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Modern Asymmetric Synthesis of α-Aminoacids

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The principal aspects of the asymmetric synthesis of α-aminoacids with a large variety of structures are surveyed and the questions of the appearance of asymmetric induction as a result of the chirality of the catalyst, the initial compound, the reagent, or the leaving group are discussed. Studies carried out in recent years using chiral reagents capable of being regenerated and catalytic methods are examined in detail. The asymmetric reactions of α-aminoacids and other methods of synthesis are discussed briefly. Examples of the synthesis of aminoacids from chiral compounds without involving the chirality centres are not considered.
The bibliography includes 299 references.

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I. INTRODUCTION

Aminoacids are widely distributed in nature and more than 500 have been discovered hitherto.[1] Despite the wide variety of the existing methods,[2,3] the search for new ways of synthesising α-aminoacids (AA) remains of current inerest, racemic AA being usually synthesised from readily available compounds under conditions ruling out multistage reactions,[4] for example:

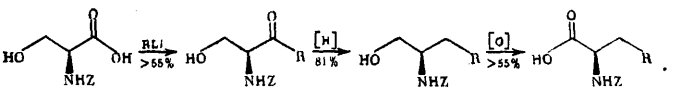
$$PhCH_2Cl + MeCONH_2 + MeCOBu \xrightarrow[Co_4(CO)_{12},110^\circ]{H_2,CO} (R, S)\text{-Phe}.$$

The development of the asymmetric synthesis of AA in recent years was dictated, on the one hand, by the need arising from the synthesis of natural products containing chiral carbon atoms with a AA fragment, and, on the other hand, by the necessity to develop the asymmetric synthesis of simple AA from available compounds using chiral reagents or catalysts capable of being regenerated.

Optically active AA are nowadays widely used as chiral synthons—chiral units—for the preparation of physiologically active substances,[5-7] including antiobiotics.[8] The application of AA successfully supplemented the use of carbohydrates[9,10] for the synthesis of natural products with a complex structure and, in contrast to carbohydrates, usually the entire AA molecule is employed without degradation. Furthermore, in view of their simpler structure, AA are usually available in the form of both stereoisomers. A large number of reactions involving the formation of a new chiral centre, induced with the aid of AA, are also known. Thus AA and their derivatives are used as cocatalysts of asymmetric reduction, the aldol reaction, and the Strecker synthesis.[11,12] The employment of polyaminoacids makes it possible to simulate successfully the action of enzymes. For example, the epoxidation of chalcones by hydrogen peroxide in the H_2O–CCl_4–poly-AA system has been carried out with an optical yield up to 96%.[13]

The reviews on the chemical asymmetric synthesis of AA[3,14,15] deal mainly with old studies concerned with the development of classical methods. The synthesis of AA has been partly considered in a number of reviews[15-20] and in monographs.[21,22]

We shall examine the principal aspects of the asymmetric synthesis of AA, elucidating whenever possible the causes of asymmetric induction, concentrating attention on syntheses using chiral reagents capable of being regenerated and on catalytic methods. Examples of asymmetric transformation without the involvement of the centre of chirality, as in the synthesis of (*R*)-AA from (*S*)-Ser[23] (see the scheme below) will not be discussed.



(*S*)-Ser (B)-AA

The questions of micellar catalysis and the use of enzymic reactions and their combinations with chemical methods for the synthesis of optically active AA have already been considered.[24-26]

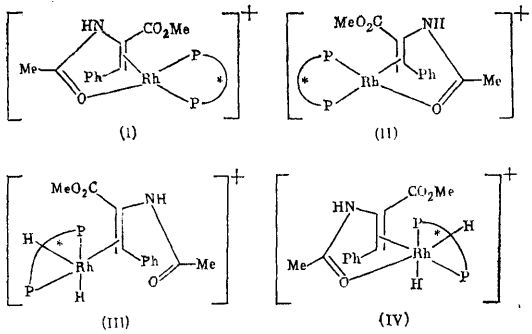
Asymmetric synthesis is the term applied to a process in which a prochiral molecule or its fragment is converted into a chiral molecule with unequal amounts of stereoisomeric products.[27] The process proceeds under the influence of a chiral reagent, the chiral component of the initial molecule, or a chiral catalyst. The interaction of the chiral and prochiral molecules inevitably results in the formation of intermediate diastereoisomeric compounds and (or) diastereoisomeric transition states, the energy difference between which actually determines the ratio of the diastereoisomers or enantiomers formed. This result is estimated in practice in terms of the diastereoisomeric (enantiomeric) excess of the reaction products or the optical yield (OY):

$$p = OY = \left|\frac{[S]-[R]}{[S]+[R]}\right| \cdot 100\% = \frac{[\alpha]_{obs}}{[\alpha]_{pure}} \cdot 100\% .$$

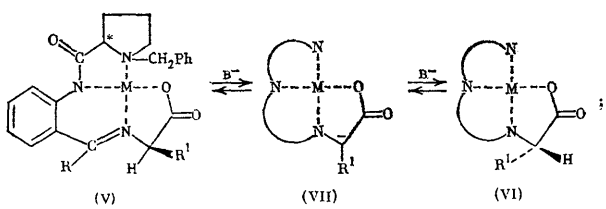
The aim of the asymmetric synthesis is to carry out the reaction with the maximum value of p for which it is sufficient to have low values of $\Delta\Delta G$, comparable to the energy of rotation about the C–C bond:

$\Delta\Delta G$, kcal mol^{-1}	0.82	1.30	1.74	2.72
p, %	60	80	90	98

Kinetically and thermodynamically controlled asymmetric syntheses are distinguished. The most striking example of kinetic control is the asymmetric reduction of *N*-acyldehydroaminoacids or chiral phosphinerhodium catalysts, where the activity of the minor intermediate diastereoisomer (I) [its content does not exceed 5% relative to compound (II)], which is higher by a factor of 10^2–10^3, determines the stereochemical course of the process and the formation of the diastereoisomer (III) with $p \geq 95\%$ [28] (Fig. 1).



As an example of thermodynamic control, we may quote the retroracemisation of the aminoacid fragment in transition metal complexes (V) of Schiff bases derived from chiral carbonyl compounds. [29–31] As a result of the epimerisation of the α-carbon atom of the aminoacid fragment, the mixture of the complexes (V) and (VI) formed initially is converted via compound (VII) into an equilibrium mixture with the ratio (V)/(VI) up to 10 : 1. After the decomposition of the mixture, AA with p up to 90% are isolated:



M = Ni, Cu; R = H, Me Ph: R^1 = Me, iso-Pr, Ph, CH_2Ph etc.

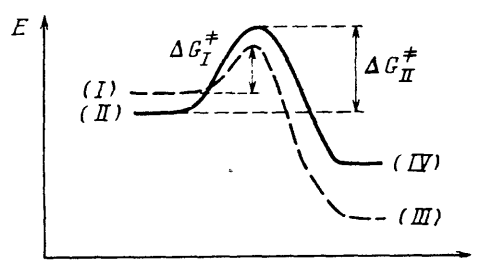
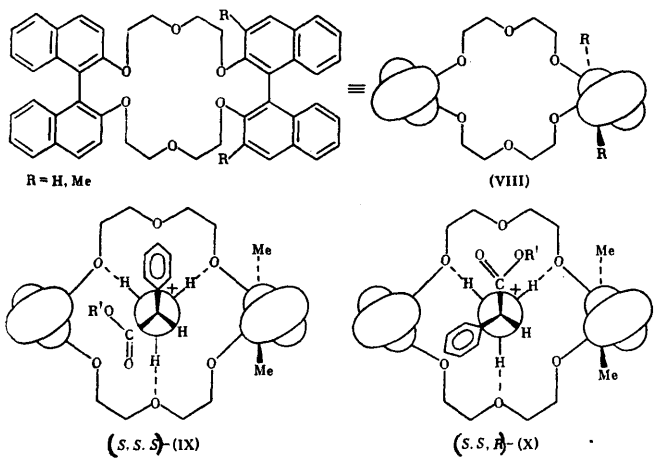


Figure 1. The energy diagram for the stage involving the formation of the rhodium hydride complex. [28]

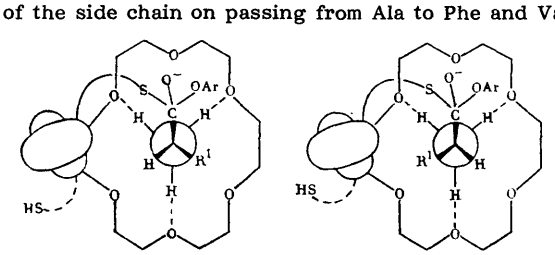
In most studies on the synthesis of AA, only the reaction result (the optical yield) is considered, without elucidating the causes of the asymmetric induction. Its manifestation is usually explained from stereochemical standpoints, [32] although the influence of electronic factors has also been demonstrated in a number of instances.

II. CHIRAL RECOGNITION AND TRANSPORT OF AMINOACIDS

The success of asymmetric synthesis is associated with the elucidation of the nature and extent of the chiral recognition in complexes of aminoacid enantiomers with chiral compounds. Crown ethers are known to form readily 1 : 1 complexes with AA. [33] The complex-forming properties of crown ethers in relation to ammonium ions have attracted attention in view of their similarity to natural ionophores—antibiotics capable of binding metals, biologically important amines, and AA. [34] The chiral recognition of amines and AA by chiral crown ethers of type (VIII) with binaphthyl fragments, [35–38] spiro-crown ethers, [39] pyridinocrown ethers, [40] various crown and azacrown compounds, [41,42] and other compounds [34,43] has been studied recently. Thus the diasteroisomers (*S,S,S*)-(IX) and (*S,S,R*)-(X) have been obtained from salts formed by AA esters with acids and from compound (VIII). The experimental value of $\Delta\Delta G$ (up to 2 kcal mole^{-1}) is actually related to the difference between the interactions of the chiral binaphthyl fragments with H or the CCOR′ group: [44]



The enantioselective thiolysis of the *p*-nitrophenyl esters of AA (AA–OAr) on treatment with an analogue of compound (VIII) containing one binaphthyl fragment with the group R = $CH_2OC_6H_4SH$ is an example of the reaction with esters of type (VIII) whose stereoselectivity can be explained by considering molecular models of the intermediate complex. [36] Comparison of the structures of (*S,S*)-(XI) and (*S,R*)-(XII) indicates that the complex (XI) is preferable because of the interaction of the chiral barrier with the hydrogen atom and not with an alkyl group of the AA, as in the case of compound (XII). This explains satisfactorily the difference between the relative thiolysis rate constants; the ratio of the constants increases from 1 to 8.3 and 9.2 respectively with increasing bulk of the side chain on passing from Ala to Phe and Val.



The transport of AA through synthetic and natural membranes, which takes place stereoselectively in living organisms through lipophilic cell membranes, is associated with the phenomenon of recognition.[44] A number of biomimetic systems—crown ethers,[35,44] their spirobiindan derivatives,[45] and azacrown ethers[34]—have been developed for the selective transport of one of the enantiomers of the AA esters in the form of the hydrochloride. The transport is from one aqueous phase to another via a liquid membrane made up of a layer of organic solvent containing the chiral transferring agent. The cation associated with the given compound, for example Na^+, is transported in the opposite direction simultaneously with the transport of the AA salt. The driving force of the process is the entropy of solution and the change in the solvation energy when an inorganic salt is replaced by an organic salt. The use of (*S*,*S*)-(VII, R = Me) in the cell (Fig.2) made it possible to isolated (0 °C, 22 h) (*S*)-PGly-OMe with *p* up to 86% in the right-hand limb from the racemate in the left-hand limb, while the use of (*R*,*R*)-(VIII) affords (*R*)-PGly-OMe with *p* up to 90%. $\Delta\Delta G$ reaches 1.96 kcal mol^{-1} for p-HO–PGly–OMe [40] and −2.15 kcal mol^{-1} for Phe–OMe.[35] Such high results have so far been obtained only for AA esters. The study of the transport of free AA has so far yielded low values of *p*, which depend greatly on the experimental conditions.[34,46] The PGly enantiomers with *p* = 91.6% have been separated by means of a liquid membrane containing a chiral crown ether and a polymer.[47]

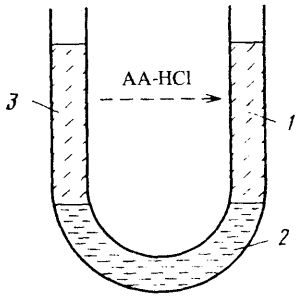
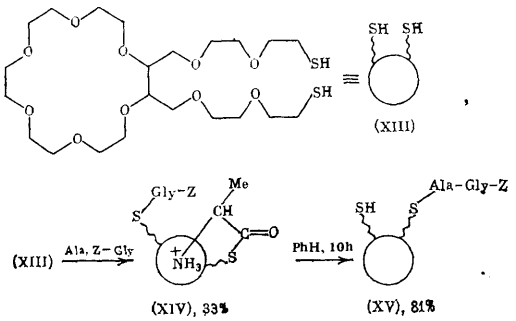


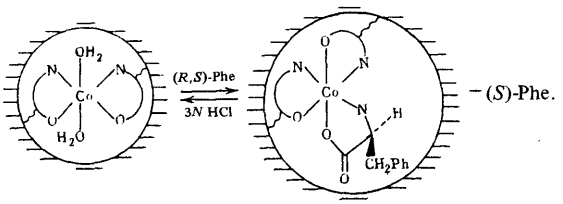
Figure 2. Cell for the phase-transfer enantioselective transport of aminoacid esters:[35] 1) 0.1 M HCl; 2) 0.027 M solution of (*S*,*S*-)- or (*R*,*R*)-(VIII) in $CHCl_3$; 3) aqueous solution of 0.08 M HCl, 0.08 M $LiPF_6$, and 0.05–0.08 M AA.HCl.

Crown ethers (XIII) with functional groups have been used as models of enzymes in the synthesis of peptides[48] (Scheme 1). The reaction involves the usual stages of peptide synthesis: the formation of a covalent intermediate, followed by the catalytic complex (XIV), and the reaction of the latter with the second substrate and the formation of the product (XV).

Scheme 1



A specific chiral environment can be created for the purpose of the recognition of AA enantiomers also by local synthesis, for example, by the copolymerisation of the cobalt(III) complex of (*R*)-Phe, containing a number of chiral groups and activated double bonds, with styrene and divinylbenzene:[50]



The polymeric gel obtained retains its initial structure of a "chiral lacuna" after hydrolysis, because, as a result of treatment with an excess of (*R*,*S*)-Phe, it forms preferentially a complex with (*R*)-Phe (*p* = 74%).

The diasteroisomeric interactions with AA are extremely varied. There is a possibility of the chiral recognition of N-Ac-PGly and N-Ac-Phe as a result of the formation of diastereoisomer solvates with tartaric acid derivatives via the formation of hydrogen bonds.[51] The study of chiral recognition in the formation of complexes with esters of (*R*)-, (*S*)-, and (*R*,*S*)-*N*-[4(1-pyrenyl)butanoyl]tryptophans in methanol and optically active octanols showed that it is associated with the differences between electrostatic, dispersion, and resonance interactions.[52]

Examples of the chiral recognition of prochiral substrates as a result of diastereoisomeric interactions, which are used for the asymmetric synthesis of AA, will be examined below.

III. ASYMMETRIC REACTIONS OF AMINOACIDS

The asymmetric transformations, sometimes referred to as *anti*- or *retro*-racemisation, include, in the stage determining the stereochemistry of the process, the inversion of the configuration of the α-carbon atom of the AA, which justifies their consideration in this review.

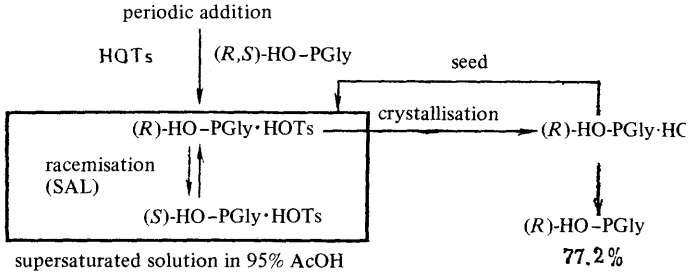
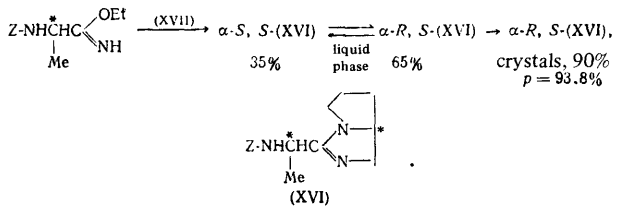


Figure 3. Schematic illustration of the asymmetric transformation of toluene-*p*-sulphonate of (*R*,*S*)-*p*-hydroxyphenylglycine.[55]

The conditions in the asymmetric transformations of *N*-Ac-Leu, *N*-butyroyl-Pro, *N*-benzoyl-PGly,[53] Ala and PGly,[54] and *p*-HO-Pgly [55] have now been worked out in detail. The essential feature of these transformations is a combination of the preferential crystallisation of one of the enantiomers in

saturated solutions of the racemate with the racemisation of the other enantiomer. Thus a supersaturated solution of *N*-Ac(*R,S*)-Leu in acetic acid with catalytic amounts of acetic anhydride was cooled at a rate of 10 K h^{-1} from 100° to 40 °C after the addition of crystals of the (*S*)-isomer as a seed. This resulted in the formation of almost optically pure (*S*)-*N*-Ac-Leu in 70% yield relative to the initial racemic mixture.[53] The toluene-*p*-sulphonate salts of (*R,S*)-*p*-HO-PGly-[(*R,S*)-HO-PGly.HOTs] are racemised using 95% of acetic acid and a catalytic amount of salicylaldehyde (SAL) [55] (Fig.3).

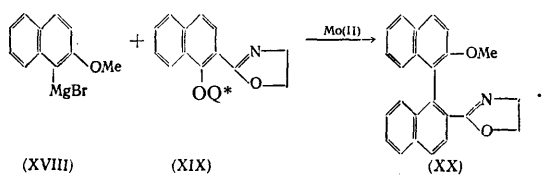
The use of the faster racemistation of intermediate Schiff base derived from the ester (*R,S*)-PGly compared with the ester of one of the PGly enantiomers, which accumulates in solution, in the presence of (+)-tartaric acid affords, as a result of the asymmetric transformation of the second kind, the pure (*R*)-enantiomer in 85% yield.[56] The transition from (*R,S*)-Ala to (*R*)-Ala via the readily epimerising imidazolines (XVI), obtained using (*S*)-2-aminomethylpyrrolidine (XVII), has been achieved:[57]



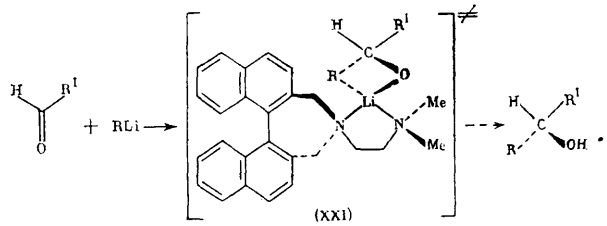
By combining the epimerisation and preferential crystallisation of the complex with $NiCl_2$, the asymmetric transformation of α-amino-ε-caprolactam (a precursor of lysine) has been carried out analogously in 50% yield (p = 96%).[58] The asymmetric transformations of AA via the intermediate formation of chiral complexes of Schiff bases with transition metals[29] are considered in Section VI.

IV. ASYMMETRIC INDUCTION BY THE CHIRAL LEAVING GROUP

Asymmetric protonation or alkylation of carbanions by chiral electrophiles is also included in the electrophilic asymmetric synthesis of AA after asymmetric transformations.[59] An example of the asymmetric induction by the leaving group in the nucleophilic aromatic substitution using 2-methoxy-1-naphthylmagnesium bromide (XVIII) as the nuclophile and the quininoxy-group (OQ*) as the leaving group in the electrophile (XIX) is known.[60] The yield of the product (XX) reached 88% (p = 95%):



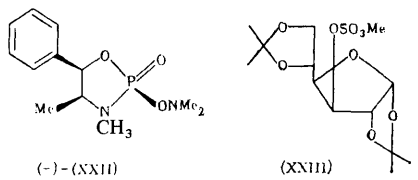
This result can be explained by the intermediate formation of two diastereoisomeric chelates with Mo^{2+}, $\Delta\Delta G$ reaching 2.4 kcal mol^{-1}. Induction by chiral lithium amides can be achieved analogously, for example, in the catalysis of the addition of alkyl-lithium to aldehydes via compound (XXI) with formation of alcohols (yield 35–75%, p = 23–95%):[61]



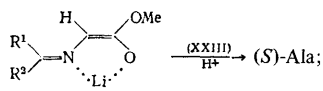
A rare instance of the use of electrophilic asymmetric amination for the synthesis of AA from the chiral reagent (XXII), prepared for (−)-ephedrine, has been described:[62]

$$PhCRCOOEtLi^{+} \xrightarrow{(-)\text{-(XXII)}} PhCR(COOEt)NMe_2;$$

R = H (yield 50%, p = 23%); R = Me (yield 56%, p = 21%);

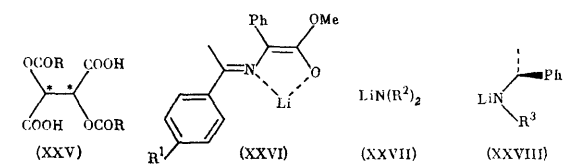


The enantioselective alkylation by compounds (XXIII) of lithium enolates obtained from a Schiff base of the glycine ester (XXIV) has been reported recently:[63]



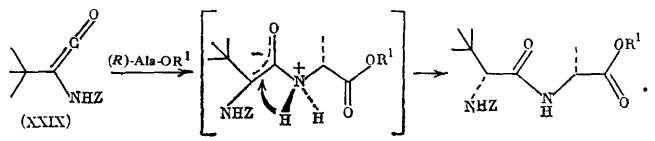
R^1	H	iso-Pr	Ph	p-$NMe_2C_6H_4$	p-$NMe_2C_6H_4$
R^2	Ph	iso-Bu	t-Bu	t-Bu	adamantyl (Ad)
Yield of (*S*)-Ala, %	50	69	72	70	90
p, %	0	35	61	66	71

The result obtained is explained by the intermediate coordination of the enolate (XXIV) to the chiral alkylating agent (XXIII), which hinders the attack on the double bond from the *re*-side, the hindrance increasing with increasing bulk of the substituents in compound (XXIV). Asymmetric protonation for the synthesis of AA has been developed in detail.[59] The essential feature of the method consists in the protonation of the lithium enolates of the Schiff bases derived from AA esters by chiral acids, which are usually (2*R*, 3*R*)- or (2*S*, 3*S*)-diacyltartaric acids (XXV):



As a consequence of the high coordinating capacity of lithium in relation to the electron-donating atoms, the product is the *syn*-enolate (XXVI), whose protonation by (*R*)- or (*S*)-(XXV) under the conditions of kinetic control affords AA enriched in one of the enantiomers. It has been established in relation to the transformations in PGly (Table 1) that the stereoselectivity increases with increasing bulk of the substituents in the amide and the acid and also with enhancement of the electron-donating character of the group in the aromatic ring of the Schiff base, which leads to the formation of a "harder" enolate. For all the AA investigated (Ala, Trp, Leu, Phe, Val, Met, PGly, NLe), the protonation

of the enolate of type (XVI) by treatment with (2*R*, 3*R*)-(XXV) yielded the (*S*)-product,[59] while the chiral acids were recovered without loss of optical activity. On double asymmetric induction using (*R*)-(XXVIII), *p* increases to 70% with a chemical yield of 90%. In the case of chiral aminocarbonyl compounds, protonation by the derivatives (XXV) proceeds with p up to 92%.[66] According to Duhamel et al.,[59] it can be used for the transformation of carboxylic acids, ketones (via enamines), allyl alcohols (via α-hydroxyketones), allyl halides (via α-halogenoketones), etc. Asymmetric protonation can be achieved also without the loss of the chiral group; for example, the reaction of phthalimido-t-butylketen (XXIX) with an (*R*)-Ala ester, results in the formation of the (*R*,*R*)-dipeptide with *p* = 70%:[67]



(XXIX)

Table 1. The influence of substituents on the optical yield of (*S*)-PGly in the reaction of compound (XXV) with the enolate (XXVI).[59,63-65]

R in (XXV)	*p*, % (R^1=H)*	R^1 in (XXVI)	*p*, % (R = t-Bu)*	R^2 in (XXVII)	R^3 in (XXVIII)	*p*, % (R^1 = H, R = t-Bu)*	(XXV)	*p*, % (R^1 = H, R = t-Bu, R^2 = Et)
Me	2.6	CN	12	C_6H_{11}	—	35	2*R*, 3*R*	70
iso-Pr	12	Cl	31	Et	—	28	2*S*, 3*S*	5.5
t-Bu	50	H	50	iso-Pr	—	50	*meso*-	24
t-$BuCH_2$	16	Me	53	—	Me	60	racemate	39
	54	MeO	57	—	Et	70	—	—
Ad	—	Me_2N	61	—	—	—	—	—

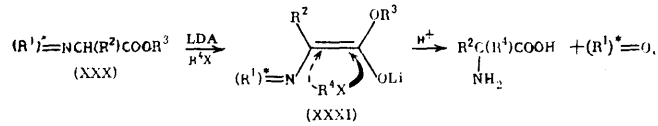
*The reaction was carried out with (2*R*,3*R*)-(XXV).

The asymmetric protonation method can be developed further using chiral polyacid. The protonation of chiral anions by achiral acids has been investigated more widely and is examined below.

V. ENANTIOSELECTIVE REACTIONS OF CARBANIONS

In recent years notable advances have been made in the asymmetric synthesis involving the enantioselective formation of C–C bonds.[68] Stabilised carbanions, which exist in the form of metal complexes are frequently used for this purpose, the complexes being obtained from carbanion compounds, for example, α-alkyl-β-ketoesters,[69] α-hydroxyesters,[70] or nitrogen-containing compounds—hydrazones[71,72] or amidines.[73] The enantioselective alkylation of such carbanions proceeds with a high value of *p*.

AA are frequently obtained by alkylating the chiral Schiff bases (XXX) derived from the simplest AA, which can be readily synthesised from chiral carbonyl compounds and AA esters.[79] The use of the Schiff bases increases the CH acidity of the aminoacid fragment of the AA [80] and makes it possible to carry out reactions even with weak electrophiles (alkyl halides), ensures the ready regeneration of the chiral carbonyl compound (R^1)*=O, and leads to comparatively high values of p (Table 2):



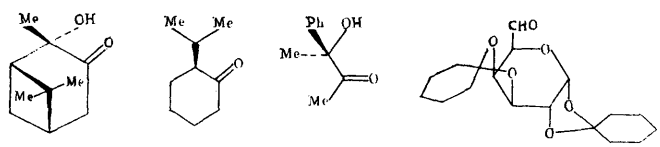
(XXX) (XXXI)

Table 2. Alkylation of chiral Schiff bases (XXX).

Chiral reagent, $(R^1)^* = 0$	R^2	R^3	R^4	Yield of AA, %	*p*, %	Refs.
(XXXII)	H	t-Bu	Me	52	83	[74]
	H	t-Bu	n-Pr	50	83	[74]
	H	t-Bu	$PhCH_2$	79	72	[74]
	H	t-Bu	$3,4\text{-}(HO)_2C_6H_3CH_2$	62	66	[74]
	H	Me	$(CH_2)_6CH{=}CH_2$	40	95	[75]
(XXXIII)	Me	t-Bu	$3,4\text{-}(HO)_2C_6H_3CH_2$	74	24	[76]
	Me	t-Bu	$PhCH_2$	55	21	[76]
(XXXII)	Me	Me	n-Pr	84	83	[77]
	Me	Me	$CH_2C{\equiv}CH$	78	52	[77]
	n-Pr	Me	Me	87	90	[77]
	n-Pr	Me	$CH_2CH{=}CH_2$	70	15	[77]
(XXXIV)	H	t-Bu	PhCHOH	67	64*	[78]
	H	t-Bu	$o\text{-}MeC_6H_4CHOH$	67	70**	[78]
(XXXV)	Me	Me	$PhCH_2$	83	83	[79]
	Me	Me	$CH_2CH{=}CH_2$	85	85	[79]
	Me	Me	$CH_2CH{=}CHPh$	65	60	[79]

**threo* : *allo* = 3 : 1.
***threo* : *allo* = 12 : 1.

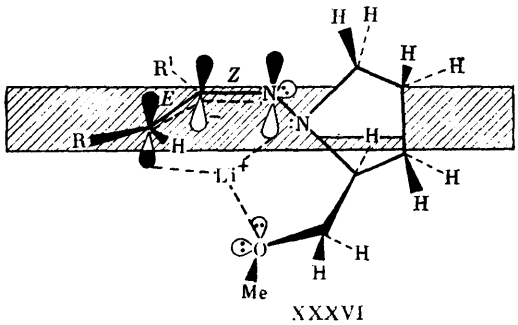
The Schiff base is deprotonated, for example, with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) to give the enolate (XXXI), which is alkylated with alkyl halides, the use of the (*S*)-reagent (R^1)* giving rise to an excess of the (*R*)-product. Asymmetric induction can be achieved for achiral Schiff bases by means of chiral lithium amides obtained from (*S*)-Pro or (*S*)-Leu, but *p* does not exceed 31%.[81] The induction is also weak when the chiral centre is moved away from the α-carbon atom of the AA by employing menthyl esters, whose derivatives afford, after deprotonation and alkylation, AA in yields of 90% and *p* = 5–55%.[82] A 48% yield of (*S*)-Ala is reached when the menthyl ester of isocyanic acid is metallated.[83] The use of other AA derivatives, for example, *N*-formyl-*N*-alkylaminoacetonitrile, likewise produces low values of *p*.[84]



(XXXII) (XXXIII) (XXXIV) (XXXV)

In another alkylation method, proposed by Enders[85] and used to synthesise AA,[71] one begins with lithiohydrazones or lithioamidines derived from (*S*)-1-amino-2-methoxymethylpyrrolidine. The structure of the lithio-derivatives of hydrazones has not been accurately established, in contrast to that of lithium enolates. The structure (XXXVI) (Fig.4) has been proposed from spectroscopic data and confirm by an MNDO calculation. The result of the electrophilic substitution of the Li^+ ion is determined by the rotation about the N–N bonds if it is assumed that the negative end of the dipole of the electrophile forms a complex with the Li^+ ion.

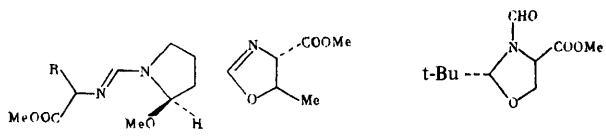
Since the electrophile attacks the anion (XXXVI) from below with formation of an (*R*)-product, then, for the more favourable *NN*-conformation in compound (XXXVI), *syn*-substitution takes place in relation to lithium. These features can be attributed also to electrophilic substitution in the amidines (XXXVII), where the preferential formation of the (*S*,*R*)-product is associated with the preferential *syn*-substitution of the lithium complex, which yields (*R*)-AA with $p = 15$ to 51%.[71] The result of the alkylation of enolates obtained from Schiff bases (XXXI) can be explained analogously.



XXXVI

Figure 4. The structure of the lithio-derivative of the hydrazone (XXXVI).[85]

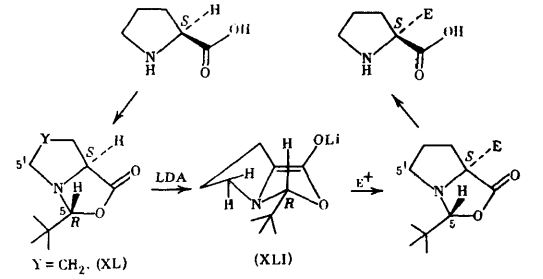
Rigid cyclic systems give rise to better results than their linear analogues. Thus the alkylation of the carbanion obtained from derivatives of the chiral 1,4-benzodiazepin-2-one yielded an AA with *p* up to 85%.[86] The advantages of the use of cyclic systems have been demonstrated particularly strikingly in two general methods of synthesis of a whole series of AA, developed by Seebach et al.[87] and Schöllkopf;[88,89] in both cases, the rigid chiral carbanion is attacked by the electrophile with an exceptionally high diastereoselectivity. The method of "self-reproducing chirality", proposed by Seebach, consists in effecting 1,3-asymmetric induction; it is convenient for the synthesis of α-C derivatives of the AA for which direct formation of enolates is impossible owing to β-elimination: Ser,[90] Thr,[91] Cys,[92,93] and Pro.[87] The principal feature of the method is the synthesis of chiral enolates from optically pure cyclic products: substituted oxazolines (XXXVIII) for Thr, oxazolidines (XXXIX) for Ser, and bicyclic compounds of the type (XL) for Pro and Cys:



(XXXVII) (XXXVIII) (XXXIX)

As shown in Scheme 2 for the adduct (XL, $Y = CH_2$),[87] the nucleophilic centre of the enolate is attacked by all kinds of electrophiles (D_3O^+, alkyl halides, carbonyl compounds, and alkenes) with restoration of the initial chiral centre and the formation of virtually only one of the possible diastereoisomers even in the case of three chiral centres (Table 3).

Scheme 2



Y = CH_2, (XL) (XLI)

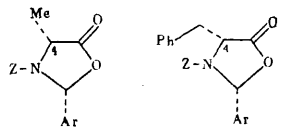
Table 3. The interaction of enolates obtained from compounds (XXXVIII), (XXXIX), and (XL) with electrophiles.

Initial compound	Electrophile	Reaction product		Refs.
		yield, %	*p*, %	
(XL), Y = CH_2	MeI	93	95	[87]
	$PhCH_2Br$	91	95	
	$MeCOOCH_2Br$	40	95	
	PhCHO	72	94	
	MeCHO	88	94	
	Me_2CO	93	95	
	$MeCOCH_2COOMe$	62	51	
		50*	95	
	»	21**	95	
(XXXIX)	$PhCH_2Br$	52	99	[90]
	MeOD	71	98	
	Me_2CO	58	99	
	PhCHO	70	99	
(XXXVIII)	MeI	94	93	[94]
	$PhCH_2Br$	93	99	
	Me_2CO	68	99	
(XL), Y=S	PhCHO	64	92	
	p-$MeOC_6H_4CHO$	68	96	
		45	88	[93]
		44	94	
	PhCH=CHCHO	48	89	

*1,2-Addition. **1,4-Addition.

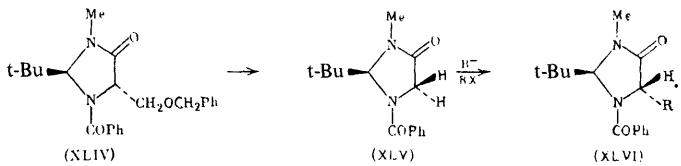
The stereochemical result is because the electrophile does not distinguish kinetically the two sides of the chiral enolate (XLI) obtained from the adduct of (*S*)-proline with pivalic aldehyde (XL). The formation of compound (XL) is rigorously distereoselective, because the existence of the (*S*,*S*)-diastereoisomer is unfavourable—in this case the pseudoaxial t-Bu group is in the eclipsed conformation relative to the 5′-CH_2 group of the pyrrolidine ring. The enolate (XLI) is formed with disappearance of the initial centre of chirality *S*-(2) and retention of the new centre *R*-(5). Presumably the Li^+ ion is coordinated to the oxygen of the enolate preferentially from the *re*-side of the plane (from below) in order to reduce the extent of the non-bonding interactions from the side of the pseudoaxial H(5) and the pyrrolidine fragment. This should lead to attack by the electrophile coordinated to the Li^+ ion from the *re*-side and the restoration of the initial centre of chirality *S*-(2), which has in fact been observed. The high stability of the carbanion (XLI) makes it possible to carry out also

the Michael reaction, for example, with cyclohexenone, whereupon adducts with p = 95% are produced.[87] The method has been extended to Ala and Phe by converting them into chiral cis-2-aryl-2-benzyloxycarbonyloxazolidinones (XLII) and (XLIII); the alkylation of their potassium enolates at C(4) by treatment with MeI and $PhCH_2Br$ afforded (*R*)- or (*S*)-α-Me-Phe after alkaline hydrolysis with hydrogenolysis.[94]



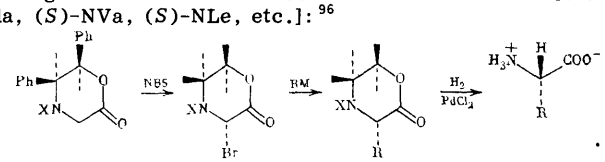
(XLII) (XLIII)

The method is applicable to the synthesis of natural AA from other AA. (*S*)-β-*O*-benzyl-Ser was converted on interaction with pivalic aldehyde into the *trans*-imidazolidinone (XLIV), which gives rise, after oxidation and decarboxylation, to the imidazolidinone (XLV) containing the Gly fragment. The alkylation of its chiral enolate with MeI or $PhCH_2Br$ (produced the (2*S*, 5*S*)-imidazolidinones (XLVI) in 51 and 45% yields respectively for p = 95%:[95]



(XLIV) (XLV) (XLVI)

The attempts to obtain the enolate from the chiral lactone (XLVII) were unsuccessful, but the generation of an electrophilic centre by passing to compound (XLVIII) made it possible to carry out the reactions with various nucleophiles, leading to the lactone (XLIX), and to isolate the AA [(*S*)-Ala, (*S*)-NVa, (*S*)-NLe, etc.]:[96]

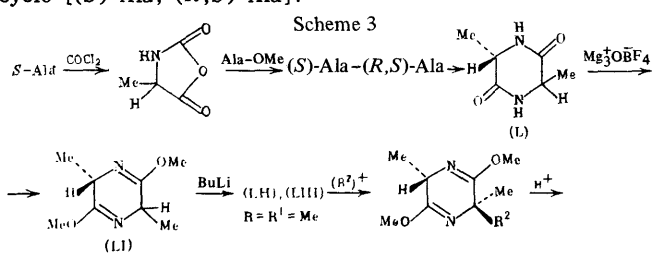


(XLVII) (XLVIII) (XLIX) $p > 96\%$

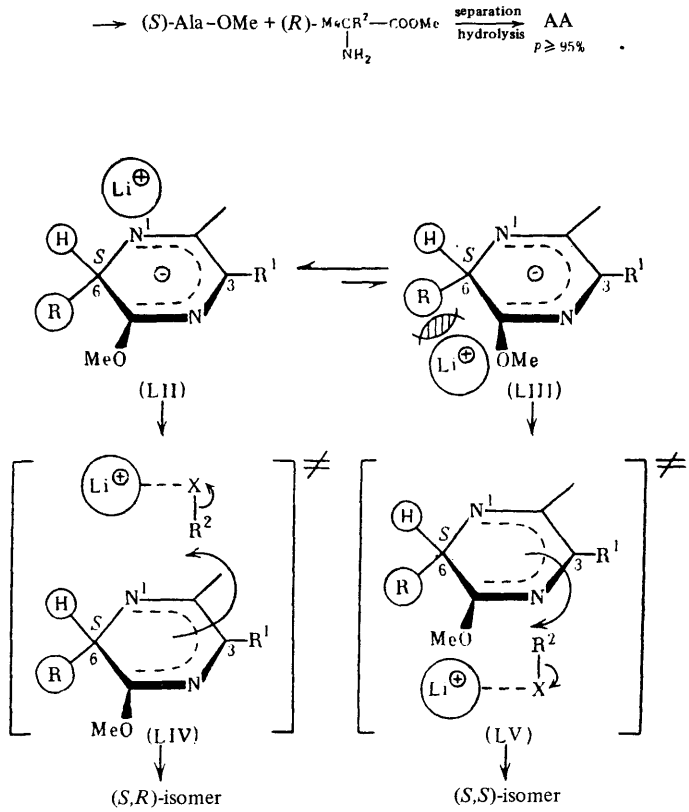
The alkylation of Asp, via acyclic enolates, gave $p = 60\%$.[97]

In Schöllkopf's method,[88,89] one initially synthesises the dioxopiperazines (L) from Gly or the available racemic AA (for example, Ala) and a chiral reagent—(*S*)-Ala, (*S*)-t-Leu, (*S*)-Val, or (*S*)-α-Me-3,4-$(MeO)_2$Phe. The dioxopiperazines are alkylated to give the bislactim ethers (LI), which exhibit a high CH acidity and form the chiral carbanions (LII) and (LIII) (Fig.5); the latter react with a wide range of electrophiles diastereoselectively with a high p value. The heterocycle obtained is hydrolysed with liberation of the auxiliary chiral reagent and of a new optically active AA in the form of an ester, as shown in Scheme 3 for the reaction with cyclo-[(*S*)-Ala, (*R*,*S*)-Ala]:[93]

Scheme 3



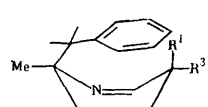
(LI)



R = Me, iso-Pr, t-Bu; R^1 = H, Me.

Figure 5. Schematic representation of the addition of an electrophile to the heterocyclic anion (LII)–(LIII).[88]

The authors assume that the dihydropyrazine anion is planar by virtue of the fulfillment of the Hückel condition and one of its diastereotopic sides is greatly shielded by the substituent R (Fig.5). It has been suggested that the Li^+ ion is close to the N(1) atom, which has the maximum electron density according to calculations. Thus the equilibrium is displaced towards compound (LII) virtue of the steric hindrance by the group R. The attack by the electrophile on the anion (LIII) is sterically hindered and the reaction proceeds mainly via the energetically more favourable state (LIV). The favourable combination of kinetic and thermodynamic factors is responsible for the high value of p (usually >95%). The role of the metal and the structure of the ion pairs were not discussed by Schöllkopf,[88,89,98] although he showed that the replacement of Li by a metal with shorter bonds [for example, $Ti(NMe_3)_3$] leads to greater asymmetric induction.[99] The structure of the alkylated products (LVI) and (LVII), obtained from compound (LII, R, R^1 = Me, R^2 = CH_2Ph) and corresponding to a folded conformation in which the benzene ring overhangs the heterocyclic ring, serves as evidence in support of the proposed mechanism.[89]



R^1 = H, R^3 = Me (LVI)

R^1 = Me, R^3 = H (LVII)

Such a structure, which is unfavourable as regards steric considerations, is realised also for cyclic dipeptides of the phenylalanine series.[100] Thus the stereoselectivity of the reactions of the chelate complexes of lithium considered in this Section is determined by the preferred introduction of the coordinated lithium atom on the *re*- or *si*-side relative to the nucleophilic centre of the anion and the subsequent electrophilic attack from the same side via the intermediate binding of lithium, which is the reason for the preferred *syn*-substitution mechanism. The knowledge and control of the steric and electronic factors in the stage determining the degree of asymmetric induction make it possible to regulate the stereoselectivity. Thus, the replacement of R = Me by R = t-Bu in compound (L) increases the stereoselectivity sharply, while the introduction of the phenyl group (R = Ph) gives rise to the opposite result.[89]

Table 4. The yields of the products of the interaction of carbanions of types (LII) and (LIII) with electrophiles.

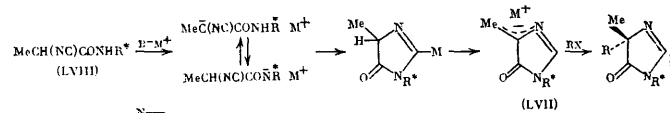
Carbanion	R¹	Yield, %	*p*, %*	Refs.
(LII), (LIII) R = t-Bu, R¹=H {from cyclo-[(*S*)-Val-Gly]}	CH(Me)OH	—	95 (91)*	[99]
	CH(Me)OH	—	85 (63)	[101]
	C(Me)$_2$OH	—	95	[101]
	CMe(Ph)OH	—	95 (38)	[101]
	CH(CH$_2$Ph)OH	—	89 (66)	[101]
	CH$_2$=CPh	90	95	[102]
	CH$_2$Ph	81	91—95	[104]
	3,4-(MeO)$_2$C$_6$H$_3$CH$_2$	91	85	[104]
	PhCH=CHCH$_2$	90	95	[104]
	CH$_2$=CHCH$_2$	88	60—65	[104]
	Me(CH$_2$)$_6$	62	75—80	[104]
	PhOCH$_2$	81	93	[105]
	MeOC(Me)$_2$	80	95	[105]
	CF(Me)$_2$	46	95	[106]
	N-Boc-(3-indolyl)CH$_2$	83	88	[107]
	CR(CH$_2$Cl)CH$_2$*O*N	90	95	[108]
(LII), (LIII) R = t-Bu, R¹ = Me {from cyclo-[(*S*)-Val-Ala]}	CMe$_2$OH	94	95	[103]
	C(Me)PhOH	93	95	[103]
	N-Boc-(3-indolyl)CH$_2$	81	95	[107]
	PhCH$_2$OCH$_2$	91	95	[109]
	PhCH$_2$	68	95	[110]
	n-C$_7$H$_{15}$	43	95	[110]
	PhCH=CHCH$_2$	80	95	[110]
	CH$_2$=CHCH$_2$	90	95	[110]
	Ph(CH$_2$)$_2$	79	95	[111]
	C[³H]$_3$	—	95	[112]
(LII), (LIII) R = R¹ = t-Bu {from cyclo-[(*S*)-t-Leu]$_2$}	Me	91	95	[113]
	CH$_2$=CHCH$_2$	78	95	[113]
(LII), (LIII) R¹ = t-Bu, R = H {from cyclo-[(*S*)-t-Leu-Gly]}	PhCH$_2$O	87	95	[114]
	n-MeOCMe$_2$	58	93	[114]
	CH$_2$=CHCH$_2$	84	93	[114]
	CH≡CCH$_2$	86	93	[114]
	t-BuOCOCH$_2$	89	93	[114]
(LII), (LIII) R = 3,4-(MeO)$_2$C$_6$H$_3$.CH$_2$, R¹ = H {from cyclo-[(*S*)-α-Me-3,4-(MeO)$_2$Phe-Gly]}	PhCH$_2$O	74	95	[105]
	MeOCMe$_2$	79	93	[115]
	CH$_2$=CHCH$_2$	70	80	[115]
	n-C$_7$H$_{15}$	—	85	[115]
from (LVIII)	PhCH$_2$	94	95	[116]
		87	95	[116]
	CH$_2$=CHCH$_2$	66	17	[116]
	cyclo-C$_6$H$_{11}$CH$_2$	20	35	[116]
from (LX) R = CMe$_3$, R¹ = 2-furyl	PhCH$_2$***	90	95	[117]
	Me***	95	90	[117]
	CH$_2$=CHCH$_2$	85	95	[118]
	PhCH$_2$	92	95	[118]
	Me	92	95	[118]

*The values of *p* (with respect to C(3) are indicated in brackets.

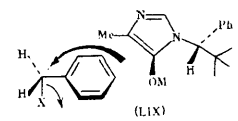
**Ti(NMe$_3$)$_3$ was used as the counterion.

***R¹ = Rh.

Cyclo-[(*S*)-Val-Gly] or cyclo][(*S*)-Val-Ala] is used most often in the Schöllkopf's method, which makes it possible to obtain various (*R*)-AA (Table 4). High optical yields have been achieved using (*S*)-t-Leu, which, however, is difficult to obtain.[89] Ketones also react with (LI) (*p* = 95%), while aldehydes react with additional induction at C′(3), (6*S*, 3*R*, 3′*S*)-diastereoisomers being formed preferentially.[101] Dehydration leads to (*R*)-α-vinyl-Ala and (*R*)-vinyl-Gly.[102,103] Hydrolysis to the AA esters proceeds without racemisation (Table 4). The large number of stages, the long reaction time, and the difficulty of separating the AA esters lead to the formation of products in yields of only 17—24% relative to the initial AA. The alkylation of the anions of chirally 1-substituted 4-methyl-2-imdazolin-5-ones (LVII), obtained from the chiral amides of carboxylic α-isocyano-acids (LVIII), also gives rise to high values of *p* when the alkylating agents are benzyl halides, but the yield falls sharply (to 17—35%) when alkyl halides are employed:[116]



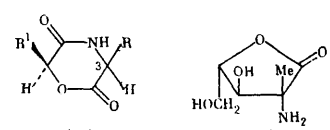
(LVII)



(LIX)

As in the alkylation of dihydropyrazine anions, the diastereoselectivity of the process is probably determined in this instance by the more favourable transition state of type (LIX).[116] The degree of asymmetric induction can be lower in this case than for the anion (LII), since the chiral centre is located further from the reaction centre and the difference between the two diastereoisomers of compound (LVII), in which the metal ion is located above and below the plane of the anion (there is a difference in the interaction of the metal with the Me and R groups), is smaller than in the case of the anion (LII) (the difference between the group *R* and the atom H).

The conversion of 2-furyl- or phenyl-glycines by condensation with hydroxyacids to the corresponding 3,6-dihydro-2*H*-1,4-oxazine-2,5-diones (LX), which react diastereoselectively with R²X via the C(3) atom, also does not differ fundamentally from the methods considered above:[117,118]



(LX)

R = Ph, 2-furyl

R¹ = CHMe$_2$, CMe$_3$

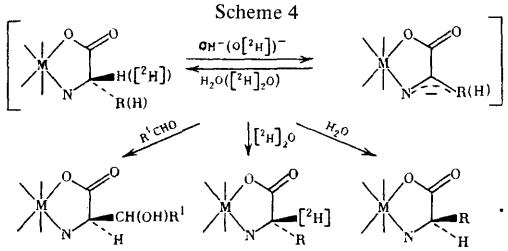
(LXI)

In view of its laborious nature, the method can be usefully employed only in the synthesis of exotic AA (see, for example, Weihrauch and Liebfritz[112]). Thus, the condensation of cyclo-[(*S*)-Ala-(*S*)-Ala] with L-glyceraldehyde yielded the biologically active lactone (LXI).[120] The use of chiral complexes of the Schiff bases derived from AA, examined in the previous Section, is more promising for the synthesis of substituted optically active AA. Interesting results may be expected also in the alkylation of the AA Schiff bases under interfacial conditions in the presence of chiral catalysts, since it is known that the alkylation of racemic phenylindanols with MeI in the presence of *N*-(*p*-trifluoromethylbenzyl)-quinine bromide gives rise to a product with *p* = 90%.[121]

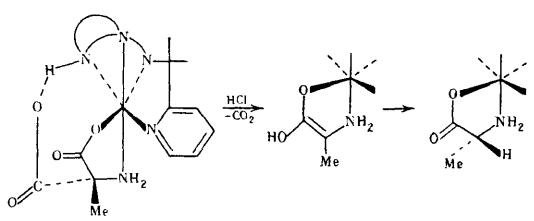
VI. SYNTHESIS AND REACTIONS OF AMINOACIDS VIA TRANSITION METAL COMPLEXES

The ligand in the chiral complexes of transition metals has a rigid orientation and X-ray diffraction analysis provides reliable information about their structure.[122] The intraligand interactions, responsible for the enantioselectivity in these systems, can therefore be assessed very accurately, which facilitates the search for useful synthetic reagents based on them. The stereochemically inert cobalt(III) complexes with amine chiral ligands and aminoacids[123,124] have been used for such purposes for years, for example the cleavage of AA.[125] The chiral recognition of the enantiomers and chiral groups in such complexes occurs mainly as a result of the sterically preferred interaction of one chiral ligand with another or with the prochiral groups of a neighbouring ligand.[126] The introduction into the complex of bonding interligand interactions, which occur for polydentate ligands, enhances the possibility of the chiral recognition of AA.[123,124] The use of chiral derivatives of amines as tetradentate ligands leads to diastereoisomeric Λ and Δ complexes of cobalt(III) with aminoacids, their ratio corresponding to the ratio of the pure AA enantiomers.[127] The epimerisation of the CH aminoacid fragment in the Λ and Δ complexes is catalysed by OH^- (Scheme 4):

Scheme 4



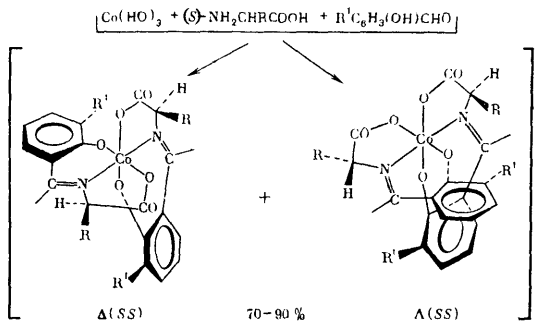
The diastereoselectivity is sometimes high and reaches Δ,*R*/Δ,*S* = 91 : 1 for the complexes with Asp.[128] Treatment of the racemic α-dichlorotriethylenetetraminecobalt(III) chloride with (*S*)-Pro and Et_3N in boiling alcohol results in 94.5% of the cobalt(III) complex, existing as the Δ complex.[129] Analogous complexes with α-amino-α-methylmalonic acid are used for the acid-catalysed asymmetric carboxylation to Ala.[129] The racemisation of the AA fragment in the isolation stage usually diminishes *p*,[130] but, for the chiral complexes with (6*R*,8*R*)-6,8-dimethyl-2,5,9,12-tetra-azatridecane[131] and *NN*-di(2-picolinyl)-(1*R*,2*R*)-diaminocyclohexanone,[132] the value of *p* corresponding to (*R*)-Ala is 66 and 78% respectively. According to Goodwin et al.,[132] the decarboxylation of the cobalt(III) pro-(*S*)-aminomethylmalonate complex affords the (*R*)-alanine complex, i.e. the α-carbon atom undergoes inversion. The mechanism involves the cyclic intermediate (LXIII):



(LXII) (LXIII)

Taking into account the data in Section IV, it has been suggested that the asymmetric induction in compound (LXIII) is effected by the selective intramolecular proton transfer to the enolate fragment from the protonated pyridinium fragment in a chiral environment. The asymmetric decarboxylation of the Λ- or Δ-tetramine complex of cobalt(III) with pyrrolidine-2,2-dicarboxylic acid gives rise to (*S*)-Pro and (*R*)-Pro with *p* = 20 and 24% respectively.[133] Asymmetric transformations of the AA fragment are possible also in the chiral complexes of dicarbonyl(η^5-cyclopentadienyl) derivatives of molybdenum and tungsten with AA.[134] These complexes are configurationally stable in a neutral solution, while in an alkaline medium rapid interconversion of the diastereoisomers is attained. The epimerisation of the AA fragment suggested[135] and led to the development[136] of the method of synthesis of chiral [^{2}H]Gly and other [2-^{2}H]AA by the enantioselective substitution of the α-proton of the AA by deuterium. It consists in the formation of ethylenediaminecobalt(III) complexes with (*S*)-AA, the separation of the diastereoisomeric complexes by chromatography, deuterium exchange by treatment with OD^- in D_2O, repeated separation of the Δ,*S* and Δ,*R* or Λ,*S* and Λ,*R* diastereoisomers, and the isolation of AA from the complexes by reduction with $NaBH_4$.[131] The chiral complexes of transition metals have also been used for the asymmetric synthesis of Thr from Gly and MeCHO in 26–33% yield and with *p* = 16–35%[137] (Scheme 4). The use of simple AA complexes of transition metals suffers from a number of disadvantages, for example, the α-amino-group of the ligand is subjected to electrophilic attack, which prevents the effective synthesis of α-substituted AA by alkylation with alkyl halides.[137] There are also difficulties in selecting the chiral ligands, since the interactions within the complex are readily smoothed out;[126] finally the CH acidity of the complexes is low.[138]

The use of chiral complexes of Schiff bases derived from AA for the synthesis of biomimetic reagents for asymmetric synthesis of AA is more successful. In these complexes, where the kinetic CH acidity of the AA fragment is high,[139] the α-amino-group is reliably protected and the polydentate ligand (the Schiff base) forms a harder complex than the free AA. The relevant studies were carried out initially mainly with stereochemically inert octahedral cobalt(III) complexes, which retain their configuration in the chemical reactions of the ligands.[127,128] The AA Schiff bases with aldehydes form planar tridentate ligands, which can be arranged perpendicularly to one another in the octahedral complexes. The complexes with Gly can be resolved into the enantiomers, while those with other AA can be resolved into diastereoisomers, for example, Λ(*SS*) and Δ(*SS*).[140]



Δ(*SS*) 70–90 % Λ(*SS*)

For the Δ(*SS*)- and Λ(*SS*)-diastereoisomers, $\Delta\Delta G = -0.45$–1.32 kcal mol^{-1} at 78 °C, which has been attributed to the energetically unfavourable interaction of the benzene ring in the Λ(*SS*)-isomers, while the introduction of the methyl group in the 3-position in salicylaldehyde (SAL) inverts the stereoselectivity owing to the interaction of the alkyl groups of the AA fragment and the 3-methyl group in the Δ(*SS*)-complexes, which is almost absent in the Λ(*SS*)-isomers.[140] These results make it possible to achieve the synthesis of the partly enriched (*R*)-[^{2}H]Gly and (*S*)-[^{2}H]Gly [147] by analogy with

the study of Keges and Legg.[136] The steric shielding of the *re*- and *si*-sides of the intermediate planar carbanion in the complexes Λ-(LXIV) (*re*-side) and Δ-(LXV) (*si*-side) with 3-Me-SAL, which hinders the attack on the pro-(*R*)-proton in the Λ-complexes and the pro-(*S*)-proton in the Δ-complexes and leads to different rates of their exchange with the ratio of the constants up to 1 : 10 (Fig.6), has also been used. Therefore, after the exchange of 50% of the hydrogen for deuterium, (*S*)-[^{2}H]Gly was isolated from the Λ-complex and (*R*)-[^{2}H]Gly was isolated from the Δ-complex with p = 20–40% [141] without the preliminary separation of the diastereoisomers, as in the study of Keges and Legg.[136] The employment of such separation made it possible to obtain the following deuteriated AA with high values of p: (*R*)-Tyr 68%, (*S*)-Tyr (94%), (*R*)-Val (96%), (*S*)-Val)98.8%), (*R*)-NVa (93.4%), (*S*)-NVa (94%), (*R*)-Met (82%), (*S*)-Met (90%), and (*R*)-Ala (90%).[141] The stereochemistry of the formation of the C–C bond obeys the same rule as that for the formation of the C–H bond, but ultimately the thermodynamically stable complex predominates in the final mixture obtained in the condensation with aldehyde. Thus (*S*)-Thr with p = 60% and (*R*)-Thr with p = 73% have been obtained by the reaction with acetaldehyde.[139,140] The interaction with methyl acrylate in H_2O at pH 11.4 afforded a mixture of complexes, after the decomposition of which (*S*)-Gly (p = 10–46%) was isolated quantitatively.[142] Thus both the kinetic acidity of the AA fragment and the enantioselectivity of the formation of the C–C and C–H bonds can be appreciably increased with the aid of chiral cobalt(III) complexes based on the Schiff bases derived from SAL and AA. The use of menthol derivatives as the carbonyl components of the Schiff bases permitted the asymmetric transformation of the AA fragment in the complexes with racemic AA with p = 22% *S* for Ala, 12.6% *S* for Val, and 11.4% *S* for Leu.[143]

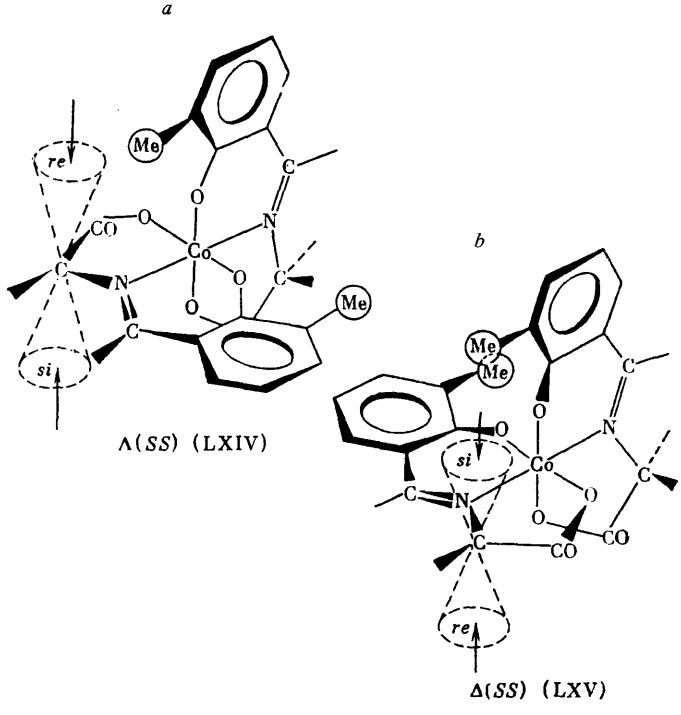
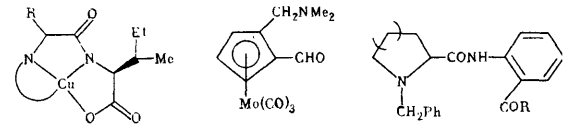


Figure 6. Steric shielding of the *re*- and *si*-sides of the carbanion formed as an intermediate in the Δ(*SS*)- and Λ(*SS*)-complexes of cobalt(III).[141]

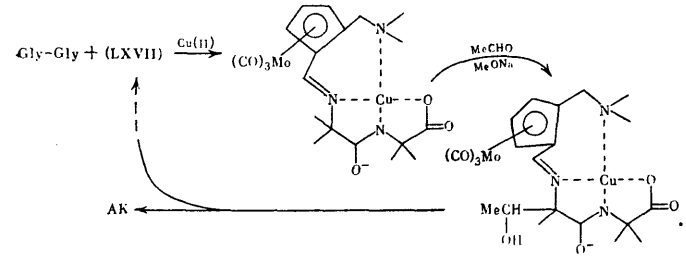
The asymmetric induction in the complexes considered was achieved as a result of the chiral disposition of the ligands within the structure of the complex, which is inert as regards substitution, but effective biomimetic reagents and catalysts[142] must be based on stereochemically labile complexes, capable of ready exchange of the ligands, which inevitably leads to the racemisation at the metal atom. In order to retain the asymmetry of such a labile system, SAL must be replaced by a chiral analogue permitting the use of Ni^{2+}, Cu^{2+}, and possibly Zn^{2+} for the asymmetric synthesis of AA. The use of optically active peptides permitted only the epimerisation of the *N*-terminal AA of the dipeptide in the copper(II) complexes (LXVI):



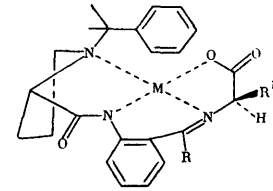
(LXVI) (LXVII) (LXVIII), n = 1, 2
R = H, Me, Ph

Dipeptides with p = 63% *S* for R = Me and 66% *S* for R = Ph have been isolated.[145] The enantiomers of 1-(*NN*-dimethylaminomethyl)-2-formylcymantrene (LXVII) [146,147] have been used as chiral reagents, capable of being regenerated, for the asymmetric synthesis and transformations of AA. Thus the interaction of (+)-(LXVII) with racemic Ala-NVa in the presence of Cu^{2+} and MeONa gives rise to a mixture of diastereoisomers whose ratio shifts towards the most favourable diastereoisomer with (*S*)-Ala (p = 55%) as a consequence of the mobility of the α-proton of the *N*-terminal AA. (*S*)-Thr (p = 92–98%) and (*S*)-allo-Thr (p = 95–100%) were isolated in proportions of 2.15–2.42 and in high yields (after the hydrolysis of the dipeptides) by condensing acetaldehyde with the complex obtained from compound (LXVII), Gly-Gly, and Cu(II):

Scheme 5



(*R*)-Thr (p = 93–96%) and (*R*)-allo-Thr (p = 100%) were obtained in proportions of 2,3 in the case of (–)-(LXVII) [146] (Scheme 5). The greater stability of the complex with (*S*)-Thr can be explained by the fact that, as a consequence of the marked distortion of the chelate rings, the alkyl substituent in the complex assumes the pseudo-axial position, in which the interaction with the aldimine hydrogen is minimal.



(*S*,*R*)-diastereoisomer (LXIX)
R = H, Me, Ph; R^1 = alkyl
M = Ni, Cu

The use of the chiral reagents (LXVIII), having a greater number of coordination sites compared with compound (LXVII), makes it possible to achieve asymmetric transformations also with AA.[29–30,148,149] In the copper(II) and nickel(II) complexes of type (LXIX), obtained in 80–90% yields from the AA and the reagent (LXVIII) in alcohol, the distortions caused by the presence of the asymmetric carbon atom are transmitted to the chelate ring, which entails different interactions of the alkyl residue of the AA and other groups in the complex.[31] These distortions, which are clearly seen in the crystalline state, are retained in solution according to spectroscopic data.[29,31]

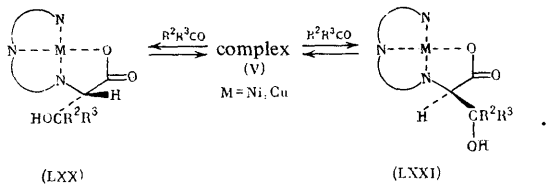
The use of such hard systems makes it possible to alter the enantioselective effects by introducing substituents R in compound (LXIX), i.e. one can alter the ratio of the diastereoisomeric complexes under equilibrium conditions. According to Belokon et al.,[31] this ratio is determined by the difference between the energies of orientation of the alkyl group of the AA towards the benzyl group (upwards from the coordination plane) for the (*S*,*R*)-diastereoisomer (LXIX) or towards the proline fragment for the (*S*,*S*)-diastereoisomer. Non-bonding interactions of the alkyl substituent with the benzyl group, shielding the apical position, are observed in the complex (LXIX), and the increase of the bulk of the group R^1 therefore diminishes the content of the complex with (*R*)-AA. The increase of the bulk of R on passing from H to Me leads to additional distortion of the metallocycles and the assumption of the pseudoaxial position by the alkyl group of the AA. Under these conditions, there is an additional increase of the excess of the complex with (*S*)-AA. The occurrence of large diastereoselective effects in the copper(II) complexes[29] and especially in the nickel(II) complexes,[30,31] reaching p = 90% for the complex with (*S*)-Val, made it possible to achieve the retroracemisation of a series of AA[29–31,150] (Table 5).

Table 5. The enantiomeric composition of the AA after the retroracemisation of the complex (LXIX) [0.2 *N* MeONa, 40° (A); 0.1 *N* MeONa, 25° (B)].

R in (V)	AA	*p*, % for (*S*)-AA		Conditions	Refs.
		Ni (II)	Cu (II)		
H	Ala	15	0	A	[29, 30]
H	Ala	15	0	B*	[31]
H	Phe	40	42	A	[29, 30]
H	Trp	64	—	A	[30]
H	Val	78	54	A	[29, 30]
H	Val	78.5	60	B	[31]
H	NVa	42	12	A	[29, 30]
Me	Ala	82	30	B*	[31]
Me	Val	76	38	B**	[31]
Me	AdAla ***	52	—	B	[31]

*0.012 *N* MeONa. **0.33 *NN* MeONa. ***AdAla = adamantylalanine.

The retention of the characteristic features of the diastereoselective effects also on formation of the C–C bond made it possible to develop a general method of diastereoselective and enantioselective synthesis of β-hydroxy-α-AA by condensing aldehydes or ketones with the nickel(II) and copper(II) complexes of glycine,[151–153] leading to the complexes (LXX) and (LXXI) (Table 6). According to Belokon' et al.,[151] the condensation of compound (V, R = Ph, R^1 = H) with aldehydes under equilibrium conditions leads to the preferential formation of the product (LXX) with the AA side chain directed away from the benzyl group and with the O atom located under the metal atom, which ensures an even greater preference for the (*S*,*S*)-diastereoisomer:

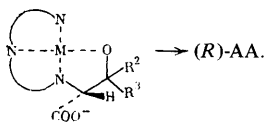


(LXX) (LXXI)

Table 6. Condensation of the glycine complex (V) with carbonyl compounds.[151]

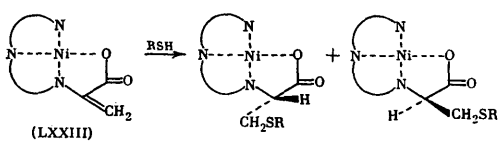
R	M	$R^2R^3C{=}O$	Base	Yield of AA, %	*threo* : *allo*	*p*, %	Configuration
Me	Ni	CH_2O	Et_3N	75–82	—	96	*S*
Me	Ni	CH_2O	MeONa	66–67	—	87–89	*R*
Ph	Ni	CH_2O	Et_3N	75	—	83	*S*
Ph	Ni	CH_2O	MeONa	95	—	88	*R*
Ph	Ni	MeCHO	MeONa	72	20:1	84	*R*
Ph	Ni	MeCHO	Et_3N	32	2:1	78	*S*
Ph	Ni	Me_2CO	MeONa	54	—	72	*R*
Ph	Ni	Me_2CO	MeONa	56	—	98	*R*
Me	Cu	Me_2CO	MeONa	55	—	70	*R*
Me	Cu	PhCHO	MeONa	67	50:1	74	*R*
Me	Ni	PhCHO	MeONa	67	34:1	82	*R*
Ph	Ni	PhCHO	MeONa	67	34:1	82	*R*
Ph	Cu	PhCHO	MeONa	59	50:1	80	*R*

The observed high value p = 95% for the diastereoisomer with (*S*)-Ser (LXX, R^2 = R = H) at low pH is in full agreement with theoretical ideas. At a high pH of the solution, only the (*S*,*R*)-diastereoisomer (LXXII) is formed, which is associated with the ionisation of the hydroxy-group in compounds (LXXI) and (LXXII) and the rearrangement of the complex with coordination of the metal to the ionised hydroxy-group:



(LXXII)

It is noteworthy that, owing to steric hindrance, the second CH_2O molecule does not add to the complex with formation of α-hydroxymethylserine—the main product in the earlier attempts to synthesis Ser from Gly.[154] The preferential formation of the *threo*-products for other aldehydes is also associated with the ionisation of the hydroxy-group at a high pH and the rearrangement of the complexes.[151] The complexes (LXX) and (LXXI) have been converted by acetylation and the elimination of AcOH into the dehydroalanine complex (LXXIII),[155] which combines with thiophenol and phenylmethanethiol via the double bond with formation of the diastereoisomeric complexes of L- and D-*S*-phenyl- or L- and D-*S*-benzyl-cysteines:



(LXXIII)

Chromatographic separation on silica after decomposition yields the enantiomerically pure L- and D-*S*-phenyl- or L- and D-*S*-benzyl-cysteines in an overall yield of 80%.[156,157] The thermodynamic CH acidity of the complexes (LXIX) reaches high values [pK_a = 19.5 (R = R^1 = H), 19.2 (R = H, R = Me), 21.2 (R = H, R^1 = $CHMe_2$), and 18.8 (R = Ph, R^1 = H) in DMSO [158]] and is comparable to the acidity of malonic ester. The high CH acidity of the complexes and their stability have been used to carry out reactions with weak electrophiles—alkyl halides, which made it possible to obtain a series of optically pure α-Me-α-AA for both the (*S*)- and the (*R*)-series[159] (Table 7):

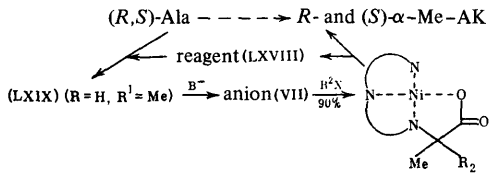


Table 7. The yields of the products of the alkylation of the complex (LXIX, R = H, R^1 = Me) by alkyl halides.[159]

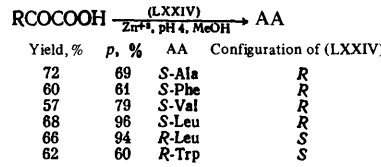
R^2X	BuLi, THF	10% NaOH, CH_2Cl_2
	(*S*, *S*); (*S*, *R*)	(*S*, *S*); (*S*, *R*)
MeI	92	
$PhCH_2Br$	51; 40	63; 31
$CH_2{=}CHCH_2Br$	56; 33	62; 22

In contrast to the known methods for the alkylation of chiral enolates,[74–79] in this case the deprotonation can be achieved not only with BuLi in THF but also with aqueous alkali under the conditions of phase-transfer catalysis. The separation of the complexes on silica yielded, after decomposition, the optically pure α-Me-AA. Under the conditions of kinetic control, the alkylation of the complex (LXIX, R = R^1 = H) by alkyl halides proceeds with a low value of *p*, which indicates a small difference between the rates of attack by the electrophile on the anion from different sides of the coordination plane. Attack from below, the side opposite to that of the benzyl group, leading to the (*S*,*S*)-diastereoisomer, is somehwat preferable.[159] The use of complexes containing the phenyl group (R = Ph), which imparts the pseudo-axial conformation to the pro-(*S*)-proton, facilitates the attack from below with formation of the (*S*)-AA fragment and increases *p* to 90%.[160]

The general method of asymmetric synthesis of AA via transition metal complexes has many advantages over other procedures. These are the ease of formation of the chiral complexes, mild conditions of the reactions with electrophiles, the high value of *p* for AA, and the virtually complete regeneration of the chiral reagent.

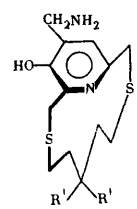
VII. CATALYTIC ASYMMETRIC TRANSAMINATION

The biomimetic approach to the synthesis of a simplified model of enzymic transamination[161] has been applied in a study[162] where the chiral pyridoxamine (LXXIV) with an *ansa*-chain in the molecule, capable of effecting the transamination of α-ketoacids to give AA with *p* up to 9.4% on catalysis by Zn^{2+}, was obtained:

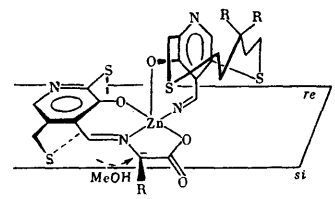


R	Yield, %	*p*, %	AA	Configuration of (LXXIV)
Me	72	69	*S*-Ala	*R*
$PhCH_2$	60	61	*S*-Phe	*R*
Me_2CH	57	79	*S*-Val	*R*
Me_2CHCH_2	68	96	*S*-Leu	*R*
Me_2CHCH_2	66	94	*R*-Leu	*S*
3-Indolyl	62	60	*R*-Trp	*S*

In the case of MeO[^{2}H], α-deuteriated AA with *p* = 40–90% are isolated:[163]

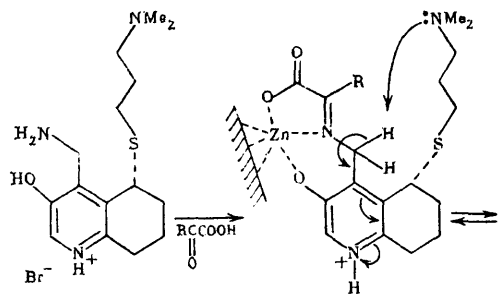


(*S*)-(LXXIV)
R' = H, Me

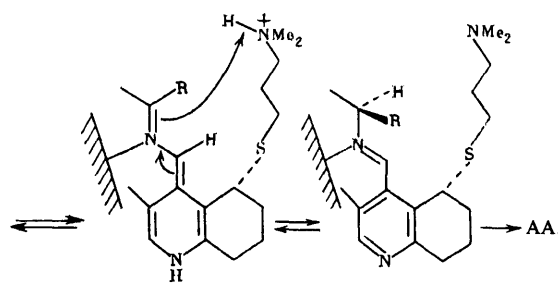


(LXXV)

The asymmetric induction can be explained by the kinetically controlled stereoselective protonation of the carbanion formed in the intermediate Zn^{2+} Λ-complex (LXXV). Best results have been obtained with the model (LXXVI), whose activity is even closer to that of an enzyme containing the ε-amino-group in a chiral environment[164]—an analogue of the ε-amino-group of lysine in the active centre of pyridoxal.[161] The dimethylamino-group in the complex (LXXVII) acts as a base for the removal of the pro-(*S*)-hydrogen from 4'-methylketimine, after which the dimethylammonium group approaches, as a consequence of the chiral structure of the complex, the same side of the intermediate (LXXVIII) and, acting as an acid, protonates the α-position from the *si*-side, giving rise to the chiral aldimine (LXXIX) with subsequent liberation of the AA.

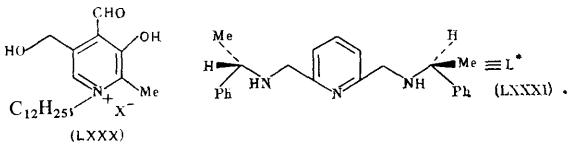


(LXXVI) (LXXVII)



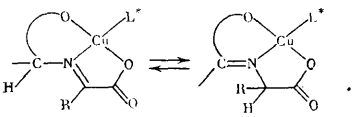
(LXXVIII) (LXXIX)

The following (*R*)-AA were obtained: Ala (yield 83%, $p = 86\%$), NVa (68%, $p = 92\%$), and Trp (89%, $p = 88\%$). The use of compound (LXXVI) accelerates the reaction by an order of magnitude owing to the intermolecular general acid—base catalysis compared with the analogue without the NMe_2 group, which a 75% yield of NVa with $p = 16\%$. Thus the chiral aldimine can be obtained in two ways—by introducing a steric hindrance through the attack by the carbanion from one side[163] or by the stereoselective protonation of the carbanion.[164] The feasibility of the method is associated with the availability of α-ketoacids and the necessity to employ a metal. The possibility of transamination also without a metal using the achiral *N*-laurylpyridoxal (LXXX) in a cationic micelle under conditions close to physiological conditions has been recently demonstrated.[165] The pyridoxal catalysis has been induced by means of a laser (3371 Å), which also leads to transamination in the absence of enzymes:[166]



(LXXX) (LXXXI).

Another approach is associated with the use of metal complexes of Schiff bases obtained from pyridoxamine and the ketoacid containing compound (LXXXI) as a chiral ligand; a diastereoselective conversion of a ketimine into an aldimine then takes place in the complex.[167] When an (*S*)-ligand is used, the values of *p* for (*S*)-Ala, (*S*)-Val, and (*S*)-Leu are respectively 54, 29, and 48%:

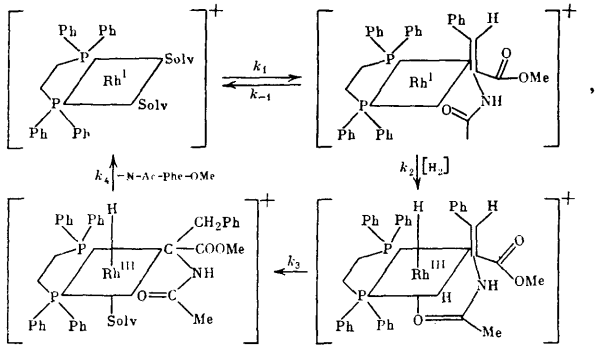


VIII. CATALYTIC ASYMMETRIC REDUCTION

The most effective way of using chiral compounds in the asymmetric synthesis of AA involves their application as catalysts.[168] Striking results have been achieved primarily in the asymmetric reduction of derivatives of prochiral αβ-dehydro-AA (Δ-AA) to the corresponding optically active AA using neutral or, more often, cationic rhodium complexes, containing chiral phosphine ligands, as catalysts.[169] In the reduction of derivatives of α-*N*-acylaminocinnamic acid (AACA), the value of *p* for many chiral phosphines is close to 100%.[170,171] The results have been described in a series of reviews[28,172-177] and monographs.[178,179] We shall examine data for the determination of the reaction mechanism, the present trends, and the prospects for the method.

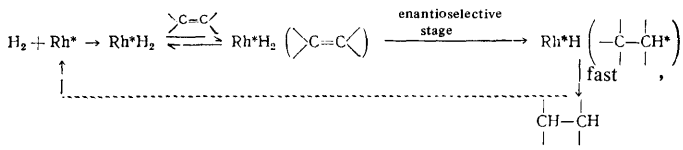
The best rhodium-based catalysts exhibit not only a high enantioselectivity but also a high activity, which approaches that of enzymes and therefore the determination of the mechanism of the reduction of AACA on the basis of the ideas of organometallic and coordination chemistry of rhodium complexes helps also in understanding the effective chiral recognition in such systems. Scheme 6 presents the mechanism of the rhodium complex-catalysed reduction of the AACA ester by Halpern's method.[28] The structure of intermediates was established by spectroscopic methods, resorting in a number of instances to X-ray diffraction;[180-183] the kinetic parameters of all the stages of the catalytic cycle have been determined.[28]

Scheme 6



In the first stage, the formation of a complex with the substrate and the ligand proceeds fairly rapidly and is almost complete even at a low substrate concentration. At 20 °C the second stage of the catalytic cycle—the oxidative addition of hydrogen to the complex—is rate determining and gives rise to a hydride complex in the form of a mixture of the two diastereoisomers (III) and (IV) (Fig.1), characterised at low temperatures as the product of the next stage—reductive elimination.[28] Examination of the structure of the principal diastereoisomer (II) [(II)/(I) > 10 : 1] in solution and in the crystalline state showed that the *re*-side of the substrate is coordinated to rhodium and that the *endo*-addition of hydrogen should give rise to the (*S*)-product, whereas the reaction leads to the isolation of the (*R*)-product with $p > 95\%$.[28] It has been shown that the preferential formation of the (*R*)-product is determined by the much higher reactivity of the minor diastereoisomer (I) (Fig.1).[28,184,185]

Ojima and co-workers[186,187] do not dispute this mechanism for the normal reduction conditions but propose an alternative pathway at high hydrogen pressures:



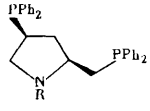
where Rh* is a rhodium complex with a chiral phosphine.

The oxidative addition of H_2 to the complex with the ligand proceeds initially and only then, in the rate-determining stage, does the substrate add on,[186,187] which also agrees with experiment.[188]

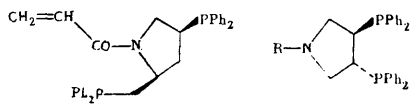
One of the important factors influencing the enantioselectivity is the hardness of the complexes (I) and (II) formed. It has been suggested that the lower yields in the reduction of the (*E*)-isomers of AACA compared with the (*Z*)-isomers are associated with the lesser degree of hardness of the complex formed.[186] Effective asymmetric reduction requires the optimum ratio of the rates of the competing reactions in the individual stages of the process, which depends very greatly on the substrate and only AACA or compounds with very similar structures satisfy these requirements.[189] Numerous findings indicating the influence of the form and conformation of the chelate phosphine rings on *p* have demonstrated that five- and seven-membered rings are preferable to six-membered rings owing to the existence of the latter in the rigid chiral C_2-twist conformation.[182,189,190] According to Butler et al.,[183] in a number of instances the size of the chelate ring is of little importance and the principal factor is the nature of the substituent in the phosphine. The main postulate important for the understanding of the stereochemical mechanism of asymmetric hydrogenation has been surveyed by Pavlov and Klabunovskii.[191] It was noted that the stereochemistry of the reaction is determined in the olefin

coordination stage with formation of a chelate complex and that the main source of discrimination between the sides of the coordinated prochiral olefin and the catalyst molecule is the chiral disposition of the benzene rings around the phosphorus atom.

A wide scale search for new and for the modification of the existing phosphine ligands, giving rise to values of p close to 100% in asymmetric reduction, has been prosecuted in recent years.[183,192–196] However, the high sensitivity of rhodium catalysts to oxygen and moisture, their high cost, their non-technological nature, and the impossibility of using them at high temperatures, limit their application. There have been only a few successful attempts to reuse a homogeneous rhodium catalyst[197] and also water-soluble diphosphines.[198,199] The problem of the synthesis of chiral organometallic catalysts free from such disadvantages is solved in general by the familiar heterogenisation methods.[200] the synthesis of the rhodium catalyst is usually achieved by introducing a chiral functional group, capable of complex formation, into the achiral matrix. However, the binding of the complexes to mineral clays significantly reduces p as a result of the selective absorption of the reduced product by the carrier.[201] Immobilisation on cellulose derivatives gives rise to a low value of p,[202] as in the case where a protein is employed as both the carrier and the catalyst.[203] The rhodium complex of BPPM, deposited on charcoal and treated with chromium acetate and Et_3N, gives rise to yields comparable to those of homogeneous reduction (p up to 86.5%), which do not fall when the catalyst is reused:[204]



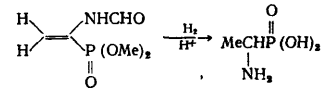
(BPPM)



(LXXXII) R = H, COPh (LXXXIII)

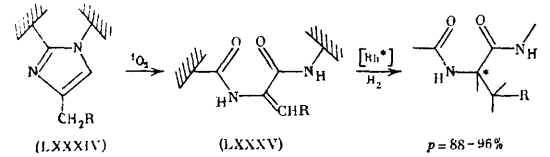
Best results have been achieved with polymers as carriers.[205,206] Thus optically active phosphine-pyrrolidine monomers (LXXXII) have been obtained, their copolymerisation with hydrophilic monomers and the divinyl monomer affording a cross-linked polymer containing 3–5% of the (LXXXII) fragments, and swelling effectively in the usual hydrogenation solvents.[205] The catalyst was obtained in the usual way by the interaction of $[RhCl(C_2H_4)_2]_2$ with an optically active polymer. Its employment yields p = 88–91% for both (R)- and (S)-N-acylated Phe and DOPA derivatives, the results being equivalent to those obtained under homogeneous reduction conditions. The essential feature of the method consists in a selection of the swellability characteristics of the polymer in the system of solvents employed such that the catalytic section of the polymer is open to interaction with the substrate and is not affected by the functional groups of the main polymer chain.[205] High results have been obtained with (R,R)-(LXXXIII), synthesised in 8 stages from (R,R)-tartaric acid with an overall yield of 36%.[207] The rhodium complex of this ligand on the Merrifield resin or SiO_2 permitted the reduction of AACA with p = 95% (catalyst/substrate = 1 : 10^4, pressure 50 bar, time h, MeOH). The hydrogenation then proceeds only slightly more slowly than under homogeneous conditions; filtration of the catalyst when the reactions have been completed makes it possible to use it more than once without loss of activity.[207] There is no doubt that the elimination of a whole series of disadvantages of homogeneous rhodium catalysts by their heterogenisation will serve in the future as a stimulus for an even wider employment of these systems. A new approach has been proposed in a study[208] in which the enantioselective hydrogenation of AACA was carried out with the aid of the achiral Wilkinson catalyst—$Rh(PPh_3)_3$—in cholesteryl tridecanoate as a chiral liquid crystal matrix. The temperature dependence of p has a maximum corresponding to the middle of the temperature range of the existence of the mesophase. The yield of Phe was 98–100% (p = 16%).

Another limitation of rhodium catalysts which prevents their wide scale use in reduction is the small number of substrates which can be used successfully. Thus, satisfactory results have been obtained for eight aminoacids: DOPA, Tyr, Phe, Trp, Ala, Lys, Leu, Val, and some of their derivatives.[171,172,209,210] Their number is now being rapidly expanded. The asymmetric synthesis of the phosphorus analogue of Ala, namely α-aminophosphonic acid, has been carried out over $[Rh\text{-}DIOP]^+$:[21]



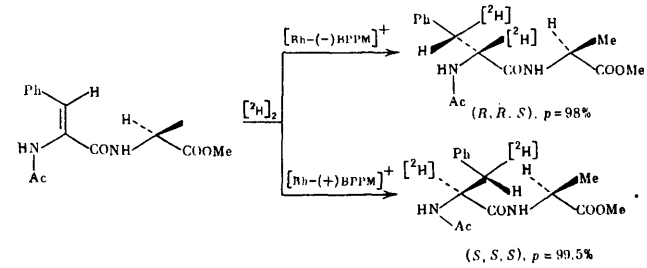
99%, p = 76%

The reduction of ten N-acyl-β-heteryl-α-aminoacrylates on this catalyst showed that 2-thienyl, 3-thienyl, 1-methylpyrrolyl, and 3-quinolinyl derivatives are reduced comparatively rapidly with p = 20–70%, while the corresponding pyridyl and imidazolyl derivatives are inactive.[212] The photochemical oxidation of cleavage of trisubstituted imidazoles (LXXXIV) with subsequent reduction of the derivatives of Δ-AA amides (LXXXV) has been achieved:[213]



(LXXXIV) R = H, $CHMe_2$, Ph. (LXXXV) p = 88–96%

Overall, the development of the asymmetric reduction stimulated also the develoomment of new ways of synthesising Δ-AA which were previously difficult to obtain.[214] On the other hand, reduction with formation of chiral dipeptides[173,179,197,215] and complex analogues of polypeptides of the type of encephalin[187,216] as well as deuteriated and tritiated polypeptides,[199,217,218] which are difficult to obtain, has also been developing on a wide scale, for example,



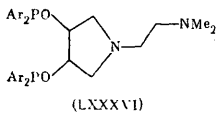
(R,R,S), p = 98%

(S,S,S), p = 99.5%

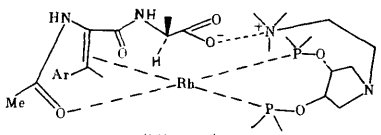
This makes it possible to modify the physiological activity of peptides by inverting the configuration of one or several chiral centres by replacing series of AA by unnatural AA, for example in enkephalin, vasopressin, etc.[187]

The effectiveness of rhodium catalysts in the synthesis of peptides differs somewhat from that for AA.[187] On the other hand, in the reduction of peptides by AACA, ligands forming seven-membered rings produce better results than those forming five-membered rings in view of their greater

flexibility, which becomes an important factor when the substrate is polyfunctional.[186] The high enantioselectivity in the reduction of *N*-terminal dehydropeptides (DHP) compared with the *C*-terminal dehydropeptides[219] and also the important role of the *N*-acyl groups, associated with the possibility of their coordination to the Rh atom with formation of a five-membered chelate ring,[218] known also for Δ-AA, has been established. The chiral AA residue in DHP has less influence, since the coordination of its carboxy-group to Rh prevents the oxidative addition of H_2.[218] A detailed study has not been made, but the principal data support the general mechanism proposed for the reduction of AACA [28] (see Scheme 3).



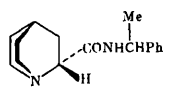
(LXXXVI)



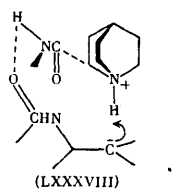
(LXXXVII)

It is of interest that, in the presence of the ω-dimethylamino-group in the ligand (LXXXVI), the diastereoselectivity is inverted also for *N*-Ac-ΔPhe-(*S*)-Phe and the (*S*,*S*)-dipeptide with p = 98% is produced.[220] This finding can be explained by the interaction between the NMe_2 group and the COOH group of the peptides, which fixes a definite disposition of the substrate on the catalyst (LXXXVII), while in the case of AACA, where the distance between the groups are large, such interaction does not occur and the yields of (*S*)-Phe are low. The only example of the reduction of bis-DHP over $[Rh\text{-}DIOP]^+$ immediately to a mixture of the Phe-Phe dipeptides (*S*,*S* + *R*,*R* and *R*,*S* + *S*,*R*) is quoted with p = 9% and 79% respectively.[221] Examples with double asymmetric induction frequently lead to high values of p. A stereochemical analysis of such induction within the framework of the interaction of two chiral reagents has been carried out.[173]

The search for effective catalysts using other metals, namely Ru,[222,223] Ir,[224] Pd,[225] and Ni and Co,[226] has been expanded recently. Systems with non-phosphine ligands are promising.[225,227] The development of effective catalysts without platinum group metals is of special interest. A reduction catalysts comprising the complex [Co(dimethylglyoxime)$_2$.base] or [Co(DMG)$_2$.B], used with a chiral catalytic system containing a tertiary amino-group in the α- or β-position relative to the amide group, has been proposed.[227] In the case of $PhCH_2NH_2$ or $P(Ph)_3$ as the base and (*S*)-*N*-[(*R*)-1-phenylethyl]quinuclidine-2-carboxamide (LXXXVII) as the chiral catalyst, the reduction of *NN*-dimethyl-5-benzylidene-hydantoin via compound (LXXXVIII) has been achieved with 93% yield and p = 79%:



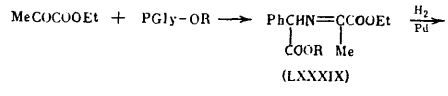
(LXXXVII)



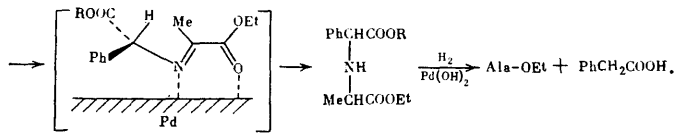
(LXXXVIII)

Thus, the asymmetric protonation of carbanions by chiral acids (Section IV) is a model reaction of the observed catalytic process. The reduction of the AACA ester [in the presence of the chiral catalytic system $CoCl_2$-(+)-neomenthyl-PPh_2-$NaBH_4$] gave p = 37% for a maximum degree of conversion of 77.5%.[228]

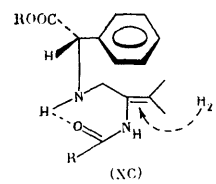
In hydrogenation on heterogeneous catalysts, two procedures are possible—firstly, the use of catalysts modified by treatment with optically active compounds capable of complex formation[229,230] and, secondly, the hydrogenation of the C=C and C=N bonds of the prochiral groups in compounds containing one or more chiral centres. Thus, hydrogenation of derivatives of the AA (LXXXIX) is well known:[231]



(LXXXIX)

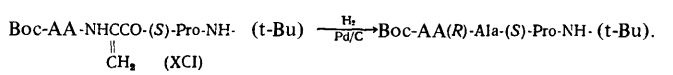


In the latest studies, the AA themselves have been used as the chiral amine,[232] but the values of p do not exceed 72% for a yield of 58%. The inadequate rigidity of the binding of the substrate to the catalyst, demonstrated by studying the influence of the solvent and temperature on transamination in compound (LXXXIX),[232] limits the application of the method. Indeed, for the more rigid cyclic systems, for example, in the reductive amination of 2-(*R*)-methylcyclohexanones over Raney nickel, p increases to 92–98%.[233] The reduction of acyclic chiral AA amides[234] or DHP [235] proceeds with low values of p, while their increase to 40–60% in the case of aromatic compounds can be explained by the formation of structures of type (XC),[235] in which one of the sides of the double bond is shielded and which are analogous to structures (LII)–(LIII), where one of the sides of the chiral carbanion is shielded.

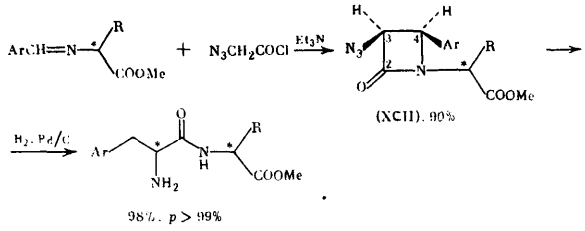


(XC)

The formation of a rigid surface chelate complex has also been proposed in a study[236] where a high value of p was obtained in the reduction of linear *N*-Ac-DHP on a nickel catalyst. Indeed the reduction of cyclic DHP on Pd/C usually affords dipeptides with high values of p (up to 96–99%).[237] Cyclo-[(*S*)-AA-(*S*)-AA] have been obtained from cyclo-[Δ-AA-(*S*)-AA]; they are hydrolysed to give (*S*)-AA. The reduction of the linear chiral tripeptides (XCI), containing the Δ-AA fragment in the middle unit, has been carried out with p = 84–93%, the use of a C-terminal substituted AA giving better results than the use of N-terminal AA:[238]



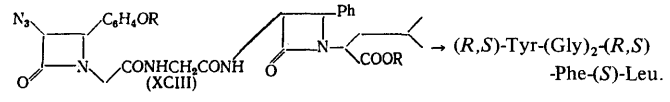
A diastereoselective synthesis of chiral peptides via β-lactams (XCII) has been developed.[239–241] β-Lactams are obtained from the Schiff bases of chiral AA and azidoacetyl chloride and are reduced after the separation of the diastereoisomers (XCII). The essential feature of the method consists in the highly selective cleavage of the N–C(4) bond in the reduction of compound (XCII) on Pd/C:



(XCII), 90%

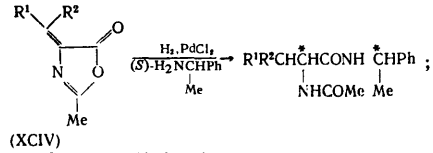
98%, $p > 99\%$

The use of Schiff bases derived from chiral amines leads to chiral AA amides.[240] The application of β-lactams as chiral synthons[9] made it possible to obtain a series of diastereoisomerically pure oligopeptides, for example a new synthesis of Leu-enkephalin from compound (XCIII) has been achieved:[240]



(XCIII) → (*R*,*S*)-Tyr-(Gly)$_2$-(*R*,*S*)-Phe-(*S*)-Leu.

The reductive ammonolysis of the azlactones (XCIV), for which the rhodium-phosphine catalysts are ineffective, makes it possible to synthesise a wide variety of natural AA.[242] The reduction of compound (XCIV) on $PdCl_2$ with subsequent ammonolysis leads to the corresponding amides *N*-acetyl-AA:

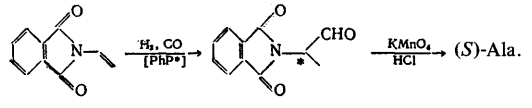


(XCIV)

R^1, R^2=H, Me, $CHMe_2$, Ar .

A yield of 98% with p = 50% (*S*,*S*) has been attained for R^1 = 3-MeO-4-$AcOC_6H_3$ and R^2 = H, which made it possible to obtain optically pure (*S*)-DOPA in 39.5% yield after recrystallisation and hydrolysis.[243]

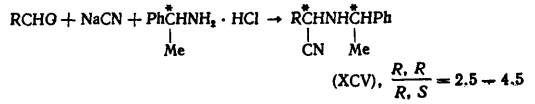
Asymmetric hydroformylation is used little in the synthesis of AA.[244] The *N*-vinyl derivatives of phthalimides have been converted into (*S*)-Ala with a yield of 33% (p = 27%)[245] and in a number of instances the yields are even lower:[246]



However, when account is taken of the latest advances in hydroformylation,[168] this application is promising.

IX. THE STRECKER SYNTHESIS

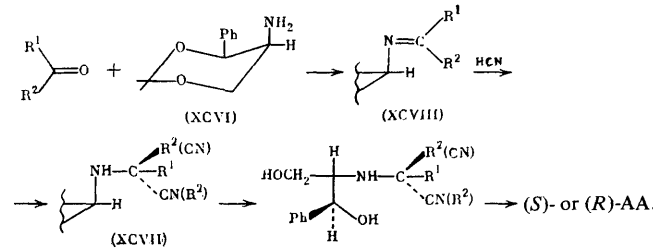
A series of reviews have been devoted to the asymmetric Strecker reaction.[2,3,15] In practice, HCN is usually allowed to react with chiral amines and carbonyl compounds[247] or with the Schiff bases obtained from them beforehand.[248] The recrystallisation of the resulting aminonitriles (XCV) using (*R*)-PhCH(Me)NH_2 makes it possible in a number of instances to raise the yield of the optically active diastereoisomers to 54%.[247] The formation of aminonitriles proceeds subject to thermodynamic control.[15]



(XCV), $\frac{R,R}{R,S} = 2.5 \div 4.5$,

The reaction of acetophenone with HCN and (*S*)-PhCH(Me).NH_2 results in the preferential formation of the (*S*,*R*)-diastereoisomer analogue of compound (XCV), while the (*S*,*S*)-diastereoisomer is formed from *p*-methoxyacetophenone.[249] If the reaction of the readily available (4*S*,5*S*)-5-amino-2,2-dimethyl-4-phenyl-1,3-dioxolan (XCVI)[250] with thiophen-2-aldehyde or thiophen-3-aldehyde and HCN is carried out in one stage, (*R*,*S*,*S*)-aminonitriles (XCVII) and respectively (*R*)-2-thienyl- or (*R*)-3-thienyl-glycine are formed preferentially, while the intermediate isolation of the imine (XCVIII) results in the preferential formation of the corresponding (*S*)-AA[248] (Scheme 7):

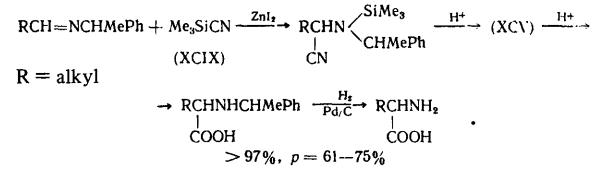
Scheme 7



(XCVI) (XCVIII) (XCVII) → (*S*)- or (*R*)-AA.

Optically pure α-Me-AA,[267] (*S*)-phenyl- and (*S*)-anisyl-Gly,[251] (*S*)-Leu, and (2*S*,4*R*)- and (2*S*,4*S*)-5,5,5-trifluoro-Leu[252] have also been obtained. The essential feature of the proposed method is the formation of diastereoisomeric readily crystallising aminonitriles (XCVII), whose ratio determines the optical yield of the AA isolated after their decomposition. In a number of instances, only the (*S*,*S*,*S*)-diastereoisomer (with R^1 = CH_2CMe_2OPh and R^2 = Me) or only the (*R*,*S*,*S*)-diastereoisomer (with R^1 = CH_2OPh and R^2 = Me) is formed.[253] In other cases the separation is carried out by recrystallisation.

The Strecker synthesis is nowadays widely used in the multistage method for the preparation of non-protein AA. Pure (*S*)-γ-carboxy-Glu has been obtained in a low yield from formylmethylmalonic ester in seven stages using (*S*)-PhCH(Me)NH_2.[254] The use of cyanotrimethylsilane (XCIX) is convenient in practice:[255]



R = alkyl

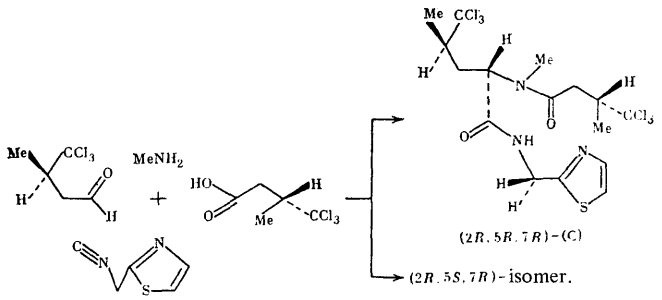
>97%, p = 61–75%

The interaction of compound (XCIX) with chiral acetals gives rise to the corresponding cyanohydrins with p = 95%.[256] Thus the Strecker synthesis continues to develop towards the use of new chiral amines in order to eliminate its principal disadvantage—the ready racemisation of diastereoisomeric α-aminonitriles. The use of chiral aminonitriles is being steadily expanded; thus they have been used to synthesise substituted α-hydroxyketones with p up to 97%.[257]

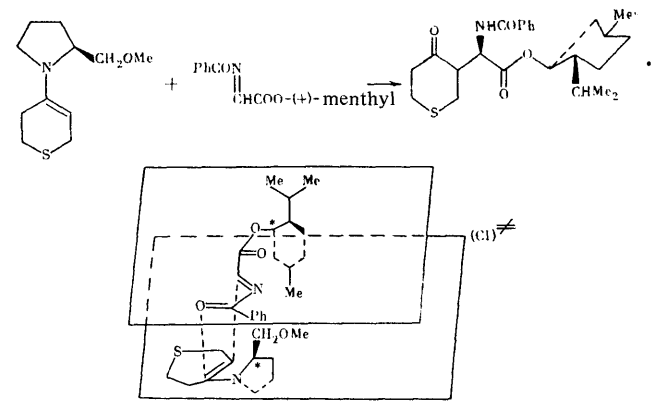
There are great possibilities in the asymmetric catalytic Strecker synthesis. The formation of benzaldehyde (*R*)-cyanohydrin in the presence of cyclo[(*S*)-Phe-(*S*)-His].H_2O takes place with p = 90% for a 40% degree of conversion (PhH, 35 °C, 0.5 h, substrate/catalyst = 1 : 1).[258] The value of p diminishes markedly with increase of the degree of conversion as a result of racemisation.[259] The attempts to carry out the absolute asymmetric synthesis of AA using cyanide compounds, modelling the prebiotic synthesis of AA,[22,260] gave low values of p.

X. OTHER REACTIONS

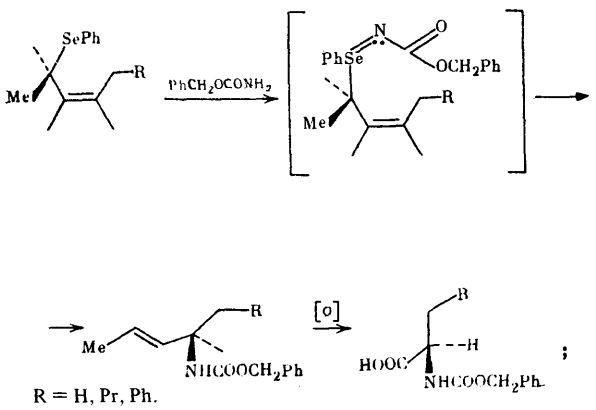
A successful example of the use of the four-component condensation by the Ugi method is provided by the synthesis of the optically pure peptide (+)-(2*R*,5*R*,7*R*)-13-demethyldysidenin (C) and its (2*R*,5*S*,7*R*)-isomer in 17 and 13% yields respectively:[261]



Enantiometrically and diastereoisomerically pure esters of γ-oxo-AA have been obtained[262] via a reaction of the Diels–Alder type, which can be explained by the transition state model $(CI)^{\neq}$.

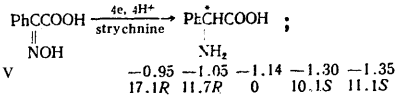


Here the cooperative effect of the two chiral substituents ensures the stereospecific course of the process and the use of (−)-menthyl ester lowers *p*.[262] The possibility of using the [2,3]sigmatropic rearrangement of substituted optically active selenides for the synthesis of *N*-substituted (*R*)-AA in yields of 58–72% and with *p* = 78–84% has been demonstrated:[263]



In the last stage, the oxidation of the double bond results in the formation of the COOH group of the aminoacid without involving the neighbouring chiral centre. In general the oxidation of alcohols and olefins to obtain the carboxy-group is widely used in the synthesis of AA from other optically active compounds: of chiral Gly from D-glucose [264] and of (*R*)-AA from (*S*)-Ser.[23]

Yet another example of the strong influence of the reaction conditions on the optical yield is provided by the electrochemical synthesis of PGly from the oxime of phenylglyoxylic acid in an acetate buffer solution in the presence of strychnine:[265]



cathodic potential, V	−0.95	−1.05	−1.14	−1.30	−1.35
p, %	17.1*R*	11.7*R*	0	10.1*S*	11.1*S*

When a graphite electrode coated with poly-(*S*)-Val is used in this reaction, $p < 2\%$.[266]

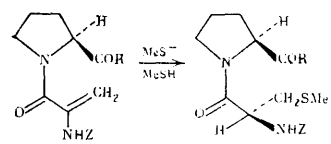
The range of photochemical asymmetric reactions investigated is limited. The first example of asymmetric photolysis, which is especially important for prebiotically valuable substrates such as AA, has been described[267] in relation to the use of (*R*,*S*)-Leu. It has been established that left-(*S*)-circularly polarised light (LCPL), obtained from a laser source with λ = 212.8 nm, effects the preferential photolysis of (*S*)-Leu, while right-(*R*)-polarised light (RCPL) effects the preferential photolysis of (*R*)-Leu. An enantiomeric excess of 1.98 has been obtained for a 52% degree of conversion with RCPL and of 2.5 for a 75% degree of conversion with LCPL. The stereocontrolled photoalkylation of the Gly residue in the peptide chain proceeds with *p* up to 40%.[268] When the reaction

$$[(S)\text{-Ala-Gly-}(S)\text{-Ala}]_n \xrightarrow[\text{toluene}]{h\nu} [(S)\text{-Ala-}(S)\text{-Phe-}(S)\text{-Ala}]_n \rightarrow (S)\text{-Phe}$$

is carried out in but-1-ene, it is possible to obtain (*R*)-NLe with *p* up to 20%:

$$[(S)\text{-Pro-Gly-}(S)\text{-Pro}]_n \xrightarrow[\text{but-1-ene}]{h\nu} (R)\text{-NLe}.$$

The biomimetic formation of Cys with high chemical) up to 95%) and optical (*p* = 85%) yields has been achieved:[269]



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Chemical asymmetric synthesis makes it possible to obtain any aminoacids with natural and non-natural structures and configurations in virtually quantitative optical yields. A particular advances has been attained in the use of general methods such as catalytic asymmetric hydrogenation and enantioselective alkylation of carbanions generated from aminoacid derivatives. In a number of instances, high optical yields have been attained with double asymmetric induction when the enantioselectivity of the process is determined by two asymmetry centres already present.

The theory of asymmetric induction has been developed to only a very slight extent, because the small differences between the energies of the diastereoisomeric transition or final states which are sufficient for the attainment of a high enantioselectivity of the synthesis are a consequence of slight steric or electronic requirements, which are as a rule difficult to take into account.

The majority of asymmetric syntheses have not been developed as preparative syntheses of aminoacids—their assessment is frequently based on the NMR or GLC analysis of the

reaction mixtures. None of the asymmetric syntheses of aminoacids has so far found a serious industrial application, while the separation of enantiomers by crystallisation is very common. Analysis of the literature shows that this is caused by, on the one hand, the high cost and the difficulty of regenerating chiral rhodium compounds, the most effective catalyst of asymmetric synthesis, and, on the other hand, by the fact that the known chiral reagents for asymmetric synthesis, capable of being regenerated, are not as yet capable of propagating the catalytic process. These deficiencies predetermine the direction of the most promising research. Certain optically active aminoacids have become a readily available and cheap source of chirality. In many methods for asymmetric synthesis, they are used as a basis for the preparation of chiral reagents and catalysts.

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During the preparation of the review for printing, additional data have appeared in literature. In particular, a chiral polymeric rhodium catalyst based on 3,4-(*R*,*R*)-bis-(diphenylphosphino)pyrrolidine has been obtained. When AACA and its methyl ester were reduced in its presence, products with *p* up to 100% were obtained.[270] The activity of the catalyst falls after repeated use. The possibility of the quantitative isolation of rhodium after the completion of the reaction has been demonstrated.[271] New data concerning the mechanism of asymmetric reduction have been published.[272] The use of a chiral polymeric platinum catalyst based on DIOP derivatives permitted the hydroformylation of *N*-vinylphthalimide with *p* up to 70%.[273] The asymmetric aldol reaction of aldehydes with isocyanates, catalysed by the chiral ferrocenylphosphine gold(I) complex, leads to AA with a high value of *p*.[274]

Poly-L-Val (2%) on CdS catalyses the synthesis of Asp from fumaric acid and NH_4Cl on UV irradiation with $p = 60\%$.[275]

A review has been devoted to the biomimetic transamination of α-ketoacids.[276]

The synthesis of AA with $p > 95\%$ from α-halogenosulphonamidoisobornyl ethers has been published.[277]

(*R*)-*N*-substituted AA have been synthesised from (*S*)-hydroxyacids.[278]

A review has been published on the regio-, diastereo, and enantiostereoselective reactions leading to the formation of a C–C bond using metallated derivatives of aminonitriles, etc.[279]

The aldol reaction of a chiral enolate containing the Gly fragment with RCHO made it possible to obtain a series of enantiomerically pure β-hydroxy-*N*-methyl-AA.[280]

The catalytic asymmetric synthesis of chiral AA amides unsubstituted in the α-amino-group from trifluoromethyl derivatives of azlactones has been achieved.[281]

The use of 2-t-butyl-1,3-oxazolin-5-ones for the synthesis of optically pure α-vinyl-,[282] α-alkyl-,[283] and β-hydroxy-AA[284] proved to be more convenient than the use of compound (XLIV), which is their analogue.

In the continuation of studies on the bislactim method of synthesis of AA, the reactions of cyclo[L-Val-Gly] with epoxides ($p > 95\%$) and Michael addition to activated olefins ($p > 95\%$), with subsequent isolation of the corresponding (*R*)-Ser[285] and (*R*)-Glu[286] have been carried out. (*R*)-Pro,[287] cyclic optically pure AA,[288,289] and various non-protein AA[290] have also been obtained. A simple synthesis of α-aminocyclopropanecarboxylic acid has been described.[291]

The use of the general asymmetric method of synthesis of AA via chiral nickel(II) complexes of type (LXIX) made it possible to synthesise enantiomerically and disastereomerically pure β- and γ-substituted Glu and (*S*)-Pro by condensing Gly with activated olefins;[292] the reaction with alkyl halides affords optically pure AA derivatives.[293]

The possibility of the electrophilic asymmetric amination of various chiral enolates, obtained from carboxylic acid derivatives, by di-t-butyl diazodiformate, has been demonstrated simultaneously in a number of studies.[294–297] The optical yield of α-hydrazinoacids and correspondingly the α-aminoacids reached 99%.

The latest reviews on asymmetric synthesis include also data on AA.[298,299]

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