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Enzyme-Catalyzed Preparation and Synthetic Applications of Optically Active Cyanohydrins

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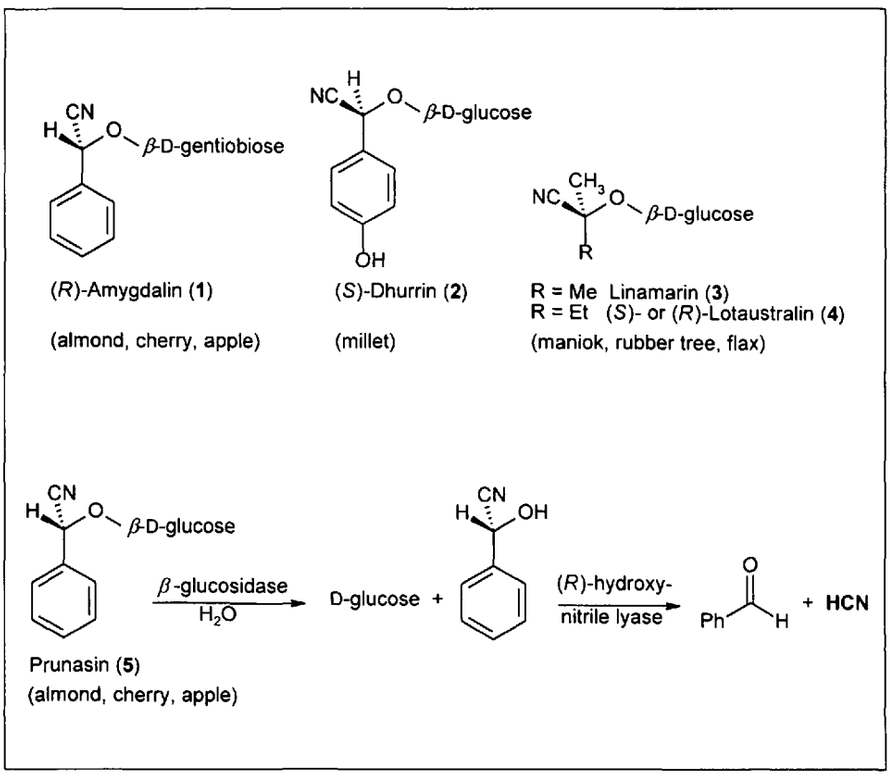
Abstract. Chiral cyanohydrins are widespread in nature as cyanoglycosides, serving more than two thousand plants and many insects as antifeedant. Fast release of HCN from cyanohydrins in cells is catalyzed by hydroxynitrile lyases (HNLs). The importance of HNLs in organic syntheses is the enantioselectivity of cleavage as well as formation of cyanohydrins by these biocatalysts. For the preparation of (*R*)-cyanohydrins from aldehydes and HCN on a preparative scale, (*R*)-PaHNL from bitter almonds proves to be the best catalyst. For the synthesis of (*S*)-cyanohydrins, the recombinant HNLs from cassava (MeHNL) and rubber tree (HbHNL) are most suitable. In organic solvents or in biphasic systems, the chemical addition of HCN to the carbonyl compounds can be suppressed, resulting in high optical yields of the obtained cyanohydrins. Stereoselective follow-up reactions of (*R*)- and (*S*)-cyanohydrins lead to other important classes of compounds with stereogenic centers. Starting from (*R*)-cyanohydrins, (*R*)-2-hydroxy carboxylic acids, (*R*)-2-hydroxy aldehydes, (*R*)-2-hydroxy ketones, (1*R*)-2-amino alcohols, and (1*R*,2*S*)-2-amino alcohols are easily obtainable in high optical and chemical yields by transformation of the cyano group. Analogous transformations are possible starting from (*S*)-cyanohydrins. Sulfonylation of the OH function in cyanohydrins allows nucleophilic substitution of the sulfonate group with complete inversion of configuration. In this way, starting, *e.g.*, from (*R*)-cyanohydrins, (*S*)-2-azido nitriles, (*S*)-2-amino nitriles, (*S*)-2-amino acids, (*S*)-1,2-diamines and (*S*)-2-sulfanyl nitriles are obtained in high optical yields.

1. Introduction

The release of HCN (cyanogenesis) as defence against herbivores is widely distributed in higher plants, including important food plants such as cassava or *Sorghum*. The highly toxic HCN is chemically masked in form of cyanohydrins, which are stabilized by *O*-β-glycosidic linkages to saccharides. During cyanogenesis (*Scheme 1*), first a specific β-glycosidase cleaves the cyanoglycoside to a carbohydrate and the corresponding cyanohydrin, which subsequently decomposes to the carbonyl compound and HCN. The latter step occurs spontaneously but also, much faster, enzymatically by action of a hydroxynitrile lyase (HNL) [1]. In *Scheme 1*, the release of HCN and the

Scheme 1



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formation of D-glucose and benzaldehyde from prunasin (**5**) represents an example of cyanogenesis in higher plants. It is interesting to note that an optically active cyanohydrin results by hydrolysis of the cyanoglucoside, and that the enzyme-catalyzed cleavage of the (*R*)-cyanohydrin requires an (*R*)-specific HNL.

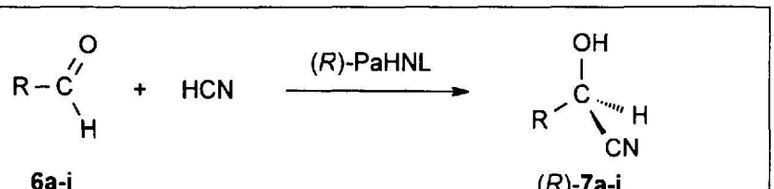
As all other catalysts, enzymes catalyze reactions in both directions. Enantioselective addition of HCN to an aldehyde in the presence of a HNL, forming an optically active cyanohydrin, could therefore be deduced from the enantioselectivity of cleavage.

One of the first asymmetric syntheses, and the first effected by an enzyme, was the preparation of (*R*)-mandelonitrile from benzaldehyde and HCN with emulsin as source for a (*R*)-HNL by *Rosenthaler* in 1908 [2]. More than fifty years later, *Pfeil* and coworkers [3] used the isolated enzyme from bitter almond (*Prunus amygdalus*), (*R*)-PaHNL [EC 4.1.2.10], and investigated the reaction in a more general way by using also other aldehydes besides benzaldehyde. All efforts to improve the optical yields of the resulting (*R*)-cyanohydrins failed, however. Especially with slow-reacting aldehydes the optical yields were very poor. As was customary at that time in enzymology, *Pfeil* and coworkers [3] used water or water/ethanol solvents and a pH of 5-6 for optimal activity of (*R*)-PaHNL. Under these conditions, the chemical addition of HCN to aldehydes resulting in racemic cyanohydrins prevails, especially when the enzyme-catalyzed addition is slow.

The decisive breakthrough for synthetic applications of this enzyme-catalyzed reaction was the discovery that the chemical addition of HCN to aldehydes is more or less suppressed in organic solvents not miscible with water. The enzyme-catalyzed reaction in organic solvents, however, is only slightly slower than in water [4]. *Table 1* demonstrates the advantage of using an organic solvent (*e.g.*, diisopropyl ether) instead of water/ethanol for the (*R*)-PaHNL-catalyzed addition of HCN to aldehydes (*Scheme 2*). In most cases, (*R*)-cyanohydrins of high optical purity are obtained [5]. For the reaction carried out in organic solvents, it is particularly advantageous to employ the enzyme adsorbed onto a suitable support, for example a crystalline cellulose like '*Avicel*'. Thus, the 'support-bound' enzyme may be filtered off after the reaction is complete and reused as catalyst.

The finding that chemical addition of HCN to aldehydes is suppressed by working in organic solvents, with the result that optically active cyanohydrins may be easily obtained, gave rise to many investigations of preparation and follow-up reactions for (*R*)- as well as (*S*)-cyanohydrins [5–9].

Scheme 2



6a-i (*R*)-**7a-i**

6,7a R = Ph
6,7b R = 2-furyl
6,7c R = 3-thienyl
6,7d R = 3-pyridyl
6,7e R = MeCH=CH
6,7f R = $MeS(CH_2)_2$
6,7g R = *n*Pr
6,7h R = $Ph(CH_2)_3$
6,7i R = Me_3C

Table 1. *Synthesis of (R)-Cyanohydrins (R)-7 by PaHNL-Catalyzed Addition of HCN to Aldehydes* **6**

	in H_2O/EtOH			in iPr_2O/*Avicel*[a])		
	Cyanohydrins (*R*)-**7**			Cyanohydrins (*R*)-**7**		
Aldehyde	Time [h]	Yield [%]	*ee* [%][b])	Time [h]	Yield [%]	*ee* [%][b])
6a	1	99	86	3	96	>99
6b	2	86	69	4	96	99
6c	–	–	–	6	95	>99
6d	2.5	78	7	3	97	82
6e	1.5	68	76	5.5	94	95
6f	3	87	60	16	98	96
6g	2	75	69	16	99	98
6h	–	–	–	45	94	90
6i	2.5	56	45	4.5	84	83

[a]) The enzyme was adsorbed on crystalline cellulose (*Avicel*).
[b]) Determined by gas chromatography on β-cyclodextrin phases after either reaction with (*R*)-α-methoxy-α-trifluoromethylphenylacetoyl chloride [(R)-(+)-MTPA chloride] to provide the diastereomeric (*R*)-(+)-MTPA esters, or after acetylation with acetic anhydride.

2. Hydroxynitrile Lyases for Synthetic Applications

The biosynthesis of cyanohydrins from α-amino acids is well established [1]. The majority (23) of the 28 cyanogenic glycosides are derived from five proteinaceous amino acids: L-valine, L-isoleucine, L-leucine, L-phenylalanine and L-tyrosine. The cyanohydrins formed by biodegradation of these amino acids contain as carbonyl compounds mainly acetone (linamarin (**3**)), butan-2-one ((*R*)-lotaustralin (**4**)), benzaldehyde ((*R*)-amygdalin (**1**), (*R*)-prunasin (**5**)), and *p*-hydroxybenzaldehyde ((*S*)-dhurrin (**2**)) (*Scheme 1*) [1]. In bitter almonds, (*R*)-amygdalin (**1**) and (*R*)-prunasin (**5**) are the main cyanogenic glycosides. Thus, benzaldehyde cyanohydrin is the natural substrate for PaHNL-catalyzed HCN release. PaHNL, however, accepts as substrates a surprising variety of other aldehydes, many of them being structurally very different from benzaldehyde. Although the substrate range of PaHNL is very broad, high optical yields are achieved in the addition reaction (*Table 1*).

Until 1987, the (*R*)-HNL from bitter almonds was the only HNL used as catalyst in the preparation of optically active cyanohydrins. Since the application of organic solvents enabled the preparation of many (*R*)-cyanohydrins in high optical yields, it was of great interest to get access to hydroxynitrile lyases for synthetic applications, which catalyze the formation of (*S*)-cyanohydrins.

An enzyme, (*S*)-SbHNL [EC 4.1.2.11], that preferentially cleaves (*S*)-cyanohydrins into aldehydes and HCN was first isolated from *Sorghum bicolor* [10]. Therefore, reactions using this enzyme in organic solvents have been investigated. It is considerably more time-consuming to isolate sufficient amounts of (*S*)-SbHNL from *Sorghum* than it is to isolate (*R*)-PaHNL from bitter almonds. Besides the problem of the more difficult accessibility, the substrate range of SbHNL is much more limited. The enzyme from *Sorghum* catalyzes exclusively the addition of HCN to aromatic and heteroaromatic aldehydes, whereas it does not accept aliphatic aldehydes as substrates [11–13]. Although clones are available from both PaHNL and SbHNL, an overexpression in other organisms (*Escherichia coli*, *Saccharomyces cerevisiae*, *Pichia pastoris*) has so far not been successful.

In order to extend the substrate range and to improve accessibility, other (*S*)-cyanogenic glycosides have been investigated in the last years with respect to applications of the corresponding enzymes in enantioselective syntheses. The (*S*)-HNLs from cassava (*Manihot esculenta*) [14] and *Hevea brasiliensis* [9] proved to be highly promising. In contrast to the (*S*)-HNL from *Sorghum*, both enzymes accept, besides aromatic and heterocyclic aldehydes, also aliphatic aldehydes and ketones as substrates [9][14]. The resulting (*S*)-cyanohydrins are obtained in high optical yields (*Scheme 3*). *Table 2* summarizes examples of (*S*)-cyanohydrins obtained with the HNL from cassava.

The (*S*)-HNLs from both *Manihot esculenta* [14][15] and *Hevea brasiliensis* [16] have been overexpressed successfully in *Escherichia coli*, *Saccharomyces cerevisiae* and *Pichia pastoris*, respectively. Hence, both recombinant (*S*)-HNLs are now available in amounts sufficient for synthetic and even technical applications. With the cloning and overexpression of the HNL from *Linum usitatissimum* an additional (*R*)-HNL has recently been developed for synthetic purposes. For some substrates, (*R*)-LuHNL seems to have advantages in comparison with the (*R*)-HNL from bitter almonds [17][18].

The properties and characteristics of the five hydroxynitrile lyases currently applied in the enzyme-catalyzed preparation of optically active cyanohydrins are listed in *Table 3*.

Numerous investigations concerning the synthesis of optically active cyanohydrins by using chiral metal complexes, cyclic dipeptides and lipases as catalysts have been published [5][7]. However, due to the easy accessibility and high optical and chemical yields, HNL-catalyzed preparations of optically active cyanohydrins are superior to other methods.

As mentioned above, the use of organic solvents for the HNL-catalyzed addition of HCN to carbonyl compounds was

Scheme 3

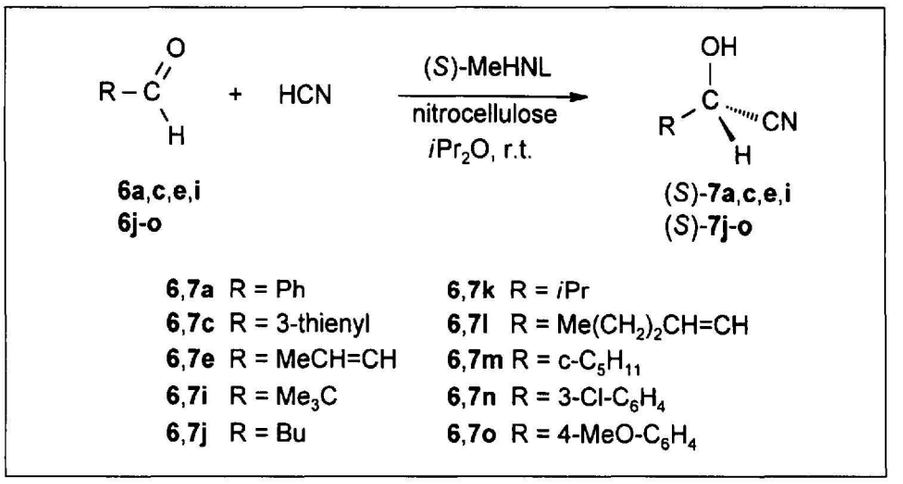


Table 2. *Synthesis of (S)-Cyanohydrins (S)-7 by MeHNL-Catalyzed Addition of HCN to Aldehydes 6 in Diisopropyl Ether* [a])

Aldehyde	Cyanohydrins (*S*)-**7**		
	Time [h]	Yield [%][b])	*ee* [%][c])
6a	7	100	98
6c	4	98	98
6e	1	100	92
6i	9	80	94
6j	4	100	91
6k	6.5	91	95
6l	3	82	97
6m	5	100	92
6n	9	100	92
6o	9.5	82	98

[a]) The enzyme was adsorbed on nitrocellulose.
[b]) The yield of **7k,n** was determined by ^{1}H-NMR spectroscopy.
[c]) Determined by gas chromatography on β-cyclodextrin phases after acetylation with acetic anhydride.

Table 3. *Properties and Characteristics of Hydroxynitrile Lyases Currently Applied in Organic Syntheses* [16][17]

Enzyme Source	Natural Substrate (Cyanogenic Glycosides)	*R/S* specificity	Molecular weight [kDa]		Optimum pH	Kinetics K_m [mM]
			Native	Subunit		
Prunus sp. (Rosaceae)	(*R*)-mandelonitrile (amygdalin, prunasin)	*R*	55–80	55–80	5–6	0.093
Sorghum bicolor (Gramineae)	(*S*)-*p*-hydroxymandelonitrile (dhurrin)	*S*	105	33 and 22	n.d.	0.55
Manihot esculenta (Euphorbiaceae)	acetone cyanohydrin, (*S*)-butan-2-one cyanohydrin (linamarin, lotaustralin)	*S*	92–124	28–30	5.4	105–119
Hevea brasiliensis (Euphorbiaceae)	acetone cyanohydrin (linamarin)	*S*	58	30	5.5–6	115
Linum usitatissimum (Linaceae)	acetone cyanohydrin (linamarin)	*R*	82	42	5.5	2.5

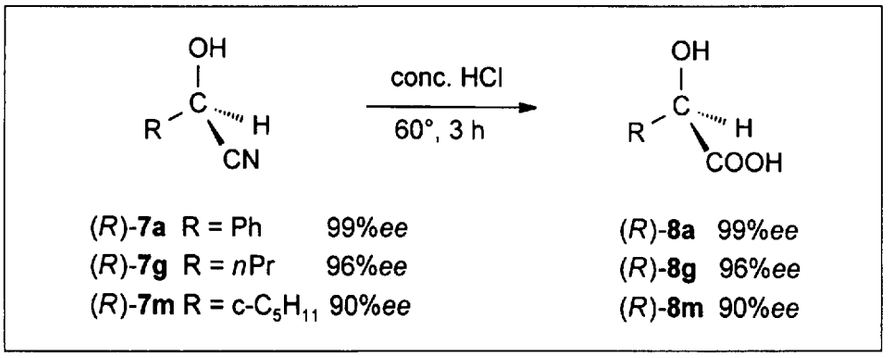
decisive for many investigations in the last years concerning optically active cyanohydrins. Several protocols for increasing the performance of the HNL-catalyzed preparation of (*R*)- and (*S*)-cyanohydrins have been developed:

a) Reactions in a biphasic system (water/organic solvent) often give optical yields comparable with those in pure organic solvents [6][19].

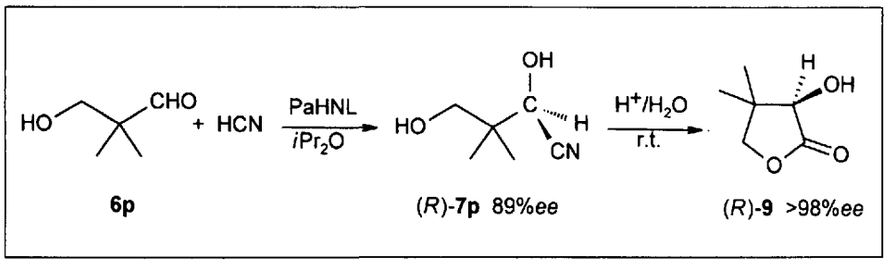
b) Acetone cyanohydrin can be used as precursor of HCN [19]. HCN can also be prepared *in situ* from NaCN with acetic acid in a biphasic system [20].

c) Isolated enzymes can be replaced for the reaction in organic solvents by whole cells, for example almond and apple meal instead of PaHNL, or *Sorghum* shoots instead of SbHNL [20][21].

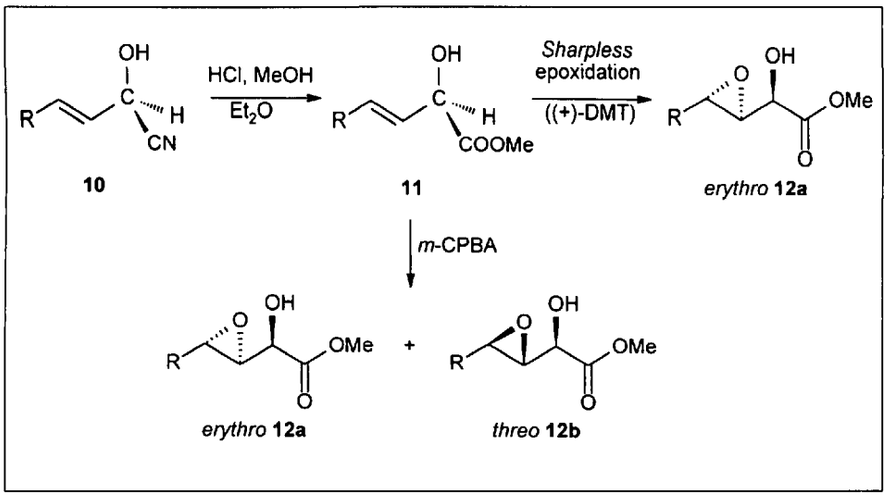
Scheme 4



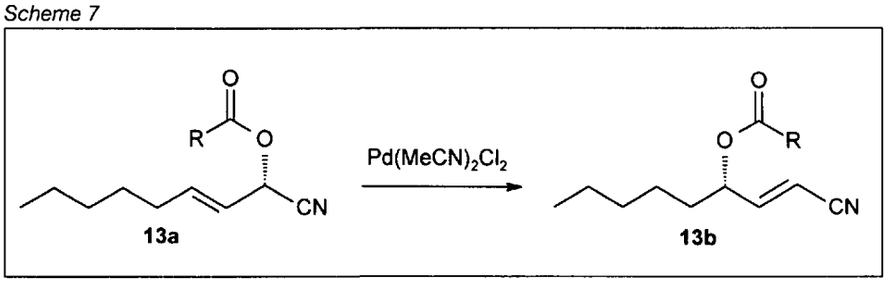
Scheme 5



Scheme 6



Scheme 7



3. Stereoselective Transformations of the Cyano Group of (*R*)- and (*S*)-Cyanohydrins

As 2-substituted carboxylic-acid derivatives, chiral cyanohydrins have a considerable synthetic potential [5–9]. Stereoselective reactions of chiral cyanohydrins lead to other important classes of compounds with stereogenic centers. In most cases, only follow-up reactions with (*R*)-cyanohydrins are described in the literature. From several examples, however, the same reaction behavior is assured for (*S*)-cyanohydrins as well [5][11].

3.1. *Hydrolysis of the Cyano Group*

Hydrolysis of chiral cyanohydrins offers an interesting general route to (*R*)- and (*S*)-2-hydroxy carboxylic acids. In concentrated hydrochloric acid, (*R*)- and (*S*)-cyanohydrins derived from aldehydes and ketones are easily hydrolyzed to give the corresponding (*R*)- and (*S*)-hydroxy carboxylic acids in excellent chemical yields and with complete retention of configuration (*Scheme 4*) [11][22]. The hydrolysis can be carried out quite simply. First, the optically active cyanohydrin is prepared in the organic solvent as described (see above). The cellulose-adsorbed enzyme is filtered off after completion of the reaction, the solvent is removed, and the crude cyanohydrin residue is directly hydrolyzed without any further purification. From the aqueous solution the hydroxy acids are extracted with diethyl ether. A comparison of the optical purity of the crude cyanohydrins and the isolated and purified 2-hydroxy carboxylic acids shows hydrolysis that proceeds virtually without any racemization (*Scheme 4*).

The preparation of (*R*)- and (*S*)-2-hydroxy carboxylic acids, respectively, *via* hydrolysis of the readily accessible chiral cyanohydrins is currently the most general approach to this important class of compounds.

The preparation of (*R*)-pantolactone *via* the corresponding (*R*)-cyanohydrin represents an interesting application of this method. *Via* the cyanohydrin (*R*)-**7p**, derived from β-hydroxypivalaldehyde (**6p**), optically pure (*R*)-pantolactone ((*R*)-**9**) is obtained in 62% yield, with respect to **6p** (*Scheme 5*) [23].

Optically active cyanohydrins **10** derived from unsaturated aldehydes are of interest due to reactions possible with the

C=C double bond. For follow-up reactions, it is often more favourable to convert the cyanohydrins according to the *Pinner* method [24a] first into the corresponding esters **11**. Epoxidation of the chiral alcohols **11** with achiral oxidants, *e.g.*, *m*-chloroperoxybenzoic acid (*m*-CPBA), yields a mixture of both possible epoxides **12a** and **12b**. With chiral (*Sharpless* titanium-tartrate system) oxidants, stereoselective epoxidation can be achieved. Using (+)-dimethyl tartrate ((+)-DMT) only the *erythro*-isomer **12a** is obtained (*Scheme 6*) [24b].

A further interesting application of unsaturated chiral cyanohydrins in the synthesis of natural products is chirality transfer from the 2- to the 4-position (*Scheme 7*) [25].

3.2. *Partial Reduction of the Cyano Group*

A partial reduction of the cyano group of optically active cyanohydrins with diisobutyl aluminum hydride (DIBALH) and *Grignard* reagents, respectively, to the corresponding imino compounds is possible (*Scheme 8*).

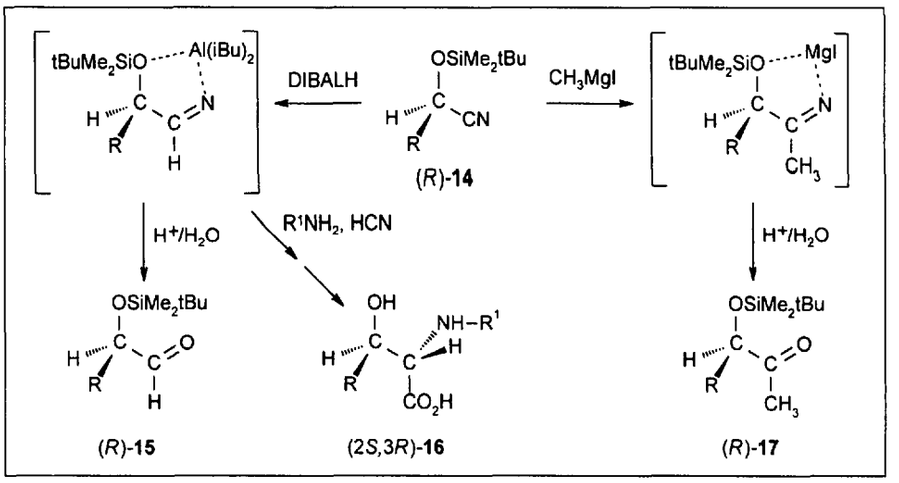
Selective hydrogenation of chiral cyanohydrins with *Raney* nickel in acidic medium occurs with retention of configuration but only moderate yields of 2-hydroxy aldehydes are obtained [26]. *O*-Protected hydroxy aldehydes (*R*)-**15** are accessible in high yields by hydrogenation of *O*-protected cyanohydrins such as (*R*)-**14** with DIBALH followed by mild acidic hydrolysis (*Scheme 8*) [27]. Besides the hydrolysis, the imino intermediates allow also other reactions. With primary amines, *e.g.*, NH_3 can be replaced by the amine (transimination) [27]. Addition of HCN to imino intermediates opens an approach to β-hydroxy-α-amino acids **16** (*Scheme 8*) [27]. Optically active 2-hydroxy ketones **17** are readily available by addition of *Grignard* reagents to *O*-protected cyanohydrins and subsequent hydrolysis (*Scheme 8*) [27].

Optically active cyanohydrins (*R*)-**14** can also be reacted with *Reformatsky* reagents (*Blaise* reaction). The primarily formed imino intermediates can be hydrolyzed under very mild conditions to give the enamines (*R*)-**18** which yield, by treatment with strong acids, the tetronic acids (*R*)-**19** (*Scheme 9*) [28][29].

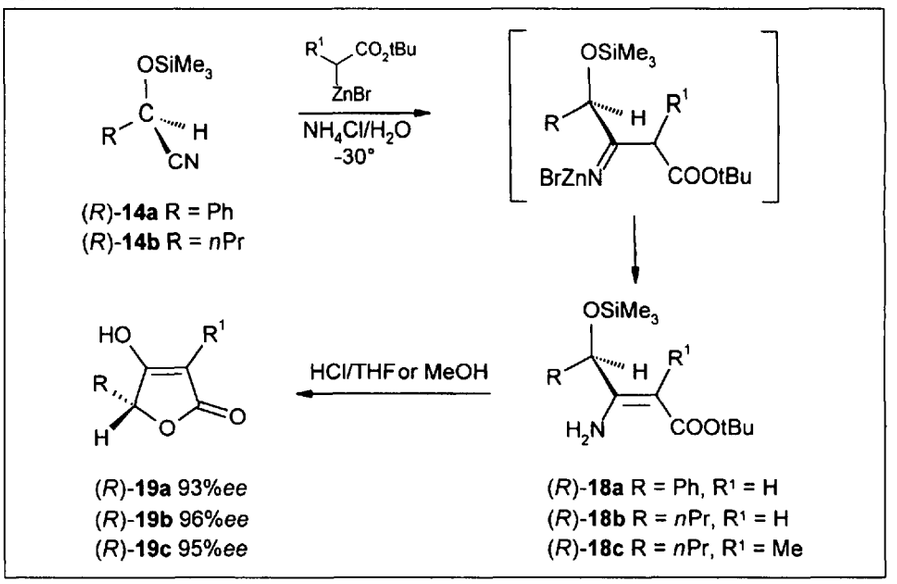
3.3. *Preparation of Chiral 2-Amino Alcohols*

2-Amino alcohols have a wide spectrum of biological activity [30]. They can be categorized as adrenaline-like compounds with one asymmetric center at

Scheme 8



Scheme 9



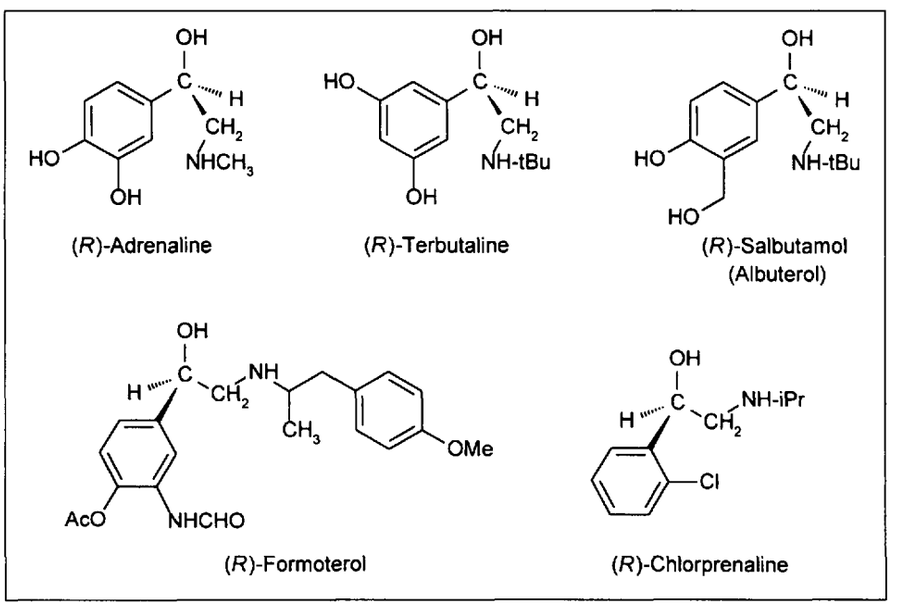


Fig. 1. *Some important 2-amino-alcohol pharmaceuticals*

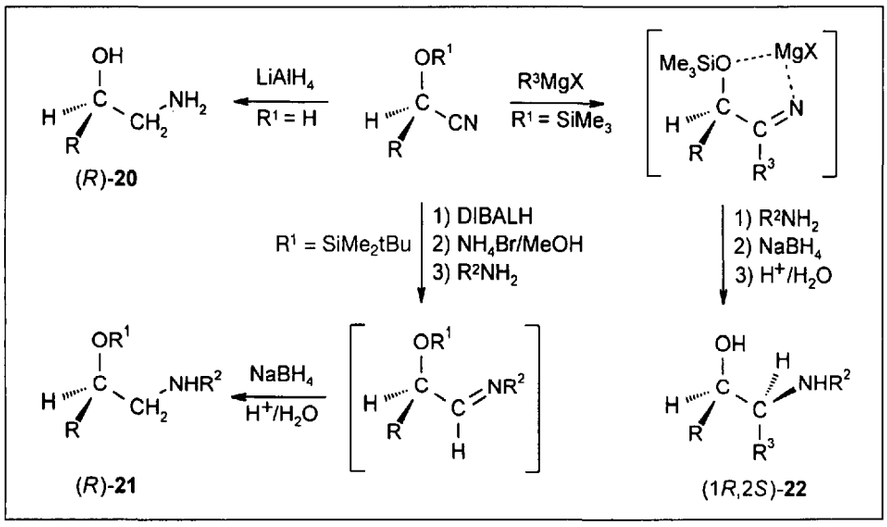
C(1) (*Fig. 1*) or as ephedrine-like compounds with two chiral centers at C(1) and C(2) (*Scheme 10*). Although it is well-known that only the compounds with (1*R*)- and (1*R*,2*S*)-configuration are responsible for biological activity, so far, predominantly racemates are applied as pharmaceuticals [30a]. Since in some cases (1*S*)-isomers seem to have noxious side effects [31], syntheses of optically pure 2-amino alcohols are gaining increasing importance.

Both free and *O*-protected optically active cyanohydrins can be hydrogenated with $LiAlH_4$ without any racemization to give adrenaline-type compounds **20** (*Scheme 10*) [3][22][32]. Use of the $SiMe_2tBu$-protecting group allows partial hydrogenation with DIBALH and transimination of the imino intermediates formed. Subsequent hydrogenation gives the pharmacologically important *N*-alkyl-substituted (1*R*)-2-amino alcohols **21** (*Fig. 1* and *Scheme 10*) [33][34].

Ephedrine-like 2-amino alcohols **22** can be prepared successfully from *O*-protected cyanohydrins by addition of a *Grignard* reagent and subsequent hydrogenation with $NaBH_4$ [35][36]. Again, NH_3 in the imino intermediate can be exchanged by primary amines (transimination). Investigations of the stereochemistry assured for both (*R*)- and (*S*)-cyanohydrins that the *Grignard* addition, the transimination, and the hydrogenation proceed without any racemization at C(1). The hydrogenation of the imino intermediate at C(2) is highly stereoselective due to a chelate-controlled reaction; *erythro* products are formed almost exclusively [36]. The preparation of (–)-L-ephedrine, which is obtained in 63% yield with respect to (*R*)-**7a** (*Scheme 11*), is an example for a straightforward stereoselective synthesis of *erythro*-2-amino alcohols. Starting from (*S*)-cyanohydrins, (1*S*,2*R*)-2-amino alcohols are obtained by this procedure [36][37].

(–)-L-Ephedrine is technically produced by a fermentation process which normally does not allow substrate variations, whereas starting from optically active cyanohydrins, almost any structural variation is possible. In *Fig. 2*, two examples of heteroaromatic analogues of ephedrine, synthesized by the described procedure, are presented [37].

Scheme 10



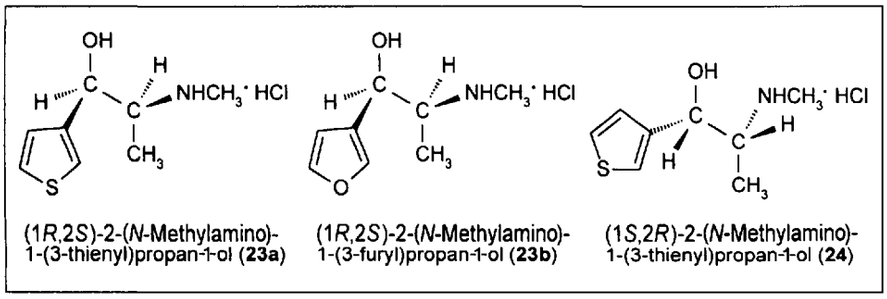
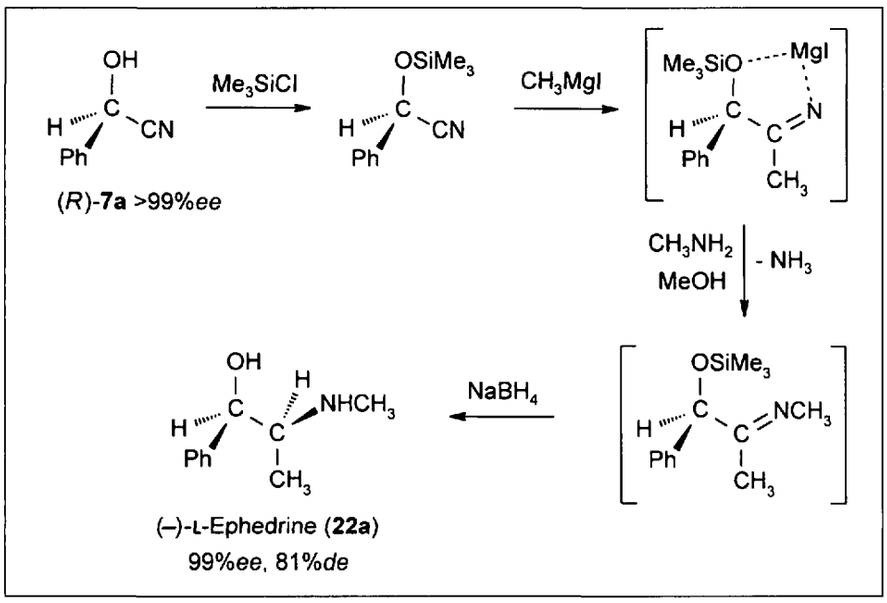


Fig. 2. *Heteroaromatic analogues of (–)-L-ephedrine*

Scheme 11



4. Stereoselective Substitution of the Hydroxy Group

The synthetic potential of optically active cyanohydrins can be extended considerably by converting the hydroxy substituent into a good leaving group, which could be exchanged stereoselectively with nucleophiles.

Nucleophilic substitutions with activated α-hydroxy carboxylic acids and esters are well established [38], but little is known about the analogous reactions of cyanohydrins [39]. 2-(Sulfonyloxy)nitriles (*R*)-**25**, easily accessible from chiral cyanohydrins (*R*)-**7** by sulfonylation (*Scheme 12*) [40], have a much higher configurational stability than the corresponding 2-halonitriles [39][40]. Sulfonylated cyanohydrins (*R*)-**25**, derived from cyanohydrins of aliphatic aldehydes (R = aliphatic), react with nucleophiles, *e.g.*, potassium

acetate (KOAc), under very mild conditions with complete inversion of configuration to give the substitution products (*S*)-**26** (*Scheme 12*) [40].

2-(Sulfonyloxy) nitriles derived from cyanohydrins of aromatic aldehydes react with weak nucleophiles, *e.g.*, KOAc, with partial racemization [40] (*Scheme 12*, R = Ph). The *Mitsunobu* reaction represents an alternative to the *O*-activation of cyanohydrins combined with nucleophilic substitution [41]. In contrast to the *O*-sulfonyl activation, *Mitsunobu* conditions work especially well for the exchange of allylic and benzylic hydroxy groups in cyanohydrins [41b]. The variation of nucleophiles in *Mitsunobu* reactions is rather limited [41c], whereas *O*-sulfonylated cyanohydrins react with various nucleophiles [40a].

In *Scheme 13*, reactions of 2-(sulfonyloxy) nitriles (*R*)-**25** with N-nucleophiles [40][42] are summarized whereas *Scheme 14* gives an overview over the reactions of (*R*)-**25** with S-nucleophiles [43].

The stereoselective synthesis of (*S*)-3,4-(methylenedioxy)amphetamines (*S*)-**37**, which are controversially discussed as psychoactive compounds [44], is another interesting example for the application of cyanohydrins as easily available chiral starting compounds. From (1*R*,2*S*)-2-amino-1-aryl alcohols, prepared as described (see *Scheme 10*), a very efficient reductive elimination of the benzylic hydroxy group was developed to give the optically pure (*S*)-amphetamine derivatives (*Scheme 15*) [44]. This is an interesting case of chirality transfer from easily available chiral cyanohydrins.

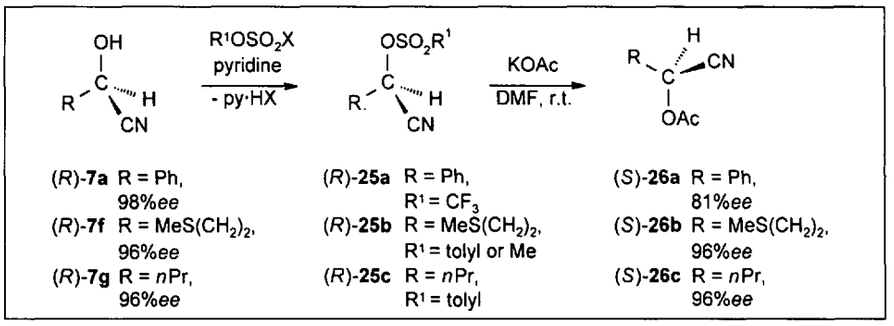
5. Conclusion

The discovery that enzyme-catalyzed cyanohydrin formation prevails over the chemical cyanohydrin formation, if organic solvents are used, gave rise to strong research activities on preparations and follow-up reactions of optically active cyanohydrins.

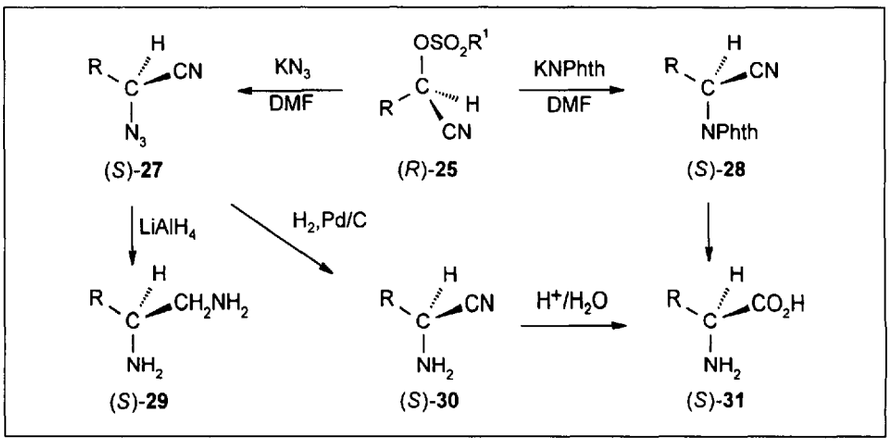
Due to the excellent accessibility and the very broad substrate range, PaHNL from bitter almonds was the enzyme of choice used for the preparation of chiral cyanohydrins. Therefore, most of the follow-up reactions were performed starting from (*R*)-cyanohydrins.

Successful cloning and overexpression of the hydroxynitrile lyases from *Manihot esculenta* (MeHNL) and *Hevea brasiliensis* (HbHNL) made available also (*S*)-HNLs, which have an equally broad substrate range as PaHNL, in sufficient amounts for applications in organic syn-

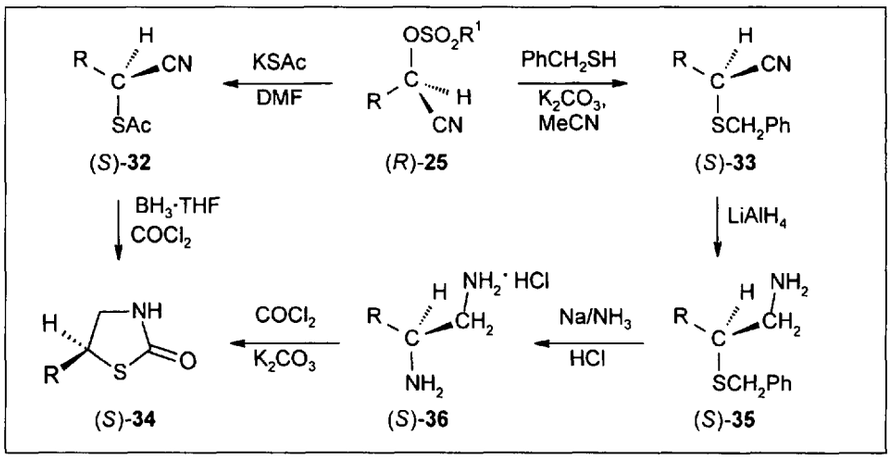
Scheme 12



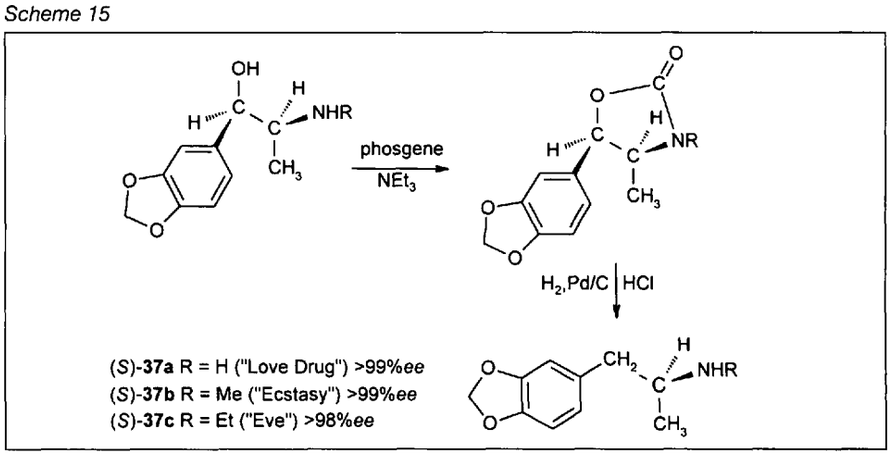
Scheme 13



Scheme 14



Scheme 15



thesis. Improvements in the practical performance of the HNL-catalyzed cyanohydrin preparation have been developed. Thus, the organic solvent can be replaced by biphasic systems in which HCN can be generated *in situ* from sodium cyanide with acetic acid in the aqueous phase. Alternatively, acetone cyanohydrin, which is safe to handle, is also suitable as precursor of HCN. Whole cells, *e.g.*, in form of almond meal or *Sorghum* shoots, can often be applied successfully instead of the isolated enzymes.

Due to the excellent accessibility, their relatively high stability and the easy handling of hydroxynitrile lyases, (*R*)- as well as (*S*)-cyanohydrins became very interesting and important as chiral starting compounds in stereoselective organic syntheses.

The present review article summarizes only the basic reaction pathways and the most important classes of compounds which can be derived from optically active cyanohydrins. All reactions described and discussed occur without racemization and with high optical induction by introducing another chiral center. A variety of biologically active compounds with stereogenic centers, *e.g.*, (1*R*,2*S*)-2-amino alcohols, are easily available in optically pure form. It can be expected that commercializing racemates and stereoisomeric mixtures of compounds as drugs will become more difficult in the future. In many cases, optically active cyanohydrins could be ideal starting materials for the selective preparation of pure stereoisomers of pharmaceuticals and plant-protecting agents.

The enthusiastic commitment of my co-workers, who are cited in the references, was decisive for the success of our work on optically active cyanohydrins during the last ten years. I would like to thank especially Drs. *Siegfried Förster*, *Harald Wajant* and *Thomas Ziegler* who played a major role in the successful development of methods for the application of HNLs as synthetically important biocatalysts. I am strongly obliged to Dr. *Angelika Baro* for her commitment in preparing the manuscript. This work was generously supported by the *Bundesministerium für Bildung und Forschung* (Zentrales Schwerpunktprogramm Bioverfahrenstechnik, Stuttgart), the *Fonds der Chemischen Industrie* and the *Degussa AG*.

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