Synthesis and application of new chiral amines in Dutch resolution
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Chapter 1
Introduction to Chirality & Resolutions

In this chapter an overview is given of the history of chirality and its consequences as well as some basic principles. Possible routes to enantiopure compounds are summarized. One of these routes, the preparation of enantiopure compounds by resolution, will be discussed in more detail. Dutch Resolution refers to the use of mixtures of structurally similar resolving agents (also called ‘families’). This chapter also describes the aspects of the first generation, second generation and reverse Dutch Resolution, and the resemblances and differences between these and classical approaches. At the end of this chapter the aim and an outline of this thesis are given.
1.1 Basic Concepts of Chirality

In 1874, the French chemist Le Bel\cite{1} and the Dutch chemist van’t Hoff\cite{2}, independently postulated that the four chemical bonds that carbon atoms can form are directed to the corners of a tetrahedral structure (Figure 1.1). This discovery proved to be the cornerstone in the study of the three-dimensional structure of organic compounds, and developed to what now is commonly referred to as stereochemistry.

![Figure 1.1 Dutch stamp of Jacobus Henricus van’t Hoff at work (left). Van’t Hoff circulated his stereochemical ideas to his colleague chemists by sending them three-dimensional paper models of tetrahedral molecules (right).](image)

In general, carbon atoms that have four non-identical groups attached to them or molecules that are not superimposable on their mirror image are said to be asymmetric, or chiral (Greek; χείρ (cheir), meaning hand). These mirror images are called enantiomers (Figure 1.2). The word enantiomer is derived from the Greek εναντιος (enantios), which means opposite. A molecule that is superimposable on its mirror image is called achiral.

We constantly encounter chirality and chiral objects in daily life; for instance shoes, scissors, screws, and spiral staircases are all examples of chiral objects. Even in our body, all amino acids (except glycine) of every protein are almost always found as the same ‘left-handed’ enantiomers, whereas all sugars in DNA, RNA, and in the metabolic pathways, are ‘right-handed’.
Chapter 1

Introduction to Chirality & Resolutions

Figure 1.2 Molecules or objects that are non-identical with their mirror image are said to be chiral. Furthermore, nearly all amino acids in the human body are left-handed.

Compounds that have the same molecular formula but different bruto chemical structures are called isomers. The classification of isomers and their description is given in Figure 1.3.

Enantiomers belong to the first class of configurational stereoisomers, the so-called optical isomers. In an achiral environment, all physical properties (e.g. melting points, boiling points, densities) of enantiomers are identical, except the direction they rotate plane-polarized light. If a solution of the optically active compound rotates the plane-polarized light clockwise (dextrorotatory), it is designated (+) or d. Therefore, a solution of the mirror image enantiomer must rotate the plane-polarized light in the opposite direction at the same magnitude, it is designated (−) or l (levorotatory). If only one enantiomeric form of a chiral molecule is present, it is called enantiomerically pure (or enantiopure). A mixture containing equal amounts of opposite enantiomers is a racemate and racemic solutions show no rotation of plane–polarized light. Racemates are frequently represented as (±).

Because enantiomers have identical physical properties, they cannot be directly separated by conventional methods (e.g. distillation, crystallization, chromatography on conventional stationary phases), but only be resolved by use of an optically pure (or enriched) chiral reagent.

There are molecules that also belong to the class of optical stereoisomers that are not mirror images of one another. These isomers are referred to as diastereoisomers (or shorter diastereomers), and contain more than one stereogenic center. As a general rule, for a molecule having \( n \) stereogenic centers, \( 2^n \) diastereomers are possible; this number is reduced to less than \( 2^n \) if meso forms, i.e. internal symmetry, of the molecule are possible. Diastereoisomers have different physical properties and therefore can be separated from one another by conventional methods.
Epimers are a special category of diastereomers. They are a pair of stereoisomers with more than one stereogenic center that differs in chirality at one and only one chiral center. A chemical reaction, which causes an interconversion in chirality at one of these chiral centers, is called an epimerization.

Figure 1.3 The relationship between different kinds of isomers.

Stereoisomers differ in the way their atoms are arranged in space, whereas constitutional isomers, the class into which all others fall, differ in the order in which atoms are bonded together.
1.2 Chirality and Bioactivity

Although enantiomers have the same physical properties, in a chiral environment, for example that of living organisms, enantiomers can show different chemical behaviour due to different chiral discrimination (diastereomeric interactions). Both carvone and limonene (Figure 1.4) provide classic examples of how enantiomerism can lead to different interactions in the human body. The enantiomers of these two odourants have different scents owing to a different 3-D fit on an odour receptor and/or on different odour receptors.

(S)-Carvone is a naturally occurring ketone that can be found in caraway seeds, and is used in the perfume industry and as a flavouring spice. (R)-Carvone is found in mint leaves. The typical spearmint and caraway odours are those of mirror molecules; caraway is the ‘right-handed’ enantiomer and spearmint is the ‘left-handed’ enantiomer.

Orange and lemon peels both contain limonene. However, the limonene molecule in orange peel is the (–)-enantiomer, and the one in the lemon is the (+)-enantiomer. And as we all know, these spatially different structures have different odours.

Similarly, chirality plays a role in the chemical communication in nature. Faranal is an insect trail pheromone of the pharaoh’s ant (Monomorium pharaonis). When a worker ant finds some food source of interest to the colony it leaves a trail of faranal which other workers pick up and follow. Only the (3S,4R)-(+) faranal is the bioactive enantiomer (of four stereoisomers).
One can imagine that the different bioactivity of enantiomers is of utmost importance in the manufacturing of pharmaceuticals; there are many examples where the stereoisomers used in drugs show differences. In the literature, the more active isomer for a given action is often referred to as the *eutomer*, whereas the other is called the *distomer*.[8] The distomer can exhibit an undesirable side effect, show no serious side effect or even have independent biological activities.[9] Examples of the latter are both enantiomers of propoxyphene, since they have independent therapeutic value. Dextropropoxyphene 1.6 (Darvon) is marketed as a painkiller, whereas the antipode levopropoxyphene 1.7 (Novrad) is a cough suppressant. Note how the mirror image relationship is reflected in their trade names.[10]

![Figure 1.5 The enantiomers of propoxyphene exhibit useful but different biological activities.](image)

In general, even if the distomer shows no unwanted side effects, it must be regarded as isomeric ballast and therefore the preparation of enantiopure drugs is preferred.
1.3 Routes to Enantiomerically Pure Compounds

In the quest for enantiopure compounds, there are three primary sources to choose from (Figure 1.6):

- The rich diversity of enantiopure compounds from the chiral pool,
- Stereoselective conversion of prochiral substrates (asymmetric synthesis), and
- Resolution of a racemate into its pure enantiomers.

These three main routes (and their sub-routes) will be described briefly in the next few sections illustrated by several examples from the literature.

1.3.1 Chiral Pool

The chiral pool consists of enantiomerically pure or highly enriched starting materials derived from natural resources, such as amino acids, carbohydrates, hydroxy acids, alkaloids and terpenes. If such a precursor is available, then it is often the most cost-effective way of introducing asymmetry. An example of using the chiral pool is the synthesis of the herbicide $(R)$-flamprop-$iso$propyl starting from one of the oldest and most well known chiral hydroxy acids, $L$-lactic acid $1.8$. After conversion to the mesylate, a single inversion step leads to the desired final product with the $(R)$-configuration (Scheme 1.1).
1.3.2 Prochiral Substrates

A potential synthesis component (synthon) is prochiral if in one reaction step a new stereogenic center is created; although this reaction can entail sub-steps (like hydrolysis of an intermediate). This reaction step can be, for example, an addition to a double bond in the molecule (e.g. prochiral olefins), or substitution of one of two enantiotopic groups (e.g. prochiral diols).

1.3.2.1 Chiral Auxiliaries\[16\]

The first strategy in asymmetric synthesis involves the use of a chiral auxiliary. In this strategy the temporary introduction of a chiral group to a prochiral substrate influences the outcome of the reaction that produces the new stereogenic center. It is preferable that both enantiomers of the chiral auxiliary are available so that it is possible to prepare both enantiomers of the final products if desired.

Once the chiral auxiliary has achieved its purpose, it can, at least in ideal situations, be removed from the molecule and re-used. Therefore the ideal chiral auxiliary should be easy to recover without any loss of enantiomeric purity. If in the removal step the chiral center of the chiral auxiliary is destroyed (immolative removal), the chiral auxiliary cannot be recycled. In this case, in the literature reference is sometimes made to a “chiral template” rather than chiral auxiliary.

One of the most well-known chiral auxiliaries in the literature are the chiral oxazolidinones applied in the Evans methodology.\[17\] A demonstration of the use of oxazolidinones as an effective chiral auxiliary is in the synthesis of key butyrolactone intermediates for the
The key step in this sequence was a highly diastereoselective alkylation of an N-acyloxazolidinone enolate.

Commercially available (4R)-benzyl and (4S)-isopropyl-2-oxazolidinones were N-acylated with dihydrocinnamic acid to give N-acyloxazolidinones (R)-1.10 and (S)-1.11. Diastereoselective alkylation with tert-butylbromoacetate gave in each case predominantly one diastereomer (1.12 and 1.13, respectively) (de ≥ 95%). After removal of the oxazolidinone moiety, the crude acid was reduced to the corresponding primary alcohol with BH₃·THF, and then converted into a lactone using TFA to afford the desired benzylbutyrolactones 1.14 and 1.15.

Scheme 1.2 Asymmetric synthesis of butyrolactones 1.14 and 1.15. Reagents and conditions: (a) NaHMDS, BrCH₂CO₂Bu; (b) LiOH, H₂O₂; (c) BH₃·THF; (d) TFA.
Another example of the use of chiral auxiliaries will be described in Chapters 3 and 4 of this thesis; enantiomerically pure (R)-phenylglycine amide proved to be an excellent chiral auxiliary in the preparation of enantiopure 1-aryl-1-butylamines and 1-aryl-3-butenylamines. These amines are valuable synthons in the preparation of biologically active compounds and will be used in Dutch Resolution experiments (as described in Chapters 5–7).

1.3.2.2 Chemocatalysis

Asymmetric chemocatalysis is a rapidly developing area, as researchers look for new ligands and catalysts derived therefrom that are more active, more selective, and more broadly applicable to bring about enantioselective reactions.

An example of the largest-scale enantioselective catalytic process at present (a capacity of more than 10,000 tons per year) is the production of (S)-Metolachlor 1.18, an important herbicide used on farmland for the control of grass weeds in row crops (e.g. corn and soybean). Of the four stereoisomers, only the two (S)-diastereomers show biological activity. The key step in the technical process is the asymmetric hydrogenation of imine intermediate 1.16 by using iridium complexed to a ferrocenyl diphosphine ligand known as Josiphos (Scheme 1.3) followed by a chloroacetylation of (S)-1.17.

This catalytic process has an exceptionally high efficiency. Under a hydrogen pressure of 80 bar and a reaction temperature of 50 °C, satisfactory enantiomeric excesses (79 % ee) and a turnover number of more than 1,000,000 can be achieved.\(^{[19c]}\)
1.3.2.3 Biocatalysis

Biological processes are usually regulated by enzymes. For instance, the digestion of food is catalyzed by enzymes. Biocatalysts used in synthetic organic chemistry include natural enzymes and unnatural modifications produced by, for example site-specific mutagenesis or gene shuffling. These systems have the potential to catalyze reactions of specific substrates with high enantio- and stereospecificity. Among the enzymes used, lipases have demonstrated a great versatility in enzymatic hydrolysis, transesterification, or aminolysis reactions. Other biocatalysts, for example lyases, have been reported for the production of pharmaceutically interesting L-amino acids.

Tyrosine phenol-lyase (TpL) is used in the production of (S)-3,4-dihydroxyphenylalanine (L-DOPA), utilized in the treatment of Parkinson’s disease and which is a precursor to the neurotransmitter dopamine. In the industrial one-pot three-component process, catechol 1.19, pyruvic acid 1.20 and ammonia are combined in a reactor in the presence of intact cells from the Erwinia herbicola containing the TpL-biocatalyst (Scheme 1.4).[19b,22]

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{O} & \\
\text{CO}_2\text{H} & \\
\text{NH}_3 & \\
\text{HO} & \quad \text{HO} \\
\text{O} & \\
\text{CO}_2\text{H} & \\
\text{NH}_2 & \\
\text{+} & \\
\text{pyruvic acid 1.20} & \quad \text{Tyrosine phenol-lyase} & \quad \text{NH}_3 & \\
\text{catechol 1.19} & \quad \text{L-DOPA 1.21} & \\
\text{NH}_2 & \\
\end{align*}
\]

Scheme 1.4 Production of L-DOPA 1.15 using tyrosine phenol-lyase.

The volumetric productivity of this process is up to 110 g.L\(^{-1}\). Over half the market need of about 250 tons of L-DOPA is produced by this enzymatic method involving TpL.[22a]

1.3.3 Starting from the Racemate – Resolutions

If a chemical reaction is performed in the laboratory with achiral starting materials and under achiral conditions, the products can be chiral but will be formed as a racemic mixture of two enantiomers. To obtain enantiopure or enantio-enriched materials, a resolution step is required. The most frequently used resolution methods will be outlined below. Another resolution method, the resolution by preferential crystallization (entrainment), will be discussed in the Chapter 2. Section 1.5 of this Chapter will deal with a relatively new technology in the field of classical resolution, referred to as Dutch Resolution, since this method will be an important constituent of this thesis.
1.3.3.1 Chromatographic Resolution

The use of chromatographic techniques in the resolution of enantiomers to obtain significant quantities of enantiomerically pure drugs and drug intermediates is a growing field of interest. Chromatographic separation relies on a difference in affinity between the (chiral) stationary phase and a mobile phase (the solvent moving through the stationary phase, the eluent). Simulated moving bed (SMB) chromatography is a continuous chromatographic multi-column separation process wherein six to eight columns are run in series. In recent years, SMB chromatography has become an alternative approach for the separation of enantiomers in quantities ranging from grams to several hundred kilograms.\(^{[24]}\)

A successful example of SMB is in the commercial scale synthesis of enantiopure (R)-miconazole 1.24 from racemic intermediate 1.22. Miconazole is used in the treatment of, for example, skin diseases and tuberculosis.

![Scheme 1.5](image)

**Scheme 1.5** The preparation of single enantiomer (R)-miconazole 1.24 by SMB-chromatography.

In the SMB process, intermediate (R)-1.22 is separated and after a substitution reaction with 2,4-dichlorobenzyl chloride 1.23, (R)-miconazole 1.24 is obtained as the single enantiomer. Unfortunately, the non-desired enantiomer could not be re-racemized.\(^{[19c]}\)
1.3.3.2 **Kinetic Resolution**\(^{(25)}\)

In a kinetic resolution process, one of the two enantiomers of the racemate is converted to another compound. Because there is a difference in the rate of conversion of either enantiomer, the starting material will be enriched in the slowest converted enantiomer if the reaction is stopped before completion. This difference in rate is induced by chemical catalysts or biocatalysts like enzymes. When the unwanted enantiomer is racemized \textit{in situ} during the reaction, a 100 % theoretical yield of the enantiopure product can be reached, and the process is referred to as \textit{dynamic} kinetic resolution.\(^{(26)}\)

A nice example of enzymatic resolution is involved in the preparation of Benazepril \ref{eq:1.28}. Benazepril is one of the most potential angiotensin converting enzyme (ACE) inhibitors, which contain an L-homophenylalanine ethyl ester in their structure.\(^{(27)}\) Recently, Regla \textit{et al.} reported a new synthetic strategy for the synthesis of the homophenylalanine (HPA) intermediate \ref{eq:1.26} by enzymatic resolution.\(^{(28)}\) Both enantiomers of \ref{eq:1.26} have potential application in the synthesis of ACE inhibitors. By using the kidney acetone powders (KAPs) derived from different mammalian species such as beef, dog, hog, rat, and sheep they were able to resolve racemic N-acetyl HPA \ref{eq:1.25} (Scheme 1.6). The beef kidney afforded the best results, providing the highest isolated yields, 41 % and 38 %, and enantiomeric excesses of > 99 % and 94 % for both L-HPA \ref{eq:1.26} and D-N-Acetyl-HPA \ref{eq:1.27}, respectively.

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {CO₂H \text{NH} \text{CO₂H}}; \\
  \node at (2,0) {CO₂H \text{NH} \text{CO₂H}}; \\
  \node at (4,0) {CO₂H \text{NH} \text{CO₂H}}; \\
  \node at (0,-2) {CO₂H \text{NH} \text{CO₂H}}; \\
  \node at (2,-2) {CO₂H \text{NH} \text{CO₂H}}; \\
  \node at (4,-2) {CO₂H \text{NH} \text{CO₂H}}; \\
  \node at (0,-4) {CO₂H \text{NH} \text{CO₂H}}; \\
  \node at (2,-4) {CO₂H \text{NH} \text{CO₂H}}; \\
  \node at (4,-4) {CO₂H \text{NH} \text{CO₂H}}; \\
  \draw[->] (0,0) -- (2,0); \\
  \draw[->] (0,-2) -- (2,-2); \\
  \draw[->] (0,-4) -- (2,-4); \\
  \node at (0,0) {\textbf{L-HPA} \ref{eq:1.26}}; \\
  \node at (2,0) {\textbf{1.27}}; \\
  \node at (4,0) {\textbf{Benazepril} \ref{eq:1.28}}; \\
  \node at (0,-2) {\textbf{1.26}}; \\
  \node at (2,-2) {\textbf{1.27}}; \\
  \node at (4,-2) {\textbf{1.27}}; \\
  \node at (0,-4) {\textbf{1.26}}; \\
  \node at (2,-4) {\textbf{1.27}}; \\
  \node at (4,-4) {\textbf{1.27}}; \\
  \node at (0,0) {\textbf{CO₂H \text{NH} \text{CO₂H}}}; \\
  \node at (2,0) {\textbf{CO₂H \text{NH} \text{CO₂H}}}; \\
  \node at (4,0) {\textbf{CO₂H \text{NH} \text{CO₂H}}}; \\
  \node at (0,-2) {\textbf{CO₂H \text{NH} \text{CO₂H}}}; \\
  \node at (2,-2) {\textbf{CO₂H \text{NH} \text{CO₂H}}}; \\
  \node at (4,-2) {\textbf{CO₂H \text{NH} \text{CO₂H}}}; \\
  \node at (0,-4) {\textbf{CO₂H \text{NH} \text{CO₂H}}}; \\
  \node at (2,-4) {\textbf{CO₂H \text{NH} \text{CO₂H}}}; \\
  \node at (4,-4) {\textbf{CO₂H \text{NH} \text{CO₂H}}}; \\
  \node at (0,0) {\textbf{KAP}}; \\
  \node at (2,0) {\textbf{1.26}}; \\
  \node at (4,0) {\textbf{1.27}}; \\
  \node at (0,-2) {\textbf{1.26}}; \\
  \node at (2,-2) {\textbf{1.27}}; \\
  \node at (4,-2) {\textbf{1.27}}; \\
  \node at (0,-4) {\textbf{1.26}}; \\
  \node at (2,-4) {\textbf{1.27}}; \\
  \node at (4,-4) {\textbf{1.27}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.6} Enzymatic resolution of (±)-Acetyl-HPA \ref{eq:1.25} with mammalian KAP in the synthesis towards Benazepril \ref{eq:1.28}.
1.3.3.3 Inclusion Resolution

A relatively new field in the resolution of racemates is inclusion resolution which is based on chiral discrimination and recognition in the crystalline phase. A chiral host molecule forms an inclusion complex preferably with one of the enantiomers by forming hydrogen bonds. The most widely applied chiral host molecules are the derivatives of tartaric acid, succinamide and lactic acid.

Recently, both enantiomers of 9,9’-spirobifluorene-1,1’-diol (SBIFOL) were conveniently obtained by inclusion resolution with 2,3-dimethoxy-N,N,N’,N’-tetracyclohexylsuccinamide (Scheme 1.7). Diol 1.29 provides potential backbones for chiral ligands in asymmetric catalysis and finds a place in molecular electronics, light-emitting materials and other areas. Racemic diol 1.29 and (2R,3R)-1.30 were mixed in a 1:1 molar ratio in ethanol at room temperature (rt). After a few minutes, the crystalline complexes were collected by filtration, and after liberation, (R)-(+) was obtained in 43 % yield (of the maximum possible 50 % yield) in an enantiomeric excess of 80 %. By repeating the procedure of inclusion crystallization once, the enantiomeric excess of (R)-(+) was further increased to 99 %. The (S)-(–) enantiomer was obtained in 99 % ee by inclusion resolution using (2S,3S)-1.30.

![Scheme 1.7 Inclusion resolution of 1.29 with (2R,3R)-1.30.](image)

1.4 Classical Resolution by Diastereomeric Salt Formation

Despite methodologies like those just described, optical resolution via diastereomeric salt formation is still the most widely used method of preparing pure enantiomers. In this section a historical overview is given and aspects that play a role in classical resolutions are discussed.
1.4.1 Louis Pasteur

Tartaric acid ("acid of grapes") is a chiral dicarboxylic acid found in wine must. It is used in the food industry to give an acid taste, and as an antioxidant. The chirality of tartaric acid was discovered in 1832 by Jean-Baptiste Biot, who observed its ability to rotate polarized light.[40]

When Louis Pasteur repeated the work of Biot in 1847 as research practice,[41] he found that one of the isomers of tartaric acid consists of equal quantities of the levo- and dextro-forms. This optically inactive form is called Racemic Acid (Greek; racemus, which means bunch of grapes). The term 'racemic' originally referred to the origin of the acid (grapes), but nowadays in chemistry it refers to an equal mixture of opposite enantiomers.

By slow crystallization of a solution of the sodium ammonium salt of tartaric acid Pasteur obtained two types of colorless mirror image crystals (Figure 1.7). By using a magnifying glass and a pair of tweezers, he separated the crystals by hand. Equimolar solutions of these separated crystals showed equal but opposite optical activity. Even though this is the first reported resolution in the literature, one can imagine that this time-consuming 'crystal picking' is not very convenient in, for example, an industrial environment.

![Image of Louis Pasteur's stamp and crystals of tartaric acid and sodium ammonium tartrate](image)

Figure 1.7 French stamp of Louis Pasteur (left). Actual crystals of the ‘right-handed’ and ‘left-handed’ enantiomorphic forms of sodium ammonium tartrate (right).

However, there was an element of luck in his (accidental) discovery. Pasteur performed his crystallization experiments on a cold day in May in the cool climate of Paris. If he would have conducted his experiments later that summer, he would not have made his revolutionary discovery for it was found that sodium ammonium tartrate only forms a conglomerate below 26 °C.[42] A conglomerate is a mixture of crystals of individual enantiomers that can, in principle, be separated mechanically.[43] Only approximately 10% of the racemic compounds form conglomerates. The majority crystallizes as true racemates with an equimolar mixture of opposite enantiomers.
1.4.2 Diastereomeric Salt Formation

A more practical, and the most frequently applied method is the ‘classical’ resolution of racemates through formation and separation of diastereomeric salts. In this strategy, an acid-base reaction is involved between a racemate and a resolving agent, which is in practice an enantiopure (single) enantiomer. If the two diastereomeric salts that are formed differ in solubility, filtration can be used to separate the diastereomeric pair. The principle of classical resolution is depicted in Figure 1.8.[44] When you start with the racemate, depicted here as two mirror-image triangles and you associate them with a “chiral figure” (the resolving agent), for instance by salt formation, you obtain two non-mirror-image figures, related as diastereomers, which can be separated by conventional methods, like crystallization, chromatography or other physical manipulation.

![Figure 1.8](image)

**Figure 1.8** Two dimensional representation of diastereomeric salt formation.[44]

For instance, when the solubilities of the two salts (the more soluble and the less soluble salt) are very different, one of the salts is insoluble and can be filtered out of the mixture, leaving the other in solution (in the most ideal case). Finally, the salt is decomposed by treatment with either acid or base, and the resolving agent can be recovered.

An illustrative example of a classical resolution employed in an industrial process, is the diastereomeric crystallization of D-phenylglycine 1.32 from the racemate developed by
Andeno (now DSM Pharma Chemicals).\textsuperscript{[45]} Optically pure \textbf{1.32} is an important intermediate in the production of semi-synthetic β-lactam antibiotics. Racemic \textbf{1.32} is easily obtained from a Strecker reaction on benzaldehyde \textbf{1.31} followed by hydrolysis of the nitrile (Figure 1.9).

\begin{figure}
  \centering
  \includegraphics[width=\textwidth]{dsmp.pdf}
  \caption{DSM process for D-phenylglycine \textbf{1.32}.}
  \label{fig:dsmp}
\end{figure}

The racemate could be successfully resolved with optically pure D-(+)-camphorsulfonic acid \textbf{1.33} (CSA) as the resolving agent in aqueous medium; the more soluble diastereomeric salt is D-(−)-\textbf{1.33}/L-(−)-\textbf{1.32} and the less soluble diastereomeric salt is the D-(−)-\textbf{1.33}/D-(+)-\textbf{1.32}. After precipitation the less soluble salt is isolated, the L-isomer is racemized in a separate step (after liberation) and can be re-used. This process is performed on more than a thousand tons scale \textit{per annum}. 

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1.4.3 Commonly used Resolving Agents

For the separation of racemic acids naturally occurring alkaloids have been used like cinchonidine 1.34, quinine 1.35, cinchonine 1.36, quinidine 1.37, brucine 1.38, strychnine 1.39, dehydroabiethylamine 1.40 and ephedrine 1.41 (Figure 1.10). Also synthetic bases like 1-phenylethylamine 1.42 and amphetamine 1.43 have been employed in resolution experiments. The advantage of synthetic resolving agents like 1.42 and 1.43 is the (commercially) availability of both enantiomers.

![Figure 1.10 Some commonly used basic resolving agents.](image)

Among the preparative methods used for obtaining enantio-enriched amines by resolution, there are procedures involving the use of acidic resolving agents like N-acetylleucine 1.44, α-bromocamphor-π-sulphonic acid 1.45, camphorsulfonic acid 1.33, phenoxypropionic acid 1.46, mandelic acid 1.47, tartaric acid 1.48 and its dibenzoyl derivative 1.49, malic acid 1.50 and pyroglutamic acid 1.51 (Figure 1.11). Also synthetic acids like L-phenylcarbamoylactic acid 1.52 can be versatile resolving agents. For instance, L-1.52
is used for the resolution of 1-(p-chlorophenyl)ethylamine, a key intermediate in the synthesis of a chiral fungicide.\[47\]

\[\text{Figure 1.11} \text{ Some commonly used acidic resolving agents.}\]

Finding a suitable resolving agent for a given substrate is not trivial. Trial-and-error and practical experience is still the best methodology since no sound theoretical basis is available. Despite many attempts, neither computer-assisted modeling,\[48\] detailed examination of the crystal structure data of diastereomeric salts,\[49\] study of the energy differences of the two diastereomeric salts,\[50\] nor empirical correlations\[51\] have made it possible to predict an appropriate resolving agent that has to be used. If a resolution process is available for a certain compound, this method does not necessarily work for other substrates with closely related structures.
1.5 Dutch Resolution

Since the original description by Pasteur in 1853,[52] the technique of resolutions by diastereomeric salt formation essentially remained unchanged. The crucial step in the development of a resolution procedure is to find a suitable resolving agent. As mentioned earlier in this chapter, selecting a suitable resolving agent to resolve a substrate of interest has been trial-and-error, guided by the experience of the experimenter, and is sometimes as much art as science.

In 1998, a new approach to classical resolution was reported whereby, instead of using one resolving agent, mixtures of structurally closely related resolving agents (so-called families of resolving agents) were added to the racemic mixture. This method was coined “Dutch Resolution”,[53] a name which has been widely adopted. Dutch Resolution certainly has something of combinatorial characteristics in it; upon the simultaneous addition of a family of resolving agents, higher de values of the first salts were obtained via this method. Success rates were 90–95 %, in general on testing only a few families of resolving agents, compared to the usual 20–30 % estimated.[23b]

1.5.1 First Generation Dutch Resolution

Examples of various enantiopure families of acidic and basic resolving agents (and their abbreviations) that are currently available are shown in Figure 1.12. Families based on substituted chalcone sulphonic acids 1.53 (J-mix), mandelic acids 1.54 (M-mix), dibenzoyltartaric acids 1.55 (T-mix), cyclic phosphoric acids 1.56 (P-mix), 1-phenylethylamine 1.57 (PE-I-mix), 1.58 (PE-II-mix), 1.59 (PE-III-mix) and the family bases on 1,2-aminoalcohols 1.60 (PG-mix) are available. Note how these homochiral families differ only on the position or nature of the substituent. However, the PE-III mix constitutes of family members in which the alkyl side-chain is varied. With these families many resolutions have been carried out readily whereas with single resolving agents resolutions were either poor or failed.

In practice, three structurally related resolving agents are used in a 1:1:1 ratio. A mixture of these resolving agents is usually found in the first isolated salts, but in non-stoichiometric ratios. Two typical examples of Dutch Resolution are shown in Scheme 1.8 and Scheme 1.9 and more examples can be found in the original Dutch Resolution article.[53a]

DL-threo-(4-methylthiophenyl)serine amide 1.61 could be successfully resolved by using 1 mol equivalent of the family of cyclic phosphoric acids 1.56, the P-(–)-mix.[54] In this case, a diastereomeric pure salt precipitated containing the desired (25,3R)-enantiomer in 99 % enantiomeric excess (ee) (Scheme 1.8, entry 4). The precipitated salt contains all three of the individual family members in a non-stoichiometric ratio. This solid solution behaviour of the resolving agents is observed in many cases of Dutch Resolution experiments. Note that each of the individual family members of the P-(–)-mix give salts with moderate ee’s (entries 1–3) and in two of the three cases the enantiomer with the opposite configuration is isolated. (entries 1 and 2).
Figure 1.12 Families of resolving agents.
The resolved phenyl serine amide can be used as an intermediate in the synthesis of thiamphenicol,[55] which is an antimicrobial substance used for the treatment of infectious diseases in cattle, pigs and poultry.

\[ \text{Thiamphenicol} \]

\[ S = 2 \times \text{yield} \times \text{de}.^{5} \]

**Scheme 1.8** Dutch Resolution of DL-threo-(4-methylthiophenyl)serine amide 1.61 with the P-(−)-Mix.

The S-factor is a measure for the resolution efficiency and is described in section 1.6.2 of this chapter.
On use of the family based on the dibenzoyltartaric acids 1.55 (T-(−)-mix) it was possible to resolve DL-2-(2-chlorophenyl)ethylamine 1.62. After two recrystallizations from ethanol a salt is obtained with > 95% ee and contains the three family members of the T-mix in a 1:5:20 ratio (Scheme 1.9). Note how phenyl- and the tolyl-substituted family members 1.55a and 1.55b are incorporated in the salt only to a small extent.

Scheme 1.9 Dutch Resolution of DL-1-(2-chlorophenyl)ethylamine 1.62 with the T-(−)-mix.

1.5.2 Second Generation Dutch Resolution

In all reported cases of the Angewandte article,[53a] the ratios of the separate resolving agents differed substantially from the originally stoichiometries. In 10 of the 46 cases, no detectable amount of at least one of the resolving agents was found in the first isolated salts; in three other cases one of the resolving agents was present in < 10 mol % in the salts. Further investigation has led to the observation that the resolutions proceed less well in the...
absence of these non- or poorly incorporated resolving agents. The suspicion arose that these non-incorporated family members might be “the dog that didn’t bark”.‡

To put this idea to the test, a model system was designed with two family members. The resolving agent present in the highest fraction is called the ‘parent resolving agent’ and the other component present in the smallest fraction is the ‘additive’. The additive is typically a poorly or non-incorporated resolving agent. This approach is referred to as ‘second generation Dutch Resolution’.⁵⁶,⁵⁷

The case studied in most detail is the resolution of racemic mandelic acid 1.47 with (S)-1-phenylethylamine 1.42 as the parent resolving agent (Scheme 1.10).⁵⁶ In this system, the more soluble diastereomeric salt is (R)-1.47/(S)-1.42 and the less soluble diastereomeric combination is the (S)-1.47/(S)-1.42 salt. A 1:1 mixture of the ortho:para-substituted family members (S)-1.63 was chosen as the additive, this mixture together with (S)-1.42 forms the original PE-II-mix 1.58 (Figure 1.12). All experiments were performed at non-optimal conditions, so any improvement could be easily detected.

![Scheme 1.10 Second generation Dutch Resolution of racemic 1.47 with (S)-1.42 in the presence of (S)-1.63 as an additive.](image)

In the absence of the additive, the resolution of (±)-1.47 with (S)-1.42 delivered a first salt with a diastereomeric excess (de) of 14 % and S-factor of 0.19 (Table 1.1, entry 1). When 10 mol % of (S)-1.42 is substituted by a 1:1 mixture of ortho:para nitro-substituted (S)-1-

‡ In “Silver Blaze” (1984), Sir Arthur Conan Doyle’s fictional hero Sherlock Holmes once solved a case because a dog that would have been expected to bark did not. Worded differently, “often, what is most important is what is not said”. This metaphor was first used by Dr. J. W. Nieuwenhuizen."⁵⁶⁵⁷
phenylethylamine \textbf{1.63}, the \textit{de} of the first isolated salt increased from 14 \% to 55 \% and the S-factor increased to 0.41 (entry 2). No detectable amount of either \textit{ortho-} or \textit{para-}(S)-\textbf{1.63} was found in the precipitated salt.

\textbf{Table 1.1} Second generation Dutch Resolution of racemic \textbf{1.47} with (S)-\textbf{1.42} in the absence and presence of (S)-\textbf{1.63} as an additive.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Resolving Agent</th>
<th>Additive</th>
<th>Additive ((%))</th>
<th>Yield ((%)^a)</th>
<th>\textit{de} ((%)^b)</th>
<th>S Factor ((%)^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-\textbf{1.42}</td>
<td>–</td>
<td>–</td>
<td>68</td>
<td>14</td>
<td>0.19</td>
</tr>
<tr>
<td>2</td>
<td>(S)-\textbf{1.42}</td>
<td>(S)-\textbf{1.63}</td>
<td>10</td>
<td>37</td>
<td>55</td>
<td>0.41</td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield of the first salt. \(^b\) \textit{de} of the first isolated salt. \(^c\) \(S = 2 \times \text{yield} \times \text{de}\).

Crystallizations in the presence of (S)-\textbf{1.63} were observed to begin at a lower temperature than with (S)-\textbf{1.42} alone. With the aid of turbidity measurements it was established that this mixture of nitro-derivatives functioned as an effective nucleation inhibitor.\(^\dagger\) For both the diastereomeric salts, nucleation inhibition was observed. By suppressing the nucleation of the more soluble diastereomer, higher resolvability can be obtained. Turbidity measurements will be described in more detail in Chapter 6.

This second generation Dutch Resolution provides an ideal resolution protocol because:

- It was found that resolutions in the presence of (S)-\textbf{1.63} give high \textit{de} values even at a higher concentration. The use of higher concentrations is particularly attractive for industrial applications, since in one batch more material can be resolved.

- The efficiency of the resolution can be enhanced by adding a sub-stoichiometric amount of a family member which acts as a nucleation inhibitor and is not incorporated. A pure salt is obtained, which after liberation of the enantio-enriched substrate affords only a single resolving agent. This is of evident benefit in recycling the resolving agent.

This second generation Dutch Resolution protocol was also used in the resolution of racemic \textit{meta-}nitrophenylbutylamine with the family of the cyclic phosphoric acids \textbf{1.56} and is described in chapter 4.4 of this thesis.

\(^\dagger\) For a more detailed description of a nucleation inhibitor see Chapter 2.8.
1.5.3 Reverse Dutch Resolution

The methodology just described can also be performed in a reverse manner, i.e. a family member of the racemate is added instead of a compound structurally related to the resolving agent. An example is the resolution of alaninol 1.64 in the presence of an enantiopure family member 2-amino-1-butanol 1.65 (Figure 1.13). Whereas the latter amine 1.65 can be successfully resolved with 1.47, the resolution of 1.64 with mandelic acid itself provides salts with low de values. In the absence of 1.65, the resolution of (±)-1.64 with (R)-1.47 delivered a first salt with a de of 13 % and S-factor of 0.11 (Table 1.2, entry 1).[54]

When racemic 1.64 is partly substituted by (R)-1.65 a mixed salt co-crystallizes containing both (R)-alaninol 1.64 and (R)-2-amino-1-butanol 1.65. Depending on the starting ratio of 1.64 and 1.65 more or less of the (R)-alaninol is incorporated in the first isolated salts (entries 2–4). Best results were obtained with (S)-1.65 as the additive; on addition of 33 mol % of (S)-1.65 a salt crystallizes which contained almost no additive. One subsequent recrystallization provided the desired enantiopure (R)-alaninol. Most likely, the (S)-family member of the racemate stereoselective hinders the crystallization of the non-desired (S)-1.64/(R)-1.47 diastereomer.*

Figure 1.13 and Table 1.2 Reverse Dutch Resolution of (±)-alaninol 1.64 with (R)-mandelic acid 1.47 using (R)- or (S)-2-amino-1-butanol 1.65 as a family member.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting ratio</th>
<th>Yield</th>
<th>de</th>
<th>S Factor</th>
<th>Mix-ratio in salt</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>100</td>
<td>–</td>
<td>43</td>
<td>0.11</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>50 (R)</td>
<td>38</td>
<td>0.71</td>
<td>25</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>25 (R)</td>
<td>34</td>
<td>0.63</td>
<td>57</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>10 (R)</td>
<td>37</td>
<td>0.65</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>33 (S)</td>
<td>24</td>
<td>0.45</td>
<td>98</td>
</tr>
</tbody>
</table>

* Unpublished results B. Kaptein, DSM Research.
1.5.4 Reexamination of Pasteur’s Work

In 1853 Pasteur reported the synthesis of optically active quinotoxine (1.66), a degradation product of quinine (1.35).[52b,58] He used alkaloid 1.66 as a resolving agent to perform the first ever resolution by diastereomeric salt formation. By treating racemic tartaric acid 1.48 with (+)-quinotoxine, Pasteur was able to precipitate preferentially the salt containing (+)-tartaric acid/(+)-quinotoxine, whereas the (–)-tartaric acid/(+)-quinotoxine salt remained in solution.

Since Pasteur obtained degradation product quinotoxine by a rearrangement reaction induced by mild treatment of quinine with sulfuric acid, it is not improbably that there was still a small quantity of starting material 1.35 present in the isolated end-product 1.66. Quinine is a perfect potential family member of quinotoxine, and this exactly fulfills the second generation Dutch Resolution protocol as described in Chapter 1.5.2. If quinine acts as a family member and suppresses the nucleation of the more soluble salt, the high stereoselectively in the precipitation process might be possibly due to nucleation inhibition.

Even today, the work of Pasteur still receives much attention. Recently, his work on the morphology of sodium ammonium tartrate was reexamined by Nakazaki and coworkers.[59] In our view, a simple experiment well worth trying is reexamination of the resolution of racemic tartaric acid with quinotoxine in the absence and presence of quinine by performing turbidity measurements.
1.6 Parameters for Evaluation

1.6.1 Enantiomeric- and Diastereomeric Excess
For a mixture of enantiomers or diastereomers, where the compositions are given as $A$ and $B$ (and $A + B = 1$), respectively the enantiomeric excess ($ee$) and the diastereomeric excess ($de$) are defined as:

\[
ee(\%) = 100 \times \frac{A - B}{A + B} \quad de(\%) = 100 \times \frac{A - B}{A + B}
\]

Hence in a 1:1 (racemic) mixture of the enantiomeric pairs, the $ee$ is 0 %.

In chiral HPLC, for instance, by integration of the peak areas the enantiomeric- or diastereomeric excesses can be calculated.

In reactions where enantio- or diastereoselectivity plays a role, it is preferable to use the terms enantiomeric ratio ($er$) or diastereomeric ratio ($dr$) to make clear the percentage of one enantiomer or diastereomer in a mixture relative to that of the other:

\[
er = \frac{A}{B} \quad dr = \frac{A}{B} \quad (and \ A + B = 100)
\]

By using a polarimeter, the enantiomer recovered can be identified by verifying the direction the plane-polarized light is rotated. By comparing the magnitude (and direction) to known experimental results, the optical purity (in %) can be determined:

\[
% \text{ optical purity} = 100 \times \frac{[\alpha]_{\text{mixture}}}{[\alpha]_{\text{pure sample}}}
\]

In this formula, the specific rotation $[\alpha]$ is defined as:

\[
[\alpha]_\lambda^T = \frac{\alpha}{c \times l}
\]
in which $\alpha$ is the observed rotation (in °), $l$ is the length of the cell (in decimeters) and $c$ is the concentration used (in g·mL⁻¹). Since usually a cell of 1 decimeter in length and several milligrams are weighed in a 10 mL flask, the formula can be rewritten as:

$$[\alpha]_T^\lambda = 10,000 \times \frac{\alpha}{w}$$

in which $w$ is the amount of sample in milligrams in a 10 mL flask. The specific rotation should always be defined together with the concentration ($c$), the solvent used, the wavelength of the polarized light ($\lambda$) and the temperature ($T$).

The optical purity corresponds to the enantiomeric excess since they both express the excess of one species over the other, e.g. an optical purity of 40 % corresponds to an $ee$ of 40 % (and thus an $er$ of 70 :30)

### 1.6.2 Resolution Efficiency

The efficiency of a resolution experiment can be expressed in terms of the resolvability ($S$). The so called $S$-factor was introduced by Fogassy[60] and is used to compare resolution processes. It is calculated by multiplying the chemical yield by the diastereomeric excess ($de$) of the first obtained salt:

$$S = 2 \times \text{yield} \times de$$

A factor 2 is introduced to adjust for the fact that the theoretical yield cannot be higher than 50 % (or 0.50). The $de$ of the first isolated salts can range between 0 and 100 % (or 1.0). Therefore, the $S$-factor must range between 0 and 1, where 1 corresponds to complete separation.

The theoretical maximum resolution efficiency can be calculated on the basis of the solubilities of the diastereomeric salts (in mol·L⁻¹), $k_{\text{more}}$ and $k_{\text{less}}$, for a given solvent.

$$S_{\text{max}} \approx \frac{k_{\text{more}} - k_{\text{less}}}{k_{\text{more}}}$$

From this equation it can be seen that the greater the difference in solubility between the two diastereomeric salts, the higher the maximum $S$-factor that could be reached.
In a binary (melting) phase diagram, the lowest melting point corresponds to the eutectic point and the corresponding composition is the eutectic composition. When a resolution is performed under equilibrium conditions, the composition of the mother liquor corresponds to the maximum solubility.

From the composition at the eutectic point, the theoretical maximum resolution efficiency is defined as:

$$S_{\text{max}} = \frac{1 - 2x_{\text{eut}}}{1 - x_{\text{eut}}} = \frac{\text{ee} \ (%\text{e})_{\text{eut}}}{50 - \text{ee} \ (%\text{e})_{\text{eut}}}$$

where $x_{\text{eut}}$ is the eutectic composition and the $\text{ee} \ (%\text{e})_{\text{cut}}$ is the enantiomeric excess of the eutectic solution.\(^{[61]}\) If the maximum S-factor is not obtained in a certain resolution process, it is most probable that the equilibrium has not been reached.

Moreover, binary phase diagrams allows calculation of the maximum yield ($R_{\text{max}}$):

$$R_{\text{max}} = \frac{0.5 - x_{\text{eut}}}{1 - x_{\text{eut}}} \times 100 \% \quad (R_{\text{max}} = 1 - 50 \%)$$

### 1.7 Chiral Pool versus Asymmetric Synthesis versus Resolution

Each approach has its specific advantages and disadvantages, and all of these strategies are used both in industrial surroundings and in research laboratories.

Low cost and high enantiopurity are two reasons for considering ‘fishing’ in the chiral pool. A possible drawback of this approach is that most natural products are available in only one enantiomeric form.

The potential of catalytic asymmetric synthesis is reflected in the Nobel Prize in chemistry 2001 awarded to W.S. Knowles, R. Noyori and K.B. Sharpless.\(^{[62]}\) In theory asymmetric synthesis, either by chiral auxiliaries or asymmetric catalysis, should be the most cost-effective method for producing single enantiomers since it has a theoretical yield of 100 %. However, this is frequently counterbalanced by the availability of only one enantiomer of the chiral auxiliary, high costs and unsuitable removal conditions of the chiral auxiliary (see also Chapter 3.1). Asymmetric catalysis is often hampered by the long time-to-market and expensive transition metals. Furthermore, even though only a small amount of catalyst is required, optimization of a catalytic process is a time-consuming process, since multiple parameters are involved (e.g. lengthy total syntheses of chiral ligands, solvent, temperature, catalyst loading and scale-up). Recently, the screening for suitable catalysts for a certain
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process has changed drastically by the introduction of high-throughput experimentation (HTE).

Even though the theoretical yield in resolution processes is 50% starting from the racemate, if the unwanted isomer can find a profitable purpose or can be racemized in situ, this method becomes highly advantageous. Although the resolution technique still is far from predictable, it has the advantage that it is a relatively simple procedure, which can often quickly be incorporated into an industrial process. In the fine chemical industry it is therefore still one of the most frequently applied methods.

1.8 Aim and Outline of this Thesis

Improvements in resolutions are not only important for industrial applications, but it is also very important to gain more insight in the resolution process. The main focus of this thesis is threefold;

a. The development of a new family of basic resolving agents based on a new synthetic strategy.

b. The use of these materials, either single or as families in Dutch Resolution experiments.

c. The use of these materials to understand the family behaviour in nucleation inhibition.

Since the possible success of Dutch Resolution lies most probably in the phenomenon of ‘nucleation inhibition’, it is therefore important to understand what is going on at the molecular level during the crystallization process of the diastereomeric salts. Therefore, a short introduction to the basic principles of crystal growth from solution will be given in Chapter 2.

In Chapter 3, the diastereoselective addition of allylzinc bromide to imines derived from \((R)-\)phenylglycine amide (\((R)-\)PGA) is described in detail. Chapter 3 deals with the reductive removal of the PGA chiral auxiliary, and in Chapter 4 the non-reductive removal is described. This general protocol proved to be widely applicable in the synthesis of a new family of substituted aromatic butylamines and butenylamines with high enantiomeric purity, which will find application in Dutch Resolution experiments. Furthermore, these chiral amines can be important building blocks in the synthesis of biologically active products and compounds of pharmaceutical interest.

Chapter 5 deals with the application of the family of arylbutylamines in the second generation Dutch Resolution of a number of racemic substrates. In these experiments, 1-phenylbutylamine was used as the parent resolving agent, and the substituted family members were used as additive.
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Chapter 6 deals with the understanding of the role of an additive in the second generation Dutch Resolution of various racemic acids with 1-phenylethylamine as the parent resolving agent. 1-Phenylbutylamine was identified to be a potential nucleation inhibitor in the resolution process of mandelic acid on the basis of turbidity measurements. Subsequently, reasonably accessible family members of 1-phenylethylamine were examined to elucidate structure/activity relationships.

In the final chapter of this thesis, the epilogue, the leads and outlook in Dutch Resolution are discussed. The development and application of novel classes of polyfunctional resolving agents is described, a class that has not been used before in resolution experiments to our knowledge. Furthermore, some recommendations for future research on ‘high-throughput screening’ of (Dutch) resolution experiments are presented.

1.9 References

Introduction to Chirality & Resolutions


Chapter 1


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Chapter 1


