Future* **1997**, *22*, 359 – 370.
[339] In other cases, use of the C_1-symmetric TADDOL **1b** provided no advantages relative to the original TADDOL **1a**.[326]
[340] Either the crotonoyloxazolidinone or the nitrone might be the electrophile, where complexation of the nitrone through the X_2Ti-TADDOLate/Lewis acid might also be worth consideration. For a frontal-orbital treatment, see ref. [308, 309, 341].
[341] K. V. Gothelf, K. A. Jørgensen, *Acta Chem. Scand.* **1996**, *50*, 652 – 660.
[342] E. J. Corey, X. M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, **1989**.
[343] R. W. Baker, G. K. Thomas, S. O. Rea, M. V. Sargent, *Aust. J. Chem.* **1997**, *50*, 1151 – 1157.
[344] T. Kanger, K. Kriis, A. Paju, T. Pehk, M. Lopp, *Tetrahedron: Asymmetry* **1998**, *9*, 4475 – 4482.
[345] S. Bruns, G. Haufe, *Tetrahedron: Asymmetry* **1999**, *10*, 1563 – 1569.
[346] F. Bertozzi, P. Crotti, F. Macchia, M. Pineschi, A. Arnold, B. L. Feringa, *Tetrahedron Lett.* **1999**, *40*, 4893 – 4896.
[347] A. Alexakis, C. Benhaïm, X. Fournioux, A. van den Heuvel, J.-M. Levêque, S. March, S. Rosset, *Synlett* **1999**, 1811 – 1813.
[348] E. A. Kretzschmar, J. Kipke, J. Sundermeyer, *J. Chem. Soc. Chem. Commun.* **1999**, 2381 – 2382.
[349] R. Hilgraf, A. Pfaltz, *Synlett* **1999**, 1814 – 1816.
[350] E. Keller, J. Maurer, R. Naasz, T. Schader, A. Meetsma, B. L. Feringa, *Tetrahedron: Asymmetry* **1998**, *9*, 2409 – 2413.
[351] D. Seebach, G. Jaeschke, A. Pichota, L. Audergon, *Helv. Chim. Acta* **1997**, *80*, 2515 – 2519.
[352] D. H. McConville, J. R. Wolf, R. R. Schrock, *J. Am. Chem. Soc.* **1993**, *115*, 4413 – 4414.
[353] For a review of the use of organocerium compounds in organic synthesis (covering the literature through 1993) and for a recent paper with relevant references, see: "Organocerium Compounds in Synthesis": H. J. Liu, K. S. Shia, X. Shang, B. Y. Zhu, *Tetrahedron* **1999**, *55*, 3803 – 3830; Z. Xiao, J. W. Timberlake, *Tetrahedron* **1998**, *54*, 4211 – 4222.
[354] K. Sugimoto, S. Aoyagi, C. Kibayashi, *J. Org. Chem.* **1997**, *62*, 2322 – 2323.
[355] N. Greeves, J. E. Pease, M. C. Bowden, S. M. Brown, *Tetrahedron Lett.* **1996**, *37*, 2675 – 2678.
[356] N. Greeves, J. E. Pease, *Tetrahedron Lett.* **1996**, *37*, 5821 – 5824.
[357] P. Müller, P. Nury, *Org. Lett.* **1999**, *1*, 439 – 441.
[358] "Rare Earth Metal Trifluoromethanesulfonates as Water-Tolerant Lewis Acid Catalysts in Organic Synthesis": S. Kobayashi, *Synlett* **1994**, 689 – 701.
[359] "Asymmetric Catalysis of Carbonyl-Ene Reactions and Related Carbon-Carbon Bond Forming Reactions": K. Mikami, *Pure Appl. Chem.* **1996**, *68*, 639 – 644.
[360] "Asymmetric Catalysis with Heterobimetallic Compounds": M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem.* **1997**, *109*, 1290 – 1310; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236 – 1256.
[361] "New Types of Lewis Acids Used in Organic Synthesis": S. Kobayashi, *Pure Appl. Chem.* **1998**, *70*, 1019 – 1026.
[362] "Reaction Engineering for Enzyme-Catalyzed Biotransformations": M. Biselli, U. Kragl, C. Wandrey in *Enzyme Catalysis in Organic Synthesis* (Eds.: K. Drauz, H. Waldmann), VCH, Weinheim, **1995**, pp. 89 – 155; S. Rissom, J. Beliczey, G. Giffels, U. Kragl, C. Wandrey, *Tetrahedron: Asymmetry* **1999**, *10*, 923 – 928.
[363] "Chiral Dendrimers": D. Seebach, P. B. Rheiner, G. Greiveldinger, T. Butz, H. Sellner, *Top. Curr. Chem.* **1998**, *197*, 125 – 164.
[364] "Towards the Chemical Synthesis of Proteins": E. Bayer, *Angew. Chem.* **1991**, *103*, 117 – 133; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 113 – 129.
[365] "Solid Phase Synthesis (Nobel Lecture)": R. B. Merrifield, *Angew. Chem.* **1985**, *97*, 801 – 812; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 799 – 810.
[366] B. Altava, M. I. Burguete, S. V. Luis, J. A. Mayoral, *Tetrahedron* **1994**, *50*, 7535 – 7542.
[367] J. Irurre, A. Fernández-Serrat, F. Rosanas, *Chirality* **1997**, *9*, 191 – 197.
[368] J. Irurre, A. Fernández-Serrat, M. Altayó, M. Riera, *Enantiomer* **1998**, *3*, 103 – 120.
[369] B. Altava, M. I. Burguete, B. Escuder, S. V. Luis, R. V. Salvador, J. M. Fraile, J. A. Mayoral, A. J. Royo, *J. Org. Chem.* **1997**, *62*, 3126 – 3134; B. Altava, M. I. Burguete, J. M. Fraile, J. I. García, S. V. Luis, J. A. Mayoral, M. J. Vicent, *Angew. Chem.* **2000**, *112*, 1563 – 1566; *Angew. Chem. Int. Ed.* **2000**, *39*, 1503 – 1506.
[370] A. Heckel, D. Seebach, *Angew. Chem.* **2000**, *112*, 165 – 167; *Angew. Chem. Int. Ed.* **2000**, *39*, 163 – 165.
[371] P. B. Rheiner, H. Sellner, D. Seebach, *Helv. Chim. Acta* **1997**, *80*, 2027 – 2032.
[372] H. Sellner, D. Seebach, *Angew. Chem.* **1999**, *111*, 2039 – 2041; *Angew. Chem. Int. Ed.* **1999**, *38*, 1918 – 1920.
[373] "Catalysts Made of Organic-Inorganic Hybrid Materials": U. Schubert, *New J. Chem.* **1994**, *18*, 1049 – 1058; O. Kröcher, R. A. Köppel, M. Fröba, A. Baiker, *J. Catal.* **1998**, *178*, 284 – 298.
[374] "Molecular Imprinting in Cross-Linked Materials with the Aid of Molecular Templates – -A Way towards Artificial Antibodies": G. Wulff, *Angew. Chem.* **1995**, *107*, 1958 – 1979; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1812 – 1832. In addition to the work of Wulff,[374] studies have also been published on "imprinting" experiments with dendrimers: M. S. Wendland, S. C. Zimmerman, *J. Am. Chem. Soc.* **1999**, *121*, 1389 – 1390.
[375] S. Itsuno, Y. Sakurai, K. Ito, T. Maruyama, S. Nakahama, J. M. J. Fréchet, *J. Org. Chem.* **1990**, *55*, 304 – 310.
[376] P. B. Rheiner, D. Seebach, *Polym. Mater. Sci. Eng.* **1997**, *77*, 130 – 131.
[377] P. J. Comina, A. K. Beck, D. Seebach, *Org. Process Res. Dev.* **1998**, *2*, 18 – 26.
[378] "Polymer Supported Reagents": A. Patchornik in *Modern Synthetic Methods*, *Vol. 1* (Ed.: R. Scheffold), Sauerländer, Aarau, **1976**, pp. 113 – 167.
[379] D. G. Blackmond, *J. Am. Chem. Soc.* **1998**, *120*, 13349 – 13353; T. O. Luukas, C. Girard, D. R. Fenwick, H. B. Kagan, *J. Am. Chem. Soc.* **1999**, *121*, 9299 – 9306.
[380] B. Schmidt, D. Seebach, *Angew. Chem.* **1991**, *103*, 1383 – 1385; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1321 – 1323.
[381] The magnesium TADDOLate mediated enantioselective addition of Grignard reagents to ketones is also free of nonlinear effects;[201] see Scheme 13j.
[382] H. Sellner, C. Faber, P. B. Rheiner, D. Seebach, *Chem. Eur. J.*, **2000**, *6*, 3692 – 3705.
[383] J. Karjalainen, unpublished experiments, ETH Zürich, **1998**/**90**.
[384] For nondendritic polymer-bound BINOLs, see: X.-W. Yang, J.-H. Sheng, C.-S. Da, H.-S. Wang, W. Su, R. Wang, A. S. C. Chan, *J. Org. Chem.* **2000**, *65*, 295 – 296.

[385] Polymer-bound ligands of the 1,2-cycloalkandiamine-bis-sulfonamide type (CYDIS, see also Section 10 and ref. [386]) and their utilization for enantioselective Et_2Zn addition to aldehydes: C. Halm, M. J. Kurth, *Angew. Chem.* **1998**, *110*, 523 – 525; *Angew. Chem. Int. Ed.* **1998**, *37*, 510 – 512; A. J. Brouwer, H. J. van der Linden, R. M. J. Liskamp, *J. Org. Chem.* **2000**, *65*, 1750 – 1757.

[386] We suggest the abbreviation CYDIS for the *trans*-**cy**clohexan-1,2-**di**amine-di**s**ulfonamide. The most frequently utilized derivative to date is the bis-triflamide,[243, 245, 247] but arylsulfonamides like the tosylamide[387] shown in Figure 17 (bottom) also produce excellent enantioselectivity in the addition of Et_2Zn to aldehydes.

[387] S. Pritchett, D. H. Woodmansee, P. Gantzel, P. J. Walsh, *J. Am. Chem. Soc.* **1998**, *120*, 6423 – 6424.

[388] a) C. R. Landis, J. Halpern, *J. Am. Chem. Soc.* **1987**, *109*, 1746 – 1754; b) "Ligand-Accelerated Catalysis": D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem.* **1995**, *107*, 1159 – 1171; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059 – 1070.

[389] N. Iwasawa, Y. Hayashi, H. Sakurai, K. Narasaka, *Chem. Lett.* **1989**, 1581 – 1584.

[390] M. DiMare, C. R. Sarko, unpublished experiments, University of California, Santa Barbara, **1994**/**95**; D.S. expresses his appreciation for personal communication.

[391] Titanate-catalyzed addition of R_2Zn or $RTi(OiPr)_3$ to aldehydes occurs from the *Si* face with (*R*,*R*)-TADDOLate, (*P*)-BINOLate, and (*R*,*R*)-CYDISate (Schemes 12 and 13 and refs. [243, 245, 247, 392, 393]); addition of Me_3SiCN to aldehydes occurs under the influence of (*R*,*R*)-titanium-TADDOLate and (*P*)-BINOLate from the *Si* face (Scheme 14 and ref. [394]); a $LiAlH_4$ derivative of the type $Li(R^*O)_2Al(OEt)H$ modified with (*R*,*R*)-TADDOL or (*P*)-BINOL reduces arylketones by hydride transfer from the *Re* face (Scheme 10 f and ref. [395]).

[392] M. Mori, T. Nakai, *Tetrahedron Lett.* **1997**, *38*, 6233 – 6236.

[393] F.-Y. Zhang, C.-W. Yip, R. Cao, A. S. C. Chan, *Tetrahedron: Asymmetry* **1997**, *8*, 585 – 589.

[394] M. Mori, H. Imma, T. Nakai, *Tetrahedron Lett.* **1997**, *38*, 6229 – 6232.

[395] R. Noyori, I. Tomino, Y. Tanimoto, M. Nishizawa, *J. Am. Chem. Soc.* **1984**, *106*, 6709 – 6716.

[396] "Specification of Molecular Chirality": R. S. Cahn, C. K. Ingold, V. Prelog, *Angew. Chem.* **1966**, *78*, 413 – 447; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 385 – 415; "Basic Principles of the CIP-System and Proposals for a Revision": V. Prelog, G. Helmchen, *Angew. Chem.* **1982**, *94*, 614 – 631; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 567 – 583.

[397] Y. M. Wang, unpublished experiments, ETH Zürich, **1990** – **1995**.

[398] Inspection of numerous crystal structures of TADDOL inclusion compounds with hydrogen-bonding acceptors (see entries in the Supporting Information) shows that guest molecules also occupy the same hemisphere (or octant) toward which the RCH group of the aldehyde points in the model suggested here ("upper left" for (*R*,*R*)-TADDOLs as host molecules). See the two examples in Figure 10.

[399] E. J. Corey, J. J. Rohde, A. Fischer, M. D. Azimioara, *Tetrahedron Lett.* **1997**, *38*, 33 – 36; E. J. Corey, J. J. Rohde, *Tetrahedron Lett.* **1997**, *38*, 37 – 40; E. J. Corey, D. Barnes-Seeman, T. W. Lee, *Tetrahedron Lett.* **1997**, *38*, 1699 – 1702.

[400] Early in 2000 we found 98 structures of acyloxazolidinones in the Cambridge Databank.

[401] See, for example, the $TiCl_4$ complex of a propionyloxazolidinone in: ref. [402].

[402] T. Hintermann, D. Seebach, *Helv. Chim. Acta* **1998**, *81*, 2093 – 2126.

[403] G. Quinkert, E. Egert, C. Griesinger, *Aspekte der Organischen Chemie*, VHCA, Basel, **1995**.

[404] E. J. Corey, Y. Matsumura, *Tetrahedron Lett.* **1991**, *32*, 6289 – 6292.

[405] See the extensive investigations carried out by the Jørgensen group (most recent publication[310] and references therein to earlier work).

[406] "Asymmetric Ene Reactions in Organic Synthesis": K. Mikami, M. Shimizu, *Chem. Rev.* **1992**, *92*, 1021 – 1050; K. Mikami, Y. Motoyama, M. Terada, *J. Am. Chem. Soc.* **1994**, *116*, 2812 – 2820.

[407] K. Nakayama, J. D. Rainier, *Tetrahedron* **1990**, *46*, 4165 – 4170.

[408] F. Toda, K. Tanaka, Z. Stein, I. Goldberg, *J. Chem. Soc. Perkin Trans. 2* **1993**, 2359 – 2361.

[409] J. Feneau-Dupont, J. P. Declercq, L. Patiny, *Bull. Soc. Chim. Belg.* **1995**, *104*, 623 – 624.

[410] D. Dubé, D. Deschênes, J. Tweddell, H. Gagnon, R. Carlini, *Tetrahedron Lett.* **1995**, *36*, 1827 – 1830.

[411] J. E. A. Luithle, J. Pietruszka, *Liebigs Ann.* **1997**, 2297 – 2302.

[412] J. E. A. Luithle, J. Pietruszka, A. Witt, *J. Chem. Soc. Chem. Commun.* **1998**, 2651 – 2652.

[413] R. H. Wallace, K. K. Zong, *J. Organomet. Chem.* **1999**, *581*, 87 – 91.

[414] P. Saravanan, V. K. Singh, *Tetrahedron Lett.* **1999**, *40*, 2611 – 2614.

[415] I. Goldberg, Z. Stein, E. Weber, N. Dörpinghaus, S. Franken, *J. Chem. Soc. Perkin Trans. 2* **1990**, 953 – 963.

[416] See the discussions in ref. [402] and [417], as well as references therein.

[417] C. Gaul, D. Seebach, *Org. Lett.* **2000**, *2*, 1501 – 1504.

[418] See also the inherent ligand exchange rates for various metallic centers, the so-called Irving – Williams series: H. Irving, R. J. P. Williams, *J. Chem. Soc.* **1953**, 3192 – 3210.

[419] "α,α-Diphenyl-2-pyrrolidinemethanol": D. J. Mathre, I. Shinkai in *Encyclopaedia of Reagents for Organic Synthesis*, *Vol. 4* (Ed.: L. A. Paquette), Wiley, Chichester, **1995**, pp. 2247 – 2250.

[420] "Asymmetric Synthesis with Chiral Oxazaborolidines": S. Wallbaum, J. Martens, *Tetrahedron: Asymmetry* **1992**, *3*, 1475 – 1504.

[421] N. A. Nikolic, P. Beak, *Org. Synth.* **1997**, *74*, 23 – 32 (*Coll. Vol. IX*, pp. 391 – 396).

[422] "The Practical Enantioselective Reduction of Prochiral Ketones": A. O. King, D. J. Mathre, D. M. Tschaen, I. Shinkai, *ACS Symp. Ser.* **1996**, *641*, 98 – 111.

[423] "Diphenyloxazaborolidine for Enantioselective Reduction of Ketones": G. J. Quallich, J. F. Blake, T. M. Woodall, *ACS Symp. Ser.* **1996**, *641*, 112 – 126.

[424] S. Itsuno, M. Nakano, K. Miyazaki, H. Masuda, K. Ito, A. Hirado, S. Nakahama, *J. Chem. Soc Perkin. Trans. 1* **1985**, 2039 – 2044.

[425] "The 'Magic' Diarylhydroxymethyl Group": M. Braun, *Angew. Chem.* **1996**, *108*, 565 – 568; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 519 – 522.

[426] D. Ridder, H. Wunderlich, M. Braun, *Eur. J. Org. Chem.* **1998**, 1071 – 1076.

[427] F. Rebiere, H. B. Kagan, *Tetrahedron Lett.* **1989**, *30*, 3659 – 3662.

[428] M. Brenner, D. Seebach, *Helv. Chim. Acta* **1999**, *82*, 2365 – 2379.

[429] S. Itsuno, M. Nakano, K. Ito, A. Hirao, M. Owa, N. Kanda, S. Nakahama, *J. Chem. Soc. Perkin Trans. 1* **1985**, 2615 – 2619; S. Itsuno, Y. Sakurai, K. Ito, A. Hirao, S. Nakahama, *Polymer* **1987**, *28*, 1005 – 1008.

[430] B. Burns, M. P. Gamble, A. R. C. Simm, J. R. Studley, N. W. Alcock, M. Wills, *Tetrahendron: Asymmetry* **1997**, *8*, 73 – 78; M. P. Gamble, A. R. C. Smith, M. Wills, *J. Org. Chem.* **1998**, *63*, 6068 – 6071.

[431] G. S. Yang, J. B. Hu, G. Zhao, Y. Ding, M. H. Tang, *Tetrahedron: Asymmetry* **1999**, *10*, 4307 – 4311.

[432] E. J. Corey, J. O. Link, *Tetrahedron Lett.* **1989**, *30*, 6275 – 6278.

[433] A. van Oeveren, W. Menge, B. L. Feringa, *Tetrahedron Lett.* **1989**, *30*, 6427 – 6430; E. J. Corey, J. O. Link, R. K. Bakshi, *Tetrahedron Lett.* **1992**, *33*, 7107 – 7110; D. K. Jones, D. C. Liotta, I. Shinkai, D. J. Mathre, *J. Org. Chem.* **1993**, *58*, 799 – 801; D. Cai, D. Tschaen, Y.-J. Shi, T. R. Verhoeven, R. A. Reamer, A. W. Douglas, *Tetrahedron Lett.* **1993**, *34*, 3243 – 3246; D. J. Mathre, A. S. Thompson, A. W. Douglas, K. Hoogsteen, J. D. Carroll, E. G. Corley, E. J. J. Grabowski, *J. Org. Chem.* **1993**, *58*, 2880 – 2888.

[434] K. Soai, Y. Kawase, *Tetrahedron: Asymmetry* **1991**, *2*, 781 – 784.

[435] S. Cicchi, S. Crea, A. Goti, A. Brandi, *Tetrahedron: Asymmetry* **1997**, *8*, 293 – 301.

[436] W. Behnen, T. Mehler, J. Martens, *Tetrahedron: Asymmetry* **1993**, *4*, 1413 – 1416.

[437] W. Trentmann, T. Mehler, J. Martens, *Tetrahedron: Asymmetry* **1997**, *8*, 2033 – 2043.

[438] L. Solà, K. S. Reddy, A. Vidal-Ferran, A. Moyano, M. A. Pericàs, A. Riera, A. Alvarez-Larena, J. F. Piniella, *J. Org. Chem.* **1998**, *63*, 7078 – 7082.

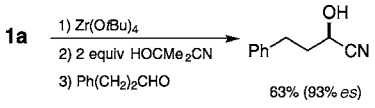
[439] S. Wassermann, J. Wilken, J. Martens, *Tetrahedron: Asymmetry* **1999**, *10*, 4437 – 4445.

[440] K. R. K. Prasad, N. N. Joshi, *J. Org. Chem.* **1997**, *62*, 3770 – 3771.

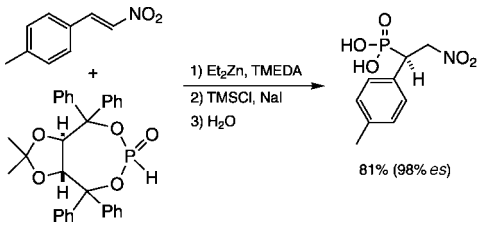
[441] I. A. O'Neil, C. D. Turner, S. B. Kalindjian, *Synlett* **1997**, 777 – 780.

[442] R. Schumacher, F. Dammast, H. U. Reißig, *Chem. Eur. J.* **1997**, *3*, 614 – 619; R. Fleischer, H. Wunderlich, M. Braun, *Eur. J. Org. Chem.* **1998**, 1063 – 1070.

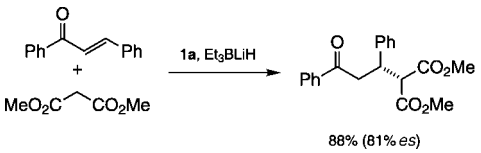
[443] T. Aratani, *Pure Appl. Chem.* **1985**, *57*, 1839 – 1844.
[444] J. M. Andrés, Y. Martín, R. Pedrosa, A. Pérez-Encabo, *Tetrahedron* **1997**, *53*, 3787 – 3794.
[445] X. Yang, R. Wang, *Tetrahedron: Asymmetry* **1997**, *8*, 3275 – 3281.
[446] D. E. Ho, J. M. Betancort, D. H. Woodmansee, M. L. Larter, P. J. Walsh, *Tetrahedron Lett.* **1997**, *38*, 3867 – 3870.
[447] H. Brunner, C. Henrichs, *Tetrahedron: Asymmetry* **1995**, *6*, 653 – 656.
[448] M. Watanabe, M. Komota, M. Nishimura, S. Araki, Y. Butsugan, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2193 – 2196.
[449] P. I. Dosa, J. C. Ruble, G. C. Fu, *J. Org. Chem.* **1997**, *62*, 444 – 445.
[450] C. Bolm. K. Muñiz Fernández, A. Seger, G. Raabe, *Synlett* **1997**, 1051 – 1052; C. Bolm. K. Muñiz, J. P. Hildebrand, *Org. Lett.* **1999**, *1*, 491 – 493; C. Bolm, K. Muñiz, *Chem. Commun.* **1999**, 1295 – 1296.
[451] At this point, too (see ref. [301]), Mukaiyama deserves a bouquet: he was the first to utilize an aminoalcohol derived from proline as an auxiliary; instead of a diarylmethanol unit on the pyrrolidine he chose dialkyl derivatives, derived from treatment of corresponding proline esters with aliphatic Grignard reagents[301] (*gem*-dialkyl effect; compare with the *gem*-dimethyl or Thorpe – Ingold effect[103]).
[452] Houben-Weyl volumes devoted to stereoselective synthesis[16] and Springer volumes on *Comprehensive Asymmetric Catalysis*.[455]
[453] Monographs by Brunner,[456] Coppola,[457] Gawronski and Gawronska (in ref. [24]), Hayashi, Tomioka and Yonemitsu (in ref. [245]), Noyori,[458] Ojima (in ref. [221]), Seyden-Penne,[459] Togni and Hayashi.[460]
[454] Review articles by Bannani and Hanessian,[244] Blaser,[461] Ito and Katzuki,[462] Kagan and Dang,[93] Koga,[204] Lucet, LeGall and Mioskowski,[463] Nugent, RajanBabu and Burk (in ref. [17]), Trost,[464] Venanzi and Togni.[465]
[455] *Comprehensive Asymmetric Catalysis I – III* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**.
[456] H. Brunner, W. Zettlmeier, *Handbook of Enantioselective Catalysis*, VCH, Weinheim, **1993**.
[457] G. M. Coppola, H. F. Schuster, *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*, Wiley, New York, **1987**; G. M. Coppola, H. F. Schuster, *α-Hydroxy Acids in Enantioselective Syntheses*, VCH, Weinheim, **1997**.
[458] R. Noyori, *Asymmetric Catalysis In Organic Synthesis*, Wiley, **1994**.
[459] J. Seyden-Penne, *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, Wiley, New York, **1995**.
[460] *Ferrocenes* (Eds.: A. Togni, T. Hayashi), VCH, Weinheim, **1995**.
[461] "The Chiral Pool as a Source of Enantioselective Catalysts and Auxiliaries": H.-U. Blaser, *Chem. Rev.* **1992**, *92*, 935 – 952.
[462] "Asymmetric Catalysis of New Generation Chiral Metallosalen Complexes": Y. N. Ito, T. Katsuki, *Bull. Chem. Soc. Jpn.* **1999**, *72*, 603 – 619.
[463] "The Chemistry of Vicinal Diamines": D. Lucet, T. Le Gall, C. Mioskowski, *Angew. Chem.* **1998**, *110*, 2724 – 2772; *Angew. Chem. Int. Ed.* **1998**, *37*, 2580 – 2627; A. Alexakis, I. Aujard, T. Kanger, P. Mangeney, *Org. Synth.* **1999**, *76*, 23 – 36.
[464] B. M. Trost, D. L. Van Vranken, *Chem. Rev.* **1996**, *96*, 395 – 422.
[465] "Nitrogen Donors in Organometallic Chemistry and Homogeneous Catalysis": A. Togni, L. M. Venanzi, *Angew. Chem.* **1994**, *106*, 517 – 547; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 497 – 526.
[466] Approximate prices (sFr mol^{-1}) for the purchase of gram quantities according to the Fluka Catalogue 1999/2000: (*R*,*R*)-tartaric acid, 10; (*R*,*R*)-diethyl tartrate, 86; (*R*,*R*)-2,3-isopropylidenedimethyl tartrate, 1700; L-alanine, 81; L-phenylalanine, 236; L-valine, 92; L-*tert*-leucine, 8146; (+)-pseudoephedrine, 418; quinine, 1330; (*R*)-BINOL, 495; (*R*,*R*)-1,2-diaminocyclohexane, 5047.
[467] a) Material for this article was assembled after several investigations in the structure, literature, and reaction databases of Chemical Abstracts Service through STN International (status at 10 February 2000) and Crossfire Beilstein (Update BS9903); b) Since completion of the manuscript for this article, we have become familiar with several especially interesting new applications of TADDOL derivatives: T. Ooi, K. Takaya, T. Miura, H. Ichikawa, K. Maruoka, *Synlett* **2000**, 1133 – 1134 [Eq. (1)]; D. Enders, L. Tedeschi, J. W. Bats, *Angew. Chem.* **2000**, *112*, 4774 – 4776; *Angew. Chem. Int. Ed.* **2000**, *39*, 4605 – 4607 [Eq. (2); TMEDA = N,N,N′,N′-tetramethyl 1,2-ethanediamine, TMS = trimethylsilyl]; J. Irurre, M. Riera, C. Amela-Cortés, *Enantiomer* **2000**, *5*, 255 – 261 [Eq. (3)]; J. Irurre, M. Riera, C. Viñas, *Tetrahedron: Asymmetry*, submitted.



(1)



(2)



(3)