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Prediction of the efficiency of diastereoisomer separation on the basis of behaviour of enantiomeric mixtures

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Abstract

The driving force of homo- and heterochiral complex formation in the mixtures of chiral compounds is, probably, effort of the system to separate the most symmetric associates from the less symmetric ones. A possible way to achieve separation of these associates is the distribution between two phases. Therefore, during the separation of (a certain part) diastereoisomers similar trends can be observed as in course of the distribution of enantiomeric mixtures between two phases, althought in the first case a third chiral compound (namely the resolving agent) is present. Of course in this case the pursuit of symmetry is not so obvious as in case of enantiomeric mixtures. It should be noted that thus the outcome may be modified by the intervention of kinetic control. One can conclude that the structure of chiral compounds encodes the result of the (optical) resolution.

Introduction

In many cases, living organisms contain only one of the two enantiomers of chiral molecules, but often racemic compounds (1:1 mixture of the two enantiomers) are obtained in the chemical syntheses. The biological activity of enantiomers may be different or even opposite, so the enantiomeric separations are necessary and inevitable. Many methods described in the literature for the separation of enantiomers involve the formation of diastereoisomers followed by liberation of the separated enantiomers. These enantiomeric separation methods are discussed and systematized in several articles.[1-10]

In the course of resolution processes, racemic compounds are reacted with another chiral reagent (resolving agent). The diastereoisomers so obtained are separated, and their decomposition affords the corresponding enantiomeric mixtures. Usually, pure enantiomers can only be obtained by further purification of these enantiomeric mixtures (Scheme 1).

Scheme 1. here

Composition of the salt crystallized during the fractionated precipitation of diastereoisomeric salts and enantiomeric mixtures is determined by the SDE[11] capacity (self disproportion of enantiomers) of the involved chiral compounds.

The most common and used methods for the separation of enantiomeric mixtures are based on the exploitation of the distribution of hetero- and homochiral associates between two phases (most often between solid and liquide or vapour phases).[12] According to the most recent research the enantiomeric enrichment can be occured

using achiral chromatography[13-16] and by separation of racemates using chiral selector on achiral[17,18] stationary phase or chiral phase chromatography (HPLC)[19], respectively.

A correlation between the eutectic composition of biner melting point diagrams of diastereoisomeric mixtures (ee_{EuDia}) and efficiency of resolution (F) was established by us (Scheme 2).[12]

Scheme 2. here

Furthermore, it was found by analyzing the results of 45 resolutions, that the average enantiomeric purity (ee_{EuDia} = 78%) of enantiomeric mixtures isolated from crystalline diastereoisomers correlates to the average value of the measured eutectic composition of the starting racemic compounds (ee_{EuRac} = 73%). At the same time, when the eutectic composition of the resolving agent is higher than the eutectic composition of racemic compound (in 29 cases), a better correlation was observed between the average value of enantiomeric purities (ee_{Dia} = 80%) of enantiomeric mixtures isolated from the crystalline diastereoisomers and the average value of eutectic compositions of enantiomeric mixtures of the resolving agent (ee_{EuRes} = 78%) (Table 1).[21]

Table 1 here

Based on these observations, we suppose that the composition of crystalline diastereoisomer is determined either by the eutectic composition of the racemic compound or that of the resolving agent and the higher ee value has more dominant effect (Scheme 3).

Scheme 3 here

Consequently, a correlation can be found between the biner melting point/composition phase diagram of the diastereoisomeric mixtures and the phase diagrams of the enantiomers which are the constituents of the diastereoisomers.

If we wish to separate the enantiomers of a racemic mixture using structurally similar resolving agent (equivalent or half equivalent amount), the isomers of the racemic compound are transformed into “quasi enantiomeric mixtures”. In the course of separation of these “quasi enantiomeric mixtures” (of diastereoisomers) the same methods based on the distribution between two phases can be used which are suitable methods for the separation of enantiomeric mixtures (also diastereoisomeric related supramolecular enantiomeric associates).[7]

Separation of diastereoisomers from melt

The mixtures of racemic compounds and resolving agents can be considered as mixtures of diastereoisomeric supramulecular structures. These diastereomeric supramolecular structures exist in solutions and in melts, therefore these diastereoisomeric associates can be separated by crystallization from melt. In this case the mixture of the racemic compound and the resolving agent is melted, then the crystalline phase - obtained by controlled cooling - can be separated by filtration (if it is possible).

An example for such a separation is the crystallization of diastereoisomeric mixture of **MEN-DBTA molecular** complex from melt incorporating menthol (**MEN**) and (*R*,*R*)-dibenzoyl-tartaric acid ((*R*,*R*)-**DBTA)** (Scheme 4).[22]

Scheme 4 here

It can be seen from the above example that the before mentioned behavior of mixed chiral compounds is valid not only for diastereoisomeric salts but for diastereoisomers in general. During resolution of racemic menthol with (*R*,*R*)-**DBTA** the parts of the diastereoisomeric complexes are kept together by weak second order interactions, only. Formation of the more stable molecular complex that crystallizes more quickly makes the separation possible.

Separation of diastereoisomers by sublimation of enantiomeric mixtures

Enantiomeric separations can be effectuated even if the mixture of diastereoisomers is obtained in a solid-solid reaction. An example is reaction of solid 2-iodo-*trans*-cyclohexanol (**ICH**) and solid (*R*,*R*)-**DBTA** for three months (Scheme 5). It was observed in the course of the fractionated vacuum sublimation[23] of the above mentioned mixture of compounds, that one of the enantiomers of **ICH** sublimated as the first fraction at realtively low temperature (T_1, Scheme 5), and the other ICH enantiomer sublimated at a higher temperature (T_2), after thermal decomposition of the molecular complex formed previously in the solid-solid reaction.

Scheme 5. here

Separation of diastereoisomers by distillation of enantiomeric mixtures

In case of resolutions using half equivalent of resolving agent it is expected, that the enantiomeric proportion of racemic compound may be separated from the corresponding diastereoisomer formed (distributed between two phases). In the reaction of methylanara (2-methylamino-1-phenylpropane, **MA**) and (*R*,*R*)-**DBTA**, after the precipitation of the diastereoisomeric salt, the residual free amin, namely (*S*)-**MA** could be obtained by distillation under vacuum[24], while the other enantiomer was obtained by the separation of the solid diastereoisomer residue (Scheme 6).

Scheme 6. here

Separation of diastereoisomers by fractionated distillation of enantomeric mixtures

This method is also suitable for fractionated separations if the resolving agent forms salt that can decompose without any damage. An adequate example for this is the resolution of racemic anara (2-amino-1-phenilpropane, **AN**) by half equivalent of the structurally related (*S*)-*N*-phtaloyl-α-phenylethylamine (**PPEA**) (Scheme 7). Again, the free, optically active base ((*R*)-**AN**) could be distilled off at T_1, then the solid diastereoisomeric salt could be decomposed at higher temperature (T_2, by ring closure

of phtaloilic derivative), so the other amine enantiomer ((*S*)-**AN**) could be distilled off in the second stage.

Scheme 7. here

Separation of diastereoisomers by extraction of enantomeric mixtures with a supercritical fluid (carbon dioxide)

In the course of a half equivalent resolution, the remaining free enantiomer may also be removed by extraction from the reaction mixture after the crystallization of the diastereoisomeric salt. This extraction can be accomplished using supercritical fluid, most often supercritical carbon dioxide. In case of resolution of *trans*-cyclohexane-1,2-diol (*trans*-**CHD**)[25] by (*R,R*)-tartaric acid ((*R,R*)-**TA**) the free enantiomeric portion was separated by extraction with supercritical CO_2 from the mixture of the excess of *trans*-**CHD** and the crystalline diastereoisomeric complex (Scheme 8). Of course, the other enantiomer can be recovered from the diastereoisomeric complex.

Scheme 8. here

Separation of diastereoisomeric molecular complexes by fractionated crystallization

The above demonstrated methods can be applied for the separation of enantiomers having asymmetric center on a phosphorous atom. For example, the resolution of several racemic alkyl-, alkoxy-, and aryl-substituted 3-methyl-3-phospholene oxides were accomplished via molecular complex formation with (*R*,*R*)-**TADDOL** (α,α,α′,α′-tetraphenyl-1,3-dioxolan-4,5-dimethanol) as the resolving agent (Scheme 9). If half equivalent of (*R*,*R*)-**TADDOL** was used, the more stable diastereoisomer crystallized which could be isolated by conventional methods, such as filtration.[26]

Scheme 9. here

Separation of diastereoisomeric coordination complexes by fractionated crystallization

In other cases, the cyclic P-chiral 3-phospholene oxides were separated into their enantiomeric mixtures by resolution with the Ca^{2+} or Mg^{2+} salts of **DBTA** (**DBTC**). As it is shown on Scheme 10, when half equivalent of resolving agent was used, the favourable diastereoisomer was precipitated. After filtration and decomplexation of the diastereoisomeric complex, enantiomeric mixture of the 3-phospholene oxide (**MPO**) was obtained. The antipode of the first isolated **MPO** enantiomer was recovered from the mother liquors of the resolutions.[27] Effectiveness of tha method was demonstrated on a series of cyclic P-chiral 3-phospholene oxides.[28]

Scheme 10. here

Separation of diastereoisomers from enantiomeric mixtures using mixtures of two immiscible solvents

Based on the above examples, formation of solid phase, solid-liquid phases or solid-gas phases systems is always necessary for the separation of diastereoisomers. Now the question is: should one achieve chiral separation between two immiscible liquid phases? The answer yes, of course. Diastereoisomers may be separated by distribution between two liquid phases.
If the racemic methylanara (**MA**) is reacted with half equivalent of sodium salt of (*R*,*R*)-tartaric acid ((*R*,*R*)-**TAN**) in a mixture of water and benzene, the enantiomer and diastereoisomer are distributed between the two liquid phases.[29]

Scheme 11. here

The aqueous phase contains the neutral salt of **TAN-MA**, while the other enantiomer can be found in the organic layer. So the separation of diastereoisomers or enantiomers can be accomplished without crystallization, using two immiscible solvents. The two solvent phases can also provide particularly good separation if the diastereoisomer can crystallize due to its insolubility in the applied two solvents.

Separation of diastereoisomers by crystallization from two immiscible solvents

The resolution of racemic Grandaxine (**GRA**) with half equivalent of **DBTA** in mixture of water and chloroform, or water and dichloromethane is an example for the separation of diastereoisomers by crystallization from two immiscible solvents.[30] The crystallization started on the boundary of solvent phases, then it is accelerated. The formed diastereoisomeric salt was filtrated, and the two phases were separated. The enantiomeric mixture containing one of the enantiomers in excess was obtained from diastereoisomeric salt, while the other enantiomer was recovered in neutral form from the organic phase. In addition, a small amount of **GRA** with racemic composition was isolated from the aqueous solution (Scheme 12). Form the ee data shown in Scheme 12. one can conclude that in this case, the eutectic composition of the racemic compound governed the efficiency of separation.

Scheme 12. here

Separation of diastereoisomers by crystallization involving the formation of solvates

It is very common during the separation of diastereoisomers, that the enantiomeric purity and yield of separation is increased when solvates were formed during the crystallization of the diastereoisomers. For example, if *trans*-chrysanthemic acid (**CRS**) is resolved with *N,N*-dimethyl-aminodiol (obtained by the transformation of an intermediate of chloramphenicol) in methanol, a methanol solvate of the diastereoisomer could be isolated in very good diastereoisomeric purity, but the yield was 52%, only (Scheme 13). Whereas the resolution was accomplished in diisopropyl ether, or methyl-isobutyl ether in the presence of methanol, the methanol solvate of the diastereoisomer was also crystallized, but both the purity and the yield increased significantly.[31]

Scheme 13. here

Separation of diastereoisomers by crystallization in the presence of a structurally related achiral reagent

Frequently, the resolution can be accomplished only via solvation. In the previous example the resolution could be carried out using another solvent. When the racemic α-phenylethylamine (**PEA**) was resolved using half equivalent of a derivative of a **PEA** enantiomer, a diastereoisomer was isolated wich contained (*S*)-**PEA** in 60% excess in acetone (Scheme 14).[32] When an achiral compound (such as urea) with related structure to one part of the resolving agent was added to the solution before crystallization, much purer diastereoisomer was isolated with an (*S*)-**PEA** enantiomeric excess of 90%.

Scheme 14. here

So the achiral solvate forming reagent - which is structurally related with either the resolving agent or the racemic compound – promoted the crystallization of diastreomer, and increased enantiomeric excess of the diasteromer.

Crystallization of diastereoisomers based on kinetic and thermodynamic control

The decisive role of kinetic and thermodynamic control was observed in the separation of enantiomeric mixtures. This phenomenon can also be found at both the separation of quasi-enantiomeric mixtures and conventional resolutions.[33,34] For example, the effect of kinetic control was observed in the resolution of Pregabalin (**PRE**) by mandelic acid (*S*)-**MA** (Scheme15). when the crystalline diastereoisomeric salt was isolated after 15 minutes crystallization, enantiomeric excess of (*S*)-**PRE** isolated from the salt was 98%, while the ee decreased significantly if the crystallization was carried out over 48 hours.
It means that the thermodynamic control has a disadvantageous effect on this process. The same phenomenon was observed in the course of the reciprocal process, when racemic **MA** was resolved by (*S*)-**PRE.** Namely, crystallization of the diastereoisomeric salt was controlled kinetically.

Scheme 15. here

In other cases it is necessary to wait until thermodynamic equilibration, because in these cases the process is controlled thermodynamically. An adequate example is the resolution of an intermediate of tamsulozin (**TAM**) with (*R,R*)-**DBTA** (Scheme 16). In this case the diastereoisomeric salt contained the (*R*)-**TAM** enantiomer in excess. However, after an hour crystallization, practically racemic **TAM** was found in the salt, but excellent enantiomeric excess could be achieved when the diastereoisomer was crystallized for 48 hours.[35]

Scheme 16. here

Conclusion

The above mentioned examples demonstrate that the properties of the involved enantiomeric mixtures determine the enantiomer (diasterepoisomer) distribution between two phases and in this way behaviour of the used chiral compounds determine the efficiency of the process during enantiomer or diastereoisomer separations. There are numerous methods of choice (solid-solid, solid-liquid, solid-gas, liquid-liquid distributions) and, of course, we should choose the most favourable method (if there are more possibilities).

We have recognized that in the resolution processes the diastereoisomers behave similarly to their constituent enantiomeric mixtures, if the resolving agent was structurally related to the racemic compound.

We demostrated that the eutectic composition of the racemate and/or the resolving agent determines the composition of the formed (crystalline) diastereoisomers even if the diastereoisomer forming chiral compounds are not structurally similar. Comparison of the average ee values of the obtained enantiomeric mixtures from series of resolutions with the average eutectic compositions of the involved chiral compounds (racemate and resolving agent) confirmed the above observation, namely the higher eutectic composition governs the enantiomer separation (Table 2).

Table 2. here

We also think that the eutectic composition of the diastereoisomer forming enantiomers determines the efficiency of the resolutions in cases of crystalline diastereoisomeric salt, molecular- or coordination complex formations and these governing effects are valid when the separation is based on the distribution between two liquid phases.

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Prediction of the efficiency of diastereoisomer separation on the basis of behaviour of enantiomeric mixtures

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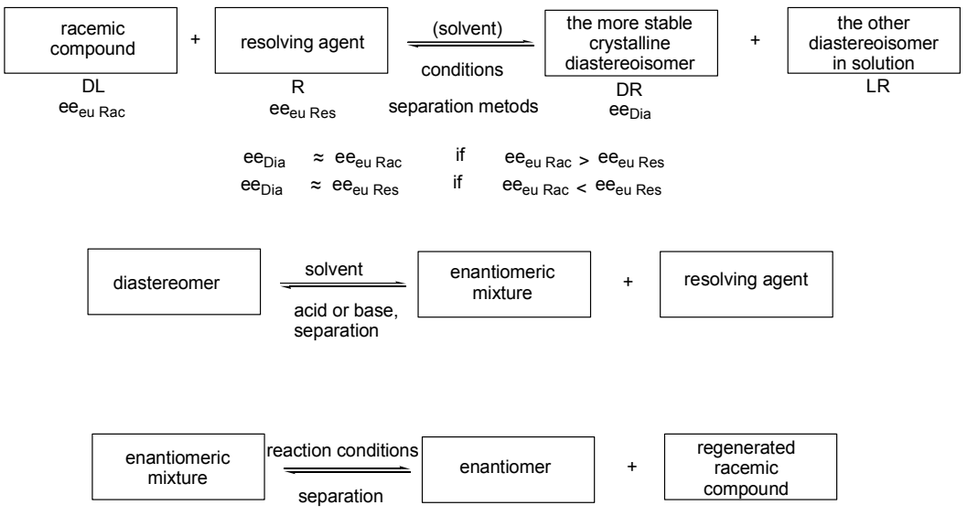
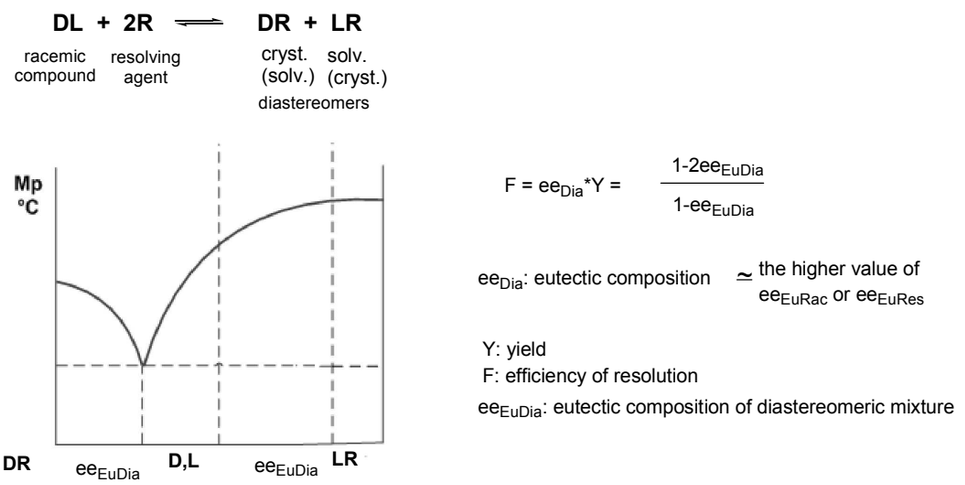
[2] *Department of Organic Chemistry and Technology, University of Technology and Economics, Budapest*



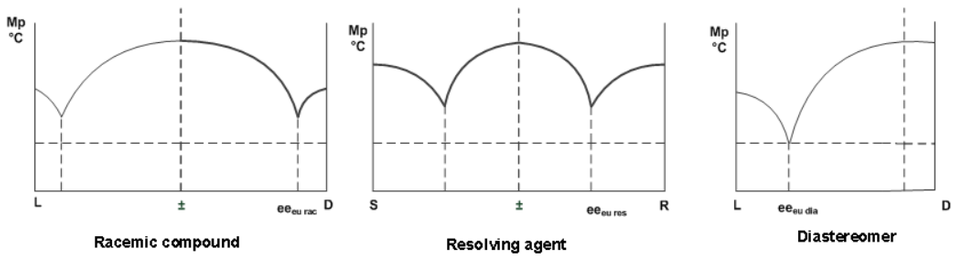
Scheme 1. General scheme for the preparation of pure enantiomers via diastereoisomeric salt formation (ee_{euRac}: ee of an enentiomer at the eutectic composition of the racemate; ee_{euRes}: ee of a resolving agent enantiomer (R or Я) at the eutectic composition; ee_{Dia}: ee of an enantiomer of the original racemate at the eutectic composition of the diastereoisomeric salt).



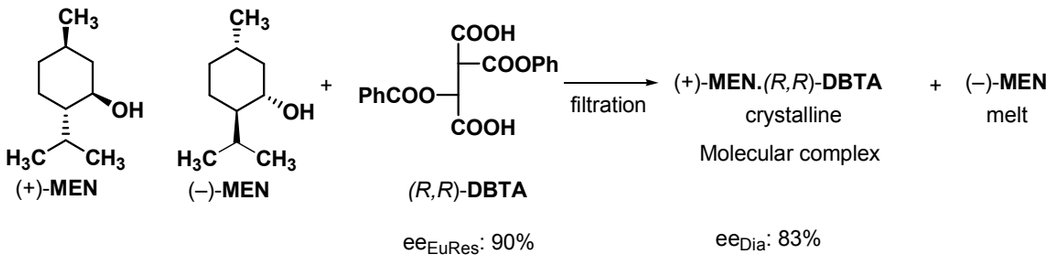
Scheme 2. Melting point/composition diagram of diastereoisomers and the relation between eutectic composition of diastereoisomeric mixture and efficiency of resolution.

Table 1: The average ee data of the investigated resolutions

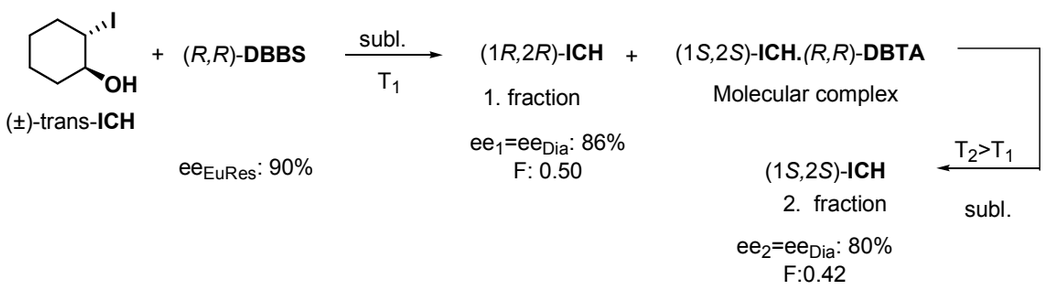
Number of resolutions	$ee_{eu\ Rac}$ (average)%	ee_{euRes} (average) %	ee_{Dia} (average)%	F (average)
45	73	70	78	0.56
29	-	78	80	0.54



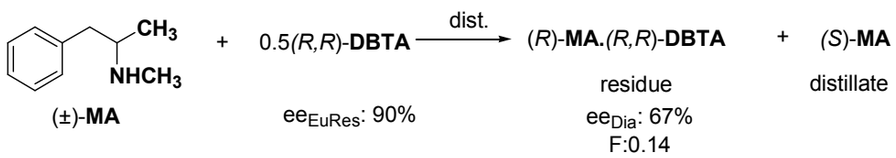
Scheme 3. The affect of the eutectic composition of racemic compound and resolving agent on the eutectic composition of diastereoisomers obtained (see also Scheme 2).



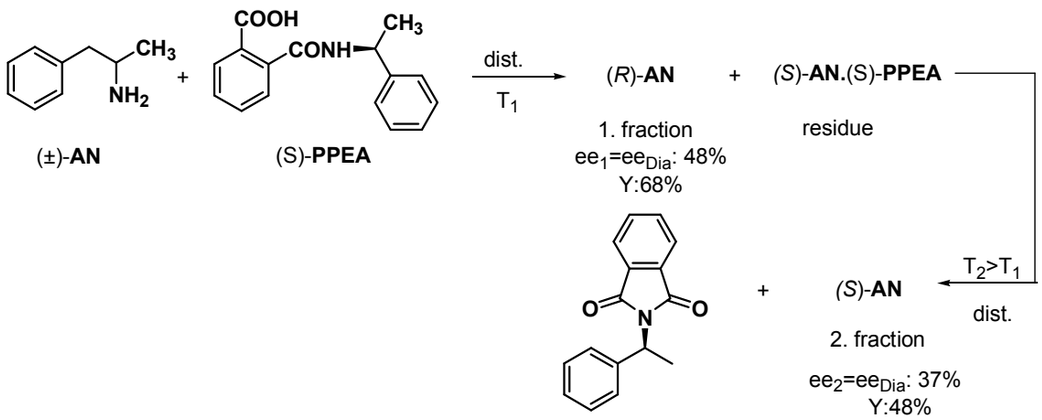
Scheme 4. Separation from melt



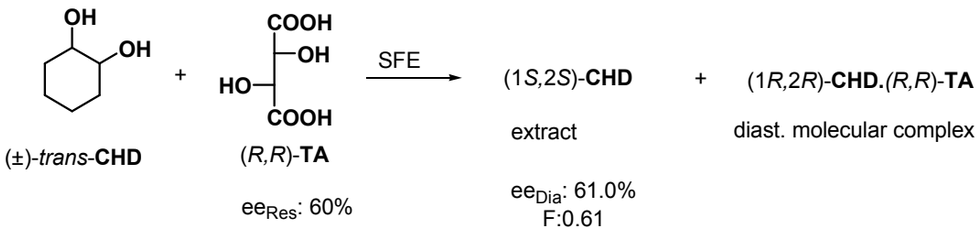
Scheme 5. Separation of diastereoisomers by fractioned vacuum sublimation.



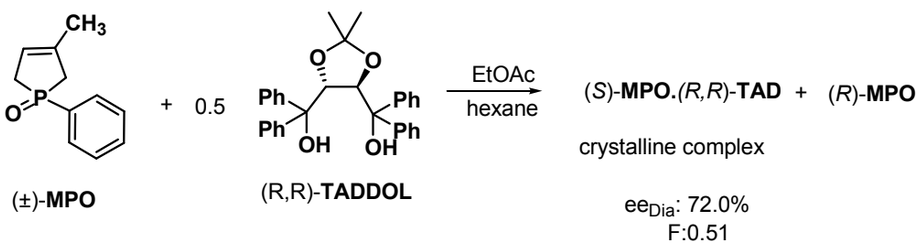
Scheme 6 Separation of diastereoisomers by distillation of enantiomeric mixture.



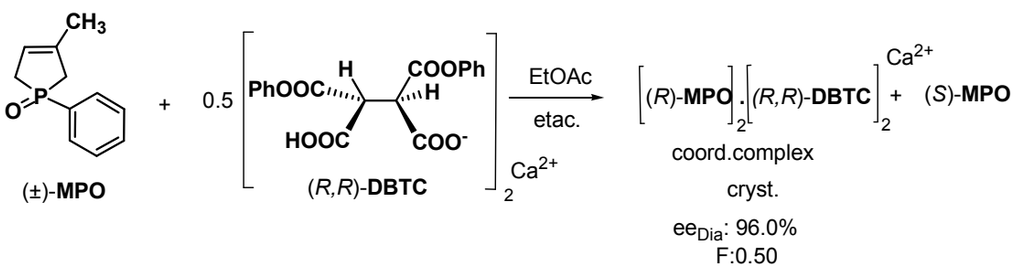
Scheme 7. Resolution of racemic **AN** *via* fractionated distillation of a mixture of free **AN** and **AN.**(*S*)**-PPEA** diastereoisomeric salt.



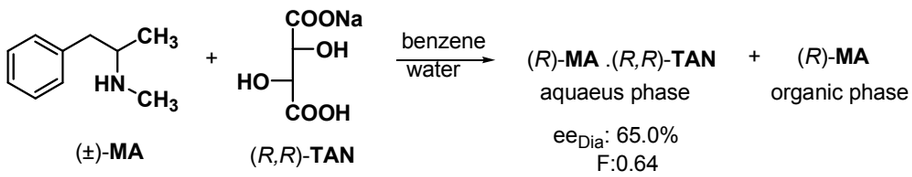
Scheme 8. Separation of the *trans*-**CHD** enantiomers via molecular complex formation followed with supercritical fluid extraction.



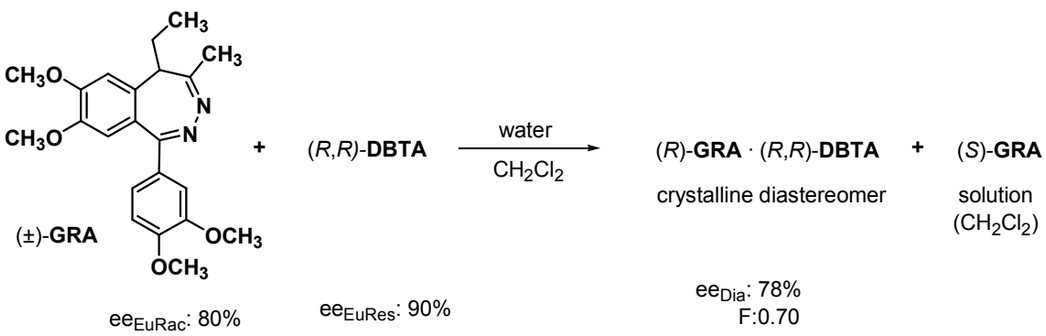
Scheme 9. Separation of diastereoisomeric molecular complexes of **MPO** by fractionated crystallization



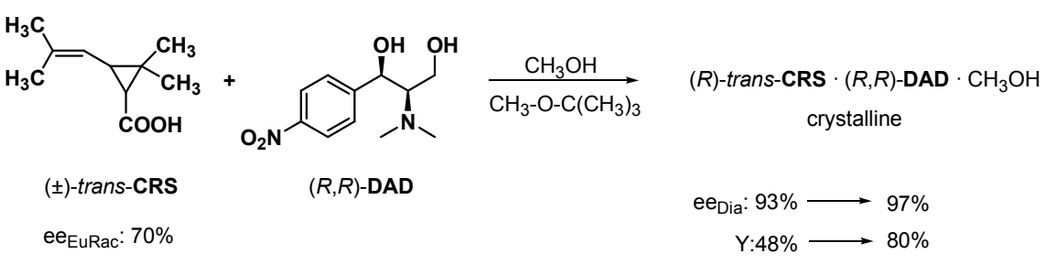
Scheme 10. Resolution **MPO** *via* diastereoisomeric coordination complex formation and fractionated crystallization.



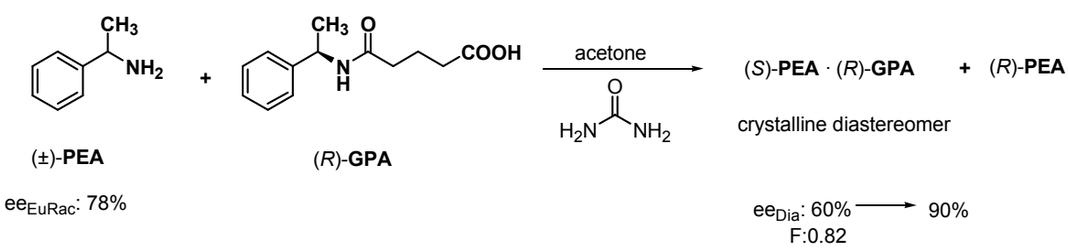
Scheme 11. Resolution of **MA** using two immiscible solvents.



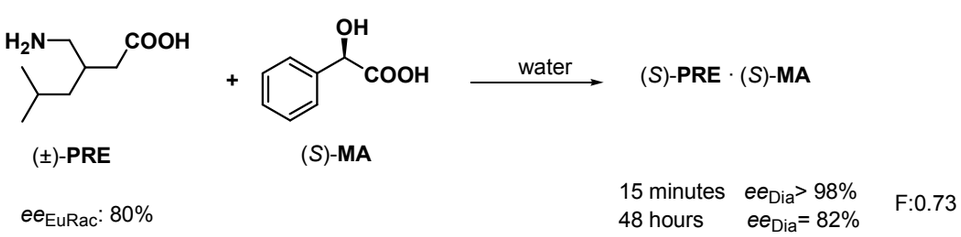
Scheme 12. The separation of diastereoisomers by crystallization from immiscible solvents



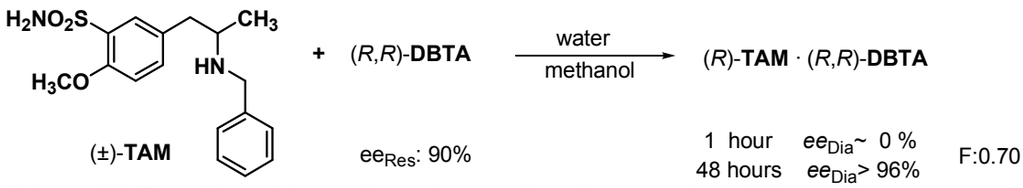
Scheme 13. Separation of diastereoisomers by crystallization involving the formation of solvates



Scheme 14. Separation of diastereoisomers by crystallization involving the formation of solvates



Scheme 15. The effect of kinetic control on the separation of diastereoisomers



Scheme 16. The effect of thermodynamic control on the separation of diastereoisomers

Table 2. The average ee data of the examined resolutions

Nr. of experiments	average value of ee_{EuRac}/ee_{EuRes} [b]	average value of ee_{Dia} [b]	average value of F
13 (10[a])	80%	78%	0.58

[a] the used compounds are not structurally related

[b] ee_{euRac}: ee of an enantiomer at the eutectic composition of the racemate; ee_{EuRes}: ee of a resolving agent enantiomer (R or Я) at the eutectic composition; ee_{Dia}: ee of an enantiomer of the original racemate at the eutectic composition of the diastereoisomeric salt.