Optical resolution methods

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Despite the large number of elaborate enantioselective syntheses for the preparation of a single enantiomer to achieve industrial and scientific goals, the separation and purification of enantiomers (components of racemic compounds) is also necessary. Hence, we present the most often used thought-provoking modern methods based on momentous recognitions (*e.g.* spontaneous resolution, induced crystallization, resolution by formation of diastereomers, resolution by formation of non-covalent diastereomers, resolution by diastereomeric salt formation, resolution by diastereomeric complex formation, "half equivalent" methods of resolution, separation by crystallization, separation by distillation, separation by supercritical fluid extraction, resolution with mixtures of resolving agents, resolution with a derivative of the target compound, enantioselective chromatography, resolution by formation of covalent diastereomers, resolution by substrate selective reaction, kinetic resolution without enzymes, kinetic resolution by enzyme catalysis, hydrolytic and redox enzymes, kinetic and thermodynamic control, resolutions combined with 2nd order asymmetric transformations, enrichment of partially resolved mixtures, role of the solvent and methods of optimization in the separation of diastereoisomers, non-linear effects and selected examples of resolution on an industrial scale).

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1. Introduction

Optical resolution (henceforth resolution) is an operation aimed at the total or partial separation into its components of a racemic mixture (henceforth racemate[1]) *i.e.* a

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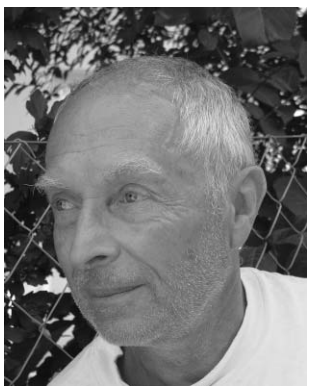
Mihály Nógrádi *(born in 1933) graduated from the Technical University of Budapest as a chemical engineer in 1957. He acquired his PhD with a thesis on the synthesis of natural flavonoids, which remained one of his main interests for a long time. His latter interest prompted him to write a textbook on stereochemistry, and a monograph on stereoselective synthesis. His cooperation with the pharmaceutical industry resulted in several patents, among them one for Ipriflavone marketed in Japan, Italy and Hungary for the treatment of osteoporosis. He has published 140 research papers.*

Elemér Fogassy



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1 : 1 mixture of enantiomers. Resolution may serve several purposes:

(i) structural studies: Pasteur's resolution experiments (1853)[2a] paved the way for the discovery of the tetrahedral orientation of the valencies of carbon (van't Hoff and Le Bel, 1874).[2b–c] Resolvability of compounds such as $R^1R^2R^3R^4N^+$ type ammonium salts and $R^1R^2R^3P$ type phosphines provided information about the configurational stability of such compounds. Racemization rates of atropisomers permits a rough estimation of the bulk of substituents in the *ortho* position to the aryl–aryl bond,

(ii) mechanistic studies: optically active compounds are powerful tools in the elucidation of the stereochemistry of reactions, especially in biochemistry. *E.g.* the inversion of configuration in S_N2 reactions was recognized by comparing the rate of racemization and isotope exchange of 2-iodooctane by Hughes and Ingold,[2d]

(iii) study of the biological activity of the individual enantiomers of chiral compounds.

(iv) separation of active and inactive (possibly harmful) enantiomers of chiral commercial products, foremost of drugs and pesticides. Nowadays the chances for registration of a new chiral drug in its racemic form are slim. Among chiral drugs approved by the FDA in 2003 more than 80% were single enantiomers. Preparation of synthetic L-amino acids as food supplements is also an important application.

1.1 History of resolution methods

The first ever resolution (in fact a kinetic resolution) was carried out by Louis Pasteur in 1848. He digested racemic tartaric acid with the mold *Penicillium glaucum* and observed that the unnatural *S*,*S* enantiomer remained unchanged. The first resolution by diastereomeric salt formation was also realized by him: he obtained (*R*,*R*)-tartaric acid from the racemate *via* its salt with (*R*,*R*)-quinotoxine.

Non-enzymatic kinetic resolution was discovered by Marckwald and McKenzie in 1899,[3] but this approach did not acquire much practical importance for several decades. In the same year Pope and Peachey described the "half equivalent" method[4] which, in numerous variations, remaines up to this day one of the most economic methods of resolution. Breathtaking advance in enantioselective synthesis and the advent of chiral chromatography in the last three decades may suggest that preparation of optically pure compounds by resolution may be obsolete, but on a large scale it still is one of the cost effective approaches, if not the most.

Absolute asymmetric synthesis, *i.e.* the production of non-racemic mixtures without a chiral aid is of high theoretical importance, first of all regarding the origin of chirality of biomolecules, but has not achieved any practical importance yet.[5–7]

1.2 Resolution and stereoselective synthesis

Two main categories of selective transformation can be distinguished:[8] (i) substrate selectivity, when selection affects two (or even more) substrates and (ii) product selectivity, when a single substrate is transformed into more than one product. Resolution is typically a substrate selective process, the substrates being the enantiomers, while stereoselective syntheses are product selective transformations.

Since enantiomers are identical in all of their scalar properties, selection between them requires a non-racemic chiral tool (reagent, catalyst, medium, *etc.*) to elicit a diastereomeric, *i.e.* non-mirror image, interaction with the components of the racemate.

2 Spontaneous resolution, induced crystallization

From a supersaturated solution of a conglomerate forming racemate one of the enantiomers may crystallize in high purity spontaneously or on seeding with the same enantiomer (preferential crystallization). The remaining solution contains an excess of the other enantiomer, which can be crystallized after concentration of the solution and repeated seeding. The process is laborious, and needs optimization and careful control of conditions. The principle of diastereomeric interaction is not violated even in this case, because interaction of the second molecule with the seed molecule of the crystal is of a diastereomeric nature for the two enantiomers.

Resolution by preferential crystallization was used in the manufacture of chloramphenicol,[9] L-dopa,[10] and (−)-menthol.[11] The latter was resolved as its benzoate, which crystallizes as a conglomerate.

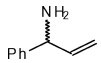
A precursor of the 1,5-benzothiazepin type calcium channel blocker diltiazem, of which only one of its four stereoisomers is active, could be resolved by alternate crystallization of the 3-amino-4-hydroxybenzenesulfonic acid salt of its *cis* diastereomer.[12] However in the manufacturing of diltiazem probably resolution with 0.5 eq. of (*S*)-naproxen is used.[13]

The method becomes more attractive when induced crystallization of one of the enantiomers is accompanied by spontaneous racemization thereby causing the total transformation of the racemate to a single enantiomer. Of the several examples, that of naproxene ethylamine salt may be mentioned giving >90% yield of one of its enantiomers.[14]

3. Resolution by formation of diastereomers

The essence of resolution is the differential interaction of the components of a racemic mixture with the single enantiomer of a chiral compound, *i.e.* the resolving agent, to form a pair of diastereomers, which have then to be separated by achiral methods. Finally the pure diastereomers have to be decomposed to yield the pure enantiomers and the resolving agent. In the following some noteworthy examples, both old and recent, of resolutions by diastereomer separation will be presented.

Table 1 Resolution of some α,β-unsaturated amines with (*S*)-2,3-isopropylideneglycerol hemiphthalate

Racemate	Yield (%)	ee (%)	*E* (%)
	80.2	>99	82
	62.9	>99	72
	41.8	98	44
	37.7	96.5	39
	0	0	0

3.1 Resolution by formation of non-covalent diastereomers

Conversion of a racemate with a single enantiomer of another chiral compound to a mixture of two diastereomers, followed by separation of the latter is the most often used method of resolution. This involves, with acidic or basic substrates, salt formation,[15] while with neutral racemates the usually less efficient complex formation can be applied. The design of resolving agents seems to be possible by crystal engineering.[16]

3.1.1 Resolution by diastereomeric salt formation.

3.1.1.1 Resolution of racemic bases. This method seems to be antediluvian, but is still the most popular for the resolution of bases. Dibenzoyl tartaric acid (**DBTA**) and di-*p*-toluoyl tartaric acid (**DPTA**)[17] are often used to separate chiral bases. An intermediate of the potent anticancer agent flavopyridol was resolved with (*R*,*R*)-**DBTA**.[18] *cis*-1-Amino-2-indanol, an intermediate for indinavir, was resolved with (*S*)-phenylpropionic acid,[19] 3-methylamino-1-(2-thienyl)propan-1-ol, an intermediate for duloxetine, was resolved with (*S*)-mandelic acid.[20]

Optimum conditions for the resolution of *N*-methylamphetamine with **DPTA** (molar ratio, solvent, *etc.*) were elaborated.[17] A similar investigation involving *N*-acetyl-phenylalanine as the resolving agent for a series of benzodiazepins was recently reported.[21]

Camphorsulfonic acid was the resolving agent for a metabolite [1-(3-hydroxy-4-methylphenyl)-2-methyl-3-(1-piperidyl)-propan-1-one] of tolperisone.[22] Tolperisone enantiomers show different biological profiles: while the *R* enantiomer is a bronchodilator, the *S* enantiomer is a central muscle relaxant.

(1*R*)-3-Bromocamphor-8-sulfonic acid [(*R*)-**BRCS**] is also an efficient resolving agent *e.g.* for a tetrahydroquinoline intermediate of the antibacterial agent flumequine.[23]

Resolution of β,γ-unsaturated amines with (*S*)-2,3-isopropylideneglycerol hemiphthalate is remarkable in that the chiral center of the resolving agent is separated by six bonds from the carboxyl group (Table 1).[24] A failure to resolve the saturated analogues of some of the substrates indicates a role of α,β-unsaturation in resolvability.

tert-Butylphenylphosphine oxide, a *P*-chiral compound, was resolved with (*S*)-mandelic acid [(*S*)-**MA**] (Fig. 1).[25]

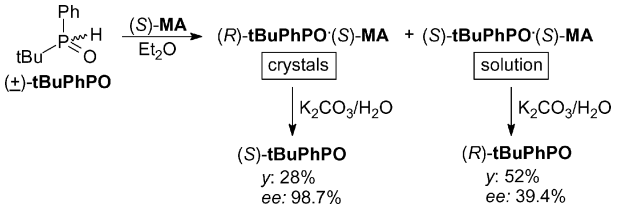


Fig. 1 Resolution of *tert*-butylphenylphosphine oxide (***t*BuPhPO**) with (*S*)-mandelic acid [(*S*)-**MA**].

3.1.1.2 Resolution of racemic acids. 1-Phenylethylamine (**PEA**) is one of the standard resolving agents for acids, among others for 3-phenyl-1-methyallenecarboxylic acid,[26] *tert*-butyl(phenyl)phosphanylthioic acid[27] and a ferrocenecarboxylic acid,[28] while 1,1′-binaphthyl-2,2′-dicarboxylic acid could be resolved with (*R*)-1-cyclohexyl-ethylamine.[29]

(1*R*,2*S*)-ephedrine (0.5 eq.) was used for the resolution of a racemic cyclopentene dicarboxylic acid.[30]

Resolution of dec-7-ene-δ-lactone (jasmine lactone) (as the Na-salt of the corresponding acid) with (1*S*,2*R*)-diphenylethanolamine is an example of a marked solvent effect, ironically water was found to be the best.[31]

The relatively inexpensive alkaloids quinine, cinchonine (**CH**), cinchonidine (**CD**) and brucine were often used to resolve racemic acids.[32] Cinchonine (**CH**) resolved a racemic phosphonic acid[33] (Fig. 2), while cinchonidine (**CD**) was used to resolve two 2-aryloxycarboxylic acids.[34] The (2-methylsulfinyl)phenyl phosphonic esters (**TPhA**) have chirogenic centers both at the P and S atoms. The doubly diastereomeric cinchonine salts of the monoester (**TPhA**, R = H) in which both P and S are chiral centers were separated by crystallization followed by reesterification, which destroyed the chirality at the P center, giving the pure (+)- and (−)-**TPhA**.

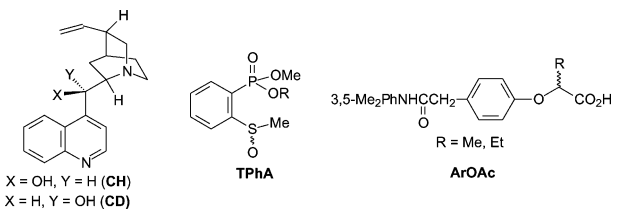
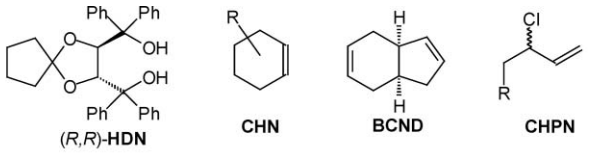


Fig. 2 Starting materials of the resolution (TPhA and ArOAc as racemic compounds, CH and CD, respectively, as resolving agents).

3.1.2 Resolution by diastereomeric complex formation. Enantioselective molecular complex formation between a resolving agent and one enantiomer of the racemate has often been exploited for resolution, especially for racemates which are not amenable to salt formation.

Racemic unsaturated hydrocarbons could be resolved by host–guest complexation with a diol [(*R*,*R*)-**HDN**] synthesized from tartaric acid (Fig. 3).[35] Although results seem to be rather poor, note that methods for the resolution of hydrocarbons are quite rare.

Some volatile chiral alcohols could be resolved by enantioselective inclusion complex formation using the bis-ketals **BKS**



Guest	Yield*	$[\alpha]_D$**	*ee**
CHN (R = 3-Me)	66	−66°	75
CHN (R = 4-Me)	55	+31°	33
CHN (R = 4-vinyl)	73	−12°	28
BCDN (R = H)	90	−16°	−***
CHPN (R = H)	48	−28°	56
CHPN (R = Cl)	42	+15°	−***

*After two recrystallizations. **Absolute configurations unknown.***Not determined.

Fig. 3 Resolution of some hydrocarbons by enantioselective inclusion complex formation with an optically active host compound [(*R*,*R*)-**HDN**].

and **BKA** derived from (*R*,*R*)-tartaric acid (Fig. 4). The racemic alcohols were mixed neat or with some toluene with the resolving agent, which selectively complexed one enantiomer, while the other one was let to evaporate. After recrystallization and thermal decomposition enantiopure alcohols were obtained in low to moderate yields (5–34%).[36] In the case of 2-hydroxypropionitril enantioselective complexation required the incorporation of one molecule of toluene.

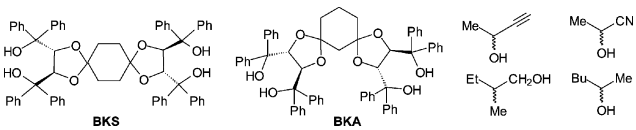


Fig. 4 Host compounds (**BKS and BKA**) derived from (*R*,*R*)-tartaric acid and some racemic alcohols resolved by enantioselective inclusion complexation.

O,*O*′-Dibenzoyl-(*R*,*R*)-tartaric acid [(*R*,*R*)-**DBTA**] forms solid molecular complexes with chiral alcohols in hexane. Although enantioselectivity is modest to low, the method deserves attention since the choice of resolution methods for alcohols is rather limited. Out of 22 alcohols enantioselective complexation was observed for 13, with ee values and yields in the range of 6–83% and 11–91% respectively.[37,38] Complexation of a racemic 3 : 2 mixture of *trans*- and *cis*-2-methylcyclohexanols with (*R*,*R*)-**DBTA** in hexane resulted both in a shift of the *trans* : *cis* ratio and in modest resolution (ee 8–42%).[39]

N-Benzyl cinchoninium chloride (**BnCH**) forms a crystalline molecular complex of very high diastereomeric purity with (*R*)-1,1′-bi-2-naphthol [(*R*)-**BINOL**] while the *S* enantiomer stays in solution (Fig. 5).[40]

Using the same technique 2-amino-2′-hydroxy-1,1′-binaphthyl was resolved with *N*-benzyl cinchonidium chloride, *i.e.* the quasi enantiomer of **BnCH**, to give the *R* enantiomer in 88% yield (ee: >99%) and the *S* enantiomer in 85% yield (ee: >99%).[41]

(*R*)- or (*S*)-1,1′-bi-2-naphthol (**BINOL**) itself can effect resolution by inclusion complex formation.[42] This was the method of choice for the resolution of a sulfoxide, namely the gastric secretion inhibitor omeprazole (**OPR**). Interestingly here it was a large excess of the chiral complexant which gave the best results (Fig. 6). The (*R*)-sulfoxide was selectively enclosed, while the *S* enantiomer could be recovered by washing the complex with diethyl ether.

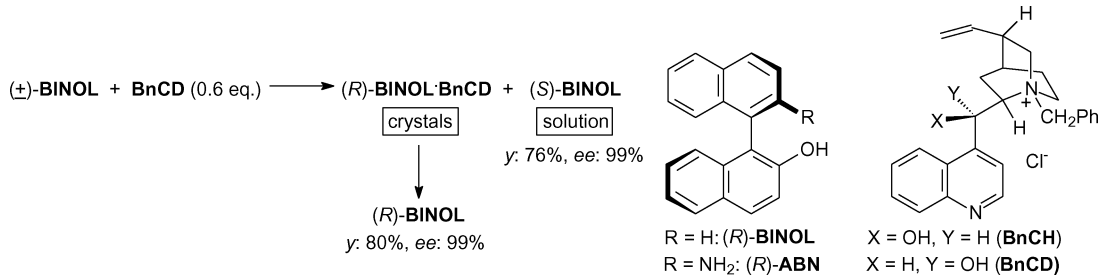


Fig. 5 Resolution of (±)-1,1′-bi-2-naphthol [(±)-**BINOL**] with *N*-benzyl cinchoninium chloride (**BnCH**).

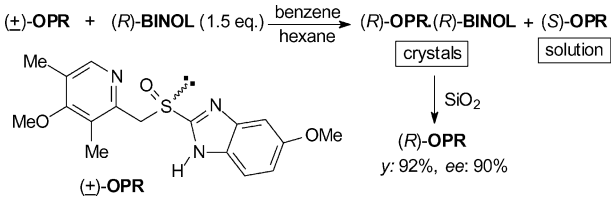


Fig. 6 Resolution of a sulfoxide by inclusion complex formation with (*R*)-**BINOL** as chiral host.

In optical resolution of chiral amino acids with chiral 18-crown-6 tetracarboxylic acid, the (+)-18C_6H_4 took very similar conformations for all complexes[43]

Chiral sulfoxides were resolved by enantioselective inclusion complex formation with dehydrocholic acid (Fig. 7).[44] Except for R = H, the predominant configuration of the included sulfoxide was *R*. After complexation, carried out in melt or in an ether solution, the uncomplexed enantiomer was washed out with ether, followed by decomposition of the complex with aqueous $NaHCO_3$ solution.

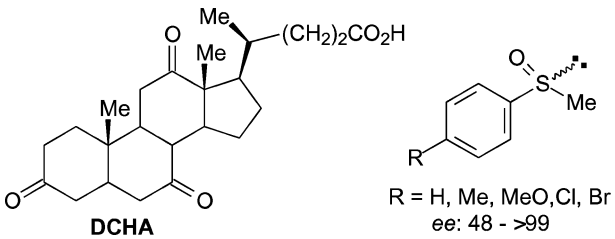


Fig. 7 Resolution of aryl methyl sulfoxides by inclusion complex formation with dehydrocholic acid (**DCHA**).

Resolution can even be achieved by forming salts with inexpensive calcium oxide. *E.g.* *O*,*O*′-dibenzoyl tartaric acid (**DBTA**) of very low ee (5–15%) can be resolved by induced crystallization of its mixed calcium salt formed with methoxyacetic acid. This salt forms conglomerate type crystals and seeding of the solution with the salt prepared from pure (*R*,*R*)-**DBTA** induces crystallization of a salt of identical chirality in 90% ee and 12% yield (Fig. 8).[45]

Seeding of the mother liquor with the salt of (*S*,*S*)-**DBTA** produces an equal amount of the antipode. Owing to the ready availability of tartaric acid enantiomers this experiment is only of theoretical interest.

Coordinative complex formation involving calcium ions has also been used to resolve 3-methoxypropionic acid and tetrahydrofuroic acid.[46] When to a solution of the neutral calcium salt of (*R*,*R*)-**DBTA** in ethanol the racemic acids were added, mixed salts precipitated, which, albeit after several recrystallizations, gave the corresponding acids in higher enantiomeric purity than by conventional resolutions with a chiral base.

The method can also be applied to resolve mandelic acid esters (Fig. 9).[47] Yields and optical purities can be high. Adding some water improves yields and ee values with the ethyl, benzyl and 2-phenylethyl esters. The process is illustrated in Fig. 9 for ethyl mandelate. Predominant configuration, yield and enantiomeric purity is much dependent on conditions (medium, additive, solvent for recrystallization). *E.g.* with methyl mandelate the *R* ester was obtained with ee > 99% and 83% yield, while the benzyl ester in toluene–acetone gave the *S* product with very low ee, in ethyl acetate–ethanol, in turn, the *R* enantiomer was obtained in high enantiomeric purity (ee 87%) but in low yield (42%).

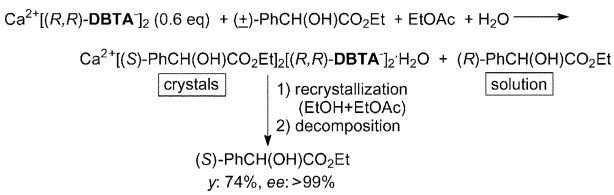


Fig. 9 Resolution of mandelic acid esters by coordination with the calcium salt of (*R*,*R*)-**DBTA**.

Formation of crystalline diastereomeric complexes with optically active organometallics offers another powerful method of resolution. In this way one can even resolve a base with another base as illustrated in Fig. 10.[48,49] A special interest of this example is that the secondary amine group in the palladium complex becomes tetracoordinated and represents an unusual center of chirality.

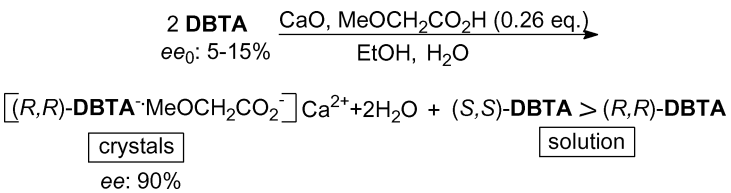


Fig. 8 Resolution of racemic *O*,*O*′-dibenzoyl tartaric acid (**DBTA**) of low optical purity by partial calcium complex formation and induced crystallization.

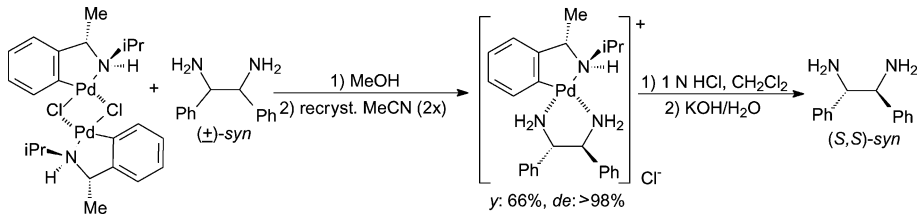


Fig. 10 Resolution of (±)-*syn*-1,2-diphenyl-1,2-ethanediamine with an *N*-chiral dimeric arylpalladium complex.

3.1.3 "Half equivalent" methods of resolution. Since even the cheapest resolving agent is relatively expensive for resolutions on a larger scale it is desirable to substitute part of it with an inorganic acid or base. The method was first proposed by Pope and Peachey who resolved 2-methyltetrahydroquinoline as the hydrochloride with 0.5 eq. of the ammonium salt of (+)-3-bromocamphor-8-sulfonic acid.[4] In such a system the solubility of the less soluble diastereomeric salt remains practically unchanged, while the other enantiomer is present as an inorganic salt, which is usually more soluble than salts with a bulky resolving agent. The method is of course only applicable to resolution of acids or bases. Its theoretical basis has been elaborated in several papers[50–53] and a monograph.[54]

3.1.3.1 Separation by crystallization. A combination of the half equivalent method and repeated resolution is shown in Fig. 11.[55] 2-Amino-1-phenylethanol, a starting material for antidiabetic drugs, was resolved with 0.25 eq. of (*R*,*R*)-**DPTA** in aq. isopropanol giving the *R* enantiomer in 62% yield and ee > 99%.[56] *trans*-2-Methylaminocyclohexanol was resolved with the same technique also with (*R*,*R*)-**DPTA**.[57]

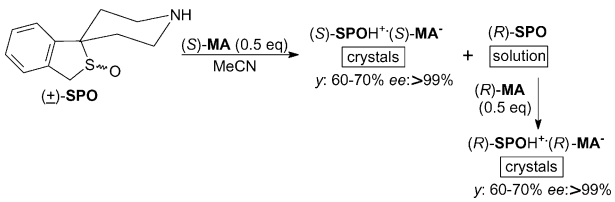


Fig. 11 Resolution of a sulfoxide with half eq. of (*S*)-mandelic acid (**MA**) followed by treatment of the mother liquor with (*R*)-mandelic acid.

3.1.3.2 Separation by distillation. Direct enantiomer separation can be achieved by distillation or fractionated distillation of a mixture of the racemate and a suitable resolving agent applied in less than equivalent amount.

Earlier it was shown that racemic unsaturated hydrocarbons can be resolved by complexation (Fig. 3).[35] One of the enantiomers preferably precipitates as a complex, while the other remains in solution. The substrate is then liberated from the solid complex by heating. Selectivity, however, is generally poor.

With distillable compounds, such as *e.g.* 1-phenylethylamine (**PEA**), the process can be simplified in such a way that the racemate is mixed with somewhat more than 0.5 eq. of a chiral agent followed by fractional distillation of the mixture. This method was applied for the separation of 2-amino-3-phenylpropane (amphetamine, **AA**) enantiomers. Seebach's ligand (**SL**) (0.52–0.66 eq.) forms a complex with the *R*-amine, while the *S* enantiomer can be distilled off. On further heating the complex decomposes and (*R*)-amphetamine can be recovered as the second fraction (Fig. 12).[58]

The optical purity of the product depends on the molar ratio of the components and whether or not an intermediate fraction is collected at the expense of yield.

Another example of the resolution of amines by fractional distillation is using 0.5 molar eq. of **DBTA** and its *p*-toluyl analogue **DTTA**.[59] On distillation the residue is mainly the more stable diasteromeric salt, while the distillate contains the other enantiomer in excess (Fig. 13). High ee values can be realized by repeating the procedure. Some amines resolved by this method and ee values after repeated resolution are shown in Fig. 13.

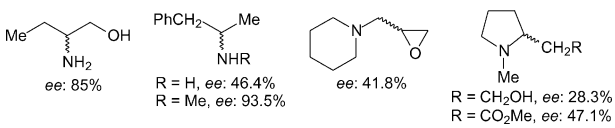


Fig. 13 Resolution of volatile amines with tartaric acid (**TA**) and its *O*,*O*′-dibenzoyl and *O*,*O*′-di-4-toluyl derivatives (**DBTA** and **DTTA**) by the distillation method.

Diastereoisomeric salt formation may also be combined with distillation as shown in Fig. 14.[58] The hemiphthalide of (*R*)-1-phenylethylamine (0.5 eq.) was added to (±)-3-phenylpropylamine [(±)-**PhPA**]. First the free amine enriched in the *R* enantiomer distilled off, then on raising the temperature, the amide decomposed and the other enantiomer could be recovered too.

3.1.3.3 Separation by supercritical fluid extraction. The finding that non-racemic products can be obtained from mixtures of

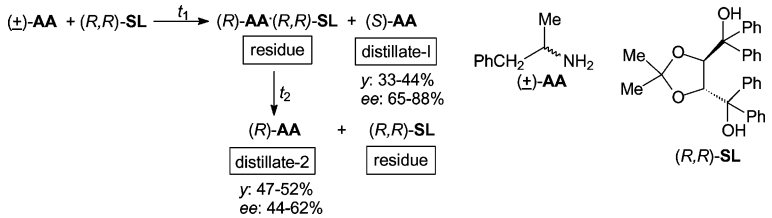


Fig. 12 Resolution of amphetamine (**AA**) by fractionated distillation using Seebach's ligand [(*R*,*R*)-**SL**] as the complexant.

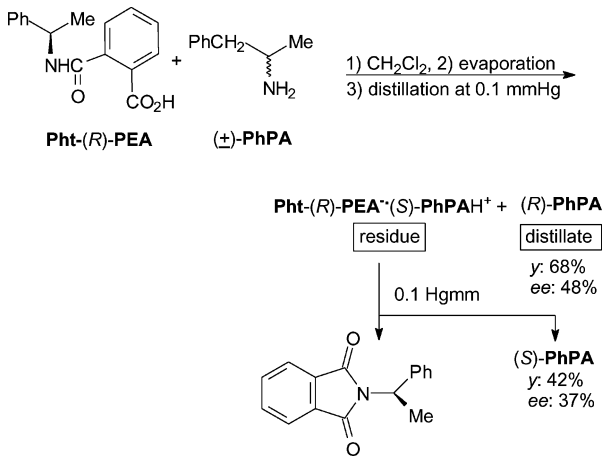


Fig. 14 Resolution of 3-phenyl-2-aminopropane using distillation at two temperatures.

free enantiomers and diastereomers by distribution between a solid and a liquid phase suggests that other methods of phase separation would also work. Thus after diastereomeric salt formation with 0.5 eq. of a resolving agent, the free enantiomer can be removed by extraction with a supercritical fluid, typically carbon dioxide.

As compared to traditional procedures this method sometimes gives better results for racemic acids even with the same resolving agent (Fig. 15). Separation is much influenced by reaction conditions,[60] and the design of the apparatus. Selectivity improves at higher pressures and temperatures. Resolution of a series of cyclopropane carboxylic acids and of ibuprofen (**IPF**) is shown in Fig. 15 and Table 2.[61,62]

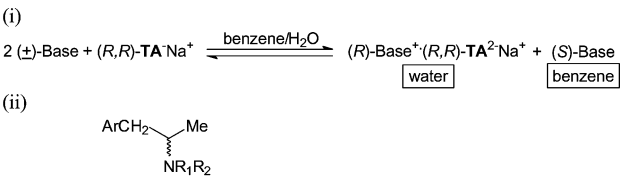
Racemic bases *e.g.* the anthelmintic tetramisole have also been separated by supercritical fluid extraction[63] of its partial salt with (*R*,*R*)-**DBTA**. Note that in this case the best results were realized with 0.25–0.35 eq. of the resolving agent. As usual, yields and optical purity were in an inverse relationship.

The resolution of *N*-methylamphetamine with (*R*,*R*)-**DBTA** was optimized regarding the molar ratio of racemate and resolving agent and at a ratio of ~0.25 ee's of 85 and 83% was realized in the extract and the raffinate respectively (yields: 47 and 48%).[64] Similar results were reported for the resolution of *trans*-2-chlorocyclohexanol by complexation with (*R*,*R*)-**DBTA** followed by extraction with supercritical carbon dioxide.[65]

If high cost of the equipment was not a severe limitation, supercritical extraction would be one of the simplest separation methods.

3.1.3.4 Resolution in a system of immiscible solvents. Enantiomer separation is also possible without crystallization using a pair of immiscible solvents based on the different solubility of diastereomeric salts and the free substrate.

A special method for enantiomer separation is reacting the racemic mixture with 0.5 eq. of the resolving agent in two immiscible solvents, one of which dissolves the free enantiomer, while the other one dissolves the diastereoisomers.[66] Such a procedure is shown in Fig. 16. Note that the concentration of



Base			Benzene phase		Aqueous phase	
R_1	R_2	Ar	*ee* %	yield %	*ee* %	yield %
H	H	Ph	49.3	49	49.6	48
Me	H	Ph	66.1	49	65.1	49
Me	H	4-O_2N-Ph	50.0	50	53.8	49
Me	H	4-H_2N-Ph	35.2	50	48.4	47
Me	H	4-Br-Ph	87.1	47	>99	40
Me	HC≡CCH$_2$	Ph	73.1	45	59.2	49

Fig. 16 Resolution of 3-aryl-2-aminopropane derivatives in a benzene–water system. (i) Scheme of the procedure, (ii) experimental results.

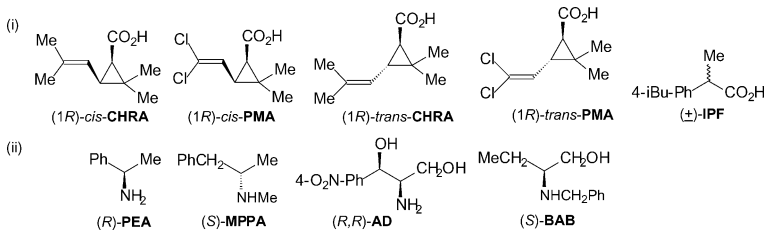


Fig. 15 Resolution of cyclopropane carboxylic acids (pyrethroid intermediates) and ibuprofen by extraction with supercritical carbon dioxide (I): (i) substrates, (ii) resolving agents.

Table 2 Resolution of cyclopropane carboxylic acids (pyrethroid intermediates) and ibuprofen (**IPF**) by extraction with supercritical carbon dioxide (II). E = extract, R = residue. For compound codes see Fig. 15

	(*R*)-**PEA**		(*S*)-**MPPA**		(*R*,*R*)-**AD**		(*S*)-**BAB**	
Racemate	E ee %	R ee %	E ee %	R ee %	E ee %	R ee %	E ee %	R ee %
cis-**CHRA**	<0.5 (*S*)	2.3 (*R*)			1.8 (*S*)	2.6 (*R*)	76.1 (*S*)	42.6 (*R*)
trans-**CHRA**					3.9 (*S*)	<0.5 (*R*)	3.1 (*S*)	12.7 (*R*)
cis-**PMA**	48.2 (*S*)	45.7 (*R*)	2.6 (*S*)	2.6 (*R*)	37.9 (*S*)	16.6 (*R*)	<0.5 (*S*)	4.4 (*R*)
trans-**PMA**	12.8 (*S*)	3.4 (*R*)			17.8 (*S*)	9.7 (*R*)	32.2 (*S*)	30.8 (*R*)
IPF	41.7 (*S*)	35.0 (*R*)	1.5 (*S*)	<0.5 (*R*)	14.0 (*S*)	11.0 (*R*)		

the substrate and the ratio of the solvents are not indifferent and have to be optimized.

Fig. 17 illustrates another example of resolution in a water–solvent system.[67] Since *cis*-**CPP** forms a racemic phase and the concentration range between the two eutectic compositions is rather broad, on recrystallization of the optically impure primary products the pure enantiomers appear in the mother liquors. The racemic portion can, of course, be recycled.

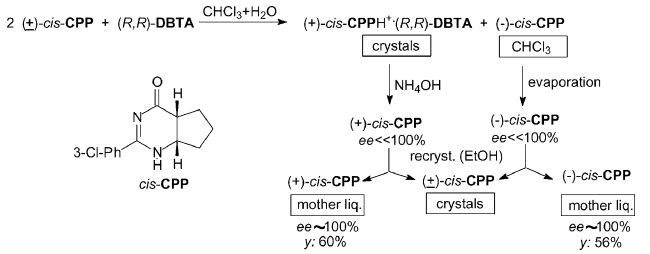


Fig. 17 Resolution process of the pyrimidine derivative *cis*-(±)-**CPP** with 0.5 eq. of (*R*,*R*)-**DBTA** in a system of immiscible solvents.

Occasionally addition of a third solvent, miscible with both phases, can significantly improve selectivity. As a consequence solubility can change significantly, which may result in much improved optical purities (Fig. 18).[68]

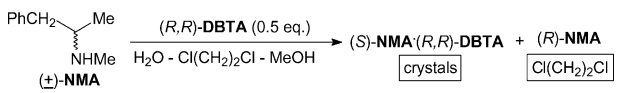


Fig. 18 Optimization of the resolution of *N*-methylamphetamine (**NMA**) with (*R*,*R*)-**DBTA** in a two-phase system by adding a third solvent.

3.1.4 Resolution with mixtures of resolving agents. A remarkable variation of the classical method of diastereoisomeric salt formation was discovered by Dutch researchers.[69,70] In the so-called "Dutch resolution (DR) technology" a mixture of resolving agents with analogous structure (called families) is applied, and the results—both in terms of enantiomeric purity and yield—may be superior to those achieved by using any of the resolving agents alone. This phenomenon implies a certain synergism of the resolving agents. *E.g.* when racemic ephedrine or another racemic base was reacted with two of the phosphoric acids shown in Fig. 19 (X = Ph and 4-Cl–Ph), 0.5 eq. of each, the salt of (1*S*,2*S*)-ephedrine containing both acids in equimolar amounts precipitated. In extremis a mixture of three cognate resolving agents in an optimized ratio was used (Fig. 19). Note that the ratio of resolving agents is different in the precipitated salt.[71]

A slight increase in ee at the expense of yield was found when some amines (*N*-methylamphetamine, its 4-fluoro analogue and 2-amino-1-butanol) were resolved with a mixture of tartaric acid and its derivatives (**DBTA, DPTA**), instead of a single resolving agent.[72]

Resolutions with several other mixtures composed of analogous resolving agents have been explored (Fig. 20).[69] Interestingly although the triads of resolving agents are applied in a 1 : 1 : 1 molar ratio, some of the components, shown boldface in Fig. 20 are not, or only to <10%, incorporated into the precipitating diastereomeric salt. It was assumed that the non-incorporated component served as a nucleation inhibitor and significant improvement of the efficiency of resolution effected by adding only 10% of the "inhibitor" supported this hypothesis.[73]

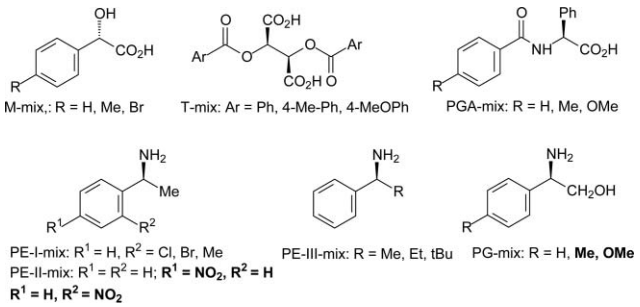


Fig. 20 Mixtures of close structural analogues (families) used as resolving agents.

Resolution of *N*-acetyl-[74] and *N*-formylphenylalanine[75] with mixtures of (*S*)-**PEA** and (*R*)-phenylglycine methyl ester, its amide and benzylamine was tried with varying success. Resolution of *N*-formylphenylalanine with a 1 : 1 mixture of the methyl ester and the amide of (*R*)-phenylglycine and its amide and benzylamine gave better results than any of the individual agents alone. The precipitated salt (yield: 79%, ee: 100%) contained, however, only the amide.[75]

Later it was also found[76] that some racemates, which could not be resolved with a given resolving agent in a pure state could be separated when mixed with another racemic or achiral compound of a similar type. *E.g.* pure racemic 4-hydroxyphenylglycine (**HPG**) and 4-fluorophenylglycine (**FPG**) could not be resolved with (1*S*)-10-camphorsulfonic acid (ee < 5%), but when mixed with racemic phenylglycine (**PG**) resolution for both was successful, although yields were low (Fig. 21). It is supposed, and supported by molecular modeling studies, that the salt of the component with low resolution efficiency forms a solid solution with the salt of its well resolvable partner.[70]

The above and other experiments are highly interesting from a theoretical point of view but their practical value is limited.

3.1.5 Resolution with a derivative of the target compound. Finding the optimal resolving agent for a target molecule has become a challenging exercise owing to the continuously widening range of commercially available resolving agents. Often, however,

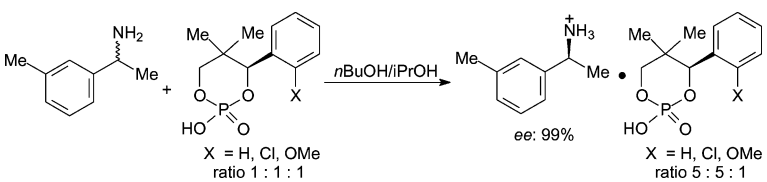


Fig. 19 Resolution of 1-(3-methylphenyl)ethylamine with a mixture of three similar resolving agents.

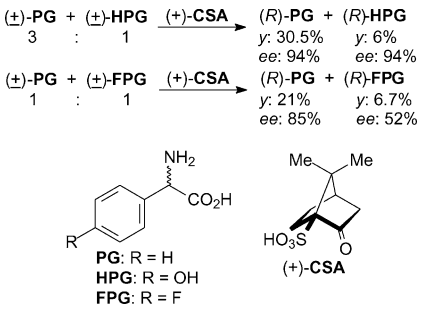


Fig. 21 Resolution of mixtures of phenylglycine (**PG**) and 4-hydroxyphenylglycine (**HPG**) as well as of **PG** and 4-fluorophenylglycine (**FPG**) with (+)-10-camphorsulfonic acid [(+)-**CSA**].

the following short-cut can be useful: it is known that about 90% of chiral compounds form a separate racemic phase,[77] which means that the crystals of the pure enantiomers are less stable (and, with very few exceptions, lower melting) than those of the racemic mixture. It can therefore be presumed that an enantiomerically pure derivative of the compound to be resolved should be an efficient resolving agent by forming a stable "quasi racemic" phase. In addition, in this way it is just the unwanted enantiomer, otherwise to be discarded, that can be put to good use.

The method seems to be quite efficient, yielding products of high optical purity and in good yield (Table 3 and Fig. 22).[78,79] The latter example[78] is noteworthy because the diastereoisomeric salt contains one molecule of one of the enantiomers and two molecules of the derivative while the other enantiomer stays in solution.

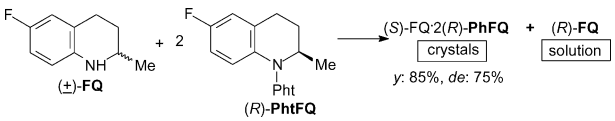


Fig. 22 Resolution of the flumequine intermediate (**FQ**) with its hemiphthalate [(*R*)-**PhtFQ**], Pht = phthaloyl.

Similarly 1-phenylethylamine[69] and its 2-, 3- and 4-methyl analogues[80] could be resolved using monoamides of (*R*)-1-phenylethylamine with oxalic, malonic and succinic acid. The highest 2-methyl derivative ee values were achieved with the succinate.

3.1.6 Enantioselective chromatography. Chromatographic separation of diastereomers is bread and butter for preparative chemists and need not be discussed here. Enantioselective chromatography developed from modest beginnings (separation of Tröger's base on lactose, 1944)[81] to a universal technique, especially after the advent of HPLC and more recently capillary electrophoresis (CE). Nowadays the determination of ee values by chiral HPLC has almost completely superseded measurement of optical rotation. For enantiomer separation both chiral mobile and stationary phases (CSP) can be used, the former rather for analytical purposes. Separation of CSPs has reached a stage of maturity permitting resolution on a multigram scale, and what is even more important, furnishing of both pure enantiomers. This is of prime importance for drug discovery, because the biological activity of both can be tested and compared. For manufacturing purposes the method still seems to be too expensive therefore we restrict ourselves to quoting some reviews.[82–84]

The introduction of supercritical fluid chromatography (SFC) with packed-CSP columns is a major step towards large scale resolution. The use of supercritical CO_2 often provides a three to five times faster separation than normal-phase HPLC.[85,86]

Simulated moving bed (SMB) countercurrent chromatography, the principle of which has already been invented in the sixties, finally offers a means for large scale chromatographic separation of enantiomers.[87–92] An apparatus built on this principle contains a circularly arranged battery of HPLC columns, through which a mobile phase is pumped. The input point of the racemic mixture and two extract points of the resolved components are continuously rotated around the system. 100 g to kgs of pure enantiomers are claimed to be producable with this apparatus.

3.1.7 Enantioselective phase transfer. By substituting one of the three hydroxyl groups of methyl cholate with a strongly basic group, and converting the other two to *N*-phenylurethane groups, phase transfer catalysts were obtained which were capable of differentiating between *N*-acyl amino acid enantiomers.[93] The hydrochloride salt of the catalyst dissolves in chloroform and on equilibration with a neutral aqueous solution of an *N*-acyl amino acid one of the enantiomers exchanges selectively with the chloride ion in the organic phase. By separating the two phases up to 80% ee can be achieved with catalyst **GCH2** (Table 4, Fig. 23).

Table 3 Resolutions by a derivative of the compound to be resolved. (Pht = phthaloyl)

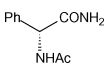
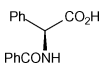
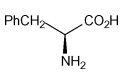
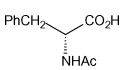
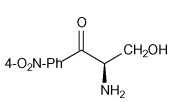
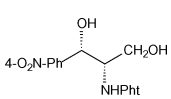
Enantiomer in the precipitated salt	Resolving agent	Yield (%)	ee (%)
		86	100
		90	95
		80	100
		95	81

Table 4 Enantioselective extraction of *N*-acyl amino acids with a guanidinium salt prepared from cholic acid (**GCH2**)

Substrate	Mol% extracted	ee % (L)
(±)-*N*-Ac-alanine	76	72
(±)-*N*-Ac-phenylalanine	93	80
(±)-*N*-Ac-tryptophane	92	72
(±)-*N*-Ac-valine	89	80
(±)-*N*-Ac-*tert*-leucine	82	44
(±)-*N*-Ac-methionine	93	80
(±)-*N*-Ac-proline	74	60
(±)-*N*-Ac-asparagine	0	—

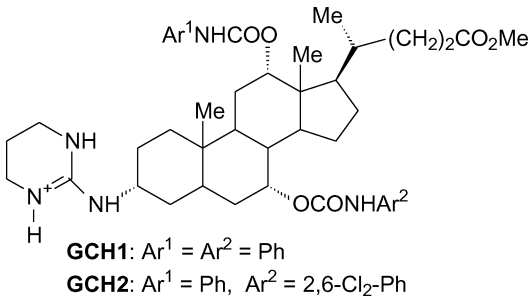


Fig. 23 Guanidinium ions **GCH1** and **GCH2**, derived from cholic acid, which are used in the enantioselective phase transfer of *N*-acetyl-α-amino acids into $CHCl_3$ from an aqueous medium.

3.2 Resolution by formation of covalent diastereomers

Covalent diastereomer formation has to be considered for molecules which are incapable of salt formation. Sometimes even with acids recourse is taken to amide formation with a chiral amine. The most often used partner for this technique is the workhorse of conventional resolutions *i.e.* 1-phenylethylamine (**PEA**). In the simplest case, diastereomeric amides are prepared and separated by fractionated crystallization. Since acids can be readily resolved by diastereomeric salt formation, here we only refer to typical papers.[94–96] Sometimes, however, as *e.g.* with δ-decalactone, a fragrant component, resolution by salt formation fails and the indirect way has to be used (Fig. 24).[31]

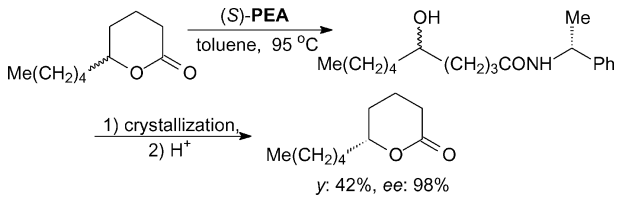


Fig. 24 Resolution of δ-decalactone by amide formation with (*S*)-**PEA**.

1-Phenylethanol proved to be useful for resolving a chiral tetracoordinated boron compound by diastereoisomeric ester formation followed by crystallization. Although the example in Fig. 25[97] also involves an acid, owing to the exotic nature of the chiral center it deserves to quoted.

The planary chiral cyclophane aldehyde in Fig. 26 was resolved by forming an azomethine with (*R*)-**PEA** followed by crystallization.

1,1′-Bi-2-naphthol enantiomers are important starting materials for enantioselective catalysts and reducing agents. An interesting way to resolve them is their transformation with L-proline to a

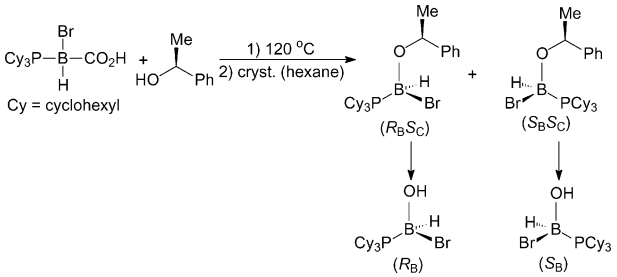


Fig. 25 Resolution of a chiral tetracoordinated boron compound by esterification with (*S*)-1-phenylethanol.

pair of diastereomeric mixed boric anhydrides. Separation of the latter followed by hydrolysis gives both enantiomers pure and in high yield (Fig. 27).[98]

Alternatively (*R*)- or (*S*)-1-(α-pyrrolidinylbenzyl)-2-naphthol can be used to form a similar pair of diastereomeric borates with **BINOL**.[99]

A very practical way of resolution *via* diastereomeric derivatives is when removal of the chiral auxiliary moves the synthetic sequence one step further, instead of regenerating the original functional group (Fig. 28).[100] After separation, each of the diastereomeric dithiolanes can be converted either to a flavan or to a flavanone.

4. Resolution by substrate selective reactions

4.1 Kinetic resolution without enzymes

Kinetic resolution discovered in 1899 by Marckwald and McKenzie[3] is a substrate selective process in which components of a racemic mixture react at different rates with a chiral reagent. Examples of efficient kinetic resolutions, apart from enzymatic processes, are rare. A nice example is the resolution of a 1,4-benzoxazine derivative by reaction with 0.5 eq. of (*S*)-naproxenyl chloride (Fig. 29).[101]

Enantioselective catalytic hydrogenation is well known, but chiral complexes may catalyze kinetic resolutions by an achiral agent too. Thus aryl alcohols were submitted to non-enzymatic kinetic acetylation in the presence of a chiral catalyst (0.5–2%,) providing efficient enantiomer separation (Fig. 30).[102]

Parallel kinetic resolution is a process in which two different chiral reagents react preferentially with one particular enantiomer of a racemate.[103] The result depends on the nature of the reagent. In the process shown in Fig. 31 both the reagents and the products are of different constitution, while in Fig. 32 the reagent is pair of diastereomers and one enantiomer of the substrate is preferentially transformed.

Parallel kinetic resolution[104] (Fig. 31) has also been carried out on both enantiomers (Fig. 33).

In the sequence presented in Fig. 33 the *S* enantiomer of 1-(1-naphthyl)-ethanol reacts practically only with chlorocarbonate (*R*)-**PMe**, while its antipode reacts only with fenchyl carbonate (*S*)-**PBn**.

An even more exotic example of parallel kinetic resolution is presented in Fig. 32. Owing to hindered rotation around the N–N bond the quinazoline **QUZ** is in fact a mixture of two diastereomers, which could be separated. Each reacted selectively

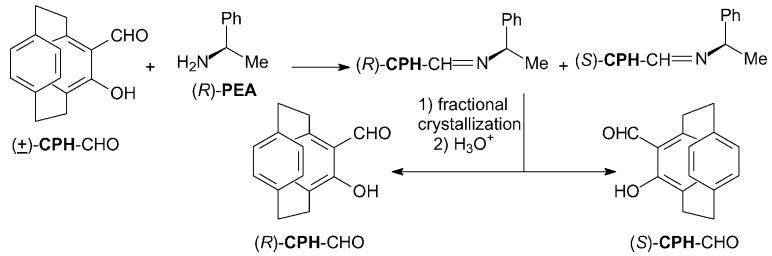


Fig. 26 Resolution of an aldehyde *via* azomethine formation with 1-phenylethyl amine (PEA).

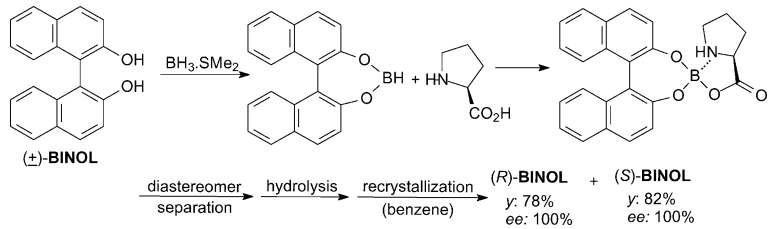


Fig. 27 Resolution of 1,1′-bi-2-naphthol by forming a pair of diastereomeric borate esters with (*S*)-proline.

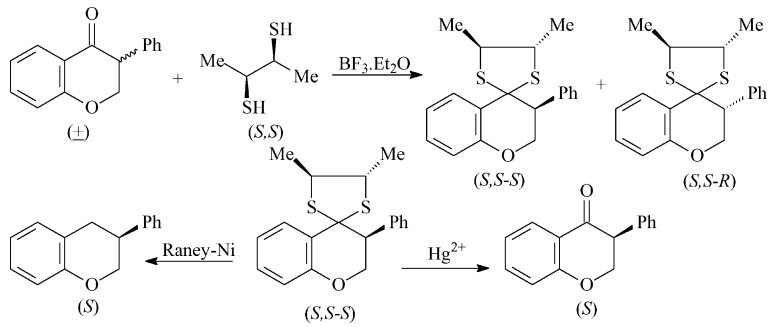


Fig. 28 Preparation of the enantiomers of flavan-4-one and flavan *via* dithiolan formation with (*S*,*S*)-2,3-butanedithiol.

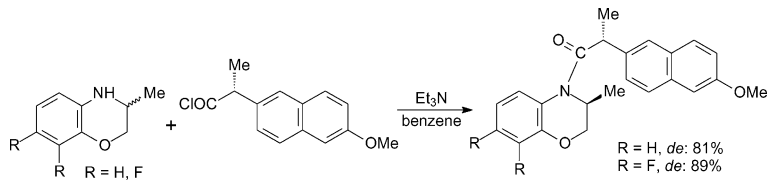


Fig. 29 Kinetic resolution of benzoxazines with (*S*)-naproxenyl chloride.

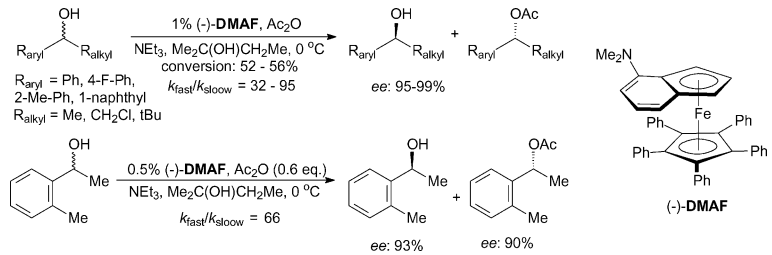


Fig. 30 Kinetic resolution of alcohols by acetylation in the presence of a planary chiral catalyst.

with only one enantiomer of 2-methylpiperidine leaving the other unreacted.[105]

When a series of (±)-*trans*-2-(alkyl,aryl)-aminocyclohexanols were reacted with *N*-chlorosuccinimide in the presence of (*S*)-BINAP, only the 1*S*,2*S* enantiomer was chlorinated, while the 1*R*,2*R* amine remained unreacted (ee: 59–97%).[106]

Finally an ingenious example of kinetic resolution should be quoted.[107] The expensive ruthenium complex of (*R*)-BINAP selectively catalyzes the hydrogenation of (*S*)-2-cylohexenol. When (1*R*,2*S*)-ephedrine was added to the system containing a racemic catalyst, the (*S*)-BINAP complex was selectively poisoned while its antipode remained active (Fig. 34).

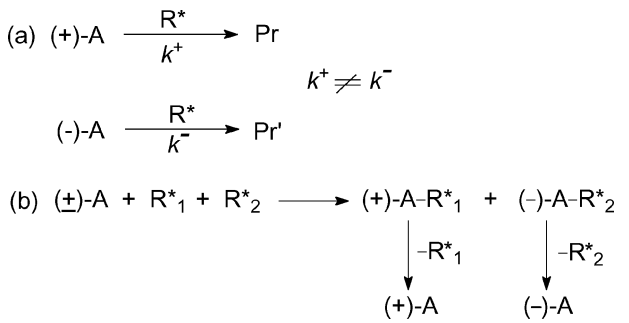


Fig. 31 Schemes for kinetic (a) and parallel kinetic resolution (b). (a) R* is a chiral reagent, Pr and Pr′ are diastereomeric products, (b) R_1* and R_2* are different chiral reagents, while (+)-A–R_1* and (−)-A–R_2* are different compounds.

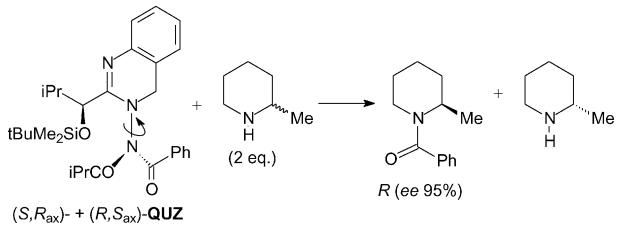


Fig. 32 Parellel kinetic resolution of an amine with a pair of axially chiral diastereomers of an acylating agent (only one shown).

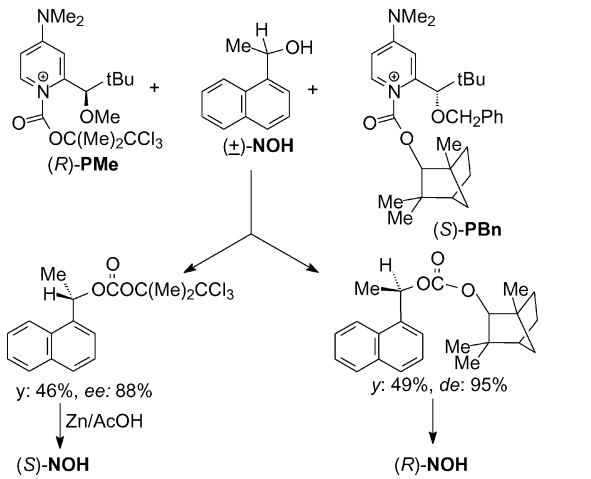


Fig. 33 An example of a parallel kinetic resolution.

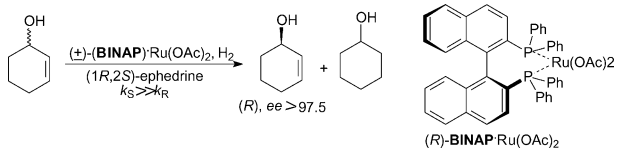


Fig. 34 Enantioselective hydrogenation of cyclohexen-2-ol with a racemic BINAP–ruthenium catalyst selectively poisoned with (1*R*,2*S*)-ephedrine.

4.2 Kinetic resolution by enzyme catalysis

In recent years, the use of biocatalysts for organic syntheses has become an attractive alternative to conventional methods and has found its way into industry where multi-kilogram to one ton magnitude is not unusual and even a thousand-ton scale is known.[108] A considerable portion of the several hundred papers in this field and several reviews (*e.g.* refs 109,110) deal with the enantioselective enzymatic transformation of racemates. It may not be surprising that the father of this technique was again Louis Pasteur, who submitted racemic ammonium tartrate to fermenting yeast which left the unnatural 2*S*,3*S* enantiomer unchanged.[111]

The advantages of resolution by enzyme catalysis are numerous: a wide selection of commercially available enzymes, most often at reasonable price, high to total selectivity, stability in organic solvents, mild reaction conditions, low burden on the environment, simple work-up. Owing to the extent of the relevant literature, this short review can only highlight a few typical examples.[112]

4.2.1 Hydrolytic enzymes. Enzymatic hydrolysis is still the most widespread technique, although it has some drawbacks (often high dilutions are required and recovery of the enzyme is problematic).

Faulconbridge *et al.* observed strong pH-dependence in *Pseudomonas cepacia* lipase catalyzed hydrolysis of β-phenylalanine ethyl ester. Increasing the pH from 7 to 8 the enantiomeric excess increased from 73% to 99% at equal conversion.[113] (Fig. 35).

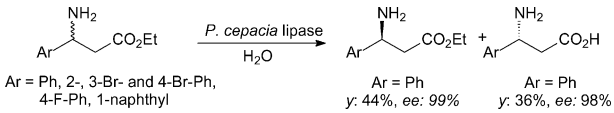


Fig. 35 Resolution of β-amino acid esters using *P. cepacia* lipase.

Lipase from *Candida antarctica* (a new "favourite") gave excellent results in the resolution of a β-lactame derivative[114] (Fig. 36).

δ-Ketoesters were successfully resolved in a phosphate buffer with a protease (α-chymotrypsin)[115] (Fig. 37).

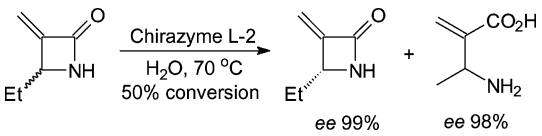


Fig. 36 Resolution of an α-methylene-β-lactam using *Candida antarctica* lipase.

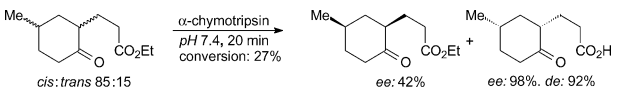


Fig. 37 Resolution of δ-ketoesters with α-chymotrypsin.

Enzymatic acylation in organic solvents may be more efficient than hydrolysis, since the enzyme can be recovered by simple filtration and by choosing an appropriate acylating agent (*e.g.* vinyl or isopropenyl acetate) the reaction becomes irreversible resulting in higher enantiomeric purities.

It has been demonstrated, that for the resolution of diols, acetylation of the secondary hydroxy group of the 1-acyl derivative is far more enantioselective than earlier methods based on hydrolysis of the diester or acylation of the diol, (Fig. 38 and Table 5).[116] Marked differences in the results between models with slightly different R groups demonstrates, however, the substrate sensitivity of enzyme systems and the need for optimization for each substrate. It has to be emphasized that total selectivity of enzyme systems is only guaranteed for their natural substrates

Table 5 Yields and ee values realized in the reactions shown in Fig. 38

Substrate	R	Method	Product I	Yield (%)	ee (%)	Product II	Yield (%)	ee (%)
(±)-1,2-Ac	*n*Bu	i	(*R*)-1,2-Ac	40	15	(*S*)-1-Ac	36	13
(±)-1,2-Ac	iPr	i	(*R*)-1,2-Ac	45	30	(*S*)-1-Ac	42	32
(±)-1-Ac	*n*Bu	ii	(*S*)-1-Ac	45	13	(*R*)-1,2-OH	46	14
(±)-1-Ac	iPr	ii	(*S*)-1-Ac	64	0	(*R*)-1,2-OH	14	4
(±)-2-Ac	*n*Bu	iii	(*S*)-2-Ac	15	22	(*R*)-1,2-OH	49	5
(±)-2-Ac	iPr	iii	(*S*)-2-Ac	60	1	(*R*)-1,2-OH	21	5
(±)-1,2-OH	*n*Bu	iv	(*S*)-1,2-OH	67	3	(*R*)-1-Ac	21	9
(±)-1,2-OH	iPr	iv	(*S*)-1,2-OH	44	32	(*R*)-1-Ac	46	31
(±)-1-Ac	*n*Bu	v	(*R*)-1-Ac	52	28	(*S*)-1,2-Ac	41	34
(±)-1-Ac	iPr	v	(*R*)-1-Ac	59	22	(*S*)-1,2-Ac	24	46
(±)-2-Ac	*n*Bu	vi	(*R*)-2-Ac	39	49	(*S*)-1,2-Ac	48	40
(±)-2-Ac	iPr	vi	(*R*)-2-Ac	53	57	(*S*)-1,2-Ac	37	100

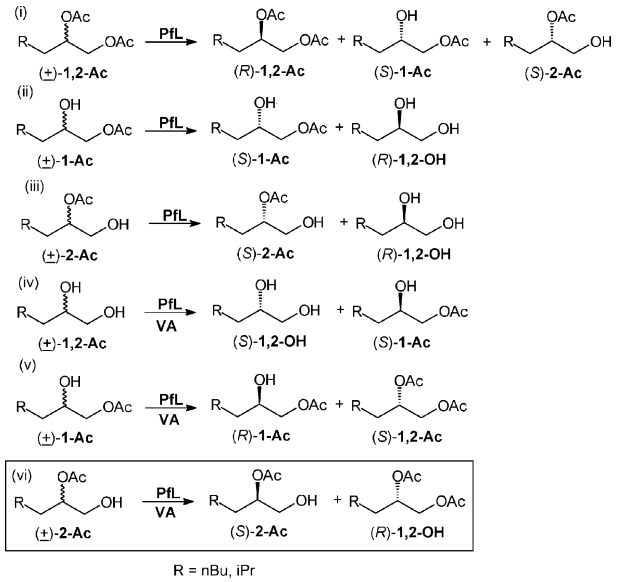


Fig. 38 Resolution of heptan-1,2-diol (R = nBu) and 4-methylpentan-1,2-diol by enzymatic hydrolysis (i–iii) and enzymatic acylation (iv–vi) and acetylation with *Pseudomonas fluorencens* lipase (**PfL**) (**VA** = vinyl acetate).

and the more the structure of a non-natural substrate deviates from that of the natural one, the less selectivity can be anticipated.

Some 1-oxyl-hydroxymethylpyrrolidines used to prepare spin labels were resolved by acetylation with various lipases.[117]

Enzymatic amidation of an achiral ester is another technique for producing optically active amino acid esters. *E.g.* in penicillin G acylase catalyzed amidation of methyl 4-hydroxyphenylacetate with racemic amino acid esters in organic solvents gives selectively the *S* amides, while the (*R*)-phenylglycine ester remains mainly unreacted (ee 75–98%) (Fig. 39).[118]

A process very promising for large scale applications uses immobilized enzymes in a flow system and supercritical carbon dioxide ($scCO_2$) as the solvent.[119] Passing a solution of racemic 1-phenylethanol and vinyl acetate in $scCO_2$ through a flow reactor packed with Novozym 435, an immobilized lipase from *Candida antarctica* gave almost quantitative yields of the unreacted (*S*)-alcohol and the (*R*)-acetate, both enantiomerically pure.

Aromatic amides were hydrolyzed with whole cells of *Escherichia coli* containing the *Pseudomonas putida* L-aminopeptidase gene.[120] The reaction was accompanied by *in situ*

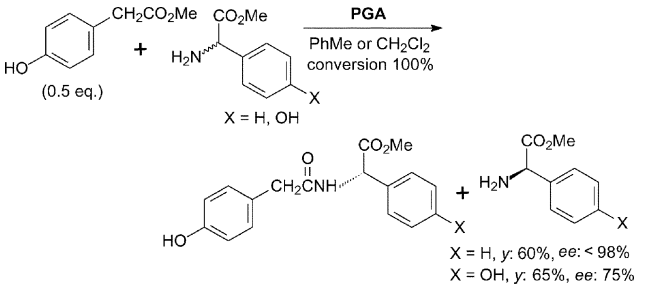


Fig. 39 Penicillin G acylase (**PGA**) catalyzed enantioselective amidation of an ester in organic solvents.

racemization of the amide which did not affect the acid permitting the obtainment of the *R* acid in 98% ee and in yields higher than 50% (Fig. 40).

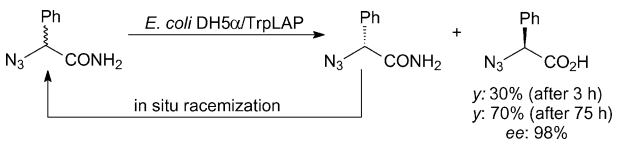


Fig. 40 Enzymatic hydrolysis of an α-azido amide combined with a second order asymmetric transformation using an *E. coli* strain containing the *P. putida* L-aminopeptidase gene (*E. coli* DH5α/pTrpLAP).

The term dynamic kinetic resolution (DKR) has been coined recently for the above process[121] which involves an enantioselective transformation combined with *in situ* racemization (spontaneous, enzyme[122] or non-enzyme catalyzed[123]).

The hemiaminal **HA** readily racemizes spontaneously *via* the open-chain form, while enzymatic acylation only transforms the *R* enantiomer (Fig. 41).[124]

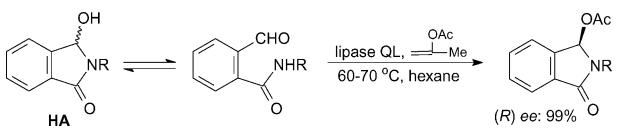


Fig. 41 Dynamic kinetic resolution of a hemiaminal by lipase catalyzed acetylation.

With chiral secondary alcohols racemization of the unreacted enantiomer can be brought about by metal catalysis as in the following example (Fig. 42).[125]

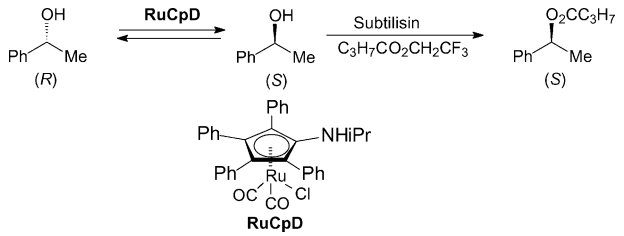


Fig. 42 Dynamic kinetic resolution of a secondary alcohol by enzyme catalyzed acetylation and metal catalyzed racemization.

4.2.2 Redox enzymes. Reduction and oxidation reactions have less synthetic relevance at the moment. This does not mean lack of interest, but rather that at present these techniques are less suitable for the production of larger quantities.

The example in Fig. 43[126] is notable in this way, that the oxidation product is reverted to the racemate by chemical reduction.

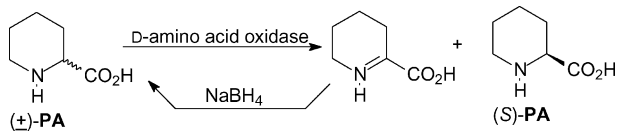


Fig. 43 Resolution of pipecolic acid by oxidation with D-amino acid oxidase and recycling of the achiral oxidation product.

4.3 Kinetic and thermodynamic control

Conventional resolution methods based on diastereomeric salt formation are usually under thermodynamic control. However, sometimes kinetic effects have also been observed and simultaneous detection of both phenomena in an induced crystallization process has been reported.[127] This example also involves induced crystallization, moreover it was triggered by a different compound. Addition of 6 mol% of L-alanine to an oversaturated aqueous solution of (±)-threonine induced, after standing for 2.5–3 hours, the crystallization of D-threonine in high ee (kinetic control). On prolonged standing, the enantiomeric purity of the product declined sharply (to 16% after 4.5 h) (thermodynamic control).

5. Resolutions combined with 2nd order asymmetric transformations. Racemization and deracemization

Racemization is an important partner process to resolution, since usually only one of the enantiomers is required and by racemization the unwanted one can be recycled. Racemization of compounds with more than a single stable chiral center cannot usually be accomplished.

With configurationally labile compounds, or in media inducing inversion of the chiral center, resolution may be accompanied by racemization of the enantiomer forming the less stable (or more soluble) diastereomer, whereby the total amount of the racemate can be transformed to a single diastereomer. The rather clumsy term for this process is second order asymmetric transformation and denotes also the very rare cases when one of the enantiomer spontaneously crystallizes and its concentration is continuously replenished by racemization of its antipode (see also dynamic kinetic resolution in Section 4.2).

An example of such a process is shown in Fig. 44.[128] The mandelate salt of the *R* enantiomer crystallizes, while its antipode racemizes yielding the pure *S* salt in high yield.

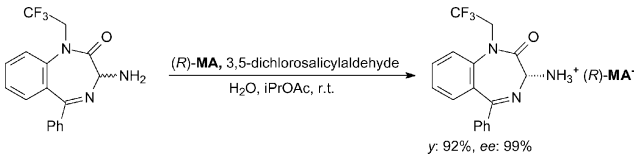


Fig. 44 Resolution of an amine with (*R*)-mandelic acid [(*R*)-**MA**] combined with a second order asymmetric transformation.

Another example of a second order asymmetric transformation is the resolution of 1,4-thiazane-3-carboxylic acid with (*R*,*R*)-tartaric acid in the presence of salicylaldehyde as the epimerization catalyst giving the salt of the pure *S* enantiomer in high yield (Fig. 45).[129]

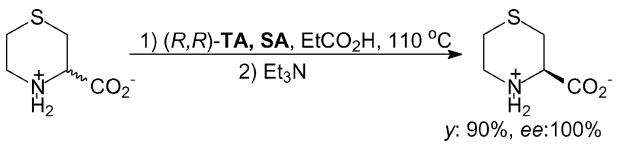


Fig. 45 Resolution of 1,4-thiazane-3-carboxylic acid with (*R*,*R*)-tartaric acid coupled with second order asymmetric transformation induced by salicylaldehyde (**SA**).

Deracemization is the transformation induced by an optically active agent of a racemic mixture to a non-racemic one without any net change in the composition of the molecule. An example is the deracemization of a number of chiral acids, such as 2-(4-isobutylphenyl)propionic acid (ibuprofen), mandelic acid and 2-phenylpropionic acid during the crystallization of their melt in the presence of 2-phenylethylbenzylamine (**MBA**) (1.5–10 eq.) and of a catalytic amount of a strong base *e.g.* 1,5-diazabicyclononene (**DBN**) (Fig. 46).[130] The preferred configuration depended, of course, on the configuration of **MBA**, *i.e.* in the case of ibuprofen (*R*)-**MBA** shifted the equilibrium towards the *R* acid and *vice versa*.

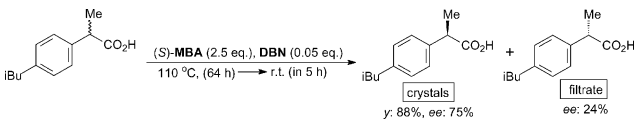


Fig. 46 Crystallization coupled deracemization of an α-arylpropionic acid (ibuprofen) in melt (optimized conditions).

Deracemization may also be effected by enzymes. The fungus *Rhizopus orizae* not only deracemizes benzoin, but the configuration of the product can even be controlled by the pH of the medium (Fig. 47).[131]

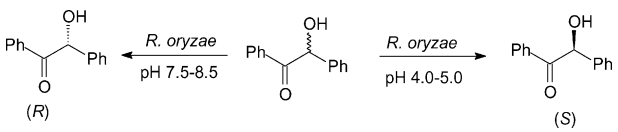


Fig. 47 pH dependent deracemization of benzoin by the fungus *Rhizopus oryzae*.

6. Enrichment of partially resolved mixtures

Optical resolutions and enantioselective reactions usually result in non-racemic but optically more or less impure products, which need further enrichment. That is, the mixture has to be separated in an optically pure and a racemic portion. This latter can then be recycled. Enrichment can be achieved by repeated resolution or, without further chiral auxiliaries, *e.g.* simply by recrystallization from a solvent, partial crystallization of a melt, selective precipitation, distillation or extraction. Enantiomeric enrichment can be characterized by the parameter *EEE* defined as follows:[132]

$$\mathrm{EEE} = op_c y/op_0$$

, where op_c and op_0 are the ee values of the enriched and initial mixture and y is the mass ratio of the enriched and initial mixtures.

The behavior of mixtures of enantiomers depends on its initial enantiomeric purity (ee_0) and whether crystals of the molecule or its derivative, *e.g.* a salt, forms a conglomerate or, apart from the two phases of the pure enantiomers, also a separate racemic phase (often called a racemate or racemic molecular compound) (Fig. 48). A survey of a large number of chiral compounds (quote ref. 77) revealed that about 80% of them form a separate racemic phase. With any method of crystallization (from melt or from a solvent) yield, optical purity and configuration of the product is controlled by the initial composition (x_0) and the phase behavior of the compound. With conglomerates always the enantiomer in excess crystallizes until the solution becomes saturated for the minor component. The theoretical upper limit of the yield of the pure enantiomer is the ee value of the starting mixture (ee_0). With compounds forming a separate racemic phase it depends on the relative position of ee_0 and the eutectic composition (ee_{eu} or x_{eu}), whether on solidification of a melt or recrystallization from a solvent it is the racemate or one of the pure enantiomers that crystallizes first.

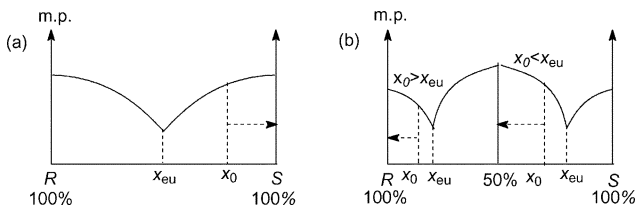


Fig. 48 Binary phase diagrams of enantiomeric mixtures: (a) conglomerate, (b) formation of a separate racemic phase ("racemate"). Arrows point to the product that crystallizes from a given composition.

Sometimes a minor modification can change the solid phase behavior of a compound. *E.g.* while (±)-1,4-benzodioxane-2-carboxylic acid forms a racemic phase, its methyl ester forms a conglomerate.[133]

Although recrystallization is usually the method of choice, sometimes simple melting is sufficient for enantiomeric enrichment (Table 6).[78,132] Followed by complete melting the mixture is cooled to an optimized temperature, kept at this temperature for a while and the crystals formed are filtered off. With conglomerate forming enantiomers it is of course the one in excess in the initial mixture which is isolated as crystals, while the other remains in the filtrate. The data in Table 6 suggest that the method works best with medium values of ee_0. Since precise control of the conditions is required, this method is not recommendable for resolutions on a small scale.

Recrystallization of non-racemic mixtures is the most straightforward enrichment procedure. Results for a series of model compounds are shown in Table 7. Note, that similarly to the melting method, depending on the phase behavior and ee_0, it is either the racemic or the (theoretically pure) enantiomer portion which crystallizes.

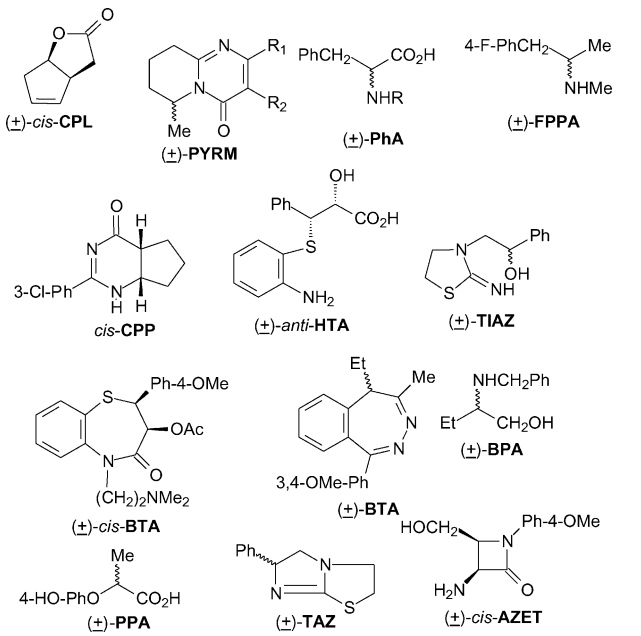


Fig. 49 Model compounds for enrichment experiments. For codes of compounds not shown here see Fig. 15.

Table 6 Enantiomeric enrichment by partial crystallization of a melt of conglomerate forming enantiomers, compound structures given in Fig. 49

		Solid phase		Liquid phase		
Racemate	ee_0	ee (%)	Yield (%)	ee (%)	Yield (%)	*EEE*[b]
CPL[a]	21.5	69.2	10.0	6.2	84.3	32.2
	29.2	72.5	39	2.6	59.0	96.8
	52.3	76.9	44.9	29.2	55.1	66.0
cis-**CHRA**	42.6	15.5	60.0	83.3	40.0	78.2
PYRM R_1=Me, R_2=Et	48.2	83.5	32.1	28.5	64.7	55.4
FQ	69.5	93.7	29.5	57.4	68.6	39.8

[a] Crystallization at 0–5 °C. [b] Calculated for the higher enriched phase.

Table 7 Enantiomeric enrichment by recrystallization from a solvent (compound codes refer to Fig. 49)

Racemate	Acid or base	ee_0	Crystals		Mother liquor		*EEE*
			ee (%)	Yield (%)	ee (%)	Yield (%)	
PhA·HCl, R = H	NH_4OH	60.6	11.4	42.5	97.1	57.0	91.3
PhA$^-NH_4^+$, R = Ac	HCl	31.0	5.2	28.1	44.0	65.0	92.3
PhA$^-NH_4^+$, R = CHO	HCl	40.1	24.3	44.2	53.1	55.3	73.2
trans-**PMA**$^-Na^+$	HCl	43.4	81.1	47.6	4.7	35.3	88.9
cis-**PMA**$^-Na^+$	HCl	25.8	10.2	35.6	36.3	58.9	82.9
BPA·HCl	NaOH	80.0	81.0	27.9	78.0	71.1	28.3
PPA$^-Na^+$	HCl	48.3	7.4	24.3	63.5	73.2	96.2
anti-**HTA**$^-Na^+$	HCl	53.2	27.7	23.4	62.4	71.0	83.3
TAZ·HCl	NaOH	80.3	5.0	12.7	99.6	65.5	81.2
cis-**AZET**·HCl	NaOH	25.8	10.2	35.6	36.3	58.9	82.9

As a modification of the above technique less than one molar equivalent of an achiral acid or base is added to the solution of the salt of the racemate, usually in water, resulting in significant enantiomeric enrichment owing to selective precipitation (Table 7).[132] Note that with high ee_0 values (*e.g.* with **BPA**) the process is inefficient.

Every available achiral method has been tested for the enrichment of partially resolved *N*-methylamphetamine of which partial hydrochloride salt formation and distillation proved to be the most effective.[134]

Apparently, except for the case of immiscible solvents, any procedure that involves some kind of distribution between phases is eligible for enantiomeric enrichment.

7. Role of the solvent and methods of optimization in the separation of diastereomers

Classical resolutions are based on the different solubility of diastereomers formed by interaction of the enantiomers with a chiral agent. The proper choice of solvent is therefore essential for an efficient separation. In this respect valuable information can be gleaned from a recent comprehensive compilation of several hundred resolutions (*e.g.* Table 8).[32]

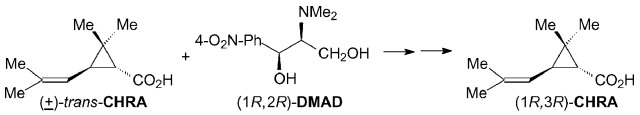
When the enrichment is carried out by recrystallization, solvent mixtures may be preferred to pure solvents. Sometimes saturating water with an immiscible solvent may bring about significant improvement. When *e.g.* mandelic acid was resolved with (*S*)-2-benzylaminobutanol in water, the ee of the *R* enantiomer increased from 36 to 68%, when water saturated with ethyl acetate was used. In ethyl acetate alone the ee of the product was only 16%.[135]

A similar solvent dependence of yield, ee, and configuration of the crystallizing enantiomer was observed in the resolution of 1-phenylethylamine (**PEA**) with (*R*,*R*)-tartaric acid. In pure methanol the salt of (*S*)-**PEA** was obtained (ee: 72%, *y*: 33%), while in water, acetonitrile and ethanol the salt of its antipode crystallized in yields of 50–88% but in very poor optical purity (ee: 4–12%).[136] When in the resolution of (±)-*threo*-methylphenidate·HCl (Ritalin®) a 1 : 1 methanol–water mixture was replaced by a 2 : 1 mixture, the ee of the product dramatically increased from 16.2 to 99.5%.[137]

Table 8 Correlation of solvent composition, yield and ee of the precipitated product in the resolution of *N*-methylamphetamine (**NMA**) with (*R*,*R*)-**DTTA** in a two-phase system

$Cl(CH_2)_2Cl : H_2O$: MeOH	ee (%)	Yield (%)
0 : 0 : 1	54.4	71.7
1 : 4 : 0	82.5	94.8
5 : 20 : 1	85.2	93.0
5 : 20 : 2	87.8	90.5
5 : 20 : 6.3	97.9	79.6
5 : 0 : 6.3	84.6	82.6

It has to be noted that solvent mixtures may play a dual role. Beside providing sufficient solubility difference of the components, they may increase yield and enantiomeric purity by being integrated into the crystal structure of the more stable diastereomer and thereby facilitate crystal growth. Fig. 50 shows the optimization of the resolution of (±)-*trans* chrysanthemic acid with a resolving agent prepared from an intermediate of chloramphenicol synthesis. 17 mixtures of miscible solvents were tested (Fig. 50).[138]



Solvent	Yield (%)	*ee* (%)
MeOH	52.5	93.1
iPr_2O–MeOH (6:1)	84.4	96.7
nBu_2O–MeOH (6:1)	99.2	83.9
Et_2O–MeOH (1:1)	86.5	99.3

Fig. 50 Resolution of *trans*-chrysanthemic acid (*trans*-**CHRA**) with (1*R*,2*R*)-1-(4-nitrophenyl)-2-*N*,*N*-dimethylamino-1,3-propanediol (**DMAD**) in miscible solvent mixtures (selected examples).

The predominant configuration of the substrate in the salt of 7-aminocaprolactam (**ACA**) with *N*-4-toluenesulfonyl-L-phenylalanine (**PhATs**) was found to be dependent on the dielectric constant of the solvent: in the range of $\varepsilon = 25–63$ it was *R*, while outside this range *S*, albeit with very poor ee values (Fig. 51).[139–141]

8. Non-linear effects

In recent years in connection with the application of enantioselective catalysts some reviews[142,143] have focused on reactions involving partially resolved chiral auxiliaries. A surprising message of these papers is that the ee values of product and catalyst often do not show a linear correlation (non-linear effect, NLE) (Fig. 52). *E.g.* a catalyst of rather low (5–9%) ee may give rise to products

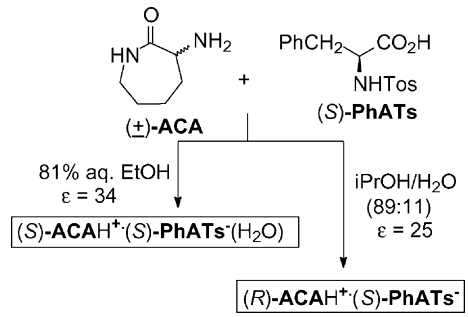


Fig. 51 Influence of the dielectric constant of the solvent on the predominant configuration of the substrate in the salt of 7-aminocaprolactam (**ACA**) with *N*-4-toluenesulfonyl-L-phenylalanine (**PhATs**).

of unexpectedly high (43–50%) optical purity as shown in Fig. 52, and Fig. 53.

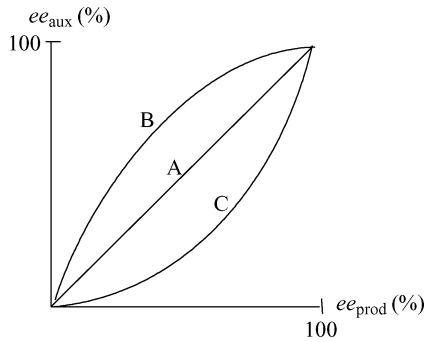


Fig. 52 Linear (A), positive (B) and negative (C) correlation between the chiral auxiliary and the product optical purity (ee_{aux} and ee_{prod}).

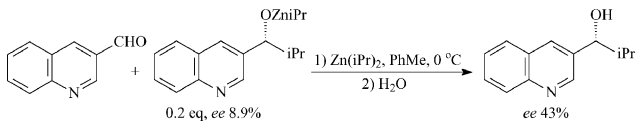


Fig. 53 (+)-NLE in the addition of diisopropylzinc to quinoline-3-carbaldehyde.

The example in Fig. 53 was selected from a very large number of examples for non-linear effects covered by the reviews quoted above.[142,143]

Data for non-linear effects in resolutions are scarce, although in the authors' opinion it may be a more general phenomenon than has been recognized.

Non-linear correlations were reported in resolutions by molecular complex formation,[144] and the distillation method.[72] When *e.g.* salts were formed from a series of achiral dicarboxylic acids (0.75 eq.) and **PEA**, marked non-linear correlation of ee_0 and the ee of the distillate was observed.[145,146]

Resolution of *N*-formylphenylalanine with (*R*)-phenylethylamine of varying optical purity (8.3–100%) was associated with a (−)-NLE: the de of the precipitating salt was always lower than the ee value of the resolving agent.[147]

9. Selected examples of resolution on an industrial scale[148]

An overwhelming majority of large scale resolutions serve the drug industry, followed at considerable distance by the production of insecticides, fragrances and food supplements. Procedures are mostly disclosed by patents but information gleaned from patent specifications have to be taken with a grain of salt. "Know-how" plays an important role in such procedures and therefore patents often fail in the second point of the oath formula: "the whole truth". The following examples are chosen rather arbitrarily and may partly overlap with those described in preceding sections.

Chloramphenicol (antibiotic)

An aminoketone intermediate of the synthesis of chloramphenicol, (±)-**AK**, was resolved with one equivalent of an acid (*S*,*S*)-**PhtAD**, prepared from the unwanted enantiomer of a later intermediate. Owing to *in situ* racemization of (*S*)-**AK**, the salt of (*R*)-**AK** was obtained in 95% yield (Fig. 54).[149]

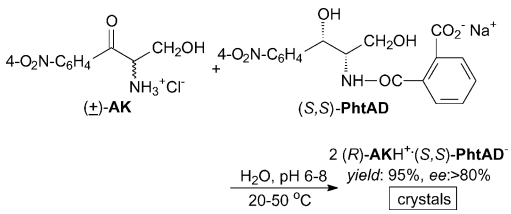


Fig. 54 Resolution of a chloramphenical intermediate.

Resolution of the aminodiol intermediate (±)-**AD** was originally performed with 0.5 eq. of *O*,*O*′-dibenzoyl-(*R*,*R*)-tartaric acid semi-*N*,*N*-dimethylamide [(*R*,*R*)-**DBTAHA**] ammonium salt,[150] but later a continuous process was invented using 0.5 eq. of the same resolving agent as the calcium salt. The components were fed to the bottom of a stirred column, while the effluent was a suspension of the salt of the required enantiomer (Fig. 55).[151]

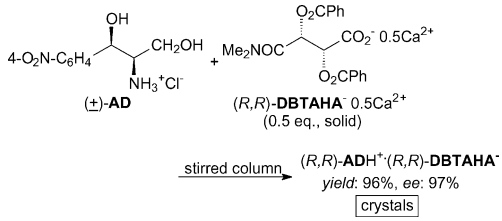


Fig. 55 Continuous resolution of the aminodiol inetrmediate (±)-**AD** of chloramphenicol synthesis using a stirred column.

α-Methyl-DOPA (antihypertensive). 2-Amino-2-(3,4-dimethoxyphenyl)-propionitrile, an intermediate of α-methyl-DOPA synthesis, was resolved with one equivalent of (*R*,*R*)-tartaric acid in water. In this case it was the salt of the unwanted *R* enantiomer which crystallized (yield 80%, ee > 95%) while the *S* nitrile was recovered from the mother liquor in similar yield and purity.[152] Treating the *R* enantiomer under the conditions of the Strecker synthesis (water, KCN, NH_4OH, NH_4Cl) effected its racemization.[153]

2-Amino-2-(4-methoxyphenyl)acetonitrile (intermediate of a semisynthetic penicilline). The racemic nitrile was resolved in a

mixture of 1,2-dichloroethane and DMF at 50 °C with (*R*,*R*)-tartaric acid (1 eq.). the salt of the *R* nitrile precipitated in 78% yield (ee: 78%) accompanied by continuous racemization of the *S* nitrile.[154]

Phenylalanine (intermediate of the artificial sweetener aspartame). This process is another example of using a derivative of the unwanted enantiomer arising from a resolution. Phenylalanine as the hydrochloride was treated with 0.5 eq. of *N*-benzoyl-(*R*)-phenylalanine in aqueous methanol to give the salt of the pure *S* enantiomer in 80% yield, while the hydrochloride of its antipode remained in solution.

Levamisol (anthelmintic). The racemate, (±)-**LEV** was resolved as the hydrochloride with 0.5 eq. of the disodium salt of (*R*,*R*)-**DBTA**.[155,156]

Naproxen (anti-inflammatory drug). Naproxen (**NA**) can be resolved as the potassium salt with 0.5 eq. of cinchonidine.[157] A much superior procedure seems to be the one using *N*-methylglucamine (**NMGA**), an inexpensive resolving agent readily available by reductive alkylation of glucose (Fig. 56).[158]

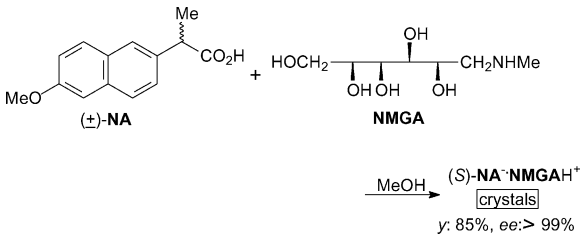


Fig. 56 Resolution of naproxen (**NA**) with *N*-methylglucamine (**NMGA**).

Acknowledgements

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