Cyanohydrins in Nature and the Laboratory: Biology, Preparations, and Synthetic Applications

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I. Introduction

Cyanohydrins now occupy a fascinating niche at the interface between chemistry and biology. On one hand, cyanohydrins have considerable synthetic potential as chiral building blocks in organic synthesis. On the other, they have a distinguished enzymatic history: probably among the first molecules on the prebiotic earth, cyanohydrins subsequently became substrates for hydroxynitrile lyases (HNLs). Advances in recent years have increased both our understanding and our exploitation of the production and utilization of enantiomerically enriched cyanohydrins.

This review covers the preparation and applications of enantiomerically enriched cyanohydrins, thus providing a timely update to previous major reviews.[1,2] However, through a consideration of some

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Robert John Hryntchyshyn Gregory graduated from the University of Cambridge, U.K., in 1994 with his B.A. degree in Natural Sciences (Chemistry), which included a molecular modeling project with Dr. Jonathan Goodman. He was awarded his Ph.D. degree in 1998 for a thesis on Biocatalytic Preparation and Chemistry of Some Novel Cyanohydrin Systems, under the supervision of Professor Stan Roberts at the Universities of Exeter and Liverpool, U.K. A subsequent Brax Limited Research Fellowship at the University of Liverpool involved the design and synthesis of mass markers as part of a project to investigate the potential of mass spectrometry in genomics and proteomics. He is currently working in the intellectual property area.

relevant roles of cyanide in nature, it also seeks to unite a biological and a chemical understanding of this important field. Such a perspective is of importance in the appreciation of cyanohydrin chemistry and in the design and rationalization of biomimetic catalysis.

Within an enzymology perspective, breakthroughs have been achieved in the production of recombinant HNLs, providing a range of effective biocatalysts for the preparation of cyanohydrins. No longer do we have only basic characterization data on these enzymes: structural and mechanistic understanding has increased dramatically, and it is now possible to speculate about their evolution. Striking similarities are emerging between HNLs and synthetic peptides, similarities that may contribute toward a greater understanding of why amino acids and peptides are so prevalent in nature's catalytic chemistry.

In addition to asymmetric catalysis by HNLs and cyclic dipeptides, preparation of cyanohydrins by lipases and by nonbiocatalytic methods are discussed, paying particular attention to more imaginative and elegant recent methods. Common themes are likewise identified in the review of applications of cyanohydrins and the scope of channeling enantiomerically enriched cyanohydrins down more adventurous synthetic avenues.

II. Racemic Cyanohydrins

Before discussing enantiomerically enriched cyanohydrins, I would like to introduce the area by reviewing cyanohydrin synthesis in the absence of chiral control. This section therefore summarizes the tools of racemic hydrocyanation (Figure 1).

The addition of hydrogen cyanide to aldehydes or ketones produces α-hydroxy nitriles or cyanohydrins.[3−5] The actual nucleophile is the cyanide ion, as was demonstrated by Lapworth in 1903, who showed that the addition of base increases the rate of reaction—one of the first organic mechanism elucidations.[6] Cyanide compounds are extremely toxic, and poisoning can occur within minutes. That prevention is easier than cure has long been recognized: Gattermann directed his students to always smoke a cigar when carrying out experiments with hydrogen cyanide since the taste imparted to the smoke in the presence of traces of hydrogen cyanide is very characteristic and allows differentiation from similar-smelling aldehydic fumes.[7]

While the direct addition of hydrogen cyanide is commonly used in industry, other methods are also popular, particularly in a laboratory environment (Figure 1). The simple addition of an aqueous solution of a cyanide salt to a solution of the substrate in acetic acid represents a simple and relatively safe procedure.[8]

In another common method, reaction with trialkylsilyl cyanide reagents may be used to give the O-silylated cyanohydrin derivatives:[9,10] *O*-TMS cyanohydrins may be hydrolyzed to the free cyanohydrins in acid. Zinc iodide[11] or 18-crown-6 with potassium cyanide[12,13] are commonly used as catalysts for trialkylsilylcyanation: ytterbium tricyanide,[14] Lewis bases,[15] and other Lewis acids[16] have also been used. This method has been employed to prepare cyanohydrins of a wide variety of carbonyl compounds including sterically hindered ketones,[17,18] α,β-unsaturated compounds,[11,14,19−21] easily enolizable ketones, and acid-sensitive ketones.[14]

A fourth method of cyanohydrin preparation is transhydrocyanation from acetone cyanohydrin to the carbonyl compound.[22−27] Reaction is assisted by basic conditions that catalyze both the decomposition of acetone cyanohydrin to acetone and hydrogen cyanide and the formation of the cyanohydrin product. Recently lanthanide(III) alkoxides have been found to be effective catalysts for this reaction, presumably due to their strong basic character although the mechanism is yet to be determined:[28] this opens the door for asymmetric catalysis in this area by the use of chiral ligands on the lanthanide. Transhydrocyanation has also been mediated by titanium-,[29,30] zirconium-,[30] and aluminum-based[29] reagents.

Other methods are used less frequently. Diethylaluminum cyanide may be used in a procedure for the preparation of cyanohydrins from relatively unreactive ketones or aldehydes.[31] Aldehydes and ketones have also been reacted with diethyl phosphorocyanidate (DEPC) and lithium cyanide to give cyanohydrin diethyl phosphates,[32] with acyl cyanides and a heterogeneous mixture of aqueous potassium carbonate and acetonitrile to give cyanohydrin esters,[33] and with triethyloxonium tetrafluoroborate and trimethylsilyl cyanide to give *O*-ethyl cyanohydrins (a special case where the intermediate carbocation is unusually stable).[34]

Having introduced several methods of cyanohydrin preparation according to the nature of the cyanating source, we shall now see how several of these methodologies are adapted in preparations of nonracemic cyanohydrins (Section IV). A plethora of

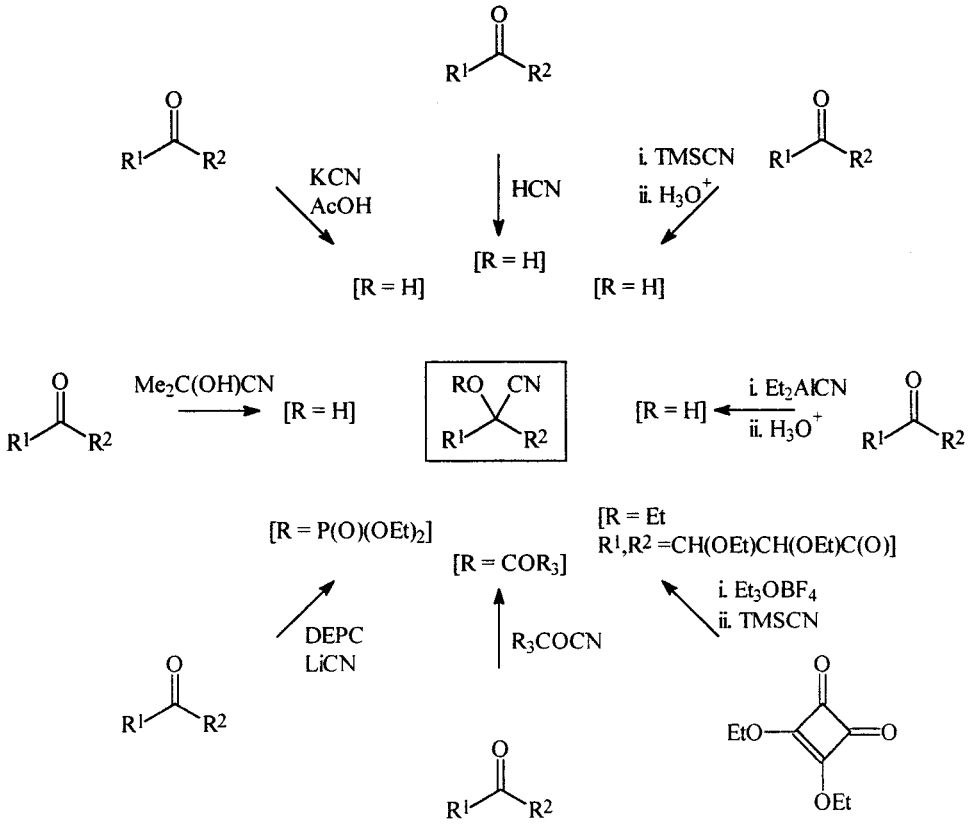


Figure 1. Methods of racemic hydrocyanation and cyanation of carbonyl compounds.

applications of these chiral units are then illustrated (Section V). But first a brief preamble to nature.

III. Cyanide in Nature

A. Prebiotic Development May Have Been Influenced by a Cyanic Soup

I would like to introduce cyanohydrins within a biological perspective by considering the first billion years of the earth's history. We cannot be certain about the composition of the atmosphere and the conditions on the surface at this time, but the energy to drive chemical reactions would certainly have been present in the form of electric storms, volcanic activity, and ultraviolet radiation (there was no ozone layer to protect the prebiotic earth).[35−38] A basic laboratory simulation of primitive conditions on the earth involves heating water, methane, ammonia, and hydrogen and supplying energy in the form of an electrical discharge or ultraviolet radiation: this yields several compounds including hydrogen cyanide, formaldehyde, amino acids, sugar precursors, and nucleoside precursors.[39−41] While such experiments should be considered very approximate models, they do suggest that the formation of basic organic molecules is very easy and furthermore that only a small range of compounds were formed during the earth's infancy. That hydrogen cyanide should be among them in what are considered to be relatively large amounts is interesting since we regard it as a very cytotoxic compound.

In fact, cyanide is only toxic within the context of higher organisms as a consequence of binding tightly to heme, thus blocking oxygen uptake in hemoglobin and electron transfer in cytochrome oxidase. To understand the influence of cyanide on evolution, we must consider life before the development of aerobic respiration and even before the appearance of the first prokaryotic cell 3.5 billion years ago. At this time the role of cyanide may have been 2-fold:

First, cyanide is considered a fundamental precursor species for biomolecules such as nitrogen bases, most directly adenine, a pentamer of hydrogen cyanide.[42,43] However, it is probable that much of the cyanide present in the early terrestrial hydrosphere and cryosphere was scavenged by ferrous ion to form ferrocyanide or by formaldehyde to form the simplest of all cyanohydrins, glycolonitrile; models of primordial organochemical processes have therefore considered the chemistry of such secondary species.[44]

Second, I infer that cyanide may have had an accelerating effect on the evolution of the first cell from RNA and protein-based systems. It is widely proposed that, following the development of RNA autocatalytic self-replication, compartmentalization was a prerequisite for the evolution of the first cell.[40,45] Thus the enzyme produced by a superior variant of RNA could be kept contained in its vicinity and could contribute selectively to the survival and development of that particular RNA variant. A secondary advantage of compartmentalization would be the ability to control the use of, and where necessary protection against, a variety of reactive chemical species. Since cyanide is such a potent ligand and thought to be present at very high abundances at this time, I suggest that it would have been one of the most important chemical species to which to adapt.

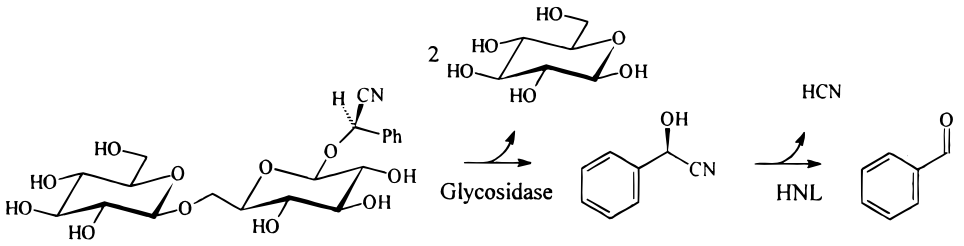


Figure 2. The cyanogenesis pathway in almonds involves the breakdown of the cyanogenic glycoside amygdalin and the cyanohydrin (*R*)-mandelonitrile.

If such a technique of coexistence with the largely cyanic soup were developed at this stage, it is reasonable to assume that some systems developed it faster than others. Surely such a significant step would have led to such huge advantages by Darwinian theory that it would represent a turning point in evolution? Thus, I speculate that the ability to survive with and use cyanide may have been one of the influencing factors in selecting the earliest RNA and protein-based systems and thence the first prokaryote from which all organisms now living on earth are derived.

B. Some Higher Organisms Perform Cyanogenesis To Liberate Hydrogen Cyanide

While the prebiotic influence of cyanide is speculative, we can observe one of its roles today in the higher organisms that employ the technique of cyanogenesis.[46,47] Over 3000 plant species and certain bacteria, fungi, centipedes, millipedes, and insects utilize this method in what was initially regarded as purely a defense mechanism. The enzymes and substrates vary between organisms, but the central molecule in this process is always a cyanohydrin, usually only slightly more complex than its distant (and quite possibly indirect) ancestor glycolonitrile. Thus, a glycosidase breaks down a cyanogenic glycoside to release the cyanohydrin whose further breakdown to hydrogen cyanide and an aldehyde or ketone is catalyzed by a hydroxynitrile lyase (abbreviated to HNL or oxynitrilase) (Figure 2).

C. Several Plant HNLs Have Been Studied

Plant HNLs have been widely studied throughout this century, and reviews have recently been published.[46,47] The 11 HNLs that have been isolated and purified so far are introduced in Table 1: the abbreviations to be used in this text are included.

Some HNL enzymes are more widely understood than others. cDNA cloning has been carried out for five genes, and recombinant enzymes have been obtained in three cases; namely, MeHNL (overexpressed in *Escherichia coli*),[59,60] LuHNL (in *E. coli* and, optimally, *Pichia pastoris*),[61,62] and HbHNL (in *E. coli*, *Saccharomyces cerevisiae*, and, optimally, *P. pastoris*).[63,64] Difficulties have been encountered with SbHNL due to complex posttranslational processing of the native enzyme.[65] Preliminary X-ray diffraction studies have been published for crystals of PaHNL,[66] MeHNL,[67] and SbHNL.[68] X-ray diffraction studies on crystals of HbHNL have now enabled the solution of the first three-dimensional structure of an HNL:[69,70] in addition, mutagenesis studies[63,71] are consistent with the assignment of HbHNL to the α/β-hydrolase fold family, which has implications for the enzyme mechanism (Section III.F).

While Table 1 represents a comprehensive summary of those enzymes that have been isolated, additional plants have been used for their HNL activity. For example, Kanerva has used crude meals from the kernels of mature apples, apricots, cherries, and plums as sources of HNL catalysis.[72,73] To detect new HNLs, it has proved not sufficient simply to screen for the presence of carbonyl compounds or hydrogen cyanide, since the breakdown of cyanohydrins may be catalyzed by enzymes other than HNLs: instead, the catalysis of cyanohydrin formation is a more reliable indicator of the presence of an HNL.[74]

D. Nature Utilizes Cyanogenesis both as a Defense Mechanism and To Provide a Nitrogen Source

Cellular or subcellular damage allows enzymes to come into contact with cyanogenic substrates to liberate the hydrogen cyanide and aldehyde or ketone. Enzymatic catalysis is not always necessary for the second step in the pathway (dehydrocyanation) since cyanohydrins are relatively unstable (particularly in basic media). The release of hydrogen cyanide has long been invoked as the defense mechanism: in fact the carbonyl product may also be toxic to herbivores and microbes.[75]

As an alternative to gaseous release, the hydrogen cyanide generated by the process may be utilized in further pathways (Figure 3). Plants may convert cysteine to asparagine in two steps: thus, during the germination of *Hevea brasiliensis*, no release of hydrogen cyanide is observed, but, the cyanogenic glycosides are used up as ultimately a nitrogen source for the amino acid synthesis of young seedling tissues.[76] A further process for refixation is the detoxification of hydrogen cyanide by reaction with thiosulfate to the less toxic thiocyanate and sulfite. Rhodanese (thiosulfate cyanide transferase) catalyzes this reaction mainly in mammals, microorganisms, and insects but also to a lesser degree in plants.[77,78]

Plants avoid the suicidal release of hydrogen cyanide by separating substrates from enzymes. Immunocytological studies of *Sorghum bicolor* and *Linum usitatissimum* have indicated that cyanohydrins are separated from HNLs on the subcellular level,[79] and separation of the glycosidase and HNL enzymes at the cellular level has been observed for *Prunus serotina*.[80,81]

Table 1. HNLs Have Been Purified and Characterized from 11 Plant Species in Six Families

species (family)	*plant (part)*	*abbreviation; EC*	*stereoselectivity*	*coenzyme*	*natural substrate(s); [cyanogenic glycoside(s)]*	*references*[a]
Prunus amygdalus (Rosaceae)	almond (nuts)	PaHNL 4.1.2.10	*(R)*	FAD	(*R*)-mandelonitrile; (amygdalin, prunasin)	8
Prunus laurocerasus (Rosaceae)	laurel cherry (seeds)	PlHNL 4.1.2.10	*(R)*	FAD	(*R*)-mandelonitrile; (amygdalin, prunasin)	48
Prunus lyonii (Rosaceae)	California cherry (seeds)	PlyHNL 4.1.2.10	*(R)*	FAD	(*R*)-mandelonitrile; (amygdalin, prunasin)	49
Prunus serotina (Rosaceae)	black cherry (seeds)	PsHNL 4.1.2.10	*(R)*	FAD	(*R*)-mandelonitrile; (amygdalin, prunasin)	50
Linum usitatissimum (Linaceae)	flax/ linseed (seedlings)	LuHNL 4.1.2.10	*(R)*	None	acetone cyanohydrin, (*R*)-2-butanone cyanohydrin; (linamarin, lotaustralin)	51
Phlebodeum aureum (Filitaceae)	fern (leaves)	PhaHNL	*(R)*	None	(*R*)-mandelonitrile; [(*R*)-vicianin]	52
Sorghum bicolor (Poaceae)	millet (seedlings)	SbHNL 4.1.2.11	*(S)*	None	(*S*)-4-hydroxy-mandelonitrile; (dhurrin)	8,53
Sorghum vulgare (Poaceae)	millet (seedlings)	SvHNL	*(S)*	None	(*S*)-4-hydroxy-mandelonitrile; (dhurrin)	54
Ximenia americana (Olacaceae)	sandalweed (leaves)	XaHNL	*(S)*	None	(*S*)-mandelonitrile; (sambunigrin)	55
Manihot esculenta (Euphorbiaceae)	cassava/ maniok (leaves)	MeHNL 4.1.2.37	*(S)*	None	acetone cyanohydrin, (*R*)-2-butanone cyanohydrin; (linamarin, lotaustralin)	56,57
Hevea brasiliensis (Euphorbiaceae)	rubber tree (leaves)	HbHNL	*(S)*	None	acetone cyanohydrin; (linamarin)	58

[a] References correspond to isolation and purification. See text for references on cloning and other work.

The storage of cyanogenic moieties in plants has implications for their use as foodstuffs for humans or animals. Numerous sudden deaths among cattle fed on immature sorghum were attributed to cyanide poisoning almost a century ago,[82] consistent with the production of hydrogen cyanide as a nitrogen source during growth. Cassava is a staple food crop for over 500 million people, and associated health hazards include Konzo, a form of tropical myelopathy caused by a combination of a low-sulfur diet and the consumption of insufficiently processed cassava products. Since the dehydrocyanation catalyzed by MeHNL may be the rate-determining step in its detoxification, the ability to manipulate the MeHNL gene has potential importance in the production of less toxic cassava food products.[57] The apricot canning, preserve, juice, and dried fruit industries produced over 650 ton of apricot (*Prunus armaniaca*) seeds in Turkey in 1995:[83] this byproduct has potential nutritional value if detoxification methods can be developed.

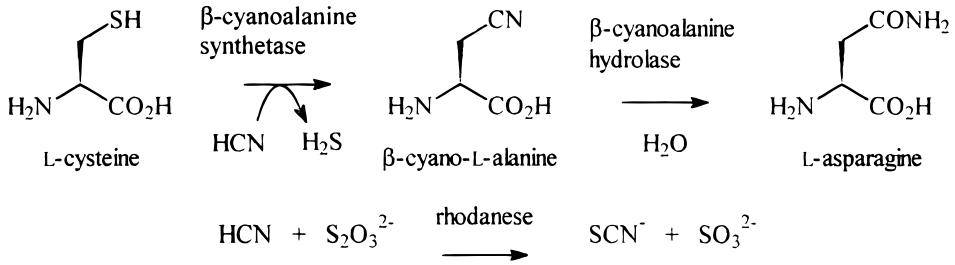


Figure 3. Hydrogen cyanide liberated by cyanogenic glycoside catabolism may be used as a nitrogen source for amino acid synthesis or refixed as less toxic thiocyanate.

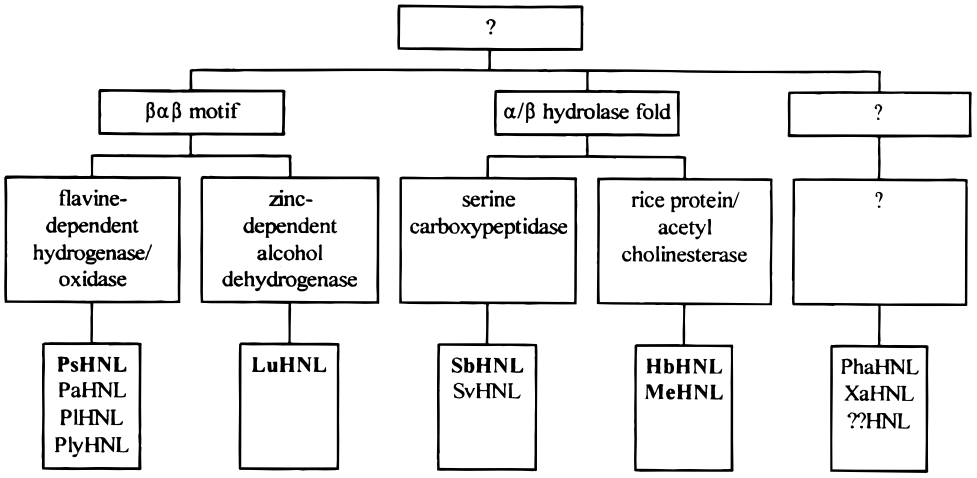


Figure 4. The ancestry of HNLs may involve divergent evolution prior to convergent evolution to result in the groups we observe today (four of which have been defined). Cloned HNLs are indicated by bold type.

E. HNLs Probably Result from both Convergent and Divergent Evolution

HNLs have been classified according to properties of the enzymes. An early classification separated the FAD-containing from the non-FAD-containing enzymes. The former have been isolated exclusively from the rosaceous stone fruits, are closely related, and have a common natural substrate, (*R*)-mandelonitrile. The traditional separation of flavoprotein and nonflavoprotein HNLs is however somewhat simplistic since the nonflavoprotein HNLs are a rather heterogeneous group and are now thought to comprise several classes.

Cloning of PsHNL,[84] SbHNL,[65] MeHNL,[59,60] HbHNL,[63,64] and most recently LuHNL[61,62] has initiated more advanced classification and evolutionary theories (Figure 4).[62] At present, four groups of HNLs, can be defined according to sequence homologies with other enzyme families; namely, various flavoproteins especially dehydrogenases and oxidases (represented by PsHNL),[84] zinc-dependent alcohol dehydrogenases (LuHNL),[61] serine carboxypeptidases (SbHNL),[65] and various hydrolases including proteins isolated from rice with as yet undetermined function (MeHNL and HbHNL).[63] Divergent evolution is evident in the observation that the former two groups share a $\beta\alpha\beta$ motif (for an ATP-binding domain)[85] but show no other overall sequence similarities and is also evident in the assignment of the latter two groups as α/β hydrolase fold enzymes (utilizing a catalytic triad of residues)[47] that are otherwise dissimilar.

It is evident that these four (and quite possibly more, as yet undefined) ancestries underwent convergent evolution to give the HNLs we see today. This is manifest not only in that cyanogenesis is enabled by enzymes of different origins but also in that there is a small range of natural substrates: most obviously, acetone cyanohydrin is a natural substrate for MeHNL, HbHNL, and the phylogenetically unrelated LuHNL.

F. HNL Mechanism Can Be Speculated at, Especially in the Cases of *Hevea brasiliensis* and *Manihot esculenta*

For most HNLs, mechanistic analysis is at a preliminary level. A common theme is the binding of aldehyde or ketone prior to the binding of and reaction with hydrogen cyanide. A putative FAD binding site has been identified for PsHNL,[84] and there has been debate over the role of FAD in the flavoproteins. In the representative PaHNL, it may not exhibit redox activity but is thought to be an important structural component in a mechanism involving a serine and a cysteine residue.[86−88] Estimates of the PaHNL active-site dimensions have been made in a systematic study of substrate ranges.[89]

1. A Nucleophilic Displacement Proposal

Significant advances in mechanistic understanding have been achieved for HbHNL. Cloning, three-dimensional structure solution, analogy to a prototypic enzyme mechanism, kinetic data, inhibition

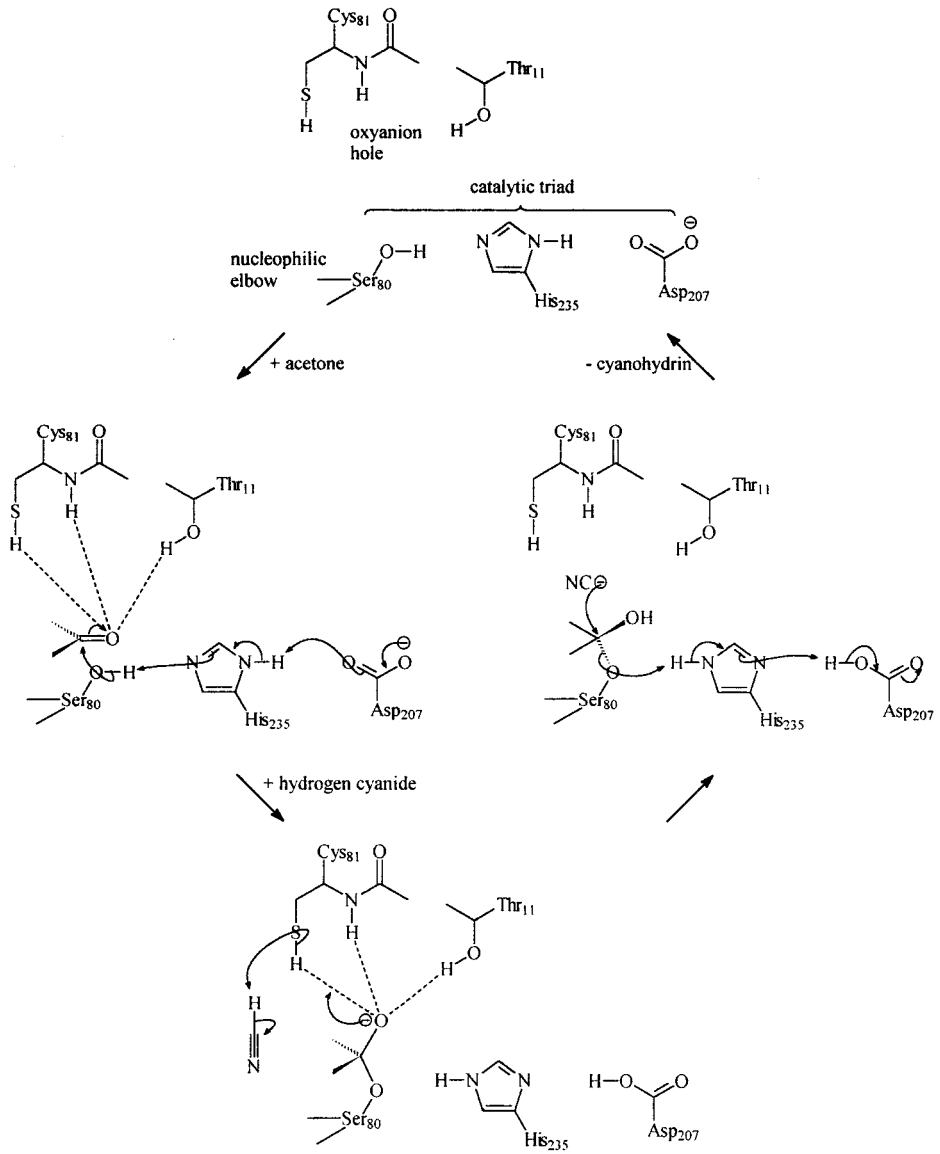


Figure 5. A proposed mechanism for HbHNL involves five key residues in the active site and nucleophilic displacement by cyanide.[70]

data, and confirmation of catalytic residues by site-directed mutagenesis have been linked together in a mechanistic proposal.[70] For clarity, this mechanism is discussed in the direction of cyanohydrin formation from acetone and hydrogen cyanide (Figure 5).

Central in the proposed HbHNL cycle is a tetrahedral intermediate formed by the nucleophilic attack of Ser_{80} onto acetone. Ser_{80} is activated by proton transfer through His_{235} to Asp_{207} (known as the catalytic triad) and is positioned at a sharp turn (the nucleophilic elbow). The negative charge on the oxygen of the hemiketal intermediate is stabilized by hydrogen-bonding to the main chain amide of Cys_{81} and the side chains of Cys_{81} and Thr_{11} in a site known as the oxyanion hole.

The second step involves incorporation of the elements of hydrogen cyanide. It is proposed that Cys_{81} plays a role in its deprotonation concomitant with protonation of the hemiketal anion. It would be reasonable to infer that the cyanide anion is somehow bound (possibly in the newly vacated oxyanion hole to some extent) to further smooth the reaction pathway, although the authors make no such proposal.[70] Nucleophilic displacement of activated Ser_{80} by cyanide anion is then possible, followed by the release of the cyanohydrin product.

The active site is deeply buried and connected to the protein surface by one narrow channel flanked by predominantly apolar residues, consistent with a mechanism involving uncharged substrates (as opposed to cyanide ion, for example) that enter and leave in a sequential fashion. The active site is much larger than required to accommodate acetone cyanohydrin as might be expected from the observation that a large range of unnatural substrates are also accepted by this enzyme.[64]

2. A Nucleophilic Addition Proposal

While mutagenesis experiments on MeHNL and the presence of analogous residues in its active site[56] might suggest the above mechanism to be applicable to other α/β hydrolase fold HNLs, a different mechanism has been put forward for MeHNL (Figure 6).[90]

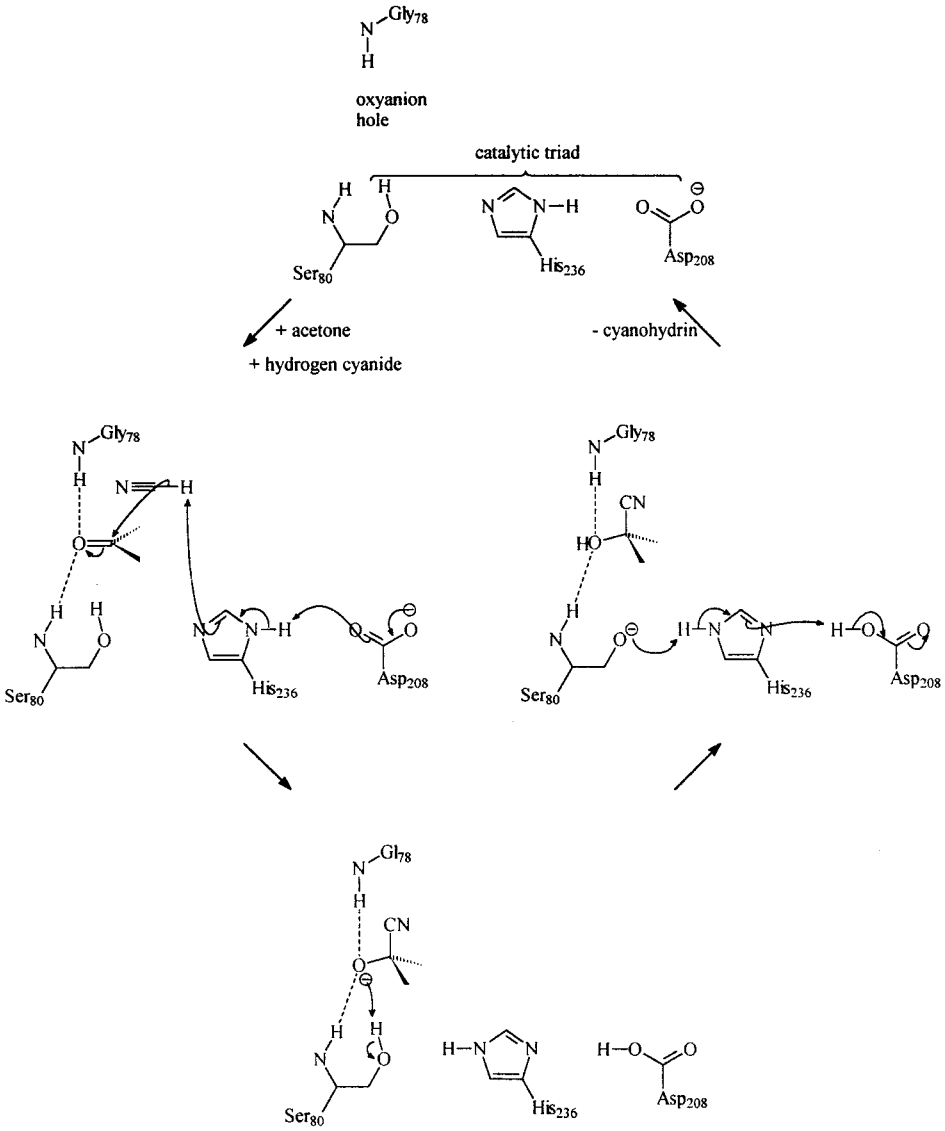


Figure 6. A proposed mechanism for MeHNL involves four key residues in the active site and nucleophilic addition of cyanide.[90]

The mechanistic proposal for MeHNL resembles the nonenzymatic racemic preparation of cyanohydrins. Binding of the carbonyl group provides Lewis acid-type catalysis for nucleophilic addition by cyanide (possibly dissociated from hydrogen cyanide by the catalytic triad). The resulting anion, stabilized and bound in its 'hole' is then protonated via the catalytic triad to give the cyanohydrin product.

Current HNL mechanistic theories require further experimental proof, and future investigations may reveal either or both hypotheses presented here to be correct or, indeed, that other mechanistic descriptions are more accurate.

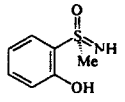
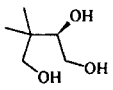
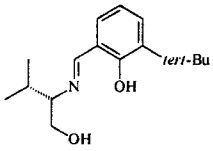
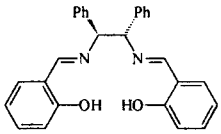
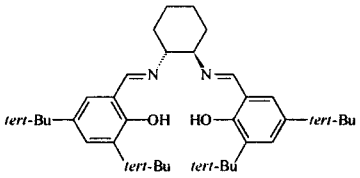
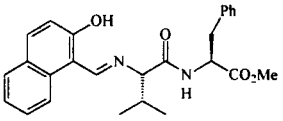
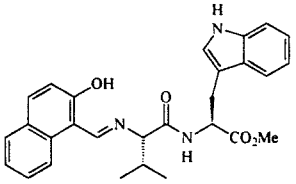
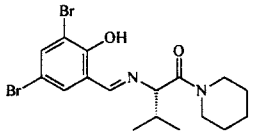
IV. Preparation of Nonracemic Cyanohydrins

Although the chemistry of racemic cyanohydrins is well-established, only relatively recently have single enantiomers been made available and utilized. Despite this, the optically active cyanohydrin field is large and subject to intensive activity by many research groups working on biotransformation by HNLs, resolution by lipases, catalysis by peptides, and nonbiocatalytic methods. Several reviews have been published, ranging from a general overview[2] to those with an emphasis on catalysis by HNLs[91,92] and a cyclic dipeptide,[1] but since the field changes very rapidly even in a few years, this section represents a significant update. The most recent commentaries by Griengl and co-workers have concentrated on preparations and applications using HNL catalysts.[93−95] The term biocatalytic is used in this section to include enzyme catalysis and biomimetic catalysis by species such as peptides (excluding complexes of peptides with metals).

A. Preparation by Nonbiocatalytic Methods

This section categorizes the nonbiocatalytic methods into three types. First, the majority of nonbiocatalytic methods in the literature involve hydrocyanation or silylcyanation of aldehydes or ketones where enantioselectivity is controlled by a chiral complex (titanium-based or other). Second, varying degrees of diastereoselective control occur where carbonyl compounds already contain a chiral center

Table 2. Some Titanium Complexes Used for the Preparation of Enantiomerically Enriched Cyanohydrins

ligand, origin of chirality and structure	*cyanating agent; selectivity; references*	*results for selected substrates[a] in % ee of (and conversion to) adduct*
sulphoximine by Kagan's method[98] 	TMSCN; (*S*); [99,100]	benzaldehyde 91 (96) cinnamaldehyde 79 (63) hexanal 89 (64)
triol from D-pantolactone 	TMSCN; (*S*); [101]	benzaldehyde 76 (92)
Schiff base from chiral β-amino alcohol 	TMSCN; (*R*); [102]	benzaldehyde 85 (67) *trans*-2-methylbut-2-enal 96 (68) other aromatic, aliphatic and α,β-unsaturated 20-91 (48-85)
salens from chiral diamines 	TMSCN; (*R*); [103]	benzaldehyde 87 (82)
	TMSCN; (*S*); [97,104,105]	benzaldehyde 86 (quantitative) other aromatic 3-92 (43-100) cinnamaldehyde 54 (quantitative) aliphatic 36-66 (quantitative) ketones 0 (0)
peptide derivatives 	HCN; (*R*); [106]	benzaldehyde 78 (94) aliphatic 54-76 (85-99) cinnamaldehyde 81 (82) other α,β-unsaturated 37-89 (28-90)
	HCN; (*R*); [96,107]	benzaldehyde 79 (99) other aromatic 85-90 (56-88)
	HCN; (*S*); [96,107]	benzaldehyde 87 (93) other aromatic 72-97 (63-96) cinnamaldehyde 62 (40)

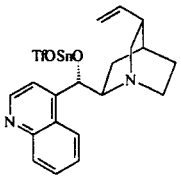
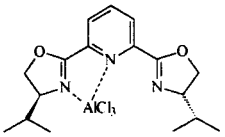
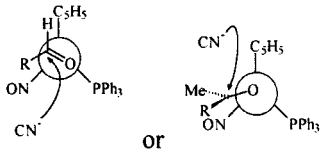
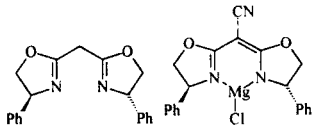
[a] Aldehydes unless specified otherwise.

of some kind. Last, a few preparative routes start from non-carbonyl precursors.

1. Chiral Complexes Control Enantioselective Hydrocyanation or Silylcyanation

Some titanium alkoxide complexes that have been used for the preparation of enantiomerically enriched aldehyde cyanohydrins are summarized in Table 2. The reactions are catalytic with respect to the titanium complex with the exception of the first entry: less than stoichiometric amounts of sulfoximine−titanium complex give very poor results. The type of stereocontrol taking place is exemplified by the proposed transition states for the peptide−titanium complexes (Figure 7).[96] Note, however, that there is much room for mechanistic speculation for each type of ligand. Significant recent work by Belokon', North, and co-workers shows that it is a

Table 3. Examples of Nontitanium Metal Catalysts for Asymmetric Cyanohydrin Synthesis

complex, origin of chirality and proposed structure	*cyanating agent; selectivity; references*	*results for selected substrates[a] in % ee of (and conversion to) adduct*
tin (II) Lewis acid from (+)-cinchonine 	TMSCN; (unspecified); [16]	cyclohexane carboxaldehyde 90 (63) benzaldehyde 0 (0)
$AlCl_3$-Pybox (from eserine) complex 	TMSCN; (*S*); [110]	benzaldehyde 86 (quantitative)
rhenium complex to give $[(\eta^5\text{-}C_5H_5)Re(NO)(PPh_3)(substrate)]^+ BF_4^-$ 	$(CH_3CH_2)_4N^+CN^-$; (*S*); [111]	benzaldehyde 90 (87) short-chain aliphatic 53-71 (78-93) *tert*-butyl methyl ketone 99 (75)
combination of a bisoxazoline ligand and a magnesium complex of a cyanobisoxazoline, both from (*S*)-phenylglycinol 	TMSCN; (*S*); [112]	cyclohexane carboxaldehyde 94 (94) other aliphatic 90-95 (57-88) benzaldehyde 52 (88)

[a] Aldehydes unless specified otherwise.

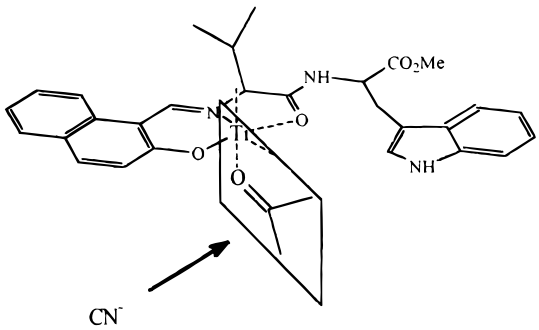


Figure 7. The titanium alkoxide complex with acyclic peptide derivatives is thought to have a typified structure with a tridentate peptide ligand and apical association to the substrate. For the derivative shown, it is the bulky tryptophan side chain that blocks the cyanation of one enantioface (row 5 in Table 2).[96]

dimeric complex[97] that promotes the fastest asymmetric reaction in the case of titanium salens (row 4 in Table 2).

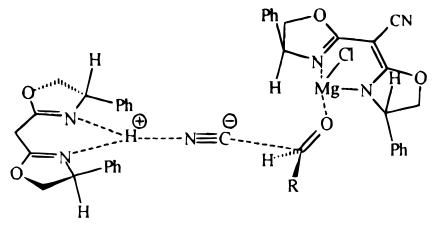
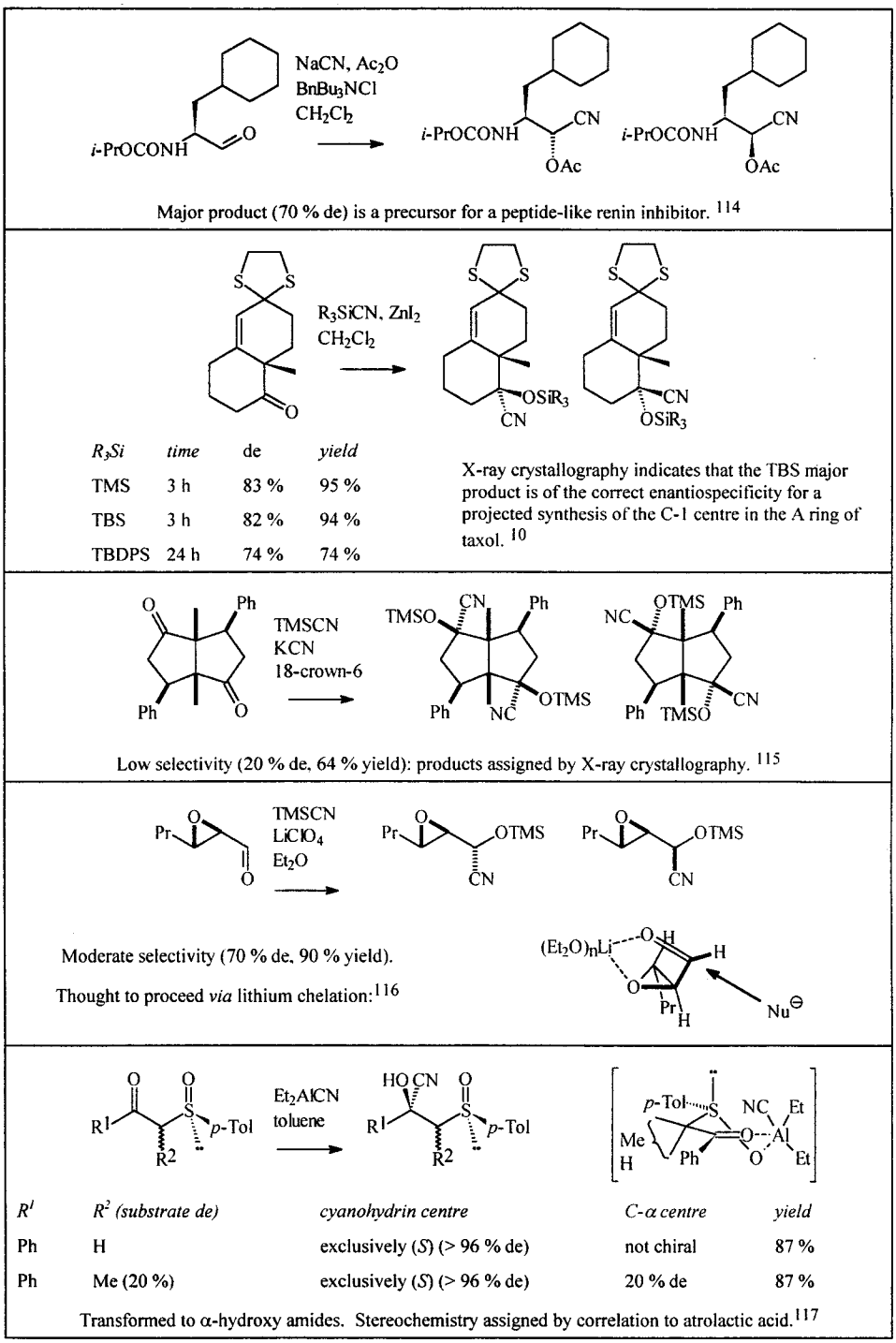


Figure 8. Corey's postulated transition state controls cyanohydrin formation via a pair of synergistic bisoxazolines (row 4 in Table 3).

Other catalysts recently reported include chiral tin Lewis acids and aluminum, rhenium and magnesium complexes (Table 3). The latter system is of particular interest since a new catalytic rationale is proposed whereby both the substrate and the cyanide are activated by binding to separate chiral sites (Figure 8), thus moving a step closer to mimicking the ideals of enzyme catalysis.

Table 4. Examples of Diastereomeric Control Showing the Major Product First, and Salient de, Conditions, Yields, Rationalizations, Applications, and References



Aside from cyanohydrin preparation, titanium-[108] and aluminum-based[109] catalysts have been used for the analogous asymmetric addition of cyanide to imine substrates en route to α-amino acid derivatives (see Section IV.B.5 for metal-free catalysts with this function).

2. Diastereoselective Hydrocyanation or Silylcyanation of Chiral Carbonyl Compounds

Some examples of diastereoselective cyanation are given in Table 4. In certain cases, notably with cyclic systems, the diastereoselectivity is predictable on steric grounds (entry 2) although heavy substitution may affect the exo preference in bicyclic systems (entry 3). Chelation to metal centers may enhance the diastereoselectivity (entries 4 and 5). In the highly diastereoselective hydrocyanation of β-keto sulfoxides, sulfur (1,3) induction of chirality predominates over C-α (1,2) control through a proposed pentacoordinate aluminum intermediate (entry 5): this constitutes a route to optically pure ketone cyanohydrins and—by anchimeric assistance of the sulfinyl group—a mild transformation to α-hydroxy amides.[113]

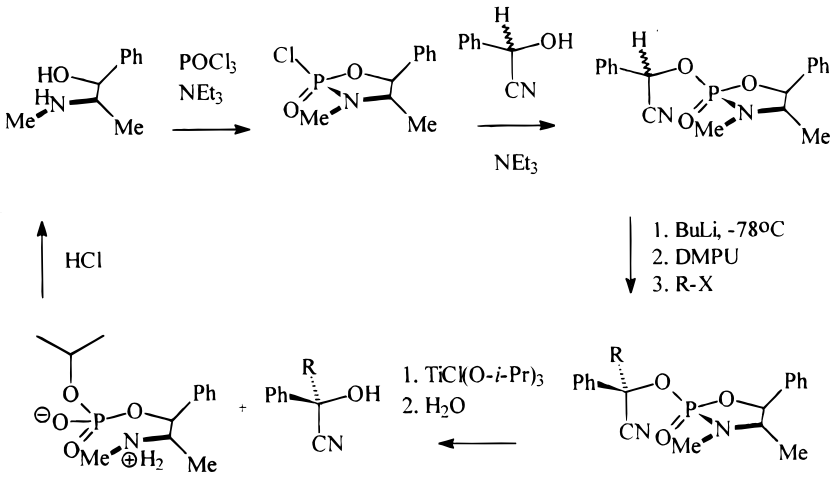


Figure 9. Schrader's chiral umpolung method for tertiary cyanohydrins from racemic mandelonitrile.[119] With R = methyl and benzyl, the optically pure (>96% ee) (*R*)-cyanohydrins are obtained in 66% and 85% yields, respectively. The phosphate is easily obtained from (+)-pseudoephedrine and may be recycled in 68% yield.

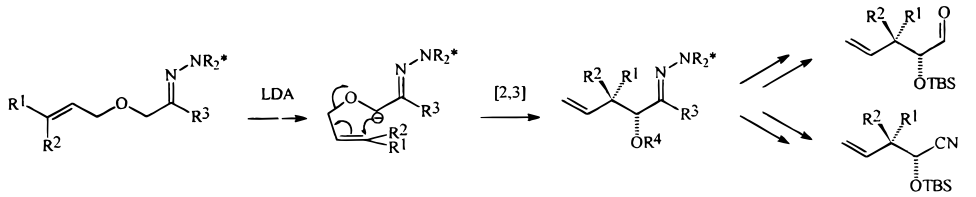


Figure 10. Enders has generated optically active γ,δ-unsaturated α-hydroxyaldehydes and cyanohydrins from α-allyloxyhydrazones (* indicates a chiral auxiliary) in high enantiomeric excesses (92−98%) and syn selectivities (88−100%).[120,121]

3. Preparation from Non-Carbonyl Compounds

Most cyanohydrin resolution methods involve enzymes (Sections IV.C and IV.D): many chemical resolution techniques are incompatible with the low stability of cyanohydrins. However, it is possible to resolve certain ketone cyanohydrins by complexation with brucine: racemic 2-hydroxy-2-phenyl-3,3,-dimethylbutanenitrile has been resolved to the (+)-enantiomer in 94% ee and quantitative yield.[118]

A more adventurous application of racemic cyanohydrins involves O-protection with a chiral phosphate and then use of the cyanohydrin derivative as a chiral umpolung reagent: deprotonation and reaction with electrophiles gives optically active tertiary cyanohydrins, following which the phosphate group can be removed (Figure 9).[119] A final, less obvious example, is an effective route from chiral α-allyloxy hydrazones to protected cyanohydrins via the [2,3]-sigmatropic Wittig rearrangement (Figure 10).[120,121]

B. Asymmetric Catalysis by Cyclic Dipeptides

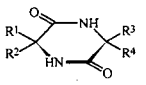
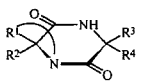
1. cyclo[(S)-His-(S)-Phe] Is the Most Effective Dipeptide Catalyst

Nature uses enzymes as precision tools to catalyze chemical transformations, and the mimicking of their highly stereospecific nature by synthetic peptides is a growing field. The advent of effective peptide catalysis was the discovery in 1979 of the first asymmetric synthesis catalyzed by cyclic dipeptides, namely, the addition of hydrogen cyanide to benzaldehyde.[122] Thus, Inoue and co-workers inferred that whereas linear peptides are unfavorable for asymmetric catalysis because of their flexible structure and variable conformation, the rigid skeleton of the 2,5-piperazinedione ring of cyclic dipeptides leads to improved enantioselectivity, especially in the case of histidine derivatives, a selection of which are illustrated in Figure 11.

The best result at this stage was obtained with *cyclo*[(*S*)-alanyl-(*S*)-histidine] or *cyclo*[(*S*)-Ala-(*S*)-His] [systematic name, (*S*,*S*)-3-(4-imidazolylmethyl)-6-methyl-2,5-piperazinedione] to give (*R*)-mandelonitrile in 10% ee; other linear and cyclic dipeptides including *cyclo*[Gly-(*S*)-His], *cyclo*[(*R*)-Ala-(*S*)-His], and *cyclo*[(*S*)-His-(*S*)-His] are even less effective (Table 5). The breakthrough came 2 years later with the discovery that *cyclo*[(*S*)-phenylalanyl-(*S*)-histidine] or *cyclo*[(*S*)-Phe-(*S*)-His] [systematic name: (*S*,*S*)-3-benzyl-6-(4-imidazolylmethyl)-2,5-piperazinedione] catalyzes the same reaction but dramatically improves the enantiomeric excess to over 90%.[123,124]

2. Cyclic Dipeptide Catalysis Has Been Studied at the Molecular Level

Inoue and co-workers proposed that the imidazole group of the histidine residue is catalytically active as a base (Figure 12) but that the peptide can also enhance racemization of the cyanohydrin by catalyzing either the reverse reaction or deprotonation of the methine group (under some conditions, enantiomeric excess decreases with time).[123,124] Jackson and co-workers additionally showed *cyclo*[(*S*)-Phe-(*S*)-His] to be the catalyst of choice against other cyclic dipeptides including *cyclo*[(*S*)-Phe-(*R*)-His], *cyclo*[(*S*)-Tyr-(*S*)-His], *cyclo*[(*S*)-MeO-Tyr-(*S*)-His], and *cyclo*[(*S*)-Ph-Gly-(*S*)-His] (see Figure 11 and Table 5);[125] provided NMR data consistent with an almost planar

in the case of *cyclo*[(*S*)-Pro-(*S*)-His]

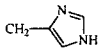
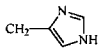
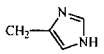
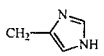
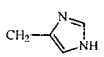
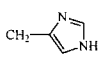
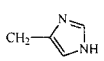
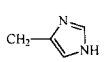
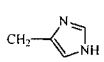
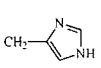
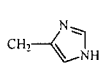
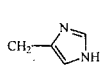
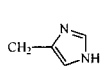
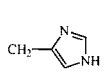
Cyclic dipeptide	R^1	R^2	R^3	R^4
***cyclo*[Gly-(*S*)-His]**	H	H		H
cyclo[(*S*)-Ala-(*S*)-His]	Me	H		H
***cyclo*[(*R*)-Ala-(*S*)-His]**	H	Me		H
***cyclo*[(*S*)-Val-(*S*)-His]**	Me_2CH	H		H
***cyclo*[(*S*)-Leu-(*S*)-His]**	Me_2CHCH_2	H		H
***cyclo*[(*S*)-Pro-(*S*)-His]**	ring N-$(CH_2)_3$	H		H
***cyclo*[(*S*)-His-(*S*)-His]**		H		H
***cyclo*[(*R*)-His-(*S*)-His]**	H			H
***cyclo*[(*S*)-Phe-(*S*)-His]**	$PhCH_2$	H		H
***cyclo*[(*S*)-Phe-(*R*)-His]**	$PhCH_2$	H	H	
***cyclo*[(*S*)-Ph-Gly-(*S*)-His]**	Ph	H		H
***cyclo*[(*S*)-Tyr-(*S*)-His]**	4-HO-$PhCH_2$	H		H
***cyclo*[(*S*)-MeO-Tyr-(*S*)-His]**	4-MeO-$PhCH_2$	H		H
***cyclo*[(*S*)-BnO-Tyr-(*S*)-His]**	4-BnO-$PhCH_2$	H		H

Figure 11. Histidine-based cyclic dipeptide catalysts investigated for hydrocyanation.

diketopiperazine ring; and enlarged Inoue's mechanistic proposal to include aryl−aryl interactions. Callant and co-workers used NMR spectroscopy and molecular modeling to propose an orientation for the catalyst, hydrogen cyanide and benzaldehyde, dependent on the theory of cyanide delivery from imidazole.[129] Kellogg and co-workers have found *cyclo*[(*S*)-(α-Me)Phe-(*S*)-His] and *cyclo*[(*R*)-(α-Me)Phe-(*S*)-His] to be comparable catalysts to *cyclo*[(*S*)-Phe-(*S*)-His], and they propose another mechanism of cyanide delivery, based on NOE studies for *p*-methoxybenzaldehyde, where the aldehyde is bound to the NH of the α-methylphenylalanine residue and not the NH of the histidine residue[130] (Figure 12).

While the unnatural *cyclo*[(*R*)-Phe-(*R*)-His] gives the opposite stereoselectivity to *cyclo*[(*S*)-Phe-(*S*)-His], the best 'natural' (*S*,*S*) dipeptide catalyst for the preparation of (*S*)-cyanohydrins is *cyclo*[(*S*)-Leu-(*S*)-His], which provides (*S*)-mandelonitrile in 85% yield and 55% enantiomeric excess.[127] The catalysts do not just work with benzaldehyde: a variety of substrates have been hydrocyanated with varying degrees of enantioselectivity (Tables 5 and 6).

The catalytic mechanism remains a confusing and incomplete but fascinating jigsaw from which a picture is slowly emerging. Questions within the puzzle involve the form of the catalyst, its inter- and intramolecular arrangement, and its catalytically active conformation. The catalyst is only active when amorphous (low crystallinity is associated with high enantioselectivity), such as is obtained by rapid precipitation (slow precipitation results in a poor catalyst):[139] activation has also been achieved by solvent evaporation, freeze-drying, and spray-drying.[140] Effective enantioselective catalysis is only observed under heterogeneous gel conditions: no enantioselectivity is observed in methanol in which the catalyst dissolves. With maximum stirring of the reaction mixture, viscosity is reduced and enantioselectivity is increased.[132] Acetone cyanohydrin and other cyanide sources in place of hydrogen cyanide result in little or no enantioselectivity.[141,142]

Inoue's method uses 2 equiv of hydrogen cyanide and 2 mol % of catalyst (prepared by rapid precipitation) in toluene at − 20 °C and represents optimized conditions, converting benzaldehyde to (*R*)-mande-

Table 5. Comparison of Different Histidine-Based Dipeptide Catalysts

catalyst	*(specificity)*	*conditions (solvent, temp, amount of HCN, amount of catalyst,[a] reaction time)*	*results for selected substrates in %; ee of (and conversion to) adduct; refs*
cyclo[Gly-(*S*)-His]	(*R*)	benzene, 35 °C, 1 equiv, 2 mol %, 44 h	benzaldehyde 3 (70)[123]
cyclo[(*S*)-Ala-(*S*)-His]	(*R*)	benzene, 35 °C, 1 equiv, 7 mol %, 47 h	benzaldehyde 10 (50)[122,123]
		toluene, −10 °C, 4 equiv, 4 mol %, 20 h	3-phenoxybenzaldehyde 26 (21)[125]
cyclo[(*R*)-Ala-(*S*)-His]	(*R*)	benzene, 35 °C, 1 equiv, 7 mol %, 47 h	benzaldehyde 8 (90)[122,123]
Z-(*S*)-Ala-(*S*)-His-OMe		benzene, 35 °C, 1 equiv, 7 mol %, 3 h	benzaldehyde 0 (80)[122]
cyclo[(*S*)-Val-(*S*)-His]	(unspecified)	unspecified	benzaldehyde <10 (unspecified)[126]
cyclo[(*S*)-Leu-(*S*)-His]	(*S*)	toluene, 0 °C, 2 equiv, 4 mol %, 6 h	benzaldehyde 27 (77)[127]
		ether, 0 °C, 2 equiv, 4 mol %, 4−24 h	benzaldehyde 55 (85)[127] other aromatic aldehydes 15−60 (66−97) undecanal 81 (93) other aliphatic aldehydes 61−74 (83−99)
cyclo[(*S*)-Pro-(*S*)-His]	(unspecified)	unspecified	benzaldehyde <10 (unspecified)[126]
cyclo[(*S*)-His-(*S*)-His]	(*R*)	benzene, 35 °C, 1 equiv, 3 mol %, 23 h	benzaldehyde 3 (50)[122,123]
		toluene, −10 °C, 4 equiv, 3 mol %, 42 h	3-phenoxybenzaldehyde 2 (90)[125]
cyclo[(*S*)-His-(*R*)-His]	(*S*)	toluene, −10 °C, 4 equiv, 2 mol %, 21 h	3-phenoxybenzaldehyde 10[b](50)[125]
cyclo[(*S*)-Phe-(*S*)-His]	(*R*)	benzene, 35 °C, 1 equiv, 2 mol %, 0.5 h	benzaldehyde 90 (40)[123]
		toluene, −20 °C, 2 equiv, 2 mol %, 8 h	benzaldehyde 97 (97)[126]
cyclo[(*S*)-Phe-(*R*)-His]	(*S*)	toluene, −10 °C, 4 equiv, 3 mol %, 21 h	3-phenoxybenzaldehyde 11 (75)[125]
Z-(*S*)-Phe-(*S*)-His-OMe	(*S*)	benzene, 35 °C, 1 equiv, 2 mol %, 3 h	benzaldehyde 1 (70)[123]
cyclo[(*S*)-Ph-Gly-(*S*)-His]		toluene, −10 °C, 4 equiv, 2 mol %, 20 h	3-phenoxybenzaldehyde 0 (30)[125]
cyclo[(*S*)-Tyr-(*S*)-His]	(*R*)	toluene, −10 °C, 4 equiv, 2 mol %, 24 h	3-phenoxybenzaldehyde 21 (61)[125]
cyclo[(*S*)-MeO-Tyr-(*S*)-His]	(*R*)	toluene, −10 °C, 4 equiv, 2 mol %, 42 h	3-phenoxybenzaldehyde 28 (74)[125]
		toluene, −5 °C, 2 equiv, 2 mol %, 24 h	4-(4-allyloxyphenylcarboxy)benzaldehyde 70 (82)[128]
cyclo[(*S*)-BnO-Tyr-(*S*)-His]	(unspecified)	toluene, −5 °C, 2 equiv, 2 mol %, 24 h	4-(4-allyloxyphenylcarboxy)benzaldehyde 20 (60)[128]

[a] Cyclic dipeptides activated by precipitation or recrystallization from protic solvents. [b] This is a surprising result since *cyclo*[(*S*)-His-(*R*)-His] is achiral, suggesting that other ee values calculated from optical rotations in this paper be treated with caution, or alternatively that *cyclo*[(*S*)-His-(*R*)-His] is a misprint for *cyclo*[(*R*)-His-(*R*)-His].

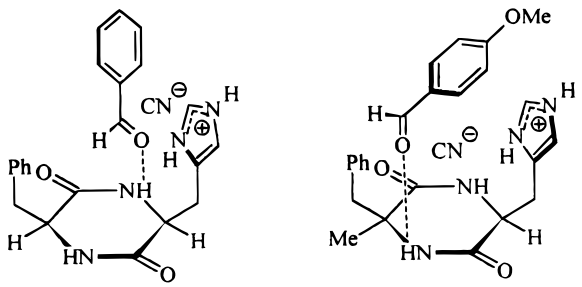


Figure 12. Mechanistic proposals for the delivery of cyanide to aldehydes catalyzed by *cyclo*[(*S*)-Phe-(*S*)-His][129] and *cyclo*[(*S*)-(α-Me)Phe-(*S*)-His].[130]

lonitrile in 97% yield and 97% enantiomeric excess (row 1 in Table 6).[126] Jackson and co-workers have obtained poorer enantioselectivities at higher temperatures,[131] and have used spectroscopic data to imply a deficiency of intermolecular hydrogen bonding and a propensity of intramolecular hydrogen bonding in the active, amorphous form of the catalyst.[143]

To investigate conformations of catalysts, North and co-workers have carried out molecular modeling and detailed NMR studies. Whereas for *cyclo*[(*S*)-Phe-(*S*)-His] the phenyl ring is thought to be folded over the diketopiperazine ring[144,145] thus shielding one face of the imidazole ring, in the case of *cyclo*[(*S*)-Leu-(*S*)-His] the imidazole ring is folded over the diketopiperazine ring and thus its other face is shielded.[146] Since the imidazole ring appears to be crucial for catalysis (the one fact on which all researchers agree), these results may go some way toward explaining why the two catalysts induce opposite chiralities.

Furthermore, the discovery that *cyclo*[(*S*)-Phe-(*S*)-His] also catalyzes the oxidation of benzaldehyde to benzoic acid led to a new mechanistic proposal based on a common aminol intermediate for both oxidation and hydrocyanation. Thus, hydrocyanation can be explained by nucleophilic attack of the imidazole ring onto benzaldehyde, leading to the aminol, which is subsequently attacked by cyanide (Figure 13).[147] This mechanism has scope for enantioselection either at the aminol formation stage or the cyanide displacement stage. In comparison with earlier mechanistic proposals, the North group suggest that the involvement of an imidazole−cyanide salt is inconsistent with their observation that interaction between catalyst and hydrogen cyanide is largely covalent.

This aminol mechanistic proposal shows striking similarities to the HbHNL nucleophilic displacement proposal (Section III.F.1) in that a center in the catalyst, possibly activated by intramolecular hydrogen-bonding, attacks the substrate to form a tetra-

Table 6. Use of *cyclo*[(*S*)-Phe-(*S*)-His]: Examples of Substrates, Activation, and Autoinduction

catalyst activation	*conditions (solvent, temp, HCN, catalyst)*	*results for selected substrates; % ee of adduct (% conversion and reaction time)*
rapid precipitation from methanol/ ether[126]	toluene, −20 °C, 2 equiv, 2 mol %	benzaldehyde 97 (97, 8 h) benzaldehyde 90 (85, 24 h)[a] 3-nitrobenzaldehyde 4 (100, 8 h) 4-methoxybenzaldehyde 99 (98, 36 h)[b] 4-allyloxybenzaldehyde 98 (96, 36 h)[b] furfural 42 (60, 8 h) other aromatic aldehydes 32−96 (45−100, 0.5−10 h) isobutyraldehyde 71 (79, 5 h) other aliphatic aldehydes 18−58 (44−96, 2.5−8 h)
recrystallization from protic solvents[131]	toluene, −5 °C, 2.5 equiv, 2 mol %	benzaldehyde 85 (79, 7 h) benzaldehyde 77 (18, 8 h) and 37 (9, 8 h)[c] 4-nitrobenzaldehyde 29 (77, 2 h) 4-methylbenzaldehyde 92 (91, 3 h) other aromatic aldehydes 32−91 (30−100, 2−24 h) furfural 79 (53, 7 h)[d] other heteroaromatic aldehydes 0−62 (23−100, 1−96 h)[e] isobutyraldehyde 17 (100, 1 h)[f] other aliphatic 14−27 (86−100, 1−8 h)[e] cinnamaldehyde 11 (65, 16 h)[f] other α,β-unsaturated aldehydes 11−34 (44−100, 2−24 h)[e] butan-2-one 19 (31, 7 h)[g] other ketones 0−17 (0−55, 21−72 h)[g]
rapid evaporation of aqueous methanol solution[132]	toluene, 5 °C, 2 equiv, 2 mol %	3-phenoxybenzaldehyde 92 (97, 6 h)
through ion exchange resin then concentration[133,134]	toluene, 0 °C, 2 equiv, 3 mol %	benzaldehyde 92, (80, 1−2 h)
methanol gel dried in critical point drier chamber[135]	toluene, 5 °C, 2 equiv, 2 mol %	3-phenoxybenzaldehyde 92 (93, 4 h)
lyophilization[136]	toluene, −15 °C, 3.2 equiv, 1 mol %	4-methoxybenzaldehyde 92 (96, 36 h) 3-phenoxybenzaldehyde 85 (92, 4 h)[h]
dried over phosphorus pentoxide[125]	benzene, 35 °C, 1.25 equiv, 2 mol %	benzaldehyde 0 (0, 1 h)
lyophilization[137] (results demonstrate enantioselective autoinduction)[137,138]	toluene, −25 °C, 2.5 equiv, 2 mol %[i]	furfural 53 (92, 7 h) seeded with 8 mol % (*S*)-mandelonitrile, 81 (95, 7 h) seeded with 8 mol % (*R*)-mandelonitrile, 50 (78, 7 h) seeded with 8 mol % methanol − 57 (94, 7 h)
	toluene, 2 equiv, 2 mol %[i]	3-phenoxybenzaldehyde 92 (94, 4 h) and 36 (66, 1 h) seeded with 9 mol % (*S*)-3-phenoxy-mandelonitrile 97 (95, 4 h)
precipitated enantiomerically impure catalyst[138]	toluene, 2 equiv, 2 mol %[i] catalyst with ee of 67%	3-phenoxybenzaldehyde 65 (81, 4 h) seeded with 9 mol % (S)-3-phenoxy-mandelonitrile, 96 (89, 4 h)
	toluene, 2 equiv, 2 mol %[i] catalyst with ee of 2%	seeded with 9 mol % (S)-3-phenoxy-mandelonitrile, 82 (43, 4 h)

Variations from the given references and conditions are as follows: [a] −5 °C.[128] [b] −15 °C, 2.5 to 3.2 equiv HCN, 1 to 2 mol % catalyst.[136] [c] −20 °C, 2 equiv HCN.[126] [d] −20 °C. [e] −10 to 22 °C. [f] 22 °C. [g] ether, unspecified temperature. [h] −25 °C, 2.5 equiv HCN, 2 mol % *cyclo*[(*R*)-Phe-(*R*)-His] catalyst.[137] [i] *cyclo*[(*R*)-Phe-(*R*)-His] [specificity (*S*)] used as catalyst in place of *cyclo*[(*S*)-Phe-(*S*)-His] [specificity (*R*)].

hedral intermediate that subsequently undergoes an S_N2 displacement with cyanide. The mechanism is further supported by solid-state NMR studies which confirm the conformation of *cyclo*[(*S*)-Phe-(*S*)-His] to have the phenyl group folded over the diketopiperazine ring in the solid state as well as in solution.[148] Nevertheless, the aminol proposal requires further experimental evidence.

3. Supramolecular Complexity Adds an Extra Mechanistic Dimension

The fact that the heterogeneous nature of the reaction medium and the amorphous nature of the catalyst have profound effects on enantioselectivity and rate suggests that reaction takes place on the surface of larger particles: diketopiperazines are well

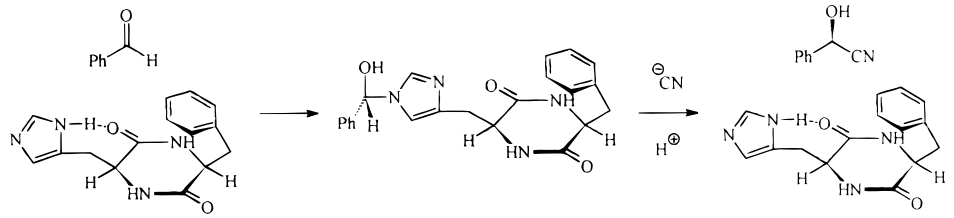


Figure 13. North's aminol mechanism for *cyclo*[(*S*)-Phe-(*S*)-His].[147]

set up for polymer formation and molecular aggregation by hydrogen bonding. Shvo and co-workers believe such aggregation to be of crucial importance: molecular modeling supports aggregation, and kinetic studies show that the reaction is second order in the catalyst, implying that two different imidazole bases in a diketopiperazine grid (whether that be dimeric, oligomeric, polymeric, or even an aggregate of polymers) participate in the reaction.[135] The umbrella idea of a peptide aggregate is a means of uniting a mechanism to deliver cyanide from one imidazole ring with a mechanism to activate aldehyde by another. The precise mechanism of aldehyde activation could involve coordination of an imidazole−hydrogen cyanide ion pair to the substrate oxygen via a dipole−dipole interaction, as proposed by Shvo.[135] Alternatively the aminol mechanism would appear to slot in here: if this were the case, the catalysis would become even more biomimetic with respect to the proposed HbHNL mechanism.

Catalysis by *cyclo*[(*S*)-Phe-(*S*)-His] is subject to enantioselective autoinduction whereby the incorporation of chiral product into the chiral catalyst promotes asymmetric reaction.[137,138,149] The increase in enantioselectivity with time (for example, with 3-phenoxybenzaldehyde in row 8 of Table 6) may imply that structural defects in the polymeric gel are self-repaired by the autoinduction process. The induction process is not observed (i.e., the ee is already at a maximum after minimum reaction time) when a cyanohydrin product is present at the start, supporting the idea of it having a role as a repairing or self-assembly agent. However, an autoinductive effect is also seen with an achiral cyanohydrin or alcohol, implying that a protic compound is sufficient for self-assembly. This process may take the form of a partial breakdown of polymer to give an oligomer or dimer,[137] which is the true catalyst, or the breakdown of hydrogen bonds within a polymer[135] to activate it while preserving its gross structure. Enantioselectivities with poor substrates may be improved by over 20% by adding a small amount (8 mol %) of a chiral aryl cyanohydrin (rows 8 and 9 in Table 6).[137] This implies that an active component of the catalyst is a complex between dipeptide and cyanohydrin product.[137] Such seeding experiments result in moderate enantioselectivities, even when largely racemic (2% ee) catalyst is used (row 9 in Table 6).

4. Lower Activity of Polymer-Bound or Covalently Modified Peptide Analogues Is a Consequence of Barriers to Aggregation

If the catalyst is a highly ordered supramolecular complex of dipeptides, one would expect that barriers to aggregation would limit the catalytic activity. This is clearly observed as detailed below and illustrated by Figure 14 and Table 7.

Covalent immobilization of *cyclo*[(*S*)-Phe-(*S*)-His] to various supports via either the benzene[128] or the imidazole[150] ring leads to poor enantioselectivities, although entrapment in a silicon-based sol−gel glass matrix still enables the formation of mandelonitrile in >94% enantiomeric excess (rows 1−4 in Table 7).[151]

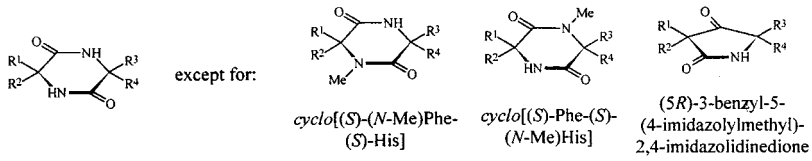
Noe and others have made several aromatic[133] (rows 5−11) and methylated[130,134] (rows 12−18) modifications to *cyclo*[(*S*)-Phe-(*S*)-His]. The presence of sterically demanding aromatic moieties results in no enantioselectivity and very low conversion, implying that such changes disturb the supramolecular ordering: only *cyclo*[(*S*)-2-thienyl-Ala-(*S*)-His] (row 7) is sufficiently isosteric to give any enantioselectivity. *N*-Methylation on the piperazine ring (rows 15 and 16) removes all catalytic activity, as would be expected through appreciable loss of hydrogen-bonding ability. Significantly, the reaction media with these peptides are clear solutions. Methylation in other positions retains some catalytic activity. (5*R*)-3-Benzyl-5-(4-imidazolylmethyl)-2,4-imidazolidinedione (bottom row), Danda's five-membered ring analogue of *cyclo*[(*S*)-Phe-(*S*)-His], furnishes (*S*)-2-hydroxy-2-(3-phenoxyphenyl)acetonitrile in only 41% enantiomeric excess.[139] Other diketoimidazolidines perform even less effectively.

5. Application of Cyclic Dipeptide Catalysis to the Strecker Amino Acid Synthesis

Lipton and co-workers have extended the use of cyclic dipeptide asymmetric catalysis to the Strecker synthesis in an elegant synthesis of α-amino acids.[152] While *cyclo*[(*S*)-Phe-(*S*)-His] does not induce chirality in the addition of hydrogen cyanide to imines, replacement of histidine with the lower homologue of arginine, (*S*)-α-amino-γ-guanidinobutyric acid, results in an effective catalyst. A guanidine side chain is more basic than an imidazole ring and is thus better able to accelerate proton transfer and to activate the imine.

Reaction of benzhydryl imines with hydrogen cyanide in the presence of 2 mol % of *cyclo*[(*S*)-α-amino-γ-guanidinobutyryl-(*S*)-histidine] furnishes α-aminonitriles (Figure 15) that on acid treatment undergo simultaneous hydrolysis and deprotection. Thus, benzaldehyde can be converted to (*S*)-phenylglycine in 97% yield and >99% ee.

The catalysis of this asymmetric Strecker reaction is different from cyanohydrin formation on two counts: under Strecker conditions, the catalyst is



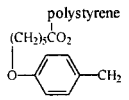
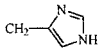
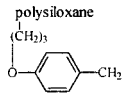
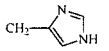
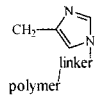
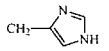
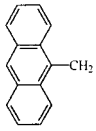
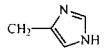
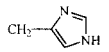
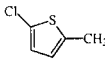
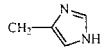
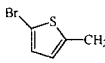
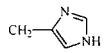
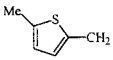
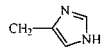
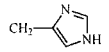
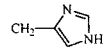
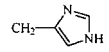
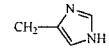
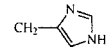
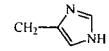
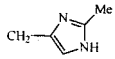
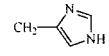
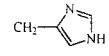
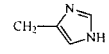
Cyclic dipeptide	R^1	R^2	R^3	R^4
***cyclo*[(*S*)-(*O*-polystyrene-attached)-Tyr-(*S*)-His]**		H		H
***cyclo*[(*S*)-(*O*-polysiloxane-attached)-Tyr-(*S*)-His]**		H		H
***cyclo*[(*S*)-Phe-(*S*)-(*N*-Merrifield polymer-attached)-His]**	$PhCH_2$	H		H
***cyclo*[(*S*)-1-naphthyl-Ala-(*S*)-His]**		H		H
***cyclo*[(*S*)-9-anthracenyl-Ala-(*S*)-His]**		H		H
***cyclo*[(*S*)-2-thienyl-Ala-(*S*)-His]**		H		H
***cyclo*[(*S*)-2-(5-chloro)-thienyl-Ala-(*S*)-His]**		H		H
***cyclo*[(*S*)-2-(5-bromo)-thienyl-Ala-(*S*)-His]**		H		H
***cyclo*[(*S*)-2-(5-methyl)-thienyl-Ala-(*S*)-His]**		H		H
***cyclo*[(*S*)-3-thienyl-Ala-(*S*)-His]**		H		H
***cyclo*[(*S*)-(α-Me)Phe-(*S*)-His]**	$PhCH_2$	Me		H
***cyclo*[(*R*)-(α-Me)Phe-(*S*)-His]**	Me	$PhCH_2$		H
***cyclo*[(*S*)-2-thienyl-(α-Me)Ala-(*S*)-His]**		Me		H
***cyclo*[(*S*)-(*N*-Me)Phe-(*S*)-His]**	$PhCH_2$	H		H
***cyclo*[(*S*)-Phe-(*S*)-(*N*-Me)His]**	$PhCH_2$	H		H
***cyclo*[(*S*)-Phe-(*S*)-(2-Me)His]**	$PhCH_2$	H		H
***cyclo*[(*S*)-(β,β-di-Me)Phe-(*S*)-His]**	$PhC(Me_2)$	H		H
***cyclo*[(*S*)-(β-Ph)Phe-(*S*)-His]**	PhC(Ph)H	H		H
(5*R*)-3-benzyl-5-(4-imidazolylmethyl)-2,4-imidazolidinedione	$PhCH_2$	H		H

Figure 14. Variations on a cyclic dipeptide theme: structurally related compounds investigated as catalysts.

Table 7. Variations on a Cyclic Dipeptide Theme: Structurally Related Compounds Investigated as Catalysts

catalyst	*(specificity)*	*method[a] ref*	*results for selected substrates % ee of adduct (% conversion and reaction time)*
cyclo[(*S*)-(*O*-polystyrene-attached)-Tyr-(*S*)-His]	(unspecified)	A[128]	benzaldehyde 30 (70, 24 h) 4-(4-allyloxyphenylcarboxy)benzaldehyde 10 (83, 24 h)
cyclo[(*S*)-(*O*-polysiloxane-attached)-Tyr-(*S*)-His]	(unspecified)	A[128]	4-(4-allyloxyphenylcarboxy)benzaldehyde 10 (70, 24 h)
cyclo[(*S*)-Phe-(*S*)-(*N*-Merrifield polymer-attached)-His]	(*R*)	B[150]	3-phenoxybenzaldehyde 0−18 (78−93, 24 h)
cyclo[(*S*)-Phe-(*S*)-His] in $Si(OMe)_4$ aerogel		C[151]	benzaldehyde 94−98 (78−80, 27 h)
cyclo[(*S*)-1-naphthyl-Ala-(*S*)-His]		D[133]	benzaldehyde 0 (<10, 1−2 h)
cyclo[(*S*)-9-anthracenyl-Ala-(*S*)-His]		D[133]	benzaldehyde 0 (<10, 1−2 h)
cyclo[(*S*)-2-thienyl-Ala-(*S*)-His]	(*R*)	D[133]	benzaldehyde 72 (40, 1−2 h)
cyclo[(*S*)-2-(5-chloro)-thienyl-Ala-(*S*)-His]		D[133]	benzaldehyde 0 (<20, 1−2 h)
cyclo[(*S*)-2-(5-bromo)-thienyl-Ala-(*S*)-His]		D[133]	benzaldehyde 0 (<20, 1−2 h)
cyclo[(*S*)-2-(5-methyl)-thienyl-Ala-(*S*)-His]		D[133]	benzaldehyde 0 (<20, 1−2 h)
cyclo[(*S*)-3-thienyl-Ala-(*S*)-His]		D[133]	benzaldehyde 0 (<20, 1−2 h)
cyclo[(*S*)-(α-Me)Phe-(*S*)-His]	(*R*)	E[130]	benzaldehyde 94 (<25, 0.5 h) 3-methoxybenzaldehyde 77 (14, 0.5 h)
		F[130]	benzaldehyde 99 (98, unspecified) 3-methoxybenzaldehyde 89 (93, 0.5 h)
		D[133]	benzaldehyde 15 (50, 1−2 h)
cyclo[(*R*)-(α-Me)Phe-(*S*)-His]	(*R*)	F[130]	benzaldehyde 32 (90, 0.5 h) 3-methoxybenzaldehyde 23 (67, 0.5 h)
cyclo[(*S*)-2-thienyl-(α-Me)Ala-(*S*)-His]		D[134]	benzaldehyde 0 (<10, 1−2 h)
cyclo[(*S*)-(*N*-Me)Phe-(*S*)-His]		D[134]	benzaldehyde 0 (<10, 1−2 h)
cyclo[(*S*)-Phe-(*S*)-(*N*-Me)His]		D[134]	benzaldehyde 0 (<10, 1−2 h)
cyclo[(*S*)-Phe-(*S*)-(2-Me)His]	(*S*)	D[134]	benzaldehyde 22 (10, 1−2 h)
cyclo[(*S*)-(*β*,*β*-di-Me)Phe-(*S*)-His]	(*R*)	D[134]	benzaldehyde 60 (20, 1−2 h)
cyclo[(*S*)-(*β*-Ph)Phe-(*S*)-His]	(*S*)	D[134]	benzaldehyde 36 (20, 1−2 h)
(5*R*)-3-benzyl-5-(4-Imidazolylmethyl)-2,4-imidazolidinedione	(*S*)	G[139]	benzaldehyde 20 (67, 3 h) 3-phenoxybenzaldehyde 41 (90, 1 h)

[a] Reaction conditions: A, toluene, −5 °C, 2 equiv HCN, 2 mol % catalyst (prepared by rapid precipitation from methanol/ether); B, toluene, −20 °C, 2 equiv HCN, catalyst (unspecified details); C, toluene, 5 °C, 2 equiv HCN, 7 mol % catalyst [encapsulated in $Si(OMe)_4$ aerogel]; D, toluene, 0 °C, 2 equiv HCN, 3 mol % catalyst (purified by ion exchange resin then concentrated); E, benzene, 25 °C, 2 equiv HCN, 2 mol % catalyst (recrystallized from methanol); F, toluene, −40 °C, 2 equiv HCN, 2 mol % catalyst (recrystallized from methanol); G, neat, 0 °C, 2 equiv HCN, 5 mol % catalyst (recrystallized from ethanol/water).

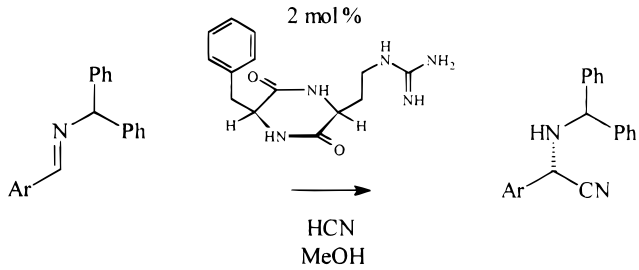


Figure 15. A cyclic dipeptide catalyzes the asymmetric step in Lipton's amino acid synthesis.[152]

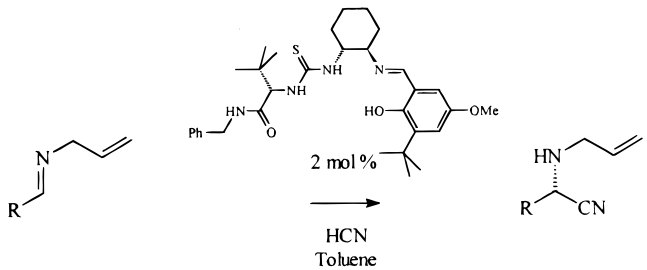


Figure 16. A Schiff base catalyst provides amino acid precursors in high yields and enantiomeric excesses (78% and 91%, respectively, for R = Ph; 70% and 85%, respectively, for R = *tert*-butyl).[153]

fully dissolved in methanol, and the enantioselectivity is the opposite to that observed by *cyclo*[(*S*)-Phe-(*S*)-His].

Within the theme of non-metal containing catalysts, a recent combinatorial approach has discovered an effective Schiff base catalyst for the addition of hydrogen cyanide to imines.[153] That its structural features are nonintuitive (Figure 16) is a further indication of the mechanistic complexities of catalytic asymmetric hydrocyanations.

C. Enzyme Methods: Preparation by Lipases

Immobilization[154] and use in organic media[155,156] have greatly expanded the potential of enzymes for practical synthetic application through maintaining or improving catalyst stability, activity, and recyclability; allowing the preparation of water-sensitive compounds; easing product recovery; and offering the possibility of medium engineering.

Figure 17. Transesterification is effective with enol esters as acylating agents: isopropenyl acetate [(R^1, R^2) = (CH_3, CH_3)], isopropenyl valerate [$CH_3(CH_2)_3$, CH_3], vinyl acetate (CH_3, H), vinyl propionate (CH_3CH_2, H), and vinyl valerate [$CH_3(CH_2)_3$, H] are commonly used.

1. Enzyme-Catalyzed Transesterification Allows the Classical Kinetic Resolution of Cyanohydrins

Esters are naturally prevalent and their preparation and hydrolysis are subject to asymmetric catalysis by a variety of esterases and lipases. Several enzymes are widely used as biocatalysts for the resolution of racemic alcohols and esters by selective esterification and hydrolysis, respectively,[157−159] collectively the most industrially applicable biotransformations.

Lipase-catalyzed esterification procedures have used various enol esters as acylating agents: vinyl and isopropenyl esters are preferable to alkyl esters because the alcohol freed in transesterification rapidly tautomerizes to volatile acetaldehyde or acetone, respectively, driving the reaction and making the process irreversible and simpler for product isolation (Figure 17).[160,161] In some cases, the acetaldehyde released may undergo an undesired side reaction whereby it deactivates the enzyme by forming an imine with the terminal amino residue of lysine, thus removing positive charge. This has been countered by immobilization via reversible alkylation, thus retaining the charge and 'immunizing' the enzyme against attack by acetaldehyde.[162] Alternatively, anhydrides have been used as acylating agents: these do not release aldehydes during transesterification.[163]

Chiral cyanohydrins are secondary or tertiary alcohols, and lipase-catalyzed resolution has been applied to the free cyanohydrins or the corresponding cyanohydrin acetates. The use of organic solvents has particularly aided this method by enhancing the stability and reducing the potential for racemization of the cyanohydrin products. In particular, selective deacylation of aliphatic (*R*)-cyanohydrins by *Candida cylindracea* lipase using hexan-1-ol as nucleophile in toluene, benzene, or acyclic ethers is an effective resolution technique, providing good to excellent enantioselectivity.[164] In contrast, porcine pancreatic lipase selectively catalyzes the acylation of (*S*)-cyanohydrins.

2. Kinetic Resolution Coupled with Cyanohydrin Racemization or Mitsunobu Esterification Theoretically Enables Quantitative Yields

The major drawback of simple kinetic resolution is that the maximum yield of each enantiomer is only 50%. While some processes use both enantiomers in further reactions, the most desirable result is usually a maximum yield of one enantiomer only. The transformation of a racemic mixture into one enantiomeric product in quantitative yield requires dynamic kinetic resolution or stereoinversion, and two methods are suitable for cyanohydrins.

Oda and co-workers have developed a one-pot synthesis of optically active (*S*)-cyanohydrin acetates from aldehydes via in-situ formation and racemization of cyanohydrins (Figure 18).[165−167] An ion-exchange resin is used to facilitate fast equilibration to convert the nonacylated (*R*)-cyanohydrin back to aldehyde. This procedure is less applicable to aliphatic cyanohydrins because they are more stable with respect to the parent ketone: the equilibrium constant is 2×10^4 M^{-1} for acetaldehyde but of the order of 33−1500 M^{-1} for aromatic aldehydes.[168]

Väntinnen and Kanerva have combined a lipase-catalyzed acylation or deacylation with a subsequent Mitsunobu esterification of the free alcohol and have applied this one-pot procedure to cyanohydrin acetates (Figure 19).[169]

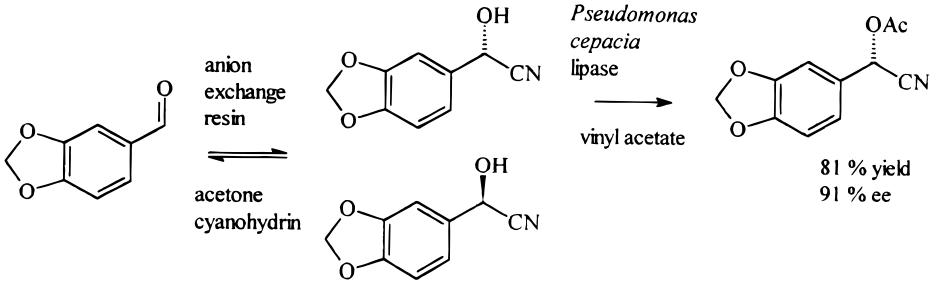


Figure 18. Piperonal may be converted to its (*S*)-cyanohydrin acetate in high yield.

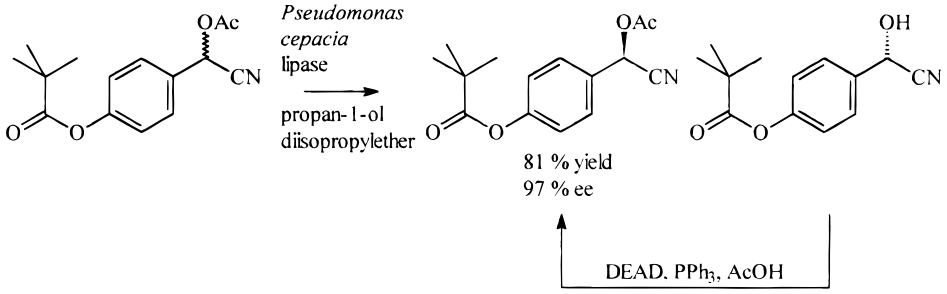


Figure 19. Biocatalytic deracemization is effective with the cyanohydrin acetate of *p*-pivalylbenzaldehyde.

Table 8. Catalytic Hydrocyanation of Aldehydes and Ketones Using Isolated or Recombinant HNLs

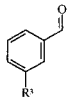
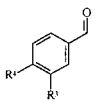
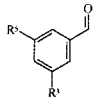
	substrate		% ee of cyanohydrin (% conversion in brackets; isolated yields where underlined) (nd = not determined/ specified); general specificity applies unless indicated otherwise by $_R$ = (R)-enantiomer preferred or $_S$ = (S)-enantiomer preferred					
			PaHNL (*R*)	apple meal (*R*)	LuHNL (*R*)	SbHNL (*S*)	HbHNL (*S*)	MeHNL (*S*)
aromatic aldehydes			99 (98)[171] 99 (95)[72] 99 (95)[172] 92 (72)[89]	99 (96)[72]		97 (97)[173] 97 (91)[174]	99 (97)[175] >99 (67)[176]	98 (100)[60]
	R^4 =	HO	96 (64)[173]	89 (66)[72]		99 (87)[174] 99 (66)[173]		
		MeO	99 (47)[171] 98 (82)[173]			71 (54)[173]	95 (49)[176]	98 (82)[60]
		PhO	95 (90)[173]	99 (92)[72]		93 (30)[173]		
		BnO	>99 (48)[177]					
		$MeOCH_2O$	94 (85)[177,178]					
			>99 (74)[177]					
		AcO	96 (85)[173] 93 (90)[177]			99 (60)[173]		
		$EtCO_2$	95 (92)[177]					
		tert-$BuCO_2$	30 (3)[72]	82 (12)[72]		0 (0)[173]		
		Me	99 (94)[173]			98 (88)[173] 78 (61)[174]		
		iso-Pr	86 (43)[72]	94 (49)[72]		37 (4)[173]		
		Me_2N	0 (0)[94]					
		Br	98 (97)[173]			44 (87)[173]		
		Cl	97 (94)[179]			54 (87)[174]		
	R^3 =	HO	97 (90)[177]			98 (90)[180] 91 (97)[174]		
		MeO	98 (85)[181]			89 (93)[174]	99 (80)[176]	
		PhO	98 (99)[172]			96 (93)[174]	99 (99)[175] 99 (9)[176]	
		$MeOCH_2O$	97 (90)[177]					
		Me				96 (80)[180]		
		F_3C	75 (76)[94]			52 (87)[2]		
		O_2N	89 (89)[179]					
		Br				92 (94)[174]		
		Cl				91 (95)[174]		
		R^2 = MeO	96 (65)[89]				77 (61)[176]	
		Cl						92 (100)[60]
		$R^3 = R^4$ = HO	21 (29)[177]					
		$R^3 = R^4$ = MeO	93 (82)[173]	93 (86)[72]		5 (34)[173]		
		R^3 = OH, R^4 = MeO	90 (35)[177]					
		R^3 = OH, R^4 = Me	98 (67)[177]					
		$R^3 = MeOCH_2O$, R^4 = MeO	83 (60)[177]					
		$R^3 = MeOCH_2O$, R^4 = Me	>98 (73)[177]					
		$R^3 = AcOCH_2$, R^4 = AcO	15 (30)[72]	82 (58)[72]				
		$R^3 = R^4$ = 	87 (23)[177]					
		R^3 =  , R^4 = 	95 (46)[177]					
		$R^3 = R^5$ = HO	69 (70)[177]					
		$R^3 = R^5$ = 	>98 (92)[177]					
		$R^3 = R^5$ = AcO	81 (89)[177]					

Table 8 (Continued)

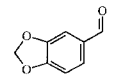
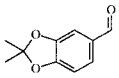
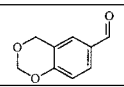
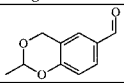
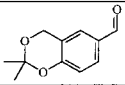
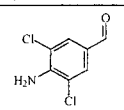
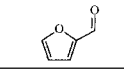
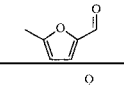
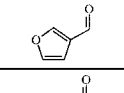
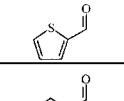
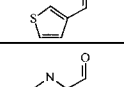
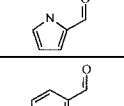
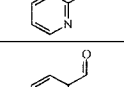
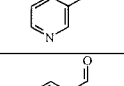
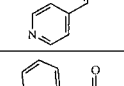
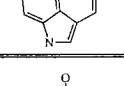
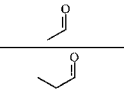
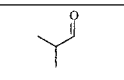
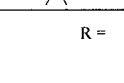
	substrate	% ee of cyanohydrin (% conversion in brackets; isolated yields where underlined) (nd = not determined/ specified); general specificity applies unless indicated otherwise by $_R$ = (R)-enantiomer preferred or $_S$ = (S)-enantiomer preferred					
		PaHNL (*R*)	apple meal (*R*)	LuHNL (*R*)	SbHNL (*S*)	HbHNL (*S*)	MeHNL (*S*)
aromatic aldehydes (contd.)		98 (88)[173] 93 (50)[182] 90 (35)[89]			89 (72)[173]		86 (84)[60]
		96 (51)[183]					
		97 (93)[177]					
		96 (60)[177]					
		30 (3)[72]	73 (6)[72]		0 (0)[173]		
		0 (0)[182]					
heteroaromatic aldehydes		99_S (96)[184] 99_S (88)[172]			80_R (80)[184] 0 (0)[180]	98_R (95)[175] 98_R (55)[176]	
		99_S (70)[171]					
		99 (96)[184]			87 (88)[184]	98 (98)[175] 99 (61)[176]	92 (98)[60]
		99_S (71)[184]			91_R (64)[184]	99_R (98)[175] 99_R (52)[176]	96_R (85)[60]
		99 (95)[184]			98 (95)[184]	99 (49)[176]	98 (98)[60]
						0 (0)[176]	
						0 (nd)[176]	
		82 (97)[2] 14 (89)[172]				0 (nd)[176]	
						0 (nd)[176]	
		0 (0)[94]				0 (0)[176]	
aliphatic aldehydes					0 (0)[180]		
				97 (87)[61]			91 (86)[60]
		83 (99)[185]		93 (100)[61]		81 (~80)[186]	95 (91)[60]
		92 (58)[89] 83 (84)[2] 73 (78)[172] 70 (73)[72]	90 (99)[72]	89 (100)[61]		67 (~80)[186]	94 (80)[60]
	R = HO	89 (84)[187]		73 (47)[61]			
	R = MeO	96 (100)[187]					
	R = EtO	73 (100)[187]					
	 R = BnO	61 (83)[187]					

Table 8 (Continued)

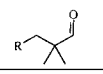
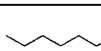
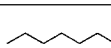
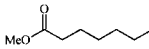
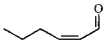
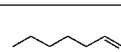
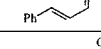
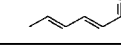
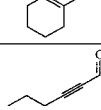
	substrate	*% ee of cyanohydrin (% conversion in brackets; isolated yields where underlined) (nd = not determined/ specified); general specificity applies unless indicated otherwise by $_R$ = (R)-enantiomer preferred or $_S$ = (S)-enantiomer preferred*					
		PaHNL (*R*)	**apple meal (*R*)**	**LuHNL (*R*)**	**SbHNL (*S*)**	**HbHNL (*S*)**	**MeHNL (*S*)**
aliphatic aldehydes (contd.)	 R = Br	89 (100)[187]					
	Cl	92 (100)[187]					
	AcO	61 (97)[187]					
		88 (81)[187]					
		98 (99)[2] 89 (100)[171] 97 (95)[72] 96 (75)[172]	99 (98)[72]	98 (91)[61]		80 (~80)[186]	88 (70)[56]
		94 (100)[185]		17 (10)[61]			
		98 (74)[179] 92 (60)[89]					
		92 (81)[188]					
		97 (100)[185]					91 (100)[60]
		91 (81)[188]					
		97 (72)[72] 67 (95)[182]	98 (71)[72]	7 (23)[61]		98 (97)[175]	
		92 (65)[89]					
		87 (98)[185]					
		96 (82)[189] 66 (33)[72]	92 (70)[72]			85 (~35)[186]	
		63 (94)[185]					
		97 (68)[89]					
		99 (90)[179] 96 (72)[89]				99 (95)[175]	92 (100)[60]
		55 (86)[182]				99 (87)[176]	
α,β-unsaturated aldehydes				74 (100)[61]		98 (92)[175] 94 (98)[190]	56 (70)[60] 47 (100)[60]
				98 (95)[61]			
		98 (99)[191] 97 (68)[172]		99 (21)[61]		86 (80)[190]	92 (100)[60]
		94 (90)[191]					
						95 (46)[190]	97 (82)[60]
						80 (35)[190]	
						99 (96)[175]	
		87 (54)[191] 0 (0)[182]		10 (20)[61]	0 (0)[142]	98 (93)[175] nd (<5)[190]	
		96 (36)[89]					
		99 (46)[89]					
		>99 (90)[191]					
						98 (62)[175] 80 (88)[190]	

Table 8 (Continued)

	substrate	*% ee of cyanohydrin (% conversion in brackets; isolated yields where underlined) (nd = not determined/ specified); general specificity applies unless indicated otherwise by $_R$ = (R)-enantiomer preferred or $_S$ = (S)-enantiomer preferred*					
		PaHNL (*R*)	**apple meal (*R*)**	**LuHNL (*R*)**	**SbHNL (*S*)**	**HbHNL (*S*)**	**MeHNL (*S*)**
composite aldehydes		88 (83)[89] 74 (88)[179]				99 (44)[176]	
		89 (33)[192]					
		22_S (27)[192]					
				10 (10)[61]		93 (88)[176]	
		90 (94)[2]					
		0 (83)[182]				0 (nd)[176]	
						12 (92)[175] 0 (nd)[176]	
methyl ketones		76 (80)[193]		95 (100)[61]			18 (91)[60]
				38 (56)[61]			
		90 (54)[193]				98 (99)[175]	
						83 (49)[175]	28 (81)[60]
		97 (70)[193] 95 (78)[194]		93 (100)[61]		74 (99)[175] 82 (30)[175]	69 (36)[60]
		94 (68)[193]					
		98 (57)[193] 98 (40)[194]				99 (86)[175]	91 (69)[60]
		84 (87)[193]		19 (54)[61]			
		98 (94)[194] 99 (73)[73]				99 (59)[175]	80 (58)[60]
		97 (80)[193]					
		98 (64)[193]					
		98 (88)[193] 98 (76)[73]					92 (39)[60]
		90 (14)[73]	93 (13)[73]			99 (40)[175]	78 (13)[60]
						89 (27)[175]	
		80 (2)[73]					
ethyl ketones		85 (33)[194]					
		90 (21)[194]					
		66 (7)[194]					
		76 (2)[194]					
		0 (0)[194]					
		20 (<1)[73]	20 (1)[73]				
other ketones		0 (67)[73]					
		85 (26)[195]					

Table 8 (Continued)

	substrate	% ee of cyanohydrin (% conversion in brackets; isolated yields where underlined) (nd = not determined/ specified); general specificity applies unless indicated otherwise by $_R$ = (*R*)-enantiomer preferred or $_S$ = (*S*)-enantiomer preferred					
		PaHNL (*R*)	apple meal (*R*)	LuHNL (*R*)	SbHNL (*S*)	HbHNL (*S*)	MeHNL (*S*)
other ketones (contd.)		nd$_S$ (1)[142]					
					0 (0)[180]		

D. Enzyme Methods: Preparation by HNLs

The enzymatic breakdown of cyanohydrins is reversible and under appropriate conditions, HNLs may catalyze the asymmetric condensation of hydrogen cyanide with aldehydes or ketones to furnish enantiomerically pure or enriched cyanohydrins, a procedure first adopted by Rosenthaler 90 years ago.[170] Whereas the natural substrates are simple cyanohydrins such as mandelonitrile and acetone cyanohydrin, HNLs also accept a range of useful and interesting unnatural substrates. The scope of the biotransformation method is largely a function of this adaptability. Table 8 is a comprehensive summary of substrates biotransformed by synthetically useful HNLs to date.

1. Substrate Specificities of HNLs

(a) The Enzyme from Almonds Dominates (*R*)-HNL Biotransformations. PaHNL (for enzyme abbreviations, see Table 1) is the most heavily researched of all the (*R*)-selective enzymes because it is easily obtained in large quantities by extraction from almonds. It accepts aromatic, heteroaromatic, saturated and unsaturated aldehydes and some ketones. The work of several research groups has clarified the broad substrate specificity and applicability. Prominent work by Effenberger[172,179,187,196] has included the partial biotransformation of simple ketones[193,194] (methyl ketones have also been resolved).[188] Kyler has estimated the active site dimensions via a systematic study of accepted substrates.[89] Brussee[171,182,191,197] and Kanerva[173,185] have made extensive use of a crude extract of almond flour as catalyst in probing substrate acceptance. In aliphatic aldehydes, a stereocenter α to the carbonyl center has been found to have little effect on the stereoselectivity of cyanohydrin formation,[72] whereas an aromatic substituent at this α position has a strong effect. Thus, (*R*)-stereochemistry at the α position may result in a small (*S*)-selectivity at the cyanohydrin center, inverting the normally observed selectivity.[192] Biotransformation of a racemic bicyclic ketone is both diastereo- and enantioselective.[195] In contrast to PaHNL, LuHNL—an alternative (*R*)-selective enzyme—has a lower availability and narrower substrate range.[51,61]

(b) (*S*)-HNLs Are Less Naturally Abundant. (*S*)-HNLs have until recently proven less synthetically applicable than PaHNL since none can be conveniently extracted from a natural source. SbHNL has a small substrate range, accepting aromatic aldehydes[8,174] but notably excluding aliphatic aldehydes: crude preparations of *Sorghum bicolor* shoots have been used as catalyst.[173,180,198] Griengl and coworkers have shown that HbHNL accepts a wide range[64,175] of aromatic, heteroaromatic, aliphatic,[176,186] and α,β-unsaturated[190] aldehydes and methyl ketones.[175] MeHNL also has a broad substrate range, accepting some ketones.[57,60]

2. The Availability of Enzymes Has Been a Limiting Factor in Their Use as Biocatalysts

Because PaHNL is so readily available and useful, few studies have been carried out on other (*R*)-HNLs. Brussee's method uses crushed, defatted almonds as an extremely cheap and convenient catalyst, requiring no immobilization.[171,182,191,197] Although purified enzyme may be required for some substrates,[187] in many cases almond meal is equally good.[185] Kanerva has extended this theme to crude meals of apples, apricots, cherries and plums, finding the former to increase the potential for sterically hindered aldehydes,[72] although it offers no improvement over almond meal for the preparation or resolution of methyl ketones.[73]

In contrast, the low availability of (*S*)-HNLs makes extraction or the use of crude preparations relatively impractical. It would take many fields of *Sorghum* to supply catalyst for one industrial-scale reaction.

The cloning and overexpression of (*S*)-HNLs is thus a significant development. The recombinant enzymes for MeHNL and HbHNL (Section III.C), together covering a large substrate range, now open up a practical biotransformation option for (*S*)-cyanohydrins.

3. Influence of Reaction Medium, Cyanide Source, and Other Factors

To maximize the enantiomeric excess of the cyanohydrin product, care must be taken to minimize the parallel chemical (nonenzymatic) condensation pathway and the racemization of products.

Simple aqueous or alcoholic solvents[182,197] allow significant chemical condensation, and ethanol is actually an inhibitor of the enzyme.[8] Better results are obtained with biphasic systems, such as ethyl acetate—aqueous buffer,[171,172,179] in which the organic solvent permits fast enzyme reaction but only slow chemical condensation. In addition, the product residence time in water is diminished, thus reducing the possibility of racemization. Other organic solvents have been used, including diethyl ether,[89] diisopropyl ether,[60,72,73,174,185,187,188,193,194,198] and methyl *tert*-butyl ether.[191] The enzyme is almost seven times more

Table 9. Some Methods for Enantiomeric Excess Determination of Cyanohydrins

method	derivative analyzed	literature examples
chiral HPLC	silylated derivatives	101, 206, 207
chiral GC	acetylated derivatives	164, 168, 185, 187, 190, 193
chiral GC	silylated derivatives	97
chiral GC	pentafluoropropionates of the reduced amino ethanols	180
HPLC	Mosher's esters	89, 102, 186
GC	Mosher's esters	96, 163, 172, 174, 193
GC	menthyl carbonates	130, 186
NMR	Mosher's esters[208]	160, 163, 188
NMR	menthyl carbonates	96
NMR	cyhalothrin esters	125, 131
NMR	cyclic phosphorus amidates	130
NMR	free cyanohydrins with $Eu(hfc)_3$	182, 197
NMR	free cyanohydrins with *tert*-butyl-phenylphosphinothioic acid as chiral solvating agent	195

active in diisopropyl ether than in ethyl acetate, and the chemical reaction plays a proportionately smaller role in the former solvent.[185] Replacing ethyl acetate with methyl *tert*-butyl ether can dramatically increase the PaHNL-catalyzed hydrocyanation of cinnamaldehyde from less than 5% to 54% conversion (87% enantiomeric excess).[191] In the absence of moisture, no catalytic activity is observed, but in the presence of excess water, the chemical condensation reaction may become significant. An optimum aqueous (pH 3.25) content is 17.5% (v/v) with respect to diisopropyl ether in the hydrocyanation of benzaldehyde with acetone cyanohydrin using *Sorghum bicolor* shoots.[198] The buffer in the biphasic systems may be at the pH optimum of the enzyme (5.5 for PaHNL) or lower.

Exclusively aqueous systems consisting of an acidic buffer represent an alternative method of suppressing the chemical condensation,[176,186,190,194,199] but this factor must be balanced against the reduced activity and stability of the enzyme at lower pH.[200,201]

Several cyanide sources have been used in biotransformations. In low pH exclusively aqueous systems, potassium cyanide is an effective reagent.[176,186,190,199] Potassium cyanide and acetic acid have been used with organic systems,[182,197] but hydrogen cyanide itself has been used in preference.[60,171,172,174,179,187,191,193,194] Rather than the separate preparation of hydrogen cyanide,[202] an organic solution may be prepared by extraction from an acidified aqueous solution of cyanide.[171]

Acetone cyanohydrin is a relatively safe and convenient source of a constant low concentration of hydrogen cyanide so that the chemical side reaction is minimized.[89,185,192,198] Simple addition of acetone cyanohydrin to the reaction flask is effective if the enzyme can catalyze its breakdown (for example, PaHNL). However, if the enzyme does not accept acetone cyanohydrin as substrate (for example, SbHNL), the reaction time is very long unless large amounts of water are present, in which case the enantiomeric excess of the product may suffer. To circumvent this problem, Kanerva has developed a method whereby hydrogen cyanide diffuses into the reaction mixture from a second flask where it may be made from acetone cyanohydrin and sodium hydroxide.[72,73,173] This method may also give improved results with PaHNL.

For optimum results in the resolution of racemic cyanohydrins by HNLs, the hydrogen cyanide released may be trapped with a second aldehyde that is reactive and able to form a relatively stable cyanohydrin. Acetaldehyde fulfills these requirements and also has the advantage that the corresponding cyanohydrin may be removed by washing with water.[73]

A small number of lyases have found application in commercial processes.[203] The use of PaHNL is one of these: Solvay Duphar (Weesp, The Netherlands) prepare (*R*)-cyanohydrins on a multi-kilogram scale using a two-phase continuous process. With recycling of the aqueous enzyme broth, the overall amount of enzyme required can be reduced to 0.04% (w/w) relative to benzaldehyde.[201] This industrial process uses hydrogen cyanide and purified enzyme.

E. Practical Considerations

The enantiomeric purity of cyanohydrins has been determined by several methods, and some examples are summarized in Table 9. Protection of cyanohydrins (Section V.A.1) improves their thermodynamic and configurational stability, and the protected derivatives may be easier to purify and analyze.

The hydrocyanation process is difficult to monitor. Aliquots cannot be quenched by common methods without disturbing the species present. In particular, this may be a problem where reactions are carried out below room temperature due to the possibility of reaction taking place between aliquot removal and its analysis. Most literature procedures have not incorporated quantitative monitoring. NMR methods may however permit simultaneous measurement of all species present.[204] Standard TLC visualization methods (such as potassium permanganate dip) are suitable for the detection of cyanohydrins. A new TLC method specific for cyanohydrins and derivatives such as pyrethroids has recently been developed.[205]

V. Applications of Cyanohydrins

Direct derivatives of the enantiomerically pure cyanohydrin functionality may themselves be synthetic targets, for example, the insecticide fenvalerate A_α (Figure 20). More commonly, however, cyanohydrins are subjected to further transformations to provide a wide variety of useful functionalized units.

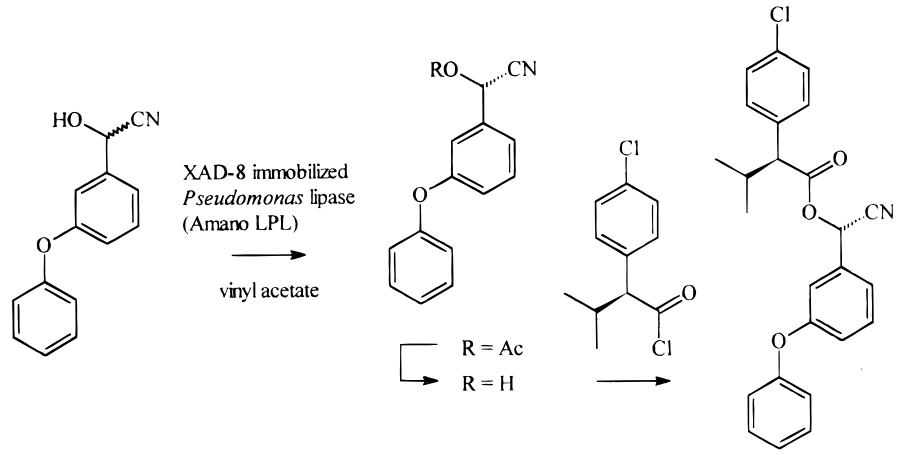


Figure 20. Lipase-catalyzed resolution and O-derivatization of 3-phenoxymandelonitrile furnishes the cyanohydrin derivative fenvalerate A_α.

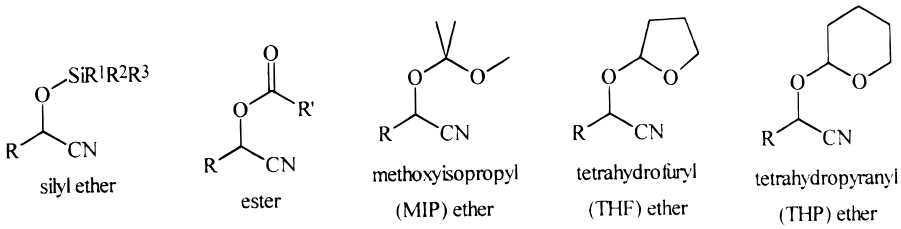


Figure 21. Several groups are commonly used to protect cyanohydrins.

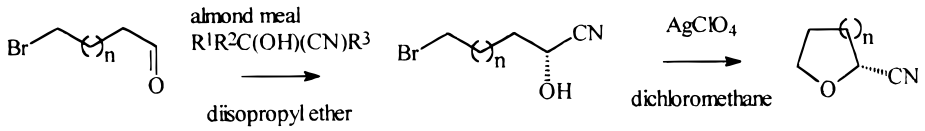


Figure 22. Asymmetric hydrocyanation of γ- or δ-bromoaldehydes provides compounds that may undergo intramolecular cyclization with silver perchlorate (n = 1 or 2).[188]

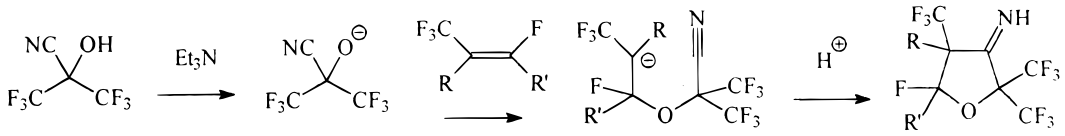


Figure 23. The formation of fluorinated 3-iminotetrahydrofurans from fluorinated olefins and cyanohydrins may proceed via nucleophilic addition of alkoxide to olefin followed by intramolecular cyclization onto the nitrile.[209]

Both the alcohol and the nitrile parts of the cyanohydrin functionality can undergo transformation to a range of groups. Unless indicated otherwise, these are general methods that proceed via racemization-free processes so that the optical activity is maintained. A third possibility is reaction at the carbon center.

A. Reactions of the Alcohol Group

The alcohol part of the cyanohydrin moiety has the capacity to act as a nucleophile or undergo nucleophilic displacement.

1. Hydroxyl Group Can Act as a Nucleophile in O-Protection or Other Reactions

This category is dominated by the use of protecting groups to escape the problems of instability, degradation, racemization, and side reactions that may be associated with unprotected cyanohydrins. Several groups are useful and compatible with attachment under acidic or neutral conditions. Trialkylsilyl chlorides and imidazole are used to give silyl ethers;[182] acid chlorides or anhydrides and pyridine produce cyanohydrin esters (though racemization may occur in some cases such as with cinnamaldehyde cyanohydrins);[176] vinyl ethers and acid catalysts furnish acetals (Figure 21).

The nucleophilicity of the alcohol group is utilized in a chemoenzymatic synthesis of (*R*)-2-cyanotetrahydrofuran and -pyran, common structural components of terpenoids, pheromones, antibiotics, *C*-glycosides, and other biologically active natural products (Figure 22).[188] An unusual reaction occurs between fluorinated cyanohydrins and olefins (Figure 23).[209]

2. Nucleophilic Displacement Yields Functionalized Nitriles

Conversion of the hydroxyl group to a good leaving group allows nucleophilic displacement with inversion of configuration. While α-halonitriles readily

Table 10. α-Sulfonyloxynitriles Undergo S_N2 Reaction with a Variety of Reagents

reagent	*product*	*references and comments*
potassium acetate	**α-acetoxy nitrile** 	211,212
potassium phthalimide	***N*-phthaloyl-protected α-amino nitrile** 	211
potassium azide	**α-azido nitrile** 	may be reduced to **α-amino nitrile** or **α,β-diamine.** 211,213
potassium fluoride	**α-fluoro nitrile** 	210
$LiAlH_4$ to produce internal nucleophile	**aziridine** 	211,214

racemize in the presence of halide ions liberated in substitution reactions, α-sulfonyloxynitriles are most suitable for these reactions since the sulfonate leaving group is less nucleophilic. Stereoselective exchange occurs with a range of nucleophiles (Table 10).

Aromatic systems are however less configurationally stable than aliphatic systems in these reactions due to a greater capacity for cation stabilization so that reactions no longer follow an exclusively S_N2 pathway. Fortunately, the displacement of sulfonate with acetate—which successfully inverts the configuration of aliphatic systems—is complemented by the Mitsunobu reaction, which inverts the configuration of aromatic[169,207] and allylic[191] cyanohydrins but retains the configuration of aliphatic systems.

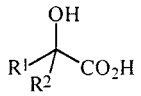
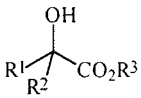
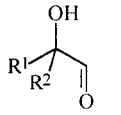
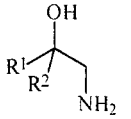
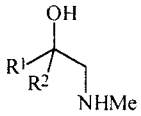
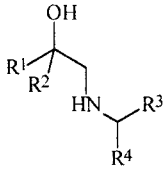
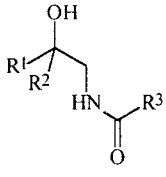
α-Fluoro acids find applicability in the synthesis of biologically active compounds, and β-fluoroamines are used in liquid crystals. While it is possible to prepare some fluoronitriles directly from the free or TMS-protected cyanohydrins,[210] the reaction via the sulfonate is milder.

B. Reactions of the Nitrile Group

1. Some Transformations Are Applicable to the Nitrile Group of Unprotected Cyanohydrins

O-Protection is not necessary for several transformations of the nitrile group including hydrolysis, solvolysis, and reduction (Table 11). On the hydroly-

Table 11. General Reactions of the Nitrile Group of O-Unprotected Cyanohydrins

transformation(s)	*reagent(s)*	*product*	*references and comments*
hydrolysis to **α-hydroxy acid**	HCl		126,179,187; performed also on ketone cyanohydrins.[193,194]
solvolysis to **α-hydroxy ester**	alcoholic HCl		126; performed also on α,β-unsaturated systems to give highly functionalized units.[191]
hydrogenation to **α-hydroxy aldehyde**	H_2, Ni		215
reduction to **β-amino alcohol**	$LiAlH_4$ or BH_3		126,179,216
reduction; reductive *N*-methylation to ***N*-methyl-β-amino alcohol**	i) $LiAlH_4$; ii) acetic formic anhydride; iii) $LiAlH_4$		183
reduction; reductive *N*-alkylation to ***N*-alkyl-β-amino alcohol**	i) $LiAlH_4$; ii) R_3R_4CO; iii) $NaBH_4$		183
reduction; *N*-acylation to **β-hydroxy amide**	i) $LiAlH_4$; ii) RCOCl		136,217

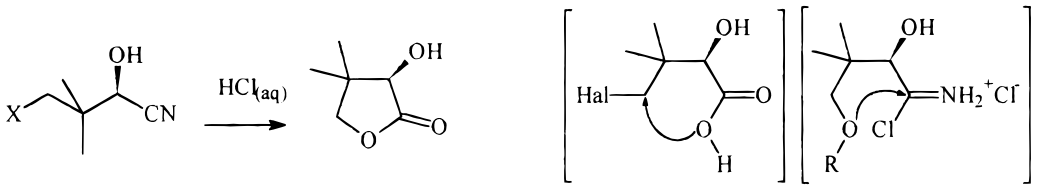


Figure 24. Hydrolysis of β-substituted pivalaldehyde (*R*)-cyanohydrins followed by in situ cyclization—by one of two mechanisms, depending on the substituent—gives (*R*)-pantolactone.

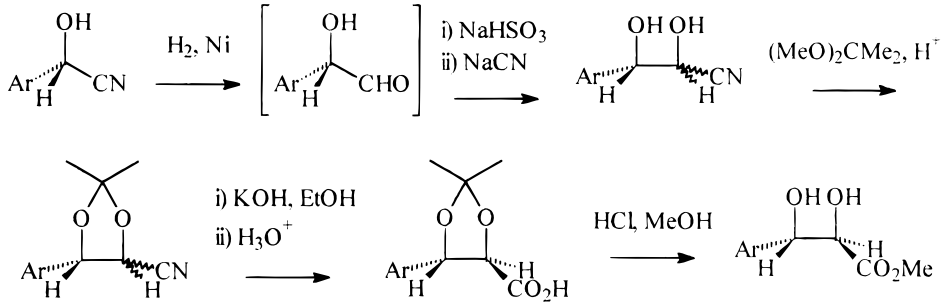


Figure 25. Epimerization at the C-2 center of a derivative of an optically pure acyloin provides *threo*-3-aryl-2,3-dihydroxypropanoic acid units, important intermediates for the preparation of diltiazem and its analogues.

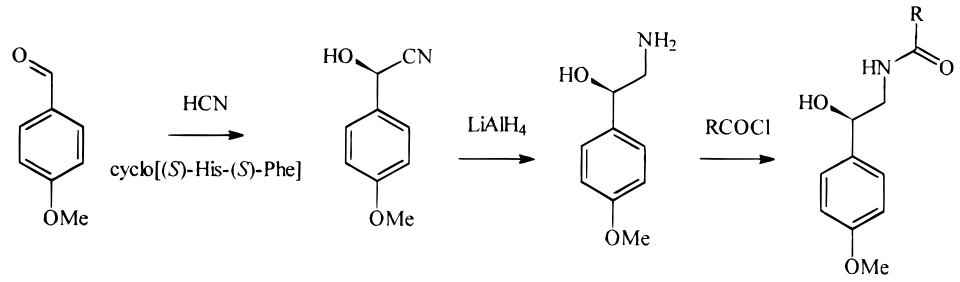


Figure 26. Optically pure (−)-tembamide (R = Ph) and (−)-aegeline (R = Ph-CH=CH) may be prepared from *p*-anisaldehyde in 70% yield.

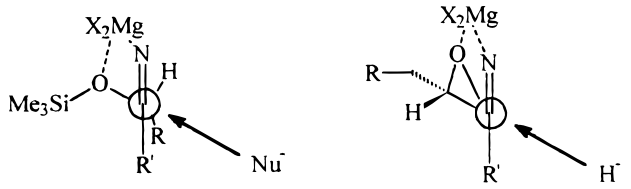


Figure 27. Diastereoselectivity of reduction or hydrocyanation of *N*-metalloimines may be controlled by the α-oxygen of the old cyanohydrin center: an epoxide has a similar stereocontrolling effect.

sis of β-substituted pivalaldehyde (*R*)-cyanohydrins, the corresponding α-hydroxy acids may undergo cyclization to (*R*)-pantolactone (Figure 24), which has applicability as a chiral building block, in chiral auxiliaries, and as a precursor for (*R*)-pantothenic acid (a constituent of coenzyme A), (*R*)-panthenol (a bactericide), and (*R*)-pantotheine (a growth factor).[187] Hydrogenation of mandelonitrile and further elaboration provides a precursor of the cardiac drug diltiazem (Figure 25).[215]

The naturally occurring hydroxy amides (−)-tembamide and (−)-aegeline have adrenaline-like and insecticidal activity. The former is a component of a traditional Indian medicine and shows hypoglycaemic activity. They can be obtained by reduction and *N*-acylation of an (*R*)-cyanohydrin (Figure 26).[136,217]

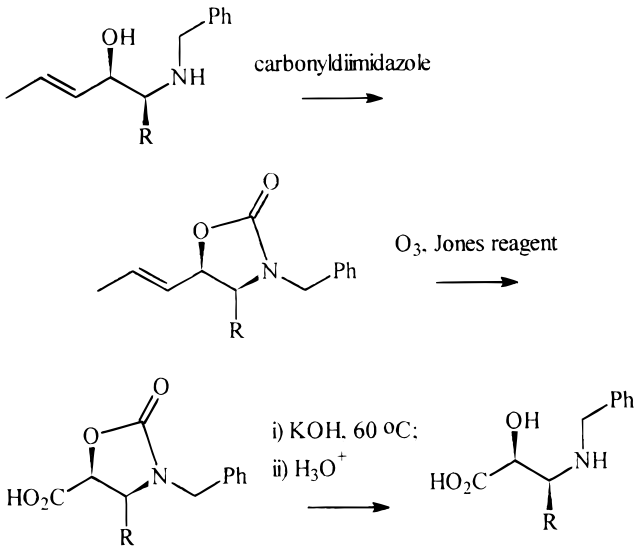
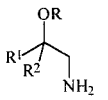
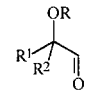
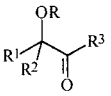
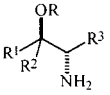
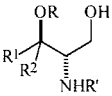
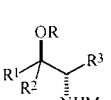
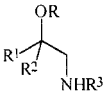
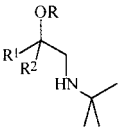
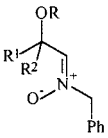
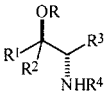
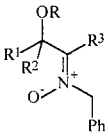
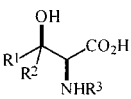
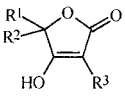


Figure 28. Further transformation of α,β-unsaturated systems provides *N*-benzyl-α-hydroxy-β-amino acids (R = H or Me).

2. O-Protected Cyanohydrins Are Tolerant of a Wider Range of Nitrile Transformations

O-Protection permits a wider range of reactions on the nitrile group and more extensive transformation (Table 12). Silyl protecting groups and mixed acetals,

Table 12. General Reactions of the Nitrile Group of O-Protected Cyanohydrins

transformation(s)	*reagent(s)*	*product*	*references and comments*
Reduction to **β-amino alcohol**	$LiAlH_4$ or BH_3		216,218
Reduction to imine; hydrolysis to **α-hydroxy aldehyde (acyloin)**	i) DIBAL; ii) H_2SO_4		with α,β-unsaturation, the double bond may migrate.[219]
Grignard; hydrolysis to **α-hydroxy ketone**	i) Grignard; ii) H_3O^+		218
Grignard; diastereoselective reduction to **α-substituted-α-amino-β-alcohol**	i) Grignard; ii) $NaBH_4$		218
Vinyl Grignard; diastereoselective reduction; *N*-protection; ozonolysis to **2-amino-1,3-diol**	i) vinyl Grignard; ii) $NaBH_4$; iii) $(BOC)_2O$; iv) O_3/MeOH; v) $NaBH_4$		components of sphingosines, dihydrosphingosines, and chloramphenicols.[178]
Grignard; diastereoselective reduction; reductive methylation to ***N*-methylated-α-substituted-α-amino-β-alcohol**	i) Grignard; ii) $NaBH_4$; iii) acetic formic anhydride; iv) $LiAlH_4$		[183]; thienyl and furyl variations of ephedrine are of pharmacological interest as possible vasodilators and bronchodilators.[184]
Reduction; transimination; reduction to ***N*-substituted-β-amino alcohol**	i) DIBAL; ii) amine; iii) $NaBH_4$		useful for (*R*)-halostachine,[206] the cardiac drug (-)-denopamine,[220] the bronchodilator salbutamol,[136] and their analogues.
Ritter reaction; reduction to ***N*-substituted-β-amino alcohol**	i) *tert*-BuOH, H_2SO_4, HOAc; ii) $LiAlH_4$		alternative to transimination, effective for the bronchodilator (*R*)-terbutaline and an (*R*)-salbutamol derivative.[177]
Reduction; transimination with *N*-benzylhydroxylamine to **α-hydroxy-aldonitrone**	i) DIBAL; ii) N-benzylhydroxylamine		1,3-dipolar cycloadditions of chiral nitrones under investigation.[221]
Grignard; transimination; diastereoselective reduction to ***N*-substituted-α-substituted-α-amino-β-alcohol**	i) Grignard; ii) amine; iii) $NaBH_4$		222,223
Grignard; transimination with *N*-benzylhydroxylamine to **α-hydroxy-ketonitrone**	i) Grignard; ii) N-benzylhydroxylamine		1,3-dipolar cycloadditions of chiral nitrones under investigation.[221]
Reduction; transimination; diastereoselective hydrocyanation; protection; hydrolysis to ***N*-substituted-β-hydroxy-α-amino acid**	i) DIBAL; ii) amine; iii) HCN; iv) carbonyldiimidazole; v) alkali; vi) acid		structural component of natural products and precursors for β-lactams.[224]
Blaise reaction and acid treatment to induce deprotection and lactonization to **tetronic acid**	i) Reformatsky reagents $BrZnCHR^3CO_2R^4$; ii) H_3O^+		[225,226]; β-amino-γ-hydroxy esters and β-amino-γ-butyrolactones are also available by this method.[227]

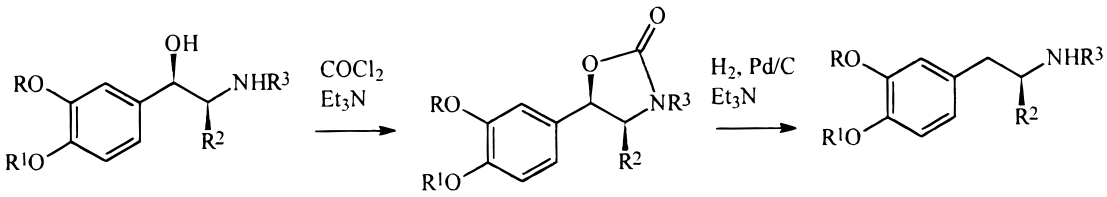


Figure 29. Derivatives of (*R*)-cyanohydrins, via a novel reduction method, provide (*S*)-amphetamines in the Ecstasy family.

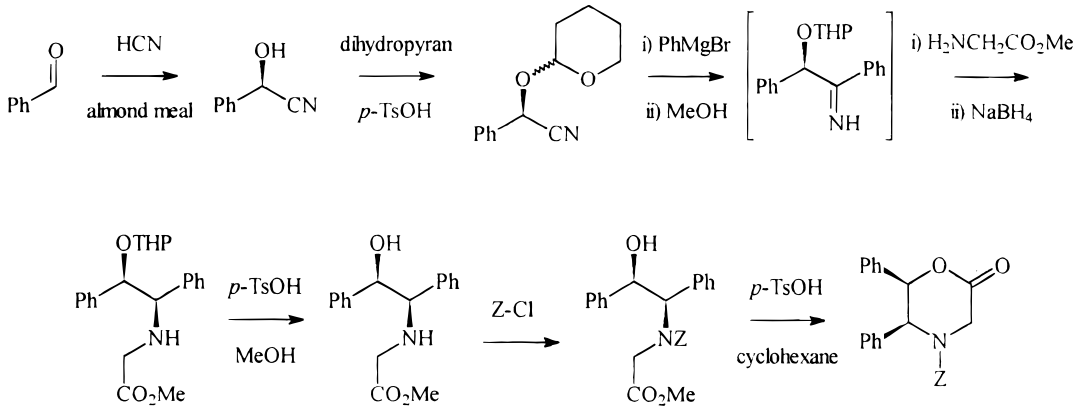


Figure 30. The Williams glycine template may be prepared in enantiomerically pure form from benzaldehyde in 48% overall yield.

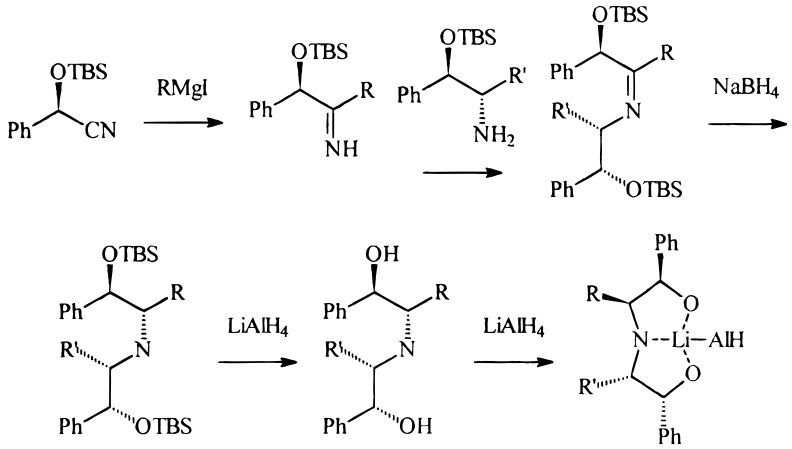


Figure 31. A chiral auxiliary for stereoselective reduction may be prepared from mandelonitrile derivatives.

in particular 2-methoxyisopropyl (MIP) and tetrahydropyranyl (THP), are especially useful since they can be introduced and removed under mild conditions, in some cases concomitant with a nitrile transformation step.

The transformation may introduce a new chiral center under diastereoselective control (Figure 27). The preferential formation of *erythro*-β-amino alcohols may be explained by preferential hydride attack on the less hindered face of the intermediate imine,[218] and hydrocyanation of the imine would also appear to proceed via the same type of transition state. Outside the cyanohydrin field, it is interesting to note that a chiral α,β-epoxy group may act as a stereocontrolling element in an analogous reduction of *N*-metalloimines in the same way.[228]

In the case of α,β-unsaturated systems, reduction−transimination−reduction or Grignard−transimination−reduction sequences may be followed by protection of the β-amino alcohol to an oxazolidinone, ozonolysis with oxidative workup, and alkali hydrolysis to give α-hydroxy-β-amino acids (Figure 28).[229] Such units are particularly abundant in biologically active compounds. Alternatively, *N*-acylation may be carried out after oxazolidinone protection, in which case the final products are α-hydroxy-β-amido acids.

Oxazolidinone protection of β-amino aryl alcohols also allows mild hydrogenation of the benzylic hydroxyl group to give a range of psychoactive amphetamines (Figure 29) that may prove to be medically useful.[230]

The Williams glycine template enables the synthesis of unnatural amino acids through diastereoselective alkylation α to its carbonyl functionality. The Grignard−transimination−reduction sequence has been used to prepare the template (Figure 30).[222]

The Grignard−reduction and Grignard−transimination−reduction sequences have been neatly combined to prepare aluminum hydride reagents from chiral diethanolamines for the stereoselective reduction of prochiral ketones (Figure 31).[231]

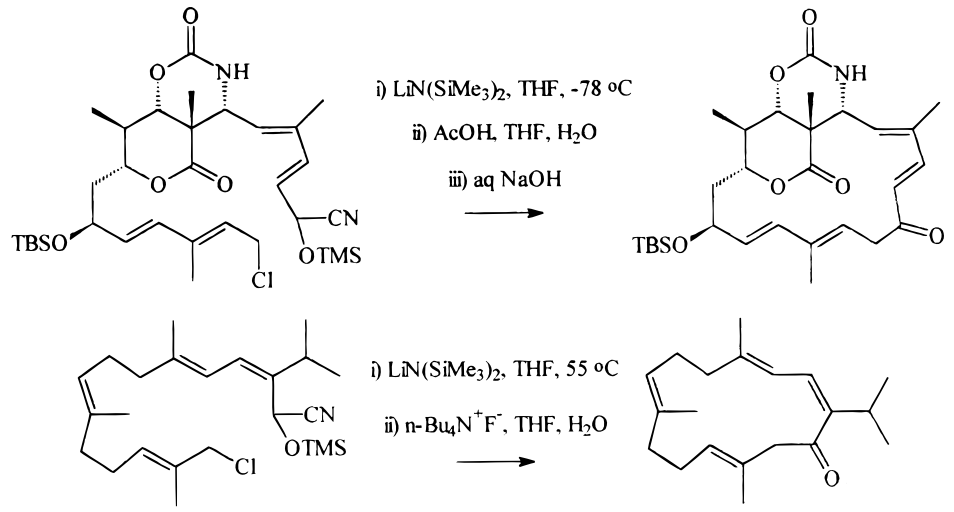


Figure 32. Stork-Takahashi macrocyclizations are key steps in syntheses of the antitumor antibiotic Lankacidin C[245] and the anticarcinogenic marine cembranoid Sarcophytotol A,[246] respectively.

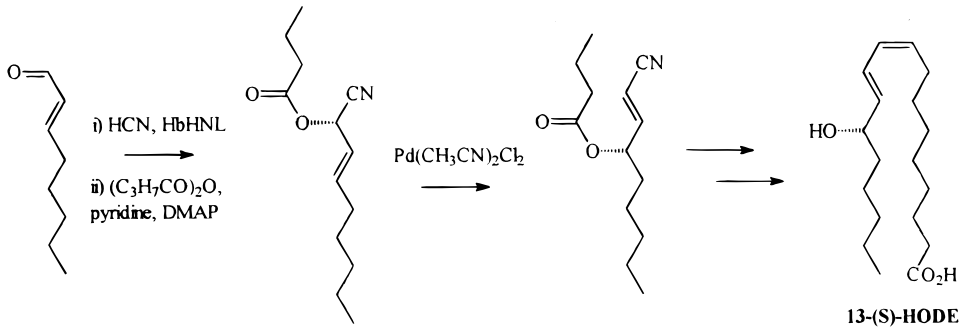


Figure 33. Asymmetric hydrocyanation of (*E*)-2-octenal followed by palladium-catalyzed rearrangement provides a precursor to synthesize 13-(*S*)-HODE in an overall yield of 11% and 99% ee.[248]

C. Reactions at the Carbon Center

The umpolung reactivity of protected cyanohydrins is mentioned briefly for completeness, although it involves the scrambling of the chiral center. Cyanohydrins are often used as acyl anion equivalents,[13,232−235] and the regioselectivity of coupling depends on the nature of secondary functionality in the umpolung reagent and electrophile.[236−241] Stork-Takahashi methodology permits macrocyclization even within highly functionalized systems (Figure 32). The alkylation of cyanohydrin 1,3-acetonides allows the construction of alternating polyol chains.[242−244]

D. Transfer of Chirality from the Cyanohydrin Center

The previous sections review the many reactions available to transform the primary functionality of cyanohydrins. Yet more scope exists to use the chiral center produced by asymmetric hydrocyanation to influence reaction on an unsaturation or other secondary functionality.[64,142] For example, α,β-unsaturated cyanohydrin esters react with transfer of chirality to γ-cyanoallylic alcohols;[106,247] this methodology has been applied to a chemoenzymatic synthesis of (*S*)-13-hydroxyoctadeca-(9*Z*,11*E*)-dienoic acid [13-(*S*)-HODE], a prostacyclin mimic that has biological activity against rice blast disease (Figure 33).[248]

VI. Conclusion

Several excellent methods are available for the preparation of enantiomerically enriched cyanohydrins. The availability of recombinant HNLs should further promote the enzyme-catalyzed method in this area of organic synthesis. Biotechnological advances may also enable other applications of HNLs on a larger scale, such as food processing. In parallel, the continuing botanical, sequence homology, and enzyme mechanism work will increase our understanding of the origins of the biological process of cyanogenesis. The link between HNL catalysis and cyclic dipeptide catalysis are becoming clearer, and the latter, a fascinating mechanistic area in its own right, may reveal itself to be useful as a model for both peptide catalysis and, more broadly, biomimetic catalysis. There is an ever-increasing need for enantiomerically pure units, and a wide variety of transformations now enable cyanohydrins to offer many viable and effective routes in organic synthesis.

VII. Acknowledgments

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