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TETRAHEDRON: ASYMMETRY REPORT NUMBER 20

Synthesis and Use of Enantiomerically Pure *tert*-Leucine[§]

Andreas S. Bommarius, Michael Schwarm, Klaus Stingl, Matthias Kottenhahn, Klaus Huthmacher and Karlheinz Drauz*

Degussa AG, Organic Chemistry R&D (IC-FE), P.O. Box 1345, D-63403 Hanau, Germany

Abstract: Owing to its bulky, inflexible and hydrophobic *tert*-butyl side chain, *tert*-leucine (Tle) finds increased use in templates or catalysts in asymmetric synthesis as well as in peptidic medicinal compounds. *(S)*-Tle, available through a large-scale enzymatic reductive amination process, has been incorporated into a variety of anti-AIDS and -cancer compounds. With two new routes to *(R)*-Tle coming available, the number of applications of both *(R)*- and *(S)*-Tle can be expected to increase considerably.

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§ *dedicated to Prof. Franz Effenberger (University of Stuttgart) on occasion of his 65th birthday*

1. INTRODUCTION AND SCOPE

According to Seebach[1], *enantiomerically pure compounds* (EPCs) can be obtained by three basic procedures:

1) resolution of racemic mixtures,
2) incorporation of molecules from the pool of natural chiral molecules (*"ex chiral pool"*-synthesis);
3) asymmetric synthesis (diastereoselective or enantioselective).

Although *tert*-leucine (Tle, 3-methyl valine, *tert*-butyl glycine) is a non-proteinogenic amino acid it is nevertheless found in Nature.[2] Fusetani and coworkers were able to isolate both enantiomers as components of antimicrobials of marine sponges.[2d-f] However, Tle is not readily available from the chiral pool, so two options remain to obtain enantiomerically pure Tle: resolution of a racemic mixture and stereoselective synthesis. Tle and its derivatives are mainly used in two areas of application, i) pharmaceutically active peptidic structures and ii) templates for asymmetric synthesis. Both the synthesis and application are covered in detail in this review.

The use of Tle and derivatives in pharmaceutical applications had been limited for a long time by its restricted availability. However, many publications and patent applications demonstrate that Tle and its derivatives now are commonly used for structural variations of drug candidates under development.

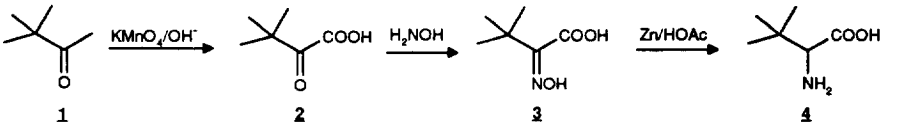
Owing to its space-filling *tert*-butyl side chain and its concomitant hydrophobicity Tle is especially important for molecular conformational control. In peptides, Tle often replaces valine, leucine or isoleucine, staying within the same chirality but offering increased hydrophobicity and additional stability against enzymatic degradation.

Steric hindrance caused by the bulky *tert* butyl side chain is the principal reason for the use of Tle or one of its derivatives in asymmetric synthesis. While in the past stoichiometric reactions have dominated asymmetric synthesis, catalytic applications are becoming increasingly important.

2. ENANTIOMERICALLY PURE Tle BY RESOLUTION OF RACEMIC MIXTURES

2.1. Synthesis of racemic Tle

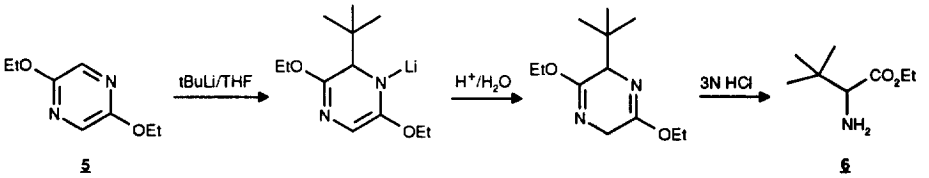
In 1914, racemic Tle was prepared for the first time by Knoop and Landmann.[3] Pinacolone **1**, treated with alkaline permanganate, yielded trimethylpyruvic acid **2** which was reacted with NH_2OH to give the corresponding oxime **3**. Reduction with zinc dust/acetic acid afforded *(RS)*-Tle **4** in an overall yield of about 60 % (Scheme 1).



Scheme 1

The yield of this laborious procedure "could not be improved" in spite of subsequent thorough investigations.[4] However, lacking more promising procedures, the general reaction sequence has been widely used with some minor modifications. Other groups have used aluminum amalgam[5] or Raney-Ni[6] for the reduction of the oxime. We have examined Pd-C as hydrogenation catalyst, however, conversion rates and yields were found to be moderate, probably owing to catalyst inactivation.[7] Reductive amination of sodium trimethylpyruvate with concentrated NH_3 and Raney-Ni at 100 atm and 60°C has been reported to yield *(RS)*-Tle·HCl[8] but without any purity data. Also, hydrogenation of the phenylhydrazone of trimethylpyruvic acid using Pd-C as catalyst did not improve yields compared to the oxime route.[9] Reduction of the oxime of ethyl trimethylpyruvate with $NaBH_4/TiCl_3$ afforded the *(RS)*-Tle ethyl ester hydrochloride in 68 % yield.[10]

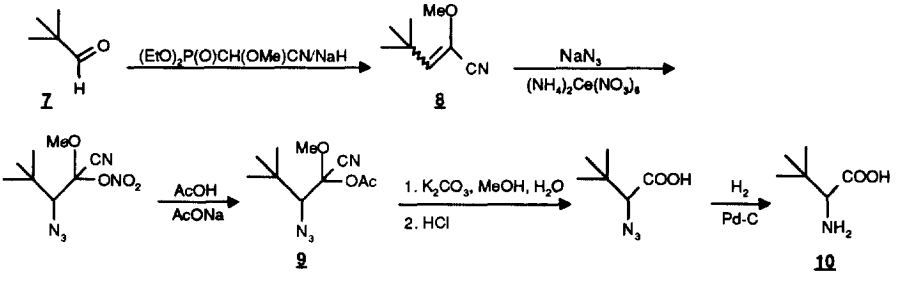
Other completely different synthetic strategies have been reported. An early synthesis consisting of *tert*-butylation of malonic ester, bromination, decarboxylation and aminolysis[11] does not appear to be very attractive. Similarly, *tert*-butylation of ethyl acetoacetate with subsequent hydrazoic acid/H_2SO_4 treatment (Schmidt rearrangement) and acid hydrolysis of N-acetyl-(*RS*)-Tle ethyl ester suffers from low purities and yields.[4] A recent synthesis of (*RS*)-Tle-ethyl ester starting from 2,5-diethoxypyrazine **5** (obtained from methylglycinate: three steps, 62 % yield) with subsequent *tert*-butylation and hydrolysis afforded the amino acid ester **6** in 70 % yield.[12] However, high cost of this procedure (owing to the prices of triethyloxonium tetrafluoroborate, N-chlorosuccinimide, *tert*-butyl lithium) and toxicity of the oxonium salt render this synthesis less attractive on a large scale (Scheme 2).



Scheme 2

Other syntheses of (*RS*)-Tle use pivaldehyde. In this context, we have investigated the preparation of (*RS*)-Tle following the classical Strecker synthesis. In the first step, pivaldehyde could be easily converted into the hydrochloride of (*RS*)-2-amino-3,3-dimethylbutyronitrile in almost quantitative yield. However, hydrolysis

requires rather drastic conditions and isolation of pure, especially salt-free (*RS*)-Tle remains laborious.[13] In another reaction sequence, pivaldehyde **7** was condensed with a Wittig reagent to give α-methoxy-β-*tert*-butyl acrylonitrile **8**. Addition of azide in the presence of ceric ammonium nitrate and subsequent treatment with acetate gave the corresponding azido acetate **9** which was hydrolyzed and hydrogenated to (*RS*)-Tle **10**.[14] However, the whole conversion requires five steps and the overall yield is only 25 % (Scheme 3).



Scheme 3

2.2. *Enantiomerically pure Tle and derivatives by resolution of racemates*

2.2.1. *Chemical processes*

Owing to the importance of enantiomerically pure Tle in biological studies, pharmaceutical applications and asymmetric synthesis, a large number of chemical resolution procedures has been published. All of them deliver enantiomerically pure or at least enriched Tle or a derivative thereof by repeated fractional crystallization of diastereomeric salt pairs.

In 1934, optically active Tle was synthesized for the first time by resolution of racemic N-formyl-Tle with brucine.[15] Subsequently, other groups published the following procedures: resolution of *(RS)*-Tle methyl[16] or ethyl ester[5] with dibenzoyltartaric acid, of N-acetyl-*(RS)*-Tle with chinchonidine and of *(RS)*-Tle-amide with tartaric acid[8], of N-thiobenzoyl-*(RS)*-Tle with brucine[4], of N-p-toluenesulfonyl-*(RS)*-Tle with brucine[5] and of N-benzyloxycarbonyl-*(RS)*-Tle with quinine or quinidine.[9] The common disadvantages of all these procedures are the tedious protection - fractionation - deprotection reaction sequences and especially the need for repeated recrystallizations to achieve sufficiently high optical purities of the intermediate diastereomeric salts which result in comparatively low overall yields.

Even a remarkably "simple optical resolution" of unprotected *(RS)*-Tle with 10-camphorsulfonic acid necessitated repeated crystallizations to obtain optically pure (e.e. ≥ 98 %) *(R)*- and *(S)*-Tle, resulting in a modest overall yield of only 23 %; the use of optically active binaphthylphosphoric acid was reported to be

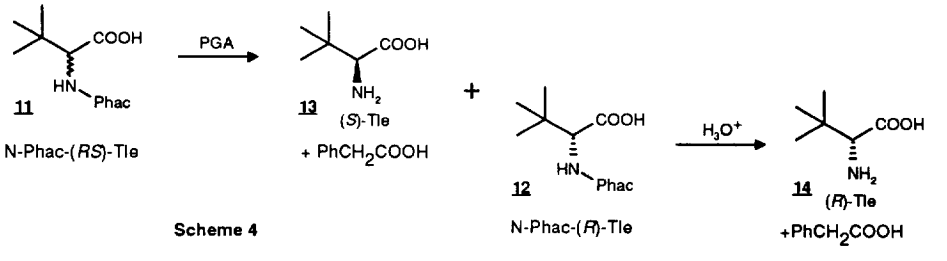
unsuitable for complete resolution.[17] Very recently, resolution of unprotected *(RS)*-Tle with optically active 1-(4-substituted-phenyl)ethanesulfonic acids has been described.[18]

2.2.2. *Biocatalytic methods*

Enzymatic resolution of racemic precursors of *(S)*-Tle by common methods has proven to be difficult:

* aminoacylase I (E.C. 3.5.1.14.) from both porcine kidney and *Aspergillus oryzae* reacts with N-acetyl- or N-chloroacetyl-*(RS)*-Tle at much less than 0.1 % of the activity compared to the rate towards its favored substrate, N-acetyl-*(RS)*-methionine;[19]
* use of amino acid amidase (E.C. 3.5.1.) from *Ochrobactrum anthropi* also is severely limited for preparative scale: the relative rate is about 1 % compared to its standard substrate, *(RS)*-phenylglycinamide.[20]

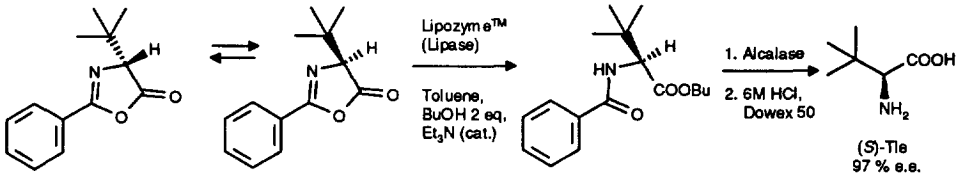
α-N-phenacetyl-*(RS)*-Tle (Phac-*(RS)*-Tle), however, seems to be an exception. Hoechst has developed a process towards *(S)*-Tle based on the hydrolysis of N-Phac-*(RS)*-Tle **11** by penicillin G acylase (PGA; E.C. 3.5.1.4.) immobilized on a phenol resin.[21] After removal of the enzymes, acidification of the solution to pH 3, and concentration to remove phenylacetic acid and N-Phac-*(R)*-Tle **12**, *(S)*-Tle **13** was obtained by extraction with ethanol/water (96 % yield). Acid hydrolysis of the remaining phenacetylated isomer yielded *(R)*-Tle **14** (e.e.-values and yields are not listed in the reference) (Scheme 4).



Scheme 4

Based on the work of both Bevinakatti[22] and Sih[23], Turner et al. developed an enantioselective hydrolysis procedure for 4-*tert*-butyl-2-phenyl-azlactone with BuOH catalyzed by Lipozyme™ (lipase from *Mucor miehei*) in toluene (Scheme 5).[24] Since the azlactone racemizes rapidly a dynamic resolution with degrees of conversion of up to 100% can be achieved. The e.e.-values of the product N-benzoyl amino acid butyl esters strongly depend on the residue in 4-position as well as on the addition of Et_3N: while the N-benzoyl-Phe butyl ester derivative could only be obtained with a 73 % e.e. (69 % chemical yield (c.y.); without Et_3N: 55 % e.e., c.y. 59 %) the *tert* butyl azlactone **15** resulted

in an enantiomerically pure N-benzoyl-Tle-OBu **16** (99.5 % e.e., c.y. 94 %, with 2 eq of BuOH, catalytic amounts of Et_3N). Probably owing to more selective enzymatic deacylation with longer chain alcohols, the e.e.-values decrease to 92.1 % with EtOH instead of BuOH and to 80 % with MeOH.

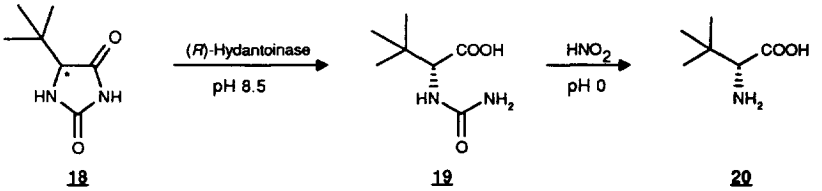


15 **16** **17**

Scheme 5

Hydrolysis and work-up of N-benzoyl-*(S)*-Tle butyl ester **16** could not be achieved by simple reflux in 6 M HCl with subsequent ion exchange chromatography over Dowex-50 (H^+) because, under those conditions, the yield was only 80 % with 73 % e.e. owing to partial back reaction to the azlactone. Instead, the ester first had to be hydrolyzed with alcalase (Novo, subtilisin from *B. licheniformis*) and then treated with 6 M HCl and ion exchange chromatography (Dowex-50 (H^+)) to yield *(S)*-Tle **17** with 97 % e.e. (Scheme 5).

Recently, Degussa has developed a convenient synthesis of *(R)*-Tle which utilizes *(RS)*-5-*tert*-butyl-hydantoin **18** and an enantioselective *(R)*-hydantoinase to open the hydantoin ring to the N-carbamoyl-*(R)*-Tle intermediate **19**. Since the hydantoin racemizes in situ the yield of the *(R)*-configured intermediate was >99 %. After an intensive screening, enzymes from suitable organisms such as *E. coli* were found which accepted *tert*-butylhydantoin as a substrate. Decarbamoylation of the biotransformation product with HNO_2 yielded an enantiomerically pure *(R)*-Tle **20** in 85.5 % yield (99.5 % e.e.) (Scheme 6).[25]



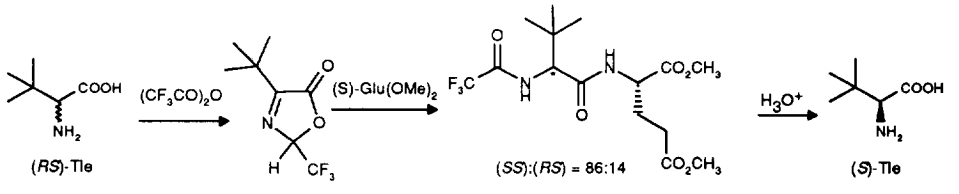
18 **19** **20**

Scheme 6

3. ENANTIOSELECTIVE SYNTHESIS OF Tle

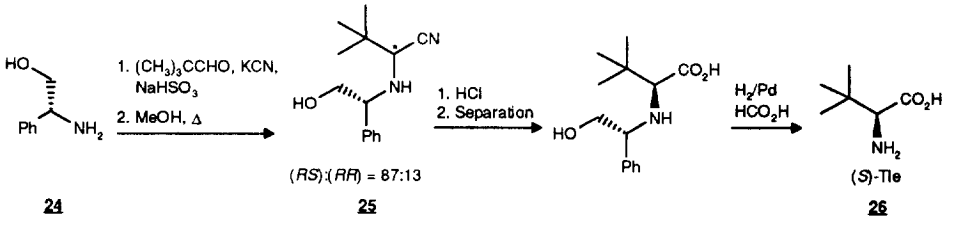
3.1. Chemical synthesis

The enantioselective conversion of a prochiral substrate into optically active proteinogenic or non-proteinogenic α-amino acids by reaction with chiral auxiliaries in catalytic or stoichiometric quantities has engaged a lot of research groups in the last decade. Two often-referenced general methods are based on the alkylation of chiral glycine enolates[26] or on the electrophilic amination of amide-[27] or ester-enolates.[28] Another method for the conversion of *(RS)*-Tle **4** into the single *(S)*-enantiomer employs the reaction of 2-(trifluoromethyl)-4-*tert*-butyl-Δ^3-oxazolinone **21** with *(S)*-dimethyl Glu leading to the two peptide diastereomers [*(SS)*:*(RS)* = 86:14] **22** (Scheme 7).[29] Separation of the *(SS)*-diastereomer and hydrolysis afforded the optically pure α-amino acid **23** in 63 % overall yield.



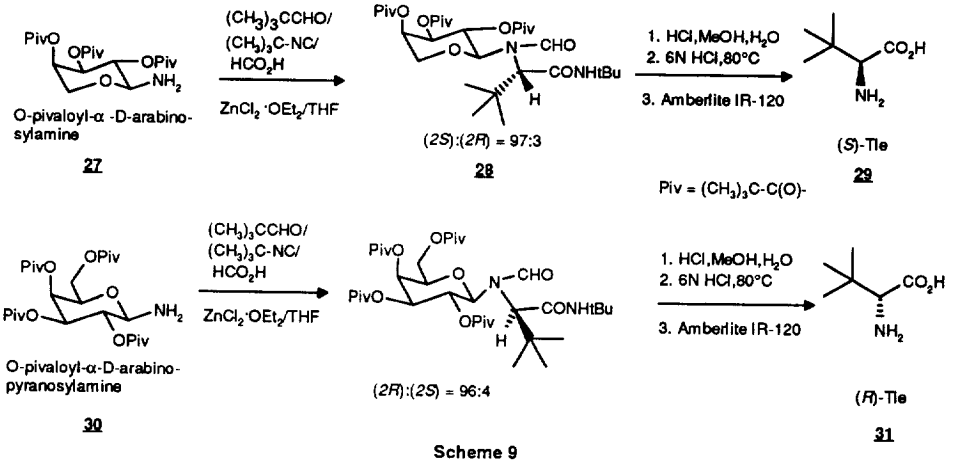
Scheme 7

An alternative pathway for the stereoselective synthesis of chiral α-amino acids can be achieved by addition of a nucleophilic carboxylate synthon to a prochiral Schiff base. The most frequently used carboxylate synthons are cyanide for the Strecker synthesis and isocyanate in the Ugi condensation. In both methods, amines were used as chiral auxiliaries for asymmetric synthesis of *(R)*- and *(S)*-Tle, respectively. By simple stirring of a mixture of *(R)*-phenylglycinol **24** as chiral auxiliary, pivaldehyde, KCN and $NaHSO_3$ in MeOH, Ogura and associates[30] obtained an equilibrium ratio *(RS)*:*(RR)* of 87:13 **25** (Scheme 8). After hydrolysis of the carbonitrile group, separation of the *(RS)*-diastereomer and removal of the chiral auxiliary by Pd-catalyzed hydrogenolysis in the presence of formic acid, enantiomerically pure *(S)*-Tle **26** was isolated.



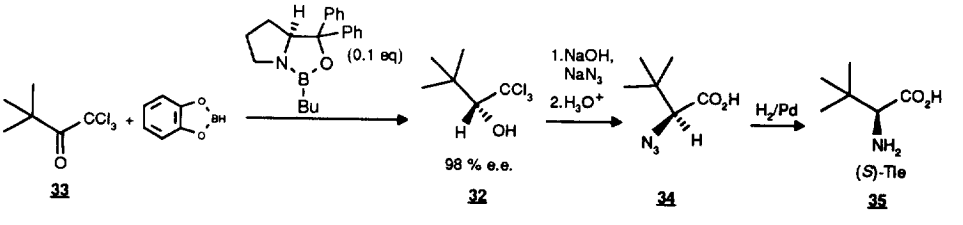
Scheme 8

Kunz and coworkers used carbohydrates as chiral templates for the synthesis of both antipodes of the non proteinogenic α-amino acid *via* Ugi condensation. By using the O-pivaloyl-α-D-arabinosylamine **27** as chiral auxiliary, the either preformed or *in situ* generated Schiff base provides a highly diastereoselective access [2*S*:2*R* = 97:3] to the *tert*-butyl substituted N-formyl-N-α-D-arabinosylamino acid *tert*-butylamide **28** (Scheme 9).[31] After application of a two-step hydrolysis *(S)*-**28** can be easily converted to the free *(S)*-configured Tle **29**. Through variation of the chiral auxiliary, using 2,3,4-tri-O-pivaloyl-α-D-arabinopyranosylamine[32] **30** instead of **27**, it is possible to get the enantiomerically pure *(R)*-Tle **31** in analogy to the previously described method.



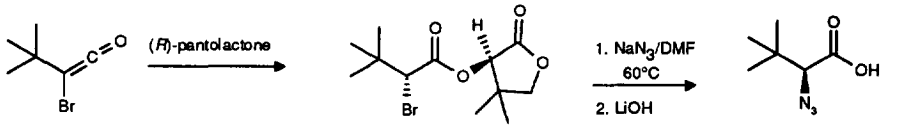
Scheme 9

A novel α-amino acid synthesis strategy pioneered in 1992 by Corey and Link[33] employs nucleophilic amination of substituted prochiral trichloromethyl ketones. *Tert*-butyl-trichloromethyl carbinol **32** was readily obtained by enantioselective reduction of the corresponding trichloromethyl ketone **33** with excellent 98 % e.e.. Treatment with NaOH and NaN_3 effected smooth conversion to the *(S)*-configured α-azido acid **34**. After subsequent reduction and recrystallization, *(S)*-Tle **35** was isolated in enantiomerically pure form (Scheme 10).



Scheme 10

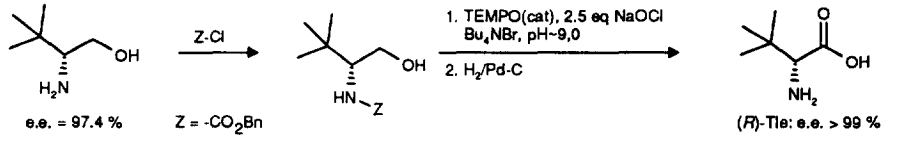
In the same year, a similar approach based on α-haloketenes as prochiral substrates was published in which the α-bromo ester precursor of the α-azido ester was obtained with *(R)*-pantolactone in good diastereoselectivity (87 % d.e.). After treatment with NaN_3 and saponification, the *(S)*-2-azido-3,3-dimethylbutanoic acid **36** could ultimately be isolated with 72 % e.e. (Scheme 11).[34]



36

Scheme 11

A procedure succeeding in synthesizing enantiomerically pure *(R)*-Tle, which has been difficult to obtain, starts from *(R)*-*tert*-leucinol **37** available by resolution (see also Section 4.1.). After protection of the amino group, the primary hydroxy function was easily, cheaply and highly selectively converted to the carboxylic acid group in the presence of catalytic amounts of 2,2,6,6-tetramethyl-piperidine-1-oxyl (TEMPO)[35] and ≥ 2.1 eq. of NaOCl in an aqueous organic two-phase system. Chemically and enantiomerically pure *(R)*-Tle **38** (e.e. > 99 %) was obtained in a 64 % overall yield after deprotection by Pd-catalyzed hydrogenolysis (Scheme 12).[36]



37 **38**

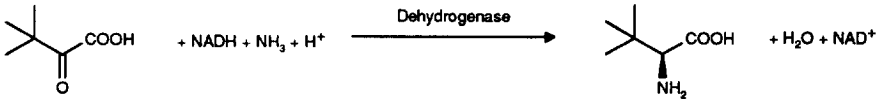
Scheme 12

3.2. Chemoenzymatic synthesis

While nonenzymatic reductive amination has been known since 1927[37], enzymatic processes to *(S)*-amino acids are much more recent. Reduction can be achieved by pyridoxalphosphate (PLP)-dependent transaminases (E.C. 2.6.1.) or by amino acid dehydrogenases (E.C. 1.4.1.) using NAD(P)H as cofactor. Both routes start from α-keto acids which are conveniently accessible by oxidation of hydroxyacids[38], by hydrolysis of acyl-cyanides[39], by hydrolysis of alkylidene hydantoins in strong alkali[40], and by oxalic ester synthesis.[41]

Transaminases use their pyridoxalphosphate (PLP) cofactors to transfer an amine nitrogen by oxidative deamination from a donor acid *via* the pyridoxaminephosphate form (PMP) to a receiving keto acid thus regenerating the resting PLP form of the cofactor. The synthetic usefulness of this reaction is diminished by the location of the equilibrium (often, $K_{eq} \approx 1$) so that complex mixtures result which often are laborious to separate. The best option for transamination is coupling with oxidative deamination of inexpensive *(S)*-amino acids such as *(S)*-aspartate to oxaloacetate which decarboxylates spontaneously to pyruvate.[42]

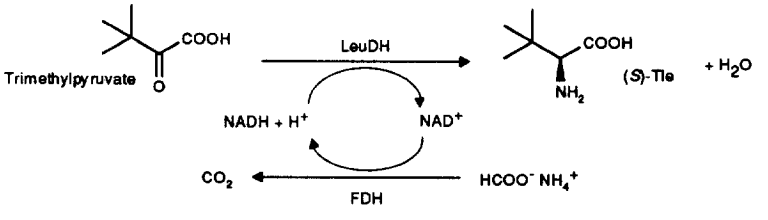
α-Keto acids can be reductively aminated to α-amino acids in a reaction with an equilibrium far on the side of aminated products ($K_{eq} = 9 \cdot 10^{12}$ at pH 11.0) (Scheme 13)[43]:



Scheme 13

As mechanistic studies on glutamate dehydrogenase (GluDH) as examples for all other amino acid dehydrogenases have shown[44], attack on the keto acid to form an intermediate imine is so specific that the resulting enantioselectivity is practically perfect. Reductive amination to *(S)*-Tle from trimethylpyruvic acid is catalyzed by leucine dehydrogenase (LeuDH) which normally catalyzes the reductive amination of branched-chain α-keto acids to the α-amino acids including unnatural amino acids such as *(S)*-Tle[45], *(S)*-β-hydroxy-valine[46], and very hydrophobic branched-chain *(S)*-amino acids.[47] *(R)*-Tle cannot be obtained through enzymatic reductive amination as corresponding *(R)*-amino acid dehydrogenases have not been found.[48] For reviews on amino acid dehydrogenases, see references 48 and 49.

Enzymatic reductive amination with NADH as cofactor can only be operated on a large scale if the cofactor is regenerated. Wandrey and Kula have developed a regeneration scheme using formate as reductant of NAD^+ generated upon reductive amination. The formate is oxidized irreversibly to CO_2 by formate dehydrogenase (FDH, E.C. 1.2.1.2.) (Scheme 14).[50]



Scheme 14

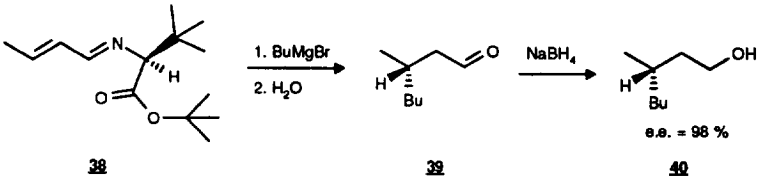
For soluble reactants and products, enzymes are preferentially immobilized in an enzyme-membrane reactor (EMR). To keep the cofactor from penetrating through the membrane, it can be enlarged with polyethyleneglycol (PEG).[51] With the advantage of quantitative use of keto acid substrate and with a suitable process of cofactor regeneration, enzymatic cofactor-dependent reductive amination of trimethylpyruvate is the route of choice for large-scale synthesis of enantiomerically pure *(S)*-Tle. Degussa operates an industrial process producing high-quality *(S)*-Tle *via* this route.

4. ENANTIOMERICALLY PURE Tle AND DERIVATIVES IN ASYMMETRIC SYNTHESIS

Enantiomerically pure Tle and its derivatives have found widespread application in asymmetric synthesis, both in stoichiometric as well as in catalytic processes. This is due to the bulky *tert*-butyl groups of these compounds which exhibit particularly strong steric hindrance in reactions proceeding on prochiral molecules or functional groups. Consequently, reagents attack preferentially from the side opposite to the *tert*-butyl group resulting in trans- or anti reaction products. Therefore, asymmetric reactions have very often shown especially high diastereo- or enantioselectivities when Tle derived compounds have been employed as chiral auxiliaries instead of the similar but sterically less demanding Val analogues.

4.1. Stoichiometric Applications

In the beginning, many investigations on the induction of asymmetry with bulky directing groups employed protected derivatives of optically active Tle itself. Thus, an early communication reported asymmetric Michael additions of Grignard reagents to α,β-unsaturated aldimines **38** derived from crotonic or cinnamic aldehyde and the *tert*-butyl esters of *(S)*-Val and *(S)*-Tle.[52] After hydrolysis, the respective aldehydes **39** were obtained and directly reduced to the corresponding alcohols **40**. The overall chemical yields ranged between 40 % and 56 %. For the *(S)*-Val derivative, a moderate optical yield of 63 % was reported, while all the reactions carried out with *(S)*-Tle-derived aldimines afforded the alcohols in 91 - 98 % enantiomeric purity (corrected with respect to 92.2 % enantiomeric purity of *(S)*-Tle) (Scheme 15).

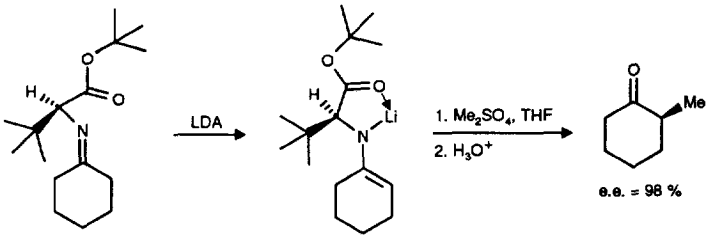


38 **39** **40**

Scheme 15

Chiral Schiff bases, prepared from benzaldehyde and amino acid esters, have been subjected to asymmetric hydrocyanation to give, after hydrolysis and oxidative decarboxylation of the amino acid auxiliary, optically active *(R)*-phenylglycine. While modest optical yields from 25 to 63 % were achieved for the intermediate N-benzyloxycarbonyl-*(R)*-phenylglycine amide with the *(S)*-Val-, *(S)*-Phe- and *(S)*-Leu-derivatives, an astonishing 96.5 % e.e. was reported when the Schiff base was prepared from *(S)*-Tle *tert*-butyl ester.[53]

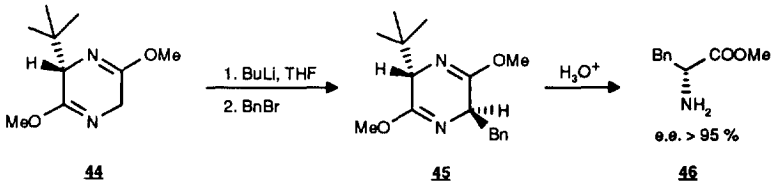
In 1978, the diastereoselective alkylation of cyclic lithioenamines **41** derived from the *tert*-butyl esters of *(S)*-Val and *(S)*-Tle imines **42** was described (Scheme 16).[54] After hydrolysis and work-up, cyclic α-alkyl ketones **43** were obtained in good yields. The optical yields were 73 % and 84 %, when the *(S)*-Val derivative was employed, but went up to 84 - 98 % with the *(S)*-Tle-based compound thus convincingly demonstrating once more the dramatic effect of increasing steric hindrance by the *tert*-butyl side chain on asymmetric induction.



42 **41** **43**

Scheme 16

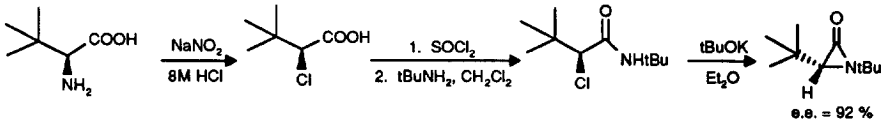
The famous bislactim ether strategy, developed by Schöllkopf and his coworkers[26b] for the asymmetric synthesis of amino acids, could be considerably improved by using Tle as the source of chirality. Thus, the *(S)*-Tle-derived bislactim ether **44** was alkylated with benzyl or heptyl bromide to give the respective adduct **45** with > 95 % d.e. in both cases (corrected with respect to 90 % enantiomeric purity of *(S)*-Tle), whereas the corresponding reactions starting from the *(S)*-Val derivative proceeded with only 92-94 % or 75-80 % d.e., respectively. The products were hydrolyzed to give *(R)*-amino acid methylesters **46** (Scheme 17).[55]



44 **45** **46**

Scheme 17

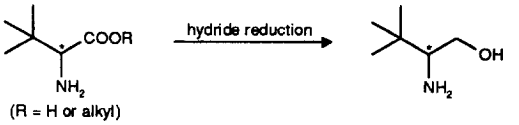
A chiral aziridinone **47** derived from *(S)*-Tle has been prepared by Quast and coworkers.[56a] Due to the high stability of this compound towards racemization, stereochemical investigations concerning ring opening,[56b] thermal reorganization and cycloadditions[56c] of this compound could be performed (Scheme 18).



47

Scheme 18

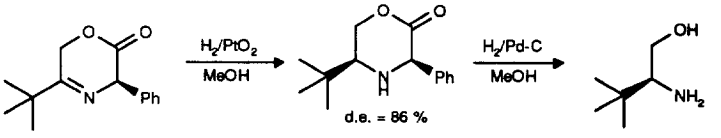
Many applications in asymmetric synthesis, however, start from enantiomerically pure *tert*-leucinol **48** as the most important derivative of Tle. This amino alcohol has been prepared for the first time by reduction of *(R)*-Tle-methylester (**49**, R = Me) with $LiAlH_4$.[16] Nowadays, enantiomerically pure *tert*-leucinol can be obtained easily and in high yields by direct reduction of optically active Tle (**49**, R = H) with $LiAlH_4$ [57] or $NaBH_4$ activated with H_2SO_4[58] or iodine (Scheme 19).[59]



49 **48**

Scheme 19

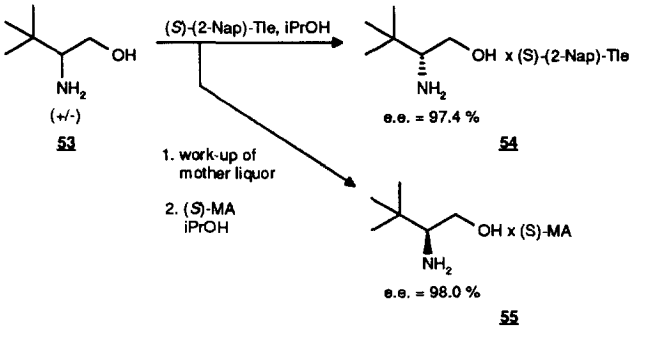
It is also possible to prepare optically active *tert*-leucinol without starting from enantiomerically pure Tle. Thus, a chiral oxazinone **50**, derived from N-benzyloxycarbonyl-*(R)*-α-phenylglycine and *tert*-butyl-halogeno-methyl-ketone, was hydrogenated using PtO_2 to give a 93:7 mixture of diastereomeric morpholinones **51**. The predominant cis-isomer was separated by chromatography and hydrogenolyzed over Pd-C to give *(S)*-*tert*-leucinol **52** (Scheme 20).[60]



50 **51** **52**

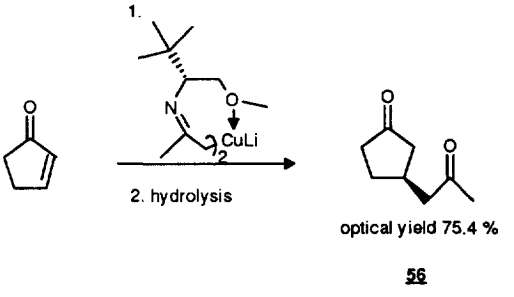
Scheme 20

Very recently, we have developed a resolution of racemic *tert*-leucinol **53** which had been obtained by reduction of trimethylpyruvic acid oxime with $NaBH_4$ - sulfuric acid (Scheme 21).[61] With N-(2-naphthoyl)-*(S)*-Tle [*(S)*-(2-Nap)-Tle] as resolving agent, a salt **54** with *(R)*-*tert*-leucinol was obtained in 70 % yield and 97.4 % e.e. Work-up of the mother liquor and treatment with *(S)*-mandelic acid [*(S)*-MA] afforded a salt **55** with the other isomer, *(S)*-*tert*-leucinol, in 63 % yield and 98.0 % e.e..



Scheme 21

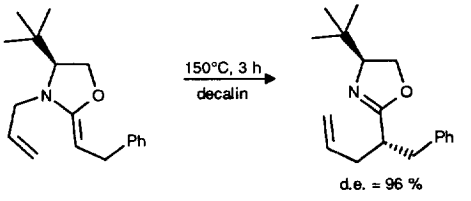
In an early study, asymmetric conjugate addition of chiral Cu azaenolates to 2-cyclopentenone and 2-cyclohexenone was investigated to give, after hydrolysis and work-up, optically active 3-acetonylcycloalkanones **56** (Scheme 22).[62] Azaenolates prepared from the methyl ethers of *(S)*-phenylalaninol, *(S)*-valinol and *(S)*- and *(R)*-*tert*-leucinol were compared. The benzyl and isopropyl derivatives gave poor optical yields for the final products ranging from 16.5 % to 28.6 %, while the *tert*-butyl-derived compounds furnished moderate optical yields between 43.6 % and 75.4 %.



Scheme 22

Asymmetric induction in the Claisen rearrangement of N-allylketene N,O-acetals **57** has been examined by Kurth and coworkers.[63] These compounds were prepared from optically active amino alcohols, and on

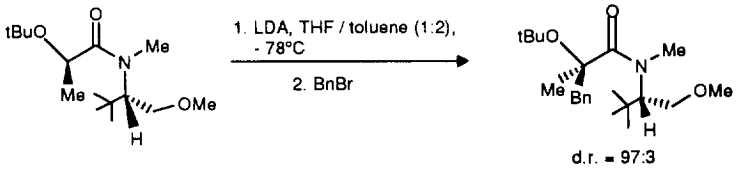
heating to 150°C the rearrangement to 2-oxazolines **58** occured with high to excellent diastereoselectivity. The best results were obtained with the *(S)-tert*-leucinol derivative (d.e. up to 96 %), which slightly exceeded the selectivities measured for the *(S)*-valinol based compounds (94 % d.e.) (Scheme 23).



57 **58**

Scheme 23

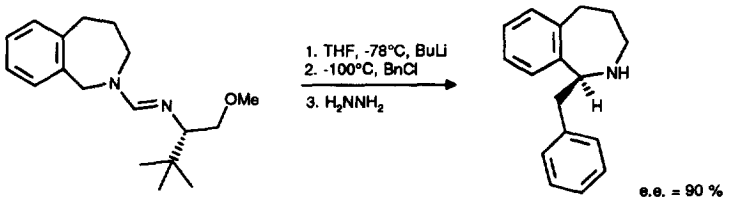
A strategy for asymmetric synthesis of α-alkylated α-hydroxy carboxylic acids utilized O-protected α-hydroxy carboxylic acid amides containing chiral amino alcohol methyl ethers (Scheme 24).[64] With the *(S)-tert*-leucinol-derived lactic acid amide **59**, diastereoselectivities from 92:8 to 97:3 were reported for the alkylation product **60** but the yields were moderate in these cases (35 - 65 %). Higher yields (97 % and 92 %) were achieved with a glyoxylic acid derivative but the diastereoselectivities dropped to 80:20 and 72:28, respectively.



59 **60**

Scheme 24

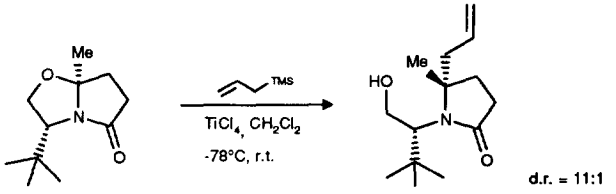
A great number of valuable contributions to the application of optically active *tert*-leucinol in asymmetric synthesis was made by Meyers and coworkers. One major area of research have been chiral formamidines which can be used to introduce a center of asymmetry adjacent to nitrogen.[65] For example, chiral 1-alkyl-2,3,4,5-tetrahydrobenzazepines have been prepared following this strategy. In a comparative experiment, the *(S)-tert*-leucinol-methyl ether derived compound **61** gave the best result (90 % e.e. for the final product, **62**), but the *(S)*-valinol derivatives were only slightly worse (88 % and 84 % e.e., respectively) (Scheme 25). With other electrophiles, up to 96 % e.e. were achieved in the alkylation of the *(S)-tert*-leucinol based formamidine.[66]



61 62

Scheme 25

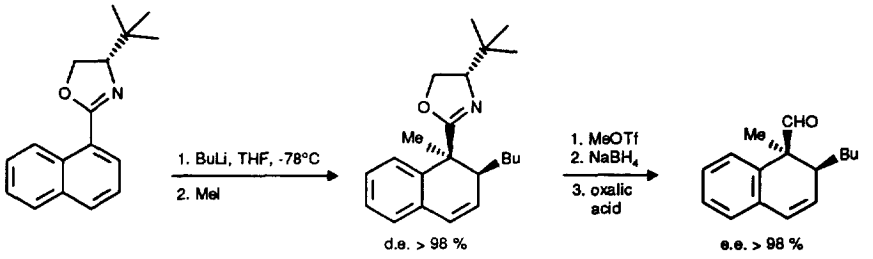
Other investigations of the Meyers group have focused on the reactions of chiral bicyclic lactams **63**.[67] For instance, the lactam prepared from an optically active amino alcohol and levulinic acid was reacted with allyltrimethylsilane in presence of $TiCl_4$ to give allylated pyrrolidinones **64**. With the alaninol-derived lactam, a diastereomeric ratio of only 1:8 was observed. When the directing group was changed, the diastereoselectivity was finally inverted and increased, resulting in a 11:1 ratio for the *tert*-leucinol based derivative (Scheme 26).[68]



63 64

Scheme 26

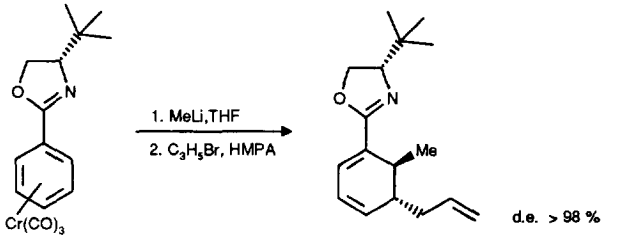
Finally, Meyers and his coworkers have explored the chemistry of 2-oxazolines and found numerous applications in asymmetric synthesis.[69] Special syntheses of starting materials include easy preparations of optically active 2-H 2-oxazolines from the corresponding amino alcohols and dimethylformamide dimethylacetal[70] and of chiral α,β-unsaturated oxazolines from ketones *via* their enol triflates and subsequent coupling with CO and the respective amino alcohols under Pd(0) catalysis.[71] In one selected example, 2-(1-naphthyl)-oxazolines **65** were subjected to tandem organolithium - methyliodide addition to give, after hydrolysis and reduction, the corresponding dihydronaphthalene aldehydes **66**. Again, the best results were obtained with the *(S)-tert*-leucinol-derived oxazoline, with diastereomeric ratios of > 99:1 for the butyl and vinyl and 95:5 for the phenyl adduct (Scheme 27).[72]



65 66

Scheme 27

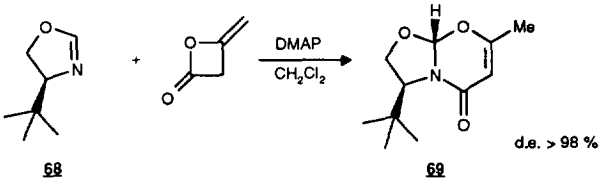
In a related investigation, this strategy could be extended to benzene derivatives by Kündig et al..[73] After complexation to $Cr(CO)_3$, an organolithium reagent was added and the intermediate trapped with allyl-bromide to give **67**. Also in this case, the *(S)-tert*-leucinol derivative gave the highest diastereomeric ratios, with > 99:1 for the reactions with methyl lithium and n-butyl lithium, respectively (Scheme 28).



67

Scheme 28

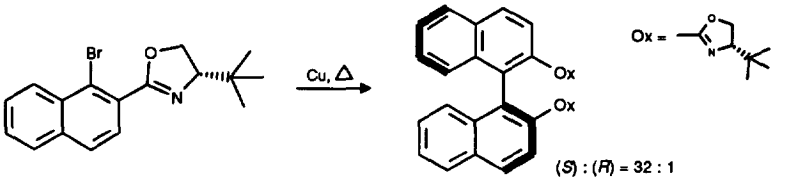
When chiral 2-H 2-oxazolines **68** were reacted with diketene, bicyclic oxazinones **69** were formed in good yields. The *(S)-tert*-leucinol derivative was obtained in diastereomerically pure form (d.e. > 98 %, compared to 92 % for the *(S)*-valinol and 86 % for the *(S)*-phenylalaninol derivative) (Scheme 29).[74]



68 69

Scheme 29

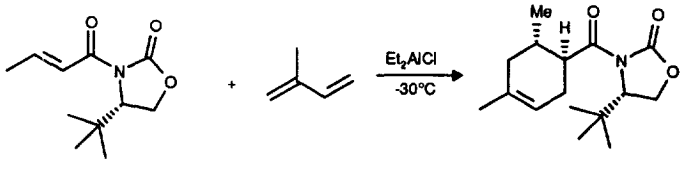
Finally, asymmetric biaryl syntheses have been investigated by Meyers and coworkers starting from oxazoline-substituted aryl compounds. Very recently, it was reported that Ullmann coupling of chiral 2-oxazoline-substituted 1-naphthylbromides **70** afforded the corresponding axially chiral binaphthyls **71** in good yields. However, the phenylglycinol-derived compound and the valinol-derivative gave only very poor diastereomeric ratios of 2:1 and 4:1, respectively. In contrast, the *(S)-tert*-leucinol based oxazoline afforded an impressive 32:1 diastereomeric ratio (Scheme 30).[75]



70 **71**

Scheme 30

Chiral 4-substituted 2-oxazolidinones, which have been investigated by Evans and his group since 1981, have been shown to be valuable chiral auxiliaries which induce high degrees of diastereoselectivity in various reactions.[76] Again, particularly high asymmetric inductions were observed with optically active 4-*tert*-butyl-2-oxazolidinone derived from *tert*-leucinol. Thus, the Diels-Alder reaction between N-crotonyl-4-*tert*-butyl-2-oxazolidinone **72** and isoprene gave a diastereoselectivity beyond the limit of detection ("very conservatively" set to > 100 : 1) (Scheme 31), and methylation of N-butyryl-4-*tert*-butyl-2-oxazolidinone afforded a 67.7:1 ratio, whereas the (S)-Val-derivative gave only 5.3:1 and 9.9:1 ratios and the *(S)*-Phe-based derivative modest 20.7:1 and 16.7:1 ratios, respectively.[77]

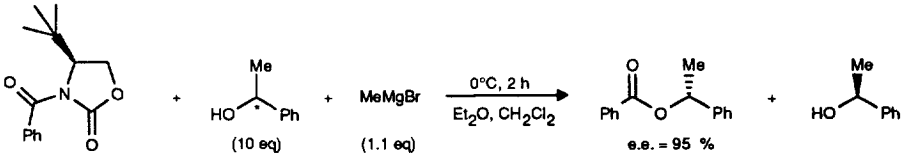


72

Scheme 31

In an extension of Evans' pioneering work it was found that the stereochemistry of the aldol reaction could be controlled by carefully adjusting the reaction conditions. While the isopropyloxazolidinone was "most effective under the anti-selective conditions" with isomeric ratios up to 95:5, under the syn-selective

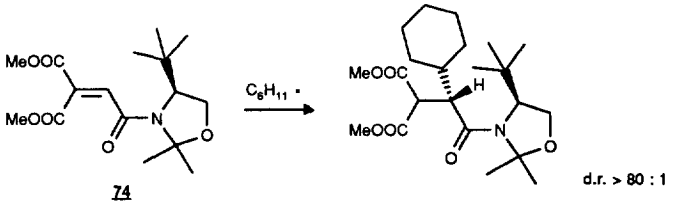
conditions the *tert*-butyl oxazolidinone gave the best results with selectivities up to 6:94.[78] The Tle-based 2-oxazolidinone was also investigated in $ZnCl_2$-accelerated radical allylation of an N-protected 2-bromo glycine derivative, but in this case the stereoselectivity was lower than with the isopropyl derivative.[79] Chiral N-benzoylated 2-oxazolidinones **73** have also proven useful for the enantioselective acylation of alcohols by kinetic resolution. With excess α-methylbenzyl alcohol (10 eq), the *tert*-butyl derivative again showed the highest selectivity (85 % e.e. for the benzoylated alcohol) compared to the isopropyl (72 % e.e.), cyclohexyl (55 % e.e.) and benzyl (57 % e.e.) oxazolidinones. Under optimized conditions, up to 95 % e.e. were obtained (Scheme 32).[80]



73

Scheme 32

Free radical additions to oxazolidine-derived acryl- and fumaramides have been studied by Porter and coworkers. Several impressive examples again showed superior diastereoselectivity induced by the *tert*-butyl substituted oxazolidine. Thus, addition of cyclohexyl radical to chiral ethenetricarboxylic acid 1,3-oxazolidinide **74** proceeded with diastereomeric ratios of 1.1: 1 with R = Ph, 10:1 with R = iPr and striking > 80:1 with R = tBu (Scheme 33).[81]



74

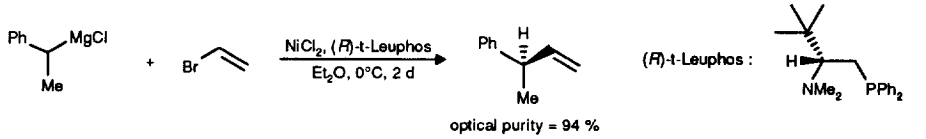
Scheme 33

In a related study, "chiral auxiliary control of tacticity in free radical polymerization" of acrylic acid derivatives was investigated. Here, the valinol- as well as the *tert*-leucinol derived oxazolidines induced the same degree of tacticity of 92 %.[82] An investigation on the chemo-, oligo- and stereoselectivity of telomerization of acryloxazolidinides, however, again gave better results for the *tert*-butyl substituted compound than for the isopropyl derivative.[83]

4.2. Catalytic Applications

Almost at the same time when research chemists started to use optically active Tle or derivatives thereof in stoichiometric asymmetric synthesis, first efforts were made to employ these compounds in catalytic asymmetric reactions. Since then, the idea has always been to prepare a derivative of optically active *tert*-leucinol which should form a suitable ligand for a metal center thus rendering highly efficient catalysts for the desired asymmetric transformations.

Kumada and coworkers synthesized chiral β-(dimethylamino)alkylphosphanes based on a variety of optically active amino acids as ligands for asymmetric Grignard cross coupling.[84] In the reaction of 1-phenylethylmagnesium chloride with vinyl bromide, the catalysts prepared from nickel chloride and the chiral phosphane ligands produced optically active 3-phenyl-1-butene **75** in good yields. A clear relationship was found between the size of the substituent at the stereogenic center in the phosphane ligand and enantiomeric purity of the product. Consequently, the ligand derived from *(R)*-Tle (which was named "*(R)*-t-leuphos" **76**) gave the highest optical purity with 94 % (corrected with respect to 88 % enantiomeric purity of *(R)*-Tle) (Scheme 34).



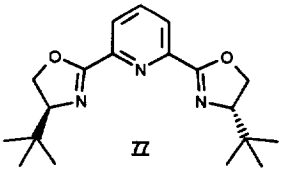
75 **76**

Scheme 34

Very recently, the enantioselective addition of trimethylsilylcyanide to aldehydes catalyzed by titanium alkoxide - chiral Schiff base complexes prepared from salicylaldehydes and various amino alcohols was reported. Corresponding cyanohydrins were obtained in moderate to high yields and e.e.-values between 22 % and 85%. Catalysts derived from *(S)-tert*-leucinol were reported to give modest e.e.-values of 40 % and 63 %, respectively.[85] However, research efforts for applications of amino alcohols in catalytic asymmetric synthesis soon concentrated on cyclic systems, especially on oxazolines. First, the suitability of bis(oxazolines) as ligands for asymmetric catalysis has been thoroughly examined for a variety of examples (for reviews, see reference 86). One of the first reactions which were investigated in detail was the Rh-catalyzed hydrosilylation of ketones. Chiral bis(oxazolinyl)pyridines **77** have been described by Nishiyama and coworkers.[57,87] The *tert*-butyl derivative gave 83 % e.e. in the asymmetric hydrosilylation of acetophenone and 79 % e.e. in the same reaction with ethyl levulinate thus being considerably less selective than the corresponding isopropyl (94 % and 95 % e.e.) and sec-butyl catalysts (91 % and 94 % e.e.). Helmchen et al. reported bisoxazolines **78** as

ligands for the same reaction[88] and found e.e.-values up to 84 % for the hydrosilylation of acetophenone with the *(S)*-phenylalaninol-derived ligand while the *(S)*-*tert*-leucinol based compound did not furnish any detectable e.e.. The same ligand system was investigated for the Ir-catalyzed transfer hydrogenation of alkyl aryl ketones by Pfaltz and his group with similar results. The isopropyl derivative gave the best e.e.-values with up to 91 % while the *tert*-butyl catalyst did not even afford significant chemical conversion (Scheme 35).[89]

Nishiyama (1989)



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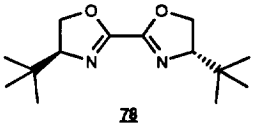


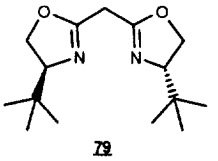
78

Helmchen (1991)
Pfaltz (1991)

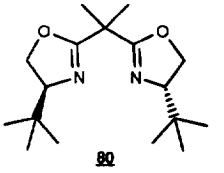
Scheme 35

In a stimulating and fascinating race for new reactions, more efficient ligands and catalysts and even higher stereoselectivities, a number of groups contributed surprising results to this highly active area of research within a very short time. Masamune and coworkers synthesized methylene-bridged bis(oxazolines) 79 as ligands for the Cu-catalyzed enantioselective cyclopropanation of various olefins with diazoacetates (Scheme 36).[90] In comparative experiments, the best result in the cyclopropanation of styrene with ethyl diazoacetate was achieved with the *(S)*-*tert*-leucinol-derived ligand which afforded the best diastereoselectivity (trans : cis = 75 : 25) and by far the best enantioselectivities for these isomers (trans 90 % e.e., cis 77 % e.e.). With styrene and l(-)-menthyl diazoacetate, the diastereoselectivity could be improved to 86:14 and the e.e.-values reached 98 % (trans isomer) and 96 % (cis isomer). Even higher diastereoselectivities and consistently high enantioselectivities were found in the cyclopropanation of other olefins with menthyl diazoacetates.

Masamune (1990)
Pfaltz (1991)
Evans (1991)
Nakamura (1995)



79



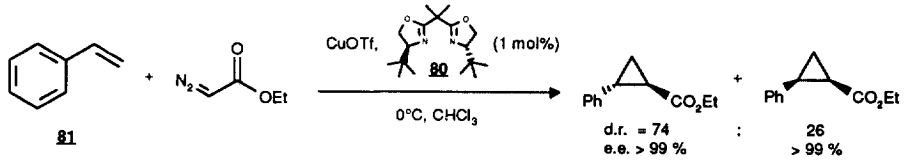
80

Evans (1991)
Masamune (1991)
Pfaltz (1995)
Andrus (1995)

Scheme 36

The group of Pfaltz also prepared these ligands for the Cu-catalyzed enantioselective cyclopropanation of styrene with menthyl diazoacetates.[89] Confirming the findings of Masamune et al., the *(S)*-*tert*-leucinol-derived methylene-bridged catalyst provided both the best diastereoselectivity (trans:cis = 87:13) and for these

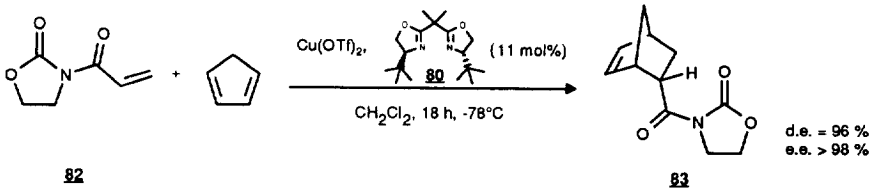
diastereomers also excellent enantioselectivities (96 % for the trans and 97 % for the cis isomer). Evans and coworkers added two methyl groups to the methylene bridge, thus providing another highly efficient ligand **80** for these reactions. For the cyclopropanation of styrene **81** with ethyl diazoacetate at 0°C, they reported a trans:cis ratio of 74:26 with impressive > 99 % e.e. for both isomers (Scheme 37).[91]



81

Scheme 37

The Evans group also studied the suitability of the dimethylmethylene-bridged bis(oxazoline)-Cu complexes for other asymmetric catalytic transformations. In enantioselective aziridinations, however, the ligand prepared from *(S)*-phenylglycinol proved to be most efficient affording e.e.-values of 70-97 %, while the *(S)*-*tert*-leucinol-derived analogue gave only 19-70 % e.e..[92] In contrast, when Diels-Alder reactions between acrylimides **82** and cyclopentadiene were investigated, the *tert*-butyl-substituted catalyst **80** again gave the best stereoselectivities with d.e.-values up to 96 % in favor of the endo addition product **83** and e.e.-values from 90 % to > 98 % for this diastereomer (Scheme 38).[93]

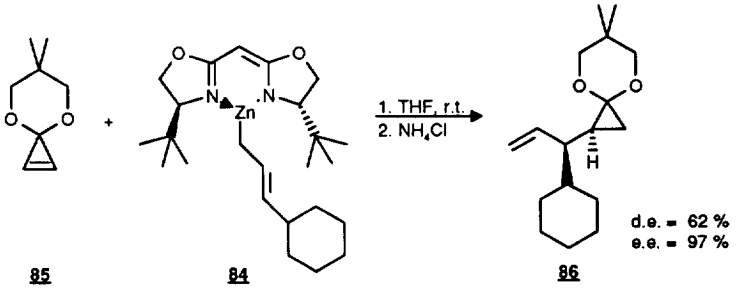


82 **83**

Scheme 38

Nakamura and associates reported excellent enantioselectivities for the allyl-zincation of cyclopropenone acetals using stoichiometric amounts of the methylene-bridged bis(oxazoline) ligand **79** first described by Masamune.[94] When addition of (E)-3-cyclohexyl-2-propenyl zinc bromide (after complexation with **79** to give intermediate **84**) to cyclopropenone 2,2-dimethyl-1,3-propanediol acetal **85** was compared, the *(S)*-valinol-derived ligand gave both moderate diastereomeric (83:17) as well as enantiomeric ratios (81:19). With the *(S)*-*tert*-leucinol analogue, diastereoselectivity was comparable (81:19) but enantioselectivity for the major

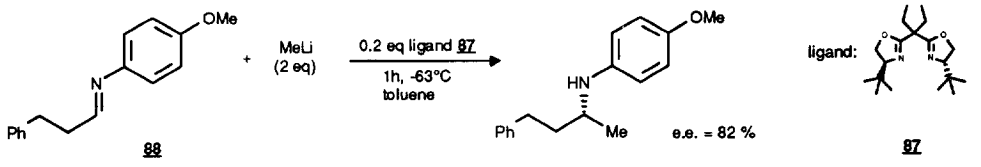
diastereomer **86** reached impressive values (98.5:1.5) (Scheme 39). In other reactions, however, both the corresponding isopropyl and phenyl ligands gave similarly high enantioselectivities (≤ 0.8:99.2).



85 **84** **86**

Scheme 39

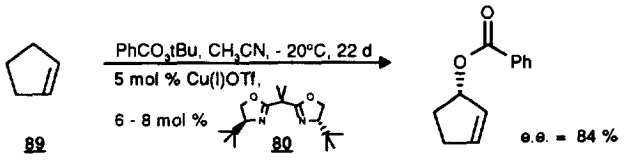
Related ligands bearing two ethyl or isobutyl groups at the methylene bridge have been examined by Denmark and coworkers in the asymmetric addition of organolithium reagents to aldimines. In a comparative stoichiometric study on the addition of methyllithium to benzaldehyde N-anisyl imine, the best enantioselectivity (85 % e.e.) was found for the bis(isobutyl)methylene bridged ligand bearing oxazoline substituents derived from *(S)-tert*-leucinol. With other substrates, the diethylmethylene-bridged bis(*tert*-butyl-oxazoline) **87** gave a maximum e.e. of 91 % with 3-phenylpropionaldehyde N-anisyl aldimine **88**. When catalytic applications were studied, this ligand still gave very good yields but enantioselectivities dropped to 51 - 82 % e.e. (Scheme 40).[95]



88 **87**

Scheme 40

Very recently, Pfaltz and coworkers reported on enantioselective Cu-catalyzed allylic oxidations of cycloalkenes with *tert*-butyl perbenzoate using the dimethylmethylene-bridged bis(oxazoline) ligands **80**.[96] In the case of cyclopentene **89**, the catalyst derived from *tert*-leucinol afforded up to 84 % e.e. while the isopropyl analog gave comparable 82 % e.e. (Scheme 41). The same reaction was investigated independently by the group of Andrus[97] who found 70 % e.e. for the benzoyloxylation of cyclopentene and 80 % e.e. with cyclohexene when the dimethylmethylene-bridged bis(oxazoline) ligand **80** derived from *tert*-leucinol was used. Cyclooctene and open-chain olefins gave significantly lower enantiomeric excesses.



Scheme 41

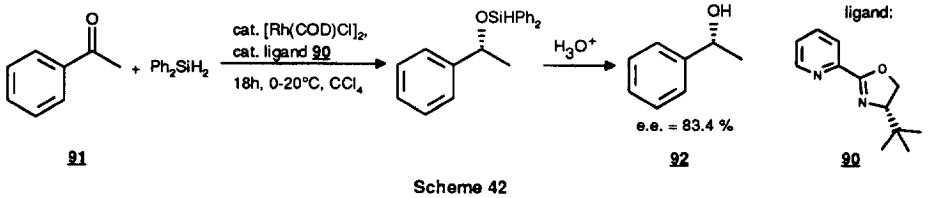
The variety of asymmetric reactions catalyzed by metal-bis(oxazoline) complexes derived from optically active *tert*-leucinol is summarized in Table 1. For comparative purposes, the corresponding values for the valinol- and phenylalaninol-derived catalysts have been added wherever available.

Table 1. Asymmetric Reactions Catalyzed by Metal-bis(Oxazoline) Complexes Derived from Optically Active *tert*-Leucinol, Valinol and Phenylalaninol

Type of Reaction	Substrate	Tle-derived ligand Yield (e.e.) [%]	Val-derived ligand Yield (e.e.) [%]	Phe-derived ligand Yield (e.e.) [%]	Ref.
Hydrosilylation	Acetophenone	92 (83)	91 (94)	-	87
Hydrosilylation	Acetophenone	n.d. (0)	n.d. (55)	59 (84)	88
Hydrosilylation	Acetophenone	< 5 (-)	89 (58)	89 (47)	89
Cyclopropanation	Styrene + ethyl diazoacetate	80 trans:cis: 75:25 (trans: 90; cis: 77)	72 trans:cis: 71:29 (trans: 46; cis: 31)	76 trans:cis: 71:29 (trans: 36; cis: 15)	90
Cyclopropanation	Styrene + (-)-menthyl diazoacetate	60 - 80 * trans:cis: 87:13 (trans: 96; cis: 97)	60 - 80 * trans:cis: 84:16 (trans: 13; cis: 5)	60 - 80 * trans:cis: 86:14 (trans: 19; cis: 9)	89
Cyclopropanation	Styrene + ethyl diazoacetate	77 trans:cis: 73:27 (trans: 99; cis: 97**)	yield not given trans:cis: 69:31 (trans: 49; cis: 45)	-	91a
Aziridination	(E)-1-Phenyl-1-propene	62 (70)	-	-	92
Diels-Alder reaction	3-Acryloyl-2-oxazolidinone + cyclopentadiene	86 endo:exo: 98:2 (endo: >98)	93 endo:exo: 96:4 (endo: 58)	-	93
Addition to imines	phenylpropionaldehyde N-anisyl imine + MeLi	81 (82)	-	-	95
Allylic oxidation	Cyclopentene	61 (84)	66 (82)	-	96

*: A yield of 60-80 % was reported for all reactions examined.
**: At 0°C, the cis-isomer was also obtained in > 99 % e.e.

The chemistry of catalysts containing ligands with only one oxazoline moiety has been a main subject of very recent research efforts, although first results with these compounds were already published in 1989 by Brunner and Obermann.[98] They synthesized 2-(2-pyridinyl)-2-oxazolines **90** derived from optically active amino alcohols and investigated the Rh-catalyzed enantioselective hydrosilylation of ketones using these ligands as chiral auxiliaries. In comparative studies with acetophenone **91** as substrate, optically active 1-phenyl-ethanol **92** was obtained, and the *(S)-tert*-leucinol derived ligand gave by far the highest enantioselectivities with 70.1 % e.e. in toluene and 83.4 % in CCl_4 (Scheme 42).

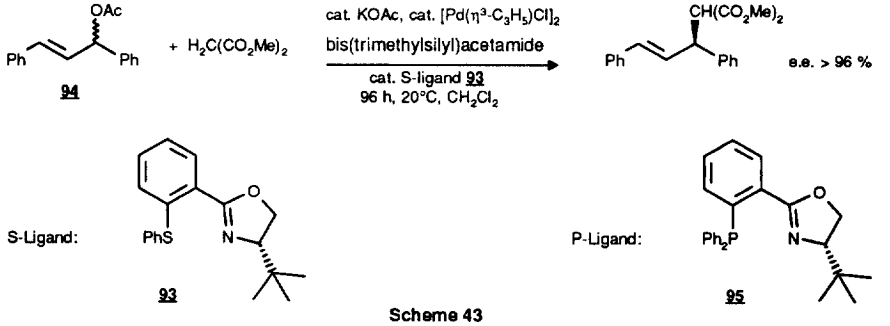


91 **92** **90**

Scheme 42

In 1993, Nicholas and coworkers reported on the preparation of 2-(hydroxyphenyl)-4-substituted-2-oxazolines derived from optically active amino alcohols designed as ligands for chiral (η^3-allyl)-Pd complexes which in turn were examined with respect to allylic functionalization.[99] The complex prepared from *(S)*-2-(2-hydroxyphenyl)-4-*tert*-butyl-2-oxazoline and $[(\eta^3$-cyclohexenyl)$PdCl]_2$ was structurally characterized by X-ray diffraction. However, in initial experiments these complexes "generally proved disappointingly unreactive toward acetic acid", tetrabutylammonium acetate and the sodium salt of dimethyl malonate.

Over the last two years, the group of Williams has published a variety of papers dealing with the suitability of P- and S-containing oxazoline ligands for asymmetric Pd-catalyzed allylic substitution.[100] For example, with *(S)*-2-[2-(phenylthio)phenyl]-4-*tert*-butyl-2-oxazoline **93**, prepared from *(S)-tert*-leucinol, e.e.-values > 96 % were achieved in the Pd-catalyzed allylic substitution of 1,3-diphenylprop-2-enyl-1-acetate **94** with dimethylmalonate, whereas the *(S)*-valinol-derived ligand afforded only 78 - 90 % e.e. (Scheme 43).[100c]

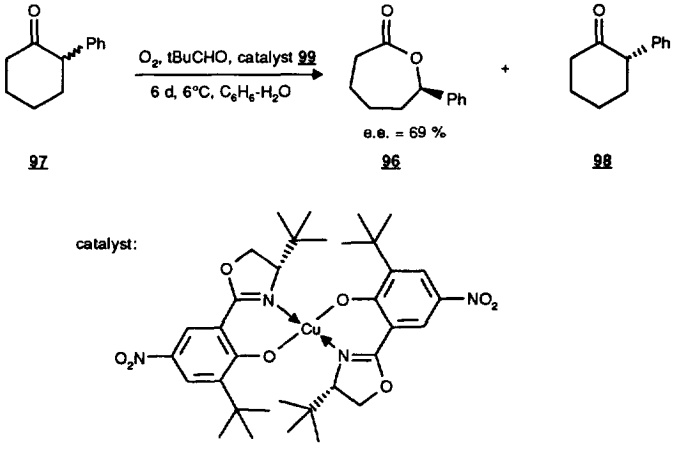


94 **93** **95**

Scheme 43

Similar results have been reported for the same reaction and catalyst system by Pfaltz and von Matt who found 94 % yield and 95 % e.e. for the P-containing *(S)-tert*-leucinol derivative **95**, 98 % yield and 98 % e.e. for the *(S)*-valinol derivative and 99 % yield and 99 % e.e. for the *(S)*-phenylglycinol based catalyst.[101] Pfaltz and Zhou investigated chiral mercaptoaryl-oxazolines as ligands in enantioselective Cu-catalyzed 1,4-additions of Grignard reagents to enones.[102] In a comparative study of the addition of n-butyl MgCl to 2-cyclohexenone, best enantioselectivities were obtained with ligands derived from *(S)*-alaninol and *(S)*-valinol (58 % e.e. & 60 % e.e., respectively) while the *(S)-tert*-leucinol-based ligand gave only poor 15 % e.e.

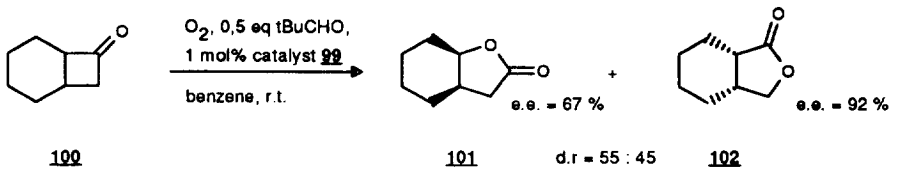
Very recently, the preparation of optically active lactones **96** by Cu-catalyzed Baeyer-Villiger-like oxidation of racemic α-substituted cyclic ketones **97** with molecular oxygen was reported by Bolm et al..[103] The remaining ketone **98** was also optically active so that the reaction corresponds to a kinetic cleavage of a racemic mixture. The best enantioselectivity (e.e. 69 %) was obtained with a catalyst **99** derived from *(S)-tert*-leucinol (Scheme 44) .



99

Scheme 44

In a subsequent investigation, the Baeyer-Villiger-type oxidation of various cyclobutanones **100** was examined using the same catalyst.[104] The reaction afforded two regioisomeric lactones with their ratio varying from 60:40 to 48:52. However, while the normal Baeyer-Villiger product **101** was obtained with 59 - 76 % e.e., the unexpected lactone **102** was formed in 92 - 95 % e.e. (Scheme 45).



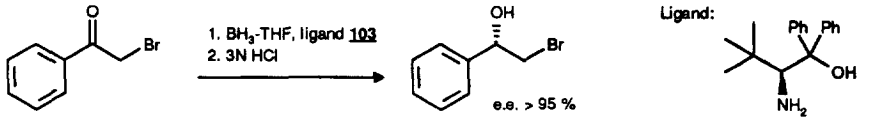
Scheme 45

The results obtained from the application of ligands with only one oxazoline moiety in metal-catalyzed asymmetric reactions are summarized in Table 2. In addition to the values for the *tert*-leucinol-derived catalysts, again the respective figures for the valinol- and phenylalaninol-based compounds are cited if available.

Table 2. Asymmetric Reactions Catalyzed by Metal-mono(Oxazoline) Complexes Derived from Optically Active *tert*-Leucinol, Valinol and Phenylalaninol

Type of Reaction	Substrate	Tle-derived ligand Yield (e.e.) [%]	Val-derived ligand Yield (e.e.) [%]	Phe-derived ligand Yield (e.e.) [%]	Ref.
Hydrosilylation	Acetophenone	90 (83.4)	85 (62.2)	95 (62.4)	98
Allylic substitution (S-containing ligand)	1,3-Diphenylprop-2-enyl-1-acetate + dimethyl malonate	92 (> 96)	96 (90)	-	100c
Allylic substitution (P-containing ligand)	1,3-Diphenylprop-2-enyl-1-acetate + Na-dimethyl malonate	99 (90)	92 (94)	96 (92)	100b
Allylic substitution (P-containing ligand)	1,3-Diphenylprop-2-enyl-1-acetate + dimethyl malonate	94 (95)	98 (98)	97 (97)	101
1,4-Grignard addition to enones	2-Cyclohexenone + n-ButylMgCl	46 (15)	67 (60)	-	102b
Baeyer-Villiger-type oxidation	2-Phenylcyclohexanone	41 (65)	57 (32)	-	103

Finally, Martens and coworkers used amino alcohols derived from *(S)*-Tle for the enantioselective catalytic borane reduction of achiral ketones.[105] With *(S)-tert*-leucinol, 85 % e.e. were achieved in the reduction of propiophenone, and *(S)*-α,α-diphenyl-*tert*-leucinol **103** afforded > 95 % e.e. in the reduction of ω-bromoacetophenone **104** (Scheme 46).



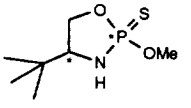
104 103

Scheme 46

5. ENANTIOMERICALLY PURE Tle AS BUILDING BLOCK OF BIOLOGICALLY ACTIVE COMPOUNDS

5.1. Insecticides

Chiral 1,3,2-Oxazaphospholidine 2-sulfides **105**, prepared from optically active amino alcohols and optically active aryl methyl phosphorochloridothionates, have shown insecticidal activity against houseflies.[106] The compounds derived from *(R)*- and *(S)*-*tert*-leucinol, however, were among the less potent substances.



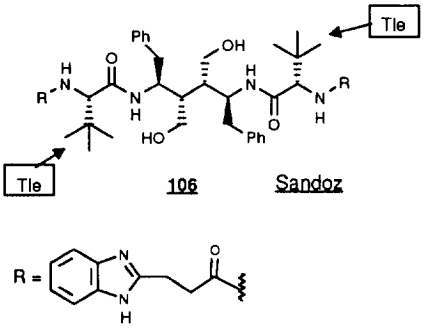
105

5.2. Pharmaceutical Applications

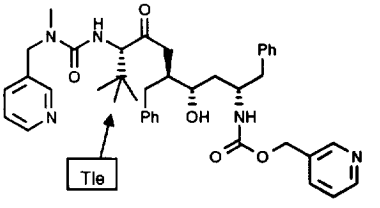
As the number of structural variations of Tle as well as the sheer number of patent applications using Tle or its derivatives is proliferating, the task of extracting relevant structures and future applications is difficult. Thus, the following selection cannot be complete and does not aim to pass judgment on chances of commercial success.

Research on antivirals shows an increasing use of Tle as component for applications such as HIV-protease inhibitors. HIV-protease is an aspartic acid protease essential for viral replication; inhibition of this enzyme leads to formation of immature, non-infectious virions[107] which renders this class of compounds promising targets for chemotherapy of HIV infections. Recent investigations demonstrate that HIV protease inhibitors are most effective for control of immunodeficiency when used in combination with reverse

transcriptase inhibitors, although even combined application is not necessarily curative but often only stops or retards progression of the disease. Most of the many different excellent inhibitors published in the literature[108,109] contain a hydroxyethylene or dihydroxyethylene replacement of the scissile amide bond of the natural substrate; phenylnorstatine[109] or an analogous structure is especially favored. To optimize enzyme inhibition (K_i) in combination with antiviral activity, numerous variations around the central dihydroxyethylene moiety were investigated at Sandoz with protected, deprotected and derivatized Val and Tle, and compound **106** was established as the most active structure which is now in clinical phase trials.[110] Abbott[111] also used Tle in its HIV-protease inhibitor **107** which is in a preclinical trial phase.



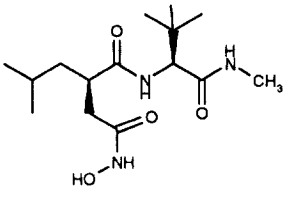
106 Sandoz



107 Abbott

During screening for orally active anti-arthritic agents, Roche identified an N-substituted Tle-N-methylamide (Ro 31-9790) **108**.[112] The structure was found to be a potent collagenase inhibitor which prevented IL-1-induced cartilage degradation in tissue culture; moreover, the structure was active in an animal model of collagen degradation.

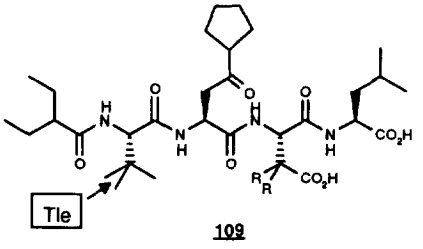
Ro 31 - 9790



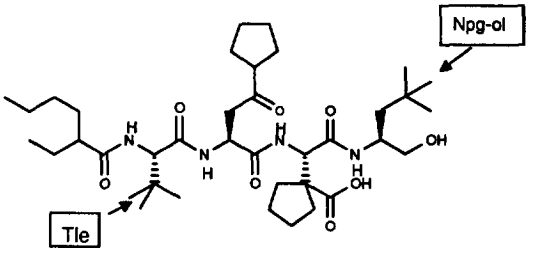
108

Herpes Simplex type viruses, responsible for genital and oral lesions, ocular diseases or encephalitis, can be fought by application of antivirals inhibiting HSV ribonucleotide reductase.[113] BioMéga/Boehringer Ingelheim[114] tested a series of different modified peptides against the known nine amino acid long C-terminal sequence of this virus. Unique structures containing Tle **109** and sometimes also *tert* leucinol or neopentylglycinol **110** were obtained with this structure-activity-related approach.[110,115] IC_{50}-values are

promising (0.6 μM for **109a** and 0.18 μM for **109b** compared to 38 μM for the original sequence), these structures are now in preclinical phases.



109



110

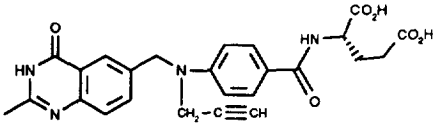
109a: R = H, IC_{50} = 0.6 +/- 0.1 μM

109b: R = CH_3, IC_{50} = 0.18 +/- 0.04 μM

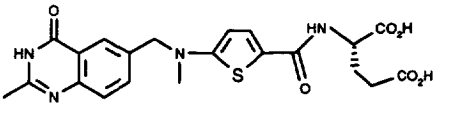
Uncontrolled degradation of cellular connective tissue by metalloproteases such as gelatinases is thought to be responsible for a variety of pathological features, with tumor metastasis as one of the most fatal examples. Celltech has developed a number of gelatinase inhibitors which might prove useful in treatment of connective tissue diseases. One of the most promising compounds found is {4-(N'-hydroxyamino)-2(*R*)-[3-(4-pyridinium)propyl]succinyl}-(*S*)-Tle amide.[116]

Thymidylate synthase inhibitors are extremely potent antitumor chemotherapy agents.[117] As tumor cells can render known inhibitors useless by acquisition of resistance to folate antimetabolites through deletion or modification of either the folate carrier or the folylpolyglutamate synthetase[118], research for compounds with potent antitumor activity but based on a different mechanism was stimulated. Among others, substitution of the glutamic acid moiety at the C-terminus (parent structures **111** and **112**) against Tle **113** showed extremely good cytotoxicity and low resistance phenomena.[113,119] However, active transport properties did not meet expectations and work was discontinued.

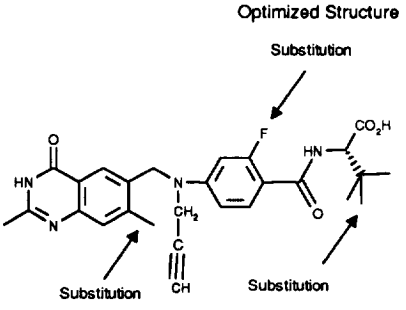
Antifolate Thymidylate Synthase Inhibitors - Parent Structures



111 ICI 198583 (IC_{50} = 0.04 μM)



112 ZD 1694 (Tomudex)



113

By isolation of depsipetide Polydiscamide A from the marine sponge *Discodermia sp.* Gulavita and coworkers found an antitumor active peptide which inhibits in vitro proliferation of the cultured human lung cancer A 549 cell line.[2c] The sequence of this peptide is Formyl-Ala-4-Br-Phe-Pro-Tle-ß-Methyl-Ile-Trp-Arg-Cys(O_3Na)-Thr-N-Me-Gln-Val-Pro-Asn.

Cholecystokinin heptapeptide analogues containing Tle or neopentylglycine (Npg) at position 5 were investigated by J. Hlavacek et al..[120] Biological activity, especially in the case of Tle substitution, was insufficient, however, therefore this modification was no success.

Despite the high failure rate of novel pharmaceutically active structures, there are and will be other Tle-containing compounds under investigation in clinical phases with exciting possibilities.

6. CONCLUSIONS AND OUTLOOK

From the above pages it is clear that Tle and its derivatives give rise to a host of applications in both the area of asymmetric synthesis as well as pharmaceutically active peptidic structures. With its *tert*iary butyl group as side chain, Tle is a unique amino acid combining hydrophobicity and sterically demanding bulkiness in the side chain with the common hydrophilic behavior of an amino acid. Nowadays, the availability of *(S)*-Tle is no longer a constraint since it is produced on large scale; with two new synthetic routes, the availability of *(R)*-Tle certainly will improve in the coming years. *(S)*-Tle today seems to be well on its way to become a regular part of any strategy seeking to modify peptides for improved pharmacological behavior. In asymmetric synthesis, a plethora of systems already exists, most of which demonstrate a higher degree of diastereo- or enantioselectivity with the *tert*-butyl derivative of the template than with any other or at least most other side chain groups. With this prospect, no doubt the importance of Tle and its derivatives will increase in the future.

ACKNOWLEDGMENTS

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