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TARTARIC ACID AND ITS *O*-ACYL DERIVATIVES. PART 2. APPLICATION OF TARTARIC ACID AND OF *O*-ACYL TARTARIC ACIDS AND ANHYDRIDES. RESOLUTION OF RACEMATES

Ludwik Synoradzki,* Urszula Bernaś and Paweł Ruśkowski

Laboratory of Technological Processes, Faculty of Chemistry
Warsaw University of Technology
Noakowskiego 3 Street, 00-664 Warsaw, POLAND
e-mail: Ludwik.Synoradzki@ch.pw.edu.pl

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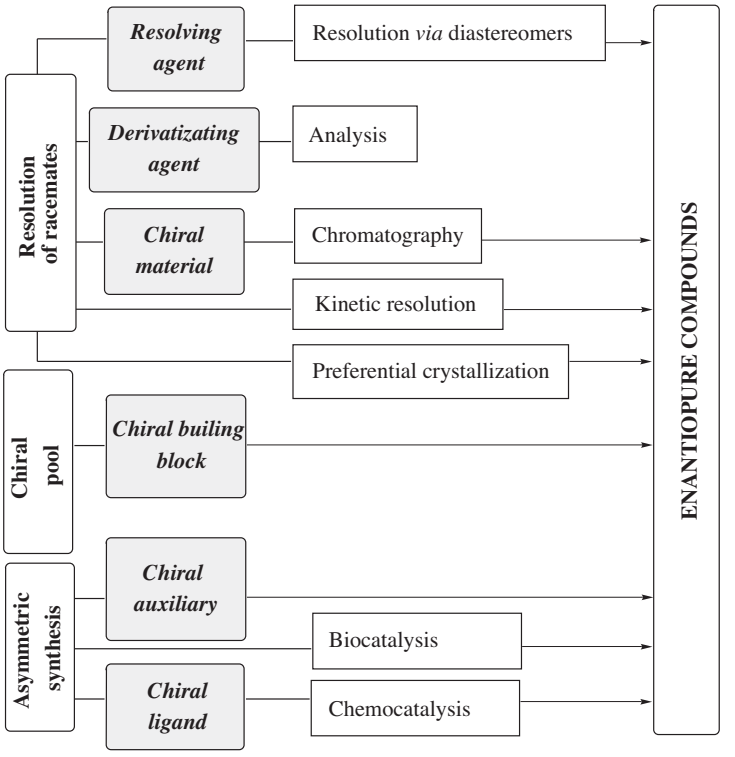
INTRODUCTION

The history and popularity of tartaric acid (**1**) and its application (*Fig. 1*) started 150 years ago with Pasteur's discovery of L and D enantiomers of **1** and of their optical activity. Toward the end of the 19th century, Pasteur successfully resolved tartaric acid into its enantiomers by manual separation of enantiomorphous tartaric acid ammonium salts and by selective crystallization of tartaric acid salt formed in the reaction of the racemate with the chiral base *cinchonicine*. The latter method was in fact the first resolution *via* diastereomeric salt formation. These innovative experiments were a cornerstone in stereochemistry in general as they introduced tartaric acid into the chemistry of chiral compounds. From this time on, tartaric acid has become popular and attractive molecule, which is still being used in all the field of asymmetric chemistry allowing one to prepare individual enantiomers on different ways.

Thus, tartaric acid **1** (*Fig. 2a*) and its acyl derivatives **2** and **3** (*Fig. 2b*) play an important role as *building blocks* in the synthesis from the chiral pool. They have been successfully used in the asymmetric synthesis as *chiral auxiliaries* or as *chiral ligands* applied in numerous catalysts.

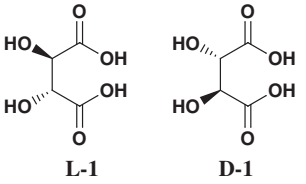
Compounds **1**-**3** also find application in chromatography as additives or templates in the formation of *chiral materials* and as a *derivatizating agent* in the sample functionalization. Despite those various uses of **1**-**3**, their utillization as *resolving agents* is the major application. Since the monograph of Gawroński and Gawrońska covers the literature concerning the use of tartaric acid in synthesis up to 1997,[1a] we decided to write this review to illustrate new examples and the continued interest in novel applications. In view of the large amount of publications and



Routes to Enantiopure Compounds with Highlighted Possibilities of Application of Tartaric Derivatives depicted in gray

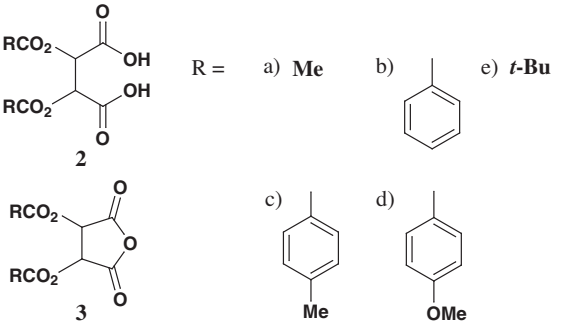
Fig. 1

of patents showing the use of tartaric acid derivatives over the last decade, this review describes only the applications of **1**-**3** in the resolution of racemates since 1998; other applications will be described in the next review.



Tartaric Acids (**1**)

Fig. 2a



Most Commonly used Diacyltartaric Acids (**2**) and Anhydrides (**3**)

Fig. 2b

I. RESOLVING AGENT

Following the US FDA policy statements (1992) which allow marketing of new chiral drugs only in enantiomerically pure forms, there has been a growing interest in the isolation of enantiomers.[2] Resolution of racemates *via* diastereomeric intermediates is still the major method, applicable also on the industrial scale.[3-5] It is based on the derivatization of racemic mixture and the subsequent separation of the resulting diastereomeric derivatives. The isolation of the diastereomers can be achieved because, contrary to enantiomers, they differ in physical and chemical properties. Therefore resolution may be accomplished *via* conventional achiral methods, such as distillation,[6] and most often crystallization, as well as by other physical manipulations such as supercritical fluid extraction for example.[7,8] Depending on the type of bonds formed between resolving agent and enantiomer, resolution can be achieved *via* diastereomeric salts (ionic), diastereomeric compounds (covalent) or diastereomeric complexes (hydrogen bond). The specific diacidic structure of **1** and **2** enables convenient formation of diastereomeric salts, in contrast to anhydrides **3** which are utilized in the preparation of diastereomeric esters and amides. The unique three-dimensional arrangement of **1** and **2** has also been used in the formation of diastereomeric host-guest type complexes. The advantages provided by the structure of **1-3** coupled with their high purity, stability and availability, make them the most widely used resolving agents. The application of other acidic resolving agents such as L-aspartic, L-glutamic, malic, mandelic, *N*-(*p*-toluenesulfonyl)glutamic and quinic acids has been described in a CRC Handbook edited by Kozma.[9]

1. Resolution *via* Diastereomeric Salt Formation

Generally, the formation of ionic bonds between the basic racemic mixture and acid **1** or **2** proceeds readily and quantitatively. Isolation of individual enantiomer from the resulting intermediate salts is also generally rapid and efficient. This makes resolution *via* diastereomeric salt formation with **1** and **2** an attractive route to obtain enantiomerically pure compounds.

The structure and stoichiometry of diastereomeric salts of amines and diacids such as **1** and **2** has been investigated.[9-13] There are acidic[14-16] and neutral[17-19] salts, depending on the number of amine equivalents bonded to the diacid (one or two for monoamines, respectively). Unfortunately, sometimes the mixed enantiomer neutral salts may also be formed, when **1** or **2** are combined with both enantiomers of an amine, leading to significant decreases in *ee*. The type of diastereomeric salt formed (1:1 or 1:2) has a considerable influence on the efficiency of resolution and may sometimes be controlled by the molar ratio of resolving agent used.[12] There are examples when *ee* of the desired enantiomer decreases[20] or increases[21] when an acidic diastereomeric salt is formed. This is the consequence of different solubilities of appropriate acidic and neutral diastereomeric salt pairs, which may be even reversed (resolution of **4** with **D-2c**).[12]

a) Resolved Compounds

Acids **1** and **2** have been employed for the resolution of numerous compounds, including primary (*Fig. 3*), secondary (*Fig. 4*) and tertiary (*Fig. 5*) monoamines.

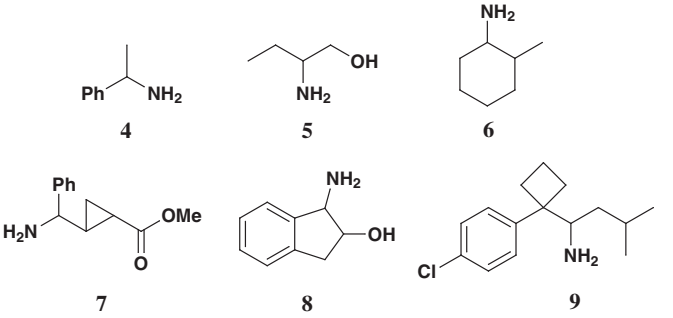


Fig. 3

Some of these amines are very simple linear or cyclic molecules. Others have more complicated structures, possessing various functional groups or condensed rings. Resolution of dimethoxyisoquinoline derivatives (**23**, **24**) (*Fig. 4*) as well as two aminooxiranes derivatives

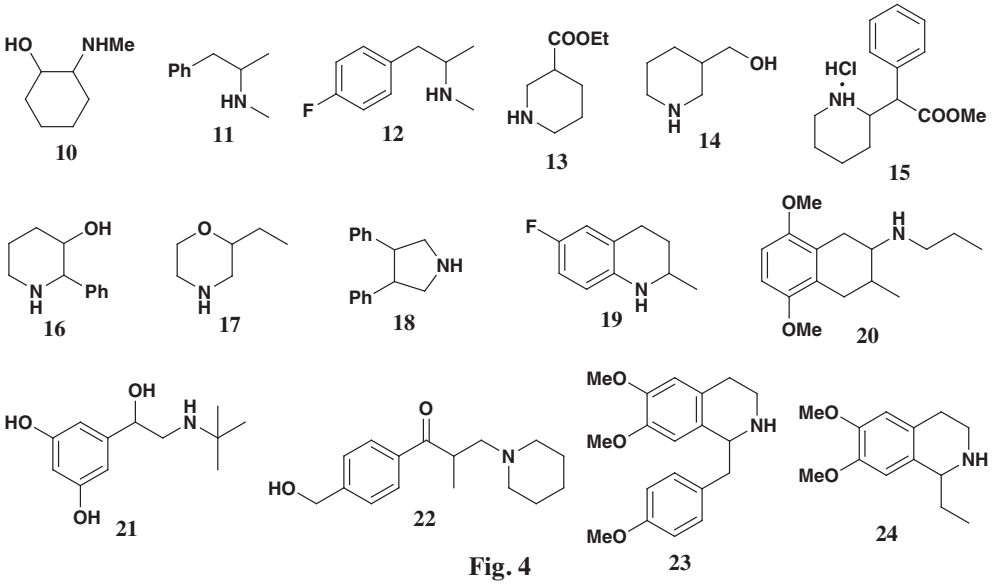


Fig. 4

(**26**, **27**) (*Fig. 5*) was achieved. Among tertiary amines resolved by acids **1** and **2**, the preparation of the enantiopure alkaloids such as *narwedine* **33** has been also reported (*Fig. 5*).[20] It appears that better resolution can be achieved, when the chiral center is close to the amine function, which forms an ionic bond with the carboxylic group of **1** or **2**.

Acids **1** and **2** are used to resolve racemates of polyamines, amines that are sterically crowded and bearing fused heterocyclic rings. Resolution of common diamines (**35**) as well as

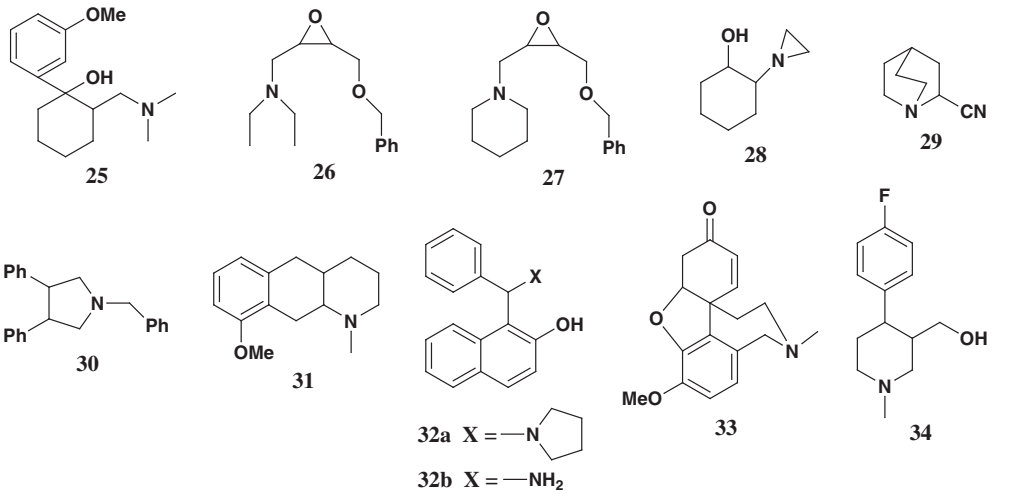


Fig. 5

more complicated tricyclic ethano Tröger's base (**39**) or benzodiazepines (**36**, **37**) was achieved with excellent results (*Fig. 6*).

Tartaric acid (**1**) may be utilized for the efficient resolution of racemic α-amino acids. It is achieved by crystallization-induced asymmetric transformation (also named 2nd order asymmetric transformation) (*Scheme 1*).[9] This strategy combines selective crystallization of less soluble diastereomeric salt with continuous racemization of its antipode in solution. The racemization is catalyzed by the addition of aldehyde (most often salicyladehyde) in carboxylic acid as a solvent. By this methodology, resolution of racemic histidine,[22] homocysteine,[23] phenylalanine,[24] phenylglicyne,[25] proline[26] with **1** and valine[27] (with **D-2b**) in high yield (>90%) and excellent optical purity (even 100%) was accomplished. This mechanism led to the production of D-amino acids from natural L enantiomers.

Resolution *via* diastereomeric salt of other compounds such as acid hydrazides and various non-amine phosphonium, arsonium and sulfonium salts with the help of **1** and **2**,[1b] as well as highly efficient chiral resolution of six-coordinate silicon (IV) complex using **2** was also described.[28]

The resolutions of optically active compounds demonstrated above were most often carried out for two purposes. For example, resolutions of α-phenylethylamine (**4**)[10,13] and of methamphetamine (**11**)[6,29,30] with the help of **1** and **2** were used as a tool in basic research. On the other hand, chiral resolutions of numerous compounds utilizing **1** and **2** reveal a practical application due to the widespread interest in development of single enantiomeric drugs. For example compounds **7**,[16] **8**,[31] **14**,[21] **31**,[32] **47**[33] play role as key intermediates in the synthesis of biologically active substances, compounds such as **9**,[34] **36**, **37**,[14] **43**[35] are potentially active and **15**,[36] **21**,[11] **25**,[37] **40**[38] play role as active pharmaceutical ingredients.

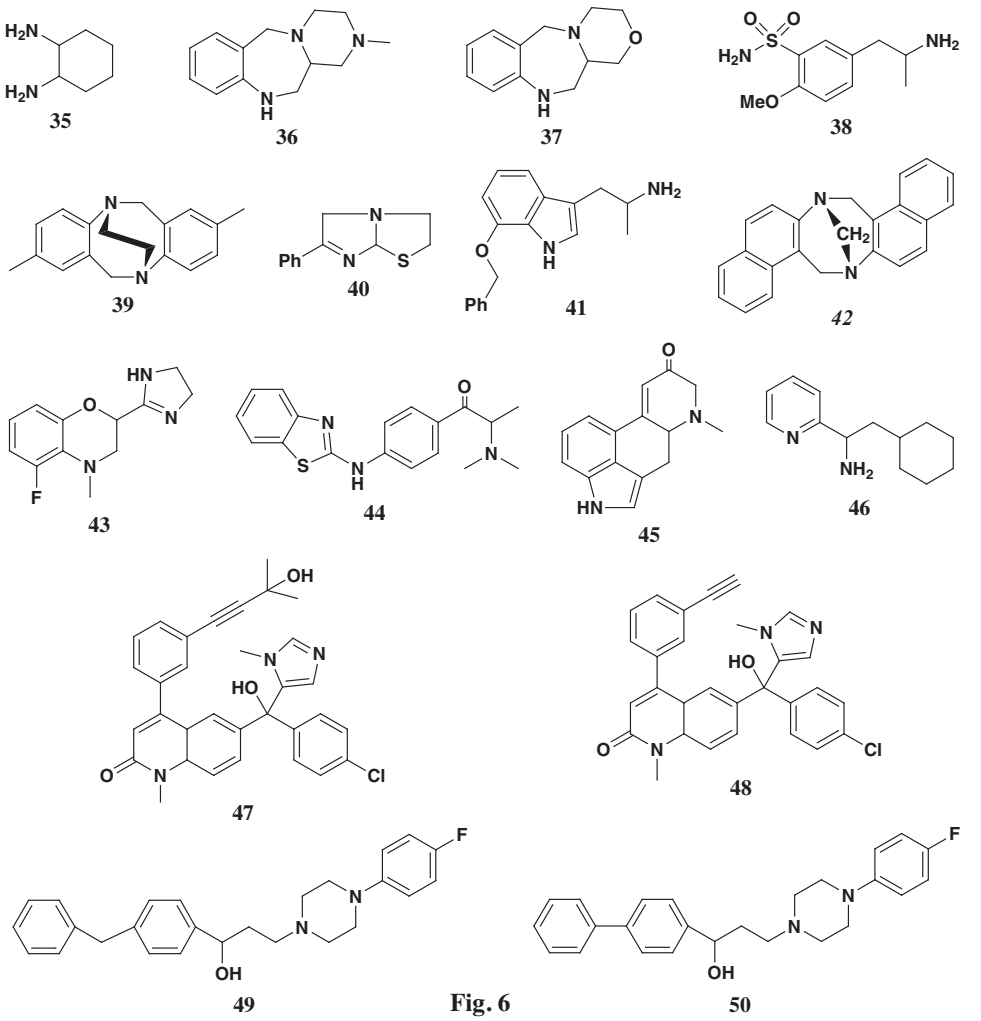
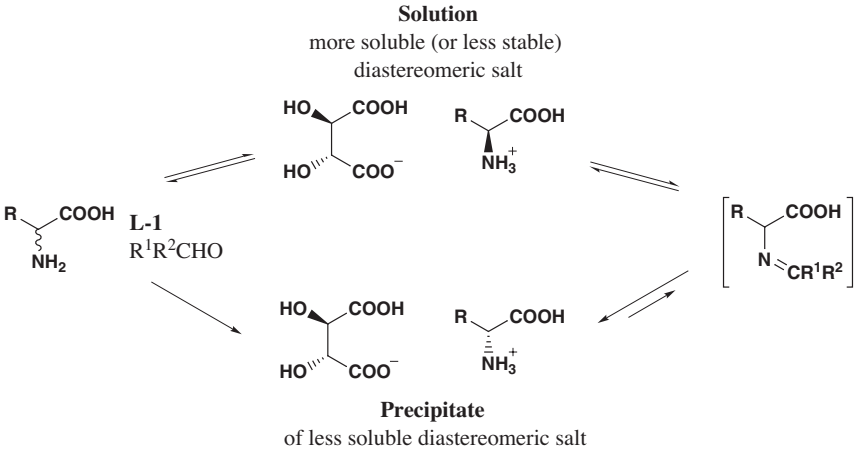


Fig. 6

The great importance of applicability of **1** and **2** in the resolutions *via* diastereomeric salt formation is also emphasized by the large number of patents' informations. During the last decade, some useful optically active pharmaceuticals was successfully resolved (*Fig. 7*), *amlodipine* (**51**) with **L-1**[39] and **D-2b**,[40] *atenolol* (**52**) (with **L-2c**),[41] *bupivacaine* (**53**) (**D-1**),[3] *ephedrine* (**54**) (**L-2**),[42] *ethambutol* (**55**) (**L-1**),[5] *nefopam* (**56**) (**L-2b**)[43] and *ramipril* (**57**) (**L-2b**).[44]

It is noteworthy that if the structure of the diastereomeric salt formed is not established (X-Ray crystallography, ^{1}H NMR, IR), it is not certain that the formation of salt actually occurs. This is implied by the fact that amines are as good as alcohols in being able to form supramolecular complexes with **1** and **2**.[45] Therefore it reveals possible that chiral resolutions of some compounds depicted in *Figures 3-6* were achieved *via* the formation of diastereomeric complexes and not of salts.



Scheme 1

b) Resolving Agent

Among tartaric acid derivatives, tartaric acid (**1**), dibenzoyl- (**2b**) and di-*p*-toluoyltartaric acid (**2c**) are most frequently used. The results of optical resolutions of previously presented amines (*Fig. 3-6*) accomplished by these acids are collected in *Tables 1-3* respectively.

Table 1. Compounds Resolved using **L-1** and **D-1**

Cmpd	Resolving agent	Isolated isomer	*ee* (%)	Yield (%)[a]	Ref.
4	**L-1**	**(–)-(*S*)-4**	72.1[b]	33.4[b]	10
6	**L-1**	**(1*S*,2*S*)-6**	92	28[b]	46
7	**L-1**	**(–)-7**	>95	41[b]	16
	D-1	**(+)-7**	>95	42[b]	
9	**L-1**	**(*R*)-9**	99	34[b]	34
	D-1	**(*S*)-9**	99	30[b]	
29	**L-1**	**(+)-29**	96	----	47
		(–)-29	97	----	
32a	**L-1**	**(*S*)-32a**	98	40	48
		(*R*)-32a	75	55	
32b	**L-1**	**(*S*)-32b**	>99	48[b]	49
35	**L-1**	**(*R*,*R*)-35**	>99.8	49	17
		(*S*,*S*)-35	>99.8	37	
38	**L-1**	**L-(–)-38**	>99	30-35	50
	D-1	**D-(+)-38**	>99		
46	**L-1**	**(*S*)-46**	>99	78[b,c]	51
47	**L-1**	**(*R*)-47**	98.4	40[b]	33
48	**D-1**	**(*R*)-48**	98.6	41[b]	33

a) Overall yield based on racemate; b) Result given for diastereomeric salt; c) Result of enantiomeric enrichment.

Table 2. Compounds Resolved using **L-2b** and **D-2b**

Cmpd	Resolving agent	Isolated isomer	*ee* (%)	Yield (%)[a]	Ref.
5	**L-2b**	**(*S*)-5**	18	----	52
8	**L-2b•H_2O**	**(+)-(*R*,*R*)-8**	99	35	31
11	**L-2b**	**(–)-11**	97.9	----	30
12	**L-2b**	**(*S*)-12**	61	----	52
13	**L-2b**	**(*S*)-13**	≥98	19	18
14	**L-2b**	**(*S*)-14**	>99	>30	21
15	**L-2b**	**(–)-15**	99.9	38	36
	D-2b	**(+)-15**	99.9	40.3	
20	**D-2b**	**(–)-(*R*,*R*)-20**	>98	25	53
24	**L-2b**	**24**	97	67[c]	54
26	**L-2b•H_2O**	**(–)-26**	>98	23[b]	55
27	**L-2b•H_2O**	**(–)-27**	96	47[b]	55
36	**L-2b**	**(–)-(*R*)-36**	≥98	24	14
	D-2b	**(+)-(*S*)-36**	≥98	20	
40	**L-2b•H_2O**	**(+)-(*R*)-40**	99.9	22	38
		(–)-(*S*)-40	99.9	27	
43	**L-2b**	**(–)-43**	98	----	35
	D-2b	**(–)-43**	97	----	
45	**L-2b**	**(–)-45**	----	38	56
	D-2b	**(–)-45**	----	20	

a) Overall yield based on racemate; b) Result given for diastereomeric salt; c) Result given for enantiomeric enrichment.

There are only few procedures describing preparation of enantiopure compounds involving the use of other diacyltartaric acids, *e. g.* dianisoyl- (**2d**)[65] and dipivaloyltartaric acid (**2e**).[66] These diacyltartaric acids are exploited only rarely, probably because they are not commercially available. It is evident that **1**, **2b** and **2c** being pure, stable, relatively cheap and available in both enantiomeric forms play important role as reliable resolving agents.

The resolution procedures entailing the use of hydrates of **2b** and **2c** has been also reported.[14,31,38] The water content has an essential and positive influence on the resolution efficiency because it is often incorporated into the crystal structure of diastereomeric salts formed.[10,11] It is postulated that the resulting salts are more stable and precipitate from the solution. Conversely, there are also some examples when the presence of water decrease the results,[63] especially when it has negative effect on the substrate, e. g. by promotion of its decomposition.

Table 3. Compounds Resolved using **L-2c** and **D-2c**

Cmpd	Resolving agent	Isolated isomer	*ee* (%)	Yield (%)[a]	Ref.
10	**D-2c**	**(+)-10**	99.9	46	19
19	**L-2c**	**(*S*)-19**	>99	27	57
21	**D-2c**	**(*R*)-21**	>99	38	11
22	**L-2c**	**(*R*)-22**	80	46[b]	58
		(*S*)-22	80	42[b]	
23	**L-2c**	**(*R*)-23**	----	45	59
25	**L-2c**	**(+)-25**	>99.5	40	37
	D-2c	**(–)-25**	>99.5	41	
28	**D-2c**	**(*R*)-28**	----	----	60
31	**L-2c**	**(4a*R*,10a*R*)-31**	>98	34	32
33	**D-2c**	**(–)-33**	97	92[b,c]	20
34	**D-2c**	**(*S*)-34**	>90	38	12
37	**L-2c**	**(–)-(*S*)-37**	95.4	34	14
	D-2c•H_2O	**(+)-(*R*)-37**	98.3	26	
39	**L-2c**	**(–)-39**	100	36	61
	D-2c•H_2O	**(+)-39**	100	37	
41	**L-2c**	**(*R*)-41**	99.5	36	62
42	**L-2c**	**(–)-42**	98	21	63
	D-2c	**(+)-42**	100	19	
44	**D-2c**	**(*S*)-44**	80	92[c]	15
49	**L-2c•H_2O**	**(–)-49**	----	20	64
		(+)-49	----	20	
50	**L-2c•H_2O**	**(–)-50**	----	37	64
		(+)-50	----	44	

a) Overall yield based on racemate; b) Result given for diastereomeric salt; c) Dynamic resolution.

c) Resolution by Formation and Fractional Crystallization of Diastereomeric Salts

Although separation of diastereomeric salts formed with **1** and **2** may be achieved by various physical methods, 'classical resolution' based on the fractional crystallization is the most widely used technique both in the laboratory and industry. The incontestable advantages of this method are the procedure and the equipment simplicity and accessibility of both enantiomers.

Resolution under Thermodynamic Control

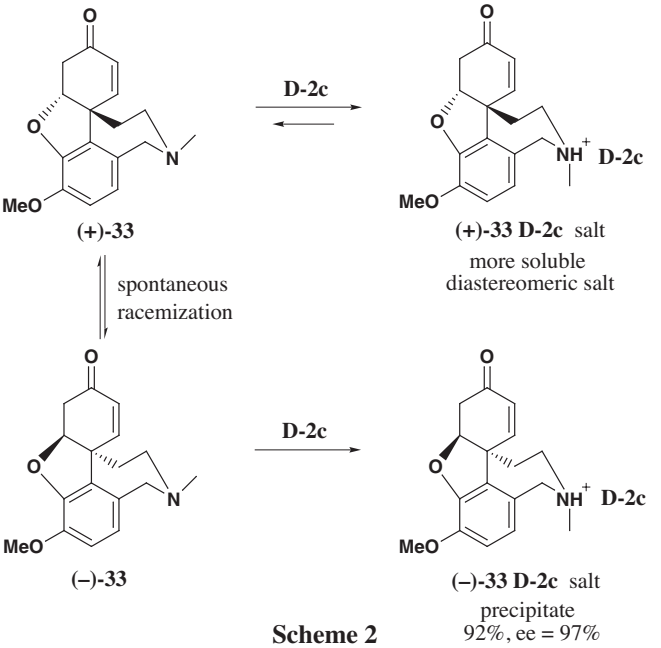
It should be emphasized that despite the fact that resolution *via* diastereomeric salts has been extensively studied, the mechanism of chiral discrimination, *i. e.* the influence of conditions on the process has not been completely explained. It is particularly interesting to determine if the

enantioselection may occur directly in the solution or not. Recently, organic solvent nanofiltration (OEN) has been used to investigate the mechanism of chiral discrimination during diastereomeric salt formation.[13] The experiment employing resolution of **4** by **D-2c** and **D-1** clearly indicated that the binding constants of each enantiomer with resolving agents are approximately equal; thus for such a system, enantioselection did not occur in the solution. It seems that in most of the chiral separations *via* diastereomeric salts, the thermodynamically controlled diastereomeric salt formation is not enantioselective and then the discrimination occurs during crystallization.

Generally crystallization is also thermodynamically controlled and depends on the differences in the solubility of diastereomeric salts formed. While three basic types of phase diagrams exist for describing the solid-liquid equilibrium of the diastereomeric salts mixture, the most effective separation occurs when the simple eutectic occurs.[67, 68]

Resolution under Kinetic Control

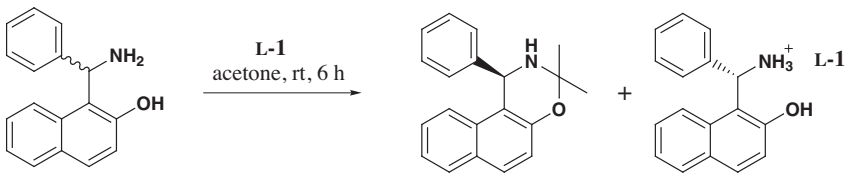
Although a classical kinetic resolution involving reaction between enantiomers and chiral reagent at different rates is not observed, in the case of diastereomeric salt formation sometimes dynamic resolution occurs. This is also a kinetic process which requires catalytic or spontaneous racemization of a substrate. Although there are only a few examples of such a kinetic chiral separation employing **1** or **2**, dynamic resolution provides much higher yields then the classical method (theoretically 100% *vs* 50%). For instance, an efficient dynamic resolution of *narwedine* (**33**) by **D-2c** was reported *(Fig. 5, Table 3)* which was followed by facile spontaneous racemization of (+)-**33** *via* prochiral dienone form (*Scheme 2*) and allowed preparation of pure (–)-**33** salt (97% *ee*) in 92% yield.[20]



Scheme 2

Similarly, resolution by **D-2c** of chiral aminoketone **44** (*Fig. 6*, *Table 3*) which was undergoing spontaneous racemization through the enol form, allowed the acquisition of desired enantiomer in 90% yield and 80% purity.[15] In the case of dynamic processes, facile crystallization of the desired diastereomeric salt has an influence on the substrate racemization equilibrium therefore induces diastereomeric resolution and increases its efficiency.

The interesting specific kinetic resolution of racemic Betti base **32b** (*Fig. 5*, *Table 1*) employing **L-1** was also reported (*Scheme 3*).[49] Resolution was based on an enantioselective deketalization of intermediate *N*,*O*-ketal compound, which was formed from racemic **32b** and acetone in the *in situ* ketalization catalyzed by **L-1**. Deketalization was also promoted by **L-1** which acted at this stage as the chiral acid promoting the enantioselective formation of **(*S*)-32b**. Thus resulting intermediate Betti base enantiomer was intercepted directly by **L-1** to form diastereomeric **(*S*)-32b** salt, which crystallized immediately, leaving in the mother liquor the opposite **(*R*)-32b** as the *N*,*O*-ketal compound.



32b

(*R*)-32b as *N*,*O*-ketal cmpd
47%, ee>99%

(*S*)-32b L-1 salt
48%, ee>99%

Scheme 3

There are also examples of kinetic control on the crystallization step, although thermodynamically controlled processes are predominant. During the resolution of **19** (*Fig. 4*, *Table 3*) with **L-2c** in ethyl acetate, the precipitate contained (*R*)- or (*S*)-enantiomer depending on the time of crystallization (respectively 5 min and 3 weeks).[57] In this case, the unwanted kinetic effect was overcome by the addition of hydrochloric acid. Similarly, time-dependent crystallization was observed in the resolution of aminooxiranes (**26** and **27**) by **L-2b** (*Fig. 5*, *Table 2*)[55] and of quinoline derivative **31** by **L-2c** (*Fig. 5*, *Table 3*)[32]. Due to the possibility of kinetic influence during crystallization, many efforts have to be made to optimize temperature and time conditions of this process, especially if it is going to be up-scaled.

d) Selection of the Resolution Optimal Parameters

Although many attempts has been made to design the best resolution conditions including computer-assisted modeling,[9] inquiry of the phase diagrams,[67,68] DSC, TG,[10] X-Ray[11] analysis of diastereomeric salts formed, the choice of appropriate resolving agent and solvent is not trivial and still is the trial and error method. Thus it is evident, that the final resolution experiment should be preceded with the wide screening of resolving agents in different solvents.[14,37,57,64]

Selection of Resolving Agent

Some authors reported an efficient preparation of enantiopure compounds by the use of resolving agent previously applied in the successful resolution of the homologous derivative.[64] This experiment, however, it appears fortuitous and, unfortunately, is not a general rule. It has been clearly demonstrated that resolutions of racemates with various resolving agents sometimes give hardly comparable results.[14,37,57] For example chiral separation of racemic **19** (*Fig. 4*) with **1, 2b** and **2c** resulted in the desired enantiomer with *ee* of 12, 2 and even 59%, respectively.[57]

In order to shorten the time-consuming selection of the appropriate resolving agent, Vries *et al*. developed the method involving a mixture of resolving agents.[69] This approach was based on the concept that during the resolution with the mixture of resolving agents, the less soluble diastereomeric salt formed with one of the 'family' members would precipitate most rapidly.[70-72] In the so called 'Dutch resolution', the tartaric acid 'family' consists of three derivatives: **2b**, **2c** and **2d**. In fact during such resolutions, it was observed that both the yield and the enantiomeric excess were superior to those obtained by the classical technique when addition of one resolving agent was employed.[73]

Table 4. Compounds Resolved using Tartaric Acid **2b**, **2c** and **2d** 'family'[73]

Cmpd	*ee* (%)	Reagent ratio in precipitated salt **2b**:**2c**:**2d**
16	99	5:1:1
17	96	0:2:1
18	99	1:3:3
30	97	6:1:1

Interestingly, it was found by analysis of the stoichiometry of crystalline diastereomeric salts, that sometimes one of the resolving agents used in the mixture of resolving agents was not present in the precipitate. However, exclusion of this apparently "useless" resolving agent from the mixture of resolving agents led to a decrease in the enantiomeric excess of the desired enantiomer.[69,73,74] This phenomenon has been extensively studied, and explained by the nucleation inhibition of this 'family' member on the crystal growth of diastereomeric salt formed with the 'parent' resolving agent.[69,74] Although the optical resolution with a 'family' of **2** may not be the universal method for screening reliable resolving agent, it evidently gives a chance of providing higher *ee* than the classical approach. It should be clearly stated that according to the originally proposed method, **1** does not belong to the tartaric acid 'family' because the presence of free hydroxy function makes it structurally dissimilar to diacylated **2b**, **2c** and **2d**.[69] However, some authors have erroneously included **1** to the 'family' resolution method.[52]

Amount of Resolving Agent

Despite a selection of the superior resolving agent, determination of its amount used in resolution procedure is also essential.[12] Most resolutions described in the literature utilize one molar equivalent of **1** or **2** for racemic amines, a ratio which favors formation of the acidic diastereomeric salts.[14,21,32,48,56,64] The use of the one-half molar equivalent (the Marckwald method) has been also described.[17,18,20,61,62,63] This resolving agent/amine ratio enables partial diastereomeric salt formation while acidic intermediate salt occurs. The Pope and Peachey method involving the use of the one-half molar equivalent of resolving agent and addition of achiral acid has been also applied.[58] Optical resolutions employing this technique are based on the formation and filtration of less soluble diastereomeric salt. In the ideal case, the more soluble diastereomeric salt racemizes in the mother liquor under the influence of achiral acid. Therefore the intermediate salt which undergo racemization may be recycled to the resolution loop and lead to significantly increased overall yield.[75] Recently, Ferreira *at al*. have postulated that with diacids such as **1** and **2**, more efficient resolutions have been achieved with the resolving agent/amine ratio above 1.5 when rather acidic diastereomeric salts were formed.[12]

Selection of Appropriate Solvent

The selection of an appropriate solvent is a crucial step for resolution because the yield and optical purity of precipitates may by dramatically different depending on the solvent used. For example, resolution of **4** (*Fig*. *3*, *Table 1*) with **L-1** in methanol gave **(–)-(*S*)-4** with 72.1% *ee* and in other solvents such as water, acetonitrile, ethanol, the opposite enantiomer predominated.[10] Similarly, crystallization of **19** (*Fig*. *4*) by **L-2c** from ethyl acetate and acetic acid provided **(*R*)-19** in 48% yield and 57% *ee* respectively; conversely, resolution from alcohols such as isopropanol, methanol, ethanol gave **(*S*)-19**.[57] This phenomenon results from the distinct differences in solubilities of diastereomeric salts in various solvents and from the solvation effect.

The solvent selection is simpler when both diastereomeric salts are accessible and their solubilities may by measured. In general, for successful resolution the solubility of more soluble diastereomeric salt in the solvent selected should be at least five times higher than the solubility of less soluble diastereomeric salt.[12] Naturally, a desired diastereomeric salt should be less soluble to easily crystallize from the chosen solvent system.

Usually, optical resolution with **1** and **2** is more efficient when more polar solvents are used.[30] It is caused by little solubility or insolubility of **2** and **1** respectively in non-polar solvents. Most frequently, methanol,[14,15,46,59,64] ethanol,[16,20,21,31,35,37,47] acetone,[48,61,63] or isopropanol, acetonitrile, ethyl acetate have been employed. Sometimes two[14,58] or even three[34] component mixtures of these solvents were also utilized. The use of water-containing (5–50%) solvent systems such as methanol,[17,60,62,73,76] ethanol,[18] acetonitrile[54,56] was also reported. The great

advantage of such systems is that an organic solvent allows the dissolution of all the reactants and water increases polarity of the system. It improves both the yield and the optical purity of the precipitated diastereomeric salt. The influence of water content in a homogenous mixture of acetonitrile-ethanol-water on resolution of *didesmethylsibutramine* (**9**) (*Fig. 3*, *Table 1*) with **D-1** was investigated.[34] The experiment confirmed that crystallization is very sensitive to the solvents' ratio (content of water) and the amount of solvent used, therefore these factors should be optimized and determined precisely. The employment of two-phase solvent system was also investigated. Resolution of racemic **11** (*Fig. 4*, *Table 2*) with **L-2b** was successfully improved by the use of water-methanol-dichloroethane system.[30] The optical purity of **(+)-11** obtained in such a three solvents mixture increased to 97.9% and is higher than the value of 54.4% which had been achieved in methanol and even than 84.6% in methanol-water system. These improved results are explained by the influence of water-immiscible organic solvent on the thermodynamic equilibrium and by the impact of additional methanol on the solubility of the precipitated salt. It is well known that significant differences in solubilities, which determine the principle of diastereomeric salts separation, arise from different molecular interaction within them. Analysis of crystal structure of diastereomeric salts formed during resolution of *terbutaline* (**21**) (*Fig. 4*, *Table 3*) with **L-2c** demonstrated that less- and more-soluble diastereomeric salts occurred in a different columnar and sheet supramolecular structure, respectively. The crystal structures of diastereomeric salts were the same, irrespective of the solvent used for crystallization. It is important note that the less-soluble salt that precipitated from the mixture contains water molecule, which stabilized the structure *via* the hydrogen bonds.[11] It seems to be an almost general rule that when the possibility to form a solvate exists, the solvated more stable diastereomeric salt precipitates. However, unexpected deviations from this pattern were also observed.[10]

Recently, the influence of solvent was investigated in the dielectrically-controlled enantiomeric resolutions with **L-1**. The experiments show that depending on the dielectric constant of the solvent mixture used, the crystal structure of diastereomeric salts formed differs, allowing for chiral discrimination.[77]

Temperature Dependence

In most cases, diastereomeric salts formation itself proceeds readily under mild conditions. This process is rapid and frequently occurs at room temperature.[35,48] Generally, higher temperatures often the boiling of the solvent,[17,20,34] are initially used because all the material have to be dissolved. Various temperatures of crystallization of diastereomeric salts formed with **1** and **2** have been used. Some procedures include controlled decrease of temperature until precipitation occurs,[34] while others allow the mixture to cool down to room temperature.[61,63] The method used depends on the nature of the process (laboratory *vs* industry) and on the technical facilities available to the experimenters.

Final Isolation of Enantiomer from Diastereomeric Salts

Filtration of crystalline solids and subsequent release of the desired enantiomer from diastereomeric salt commonly constitute the last step of resolution. The latter is achieved by a decomposition of tartrate salt, which is most often carried out in an aqueous basic solution at room temperature. Most frequently, sodium hydroxide,[14,32,37,56,62,64] sodium bicarbonate[46,47,61] and sodium carbonate[48] were used. In the case of base-mediated racemization of undesired product or the necessity to reuse **1** or **2**, diastereomeric salts were decomposed by acidification.[31] After decomposition of diastereomeric salt, the product was isolated by extraction with dichloromethane,[37,47,48,61,63,64] ethyl acetate,[14] ether,[32] chloroform.

There are examples of very efficient resolutions by this procedure where products of high *ee* were obtained directly.[32,46,48,56] However, sometimes recrystallization of diastereomeric salt,[14,37,47,61,62,64] product[59] or both[63,36] was necessary. In few cases, only repeated fractional crystallization provided compounds of desired purity.[21,53] There have also been some procedures, which omitted the decomposition step, because diastereomeric salts isolated from solution were directly used in the next reaction step.[15,16,18,21] In the case of *narwedine* (**33**), which racemizes as a free base, the pure product may be isolated only as a salt (*Scheme 2*).[20]

e) Alternative Methods of Separation of Diastereomeric Salts

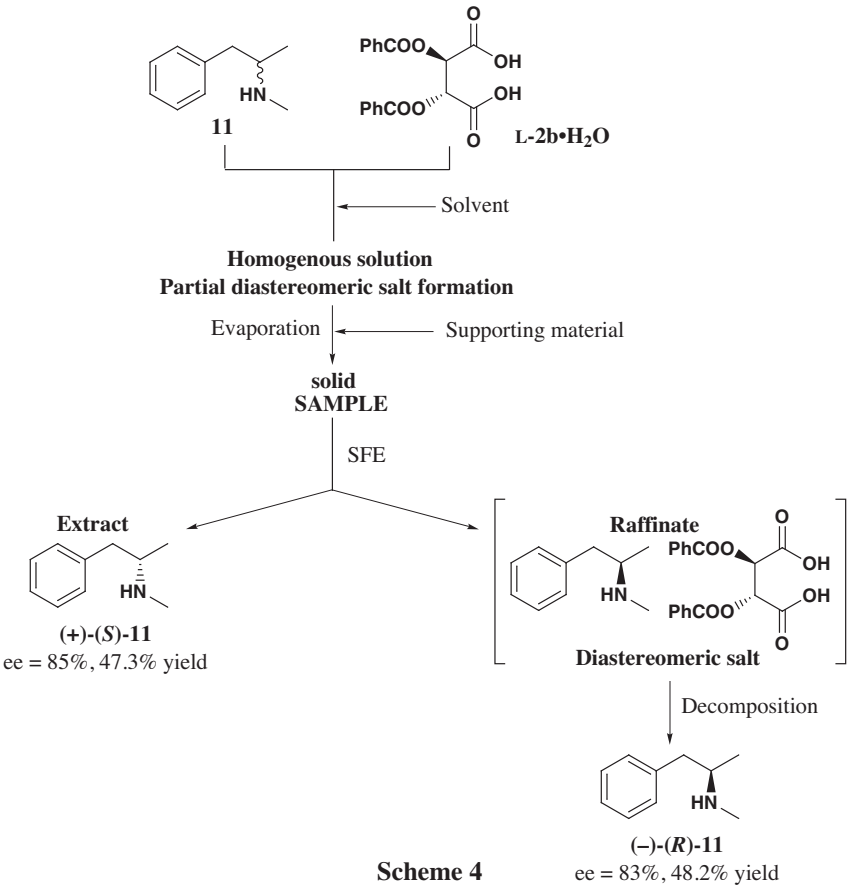
Distillation

Due to the crystalline character of most of the salts formed with **1** and **2**, isolation of the desired product by distillation from the mixture is impossible. Therefore this method involves partial diastereomeric salt formation with half a molar amount of **1** or **2**. The unengaged enantiomer distills off while diastereomeric salt of its antipode remains in the residue. By use of this methodology successful resolutions of **11** (*Fig. 4*) with **L-2b** and **L-2c**[6] as well as **5** (*Fig. 3*, *Table 2*) and **12** (*Fig. 4*, *Table 2*)[52] have been accomplished, comparable or superior of those obtained by conventional crystallization. This process seems to be attractive for industrial applications because of the solvent elimination and mild conditions. The only limitation is the nature of resolved compounds, where one of them has to be an easily distillable liquid.

Supercritical Fluid Extraction

The alternative new method of isolation is supercritical fluid extraction (SFE). Reaction of racemate with less then one equivalent of the resolving agent and subsequent partial diastereomeric salt formation is followed by SFE of unreacted enantiomer. By use of this technique, the resolution of racemic *tetramisole* (**40**) (*Fig. 6*, *Table 2*) by **L-2b•H_2O** was successfully accomplished,[8] and the preparation of both enantiomers of **11** (*Fig. 4*) (*Scheme 4*)[29] was achieved with results comparable to those obtained by the 'classical resolution'.

The effect of the molar ratio, extraction pressure and temperature on the efficiency of resolution was examined.[8,29] The significant influence of achiral support on the resolution was



Scheme 4

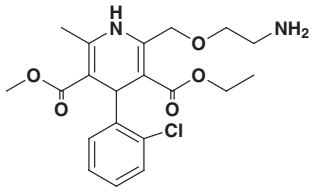
also investigated, showing that better results may be achieved in the presence of activated carbon.[38] The SFE technique is a very promising one with efficient availability of both enantiomers and use of supercritical fluid. Advantages of this process makes it very attractive also for industry.

f) Industrial Aspect

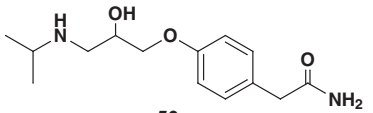
Although resolution *via* diastereomeric salts crystallization on the industrial scale is sometimes a space- and time-consuming process, it still remains the most common route to obtain pure enantiomers. This approach offers several advantages: the process is straightforward and the racemic substrate as a product of classical non-asymmetric synthesis is readily available and relatively inexpensive. The resolution method eliminates impurities other than the resolving agent itself.[3] Although the theoretical yield of resolution is only 50%, racemization of unwanted enantiomer and its recycling to the resolution loop makes this method economically attractive.[18,62]

Recovery of the resolving agent, especially when the D-isomer of **1** or **2** is used, may also increase economical benefits. This may be achieved by isolation of **1** or **2** by acidification, extraction and subsequent crystallization from aqueous solution obtained after basic decomposition of diastereomeric salt.[31,37,60] The important parameter, which affects the recovery of diacyltartaric acid **2** is the pH of alkali used. In solutions with pH higher than 9, quite a rapid unwanted hydrolysis of ester functionalities of **2** may occur.[37] Other processes for the recovery of **1** and **2** involving the acid-mediated hydrolysis of diastereomeric salt have been also reported.[78,79]

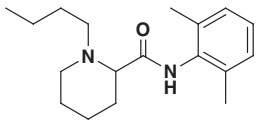
Many various active pharmaceutical ingredients and agrochemicals are produced employing separation of diastereomeric salt by crystallization (*Fig 7*). A very convincing case is the synthesis of *ethambutol* (**55**), a popular tuberculostatic drug produced with worldwide sale over $ 50 milions,[5] which involves the resolution by **L-1**. One of the most spectacular examples of the **2b** efficiency is the preparation of one of the 32 isomers in the production of *ramipril* (**57**), an important drug against hypertension.[44]



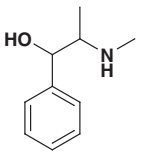
51
Amlodipine



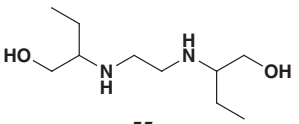
52
Atenolol



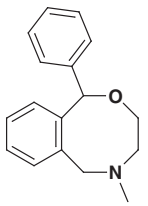
53
Bupivacaine



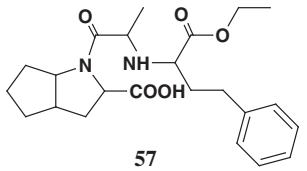
54
Ephedrine



55
Ethambutol



56
Nefopam



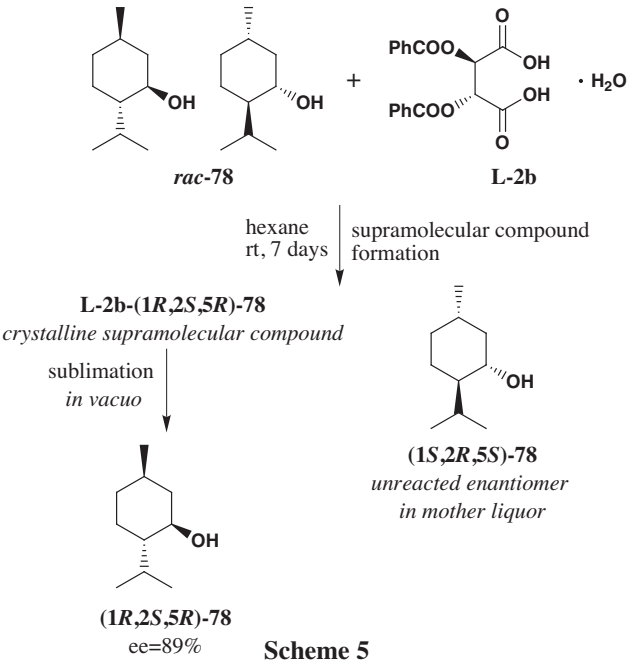
57
Ramipril

Fig. 7

Industrially, the technology may involve resolution of diastereomeric salts at various stages. Sometimes, resolution is used at the beginning of the multi-step process. Then the following steps must be carried out enantioselectively so that the desired configuration of the product is retained. (**55**,[5] **57**[44]). Alternatively, the resolution is the final stage (**53**)[3] of the multistep synthesis in which case it is important that the unwanted enantiomer be racemized and recycled. However, the latter resolution may be problematic and expensive, if racemization of the unwanted isomer does not proceed easily.

2. Resolution *via* Diastereomeric Complex Formation

Recently, it has been shown, that optical resolution of racemates can also be achieved *via* diastereomeric complex formation (*Scheme 5*).[80,81] This is of great relevance because it enables the resolution of neutral compounds, that is a process which is still complicated.[80-93]



Scheme 5

a) Resolved Compounds

Although the method applying the host properties of **1** and **2** is relatively unexplored, many diverse non-basic compounds were successfully resolved by diastereomeric complexes with those resolving agents (*Fig. 8*).[80,81,83-87,90-93] The most promising optical resolutions *via* diastereomeric complex formation are based on one-step preparation of enantiopure alcohols. Tartaric derivative **L-2b** was employed for resolution of aliphatic secondary alcohols (**58**-**65**, **80**) as well as various 2-*trans*-substituted cyclohexanols (**66**-**76**). Resolution of other non-basic compounds such as chiral phosphine oxides (**83**-**85**) was also achieved by formation of diastereomeric inclusion complexes with **2b** (**83**)[83] and **2c** (**84**).[84] It was clearly demonstrated that in case of resolution *via* diastereomeric complex formation, the structures of resolving agent and compounds resolved (host-guest) are fundamental. X-ray and thermoanalytical studies of supramolecular compounds formed between chiral alcohol and **2** indicated that discrimination occurs during crystallization and that the architecture of crystal thus formed is essential for resolution efficiency.[72,81,86-88] The ability and enantioselectivity of molecular complex formation depends on the space filling of the alcohol side-chain or ring.[87] The DSC and TG analysis proved that the thermal stability of diastereomeric complexes is directly connected with its enantioselectivity, the more stable the adducts the better the *ee*.[81,86,87] Among secondary alcohols, only butanols and pentanols form supramolecular compounds with **L-2b•H_2O**, while alcohols with longer chain do not react. Enantioselectivity of crystalline diastereomeric complexes with branched 2-alkanols *(e. g.* 3-methyl-2-butanol and 4-methyl-2-pentanol) is higher than those of

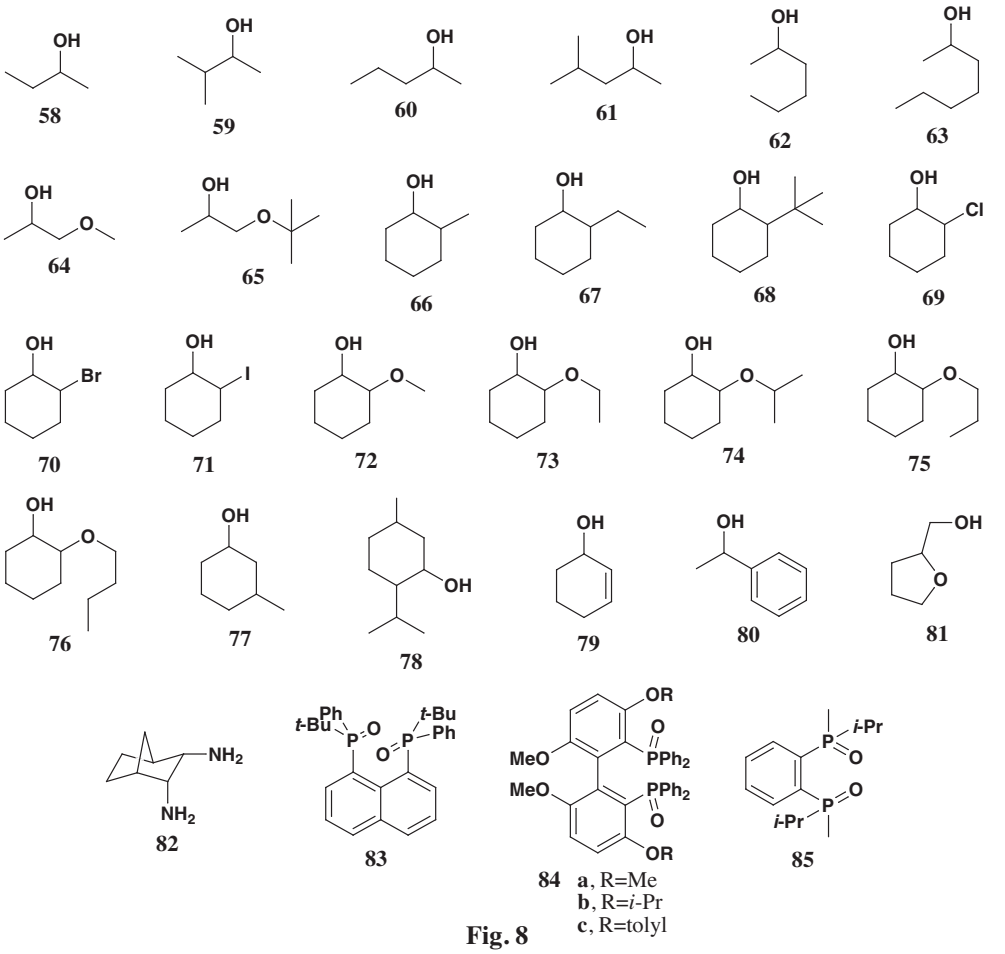


Fig. 8

complexes with unbranched 2-alkanols and the thermal stability of the former is also higher.[86,87] It has been demonstrated that supramolecular compound formation is *trans*-selective, *i. e.* (+)-menthol ((**1*S*,2*R*,5*S*)-78**) formed a supermolecular compound while (+)-*iso*-menthol ((**1*S*,2*R*,5*R*)-78**) did not form the corresponding adduct.[86] In case of *trans*-2-alkoxy- and *trans*-2-alkylcyclohexanols, the enantioselectivity also depends on the size of the alkoxy or alkyl groups.[86,87]

The interesting complexive properties of **1** and **2b** have been also applied to the resolution of racemic diethanolamine by diastereomeric complex formation with the corresponding copper complexes (*Fig. 9*).[85]

It has been also found that **2b•H_2O** may be employed to separate stereochemical isomers (*Fig. 10*).[89,90] Complex formation of some *cis-trans* mixtures of 4-alkylcyclohexanols with **2b•H_2O** showed that efficient enrichment with the *trans*-isomer was achieved.

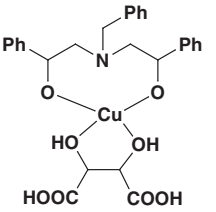
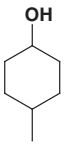
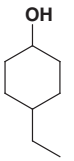
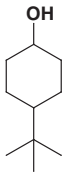


Fig. 9

Initial stereoisomer ratio

***cis*-87** 33%	***cis*-88** 34%	***cis*-89** 9%
***trans*-87** 67%	***trans*-88** 66%	***trans*-89** 91%

Stereoisomer ratio from complex

***cis*-87** 25%	***cis*-88** 7%	***cis*-89** 8%
***trans*-87** 75%	***trans*-88** 93%	***trans*-89** 92%

Fig. 10

b) Resolving Agent

The optical resolutions *via* diastereomeric complexes of previously discussed compounds (*Fig. 8*) with different resolving agents are collected in *Table 5*. The ability of **1**, **2b** and **2c** to form inclusion complexes was elaborated by thermoanalytical studies. Although the complexive properties of **1** are well known, resolutions applying natural **1** failed. The efficiency of **2b** is probably because hydrophobic cave in the diastereomeric crystal lattice, which is required to capture guest molecule, is formed from the benzoyl groups of acylated **1** oriented parallel to it.[88]

The interesting observation was that **2c** which is structurally related to **2b**, captured chiral alcohols less strongly. Thus, the resolutions with **2c** were less effective than those with **2b**.[91] It was postulated that during the chiral recognition process, the weaker second order (*e. g.* van der Waals) interactions are essential, since both **2b** and **2c** have the same possibility to form strong hydrogen bond.[91] The great ability of **2b** to form supramolecular compounds stems from its ability to act both as a proton donor and as a proton acceptor. It may also play role both in a hydrophobic interaction due to the two benzoyl groups as well as in a hydrophilic interaction because the other part of molecule contains polar carboxylic functions.[81,86] Several optical resolutions revealed, that the monohydrate of **2b** is even more efficient than anhydrous **2b**. It seems

Table 5. Compounds Resolved *via* Diastereomeric Complex Formation with **2**

Cmpd	Resolving Agent	Isolated Enantiomer	*ee* (%)	Yield (%)[a]	Ref.
58	**L-2b•H_2O**	----	poor	----	86, 87
59	**L-2b•H_2O**	----	poor	----	86, 87
60	**L-2b**	**(–)-60**	21		80, 86, 87
	L-2b•H_2O		29		
61	**L-2b**	**(+)-61**	24[81]		81, 86, 87, 91
	L-2b•H_2O		28[87]		
62	**L-2b•H_2O**	----	5	----	86
63	**L-2b•H_2O**	----	0	----	86
64	**L-2b•H_2O**	----	7	----	86
65	**L-2b•H_2O**	----	0	----	86
66	**L-2b•H_2O**	----	----	----	86
67	**L-2b•H_2O**	----	----	----	86
68	**L-2b•H_2O**	----	no complex[b]		86
69	**L-2b•H_2O**	**(+)-(1*S*,2*S*)-69**	35	----	86, 87
70	**L-2b•H_2O**	**(+)-(1*S*,2*S*)-70**	56	----	86, 87
71	**L-2b•H_2O**	**(+)-(1*S*,2*S*)-71**	61	----	86, 87, 91
	L-2c•H_2O		22	62	
72	**L-2b•H_2O**	----	no solid phase[c]		85
73	**L-2b•H_2O**	**(–)-(1*R*,2*R*)-73**	50	----	86, 87
74	**L-2b•H_2O**	**(–)-(1*R*,2*R*)-74**	15	----	86, 87
75	**L-2b•H_2O**	**(+)-(1*S*,2*S*)-75**	44	----	86, 87
76	**L-2b•H_2O**	----	0	----	85
77	**L-2b•H_2O**	----	no solid phase[c]		85
78	**L-2b**	**(+)-(1*R*,2*S*,5*R*)-78**	69[80]		80, 81, 91
	L-2b•H_2O		83[80]		
79	**L-2b•H_2O**	----	21	----	85
80	**L-2b•H_2O**	----	0	----	78
81	**L-2b**	**(–)-81**	30[79]	poor	80, 81, 85
	L-2b•H_2O		28[79]	poor	
82	**L -2b**	**(*S*,*S*)-82**	pure	16	92
83	**D-2b**	**(+)-(*R*,*R*)-83**	pure	30	83
		(–)-(*S*,*S*)-83	pure	37	
84a	**D-2c** and **L-2c**	**(–)-84a**	pure	91	
84b	**D-2c** and **L-2c**	**(+)-84b**	pure	77	84
84c	**L-2b**	**(+)-84c**	pure	68	
85	**D-2b**	**(*R*,*R*)-90**	99	35	93

a) Yields based on half amount of racemate; b) An isolated precipitate was not an expected complex; c) No precipitate was observed.

that the use of monohydrate facilitates complex formation, even though the supramolecular crystals obtained with **2b•H_2O** do not contain water molecules. Analysis of the crystal lattice reveals that water is displaced by the guest alcohol molecule.[80]

c) Techniques of Resolution via Complex Formation

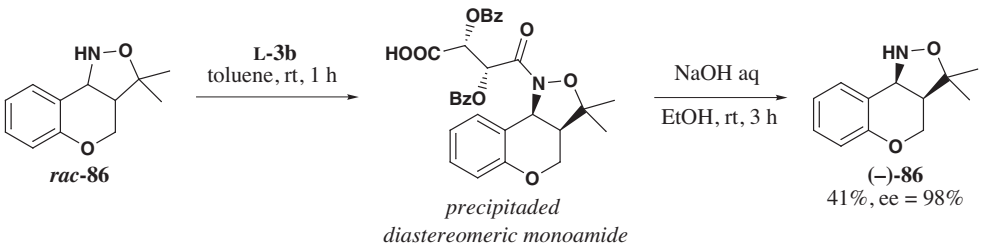
The interesting suspension method for resolution by inclusion complexation was proposed by Toda.[94] The procedure involves the use of an inert solvent such as hexane or water, which dissolves only the resolved guest compound. The powdered-host resolving agent remains suspended in the solvent and its transformation occurs on a liquid-solid phase over a few days at room temperature without stirring. The method involves subsequent heating the filtered diastereomeric complex *in vacuo*, which produces desired enantiomer in free form. This technique was successfully used by Kozma's group for resolution of chiral alcohols with tartaric **2** derivative.[80,81,86,87,89,91] Supramolecular complex formation was achieved with half amounts of **2b•H_2O** or **2c•H_2O**, and the unengaged enantiomer of the resultant diastereomeric complex remained in the mother liquor. Resolution of racemic menthol (**78**) by diastereomeric supramolecular compound formation with **L-2b•H_2O** has been presented in *Scheme 5*.[80,81]

Recently, it was demonstrated that supramolecular compound formation may occur without solvent, in a melt of the racemate. In case of **78**, resolution was more efficient than those in hexane solution.[95] Resolution by complexation may be also carried out using a procedure characteristic for diastereomeric salt formation namely by dissolution of all materials in a polar solvent and subsequent recrystallization of precipitate.[83,84]

3. Resolution *via* Diastereomeric Compound Formation

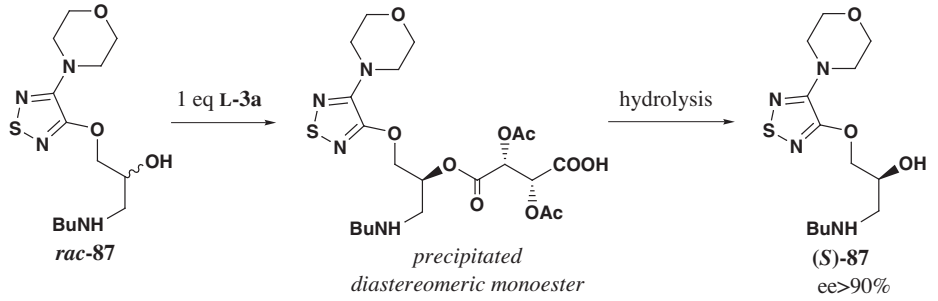
Acylated tartaric acid derivatives are also able to form covalent diastereomers, mainly monoamides, monoesters and imides.[1c] Resolutions *via* diastereomeric compounds are carried out with anhydrides **3a** or **3b**, which after the nucleophilic attack of amine or alcohol undergo subsequent ring opening and yield appropriate diastereomeric monoamides or esters, respectively. Due to the covalent diastereomers preparation, which is in general more complicated than the formation of diastereomeric salts or complexes and involve additional operation before and after the resolution step, this method is far less frequently used. During last few years, there have been only a few examples of single enantiomer production by application of this method. Efficient optical resolution of racemic benzopyrano[4,3-c]isoxazolidine (**86**) with **L-3b** was achieved *via* the formation of diastereomeric monoamides (*Scheme 6*).[96] Compound **3a** was used for the preparation of single enantiomer of *timolol* [(***S***)-**87**)] *via* preferential crystallization of its diastereomeric monoester (*Scheme 7*).[97]

Formation of diastereomeric amides and esters with anhydrides **3a** and **3b**, although not as popular as other classical resolution methods, is widely exploited in analytical chemistry. Compounds **3a** and **3b** are often used as the derivatizating agents for chiral amines and alcohols;



Scheme 6

the diastereomeric compounds they formed are stable and, in general, it is possible to assay them by chromatographic techniques for example. The latter application of **3** will be presented in the next section.



Scheme 7

II. DERIVATIZATING AGENT

Another important application of tartaric acid derivatives is their use as derivatizating agents (*Fig. 1*) to form diastereoisomers which can be analyzed. Derivatization of many chiral alcohols and amines has been be achieved with tartaric anhydrides **3**, and the covalent diastereomers formed, monoesters and monoamides respectively, were determined.[98-106] Through the formation of these diastereomeric compounds, enantiomeric excesses,[98,99] yields[100] and configurations[104] of the starting chiral alcohols and amines has been assayed. Derived diastereomeric monoesters and monoamides of **3** were most often analyzed using liquid chromatography with achiral columns,[98,100-102] but other methods like ^{1}H NMR[98,99] or X-Ray[103] were also exploited. Derivatization with **3** may be used in a laboratory[98,99] as well as in medicinal advanced analyses of biological materials.[100] The most frequently utilized derivatizating agents has been compounds **3** because the covalent diastereomers formed are more stable; however, derivatization to diastereomeric complexes is also known. For example the use of **L-2a** in the determination of the enantiomeric composition of some phenothiazine derivatives by ^{1}H NMR analysis of their diastereomeric hydrogen associates has been reported.[104] The use of **1**-**3** group in the formation of chiral chromatographic materials is illustrated in Section III.

1. Derivatization of Alcohols

Determination of the enantiomeric purity of 1-hydroxyindolizidines (**88**)[98] and of 6-hydroxyindolizidines (**89**)[99] after conversion to diastereomeric acetyl or benzoyl tartaric monoesters was achieved, respectively (*Fig. 11*).

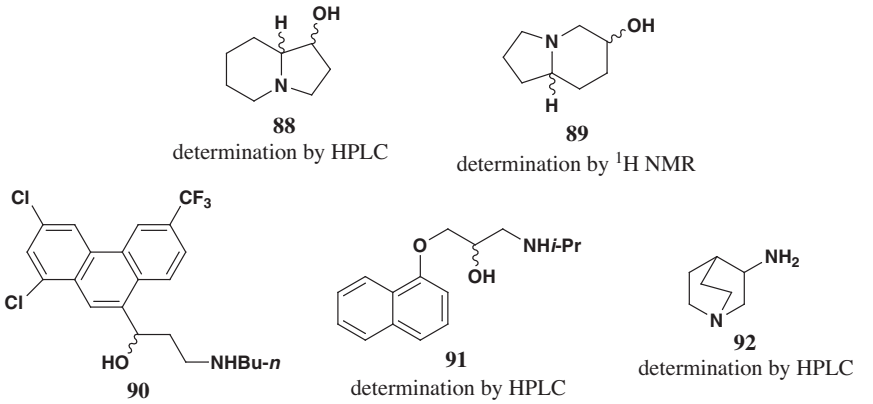


Fig. 11

The use of **3** as derivatizating agent in medicinal analyses has been also reported. By the pre-column derivatization to diastereomeric monoesters, the farmacokinetics of an anty-malarian drug *desbutylhalofantrine* (**90**) in rat plasma was studied.[100] Similarly determination of some, β-blockers, *e. g. propranolol* (**91**) in biological fluids was accomplished by derivatization with anhydride **L-3a** and subsequent analysis on reversed-phase chromatography of the tartaric monoesters thus formed (*Fig. 11)*.[102,105,106]

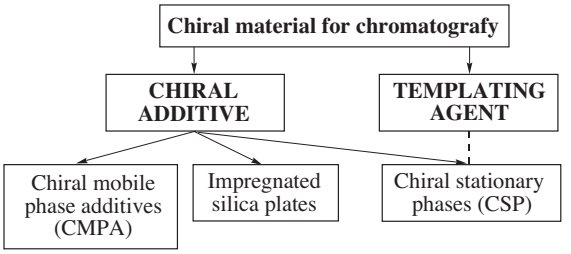
Mild conditions and low temperatures of the reaction of alcohols with anhydrides **3** are great advantage of derivatization with these compounds. Although it is known that bulkiness of substituent group may increase the separation factor (1.61, 2.86 and 3.48 for separation of celiprolol alkanolamine with **3a**, **3b** and **3c** respectively),[106] the less crowded **3a** is most often used because of its higher reactivity and the simplicity of ring-opening and of monoesters formation.

2. Derivatization of Amines

Despite the possibility of **3** to similarly form diastereomeric monoamides with amines, such a derivatization has been rarely reported. One example is the determination of enantiomeric composition of 3-aminoquinuclidine (**92**) by HPLC separation of its diastereomeric monoamides formed with **L-3b** (*Fig. 11*).[1d]

III. CHIRAL MATERIAL FOR CHROMATOGRAPHY

The chiral recognition ability of tartaric acid moiety has been widely used in chromatographic techniques (*Fig. 12*). Chromatographic resolution of enantiomers for analytical and



The Use of **1** Derivatives as Chiral Discriminating Agents in Chromatographic Materials

Fig. 12

preparative purposes with help of **1**-**3** has probably been started from the application of thin layer chromatographic impregnated silica plates.[107,108]

Then amides[109] and esters[110] of **1** were used as an effective chiral mobile phase additives. The scope of application was enhanced when it was noted that derivatives of **3** might function as chiral selector indeed.[111] Thus, many chiral materials derived from **3** were synthesized and evaluated as chiral stationary phases in liquid chromatography. All of these chromatographic materials employ the tartaric acid moiety as an additive to the achiral support (silica plates, CSP) or eluent (CMPA). A novel application is the use of **1** and **2** as a templating agent in the synthesis of chiral polymers.[112]

1. Chiral Additive

The role of **1**–**3** as chiral additives in chromatographic applications consists in the addition of chirality contributed by the tartaric moiety to the achiral support. In these systems, tartaric molecules are responsible directly for molecular recognition and discrimination of solute enantiomers, by dual hydrogen bonds and diastereomeric complexes formation.

a) Impregnated Silica Plates

A well-known application of **1** and **2** as chiral additives is their use in the preparation of impregnated silica plates. For example the resolution of phenylthiohydantoin amino acids by TLC on impregnated by **L-1** silica plates was reported.[107] Preparative enantiomer separation of chromenone-benzoxazole receptor racemic mixture was achieved using TLC **L-2c** impregnated plates. The enantiomerically pure compounds were recovered from silica gel as diastereomeric **2c** complexes.[108]

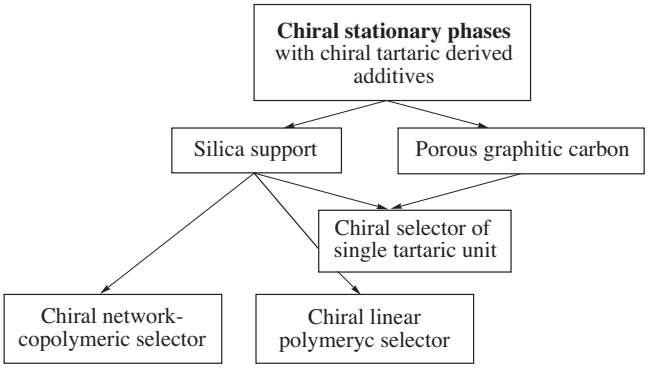
b) Chiral Mobile Phase Additives

The use of **1** derivatives as chiral mobile phase additives has been already known for half a century.[113] Diesters and diamides of **1** have been used as chiral additives in liquid chromatography to the aqueous and non-aqueous eluents, respectively.[109,114] The chiral recognition of a wide range of enantiomers is caused by the great ability of those derivatives to form dual

hydrogen bonds *via* its hydroxy groups and amide or ester units. This application is still of importance, while enantio-separation of alkyl tropate with di-*n*-propyl ester of **L-1** as CMPA by HPLC was recently reported.[110]

c) Chiral Stationary Phases

Generally, the chiral-stationary-phases (CSP) for liquid chromatographic resolution are prepared by surface modification of porous support material (silica, porous graphitic carbon) by the coating or bonding of an appropriate chiral additive. The chiral discrimination by the tartaric moiety may be achieved by single unit incorporated on the support[109,111,115] as well as chiral polymers immobilized on silica (*Fig. 13*).[116-122]



Chiral Stationary Phases Based on Tartaric Derived Chiral Additives

Fig. 13

Over two decades ago, it was found that the tartaric unit is a successful component of silica CSP.[111] In such a system, tartaric acid is covalently bonded to the silica gel surface *via* the corresponding tartramide, subsequent silane formation and its reaction with porous silica gel (*Fig. 14*). All three routes to such tartaric-based CSP's involve the use of the corresponding **3** derivative and its aminolysis as a first step, thus differing in the methods of silane formation.[109,111,200]

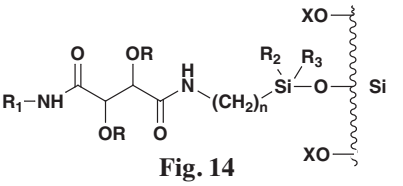


Fig. 14

The preparation and application of many chiral silica sorbents based on covalently-linked tartaric acid has been reported (*Fig. 14*, *Table 6*) and evaluated as CSP's in LC, HPLC or even SFC (supercritical fluid chromatography).[121] It was noted that chiral recognition is probably caused by the formation of diastereomeric complex between tartaric unit and enantiomer *via* hydrogen bonds.

The use of such CSP's has led to the successful separation of various compounds including β-hydroxycarboxylic acids,[111] α- and β-amino acids, α- and β-hydroxycarbonyl compounds, amines and 1,2-diols.[109]

Table 6. Silica CSP's with Tartaric Unit as Chiral Selector

CSP[a]	R	R^1	n	R^2	R^3	X	Ref.
1	H	$CH(CH_3)_2$	11	CH_3	CH_3	$Si(CH_3)_3$	109
2	H	$CH(CH_3)_2$	11	CH_3	CH_3	H	109
3	H	$CH(CH_3)_2$	3	OH	O~|Si	H	109
4	H	$CH(CH_3)_2$	3	CH_3	O~|Si		111
5	PhC(O)	$(CH_2)_3CH_3$	3	CH_3	CH_3	H	120
6	H	$(CH_2)_3Si(CH_3)O$~|Si	3	CH_3	CH_3		120

[a] see *Fig. 14*

The monoamides of **1** (*Fig. 15*) have also been used as an ionically bonded chiral selector *via* adsorption to the amino-propyl silica gel. This unique chiral selector served as a bifunctional discriminating agent, while it was also used as a coating agent of silica ligand-exchange CSP.[116]

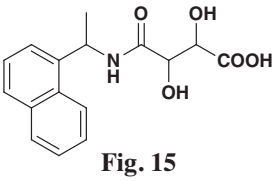
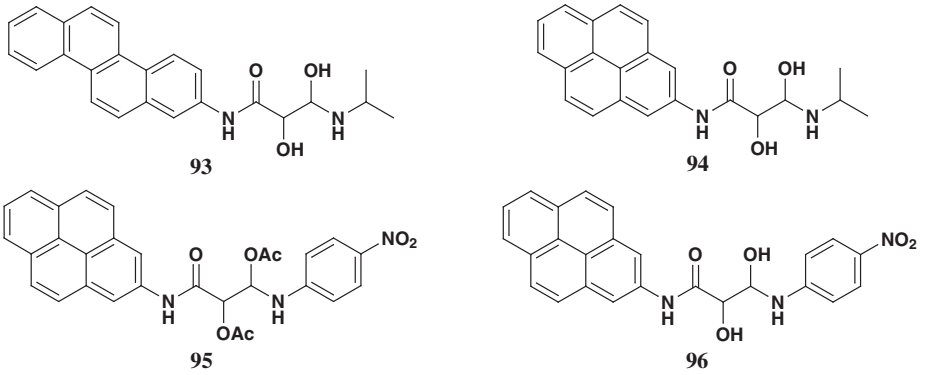


Fig. 15

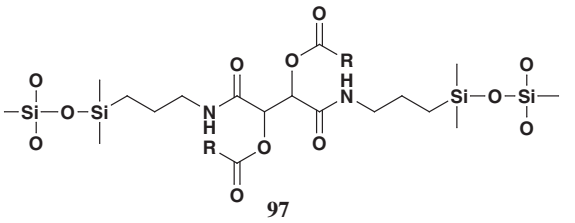
The success of silica CSP obtained by the chemical modification with tartaric additives prompted the use of these derivatives as chiral selector linked to other supports such as porous graphitic carbon (PCG). Although structurally related to the tartaric acid amides used as silica gel modifiers, the appropriate selectors (**93-96**) are different in that they contain large aromatic components (1-pyrenyl, 2-chrysenyl) (*Fig. 16*) whose presence is necessary for the chosen chiral selector to be absorbed on PCG, which has no functional group and cannot form a covalent bond itself. Four such CSP's were synthesized and introduced as HPLC packing material exhibit excellent enantioselectivity for various type of compound.[115]

The spectacular successes were the investigations on the novel chiral network-polymeric CSP's based on the tartaric moiety.[118,122] These novel sorbents contain chiral-branched polymer with the tartaric unit as chiral selector (*Fig 17*). Preparation of this CSP involved polymerization of *N,N'*-diallyl-L-tartaric diamide with functional hydrosilane and subsequent immobilization of the formed chiral polymer to vinyl-silica.



Porous Graphitic Carbon CSP's with Tartaric Unit as Chiral Selector

Fig. 16



R = a) Ph, b) 4-Me-Ph, c) 3,5-$(Me)_2$-Ph, d) 4-*t*-Bu-Ph, e) 4-Ph-C_6H_4, f) 4-Ph-O-C_6H_4, g) 2-Ph-O-C_6H_4

Chiral Selector Based on Copolymeric Bond of Tartaric Moiety and Hydrosilane

Fig. 17

Various acyloxy substituents were investigated for chiral discrimination ability (*Fig. 16*). *O,O'-bis*-(3,5-Dimethylbenzoyl)-*N,N'*-diallyl-L-tartaric diamide (**97c**) and *O,O'-bis*-(4-*tert*-butylbenzoyl)-*N,N'*-diallyl-L-tartaric diamide (**97d**) were found to be excellent CSP components.[118,121] These novel network-polymeric materials have found application as commercially available chiral column packings of Kromasil CHI-DMB and Kromasil CHI-TBB, respectively. Application of these columns include separation of various acidic, basic and neutral compounds, e. g. of amino acids[119] as well as compounds of pharmaceutical importance as *bupivacaine*, *ibuprofen*, *naproxen* and *tocainidine*.[121]

Due to the great applicability of these network-polymeric selectors based on **1**, another investigation was carried out to compare the enantioselectivity of commercially available Kromasil CHI-DMB with other selectors based on similar units.[117,123] Neither analogous CSP with twin dimeric tartaric selector nor linear tartaric polyamide gave comparable separating factors.[117] Similarly, CSP obtained by adsorption of analogous selector on PCG was examined and showed lower discriminating ability.[123]

2. Templating Agent

In an effort to prepare new materials applicable as chiral materials in chromatography, the use of organic molecules as templates has been investigated. For example chiral polyaniline was synthesized through L- or D-**1** and L- or D-**2b** and evaluated as chiral stationary phase.[123] Polymer-doped with chiral tartaric molecules has been subsequently removed dedoped *via* extraction leaving a chiral cave. Thus the obtained chiral recognition polymer preferentially traps enantiomers from racemic mixture, as was proved by the resolution of some amino acids.

IV. SUMMARY

Tartaric acid **1** and its derivatives **2**, **3** are very popular and attractive molecules which have been and are still being used in all the field of asymmetric chemistry. The major use of **1** and of *O*-acyl tartaric acids **2** and anhydrides **3** in the resolution of racemates illustrated with examples from 1998 to present has been described.

Compounds **1** and **2** are most often used as resolving agent for racemic mixtures of amines, and other compounds of basic character. Depending on the properties of compounds, the resolution can proceed *via* diastereomeric salt formation, *via* diastereomeric complex formation or rarely *via* diastereomeric compound formation. Numerous compounds resolved with amino function have been grouped according to their structure; several resolutions of racemic α-amino acids and various non-amine phosphonium, arsonium and sulfonium salts were also reported.

The role of resolving agent, some mechanistic aspects and the selection of optimal parameters of the most often used method of separation of diastereomeric salts by crystallization have been discussed. Alternative methods of separation of diastereomeric salts such as distillation and supercritical fluid extraction, as well as industrial aspect of separation have been mentioned. Among tartaric resolving agents, tartaric acid (**1**), dibenzoyl- (**2b**) and di-*p*-toluoyltartaric acids (**2c**) are the most frequently used; however, dianisoyl- (**2d**) and dipivaloyltartaric acids (**2e**) have also been exploited.

An important disadvantage of racemates resolution is the 50% loss of unwanted enantiomer. Thus, the most exciting method is a dynamic diastereomeric salt resolution, a kinetic process which involves catalytic or spontaneous racemization of a substrate. It allows the resolution in nearly 100% yield while classical resolution has a 50% limit.

Anhydrides **3**, especially **3a**, have been most often used as the derivatizating agents of chiral alcohols and amines resulting in the functionalization of enantiomers, which makes their analysis possible. The covalent diastereomers formed are more stable; however, derivatization to diastereomeric complexes is also known. Interestingly, pre-column derivatization with chiral **3** permits the determination of diastereomers by liquid chromatography with achiral columns. Analyses using chiral columns have also been exploited.

The application of **1**-**3** in chiral materials for chromatography, *e. g.* as additives in mobile phases, impregnated silica plates or chiral stationary phases (CSP) is a result of their

important function as chiral selector. The most modern CSP, beside single unit incorporated to the support, may be achieved by chiral polymers immobilized on silica. As a result of continuous search for new materials for chromatography, promising information on chiral templates obtained by doping and de-doping of some polymers with tartaric units has been reported.

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