Asymmetric Syntheses with Amino Acids

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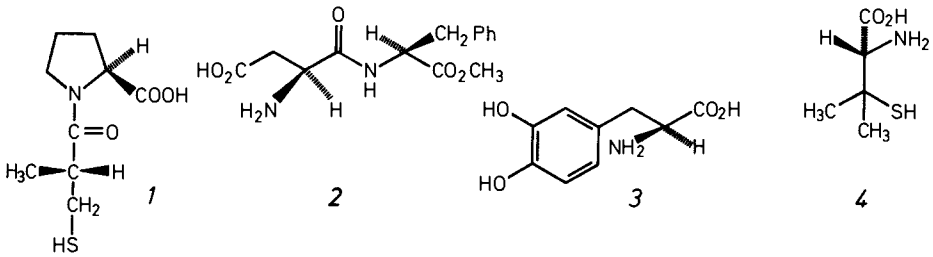
1 Introduction

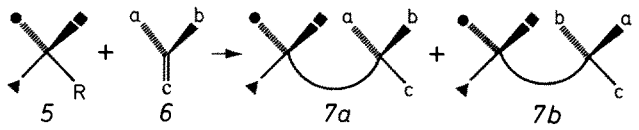
1.1 Why Asymmetric Syntheses? Definition

The synthesis of enantiomerically pure organic compounds presents a challenge to academic and industrial chemist alike. The art of organic synthesis has reached a point where it is perfectly conceivable to prepare by total synthesis many sophisticated compounds especially useful for their biological properties. For example, captoril (1) is an orally active antihypertensive agent having a unique inhibitory action on angiotensin-converting enzyme. Dipeptide (2) is a sweetening agent (aspartame) which recently appeared on the market. L-dopa (3) is active against Parkinson's disease and amino acid D-penicillamine (4) has shown favorable effects on the clinical aspects of rheumatoid arthritis. Many biologically active compounds have one or more asymmetric centers, the specific activity being related only to one stereoisomer. The drug (1) having (S,S)-configuration, for example, is about 100 times more active than the corresponding diastereomer with (R)-configuration in the side chain [1]. Other examples for molecules exhibiting different biological activities of the stereoisomers include pheromones [2], herbicides [3] etc. However, surprisingly, of the numerous drugs prepared by total synthesis that contain at least one asymmetric center, only about 20% have so far been used in sterically pure form.

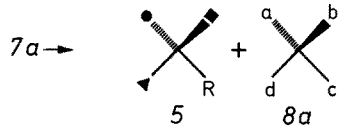


It is therefore of prime importance to be able to control the formation of asymmetric centers during the course of the synthesis. Especially delicate is the formation of the first asymmetric center in an achiral molecule. The methods of asymmetric synthesis try to solve this problem.

"Asymmetric synthesis" is a term first used in 1894 by E. Fischer and defined [4] in 1904 by W. Markwald as "a reaction which produces optically active substances from symmetrically constituted compounds with the intermediate use of optically active materials but with the exclusion of all analytical processes". A modern definition was proposed [5] by Morrison and Mosher: "An asymmetric synthesis is a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereosiomeric products (enantiomeric or diastereomeric) are formed in unequal amounts. This is to say, an asymmetric synthesis is a process which converts a prochiral [6] unit into a chiral unit so that unequal amounts of stereoisomeric products result". When a prochiral molecule

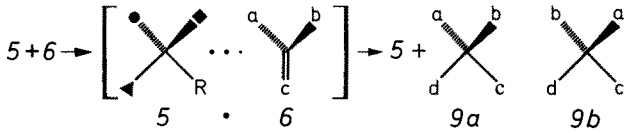


Eq. (a)



Eq. (b)

Eq. (c)



Eq. (d)

(6) reacts with a chiral reagent (5) to form a new center of chirality, two diastereomers, (7a) and (7b) [Eq. (a)], are formed. The ds value (%) is used as a measure of the diastereoselectivity of the reaction:

$$\text{ds} = \frac{[7a] - [7b]}{[7a] + [7b]} \times 100\%$$

If only one of the two diastereomers (7a) or (7b) is formed, the reaction is considered stereospecific (ds = 100%). In the subsequent course of the synthesis (7a) or (7b) may be cleaved with the formation of a new enantiomer (8a) or (8b), whereby chiral reagent (5) is either recovered [Eq. (b)] or decomposed [Eq. (c)].

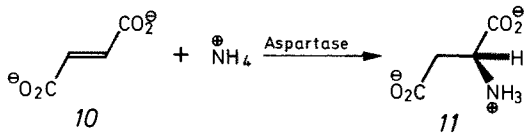
If equivalent or catalytic amounts of a chiral molecule (5) react with a prochiral molecule (6) — the complex (5) · (6) is formed as an intermediate — to give the new chiral compounds (9a) and/or (9b), one speaks of an enantioselective reaction [Eq. (d)]. The enantioselectivity of such a reaction is given by the enantiomeric excess (ee) or by the optical yield:

$$\text{ee} = \frac{[9a] - [9b]}{[9a] + [9b]} \times 100\%$$

$$\text{optical yield} = \frac{\alpha}{\alpha_0} \times 100\%$$

α = measured rotation of the product
α_0 = rotation of the pure enantiomer

By far, the best asymmetric synthesis is done in nature by enzymes [7]. These have also found industrial application [8], e.g. the stereospecific amination of fumaric acid (10) to (S)-aspartic acid (11):



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However, a considerable effort has been put forward by chemists to achieve comparable results. There is the challange to develop chemical systems as efficient as enzymic ones. For many years it had been questioned whether high optical yields could be effectively attained by organic chemists without the aid of enzymes. *However*, an increasing amount of recent results demonstrates that versatile and efficient non-enzymatic asymmetric syntheses are indeed possible.

The ever-increasing knowledge in synthetic methology for asymmetric synthesis is exemplified by the numerous reviews that have appeared in literature, in particular, the recent ones by Morrison and Mosher [5], Scott and Valentine [9], Meyer [10], Kagan and Fiaud [11], Otsuka and Tani [12], Apsimon and Sequin [13], Fischli [14], Wynberg [15], Masamune and Choy [16] and Heathcock [17]. These reviews, however, did not cover in depth the recent advances in asymmetric synthesis by chiral amino acid reagents. The enantiomerically pure educts of asymmetric syntheses, the chiral units (5), can either be prepared in the laboratory or be isolated from natural products. Thus, the chemist has at his disposal a large number of chiral units among the natural products. In particular, carbohydrates [18], terpenes [19], α-hydroxycarboxylic acids [20], alkaloids [21], biogenic amines [22] and amino acids [23] have found application as building blocks for asymmetric syntheses. A disadvantage in the use of carbohydrates, alkaloids and terpenes, which can rarely be obtained in both enantiomeric forms, does not exist in the case of α-hydroxycarboxylic acids such as lactic, mandelic, malic and tartaric acid.

In the present review we concentrate on the induction of asymmetry for the case in which the chiral reagent (5) is represented by an *amino acid* or a derivative thereof. Only those papers are considered in which the formation of a *new* center of asymmetry is induced. This can take place with the simultaneous incorporation of the chiral amino acid (or a derivative thereof) in the target molecule or by the action of catalytic amounts of this amino acid on a prochirale molecule. Reactions in which only the asymmetric center of the amino acid is modified without the stereoselective appearance of a new chiral center, have not been considered. Enzymatically catalyzed transformations [24] of molecules are not treated here.

1.2 Commercial Significance of Amino Acids

During recent years, the industrial manufacture of chiral amino acids has been actively developed throughout the world. The total amino acid market volume is estimated

at US $ 1.2 billion in 1982 [25]. Their chief consumers have been the pharmaceutical industry, the food industry, in which sodium (S)-glutamate is used as a flavour intensifier, animal husbandry, and poultry farming, where (S)-lysine and (RS)-methionine are used to increase the food value of protein feeds [26]. The (S)-amino acids used most frequently [27] are obtained by fermentation [28], extraction of protein hydrolyzates, enzymic syntheses [28], or enzymic cleavage of racemates. There are also specific production processes [29] for the nonnatural (R)-amino acids, including homogeneous asymmetric hydrogenation of N-acyl dehydroamino acids [30]. Thus, most amino acids are available in significant quantities in two enantiomeric forms. However, in most cases, the natural enantiomer is available at a lower price than the unnatural one. This is mainly the result of a small demand for these products.

An interesting relationship exists between supply and current market price of natural chiral amino acids [31]. The greater demand induces lower cost, and the lower cost stimulates the greater demand. Therefore, one can also expect lower prices for unnatural amino acids if the demand expands.

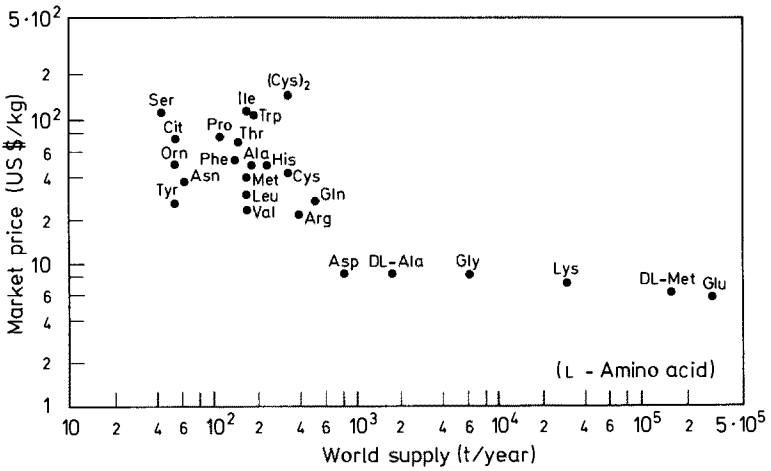


Fig. 1. Relationship between Supply and Current Market Price of chiral Amino Acids (1980)

Sources of Amino Acids

The chiral amino acids which are appropiate for use in synthesis must either be available commercially or be prepared readily from cheap precursors. Apart from the usual chemical suppliers, Ajinomoto (Tokyo, Japan), Degussa AG (Frankfurt, Federal Republic of Germany), Kyowa Hakko and Tanabe Seiyaku (both Tokyo, Japan) can offer the full range of amino acids and a number of derivatives from technical scale production.

2 Induction of Asymmetry by Catalytic Amounts of Amino Acids or their Derivatives

Although the use of enzymes as chiral catalysts will undoubtedly increase as they become more available, nonenzymic catalytic asymmetric synthesis is a very powerful tool in organic chemistry.

Until 1968, not a single nonenzymic catalytic asymmetric synthesis had been achieved with a yield above 50%. Now, barely 15 years later, no fewer than six types of reactions can be carried out with yields of 75–100% using amino acid catalysts, i.e., catalytic hydrogenation, intramolecular aldol cyclizations, cyanhydrin synthesis, alkylation of carbonyl compounds, hydrosilylation, and epoxidations.

In all reactions treated in this section the chiral educts are used only as catalysts. Thus, the reactions closely resemble an enzymatic process, i.e., an optimal process in which a small amount of chiral information is sufficient to direct a large number of molecules through the desired transformations in accordance with Eq. (d).

2.1 Homogeneous Asymmetric Hydrogenation

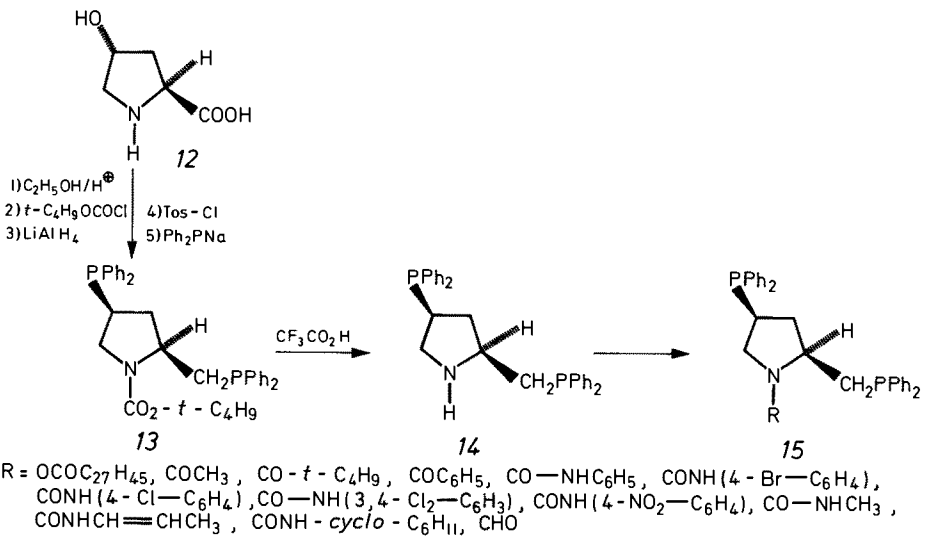
Asymmetric hydrogenation has been reviewed several times [32], and a very complete review through 1980 has appeared recently [30]. We present only the main results and new developments here.

2.1.1 Preparation of the Catalysts

Besides a considerable number of chiral Wilkinson-catalysts prepared from chiral α-hydroxy acids [33], carbohydrates [34], stereoids [35], and ferrocenylphosphines [36], many functionalized chiral biphosphanes based on amino acids have also been developed. The first optically active tertiary phosphane was synthesized in 1961 by Horner et al. [37].

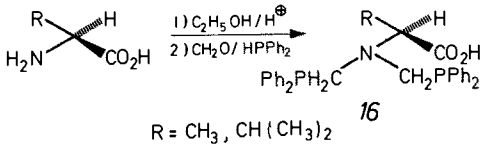
Knowles et al. [38] prepared the first chiral Wilkinson complexes with an outstanding inductive activity. The vigorous development in this area is covered by an excellent review article [39].

In 1976, Achiwa [40] synthesized the first functionalized chiral biphosphanes starting with an optically active amino acid, namely 4-hydroxy-(S)-proline (12).

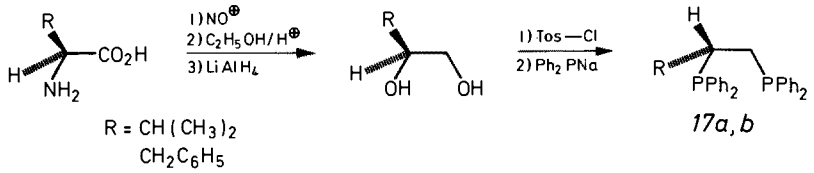


(2S,4S)-N-tert-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphino-methyl-pyrrolidine (BPPM) (13) is an excellent bisphosphane and is also the starting material for the synthesis of PPM (14). The chiral bisphosphanes (15) have been prepared by reaction of (14) with either acid chlorides or isocyanates.

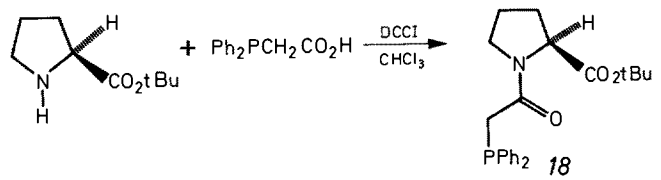
The α-amino acids (S)-alanine and (S)-valine can be converted into N,N-bis-(phosphinomethyl) derivatives (16) in a modified Mannich reaction [42].



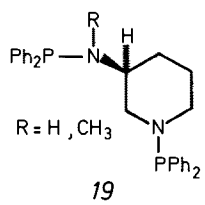
The chiral ligands (R)-Val-Phos(17a) and (R)-Phe-Phos (17b) have been synthesized from (S)-valine and (S)-phenylalanine, respectively, in an industrial laboratory [43].



Chiral, N-substituted diphenylphosphinoacetamides (18) were prepared by the acylation of (S)-amino acid esters with diphenylphosphinoacetic acid [44].



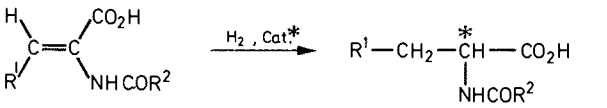
New aminophosphines (19) were obtained from (S)-ornithine recently [45].



Takeuchi and Ohgo have reported a less stereoselective catalyst system based on (S)-N-methylproline [46].

2.1.2 Homogeneous Asymmetric Hydrogenation of C=C Double Bonds

In recent years, asymmetric hydrogenation of prochiral olefins, using rhodium (I) complexes with chiral phosphine ligands as catalysts, has been extensively investigated. Namely the asymmetric hydrogenation of α-acylaminocinnamic acid or α-acylamino-acrylic acids for obtaining optically active N-acyl-α-amino acids (20) has found interest [47]. In this reaction it is especially gratifying to see that e.e. 80—99% could be obtained [40, 41, 43, 45, 48] employing rhodium (I) complexes formed from $[Rh(COD)Cl]_2$ (COD = cyclooctadiene) and the chiral phosphines (13–19). L-Dopa (3) is now manufactured by such a process [38]. This represents the first nonenzymic industrial asymmetric synthesis.



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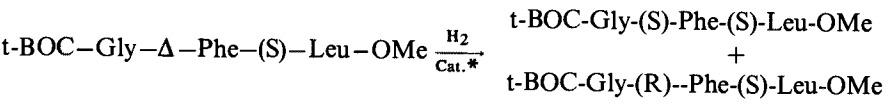
R^1 = H, alkyl, aryl R^2 = CH_3, $OCH_2C_6H_5$, C_6H_5

It has recently been demonstrated that a *stereoselective synthesis of dipeptides* by hydrogenation of the corresponding monodehydropeptides (N-protected free acids or methyl esters) is possible. In this reaction, chiral catalysts, for example BPPM (13), in the form of a Wilkinson complex have been used. These are superior to the corresponding DIOP complexes (DIOP = P,P'-[2,2-dimethyl-1,3-dioxolane-4,5-bis(methylene)] bis(diphenylphosphane). A d.s. value of 90—99% was generally obtained [49].

Dehydropeptides (21) were employed for the asymmetric hydrogenation, catalyzed by chiral rhodium complexes of the hydroxyproline derivative (13). It was reported that the stereoselectivity is satisfying (ds = 90–95%) [50].



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Stereoselective Hydrogenation of Other Prochiral Olefins

Optical yields are always low in asymmetric reduction of simple olefins where no polar groups are close to the double bond [41a, 51].

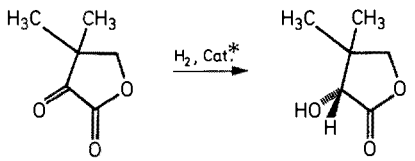
2.1.3 Homogeneous Asymmetric Hydrogenation of C=O Double Bonds

Carbonyl groups are not reduced with classical Wilkinson catalysts. However, some cationic rhodium complexes show catalytic activity [52]. There are only a few examples of asymmetric hydrogenation of ketones. Addition of base to a neutral rhodium complex is also a way to produce a catalyst for ketone reduction [44]. Acetophenone

was hydrogenated with low enantioselectivity, using rhodium complexes of (S)-proline derivative (18) [44].

Especially high optical inductions have been achieved with catalysts which contain BPPM (13), PPM (14) or (15) as chiral ligands. Pyruvic acid esters were usually hydrogenated to lactic acid esters in quantitative chemical yield with an enantiomeric excess of 65–75% [41a,53]. However, this method is not of technical significance, since chiral lactic acid derivatives may be produced more conveniently by biotechnological processes.

(R)-(—)-Pantolactone (22), a key intermediate for the preparation of the vitamin pantothenic acid, has been obtained with high stereoselectivity (e.e. = 87%) by the asymmetric hydrogenation of the corresponding ketopantotyllactone in the presence of a rhodium complex of BPPM (13) [54].



22

A smaller e.e. value is obtained with Rh-(14) and Rh-(15) [54] in this reaction. Moreover, in one case the undesired enantiomer of (22) is obtained.

2.2 Heterogeneous Asymmetric Hydrogenation

Nickel and other transition metal catalysts, when "modified" with a chiral compound such as (R,R)-tartaric acid [55], become enantioselective. All attempts to modify solid surfaces with optically active substances have so far resulted in catalysts of only low stereoselectivity. This is due to the fact that too many active centers of different structures are present on the surface of the catalysts. Consequently, in asymmetric hydrogenations the technique of homogeneous catalysis is superior to heterogeneous catalysis [56]. However, some carbonyl compounds have been hydrogenated in the presence of tartaric-acid-supported nickel catalysts in up to 92% optical purity [55].

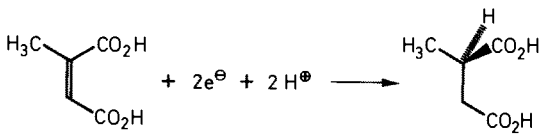
An excellent review of the problems of the enantioselective heterocatalytic hydrogenation of prochiral double bonds, covering the literature up to 1970, has been compiled by Izumi [57]. Raney nickel catalysts modified with chiral amino acids or dipeptides gave only very moderate enantiomeric excesses of between 0 and 10% in the hydrogenation of olefins, carbonyl compounds or oximes [57]. Only Raney nickel modified with (S)-tyrosine furnished a higher enantiomeric excess in the products [58].

2.3 Electrochemical Asymmetric Syntheses

Pioneer work in the field of electrochemical asymmetric synthesis was done by Gourley et al. [59] using optically active alkaloids as chiral auxiliaries. Afterward,

Miller and his co-workers [60] reported surprisingly high optical yields, close to 50%, in the reduction of 2-acetylpyridine in the presence of strychnine. They also prepared chemically modified electrodes with optically active amino acids and attempted asymmetric induction in both reduction and oxidation [61]. The best optical yield, only 14.5%, seemed to be obtained in the reduction of 4-acetyl-pyridine on a graphite cathode modified with (S)-phenylalanine methyl ester.

Nonaka et al. [62] examined the asymmetric reduction of open-chain olefins in the presence of optically active amino acids. In the best case (R)-methylsuccinic acid (23) was formed in 2.4% and 53% optical and chemical yields, respectively, from citraconic acid (24) in the presence of (R)-cysteine.



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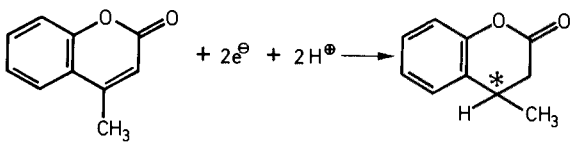
As reported in 1983, the same group was able to improve the optical yield of the reduction of (24) to 25%, while carrying out the electrochemical reduction at a poly-(S)-valine-coated graphite cathode [63]. In the reduction of 4-methylcoumarin (25) on this cathode an optical yield of 43% was achieved; the (S)-configurational enantiomer (26) was formed in excess [63].



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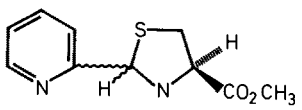
2.4 Enantioselective Hydrosilylation [64]

Acetophenone was enantioselectively hydrosilylated using a catalyst prepared from $[(COD)Rh\ Cl]_2$ and the (R)-cysteine derivative (27). (27) is the condensation product of (R)-cysteine methyl ester and 2-pyridinecarboxaldehyde.



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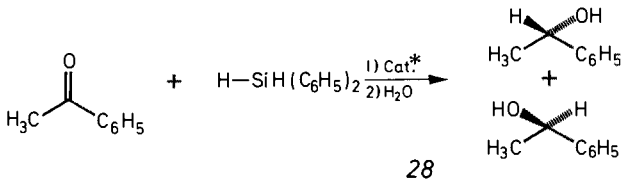
The enantioselective hydrosilylation is carried out between −20 and +20 °C; 1-phenylethanol (28) is obtained in 98% chemical yield with an e.e. value of 87%. The inductive power of the catalyst system [(COD)Rh Cl]$_2$/(27) (Rh: (27) ≈ 1:13) is surprising, since (27) was only obtained as a mixture of two diastereomers (58:42), according to ^{1}N-NMR-data.



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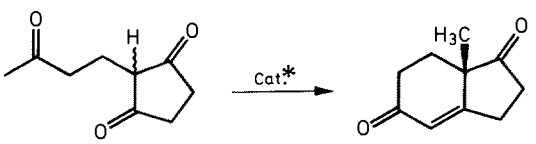
The main product is always the (R)-enantiomer of (28) [64]. Employing other chiral catalysts, e.g. Schiff bases prepared from (S)-alaninemethyl ester or (S)-valinemethyl ester and 2-pyridinecarboxaldehyde in form of their rhodium complexes, in the same reaction, no or only very low asymmetric induction was observed.

2.5 Asymmetric Aldol Addition

The efficient asymmetric intramolecular aldolization of certain triketones with a reflective symmetry axis using chiral amino acid catalysts has been reported with a view at obtaining optically active steroids.

Starting with the fundamental work of Wiechert et al. [65] and Hajos et al. [66], more than 15 amino acids have so far been used as chiral auxiliaries. It is remarkable that in most cases catalysts of the (S)-series, to which most natural α-amino acids belong, induce (S)-configuration. Chiral auxiliaries of the (R)-series, on the other hand, lead predominantly to products having an (R)-configuration.

Most workers in the field have investigated the asymmetric cyclization of 2-methyl-2-(3-oxobutyl)-1,3-cyclopentadione (29). The resulting enedione (30) was used as the C,D-unit in the total syntheses of steroids having a natural configuration [67]. With (S)-proline, (30) was obtained with an enantiomeric excess of 95% in almost quantitative chemical yield [67d].



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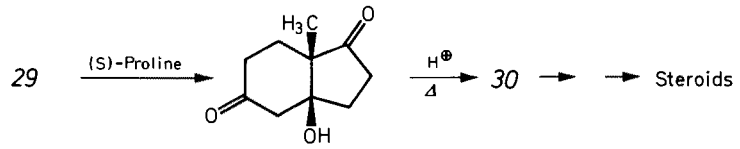
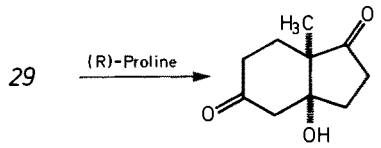
Hajos and Parrish [66] have shown that in the presence of only 3 mol-% of (R)- or (S)-proline in DMF at room temperature (29) is converted into the aldols (31a)

and (31b), respectively. These readily eliminate water upon heating with p-toluenesulfonic acid in benzene.



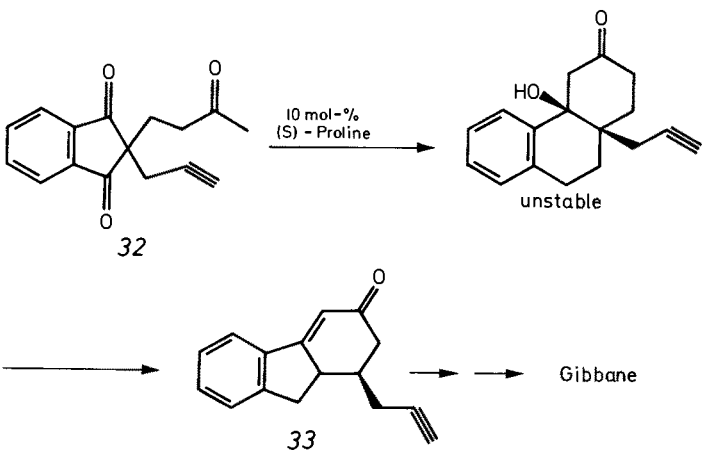
31a



31b

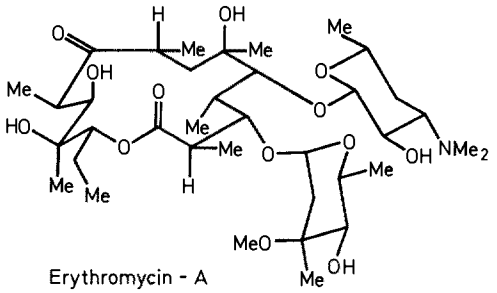
The best chemical and optical yields in the above reactions are obtained by using (S)- or (R)-proline. Some 19-norsteroids are prepared on an industrial scale from products of intramolecular aldol additions catalyzed by (S)-proline [68].

Takano et al. [69] exploited the asymmetric aldolization for the synthesis of more functionalized chiral products which possess units suitable for the construction of certain tetracyclic triterpenes, such as gibberellins and kaurenes. They described the enantioselective synthesis of the tricyclic enone (33) from the symmetric triketone (32) and its conversion into the gibbane framework. Again, (S)-proline was used as the catalyst.

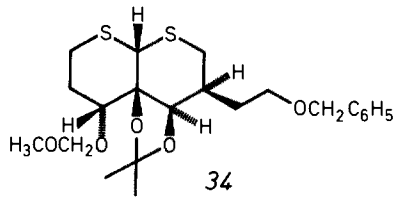


In his 1956 article in "Perspectives in Organic Chemistry", the late Professor R. B. Woodward characterized the macrolide antibiotic erythromycin as a synthetic challenge which is ". . . quite hopelessly complex, especially in view of its plethora of asymmetric centers" [70]. Twenty-five years after making this dismal prognosis,

R. B. Woodward and forty-eight coworkers have overcome this obstacle by using an ingenious strategy.



The dithiadecalin (34) was used to provide the carbon backbone for C-3 to C-8 and C-9 to C-13. Compound (34) was obtained in an optically active form by a route involving an enantioselective (36% e.e.) aldol cyclisation catalyzed by (R)-proline [71].

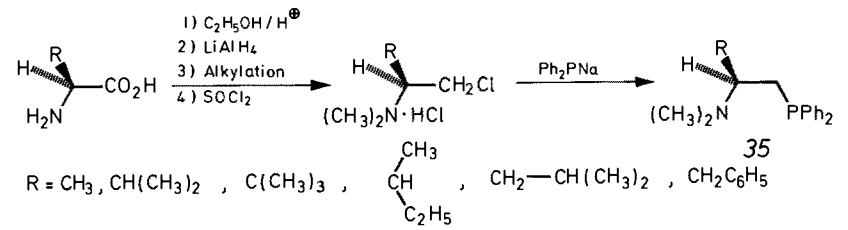


34

Until 1968, not a single nonenzymic catalytic asymmetric synthesis had been achieved with an enantiomeric excess above 50%. Now, the intramolecular aldol cyclisation, catalyzed by chiral amino acids has proven to be a very useful synthetic tool. This reaction was extensively covered by two reviews [23,68]. Two more papers [72], published recently, should also be cited.

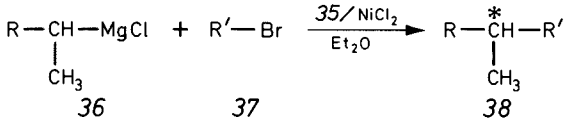
2.6 Asymmetric Grignard Cross-Coupling Catalyzed by Chiral Phosphine-Nickel Complexes [73]

Hayashi et al. [74] described a process of kinetic resolution in the coupling of Grignard reagents R*Mgx (having a chiral center at the point of attachment to the metal) with various alkenyl halides under the influence of chiral phosphine-nickel complexes. Chiral amino acid derivatives (35) were used as ligands.



35

The reaction of 1-phenylethyl-, 2-octyl-, and 2-butyl-magnesium chloride (36a, b, c) with vinyl bromide (37a), (E)-β-bromostyrene (37b), 2-bromopropene (37c), and bromobenzene (37d) was carried out in the presence of 0.5 mol-% of a nickel catalyst prepared in situ from nickel chloride and the chiral ligand (35).



36 37 38

R = C_6H_5, n-C_6H_{13}, C_2H_5

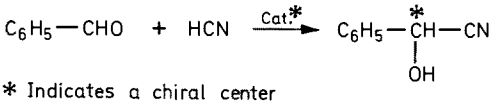
R′ = $CH{=}CH_2$,  , C_6H_5, $C(CH_3){=}CH_2$, C_6H_5

* Indicates a chiral center

The products (38) where obtained with relatively high stereoselectivity (in some cases e.e. $\geqq 80\%$).

2.7 Asymmetric Cyanohydrin Syntheses

Chemists in Japan have studied an asymmetric cyanohydrin synthesis: addition of hydrogen cyanide to benzaldehyde using synthetic peptides as catalysts [75].



* Indicates a chiral center

This reaction is known to be catalyzed by the enzyme oxynitrilase to produce the optically pure cyanohydrin [76]. Since this reaction proceeds with a base catalyst, Jnoue et al. [75] used cyclic and linear dipeptides containing (S)-histidine. The catalysts employed are as follows: benzyloxycarbonyl-R-(S)-histidine methyl ester with R = (S)-alanyl, (R)-alanyl, (S)-phenylalanyl,[Z-(S)-Ala-(S)-His-OCH_3, Z-(R)-Ala-(S)-His-OCH_3, and Z-(S)-Phe-(S)-His-OCH_3] as linear dipeptides, and cyclic (S)-histidine containing dipeptides Gly—(S)—His,

(S)—Ala—(S)—His, (R)—Ala—(S)—His, (S)—His—(S)—Phe, and

(S)—His—(S)—His.

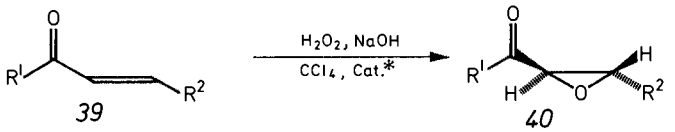
When (S)—His—(S)—Phe was used in a mole ratio to benzaldehyde of about 1/50, the enantiomeric excess of mandelonitrile was very high (90%, rich in (R)) in the early stage, but decreased with reaction time.

In sharp contrast, the corresponding linear dipeptide Z-(S)-Phe-(S)-His-OCH_3 exhibited only very low stereospecificity (0.6% e.e., rich in (S)) in the addition of

hydrogen cyanide to benzaldehyde. Thus, the rigid structure of the 2,5-piperazinedione ring of the cyclic dipeptide is very important for the asymmetric addition. The flexible linear dipeptide is disadvantageous [75].

2.8 Enantioselective Epoxidations

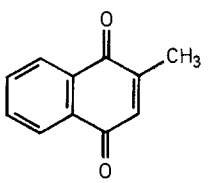
The asymmetric epoxidation of several chalcones (39) and other electron-poor olefins in a triphase system (water/organic solvent/chiral polyamino acid) afford optically active oxirans with optical yields of up to 96%. The influence of the molecular structure of the catalysts and substrates, the solvent, and the temperature on the stereochemistry was investigated by a group of chemists from Italy and Spain [77].



39 40

R^1, R^2 = phenyl or substituded aryl

The epoxidation of (39) generally occurs with good chemical conversions and high optical yields [77]. When poly-(S)-alanine is employed as chiral catalyst, the reaction is practically stereospecific. Similar good results were obtained with poly-(S)-leucine and poly-(S)-isoleucine, whereas poly-(S)-valine not only reduces the chemical yields, but also greatly affects the asymmetric synthesis. Both poly-(S)-phenylalanine and the dipeptide (S)-Ala-(S)-Ala give almost racemic oxiranes (40). The structure of the substrate also plays an import role in determining the amount of asymmetric induction. Poly-(S)-amino acids are much less effective catalysts in the epoxidation of systems other than chalcone (39) and other related electron-poor olefins, such as 2-methyl-1,4-naphthoquinone (41) and 1-phenyl-2-nitro-propene (42).



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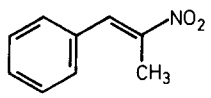
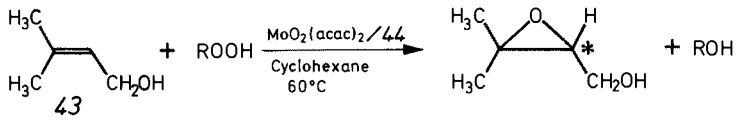


42

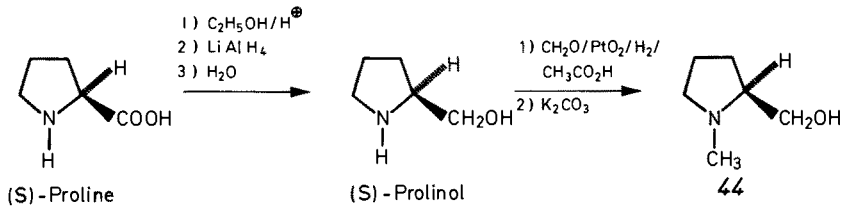
Enantioselective epoxidation of allylic alcohols using hydrogen peroxide and chiral catalysts was first reported for molybdenum [78] and vanadium [79] complexe. In 1980, Sharpless [80] reported a titanium system. Using a tartaric acid derivative as chiral auxiliary it achieves almost total stereoselection in this reaction.

During the investigation of the molybdenum-catalyzed epoxidation of the allylic alcohol (43) mediated by a chiral (S)-proline derivative (44). S. Coleman-Kammula

and E. Th. Duim-Koolstra observed that the stereoselectivity decreased with increasing conversion.



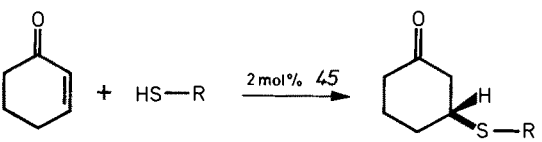
The ligand (S)-N-methylprolinol was used in a 2:1 molar ratio to the $MoO_2(acac)_2$ catalyst (1 mol % on the allylic alcohol (43) in the epoxidation of 3-methyl-2-buten-1-ol (43) with cumene hydroperoxide in cyclohexane solvent.



The chiral ligand (44) was prepared starting from the cyclic α-amino acid (S)-proline [80]. Recently, similar chiral catalysts and related molybdenum complexes involving optically active N-alkyl-β-aminoalcohols as stable chiral ligands and acetylacetone as a replaceable bidentate ligand, were designed for the epoxidation of allylic alcohols with alkyl hydroperoxides which could be catalyzed by such metal complexes [81].

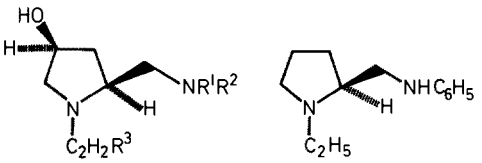
2.9 Enantioselective Michael Addition of Thiols to 2-Cyclohexen-1-one

Chiral aminoalcohols (45), derived from (2S, 4S)-4-hydroxyproline and (S)-proline, respectively, were found to be superior catalysts for the enantioselective 1,4-addition of arylthiols to 2-cyclohexen-1-one to yield 3-arylthiocyclohexanones (46) [82].



In the best case the optically active adduct (46) was obtained in 88% optical yield. The ketone (46) was made optically pure when recrystallized twice from pentane.

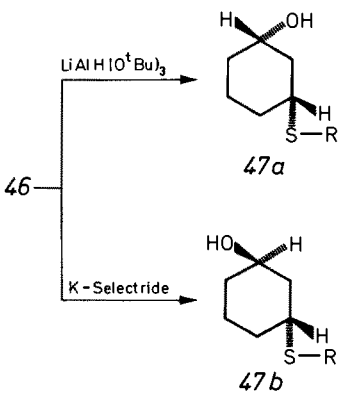
The same authors [83] used the chiral ketone (46) as substrate for the preparation of optically active cyclohexanol derivatives (47) which may be useful intermediates in the synthesis of chiral natural products, such as (—)-mesenbranoene, (+)-2-carene etc.



45a 45b

R^1 = H, CH_3
R^2 = Aryl, Cyclohexyl
R^3 = H, C_2H_5

It is noteworthy that (47a) was obtained almost exclusively (e.e. = 96%) by employing $LiALH(O^+Bu)_3$, while (47b) was obtained by reduction with K-selectride in 92% e.e. [83].



47a 47b

3 Stoichiometric Asymmetric Syntheses

In the preceding Section we considered the catalytic asymmetric synthesis. In this connection the induction of asymmetry by catalytic amounts of "chiral information" (= amino acids or their derivatives) was treated. The chiral information was transferred into a prochiral substrate.

In Section 3 we turn to reactions which require at least equimolar amounts of chiral information for the induction of asymmetry in the products. The newly formed asymmetric center can be induced by either intramolecular or by intermolecular interactions. Having served its stereochemical purpose, the amino acid moiety may be destroyed so that it does not exist as a discrete entity in the product, although sections of it may survive.

In another case the amino acid is used as a chiral reagent in stoichiometric amounts. Thus, the reagent is preferably recovered and recycled.

We do not address the chiral template method in this article.

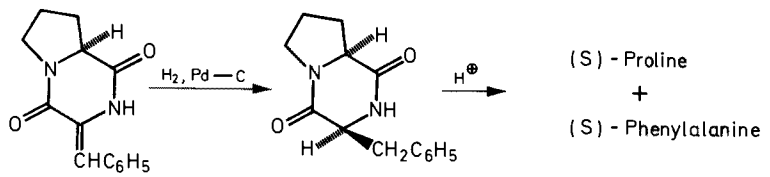
3.1 Hydrogenations

3.1.1 Asymmetric Hydrogenation of C=C Double Bonds

If an asymmetric hydrogenation of C=C bonds is desired in the presence of achiral catalysts, chiral information is required to be present in the substrate. Peptides and cyclopeptides containing dehydroaminos acid units are very good substrates achieving quite high stereoselectivities upon asymmetric hydogenation on 10% Pd-C or other achiral catalysts [49a, 84].

The optical yields have been as high as 61% for the hydrogenation of open-chain dehydrogeneous or heterogeneous phase.

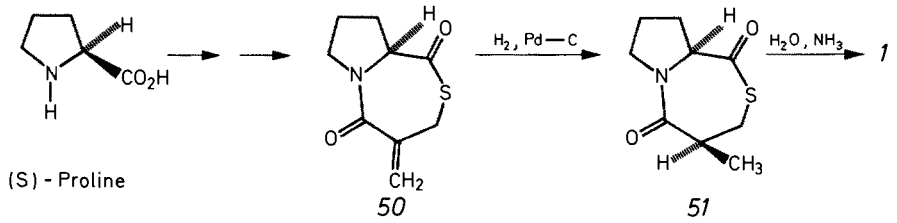
However, excellent optical yields have been obtained for the hydrogenation of cyclodipeptides. As early as 1944, M. Bergmann and J. E. Tietzmann [84m] obtained the diketopiperazine of (S)-phenylalanyl-(S)-proline (49), while hydrogenating dehydrophenylalanyl-(S)-proline diketopiperazine (48).



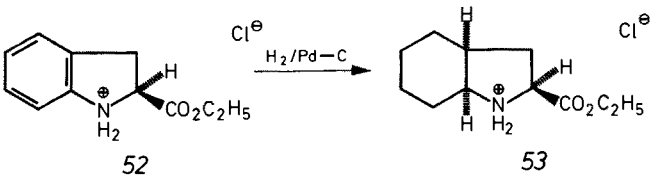
48 49

Hydrolysis of the resulting (S,S)-cyclodipeptide (49) (e.e. >90%) affords (S)-phenylalanine and the chiral inductor (S)-proline [84h].

Captopril (1), an approved antihypertensive drug, was prepared from (S)-proline. The key step in an elegant asymmetric synthesis of (1) was a hydrogenation of (50) to give (51) which is hydrolyzed to afford (1) [85].

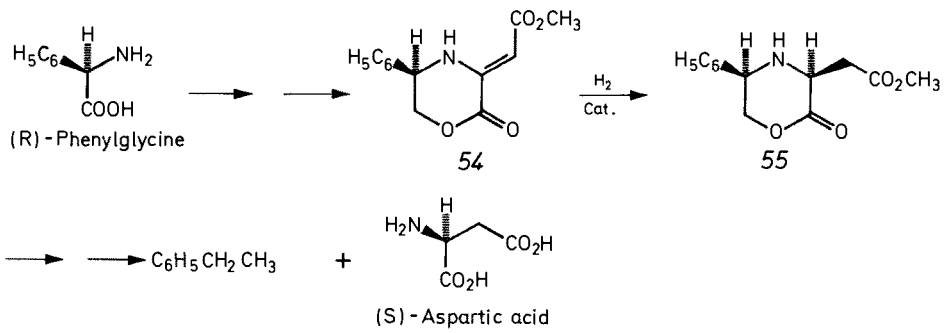


(S)-2-carbethoxy indolene hydrochloride (52) was catalytically hydrogenated (Pd-C) in ethanol to (2S, 3aS, 7aS)-2-carbethoxy perhydroindole hydrochloride (53) which was purified by crystallization [86]. (53) was used in the synthesis of a potent inhibitor of the angiotensin converting enzyme.



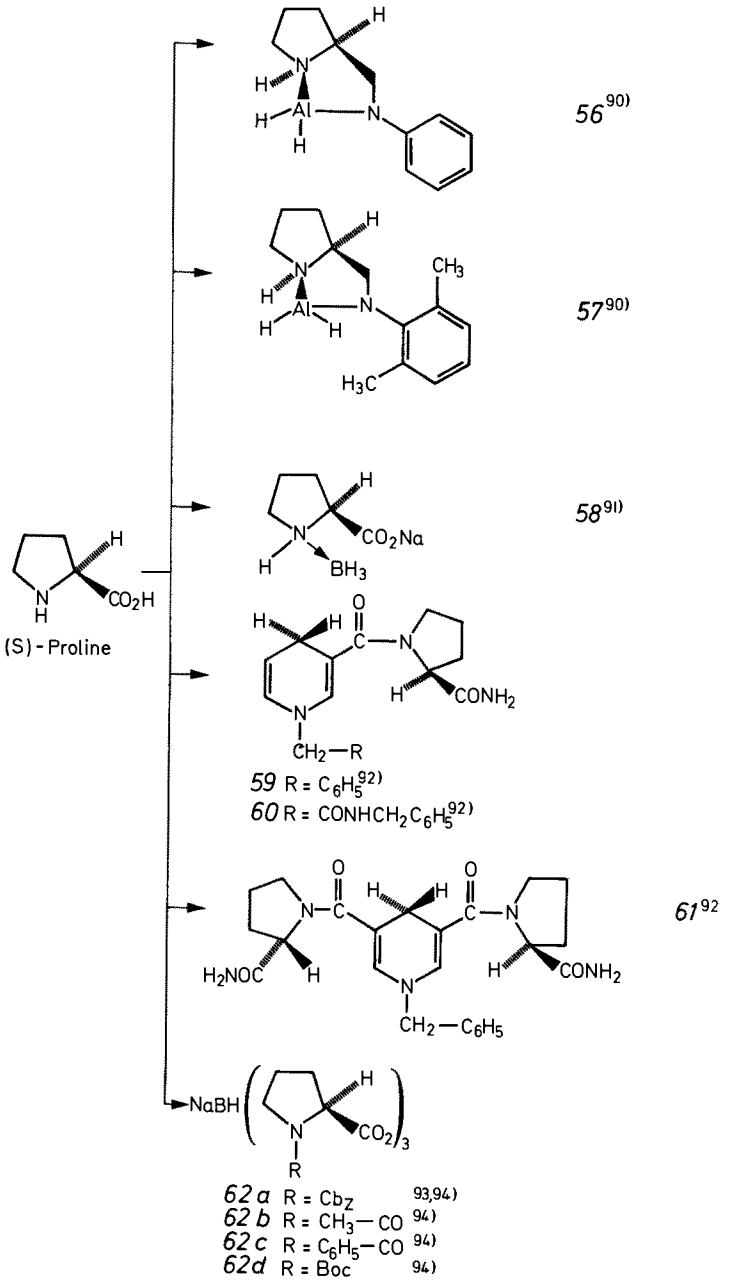
Stereoselective addition of hydrogen to a C=C double bond of an (S)-proline derivation was applied in the total synthesis of gephyrotoxin, a biologically active alkaloid [87]. Optically active pyrrolizidine bases have been synthesized by Robins and Sakdarat [88] from chiral hydroxyproline derivatives by hydrogenation (ds > 60 %).

In the asymmetric hydrogenation of the (R)-phenylglycine derivative (54) in the presence of an achiral catalyst the stereoselectivity was reported [89] to be low. The lactone (55) could subsequently be converted into (S)-aspartic acid [89]. This reaction sequence is an example of the intramolecular transfer of chirality with subsequent disappearance of the original chiral center.

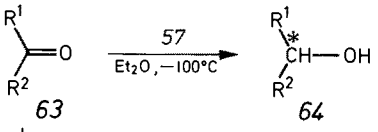


The reducing agents (*56*) to (*62*), derived from (S)-proline, are eminently suitable for the hydrogenation of prochiral CN and CO double bonds.

The prochiral ketones (63) were reduced with (57) at low temperature in high chemical (82–97%) and optical (31–96%) yields [90] to the (S)-alcohols (64). The chiral precursor or (57) can be recovered.



When the ketone (65) was treated with the chiral reagent produced by decomposing $LiAlH_4$ with (S)-2-(anilinomethyl) pyrrolidine, the alcohol (66) obtained in 60% yield. The optical yield could be determined as 62% e.e. [95].



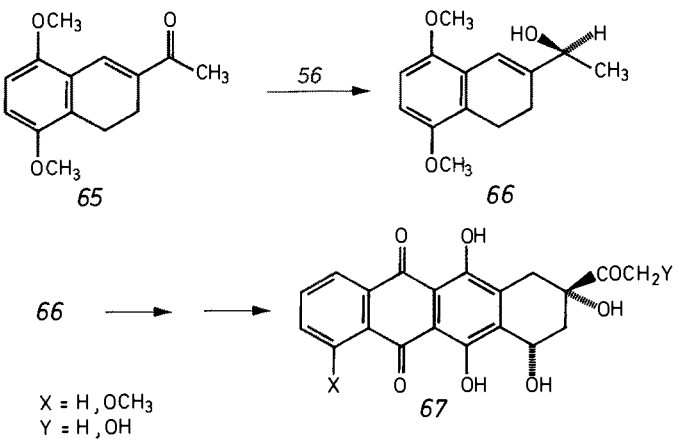
63 64

R^1 = n - C_6H_{13}, $CH_2C_6H_5$, C_6H_5
R^2 = CH_3, C_2H_5, i - C_3H_7

The chiral alcohol (66) is a valuable intermediate for the asymmetric synthesis of optically active anthracyclinones (67). These aglycones of anthracycline antibioties are currently attracting much attention because of their promising anticancer activities.

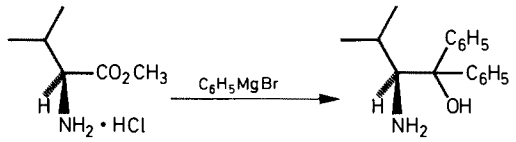
(58) reduces aryl alkyl ketones as well as prochiral dialkylketones to the corresponding chiral alcohols in chemical yields of 66 to 92% and optical yields of up to 62% [91].

High stereoselectivities (94–100%) are attained in the reduction of aromatic ketones by use of a new chiral borane complex with (S)-2-amino-3-methyl-1,1-diphenylbutan-1-ol,(S-68) readily prepared in two steps from (S)-valine, in an experimentally convenient procedure [96]. (S)-Valine methyl ester hydrochloride was converted with excess of phenylmagnesium bromide into (S-68). The same treatment of (R)-valine gave (R-68). In a typical asymmetric reduction the reagent, prepared from (S-68) and borane, and the ketone (69) in tetrahydrofuran were kept at 30 °C for some hours. The corresponding alcohols were obtained in high optical purity. (S-68) could be recovered to more than 80% without racemization [96].



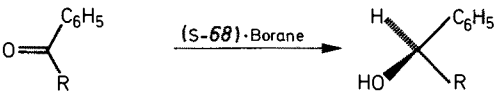
It is of particular interest that the borane complex of (S-68) produces the (R)-alcohol, while the reversed stereoselectivity with the same degree of asymmetric induction

was achieved by use of the reagent from (R-68). Since both (S-68) and (R-68) are readily accessible from the corresponding amino acids (S)-valine and (R)-valine, respectively, this method allows both enantiomers of secondary alcohols to be synthesized readily from aromatic ketones.



(S)-Valine methyl ester hydrochloride

S-68

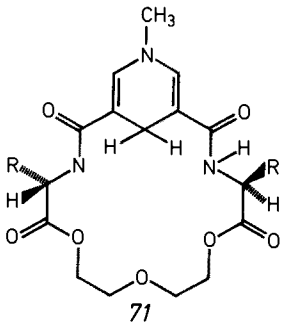


69

70

R = CH_3, C_2H_5, n-C_3H_7, n-C_4H_9

A number of chiral macrocyclic crown ligands have been synthesized by using amino acids as the chiral natural source. Thus, macrocyclic compounds which have a 12-, 15-, or 18-membered ring have been prepared from α-amino acids to introduce chirality into their rings or the side chains [97]. Most chiral crowns derived from amino acids have not as yet been evaluated for their ability to effect chiral recognition or act as catalysts. Kellog [97a] used the dihydropyridine crowns (71) to cause asymmetric reduction of a number of aromatic ketones. Optical yields as high as 86% have been achieved using these macrocycles.

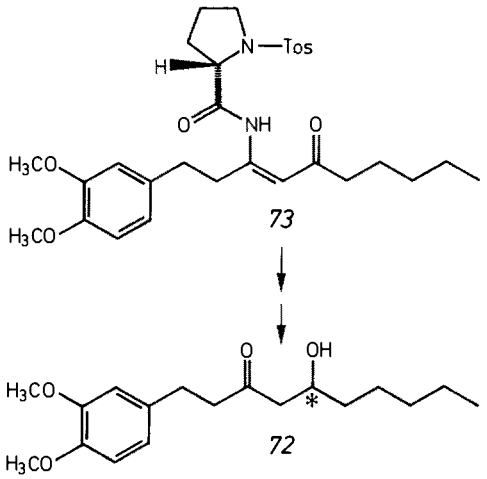


71

Recently, Inouye et al. [92] reported that NADH model compounds (59, 60, 61) carrying one or two (S)-prolinamite moieties as the asymmetric center showed virtually complete stereoselectivity in the asymmetric reduction of several ketones.

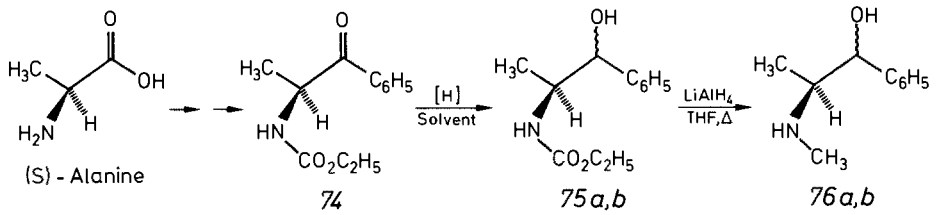
The natural product (+)-(S)-gingerol (72) was synthesized using 3,5-disubstituted

isoxazole as masked β-keIol. Reductive fission of the labile N—O bond of the isoxazole gave an enamino-ketone which was converted into the vinylogous imide (73) using N-tosyl-(S)-prolyl chloride. Reduction of (73) gave (72) in 30–40% optical yield [98].



α-N-Acylamino acids have been developed as useful reagents for the preparation of optically pure α-aminoalkyl aryl ketones. Protection of the amino group as the ethoxycarbonyl derivative (74) [99] allows (S)-alanine to serve as an effective educt for the asymmetric synthesis of a variety of structures containing the phenylethylamine backbone. Thus, N-acyl-(S)-alanine chloride undergoes Friedel-Crafts acylation.

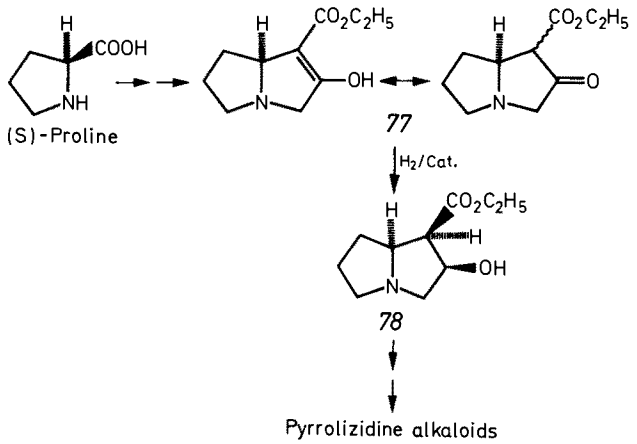
Table 1. Reduction of (S)-2-[(Ethoxycarbonyl)amino]propiophenone (74) to Ephedrine (75a) and Pseudoephedrine (76b)



Reducing agent [H]	Solvent	Ephedrine *75a* / Pseudoephedrine *76b*
$NaBH_4$	CH_3OH	4 : 1
$LiAlH_4$	THF	4 : 1
Li selectride	THF	1 : 1
Pd - C/H_2	C_2H_5OH	2 : 1

These intermediates were used to synthesize optically pure ephedrines and amphetamines without recourse to resolution, since the chirality of the amino acid educt was entirely conserved throughout the process. The reduction of (S)-2-(ethoxycarbonyl)amino-propiophenone (74) first produced a mixture of alcohols (75a, b) [99]. Lithium aluminium hydride reduction then produced the desired secondary amino alcohols (76a, b). Table 1 illustrates the reduction scheme and the diastereomer ratios obtained [99].

Dieckmann cyclization of (S)-N-2-di(carboethoxymethyl)pyrrolidine, made from (S)-proline, produced (8S)-1-carboethoxypyrrolizidin-2-one (77). Upon catalytic hydrogenation, (78) was obtained as the main product in high diastereoselectivity [100].

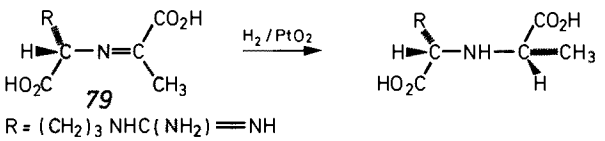


(78) serves as a key intermediate in the synthesis of (—)-isoretronecanol, (—)-trachelanthamidine, (—)-supinidine, and other pyrrolizidine alkaloids [100].

A related asymmetric reduction directed by a chiral center from a (S)-proline moiety was reported by Budzikiewcz et al. earlier [101].

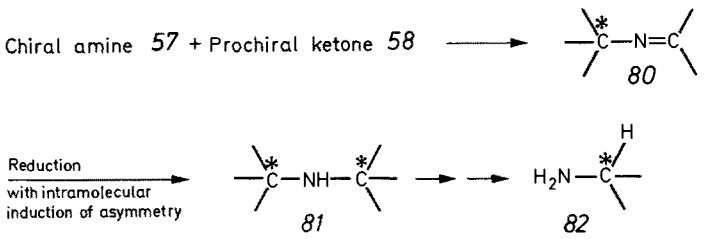
3.1.3 Asymmetric Hydrogenation of C=N Double Bonds

Knoop and Martius [102a] reported the asymmetric hydrogenation of the Schiff base obtained from (S)-arginine and pyruvic acid as early as 1939.

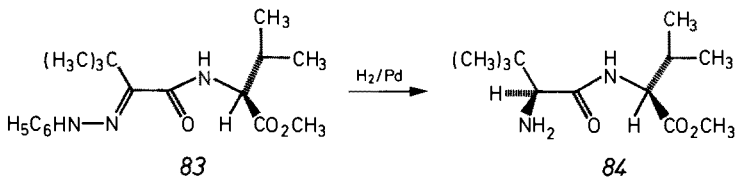


The asymmetric transamination from chiral α-amino acids [102] and amino acid derivatives (57) (esters [86, 103], amino alcohols [104]) to carbonyl functions in prochiral substrates (58) (α-keto acids [102], α-keto esters [86, 103], ketones [103b, d] was described

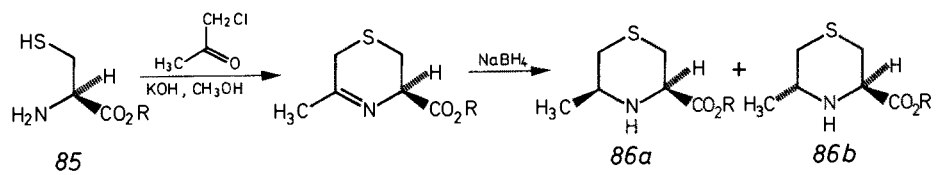
in many papers. In each case, a Schiff base (80) is an intermediate. The optical yield in the reduction was as high as 87% and was measured either from compounds (81) or (82).



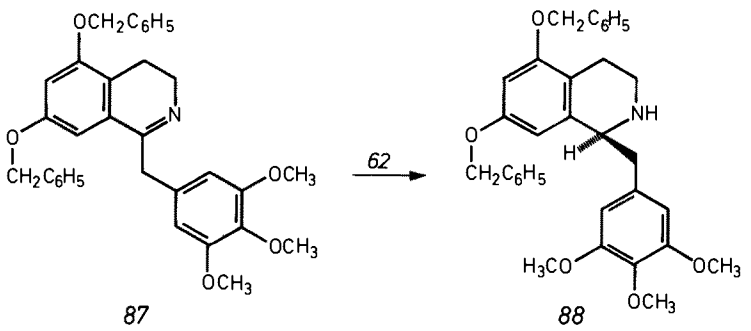
The asymmetric hydrogenation of the phenylhydrazone of methyl-N-(3,3-dimethyl-2-oxobutanoyl)-(S)-valinate (83) was investigated using palladium catalysts [105]. The absolute configuration of the newly formed t-leucine moiety in (84) was found to be (S). The diastereoselectivity in the hydrogenation step was shown to be as high as 56%.



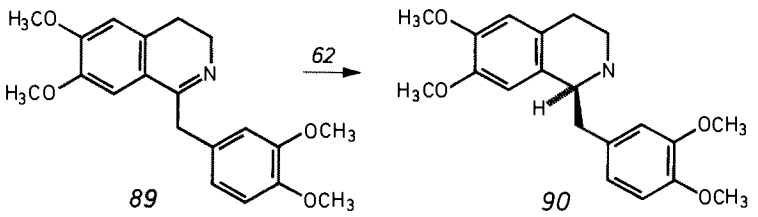
Condensation of (R)-cysteine methyl ester (85) with monochloroacetone followed by reduction with sodium borohydride yielded (3R,5S)-5-methyl-1,4-thiazane-3-carboxylate (86a) and its (5R)-methyl isomer (86b) in a ratio of 3.1:1 [106]. The use of (R)-cysteine isopropyl ester instead of the methyl ester (85) gave the corresponding (5S)-methyl isomer (86a) more stereoselectively.



N. Mohr and H. Budzikiewicz [107] described another example of an asymmetric reductive amination using a (S)-proline moiety as chiral inductor.



The 1-substituted 3,4-dihydroisoquinoline (87) was reduced with chiral reducing agent (62) to the corresponding alkaloids (88) in excellent optical yields (e.e. = 60 to 87%) [94].



(88) is an intermediate in the synthesis of a positional isomer of trimetoquinol with respect to the hydroxy groups and is currently under clinical trials as an orally effective bronchodilator [94].

Triacycloxyborohydrides (62), derived from $NaBH_4$ (1 equiv.) and (S)-N-acyl-proline (3 equiv.), were found to reduce 3,4-dihydropapaverine (89) in tetrahydrofuran to (S)-norlaudanosine (90) hydrochloride in 60% optical yield [93]. In some cases (90) was obtained in even higher optical purity (e.e. = 70–86%).

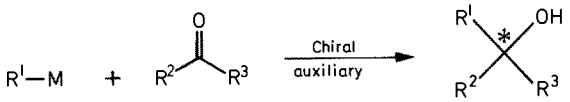
3.2 CC Bond-Forming Reactions

The development of efficient and highly selective methods for carbon-carbon bond formation has been and continues to be a challenging and exciting endeavor in organic chemistry. Especially in the field of asymmetric synthesis, the chemical community has seen a real breakthrough in the past 10 years. Several processes routinely allowing asymmetric inductions of greater than 90% e.e. are now at our disposal. In this Section, asymmetric C–C bond-forming reactions are considered in which amino acids or amino acid derivatives are used as chiral auxiliary reagents.

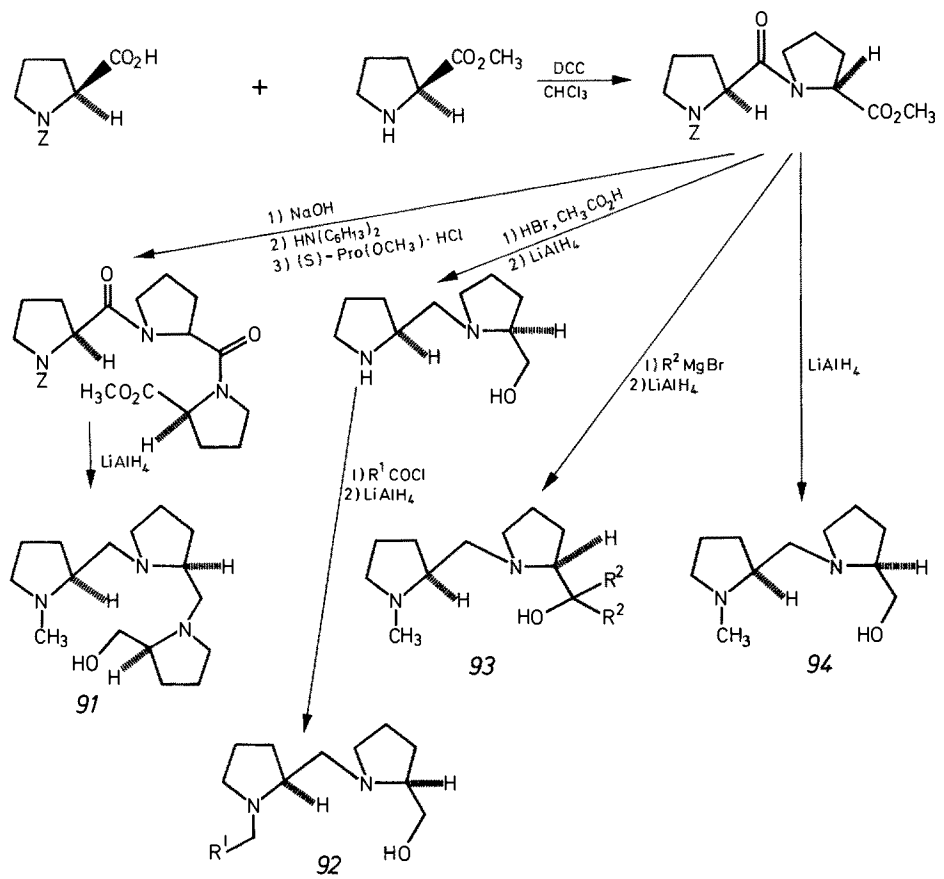
3.2.1 Reactions at the Carbonyl Group

1,2-Additions of Organometallic Compounds:

The formation of chiral alcohols from carbonyl compounds has been fairly widely studied by reactions of aldehydes or ketones with organometallic reagents in the presence of chiral ligands. Mukaiyama et al. [108] obtained excellent results (up to 94% e.e.) in at least stoichiometric addition of the chiral auxiliary to the carbonyl substrate and the organometallic reagent.

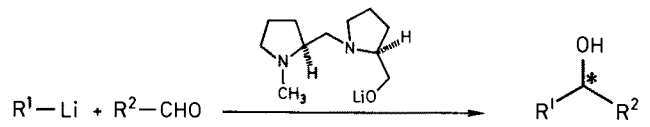


Various chiral diaminoalcohols (91, 92, 93, 94) were synthesized starting from commercially acailable (S)-proline. The enantioselective addition of organometallic compounds to aldehydes in the presence of the aminoalcohols was investigated.



The enantioselective addition of alkyllithium to aldehyde in the presence of the lithium salt of diaminoalcohol (94) yielded optically active secondary alcohols as shown in Table 2.

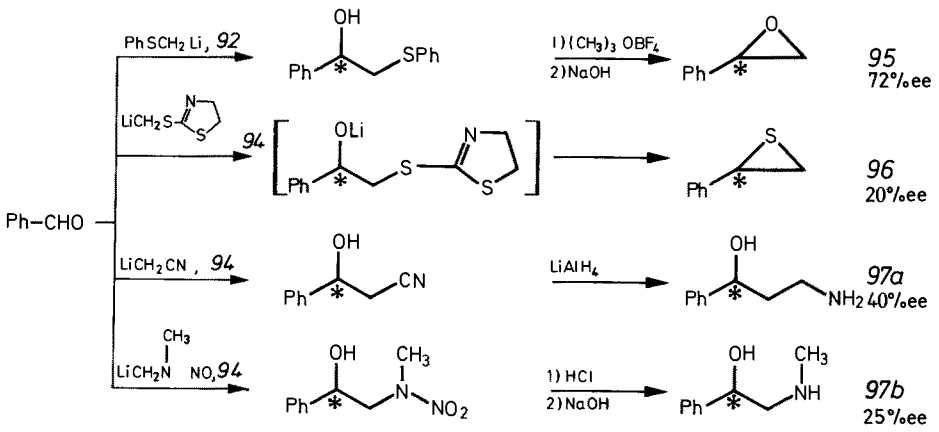
Table 2. Enantioface-differentiating Addition of Alkyl Lithiums to Aldehydes [109]

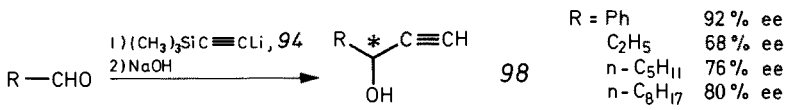


R^1	R^2	Yield (%)	ee(%)	Config.
CH_3	C_6H_5	81	40	R
C_2H_5	C_6H_5	59	54	S
n-C_3H_7	C_6H_5	64	60	S
n-C_4H_9	C_6H_5	77	95	S
n-C_4H_9	i-C_3H_7	57	80	S

L. Colombo et al. [110] synthesized two related (S)-proline derivatives and used them as chiral ligands for lithium in reactions of n-butyllithium with benzaldehyde. 1-Phenyl-1-pentanol was obtained with moderate optical purity (4–33% e.e.). Both nitrogen atoms as well as the free hydroxy group in ligands (91) to (94) appear to be essential centers for coordination with the alkali metal.

By the extension of the above-mentioned stereoselective asymmetric addition of alkylithiums to other organolithium reagents such as lithium salts of methyl phenyl sulfide, 2-methylthiazoline, trialkylsilylacetylene, N-nitroso-dimethylamine, and acetonitrile, chiral oxiranes (95) [111], thiiranes (96) [111], acetylenic alcohols (98) [112], and amino alcohols (97) [111] were readily obtained.

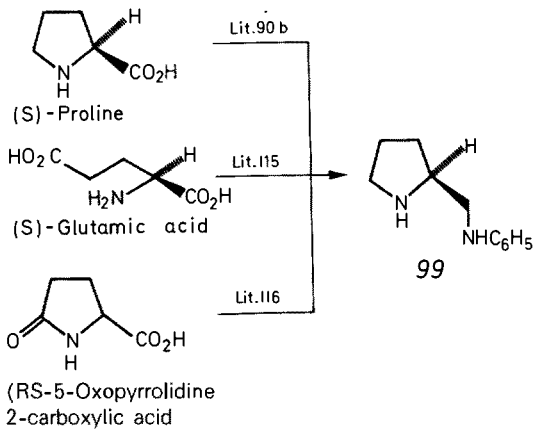




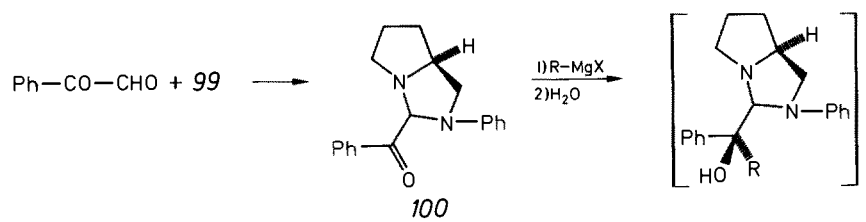
Some of the chiral acetylenic alcohols (98) were successfully converted to γ-ethyl-γ-butyrolactones, insect pheromones of *Trogoderma*. In addition, they are important intermediates for the synthesis of products with antibacterial activity [113].

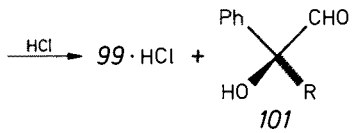
Aside from alkyllithium compounds, only dialkylmagnesium compounds gave high optical yields of the alcohols using ligand (94) as chiral auxiliary [109c, 114].

The diamine (99) was prepared from (S)-proline [90b] or (S)-glutamic acid [115] maintaining the asymmetric center. Racemic 2-(anilinomethyl)pyrrolidine, prepared from (RS)-5-oxopyrrolidine-2-carboxylic acid, was effectively resolved into a pair of enantiomers by fractional crystallization of its mandelic acid salt [116]. Moreover, the preferential crystallization of its 4-hydrobenzoic acid salt was found to produce both enantiomers in high optical purities by alternate seeding [116].



The diamine (99) was applied [117] to the synthesis of chiral α-hydroxyaldehydes. Thus, treatment of the aminal (100), prepared from the chiral diamine (99) and phenylglyoxal, with the Grignard reagent affords the hydroxyaminal, which in turn was hydrolyzed to yield α-alkyl-α-hydroxyphenylacetaldehyde (101). The chiral auxiliary was recovered [117].

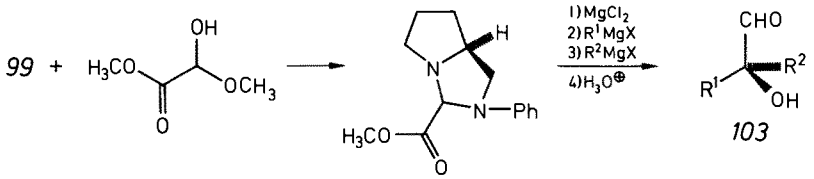




101

R = CH_3 (34% ee), C_2H_5 (92% ee), i-C_3H_7 (40% ee), n-C_4H_9 (88% ee), sec.-C_4H_9 (42% ee)

Mukaiyama et al. developed a rather general and versatile method for the preparation of optically active α-hydroxyaldehydes by using the diamine (99) as chiral adjuvant. Thus, one Grignard reagent (R^1MgX) is reacted with the aminal (102) of methyl glyoxylate. In the next step a second kind of Grignard reagent (R^2-MgX) is diastereoselectively added to the ketoaminal, and the desired chiral α-hydroxyaldehyde (103) is obtained by hydrolysis [117, 118].

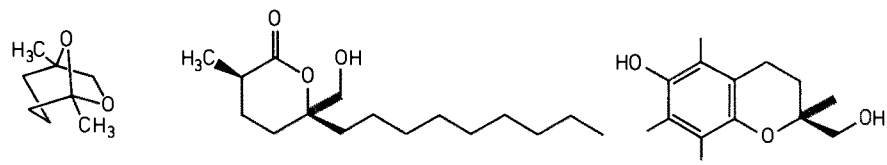


102 103

If, according to the CIP rules, R^1 has a higher priority than R^2, (103) has an (S)-configuration; otherwise it has an (R)-configuration.

This synthetic principle was used by Mukaiyama et al. in the asymmetric total synthesis of
frontalin (104) [119], a pheromone of several species of beetles belonging to the genus *Dendroctonus*,
a marine antibiotic, (—)-malyngolide (105) [120], discovered in the marine blue-green alga, *Lyngbya majuscula Gomot*, and
an α-tocopherol precursor (106) [121].

The aminal (102) was always a key intermediate in the synthesis:

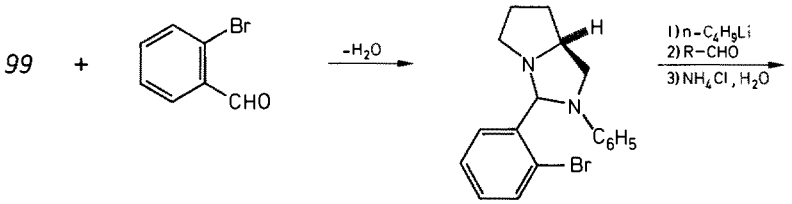


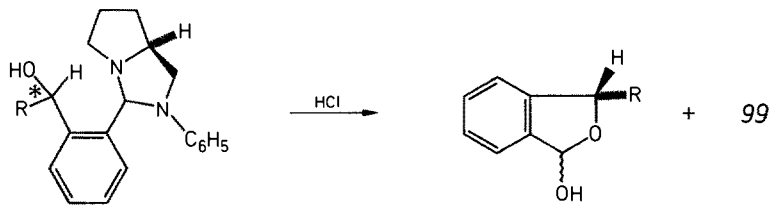
(+)-Frontalin 104 (-)-Malyngolide 105 Vitamin E Precursor 106

Chiral β-formyl-β-hydroxycarboxylic esters were also obtained by the employment of either lithium or zinc enolate of ethyl acetate in place of Grignard reagents in the above-mentioned reaction in moderate to excellent optical purity (62 to 92% e.e.) [122].

Asymmetric synthesis of 2-oxaindane is also achieved by utilizing the aminal (107), prepared from 2-bromobenzaldehyde and the chiral auxiliary (99). Various chiral

3-alkyl-1-hydroxy-2-oxaindanes (108) were obtained by the reaction of the lithium salt, prepared by treatment of the aminal (107) with n-butyllithium, to aldehydes and subsequent hydrolysis.

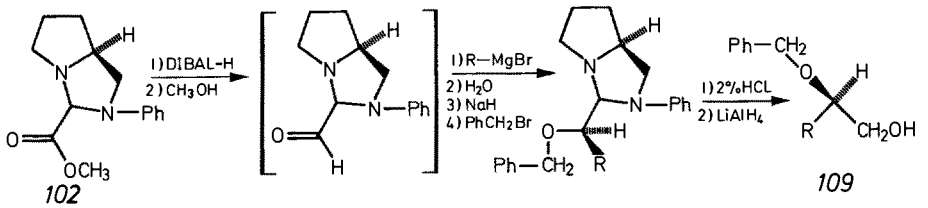




108

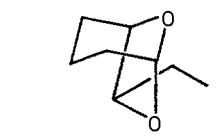
R = C_2H_5 (88% ee), i-C_3H_7 (90% ee), n-C_4H_9 (87% ee), n-C_8H_7 (90% ee), CH_3—CH=CH (20% ee)

Recently, M. Asami and T. Mukaiyama [124] synthesized α-benzyloxyaldehydes (109) having a chiral tertiary center at the α-carbon atom in high enantiomeric excess by successive treatment of the aminal (102) with diisobutylaluminium hydride (DIBAL-H) and Grignard reagents. The asymmetric reaction is applied to the total synthesis of *exo*-(+)-brevicomin (110), the principal aggregation pheromone in the frass of the female western pine beetle (*Dendroctonus brevicomis*).



102

109



exo-(+)-Brevicomin

110

The chiral azomethine compounds (111) were synthesized by condensation of (S)-valinol with benzaldehyde and substituted benzaldehydes, respectively [125]. The

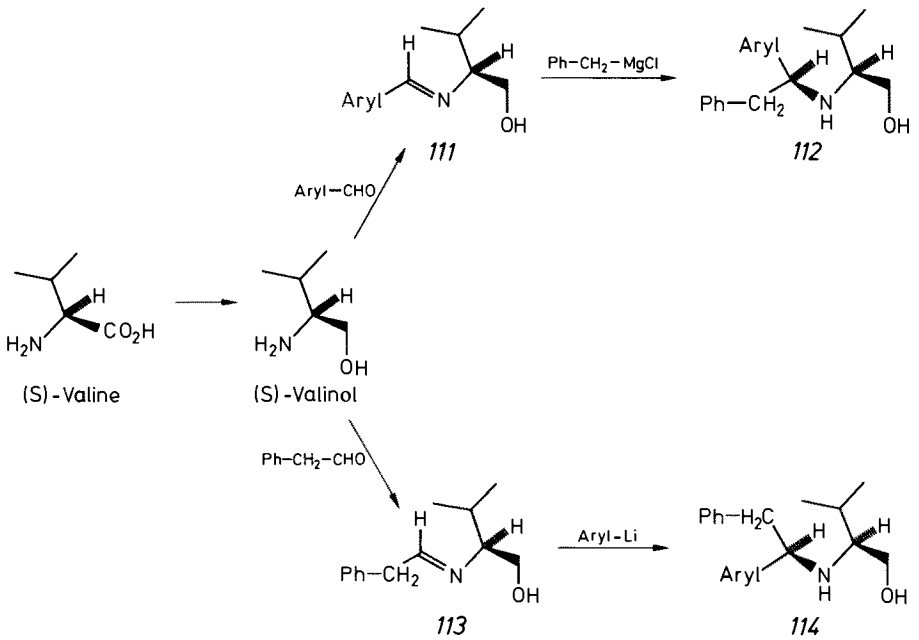
products of 1. these reactions consisted solely of the E isomers due to the difference of bulkiness between the hydrogen atom and aryl group. The reaction of these chiral azomethines (111) with benzylmagnesium chloride produced α-substituted phenethylamines (112) in good yields. No other diastereomer was detected by TLC, GC, and NMR in any case [125].

On the other hand, azomethine (113) was synthesized by condensation of (S)-valinol with phenylacetaldehyde in good yield. The reaction of this chiral azomethine (113) with aryllithium afforded again chiral α-substituted phenethylamines (114). The relationship between (112) and (114) was diastereomeric, due to the different configurations at the newly created chiral center at the 1-position. The diastereoselectivity is more than 98%, because the other diastereomer was not detectable in any case [125].

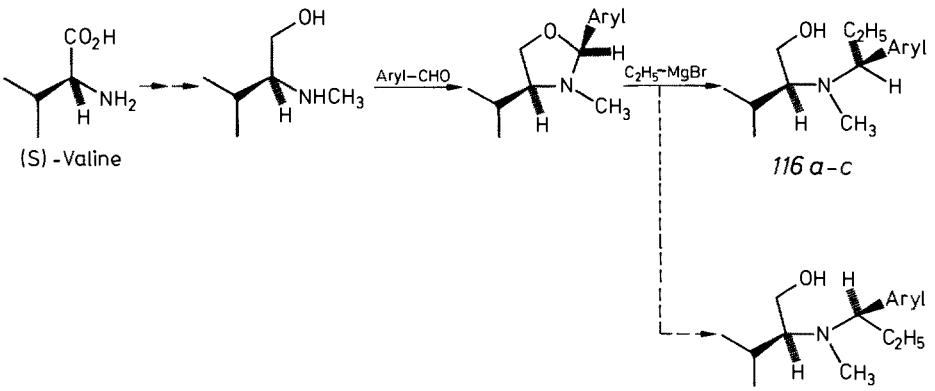
It seems that these asymmetric reactions include two important stereoselective steps:

a) Condensation of (S)-valinol with aldehydes leads to the E isomer at the C=N bond.
b) Complexation of the chiral azomethines (111) or (113) with the magnesium or lithium reagents leads to a highly stereoselective attack.

Similar results [126] were obtained when related optically active azomethines were synthesized from (S)-alanine, (S)-leucine, and (S)-isoleucine *via* (S)-2-aminoalkanols. On the other hand, the aminoalkanols having (R)-configuration were synthesized from (R)-amino acids, i.e., (R)-alanine and (R)leucine [126]. Again, the asymmetric reaction of the chiral azomethines with Grignard reagents was found to be extremely highly stereoselective. However, the reactions of the azomethines derived from (S)- and (R)-alanine with benzylmagnesium chloride afforded only poor stereoselectivity.



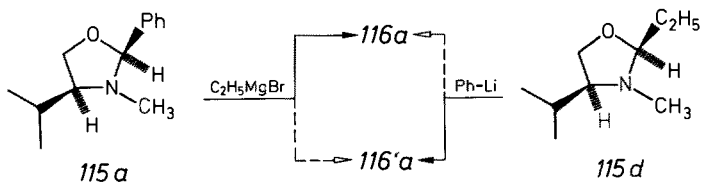
Recently, new chiral oxazolidines (115a–c) were synthesized by the condensation of (S)-N-methylvalinol with some aldehydes [127]. According to NMR-spectra, only one diastereomer was obtained in this reaction, suggesting again that the isopropyl group of optically active (S)-valine produces very high asymmetric induction. The reactions of (115a–c) with ethylmagnesium bromide produced optically active amines (116 and 116') in good yields [127]. These reaction products were elucidated to consist of a mixture of two diastereomers. The major component (116) was formed with 58 to 80% ds.



On the other hand, the oxazolidine (115d) was synthesized by the condensation of (S)-N-methylvalinol with propionaldehyde in a stereospecific manner. Reaction of (115d) with phenyllithium produced (116'a) as the major product, while (116a), the diastereomer, was the minor product. The ratio of major to minor product was estimated to be 89:11 [127].

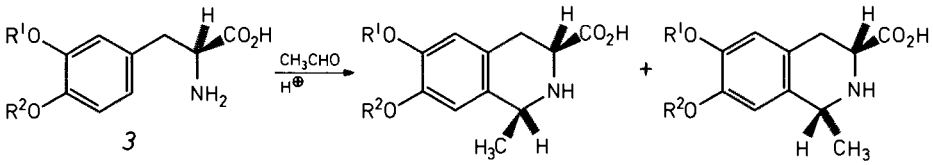
The mechanism of this interesting asymmetric synthesis may be assumed to be as follows:

First, the magnesium atom of the Grignard reagent attaches to the lone pair of 1-position oxygen from the less sterically hindered side. Then, the ethyl anion attacks the 2-position carbon from the same side, because the reaction of (115a–c) with ethylmagnesium bromide produced the (1S, 1'S)-configuration amines (116a–c) as the major products. On the other hand, the minor component (116'a–c) is considered to be formed by attack of ethyl anion at 2-position from behind.



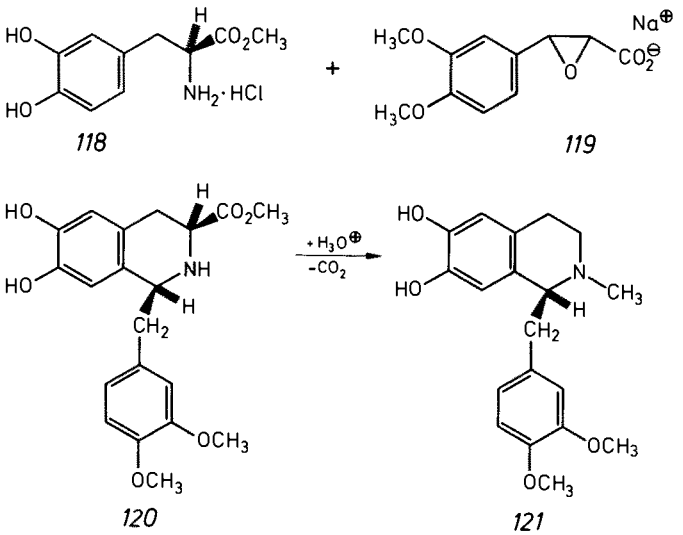
Reactions of the Pictet-Spengler Type:

Various symptoms of ethanol intoxication, dependence and withdrawal may be caused by the reaction of acetaldehyde, the primary metabolite of ethanol, with compounds possessing a β-arylethylamine structure to produce pharmacologically active tetrahydroisoquinolines. Thus, phenylalanine, tryptophane and histidine can react with aldehydes in a reaction of the Pictet-Spengler type. The reaction products are tetrahydroisoquinolinecarboxylic acid derivatives, tetrahydro-β-carbolines, and tetrahydroimidazopyridines, respectively. Such carbolines were synthesized as early as 1948, but from racemic tryptophane [128]. Later, Brossi et al. [129] reported a Pictet-Spengler condensation of (S)-Dopa (3) and of its 0-alkyl derivatives with acetyldehyde. This reaction occurred with asymmetric induction and gave rise predominantly to the tetrahydroisoquinolinecarboxylic acids (117a) (ds = 80%) in which the carboxyl and methyl groups are in the cis position to one another. Thus, the asymmetric center of the amino acid (3) induces the configuration at C-1 with high stereoselectivity.



3 $R^1 = R^2 = H, CH_3$ 117a 117b

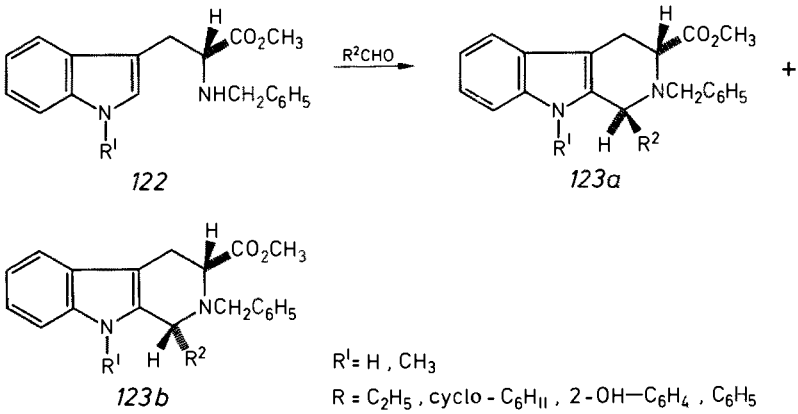
S. Yamada and co-workers [130] obtained tetrahydroisoquinoline (120) by the condensation of (S)-dopa methyl ester hydrochloride (118) with the carboxylate (119), a precursor of 3,4-dimethoxybenzaldehyde, in high stereoselectivity (ds = 76%). (120) was decarboxylated to yield a natural product named (S)-laudanosine (121) [131]. (R)-Laudanosine [132] and (S)-reticuline [133] have been obtained by the same method. Rapoport et al. [134] synthesized some 8- and 13-methylberberine alkaloids starting from (117a) ($R^1 = R^2 = H$).



118 119 120 121

In a series of papers, Cook et al. [135] described the Pictet-Spengler reaction of (S)-tryptophan derivatives (122) and the appropriate aldehydes in benzene to form exclusively tetrahydro-β-carbolines (123a). On the other hand, Grigg et al. [136] reported that in the condensation described by Cook et al. [135] the presence of a Bronsted acid is essential. Otherwise the Pictet-Spengler reaction occurs extremely slowly, if at all. Grigg et al. [136] obtained in a model reaction the tetrahydro-β-carbolines (123) as a stereoisomeric mixture of (123a) and (123b) in a ratio of 1:1.2. Several other groups [137] have also investigated the ratio of cis/trans isomers produced in the Pictet-Spengler reaction of tryptophan derivatives with aldehydes. However, in all of the reactions discussed, mixtures of cis and trans diastereomers were reported with the exception of the harman substitution pattern (1-methyl) and, in fact, Brossi et al. [138] have isolated cis and trans isomers (1-methyl-3-carboxyl) in this series. Only Cook et al. [135] found that the Pictet-Spengler reaction of N_b-benzyltryptophan methyl ester with aldehydes occurs in a stereospecific fashion.

A base-catalyzed Pictet-Spengler reaction of (S)-histidine with benzaldehyde was recently reported to yield a mixture of diastereomers, 59% trans and 22% cis [139].



122 123a

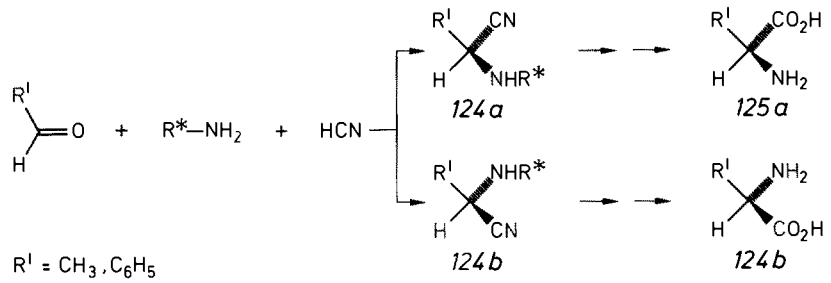
123b

R^1 = H, CH_3

R = C_2H_5, cyclo-C_6H_{11}, 2-OH—C_6H_4, C_6H_5

Asymmetric Strecker Syntheses:

When an aldehyde is allowed to react with an optically active amine and hydrocyanic acid, one of the two diastereomeric amino nitriles, (124a) or (124b), may be formed in excess. To prepare the chiral amino acids (125a) or (125b), the nitriles (124a) and (124b), respectively, are hydrolyzed with mineral acids, whereupon R* is split off. However, this asymmetric synthesis of amino acids has no industrial significance.



124a 125a

124b 124b

R^1 = CH_3, C_6H_5

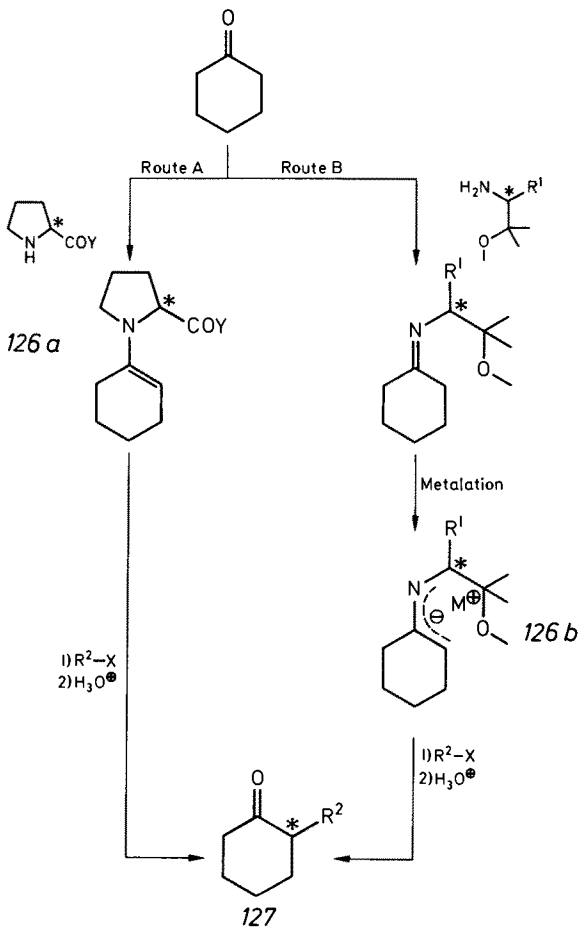
Most commonly, α-phenylethylamine is used as chiral amine in the asymmetric Strecker synthesis. Amino acid derivatives have also been used quite successfully as chiral amines. Especially (S)-tert.-butylglycine tert.-butyl ester was proven to be a powerful chiral inductor [140]. The optical yields were as high as 96.5%. The best results were obtained in nonpolar solvents such as n-hexane [140].

The asymmetric Strecker synthesis was also applied in the preparation of other chiral products. In these reactions japanese chemists [141] always used amino acid derivatives as the chiral amine component which is responsible for the induction of asymmetry.

3.2.2 Reactions at the α-Carbon Atom of Carbonyl Groups

Alkylation of Imino- and Enamino Compounds:

Methods which allow the construction of carbon-carbon bonds α to the carbonyl group and simultaneously generate a new asymmetric center at the α-position, belong



to the most important synthetic operations. A milestone in this field was the introduction of metalated imines as reactive enolate equivalents by Wittig et al. [142] and Stork et al. [143]. Metalated hydrazones have proven to be of similar synthetic utility in organic synthesis.

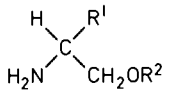
To obtain an asymmetric induction during C–C bond formation, one needs an enantiomerically pure amine compound.

In 1968, Horeau et al. [144] reported an enantioselective methylation of cyclohexanone via an optically active terpenylimine to yield 2-methylcyclohexanone with 72% enantiomeric excess. The following deals only with those chiral amino compounds that are derived directly from amino acids [145].

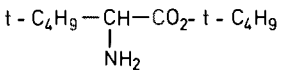
The alkylation of caclohexanone has been studied as a model reaction in detail. Generally, enamino compounds (126) are allowed to react with alkyl halides or α,β-unsaturated carbonyl compounds. The enamine (126a) is prepared directly from the ketone and a chiral secondary amine (route A). A "metalloenamine" (126b) can be synthesized from chiral azomethine, derived from the model ketone and a primary chiral amine (route B). The primary amine used for the formation of (126b) must possess an oxygen function. This oxygen function plays a key role in the coordination of the lithium ion in the complex (126b).

2-Alkylated cyclohexanones (127) have been obtained by this procedure with 72–98% enantiomeric excess [146]. If cyclohexanone is replaced in this model reaction by acyclic aldehydes, the e.e. value drops significantly, to 42–54% [146].

A series of chiral amines derived from amino acids has been used; the best optical yields have been obtained with phenylalanine derivatives (128) ($R^1 = CH_2C_6H_5$) and tert-leucine tert-butyl ester (129) [146].



128

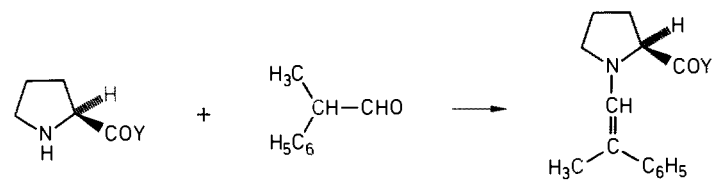


129

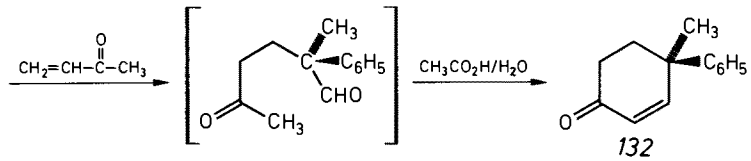
R^1 = C_6H_5, $CH_2C_6H_5$, i - C_3H_7, $CH_2CH(CH_3)_2$, cyclo - $C_6H_{11}CH_2$, CH_3CH_2

R^2 = H, CH_3, $CH_2CH_2OCH_3$, $CH_2CH_2N(CH_3)_2$, $CH_2CH_2OCH_2CH_2OCH_3$, $CH_2CH_2CH_2OCH_3$

The Stork reaction between methylvinyl ketone and enamine (130) derived from (S)-proline derivatives (131) is of particular interest since chiral cyclohexenones can be obtained. These are useful in many natural product syntheses. Optical yields of 20–50% have been reported [147].



131 130

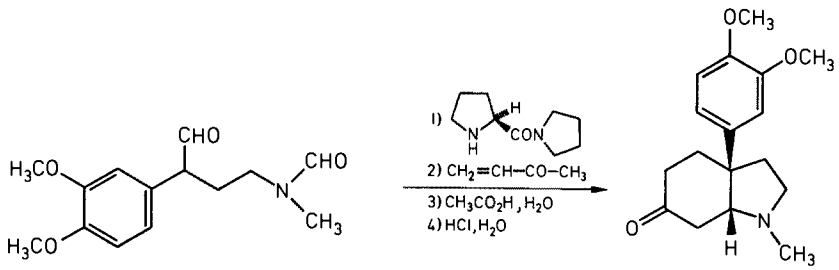


132

Y = O-t-C_4H_9, $N(CH_3)_2$, $N(C_2H_5)_2$, N

The alkylation of enamines (126a) (Y = OCH_3, OC_2H_5, O-t-C_4H_9) derived from (S)-proline esters was first described by Yamada et al. [148].

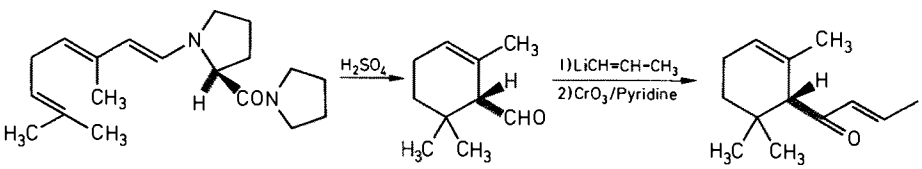
Activated olefins (acrylonitrile, methyl acrylate), and halides such as allyl bromide and ethyl bromoacetate were used as electrophiles. In nonpolar solvents, the enamines (126a) were alkylated with high enantioselectivity, but poor chemical yields. In polar solvents, the chemical yields were acceptable, the optical yields poor [148]. A similar reaction sequence has been used successfully for the synthesis of (+)-mesembrine (133) [149].



133

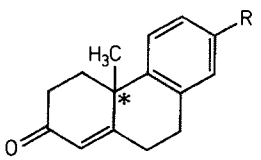
In the asymmetric synthesis of 4,4-disubstituted cyclohexenones of the type (132) it was possible to raise the optical yield to a maximum of 54% by varying the structures of the carbonyl compounds [150] and of the proline derivatives (131) [151].

The acid-catalyzed cyclization of the chiral enamine (134) produces (R)-α-cyclocitral (135) and hence (R)-trans-α-damascone (136) in 33% enantiomeric excess [152].



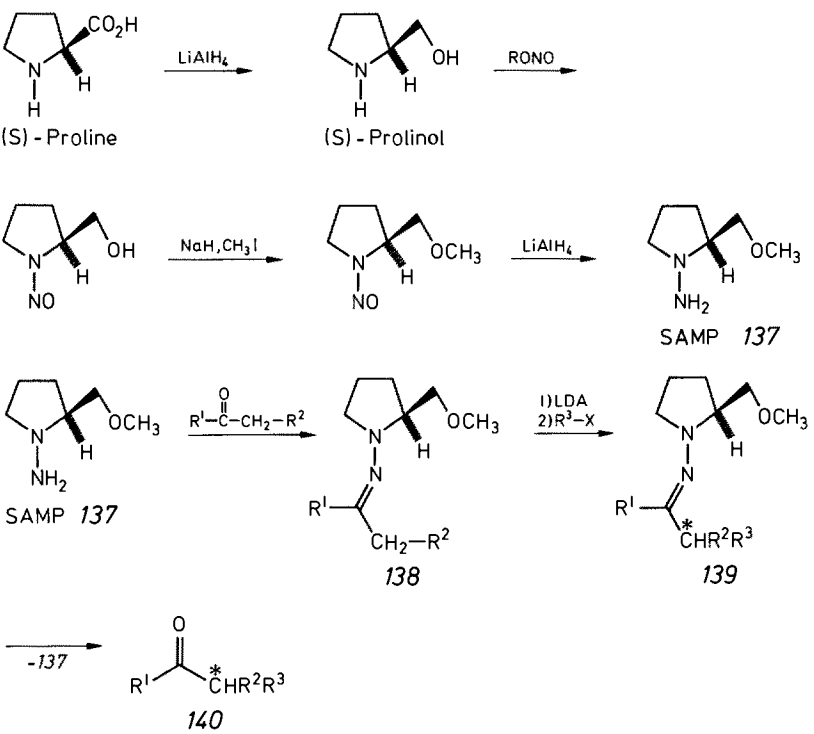
134 135 136

Other natural products in the form of chiral diterpenes and steroids, such as podocarpic acid [153], (R)- and (S)-$\Delta^{1,9}$-2-octalone [154] and vincamine [155], have been prepared from (132) via the phenanthrone derivatives (137).



137

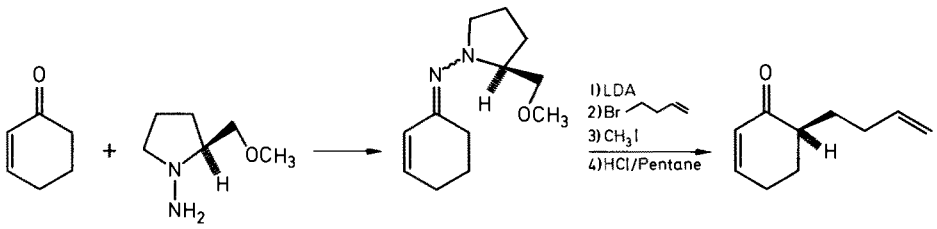
In late 1975, Enders et al. [156] started a research project directed towards the development of a new synthetic method for asymmetric carbon-carbon bond formation. A new chiral auxiliary, namely the (S)-proline derivative SAMP (137), was allowed to react with aldehydes and ketones to give the hydrazones (138), which can be alkylated in the α-position in an diastereoselective manner [157,158]. Lithiation [159] of the SAMP hydrazones (138), which are formed in excellent yields, leads to chelate complexes of known configuration [160]. Upon treatment of the chelate complexes with alkyl halogenides the new hydrazones (139) are formed. Cleavage of the product hydrazones (139) leads to 2-alkylated carbonyl compounds (140).



For the cleavage reaction two methods have been described: ozonolysis at −78 °C, which can be used to recycle the chiral information (137), or acid hydrolysis in a two-phase system. No racemization of the product ketone was observed under these conditions.

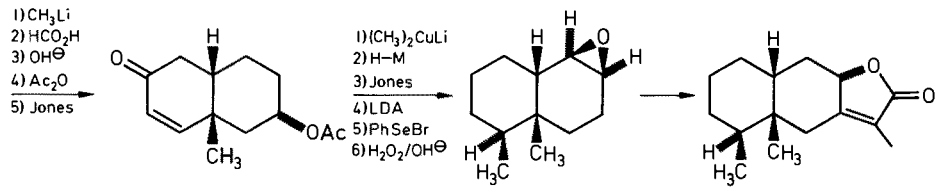
A number of optically active cyclic ketones have been prepared this way. The overall chemical yields in all cases (cyclopentanones, cyclohexanones, cycloheptanones, and cyclooctanones) were good; the enantiomeric excess in some cases exceeded 95% and was generally satisfying to excellent.

Pennanen [161] used the SAMP-hydrazone method in a total synthesis of the sesquiterpene (+)-eremophilenolide (143). The key step in the synthetic scheme was the enantioselective α'-alkylation of cyclohexanone. Thus, with cyclohexanone SAMP (137) readily gave the hydrazone (141), which was subjected to lithiation with lithium di(isopropyl)amide (LDA), followed by treatment with 4-bromo-1-butene. The regeneration of the keto group was performed with methyl iodide/HCl producing the enone (142) which was converted to (143) in several steps. The stereochemistry of all intermediates was controlled by the asymmetric center in (142). In other words: the absolute configuration of (143) having *four* asymmetric carbon atoms is derived from the chiral information incorporated in (142), and this was induced by the influence of the chiral amino acid (S)-proline via SAMP (137). The optical purity of the sesquiterpene (143) which was obtained by the SAMP-method was found to be high (89% e.e.).



SAMP *137* *141* *142*

ee = 89% (R)[162]

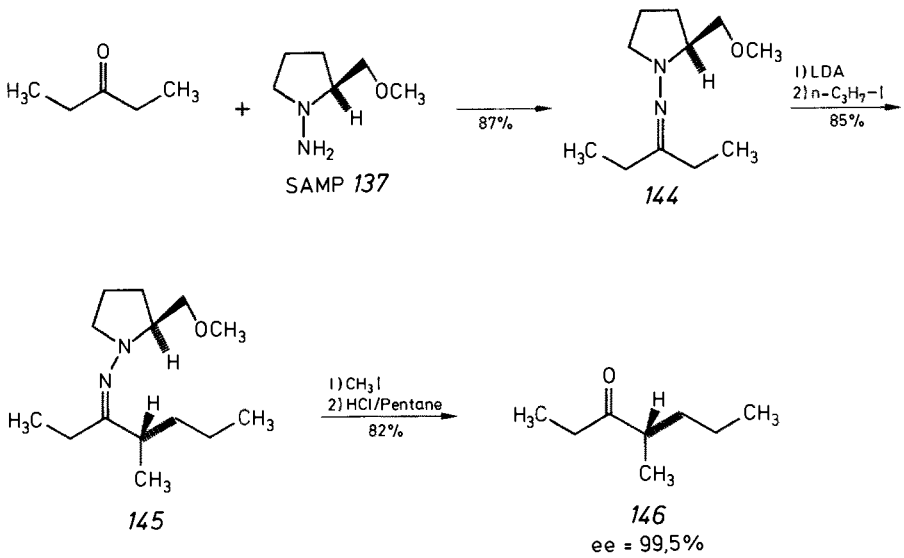


143

In the case of the asymmetric syntheses of conformationally much more flexible aldehydes and acyclic ketones applying the SAMP-method, the control of both metalation and alkylation selectivity is necessary to reach an excellent overall stereoselectivity. A variety of acyclic ketones can be prepared via the related SAMP-hydrazones in good chemical yields and routinely with overall enantioselectivities of 94–99.5% e.e.

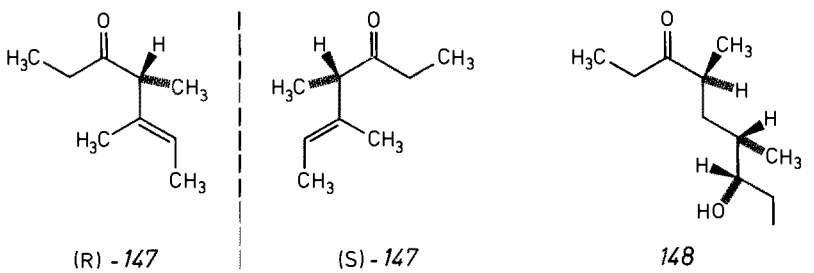
(S)-4-methyl-3-heptanone (146), the alarm pheromone of the leafcutting ant *Atta texana* is about 400 times more active than its optical isomer. This acyclic ketone (146) could be prepared by simply starting from diethyl ketone and propyliodide.

Transformation of diethyl ketone to the corresponding SAMP-hydrazone (144) followed by metalation with LDA and trapping with propyliodide produced the (ZSS)-diastereomer of the product hydrazone (145). This was then cleaved to produce the pheromone (146) in 60% chemical yield with 99.5% enantiomeric excess.



Thus, even in this flexible acyclic back-bone case, the electrophilic substitution occurs with almost complete asymmetric induction, which means that both deprotonation selectivity and alkylation selectivity are almost 100%.

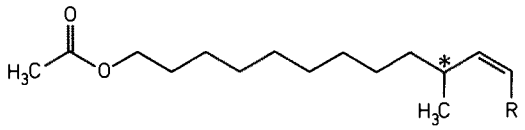
The (R)- and (S)-enantiomers of (E)-4.6-dimethyl-6-octene-3-one (147), a defense substance of spiders (known commonly as "daddy longlegs" *Leiobunum vittatum* and *L. calcar*) were recently synthesized by Enders and Baus [163] using the (R)-proline derivative RAMP and the (S)-proline derivative SAMP (137) as chiral auxiliary, respectively. (S)- and (R)-enantiomers of (147) have been obtained in an overall chemical yield of 70% and in very high stereoselectivities of ≧95% e.e., respectively.



In an elegant asymmetric synthesis of natural serricornin (148) by Mori et al. [164], an overall enantioselective alkylation of diethyl ketone via its SAMP-hydrazone (144) was again the key step. (148) is the sex pheromone of the female cigarette beetle, *Lasioderma serricorne F.*

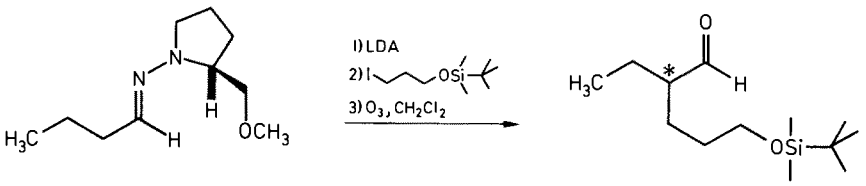
As expected for the SAMP-alkylation, the (4S)-configuration was generated in excess. Thus, the absolute stereochemistry of (—)-serricornin (148) could be determined to be (4S,6S,7S). Other synthetic stereoisomers of serricornin prepared by Mori et al. [165] were almost devoid of pheromone activity.

Bestmann et al. [166] used the SAMP/RAMP-hydrazone method very successfully in their synthesis of both enantiomers of methylsubstituted pheromone analogues (150) of *Lepidopetra* species *Manestra* brassicae (R = n-C_4H_9), *Argyrotaenia velutinana*, *Ostrinia nubilalis* and *Tortrix viridana* (R = C_2H_5).

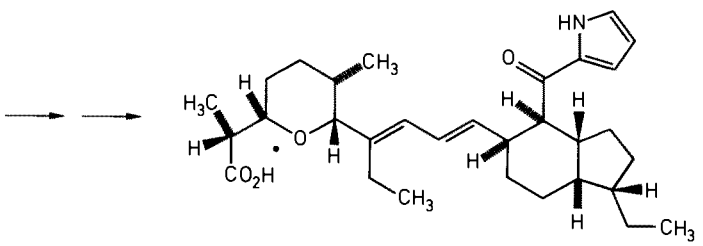


150

Recently, Nicolaou et al. [167] reported an elegant asymmetric synthesis of the ionophore antibiotic X-14547 A (153) isolated at Hoffmann-La Roche from *Streptomyces antibioticus NRRL 8167.* The key step in this synthesis was an enantioselective α-alkylation of n-butanal via its SAMP-hydrazone (151) to produce the intermediate (152). The asymmetric induction as determined by NMR-spectra of the product SAMP-hydrazone, was 95% e.e.

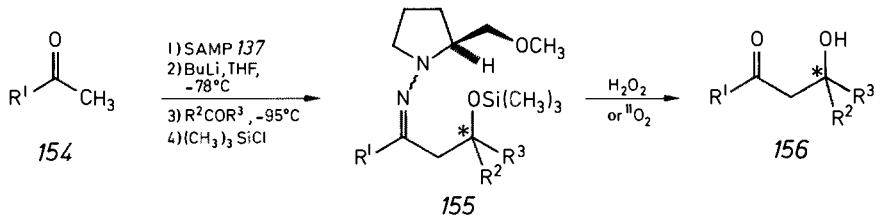


151 152



153

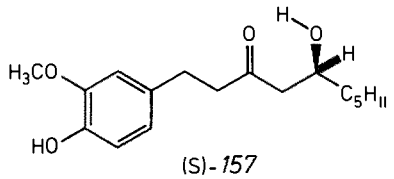
Regiospecific and enantioselective aldol reactions [168] were also performed with SAMP (137). Lithiated hydrazones obtained from ketones (154) as described above were alkylated with carbonyl compounds and the adducts then treated with chlorotrimethylsilane. The resulting trimethylsilylethers (155) were finally oxidatively hydrolyzed to yield the chiral β-hydroxyketones (156) (e.e. = 31–62%) [168].



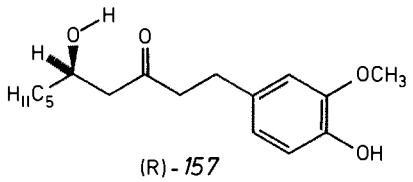
154 155 156

In cases involving unsymmetrical ketones (154) ($R^1 \neq CH_3$), the C–C bond formation occurs regiospecifically at the less substituted alkyl group in α-position to the carbonyl function.

[6]-Gingerol (157), the pungent principal of ginger, was prepared by this method from the cheap starting materials vanillin, acetone, and n-hexanal. 36% e.e. of the (R)-compound [using SAMP (137)] and 39% e.e. of the naturally configurated (S)-gingerol [using the mirror image of SAMP (137), e.g. RAMP] were reached [169]. Yashibushiketol (158), occurring in the tree *Alnus firma*, was obtained only with a low e.e. value via SAMP (137) [170].

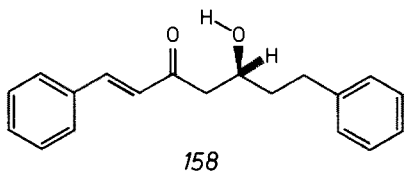


(S)-157



(R)-157

[6]-Gingerol, natural configuration

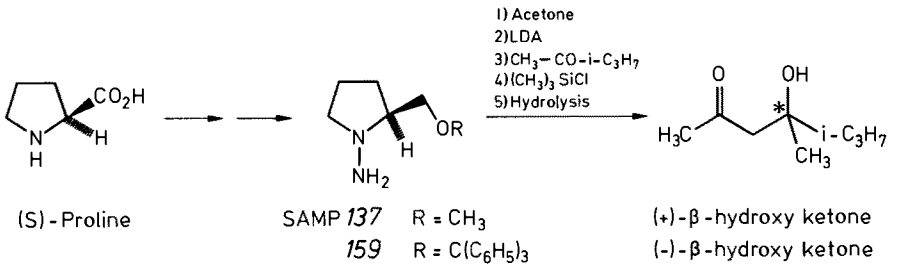


158

Yashibushiketol

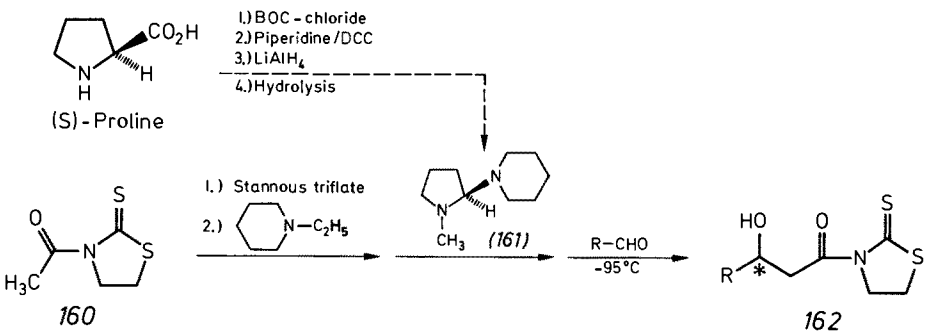
One way to achieve a higher stereoselectivity in these aldol reactions could obviously be the variation of the alkoxy group on the pyrrolidine sidechain of the chiral auxiliary. Thus, Enders and co-workers synthesized the SAMP-analogue (159). While acetone-SAMP-hydrazone leads to a (+)-β-hydroxyketone in 47% e.e., the corres-

ponding acetone-(159)-hydrazone, bearing the sterically demanding trityl group, gave rise to its enantiomer (—)-β-hydroxyketone in only 38% e.e. This result is not easy to explain. Further investigations are necessary to achieve a better understanding of this phenomenon.



A highly enantioselective aldol-type reaction forming various β-hydroxycarbonyl compounds (162) from 3-acetylthiazolidine-2-thione (160) and achiral aldehydes was achieved via divalent tin enolate employing a chiral diamine (161) derived from naturally occurring (S)-proline as ligand [171]. Thus, stannous triflate was treated with (160) in the presence of N-ethylpiperidine as a base. (S)-1-Methyl-2-[(piperidin-1-yl)-methyl] pyrrolidine (161), the chiral auxiliary, was added and the resulting reaction mixture was cooled. Then, an aldehyde was added and, after the usual work up, the reaction mixture afforded the corresponding aldol-type product (162) in good yield and stereoselectivity. In some cases, optical purities of more than 90% enantiomeric excess were achieved by Iwasa and Mukaiyama [171].

Table 3. Enantioselective Aldol-Type Reaction of (160) to yield (162)



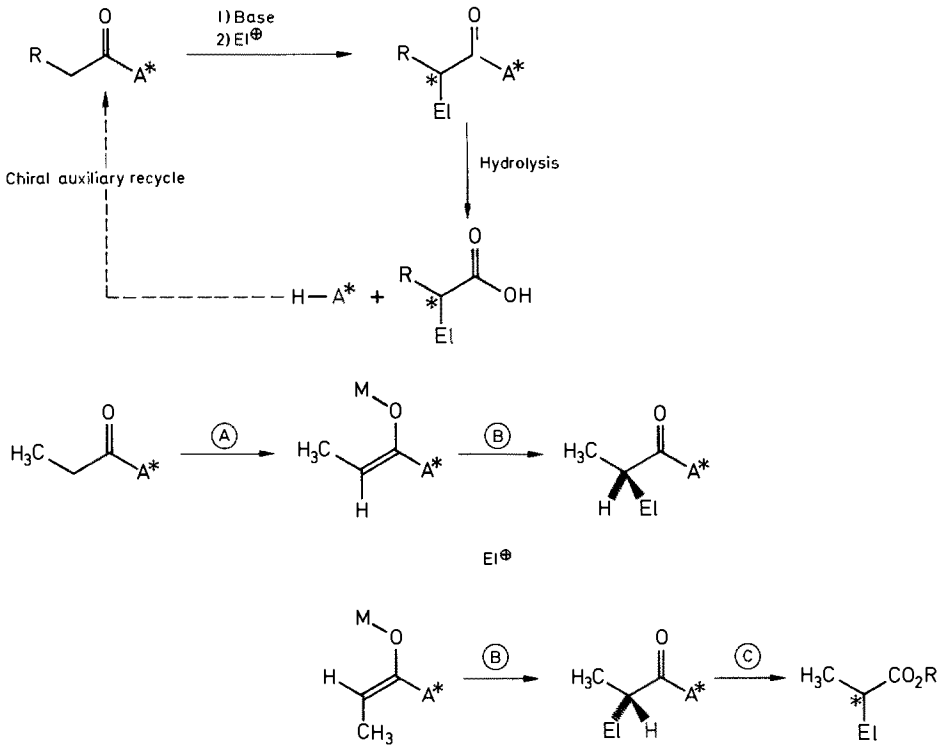
R—CHO	162	
	Yield (%)	Optical purity (%)
C_6H_5—CHO	79	65
i-C_3H_7—CHO	63	>90
$C_6H_5CH_2CH_2$—CHO	76	>90
cyclo-C_6H_{11}—CHO	81	88
C_2H_5—CHO	70	90
n-C_5H_{11}—CHO	65	90

Iwasawa and Mukaiyama have previously reported the first example of forming highly optically active aldols from aromatic ketones and various aldehydes, again via divalent tin enolates employing chiral diamines derived from (S)-proline as ligands [172].

Enders et al. [173] transformed open chain and cyclic β-ketoesters into the corresponding SAMP-hydrazones. Metalation with n-butyllithium, followed by trapping of the intermediate "anions" with alkyhalides generates esterhydrazones which upon cleavage by ozonolysis finally leads to optically active β-ketoesters. While the overall chemical yields are good, the enantiomeric excesses of 18–60% are relatively low.

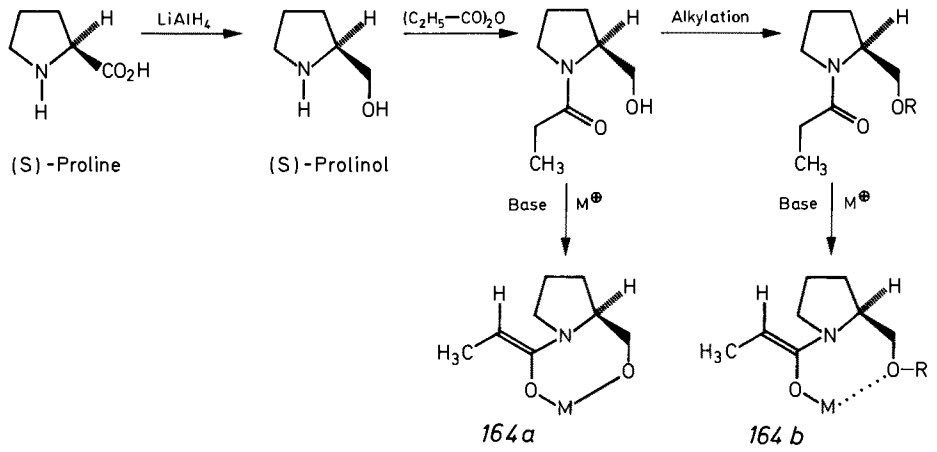
Enders and Lotter [174] developed an asymmetric synthesis of α-hydroxyketones and vicinal diols using the (S)-proline derivative (S)-1-formyl-2-methoxymethylpyrrolidine as chiral auxiliary. However, the α-hydroxyketones and vicinal diols, respectively, were only obtained with low stereoselectivity.

Alkylation of Enolates: Asymmetric syntheses involving enolate reactions such as alkylations, aldol additions and acylations in which the chiral auxiliary A*-H is both readily obtained and easily recoverable after the desired bond construction had been achieved by Evans et al. [175].



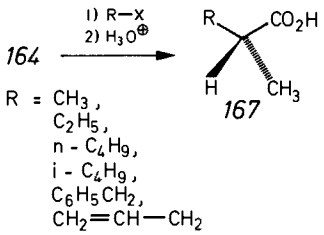
The major obstacles presented by the overall objective to create carbon-carbon bonds asymmetrically via chiral enolates are therefold in nature: Given the carbonyl derivative (163), the chiral auxiliary moiety A* must provide a strong bias for a highly selective enolization process **A**; it must also provide a strong topological bias for

enolate diastereoface selection in the bond construction **B**; and finally its nondestructive removal **C** must be carried out with minimal racemization under mild conditions.



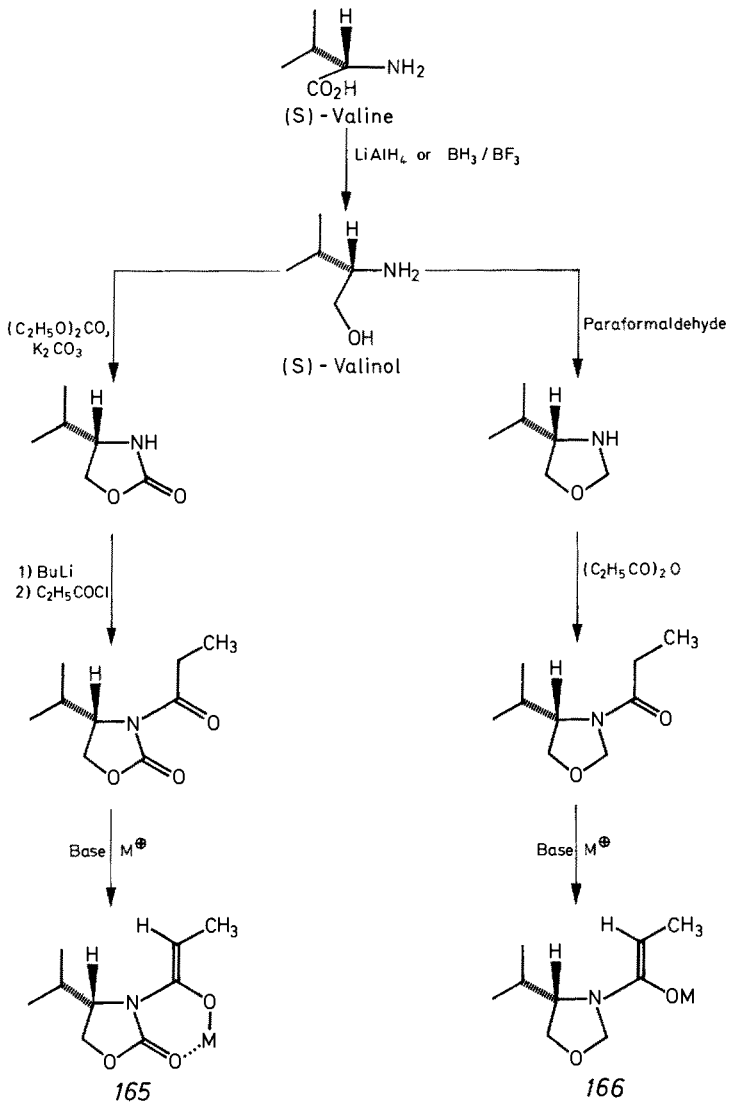
The chiral auxiliaries H-A* developed by Evans et al. [176] were derivatives of naturally occurring amino acids. The (S)-proline-derived amide enolates (164) as well as the (S)-valine-derived amide enolates (166) and imide enolates (165) have proven to be exceptionally versatile chiral nucleophiles.

The highly nucleophilic (S)-prolinol amide enolate (164) (M = Li) was alkylated employing a range of alkyl halides. The carboxylic acids (167) were obtained in chemical yields of 78–96% and outstanding optical yields [177].

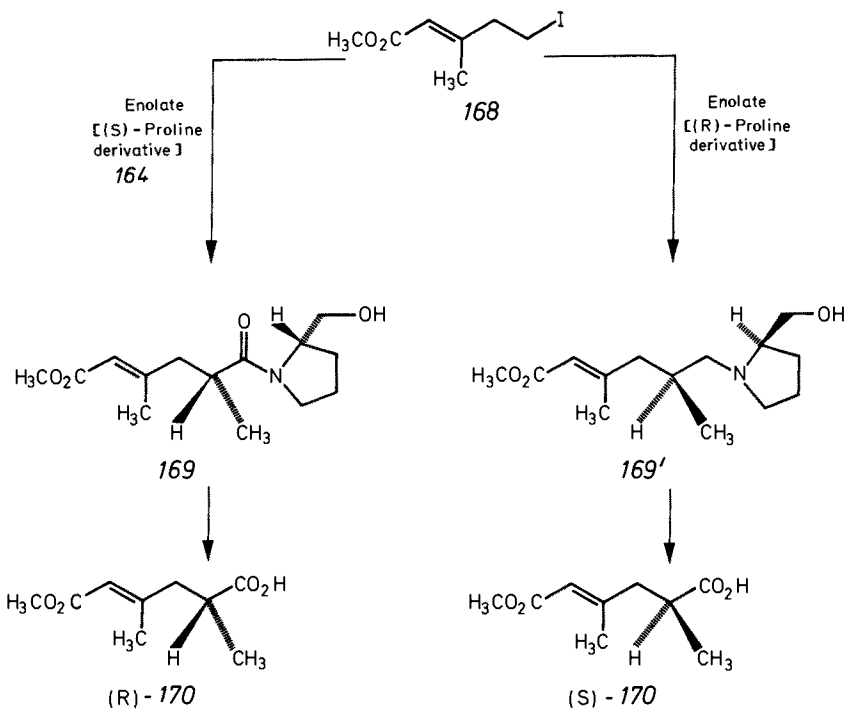


Recently, both enantiomeric forms of callosobruchusic acid (170), a pheromone of the azuki bean weevil, *Callosobruchus chinensis* L., which induces the male to extrude his genital organ and to attempt copulation, were synthesized by Mori et al. [178], applying Evan's alkylation method in natural product synthesis as the key step. Thus, (S)-prolinol propionamide was converted to its enolate (164) by treatment with LDA.

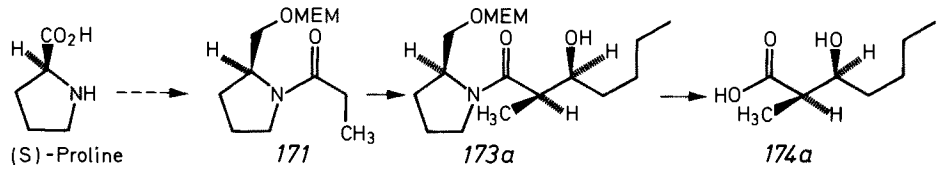
Then it was alkylated with iodide (168) in the presence of HMPA. Finally the reaction was quenched to produce (169) in 46% yield with 96.6% diastereomeric purity. The amide (169) was hydrolyzed to produce (R)-(170) with 93% e.e. In the same manner, by alkylating (R)-prolinol propionamide with (168), the amide (169') was obtained. Acid hydrolysis of (169') produced (S)-(170) with 92% e.e.

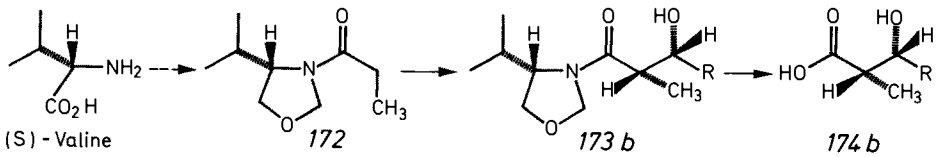


Not surprinsingly, the aldol addition of the lithium enolates derived from these systems proved to be unsatisfactory. However, the derived zirkonium enolates in these and related systems have proven to be exceptional [176]. The amides (171) and (172), each of which is readily derived from (S)-proline and (S)-valine respectively, exhibit good stereoselectivity with a range of aldehydes. The optical purity of the β-hydroxy amides (173) was very good (>95% e.e.). However, this method has a limitation which has been associated with the acidic conditions that are required to hydrolize these chiral amides (173) to their derived carboxylic acids (174). While



this is not a problem in simple systems, in more complex cases where acid labile protecting groups are present, these hydrolytic conditions have proven to greatly limit these enolate systems [175].





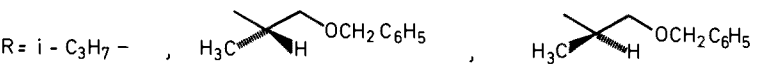
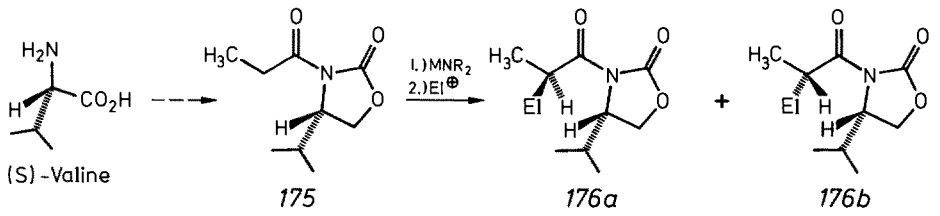
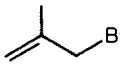
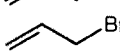


Table 4. Stereoselective Alkylation of the Chiral 2-Oxazolidones (175)

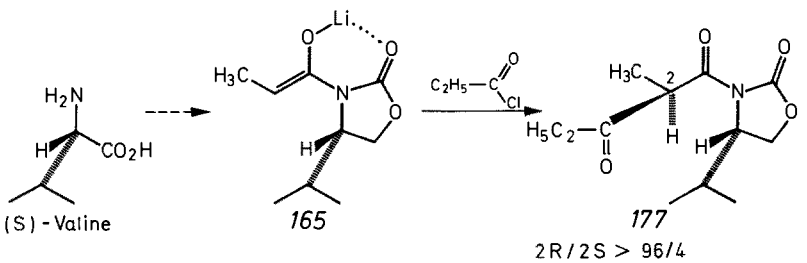


Electrophile	Metal	Ratio *176a* : *176b*	Yield (%) [a]
$C_6H_5CH_2Br$	Li	120 : 1	75
	Li	98 : 2	62
	Li	98 : 2	71
	Na	99 : 1	-
$C_6H_5CH_2OCH_2Br$	Li	98 : 2	77

a) *176a* : *176b* > 99 : 1

Due to these limitations Evans et al. focussed on the exploration of imide-derived enolates (165). They expected these systems to react stereoselective in carbon-carbon bond formation and that the derived imides might be readily hydrolized or reduced under the mild conditions required for the construction of complex products. One of the two chiral 2-oxazolidones (175) chosen for study by Evans et al. [179] is derived from (S)-valine and was readily prepared from this inexpensive commercially available α-amino acid having an optical purity exceeding 99%. The preparation of the related imide-derived enolate (165) is shown in the next scheme. Alkylation reactions employing (175) resulted in excellent diastereoface selection, as summarized in Table 4 [179].

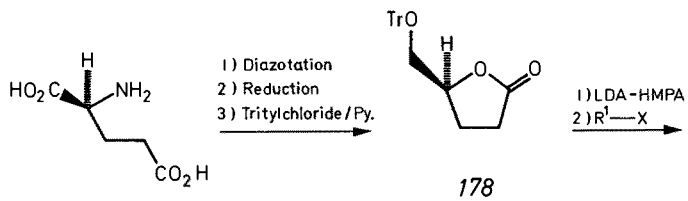
To date, Evans and co-workers have examined a series of transformations that result in the mild, nondestructive removal of the oxazolidone auxiliaries from (176). Basic hydrolysis, transesterification, and reduction of (176) are all viable chemical operations in these systems.



Besides alkyl halides, other electrophiles have been allowed to react with the imide-derived enolate (165). For example acylation of (165) with propionylchloride afforded the chiral β-keto imide (177) in 95% yield with high stereoselectivity [175].

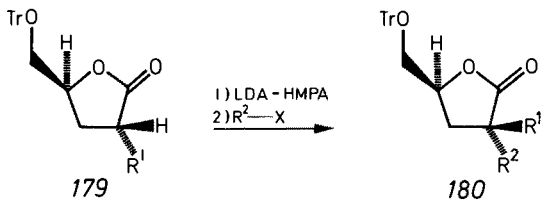
From the illustrated (S)-valinol imide (175), the derived dibutylboryl enolates undergo condensation with a broad range of aldehydes in greater than 99% asymmetric induction for both newly formed asymmetric centers [180]. Evans et al. have shown that the propionyl sidely chain in (175) may be replaced by other alkanoyl substituents without loss of stereoselectivity in the aldol type reaction [180].

The chiral lactone alcohol derivative (178) [181] can be readily prepared from natural (S)-glutamic acid, the cheapest chiral α-amino acid. Lactone (178) was alkylated to yield optically active 3-substituted lactone alcohol derivatives, (179) and (180), which were intermediates in the stereoselective synthesis of various natural products [182].



(S)-Glutamic Acid

178



179 *180*

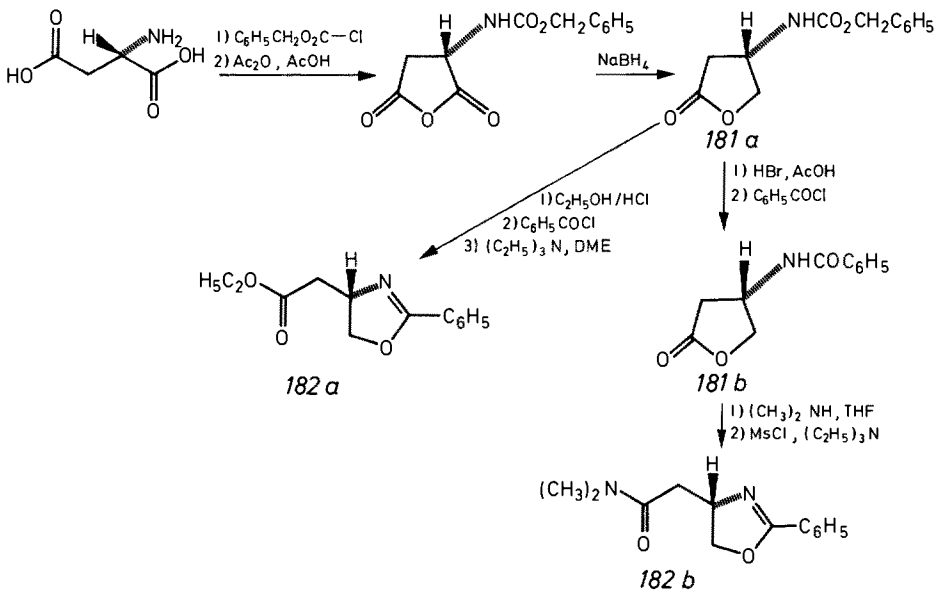
R^1 = CH_3 , C_2H_5 , n - C_3H_7 , CH_2—CH=CH_2 , $CH_2C_6H_5$

R^2 = CH_3 , C_2H_5 , n - C_3H_7 , CH_2—CH=CH_2 , $CH_2C_6H_5$

Both (179) and (180) were obtained with excellent stereoselectivity [183] (d.s. ≧92%; most cases >98%).

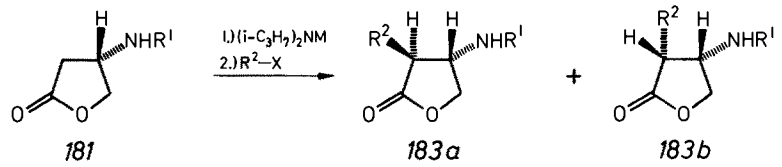
The chiral lactone (178) has been used for the synthesis of a variety of natural products, such as sugars, lignans, terpenes, alkaloids, and β-lactams as a chiral building block [182c, 184]. The use of (178) as a powerful inductor of asymmetry was mainly established by Takano et al. [181–184]; one can expect more highly interesting reports from this group.

(S)-Aspartic acid has been converted to derivatives (181) and (182) which undergo alkylation reactions with stereoselectivities that are enantiomerically complementary [185].



With multigram quantities of compounds (181) and (182) in hand, attention was turned to the stereoselective alkylation of their derived enolates. The lactones (181) were smoothly transformed to their corresponding dianions which subsequently suffered alkylation favoring the expected trans product (183a) [185].

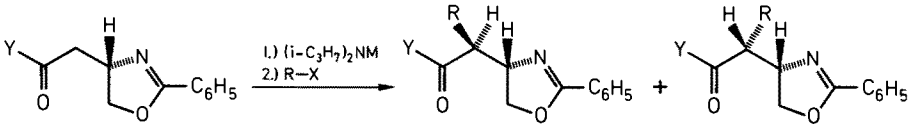
Table 5. Enantioselective Alkylation of (S)-Aspartic Acid Derivatives (181a, b)



R^1	M	R^2-X	Ratio 183a : 183b	Yield (%)
$CO_2CH_2C_6H_5$	Li	CH_3I	88 : 12	97
$CO_2CH_2C_6H_5$	MgCl	CH_3I	88 : 12	88
$CO_2CH_2C_6H_5$	Li	$CH_2=CHCH_2Br$	88 : 12	80
COC_6H_5	Li	CH_3I	91 : 9	77

Alternatively, it was expected that chelation with the β-nitrogen in the enolates resulting from oxazolines (182) would impose a diastereofacial bias opposite to that found in the lactones (181). Deprotonation of (182) afforded enolates which were

Table 6. Enantioselective Alkylation of Oxazolines (182), derived from (S)-Aspartic Acid



182 184a 184b

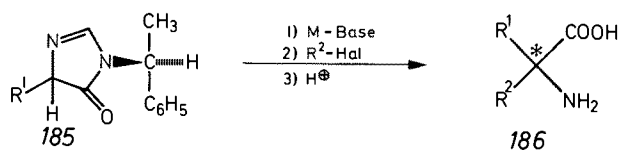
Y	M	R—X	Ratio 184a : 184b	Yield (%)
OC_2H_5	MgCl	CH_3I	66 : 34	84
OC_2H_5	Li	CH_3I	67 : 33	81
$N(CH_3)_2$	MgCl	CH_3I	76 : 24	100 (crude)
$N(CH_3)_2$	Li	CH_3I	83 : 17	78
$N(CH_3)_2$	Li	$C_6H_5CH_2Br$	92 : 8	87
$N(CH_3)_2$	Li	$CH_2{=}CH{-}CH_2Br$	94 : 6	67

sufficiently reactive to undergo alkylation reactions at low temperatures without activating agents such as HMPA. As illustrated in Table 6, the expectations of McGarvey et al. [185] were realized as the antiisomer (184a) predominated. The best asymmetric induction was exhibited by the lithium enolate of amide (182b) [185]. Since diastereomeric alkylation products (184) may often be resolved by simple column chromatography, one can easily isolate isomerically pure compounds.

A related approach was recently successful for the stereocontrolled synthesis of an antibiotic. In this synthesis the Japanese chemists used (S)-3-[(benzyloxycarbonyl)-amino]-4-(methoxycarbonyl)butyric acid as chiral auxiliary [186].

α-Alkylations of α-Amino Acid Derivatives: Optically active α-alkyl-α-amino acids deserve attention because of their documented or potential biological activity. Some are valuable pharmaceuticals, such as (S)-α-methyldopa. Others are interesting as enzyme inhibitors. In fact, enzyme inhibition studies with non-proteinogen amino acids have furnished valuable information about the mode of action of certain enzymes. Obviously, there is a demand for chiral non-proteinogen amino acids both for pure and applied organic or bioorganic chemistry.

Schöllkopf et al. [187] synthesized α-alkyl-α-amino acids (186) by the alkylation of chiral 1-substituted 2-imidazolin-5-ones (185), which can be prepared from α-amino acid (S)-phenylethylamides and orthoformic esters. The optical yields of the products (186) were in many cases higher than 95%.



185 186

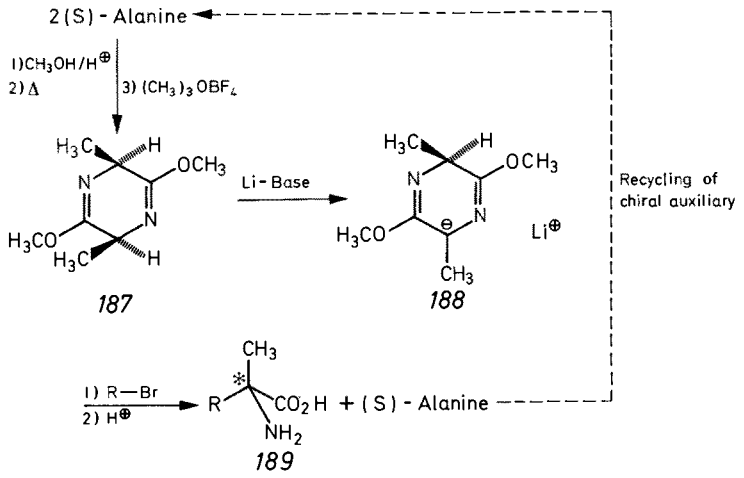
R^1 = CH_3, C_2H_5, n - C_3H_7, i - C_3H_7, n - C_4H_9, $CH_2CH{=}CH_2$, CH_2 - Aryl
R^2 = CH_3, i - C_3H_7, n - C_4H_9, $CH_2CH{=}CH_2$, $CH_2CO_2C_2H_5$, CH_2 - Aryl

Excellent reviews covering the enantioselective synthesis of non-proteinogenic amino acids via metallated *bis*-lactim ethers of cyclic dipeptides (2,5-diketopiperazines) (187) have been compiled by Schöllkopf [188].

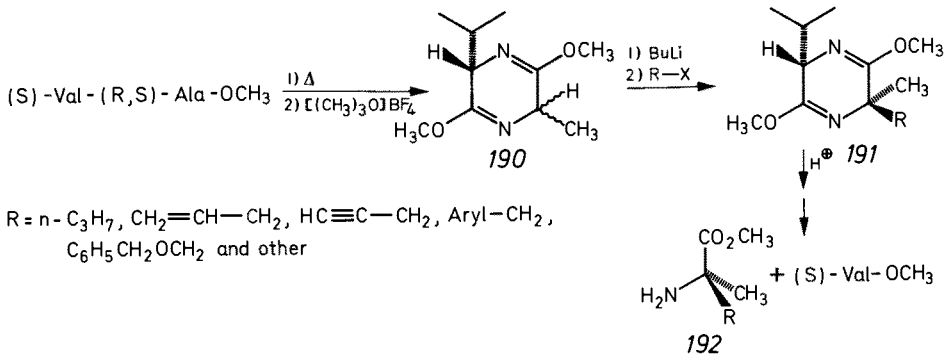
Bis-lactim ethers (187) contain a chiral inducing center, an acidic carbon-hydrogen bond, and two sites susceptible to hydrolysis. They may react with BuLi to give lithium compounds of type (188), which possess a prochiral carbon atom. Lithium compounds, like (188), smoothly add electrophiles (such as alkylating agents or carbonyl compounds) with outstanding diastereoface differentiation. In many cases the d.s.-value of the adduct exceeds 95%. On hydrolysis, the adducts were cleaved, liberating the chiral auxiliary and the desired products, the optically active amino acids (189) or amino acid methyl esters. The recovered chiral auxiliary (also an amino acid or an amino acid methyl ester) and the target molecule (189) are separable either by fractional distillation (esters) or by chromatography (free acids). In Scheme 93 the enantioselective synthesis of α-methyl amino acids is given as an example for a successful application of Schöllkopf's now well-established *bis*-lactim ether method.

"Symmetrical" *bis*-lactim ethers of type (187) — built up from two identical amino acids — do have one disadvantage, inherent in the system: only 50% of the chiral auxiliary — in this case (S)-alanine — is recovered; the other 50% is first racemized via (188) and finally incorporated in the product (189). To avoid this disadvantage Schöllkopf et al. have developed methods to synthesize "mixed" *bis*-lactim ethers, starting from two different amino acids, e.g. (S)-valine and (R,S)-alanine. Thus, the authors obtained cyclo [(S)-val-(R,S)-ala] and prepared the related *bis*-lactim ether (190).

The *bis*-lactim ether (190) was metallated with BuLi regiospecifically in the alanine part of the molecule to produce, after the reaction with alkyl halides, the (3R)-adducts (191) with ds > 95%. Upon hydrolysis the (R)-α-methyl amino acid esters (192) were obtained with e.e. values >95% [189].



R = i - C_3H_7, $CH_2CH{=}CH_2$, CH_2 - Aryl, $C(OH)(C_6H_5)_2$, n - C_8H_{17}, Cinnamyl

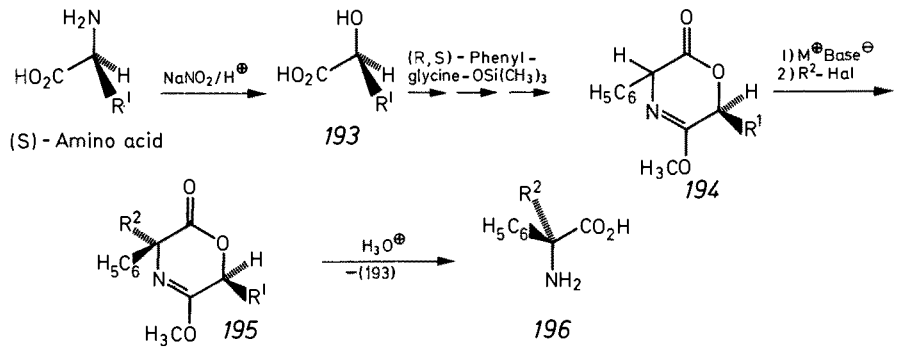


R = n-C_3H_7, $CH_2{=}CH{-}CH_2$, $HC{\equiv}C{-}CH_2$, Aryl$-CH_2$, $C_6H_5CH_2OCH_2$ and other

Applying the *bis*-lactim ether method, Schöllkopf and co-workers synthesized enantioselectively

— α-unsubstituted amino acids from cyclo [(S)-val-gly] [188],
— (S)-cystein derivatives [188,190] with the *bis*-lactim ether of cyclo [(S)-val-gly] [188],
— (S)-α-methyl-cystein derivatives [190,191] using (190) as chiral auxiliary reagent,
— α-methyl serines and α-alkenyl serines by allowing (188) to react with ketones and aldehydes [188,192], respectively,
— (2R)-serines starting with the *bis*-lactim ether of cyclo [(S)-val-gly] [193].

3,6-Dihydro-3-phenyl-2*H*-1,4-oxazin-2-ones (194) [194] were synthesized from (R,S)-phenylglycine and (S)-2-hydroxyalkanoic acids (193), the latter derived from (S)-amino acids. The heterocycles (194) contain an endocyclic chiral center at C-6. Metallation of (194) and subsequent treatment with alkyl halides produced the adducts (195) in good chemical yields and with d.s. values from 50 up to more than 95% due to an asymmetric induction. On hydrolysis of the heterocycles (195), the 2-hydroxy-alkanoic acids (193) and the optically active (S)-α-alkyl-α-phenylglycines (196) were liberated [194].

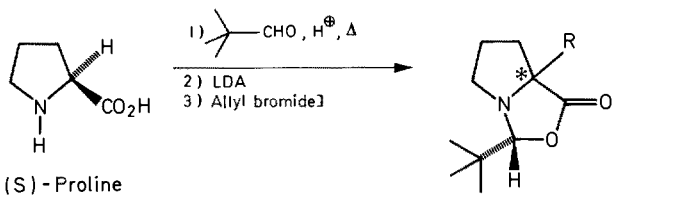


R^1 = i-C_3H_7, t-C_4H_9, C_6H_5, $CH_2C_6H_5$ R^2 = CH_3, $CH_2{=}CH{-}CH_2$, $C_6H_5CH_2$

The asymmetric methylation of N-benzylidene-(R,S)-phenylalanine methyl ester was carried out [195] in the presence of lithium salts of secondary amines derived from

(S)-proline. The lithium amides of *poly*-(imino-1-isobutylethylene) and its corresponding low-molecular-weight model compound, derived from (S)-leucine, were similarly used in order to examine the polymer effects with regard to the stereoselectivity. After acetylation, N-acetyl-α-methylphenylalanine was obtained in max. 31% optical yield [195].

Seebach and Naef [196] generated chiral enolates with asymmetric induction from α-heterosubstituted carboxylic acids. Reactions of these enolates with alkyl halides were found to be highly diastereoselective. Thus, the overall enantioselective α-alkylation of chiral, non-racemic α-heterosubstituted carboxylic acids was realized. No "external" chiral auxiliary was necessary in order to produce the α-alkylated target molecules. Thus, (S)-proline was refluxed in a pentane solution of pivalaldehyde in the presence of an acid catalyst, with azeotropic removal of water. (197) was isolated as a single diastereomer by distillation. The enolate generated from (197) was allylated and produced (198) with a d.s. value >98%. The substitution (197) → (198) probably takes place with retention of configuration [196].



(S)-Proline

197 R = H
198 R = CH_2—CH=CH_2

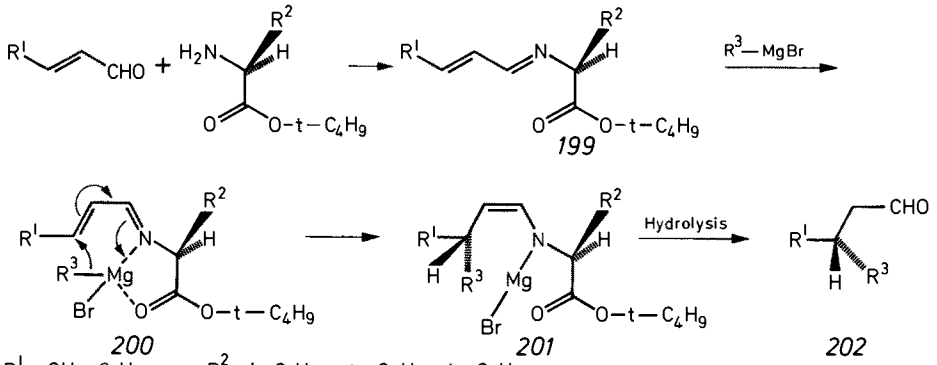
A group at the Academy of Sciences in Moscow [197] has synthesized chiral threonine. Derivatives of cyclic imino acids form copper complexes with glacine and carbonyl compounds. Hydroxyethylation with acetaldehyde and decomposition of the resulting complexes produced threonine with an optical purity of up to 97–100% and with *threo/allo* ratios of up to 19:1 [197]. The chiral reagents could be recovered and re-used without loss of stereoselectivity. The mechanism of this asymmetric synthesis of amino acids *via* glacine Schiff base/metal complexes was also discussed [197].

3.2.3 Reactions at the β-Carbon Atom of Carbonyl Groups

Michael-Additions: The most important application of this type of reaction is the carbon-carbon bond formation β to a carbonyl function by the addition of carbanion. The asymmetric version of the Michael-addition has been known since 1973. An optically active vinyl sulfoxide served as chiral auxiliary [198].

The first Michael-addition with induction of asymmetry under the influence of an chiral amino acid derivative was reported by Koga et al. [199] in 1976. Thus, the 1,4-addition of Grignard reagents [199a] and potassium diethyl malonate [199b] to chiral α,β-unsaturated aldimines (199) was realized. It was suggested that acting as a base to give a metallodinamine, the Grignard reagent produced a chelated complex (200) which transfers an alkyl group to the adjacent electrophilic position of the

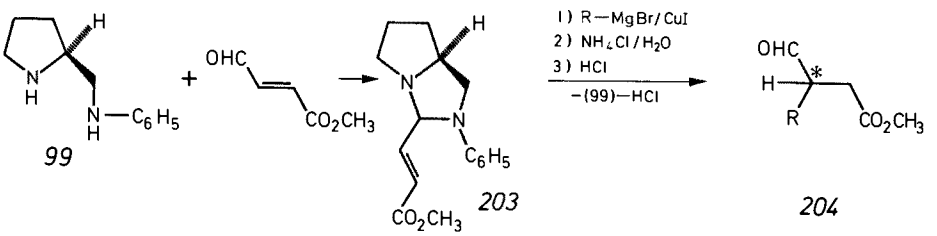
aldimine to produce (201). Hydrolysis produced the (R)- or (S)- aldehyde (202) in high optical yield (63–98%) depending upon the configuration of the chiral α-amino acid auxiliary. Alternatively, the enantiomer of (202) could be obtained by simply exchanging the R^1 group in aldimine (199) for the R^3 group in the Grignard reagent while retaining the same chiral amino acid reagent.



199 200 201 202

A useful method for the diastereoselective and enantioselective synthesis of *trans*- and *cis*-1,2-disubstituted cycloalkanecarboxaldehydes was devised by Koga et al. [199f] starting from cycloalkanecarboxaldehydes. (S)-*tert.*-Leucine *tert.*-butyl ester, a highly effective chiral auxiliary reagent, could be recovered for recycling without any loss of optical purity in a reaction sequence similar to that in the acyclic synthesis of (202).

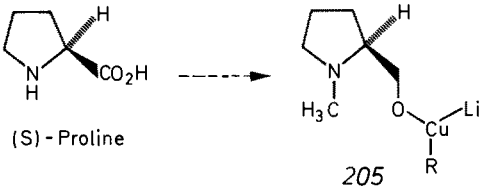
Mukaiyama et al. [200] synthesized optically active 3-substituted succinialdehyde acid esters (204) via a Michael-addition. The methyl ester of fumaraldehydic acid was converted into the corresponding aminal (203) by treatment with the (S)-proline-derived chiral diamine (99). The Michael-addition of Grignard reagent to the aminal, followed by hydrolysis produced stereoselectivily 3-substituted succinaldehydic acid ester (204) in good yield.



99 203 204

R = C_2H_5 (93%ee), $CH_3(CH_2)_2$ (89%ee), i-C_3H_7 (85%ee), n-C_4H_9 (93%ee), n-C_5H_{11} (92%ee), $C_6H_5CH_2$ (35%ee)

In the reaction of 2-cyclohexenone and of 4-phenylbut-3-en-2-one with chiral organocuprates of type (205), optical yields of only 5% and 15%, respectively, were obtained [201]. Methylation of 1,3-diphenyl-2-propene-1-one with (205) (R = CH_3) produced (S)-1,3-diphenyl-1-butanone in 68% enantiomeric excess [202].



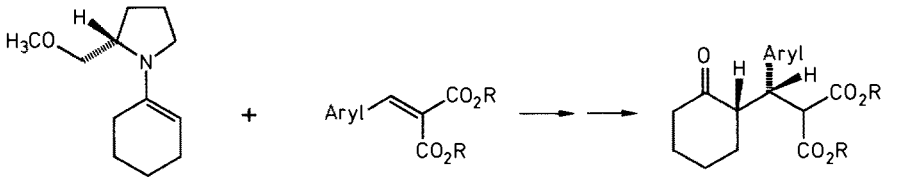
205

When (2S)-1-(1-cyclohexene-1-yl)-2-(methoxymethyl)pyrrolidine (206), enamine from cyclohexanone, and (S)-proline-derived (2S)-(methoxymethyl)pyrrolidine is added to the Knoevenagel condensation products (207), mainly one of the possible four diastereomers is formed. The diastereomeric purity was found to be excellent (d.s. > 90%) [203]. The stereochemical course of this highly effective asymmetric synthesis allowed the synthesis of the optically active target molecules (208). A possible mechanism discussed by Blarer and Seebach [203].

In related asymmetric Michael-additions of enamine (206) and 2-aryl-1-nitroethylenes, only one of the four possible enantiomerically pure diastereomers was formed [204]. Hydrolysis of the crude primary products furnished α-alkylated cyclohexanones of >90% enantiomeric excess [204].

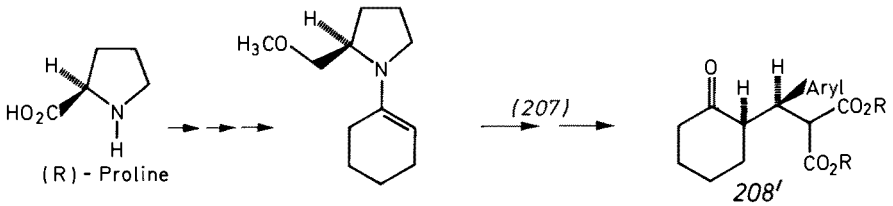
Instead of introducing the (S)-proline-derived chiral auxiliary (206), its enantiomer in the Michael-addition, the authors obtained the enantiomeric product (208') having opposite optical rotation compared to (208).

Table 7. Asymmetric Michael-Addition of Knoevenagel Condensation Products

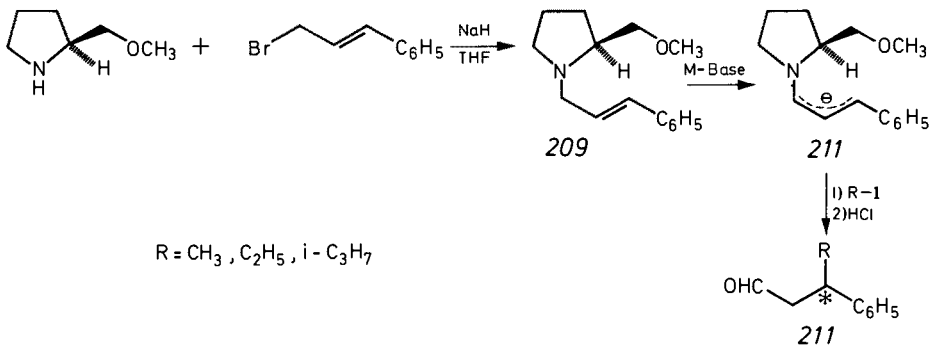


206 207 208

		Ketodiester *208* crude		
Aryl	R	Yield (%)	ds (%)	ee (%)
C_6H_5	C_2H_5	70	>95	95
C_6H_5	CH_3	76	>95	92
4-Cl—C_6H_4	CH_3	53	88	80
4-NO_2—C_6H_4	CH_3	35	88	83
3,4-(OCH_2O)—C_6H_3	CH_3	35	95	82



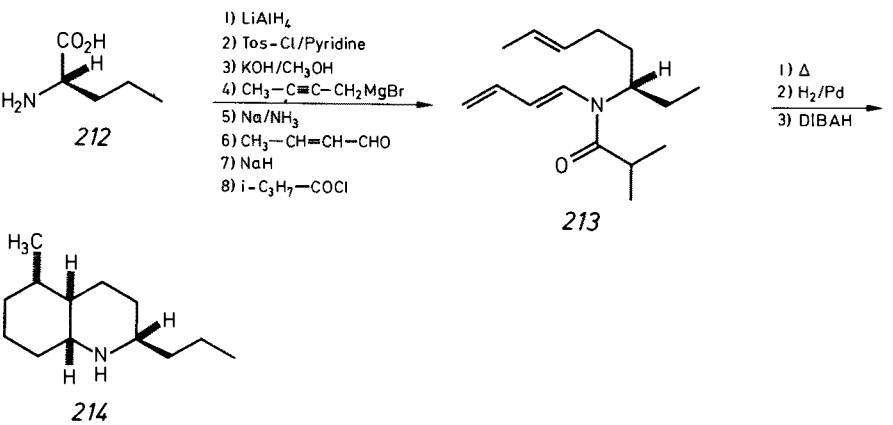
Enders et al. [205] metalated the (S)-proline-derived chiral allylamines (209). The resulting homoenolate (210) was subsequently alkylated. Upon hydrolysis β-substituted aldehydes (211) were obtained (e.e. = 64–67%).



The bacteriostatic gliotoxin was prepared [206] by a total synthesis involving an asymmetric Michael-addition. A chiral amino acid derivative served as chiral auxiliary in the key step.

3.2.4 Cycloadditions

The use of a chiral dienophile or enophile in the Diels-Alder reaction effects asymmetric induction. This asymmetric Diels-Alder chemistry, pioneered by Korolew and

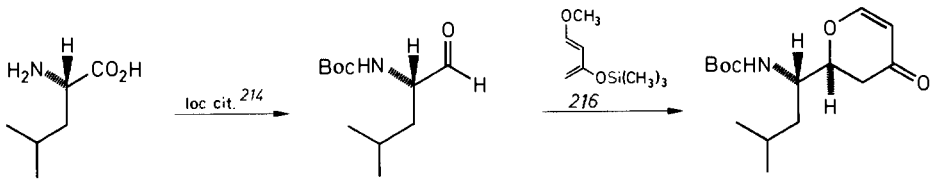


Mur [207], has received renewed interest in recent years. A fine review covering the intermolecular asymmetric Diels-Alder reaction was compiled by Mori [208]. In this article the use of terpenes and carbohydrates as chiral auxiliaries is discussed; no amino acid derivatives are mentioned in this context. A chiral α-hydroxycarboxylic acid derivative was also used to achieve an asymmetric Diels-Alder reaction [209]. High asymmetric induction could be detected in the intramolecular Diels-Alder reaction of chiral molecules.

Thus, (2R)-pumiliotoxin C (214) has been prepared from (R)-norvaline (212). The asymmetric center in the triene (213) controls the configuration at three carbon atoms [210]. α-Kainic acid, isolated from the algae *Digena simplex* and *Centrocerus clavulatum*, was prepared by total synthesis. Its enantioselective synthesis involved a stereocontrolled intramolecular cycloaddition of a (S)-glutamic acid [211]. Asymmetric cycloadditions also play a decisive role in the synthesis of chiral cytochalasins. In this case [212] the primary chiral information was carried by (S)-alanine and (S)-phenylalanine, respectively.

The (S)-leucine derivative (215) was allowed to react with diene (216) to afford the *threo* isomer (217) as the major product (d.s. = 80%) [213]. Mukaiyama et al. [215] have reported the total synthesis of the sesquiterpene (+)-farnesiferol, starting from (R)-phenylglycinol, a derivative of the amino acid (R)-phenylglcine. They key step of this synthesis was an asymmetric Diels-Alder reaction.

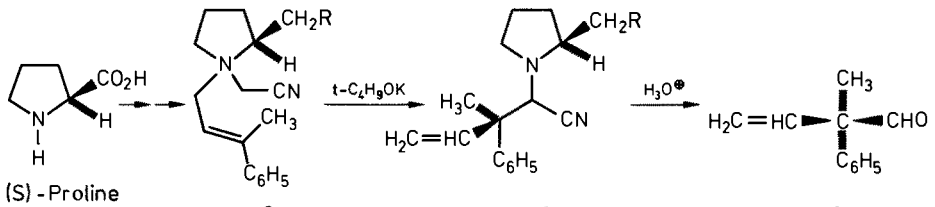
Baggiolini et al. [216] have succeeded in synthesizing the vitamin d-biotin from (RR)-cystine *via* intramolecular [3 + 2] cycloaddition with a d.s. value of 80%. Danishefsky et al. [217] synthesized pretyrosine, the biosynthetic precursor of (S)-tyrosine, by a [4 + 2]-cycloaddition applying an (S)-glutamic acid derivative as chiral auxiliary. Phenylglycine was used as the source of the chiral information in an asymmetric variation of a 1,3-dipolar cycloaddition, as reported by Grigg and Kemp et al. [218].



(S)-Leucine 215 217

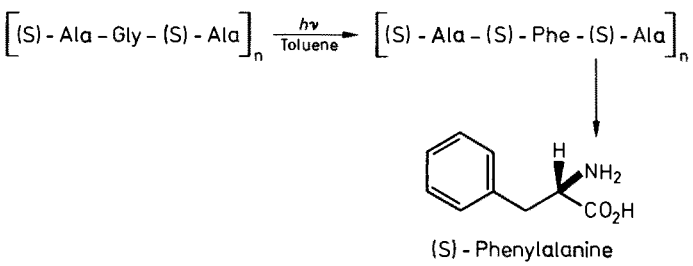
3.2.5 [2,3]-Sigmatropic Rearrangements *via* Chiral Ammonium Ylides

The [2,3]-sigmatropic rearrangement of (E)-(218a), a derivative of the chiral cyclic α-amino acid (S)-proline, produced the aminonitrile (219) in a stereoselective manner. Saponification of (219) yielded (+)-2-methyl-2-phenyl-3-butenal (220) with an enantiomeric excess of 90% [219]. In replacing the benzyloxymethyl moiety in (218a) by a methyl group, the optical purity of the chiral aldehyde (220) obtained in the corresponding reaction sequence decreases considerably [219].



3.2.6 Stereoselective Photochemical Syntheses

Asymmetric synthesis, either enantioselective or diastereoselective, has seldom been performed by photochemical reactions. One of the first examples that may be classified as a photochemical asymmetric synthesis is the photoalkylation of the most simple amino acid, glycine. Elad and Sperling [220] demonstrated that, if glycine is part of a polypeptide chain, there is good control (up to 40% e.e.) in the creation of the new chiral center. A radical mechanism operates after the first step of photoinitiation of the process.



Thus, glycine, as part of a peptide chain, was stereocontrol-alkylated by irradiation in the presence of toluene. The new asymmetric center was induced by (S)-alanine moieties in the peptide chain.

The protoberberine alkaloid, xylopinine, has been synthesized in an optically active form by Kametani et al. [221]. A key reaction in this synthesis was the photochemical cyclization of the optically active amino acid derivative 1,2,3,4-tetrahydro-6,7-dimethoxy-3-methoxycarbonyl-1-methylene-2-veratroylisoquinoline with 1,3 asymmetric induction (d.s. $<50\%$). Eschenmoser et al. [222] discovered a photochemically-induced secocorrin → corrin cycloisomerization; an (S)-glutamic acid derivative served as the source of chiral information in this transformation.

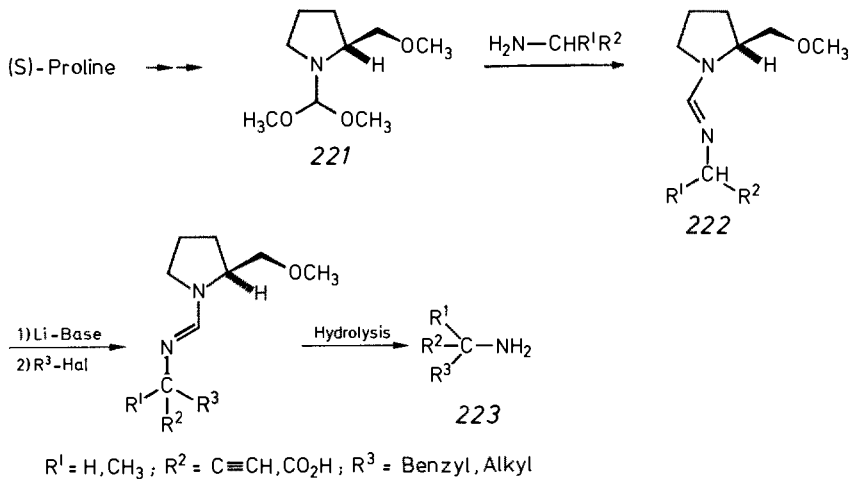
3.2.7 β-Lactam Syntheses

The asymmetric synthesis of β-lactames is still of interest to many organic and pharmaceutical chemists because of the great importance of these antibiotics. A detailed

discussion of the numerous β-lactam syntheses which involves the induction of asymmetry by chiral amino acids is beyond the scope of this review article. Therefore, the reader is referred to reviews [223] and some more recent original publications describing the asymmetric synthesis of β-lactames starting from chiral amino acids, particularly serine [224,225], threonine [225,226], asparagin [227], and aspartic acid [228].

3.2.8 α-Alkylation of Amines

Kolb and Barth [229] synthesized α-substituted optically active amines or amino acids (223). Again the authors employed a derivative of naturally occurring (S)-proline, namely (—)-(S)-1-dimethoxymethyl-2-methoxymethyl-pyrrolidine (221) as chiral auxiliary agent. The metalation of the amidines (160) leads to azaallyl anions homologous with (222). After alkylation and hydrolysis, the desired α-substituted amines and amino acids, respectively, are obtained with some stereoselectivity.

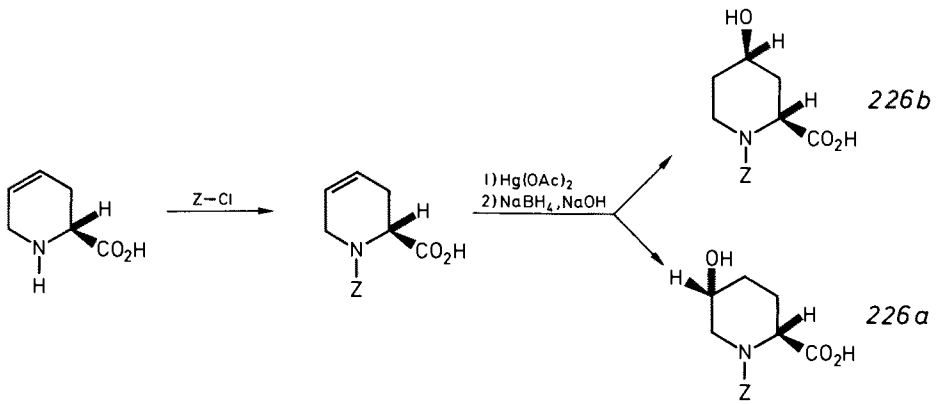


3.3 Other Reactions Taking Place with the Transfer of Asymmetry

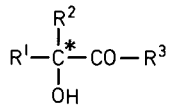
In this Section we will mainly concentrate on stereoselective addition reactions involving the transformation of sp^2 carbon atoms in C=C, C=O and C=N functions to sp^3 hybridization; these reactions do not include hydrogenation- and reduction-type transformations which were addressed in Sect. 2.1, 2.2, and 3.1.

3.3.1 Addition of XH-Compounds to C=C Double Bonds (X = O,S,Halogen)

The naturally occurring chiral amino acid (S)-baikiain (224) is an attractive substrate for the preparation of 5- or 4-substituted pipecolinic acids. (S)-Baikiain (224) is a non-proteinogenic imino acid which can be isolated from in Rhodesian teak wood (*Baikiea plurijuga*). After protecting the nitrogen function of (224), Callens, Anteunis, and Reyniers [230] have oxymercurated (225) using $Hg(OAc)_2$. After reductive work-up with $NaBH_4$/NaOH the authors isolated a 7:3 mixture of Z-(2S,5R)-5-hydroxy-pipecolic acid (226a) and Z-(2S,4R)-4-hydroxy-pipecolic acid (226b).

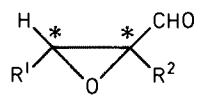


Terashima et al. [231] reported an asymmetric halolactonization reaction. This highly stereoselective reaction permits the synthesis of intermediates for the preparation of chiral α,α-disubstituted α-hydroxycarboxylic acids (227) [231c], α-hydroxyketones (228) [231c], functionalized epoxides (229) [231d,e] and natural products [231h,j]. Only amino acids have so far been used as a source of the chiral information in the asymmetric halolactonization reaction. Again, the best results have been obtained by using cyclic imino acid enantiomers, namely proline.



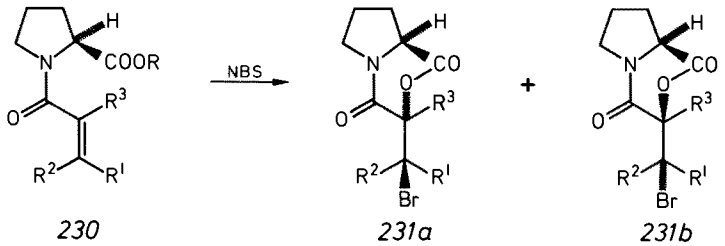
227, R^1, R^2 = Alkyl or Aryl, R^3 = OH

228, $R^1, R^2 R^3$ = Alkyl or Aryl

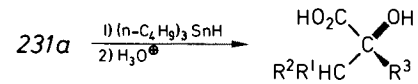


229, R^1, R^2 = Alkyl or Aryl

α,β-Unsaturated N-acyl-(S)-prolines (230) were treated with N-bromo-succinimide (NBS). The halolactonization leads to the formation of a mixture of diastereomeric lactones (231a) and (231b), (231a) being the major product (d.s. > 90%) [231].



230 *231a* *231b*

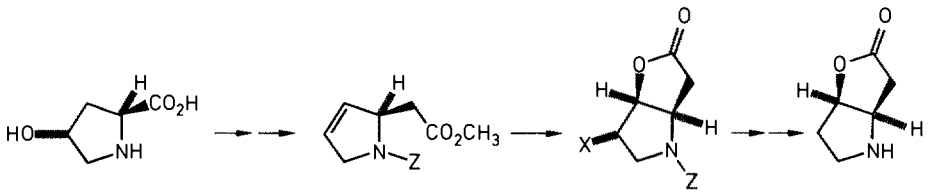


R^1 = H, CH_3, n-C_6H_{13}, C_6H_5; R^2 = H, CH_3; R^3 = CH_3

The asymmetric induction in the formation of (231) proceeds *via* a bromonium ion [231c]. Debromination of (231a) with tri-*n*-butyltin hydride followed by saponification gave the chiral α-hydroxycarboxylic acid (232) in high optical purity. (S)-proline was recovered for recycling.

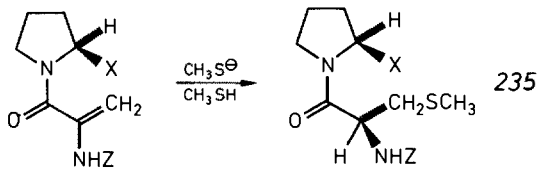
In the total synthesis of an anthracycline antibiotic, the key step was an asymmetric halolactonization reaction. The corresponding bromolactones were formed with high stereoselectivity (d.s. > 90%). (S)-Proline was used as chiral auxiliary.

The 4-hydroxy-(S)-proline-derived acid (232) was subjected to electrophilic lactonization either with J_2-KJ-$NaHCO_3$ to yield the iodolactone (233a), or benzeneselenyl chloride to give the phenylselenolactone (23b). Reductive removal of X from these products was achieved with tri-*n*-butyl- or triphenyltin hydride, followed by hydrogenolysis to yield (234) with at least 99% optical purity [231j].



Stereoselective formation of 3-alkyl-6-methoxy-2,5-piperazine-dione derivatives by the addition of methanol in the presence of NBS to 3-alkyl-6-alkylidene-2,5-piperazinediones was recently reported by Shin et al. [232]. The asymmetric induction in this reaction was accomplished by the chiral center of a derivative of the natural proteinogenic chiral amino acid threonine.

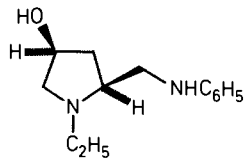
While investigating the biomimetic formation of cysteine, Schmidt et al. [233] added thiolates to N-protected chiral α-aminoacrylic acid derivatives (dehydropeptides). (235) was obtained in optical yields up to 90%.



X = $CONHCH_3$, $CONH_2$, $CON(CH_3)_2$; Z = $C_6H_5CH_2OCO$

An analogue of the drug captopril (1) was prepared by Vasella et al. [234] by a similar approach. In this case the diastereoselectivity was very low.

The asymmetric addition of thiolates to 2-cyclohexenone was induced in an intermolecular induction process by catalytic amounts of the 4-hydroxy-(S)-proline derivative (236) [235].

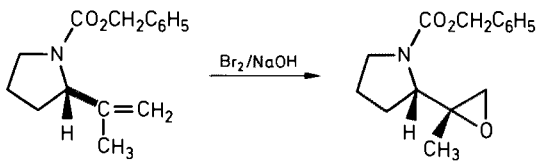


236

Recently, tryptophane has been converted to the methyl ester of lysergic acid in ten steps, involving a stereoselective HBr-addition to a C=C double bond [236].

3.3.2 Epoxidation

A stereoselective total synthesis of dendrobatide toxin 251 D was developed by Overman et al. [237] involving an epoxidation of the (S)-proline derivative (237) to furnish the oxirane (238) as major product. In their approach towards the total synthesis of the same natural product Thomas et al. [238] investigated the stereoselectivity of the epoxide formation from (S)-5-acetylpyrrolidin-2-one and dimethyloxosulfonium methylide. A diastereoselectivity of d.s. 50–60% was achieved [238].



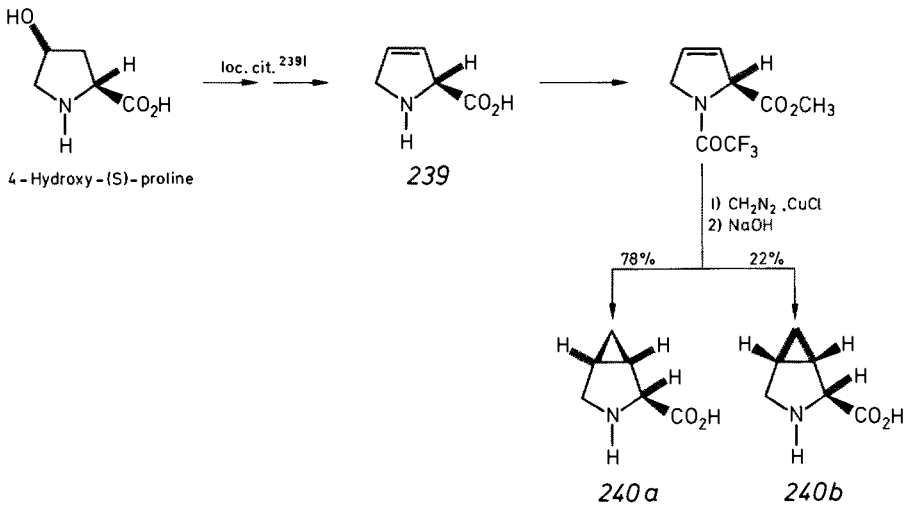
237 238

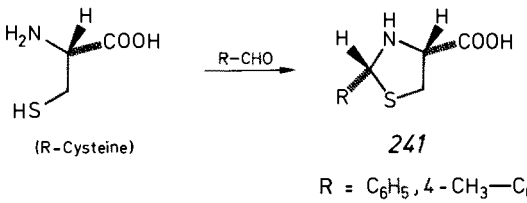
3.3.3 Carbene Addition to a C=C Double Bond

The observation that *cis*-3,4-methylene-(S)-proline (240a) isolated from *Aesculus parviflora* (the buckeye chestnut of the USA) had significant effects on pollen viability, has initiated renewed interest in the chemistry of this cyclic imino acid. Thus, 4-hydroxy-(S)-proline was converted [239] into (S)-3,4-diadehydroproline (239), and its N-trifuoroacetyl methylester was successfully reacted with diazomethane to yield, after deprotection, the desired target molecule (240a) as the major product. A minor product was *trans*-3,4-methylene-(S)-proline (240b) [240].

3.3.4 Addition of X—H-Compounds to C=O Double Bonds (X = S,N,O)

Reactions of carbonyl compounds with vicinal aminothiols, particularly with (R)-cysteine and (S)-penicillamine (4), are of chemical, biochemical, and pharmacological interest and have been investigated extensively. When (R)-cysteine was condensed with benzaldehydes, the corresponding thiazolidine compound (241) was obtained in almost quantitative yield [241]. This reaction occurs stereospecifically [241].





The increasingly accepted hypothesis that acetaldehyde may be the causative agent in initiating the multitude of acute pharmacological and chronic pathophysiological effects of alcohol prompted Nagasawa et al. to seek methods to reduce its blood levels. One possibility would be the administration of (S)-penicillamine (4), a compound related to cysteine. The condensation of this amino acid with acetaldehyde produced 2,5,5-trimethylthiazolidine-4-carboxylic acid [242]. The chirality of this compound was deducted by NMR analysis to be 72% 2S, 4S and 28% 2R, 4S. Thus, this result is consistent with the configuration found previously for the thiazolidines formed from (R)-cysteine and aldehydes [241].

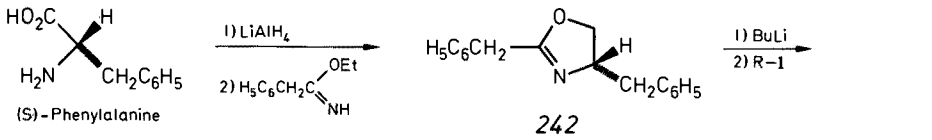
An asymmetric synthesis of the vitamin (+)-biotin has been reported [241a] using thiazoline (241) as substrate.

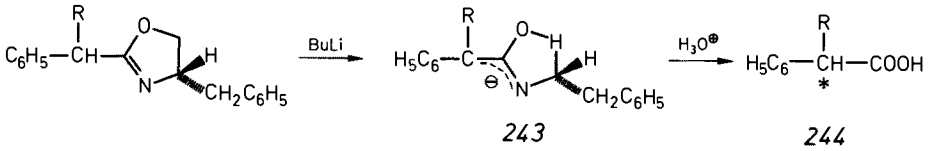
Addition of (S)-α-amino acids to β,β-dibromo-α-imino acids proceeded to produce the corresponding optically active α,α-diamino acid derivatives with d.s. = 33 to 85% [243].

The diastereoselective condensation of pivalaldehyde and (S)-proline was described by Seebach and Naef [196] to yield (197).

3.3.5 Equilibration and Stereoselective Protonation

In the synthesis of optically active 2-phenylalkanoic acids (244), a derivative of (S)-phenylalanine was used as a chiral auxiliary [244]. The carboxylic acids (244) were obtained in optical yields of up to 53%.

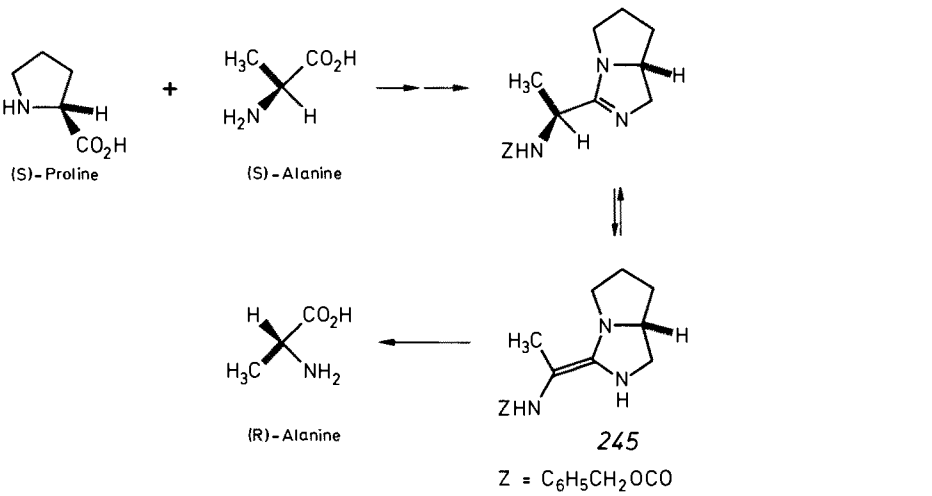




R = CH_3 , C_2H_5 , i - C_3H_7 , n - C_4H_9, n - C_5H_{11}

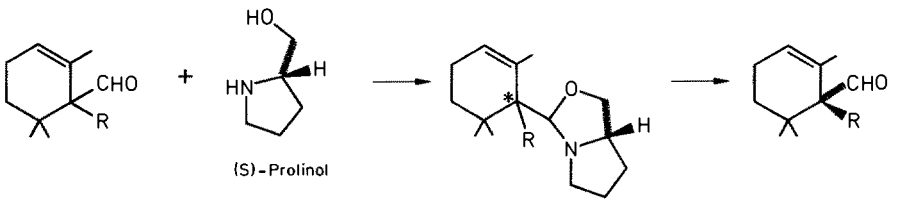
Chiral oxazolines (242), which had been originally used by Meyers et al. for asymmetric synthesis, were also applied for the asymmetric transformation of 2-chloroalkanoic acids to produce chiral 2-chloroalkanenecarboxylic acids in 45–73% optical yield [245].

Imidazolines (245) have been prepared from (S)-alanine and (S)-proline. Upon hydrolysis (R)-alanine was obtained. This result can be explained in terms of epimerization and stereoselective protonation with asymmetric induction by the chiral center originating from (S)-proline [246].



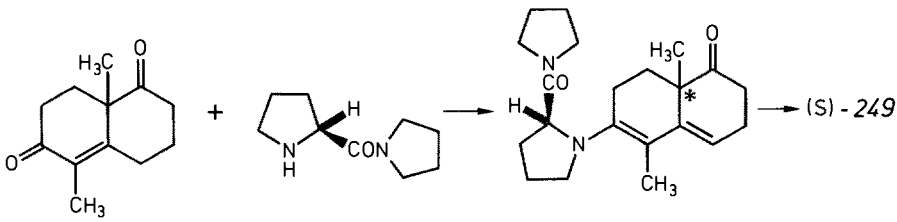
(R)-Alanine was obtained from (245) in an optical yield of up to 94% [246]. Non-natural alanine can, of course, also be obtained from racemic alanine in this reaction sequence.

Racemic 6-benzoyloxycyclocitral (246) has been converted to (S)-6-hydroxycyclocitral (248) *via* the oxazolinone (247). (248) was obtained in 63% enantiomeric excess [247].



246 R = H, $OCOC_6H_5$ 247 R = H, OH 248 R = H, OH

By heating the racemic Robinson annelation product (249) with an equimolar amount of (S)-proline pyrrolidide (250), the related dienamine (251) was obtained, which, upon hydrolysis was converted to (S)-(249) [248].

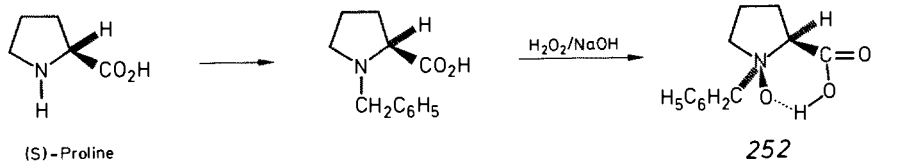


249 250 251

Kinetics and stereochemistry of deuterium exchange of the α-hydrogen of an amino acid moiety in metal complexes of amino acid Schiff bases with *ortho*-hydroxyacetophenone have been studied by Belokon et al. [249].

3.3.6 Nitrogen, Phosphorus and Sulfur Atoms as Asymmetric Centers

Chiral N-Oxides [250]: In the reaction of N-benzyl-N-methylamino amino acids with H_2O_2 in alkaline water solution, mixtures of diastereomeric N-oxides, containing new centers of chirality on nitrogen atoms, were obtained. The reaction was performed with the corresponding derivatives of (S)- [or (R)] alanine, (S)- [or (R)] leucine, (S)- [or (R)] phenylalanine, and (S)- [or (R)] proline, respectively. In the reaction a distinct stereoselectivity could be observed: for alanine, leucine, and phenylalanine derivatives the formation of $N_{(S)}C_{(S)}$, or correspondingly $N_{(R)}C_{(R)}$ diastereomer is favoured. The reaction of (S)-proline derivatives leads, however, exclusively to the $N_{(R)}C_{(S)}$ stereoisomer (252); on the other hand, (R)-proline yielded stereoselectively the $N_{(S)}C_{(R)}$ compound (253).



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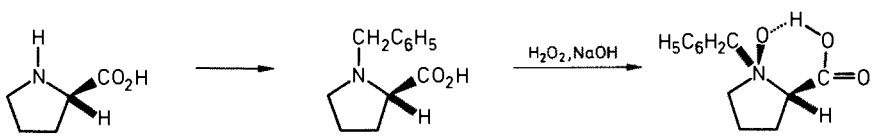
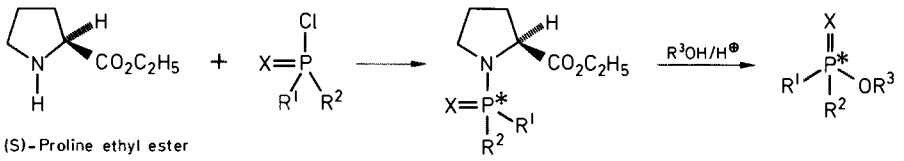


253

Chiral Phosphorus Compounds: Koizumi et al. [251] have prepared a series of chiral organophosphorus compounds (256) in which the phosphorus atom is the asymmetric center, whereby amino acid derivatives were used as chiral auxiliary reagents.

The reaction of phosphonic acid chloride (254) with (S)-proline ethyl ester afforded a mixture of diasteromeric amides (255) in high diastereoselectivity. The diastereomers (255) can easily be purified by chromatography. The chiral, practically optical pure organophosphorus compound (256) was obtained from purified (255) by acid alcoholysis.



254 255 256

X = O, S
R^1 = CH_3, C_6H_5, OC_6H_5
R^2 = C_2H_5, n-C_4H_9, C_6H_5, OC_6H_5
R^3 = CH_3, C_2H_5, n-C_3H_7, i-C_3H_7

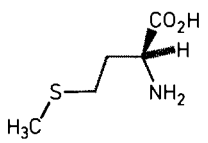
Some diastereoselectivity was also observed in the reaction of (S)-prolinol with the dichloride (257) leading to the chiral organophosphorus compounds (258).

257 258a 258b

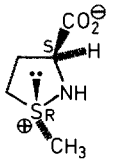
X = O, S

Chiral Sulfur Compounds: Dehydromethionine was first prepared by Lavine [252], who correctly assigned its structure (without regard to relative stereochemistry). An analysis of the crystal structure of the racemic compound revealed the carboxy-group to be on the opposite side of the ring to the S-methyl group. The structure of the dehydromethionine derived from (S)-methionine is therefore that of compound (259), having the (1R,3S)-configuration [253]. (259) is readily obtained by oxidizing (S)-methionine with iodine in methanol, and although this oxidation normally pro-

duces sulfoxides from sulfides, (259) is formed because of intramolecular attack by the amino-group in a sulfonium iodide intermediate. The stereochemistry of the conversion [253b] of dehydromethionine (259) into methionine sulfoxide (260) was also studied. Dehydromethionine (259) was treated with alkali hydroxide in water and, after neutralization, the addition of acetone led to the precipitation of (260). This produced methionine sulfoxide (260) in yields of 80–85 % and with $[\alpha]_D^{24} = +120°$ (C = 1.8 in 1N hydroxychloric acid), compared with the highest reported value for (S)-methionine-(S)-sulfoxide (260) of +131°. Thus, the preparation of (260) from (S)-methionine *via* (1R,3S)-dehydromethionine (259) is not as stereospecific as the oxidation of (S)-methionine with H_2O_2 [252] or gold (III) chloride [254]. However, it has the advantages of being rapid, experimentally simple, and of using radily available, cheap starting materials [253b].



(S)-Methionine



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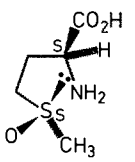

260

Other sulfoxides of high optical purity have been derived from enantiomers of cysteine [255] and methionine [256].

3.3.7 Miscellaneous

Recent developments regarding the utility of chiral amino acids in asymmetric synthesis of natural products were reported. Examples of such syntheses are the preparation of carbohydrates from (S)-glutamic acid [257], (S)-alanine [258], or (S)-threonine [259], and syntheses of alkaloids [260], terpenes [261], peptide [262] derivatives, and toxines [263].

A chiral recognition was observed in aminolysis of 3-acyl-4(R)-methoxycarbonyl-1,3-thiazolidine-2-thione, a derivative of (R)-cysteine, by racemic amines to give an optically active amide [(S)-excess] and amine [(R)-excess] [264]. In the reaction of cyclic *meso*-1,3-diols with chiral N-protected phenylalanyl chlorides, Yamada et al. [265] observed the preferential formation of one of the two possible diastereomeric monoesters, which has been used for the synthesis of optically active steroids [266] and prostaglandins [267].

The asymmetric synthesis of (1R,3S)-*cis*-chrysanthemic acid was reported by Mukaiyama et al. [268]; (R)-phenylglycinol was used as chiral auxiliary.

Asymmetric transformations of α-amino acids promoted by optically active metal complexes have been reported by several groups [269]. The control of the stereoselective hydrolysis reactions of racemic esters by chiral micellar compounds prepared from amino acids has been intensively investigated [270].

4 Concluding Remarks

Asymmetric synthesis has evolved rapidly during recent years. Most of the progress is registered in synthetic methods; less emphasis has been given to theoretical concepts and mechanistic studies. Methods have been devised for achieving optical yields exceeding 95%. A number of stochiometric reactions with respect to the chiral auxiliary moiety are now highly efficient.

A trend in asymmetric synthesis is the utilization of cheap chiral products such as amino acids, hydroxy acids, sugars, or terpenes as starting materials or catalysts. Nature provides us with a wide range of these optically active natural compounds ("chiral pool"). Particularly frequent use is made of sugars and naturally occurring hydroxycarboxylic acids such as tartaric acid and malic acid. In recent years, however, increasing use has been made of amino acids as educts in asymmetric syntheses. Until 1981, the induction of asymmetry by amino acids was the subject of roughly 250 original papers, most of which were published in the last ten years. Surveying the existing literature to date (September 1983) it is notable that by now 400 research reports have been published which deal with the topic of this review. Thus, drastically increasing use has been made of amino acids as educts in asymmetric syntheses. One reason for this development is the growing interest in asymmetric synthesis as such. Another reason should also be noted: amino acids are particularly versatile chiral compounds, most are available in significant quantities and — other than in the case of sugars and hydroxycarboxylic acid — both enantiomers of many amino acids are being produced or could be produced on an industrial scale.

Strikingly high stereoselectivities have been achieved in asymmetric syntheses with optically pure proline or proline derivatives, probably due to the rigidity of the five-membered ring. Other preferably used chiral auxiliaries include (S)-phenylalanine, (S)-valine and tert.-(S)-leucine.

From an industrial chemist's point of view the use of proline, phenylalanine, valine, and other commercially available amino acids, is fine. To date, however, tert.-(S)-leucine is still an exotic compound. It should also be noted that the recycling of the chiral amino acid moiety is of importance for possible technical processes. On the other hand, the recovery of the chiral auxiliary sometimes does not make sense, especially in syntheses which the require the use of stochiometric amounts of expensive reagents, e.g. LDA.

Traditionally, amino acids have been utilized in the mainstream of organic chemistry primarily as building blocks for peptide syntheses. One may expect that in the future the use of amino acids as starting materials for non-peptide compounds will be a subject of ever-increasing interest. Many chiral target molecules with widely variable structures will be prepared from amino acids in the future.

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