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BASF's ChiPros® chiral building blocks

The cornerstones of your API syntheses!

INTRODUCTION

Although chirality in naturally occurring molecules is as old as life, it took a long time to recognize that one enantiomer in pharmaceutically active compounds is usually superior to its antipode regarding biological activity and/or toxicity (1). Cases of severe side-effects in the early 1960s caused by the "wrong" enantiomers in racemic mixtures of active pharmaceutical ingredients (APIs) spurred the breakthrough in using and manufacturing enantiomerically pure APIs. An important factor for shifting from racemic mixtures of APIs to single-enantiomeric actives was the publication of FDA guidelines (2) which encourage the development of chirally pure drugs.

In addition to new chemical entities which were originally launched as single enantiomers, active life-cycle management has led in several cases to the re-launch of the pharmaceutically active enantiomer of an originally racemic mixture, the so-called *racemic* or *chiral switch*.

About 40 percent of existing pharma compounds are chiral molecules. Of the drugs (excluding biologics) newly launched from 2000 to 2004, 56 percent were single enantiomeric (3). Similar data have been published for molecules in development in 2006 at AstraZeneca, Pfizer and GSK (4). In most of the cases, the process chemists bought chiral starting materials rather than generating the stereocenters themselves. Specialized suppliers, such as BASF under its ChiPros® label, offer such chiral building blocks based on market needs and customer requests.

As a consequence, enantiomerically pure intermediates presently constitute an important market: In 2006, CPA published their evaluation of the 2005 global market (5) attributing sales of €5.8-6.5bn to advanced intermediates. In this article, we are going to present an overview of the most important chemical classes of chirally pure building blocks (synthons) for APIs and the different synthetic ways for manufacturing them.

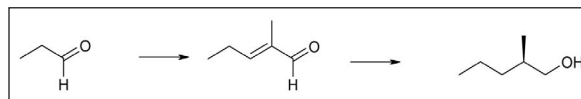
CHIRAL ALIPHATIC AND CYCLOALIPHATIC ALCOHOLS

Chiral aliphatic and cycloaliphatic alcohols form a versatile class of chiral synthons, since they can be incorporated into the API structures directly as esters or ethers.

They can be starting materials for the formation of amines, amides, thiols, thioethers. In addition, after transforming the hydroxyl function into a leaving group by way of mesylation,

tosylation or triflation, they can be used to form new C-C bonds, e.g. through reaction with organometallic reagents such as Zn-catalyzed Grignard reaction (6), ethynylation, reaction with cyanides etc.

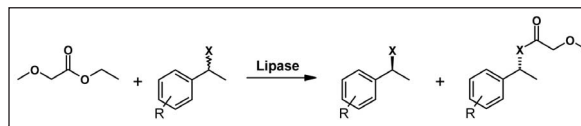
Many manufacturing routes make use of asymmetric hydrogenation methods (7). As an example, the products of aldol condensations are often suitable starting materials for the desired alcohols:



Scheme 1. Synthesis of (R)-2-methylpentanol

Other starting materials may stem from other condensation or annulation reactions. Secondary ketones can also be hydrogenated at high enantiomeric excesses (see following section) (8).

The two most important biocatalytical processes for the formation of chiral alcohols apply lipases and dehydrogenases, respectively (9). The latter offer the advantage that starting from a prochiral precursor ketone, only the requested enantiomer is obtained. Switching to the antipodal stereoisomer, however, means that an alternative enzyme must be found. Enzyme-catalyzed acylations using lipases, on the other hand, achieve the resolution of racemic mixtures of alcohols but with an inherent 50 percent maximum yield of the total amount of starting material.

Scheme 2. X = OH, NH₂. R = F, Cl, Br, Me, OCH₃, (OCH₃)₂, CF₃, (OCF₃)₂, ...

One enantiomer of the racemic mixture remains unchanged whilst the antipodal enantiomer is esterified and is separated from the alcohol during work-up.

Using vinyl esters as acylating agents makes the formation of the ester (or, more precisely: the transesterification) an irreversible process, as the vinyl alcohol released during the reaction rapidly tautomerizes into acetaldehyde.

Thanks to a variety of commercial and proprietary enzymes at its disposal, BASF offers a wide range of aliphatic and cycloaliphatic single-enantiomer alcohols under the ChiPros® brand.

Some of them are shown in Figure 1.

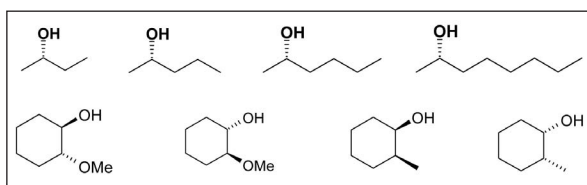


Figure 1. Single-enantiomer aliphatic and cyclo-aliphatic alcohols

CHIRAL ARYL-SUBSTITUTED ALCOHOLS

Chiral aryl-substituted alkanols are accessible either by chemocatalytic routes and/or enzymatic processes. The selection of the best process usually depends on availability of substrates, catalysts or enzymes, completeness of reaction, achievable optical purity, ease of work-up and scale-up capability. Due to the variety of technologies available, BASF can always choose the best route: Whilst (R)- and (S)-1-(1-naphthyl)ethanol (**1** and **2**, resp.; see Figure 2) are made by the chemocatalytic route, both enantiomers of 1-phenylethanol (**3** and **4**) are produced enzymatically (lipase-catalyzed resolution of the mixture of racemic alcohols). For the thiophen derivative **5**, reducing the precursor ketone with dehydrogenase is most favourable.

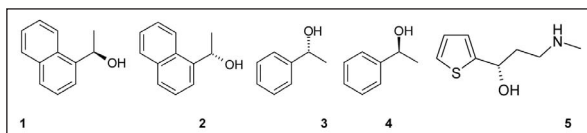


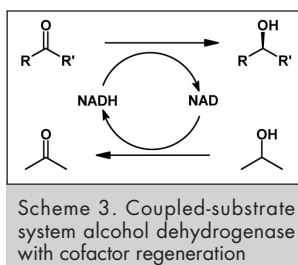
Figure 2. Chiral aryl-substituted alcohols

The general pathway for dehydrogenase-catalyzed reduction is as described in Scheme 3.

Since all naturally occurring reduced cofactors (complex hydrides) are prohibitively expensive when used in stoichiometric quantities, NADH (in this case; NAD(P)H, FAD and FMN are other examples of cofactors) is used in only catalytic amounts. The oxidized cofactor is regenerated in a redox reaction by oxidizing a hydrogen donor. The regeneration can be done either in a coupled-enzyme system (formate dehydrogenase and glucose dehydrogenase are widely used) or in a substrate coupled system where a single enzyme reduces the product substrate and in parallel oxidizes the auxiliary substrate while recycling the cofactor. A cheap alcohol of low molecular weight can often be used as auxiliary alcohol. Removing the resulting volatile ketone from the reaction mixture shifts the equilibrium to the product side (10). This is not necessary when GDH or FDH is used for cofactor regeneration.

Since choosing the best suited catalyst still relies more on empiric selection processes than theoretical predictions, we have established testing facilities which allow the rapid and efficient screening of a huge range of chemical catalysts (11).

This enabled us to find synthetic routes to both enantiomers of 1-[3,5-bis(trifluoromethyl)phenyl]ethanol **6** and **7**, (S)-1-(3-nitrophenyl)propan-1-ol (**8**) and other alcohols:



Scheme 3. Coupled-substrate system alcohol dehydrogenase with cofactor regeneration

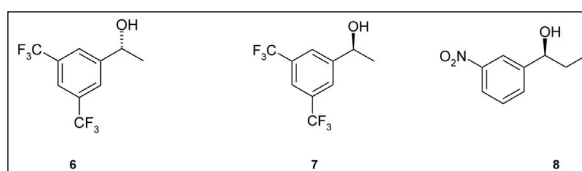
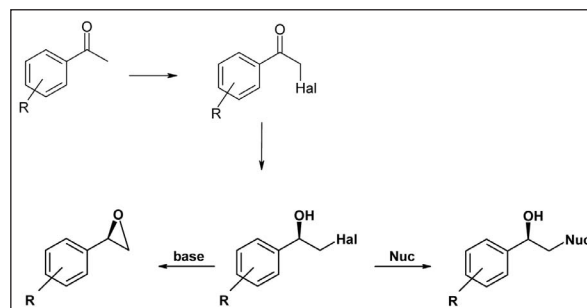


Figure 3. Chiral aryl-substituted alkanols

CHIRAL OXIRANES

There are several alternative routes towards chiral aryl-substituted oxiranes, among them Jacobsen's asymmetric epoxidation (12) or his hydrolytic kinetic resolution (HKR) (13) method, Sharpless's asymmetric epoxidation (14) using *tert*-butylhydroxy-peroxide and catalytic titan(IV)-isopropylate/diethyl tartrate complexes, complemented by Shi's reaction (15) using peroxomonosulfate with a chiral ketone as catalyst, or among the enzymatic methods, application of epoxide hydrolases, lipases or monooxygenases (for a review of these methods, see Lit. (9)). These methods are often limited in their substrate scope, require expensive catalysts, may require cryogenic reaction conditions, reach only moderate optical purities (15ii), or even pose safety and/or corrosion hazards due to the use of peroxides and hypochlorites. When carbonyl compounds are used as starting materials, keeping the competing Baeyer-Villiger oxidation at bay may be an issue (15ii). It is always necessary to compare the chemical and cost efficiency of alternative synthetic routes. In some cases, chiral intermediates may be accessible via chemical catalytic processes but this may not be the optimum way. To cite just one example, R. Noyori et al. (16) reported a synthesis of substituted, optically active styrene oxides via asymmetric reduction using chiral rhodium catalysts but at a low S/C ratio of 1,000 to 5,000. We found that stereoselective reduction of alpha-chlorinated acetophenones using dehydrogenases affords a very versatile and more cost-efficient access to a wide range of oxiranes, including both enantiomers of styrene oxide as well as very differently substituted phenyl oxiranes and their chlorohydrins (chloro-ethanols):



Scheme 4. Stereoselective synthesis of oxiranes and chlorohydrins

Examples:

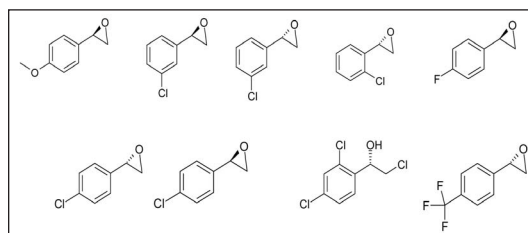


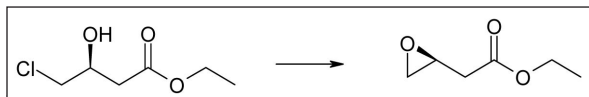
Figure 4. Chiral oxiranes and chlorohydrins

Oxiranes and chlorohydrins are very valuable building blocks which allow derivatization:

- by forming carbon-hetero atom bonds (through reactions with alcohols, ammonia, amines, phenolates and so forth)
- or by forming new carbon-carbon bonds (through reactions with cyanide, malonates, allyl silyl reagents, metal-organic reagents, e.g. Mg, Zn, Li organyls).

CHIRAL α - AND β -HYDROXY ACIDS, ESTERS AND AMIDES

Enantiopure α - and β -hydroxy acids and esters are versatile building blocks for the preparation of a wide range of active pharmaceutical ingredients by incorporating them as esters, amides or ethers or after further derivatization, as diols, amino alcohols, thioethers. 4-Chloro-3-hydroxy butanoic acid esters can be converted into oxirane butanoates which can be further derivatized:



Scheme 5. Synthesis of ethyl (S)-3,4-epoxybutanoate

Hydroxy acids are accessible via a range of biotransformations, among them are the stereoselective hydrolysis of the racemic ester precursor or reduction of the corresponding keto esters. Hydroxynitrile lyase (HNL) processes catalyze the stereoselective addition of HCN to aldehydes and ketones yielding single-enantiomeric *nitriles* (9). Application of nitrilases (or a combination of nitrile-hydratase plus amidase) allows the transformation of the starting material into the desired enantiomer of the corresponding *acid* in a dynamic kinetic resolution because the racemization of the intermediate cyanohydrin occurs faster than the enzymatic hydrolysis. This biotransformation yields mandelic acid as well as substituted mandelic acids, e.g.:

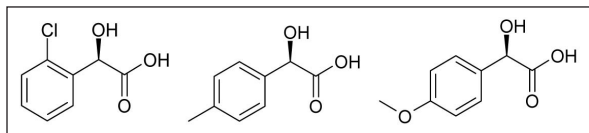


Figure 5. Substituted (R) mandelic acids

BASF developed proprietary processes based on dehydrogenases to offer access to a wide range of α - and β -hydroxy esters, starting from readily available keto esters. Due to the large range of enzymes available, both enantiomers can normally be made. Another established technology is the enzymatic resolution using lipases which only acylate one enantiomer. The acylated stereoisomer can easily be separated from its alcohol antipode. If feasible, the unwanted enantiomer may be racemized with a racemase so that the substrate can be completely transformed into the desired product (17). Examples from the ChiPros range are shown in Figure 6.

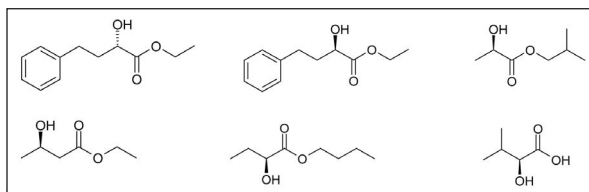
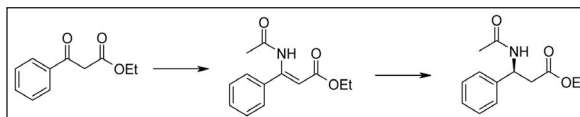


Figure 6. Chiral α - and β -hydroxy acids and esters

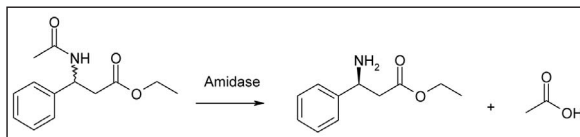
CHIRAL α - AND β -AMINO ACIDS, AMIDES AND ESTERS

Application of amidases and/or asymmetric hydrogenation offer a catalytic route to optically pure amino acids. Readily accessible β -keto esters are converted into the N-acylated enamines and then submitted to asymmetric hydrogenation. Deprotection is achieved with a suitable amidase which not only allows the selective hydrolysis of the acetamide under

mild conditions but also increases the optical purity of the resulting single-enantiomer β -amino acid ester:



Scheme 6. Asymmetric hydrogenation of N-acylated enamines



Scheme 7. Stereoselective hydrolysis of racemic or enantiomerically enriched N-acyl amino acids

Using purely biocatalytic processes or combinations of chemical catalysis and enzymatic biotransformations, molecules such as **9** and **10** are available on lab to commercial scale.

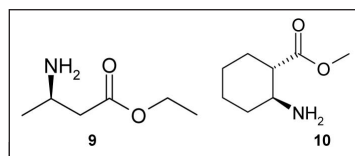
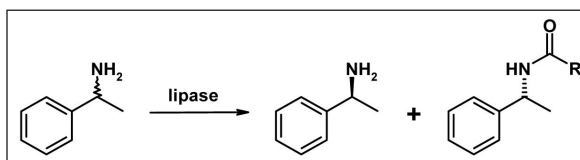


Figure 7. Chiral β -amino acids

CHIRAL AMINES

Chiral amines play an important role in stereoselective organic synthesis. They are used directly as resolving agents, building blocks or chiral auxiliaries (18-20).

While classically available through racemic resolution with optically active acids, biotechnological approaches also open a way to chiral amines (9). BASF's optimized lipase-catalyzed route to optically active amines (Scheme 8) can be run at several thousand tons scale.



Scheme 8. Lipase-catalyzed resolution of racemic amines

Due to the wide range of substrates tolerated by the enzymes, a large variety of different chiral amines is commercially available. A few examples are listed below:

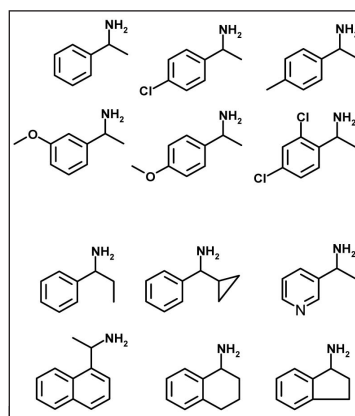


Figure 8. Aryl alkyl amines

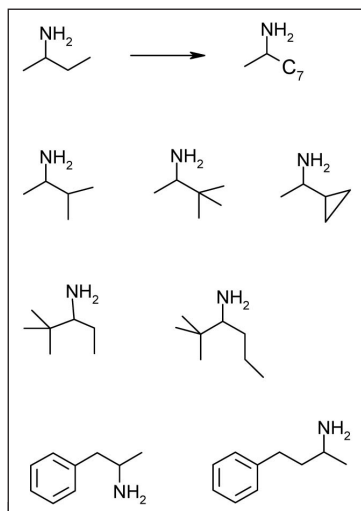


Figure 9. Alkyl amines

BASF's kinetic resolution process gives not only access to chiral amines but also to chiral aminoalcohols. Both product classes can be produced from lab to multi-ton scale.

OUTLOOK

BASF continues establishing new catalytic processes. We are also collaborating with universities and research institutions in order to find new and improved synthetic methods. Enoate reductases (21-23) are a next step towards expanding the scope of industrial biocatalysis.

CONCLUSION

As the saying goes, "When all you have is a hammer, everything looks like a nail". But in the pharmaceutical business, it is important that suppliers of single-enantiomer intermediates do not rely solely on one technology (be it asymmetric catalysis or biotransformation) – they should be in a position to choose the best suited technology regarding quality and economic and ecological efficiency. It is equally important that the process can be scaled up from laboratory to technical quantities as the pharma project advances – and that the supplier is able to provide the required quantities. BASF integrates discovery and development of chemical and biological catalysts, screening, process scale-up and production from lab to technical scale.

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