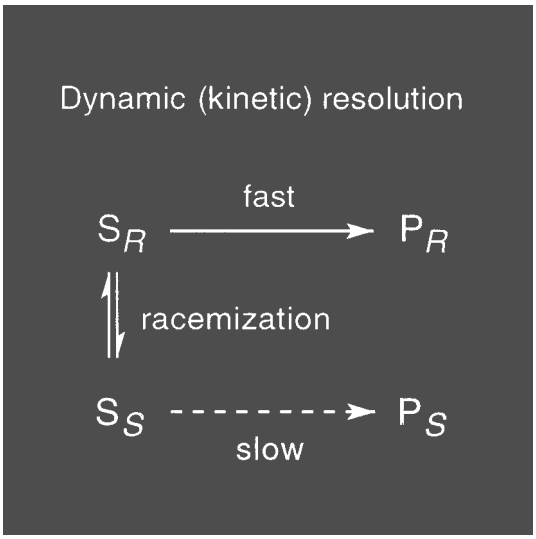
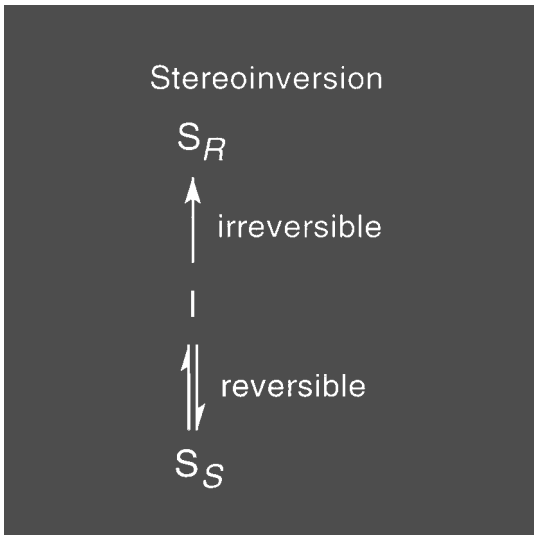
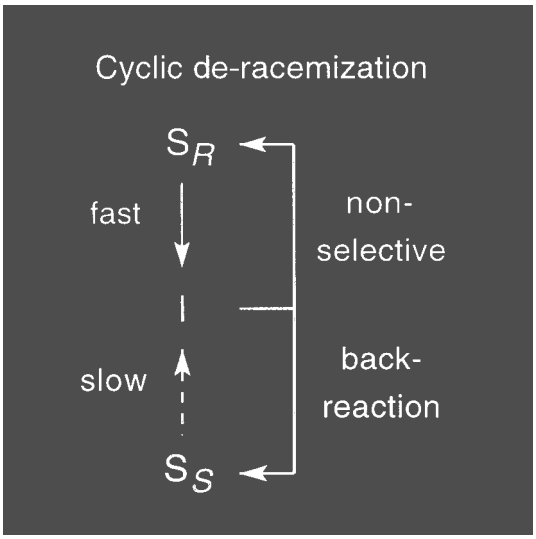
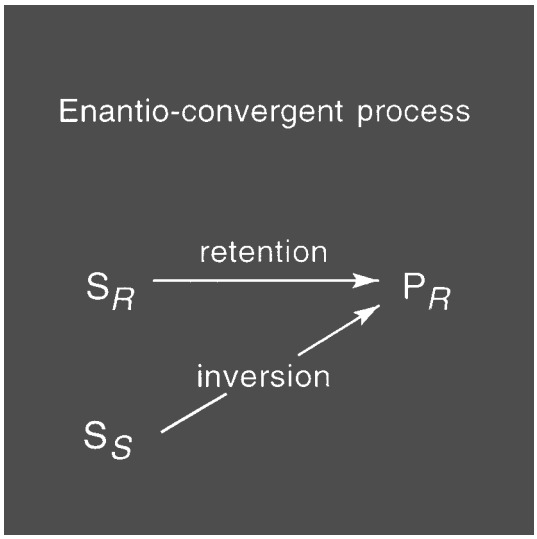
Transformation of a Recemate into a Single Stereoisomer









S_R, S_S = substrate enantiomers

P_R, P_S = product enantiomers

I = achiral intermediate

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Non-Sequential Processes for the Transformation of a Racemate into a Single Stereoisomeric Product: Proposal for Stereochemical Classification

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Abstract: Non-sequential processes which allow the transformation of a racemate into a single stereoisomeric product without the occurrence of an "undesired" isomer are classified according to their underlying stereochemistry. A re-definition of the term "de-racemization" is proposed.

Keywords: asymmetric catalysis · kinetic resolution · stereochemical classification · stereoinversion

Introduction and Background Information

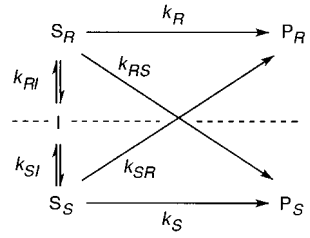
Driven by the demand to enhance the economic balance of chemical processes, there has been an increased interest in the transformation of racemates into a single stereoisomeric product without the occurrence of an undesired isomer. Despite numerous efforts to transform an unwanted isomer into the desired final product, for example by re-racemization or via independent enantio-convergent synthesis, processes based on the separate use of two enantiomers are far from being economically optimal and certainly lack elegance.

To date, the resolution of racemates is still one of the major methods for the production of enantiopure compounds on an industrial scale. Although numerous methods exist which are highly efficient in terms of enantio-discrimination, the maximum theroretical yield of 50% for each enantiomer sets a low ceiling on the productivity of such processes. In order to overcome this limitation, considerable effort has been devoted to create processes which afford the product with the same high enantiomeric purity, but in significantly improved chemical yields. After all, in an ideal process, all of the starting material is used and the occurrence of an undesired stereoisomer is entirely avoided.

During the past few years, a number of strategies have been developed that allow the conversion of both enantiomers from a racemate into a single stereoisomer in a concurrent and non-sequential fashion.[1, 2] The majority of them belong to the so-called "asymmetric transformation of the second kind".[3]

According to Kuhn,[4] an "asymmetric transformation of the first kind" involves the equilibration of stereoisomers (usually enantiomers in this context[5]) without concomitant separation. These processes are of limited practical value, since enantiomerically enriched material cannot be obtained due to the equilibrium reaction. However, in case a second (additional) process is applied, which ensures that one stereoisomer is withdrawn from the equilibrating mixture, a single stereoisomer may be obtained as the sole product. Kuhn termed such a process an "asymmetric transformation of the second kind". Incidentially, in the classic definition, the word "order" is improperly used. It originates from an incorrect translation of the German word "Art", the correct meaning in this context being "kind" rather than "order".[6]

All of the major techniques, which are discussed in this paper, can be described by the general pathways depicted in Scheme 1. In this concept, we want to propose clear definitions of such asymmetric processes and (re)define several terms which have often been used in a wrong or ambiguous way.



Scheme 1. General pathways for the asymmetric transformation of a racemate. S_R, S_S = substrate enantiomers; P_R, P_S = product enantiomers; I = achiral/prochiral intermediate, may be transition state; k_R, k_S = rate constants (proceeding through retention of configuration); k_{RS}, k_{SR} = rate constants (proceeding through inversion of configuration); k_{RI}, k_{SI} = rate constants for removal of chiral center; ---- = plane of symmetry.

The central problem for the transformation of both enantiomers into a single stereoisomeric product is caused by the presence of a plane of symmetry, which is separating both enantiomers of the racemic mixture $S_R + S_S$ (Scheme 1). In order to transform all of the material into a single

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stereoisomer (P_R), half of the material (e.g. S_S) has to cross the plane of symmetry, which can be accomplished in two ways:

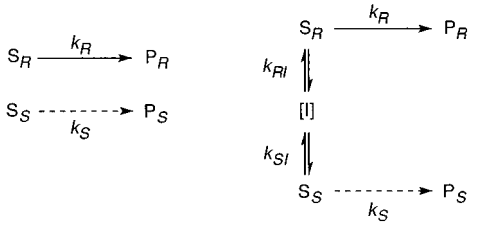
i) Interconversion of S_S to S_R would effect racemization. This may take place in a direct, equilibrium-controlled fashion with I representing an achiral transition state of a "classic" racemization and k_{RI} would be equal to k_{SI}.[7] Alternatively, interconversion of S_S and S_R may occur via an equilibrium-controlled two-step oxidation–reduction sequence and again, k_{RI} equals k_{SI}. In this case, I would be an achiral intermediate species, such as a ketone, or imine, respectively. In a second (independent) step, one of the equilibrating substrate enantiomers (S_R) may then be transformed to the final product P_R in an enantioselective fashion by "pulling" $S_R \rightleftharpoons S_S$ out of the equilibrium. Typically, this approach has been verified for dynamic (kinetic) resolutions.

   In case the interconversion of enantiomers via oxidation–reduction is a non-equilibrium process (i.e., $k_{RI} \neq k_{SI}$), an additional second step forming P_R is not required and the final product consists of S_R. These transformations are referred to as "stereoinversion".

ii) Instead of converting S_S into P_R via S_R, direct transformation of S_S to P_R is more straightforward. Thus, a process may be envisaged, in which each enantiomer is transformed via an (enantiospecific) independent pathway described by k_R and k_{SR} to give P_R. Due to the fact that k_{SR} is crossing the plane of symmetry, this reaction has to take place with *inversion* of configuration, whereas k_R is acting with *retention*. Since both starting enantiomers are finally combined in P_R, these transformations have been termed "enantio-convergent".

Kinetic and Dynamic (Kinetic) Resolution

Kinetic resolution is based on the difference of reaction rates (k_R, k_S) of enantiomers (S_R, S_S) during the transformation to P_R and P_S by a chiral catalyst via diastereomeric transition states (Scheme 2).[8] Due to the fact that two enantiomeric



Scheme 2. Kinetic and dynamic (kinetic) resolution of a racemate. S_R, S_S = substrate enantiomers; P_R, P_S = product enantiomers; k_R, k_S = rate constants; $k_R \gg k_S$, preferably irreversible; [I] ≅ achiral transition state of racemization; $k_{RI} \geq (k_R + k_S)$; $k_{RI} = k_{SI}$.

species are reacting simultaneously at different rates, the relative concentration of S_R/S_S and P_R/P_S is changing as the reaction proceeds and, as a consequence, the enantiomeric composition of S and P becomes a function of the conversion. The mathematical basis for the treatment of the kinetics was laid by Fajans[9] and later further developed for chemo-catalysis by Sharpless[10] and for bio-catalyzed resolutions by Sih.[11] In order to facilitate the optimization of kinetic resolutions in practical applications, computer programs are available.[12] Recovery of the formed product P_R and the unreacted enantiomer S_S in nonracemic form constitutes a kinetic resolution.

A significant breakthrough to overcome the 50% yield barrier in kinetic resolution was achieved by the development of dynamic (kinetic) resolution (Scheme 2). The latter combines the resolution step with an in situ equilibration (racemization) of a chirally labile substrate S_R/S_S. As a consequence, as the faster reacting enantiomer (S_R) is depleted during the enantioselective reaction, the equilibrium of S_R/S_S is constantly re-adjusted by racemization of the slow-reacting counterpart S_S. To indicate the non-static character of this process, the term "dynamic resolution" has been coined.[13–16] It is conceivable, that the kinetic balance of the two concurring reactions is of crucial importance for the success of a dynamic kinetic resolution. As a rule of thumb, the racemization of the substrate should occur at an equal or higher rate than the asymmetric catalytic reaction. The mathematical treatment of the kinetics has been developed by Noyori et al.,[17] computer programs for analysis and optimization of practical applications are currently being developed.[18]

Based on the underlying kinetics, a high *ee* for P (ee_P) in a dynamic kinetic resolution can only be achieved for reactions displaying excellent selectivities. For example, E values of ≈19 and ≈40 lead to an ee_P of 90 and 95%, respectively, whereas for an enantiomeric excess of 98%, a selectivity of E ≈100 is required.

In dynamic (kinetic) resolutions showing high enantioselectivity ($k_R \gg k_S$), the magnitude of racemisation ($k_{RI} = k_{SI}$) has the following influence on the overall performance of the process:

i) If $k_{RI} \geq k_{SI} \gg k_R$, a *fast* and *selective* process is ensured, because S_S is transformed into S_R at a sufficient speed which is not rate-limiting to k_R,

ii) if $k_R > k_{RI} = k_{SI} > k_S$, then the racemization rate controls the *speed* of the process, because the formation of S_R from S_S now becomes rate-limiting. On the other hand, the stereoselectivity is not impeded, because (at high selectivity) the transformation of S_S into product P_S is too slow in comparison to the main pathway (i.e., $S_S \rightarrow S_R \rightarrow P_R$) to build up significant amounts P_S.

iii) Only if $k_R \gg k_{SI} > k_{RI} = k_{SI}$, the process will be *slow* and *non-selective*, because then it represents a kinetic rather than a dynamic resolution.

The number of examples for dynamic (kinetic) resolution has increased dramatically during the past few years by making use of a combination of (chemo-catalytic) in situ racemization of substrate and (bio-catalytic) enantioselective transformations. An evaluation of the processes described so far reveals that the critical point is the compatibility of both reactions. The most successful strategies are outlined below.

In situ racemization via protonation/deprotonation: The easiest and hence most widely used method for in situ racemization involves acid/base-catalyzed enol(ate) formation. Since the pH window of biocatalysts is rather narrow, it is not surprising that successful applications were found for

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chirally labile centers which may be racemised under weakly alkaline or acidic conditions, usually in the α-position to a carbonyl group. Numerous α-substituted carboxylic acid derivatives (such as esters, hydantoins, oxazolinones, etc.)[19] and α-substituted ketones[20] were dynamically resolved in this way.

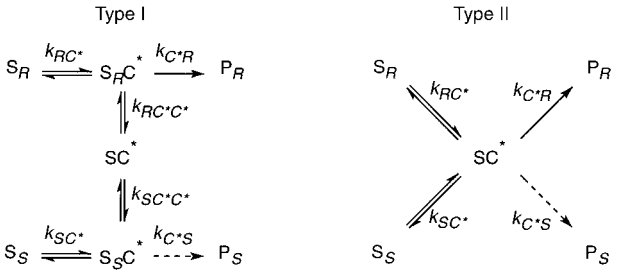
In situ racemization via addition/elimination: For chirally stable centers, such as *sec*-alcohols and amines on a *sec*-carbon atom, racemization by acid/base catalysis is not feasible except for specially "activated" *sec*-alcohol derivatives (e.g. acyloins).[21] However, several chemically labile derivatives of *sec*-alcohols, such as cyanohydrins,[22] hemiacetals (lactols),[23] hemiaminals,[24] and hemithioacetals[25] are prone to undergo reversible addition/elimination under mild conditions. This latter property has been used for the dynamic resolution of such derivatives. The enantioselective biocatalyzed reaction for this type of substrates usually involves the remaining hydroxyl group, for example by acylation. In rare cases, also nitrile hydrolysis has been applied.[26]

In situ racemization via oxidation/reduction: A useful alternative for the racemization of chemically stable *sec*-alcohols and amines on a *sec*-carbon atom is accomplished via a (reversible) oxidation–reduction sequence by transition metal catalysts based on Ru,[27] Rh, Ir, Al,[28] or Pd.[29] Depending on the equilibrium, the achiral intermediate (i.e., a ketone or imine, respectively) can be detected at low concentrations. The dynamic resolution of *sec*-alcohols based on this principle has been shown to be quite powerful in that it is also applicable to substrates possessing more than one stereocenter, such as a mixture of D/L- and *meso*-forms, which lead to the formation of a single (diastereomerically pure) enantiomer.[30]

In situ racemization via nucleophilic substitution: A rather scarcely used method for in situ racemization is based on the (reversible) nucleophilic substitution of a *sec*-halogen which is susceptible to nucleophilic displacement by the same halide, when situated in an electronically activated position, such as α to a carboxyl group. This fact has allowed for the dynamic resolution of α-halocarboxylic esters.[31] The carboxylate formed through enzyme-catalyzed enantioselective hydrolysis is stable to racemization under these conditions. This recently discovered method has a potential which has yet to be exploited in more detail.

Dynamic (Kinetic) Asymmetric Transformation and Dynamic Thermodynamic Resolution

At first sight, "dynamic (kinetic) asymmetric transformation"[32, 33] (also abbreviated as DYKAT[34]) and "dynamic thermodynamic resolution" of a racemate[35] look almost identical to dynamic (kinetic) resolution, and, as a matter of fact, the use of these terms has created considerable confusion.[36] Two subtypes of DYKAT can be drawn (Scheme 3):



Scheme 3. Principles of dynamic (kinetic) asymmetric transformation and dynamic thermodynamic resolution of enantiomers. S_R, S_S = substrate enantiomers; P_R, P_S = product enantiomers; S_RC^*, S_SC^* = diastereomeric intermediates; C* = chiral catalyst; SC* = chiral intermediate; k_{RC^*}, k_{SC^*}, k_{C^*R}, k_{C^*S} = rate constants for formation/reaction of intermediates; $k_{RC^*C^*}$, $k_{SC^*C^*}$ = rate constants for interconversion of intermediates.

Type I: Two enantiomers of the starting material (S_R, S_S) are subjected to the action of a chiral catalyst (C*) forming diastereomeric complexes S_RC^* and S_SC^*. The latter intermediates are configurationally stable on the time scale of the subsequent reaction forming final products P_R and P_S. To this point, the whole process would constitute of a kinetic resolution. This "static" system can be turned "dynamic", if an equilibration of intermediates S_RC^* and S_SC^* via SC* is taken into account and, as a consequence, a 100% thereotical yield of a single stereoisomer (P_R) can be envisaged. In Type I processes,[33, 34]

i) the selectivity depends not only on the ratio of k_{C^*R}/k_{C^*S}, but also
ii) on the relative population of the (diastereomeric) intermediates S_RC^* and S_SC^*.
iii) The latter is determined by a) the relative rate of formation (k_{RC^*}/k_{SC^*}) and b) the (unequal) interconversion ($k_{RC^*C^*}/k_{SC^*C^*}$) through a single enantiomeric intermediate SC*.

Despite some similarities to dynamic (kinetic) resolution, these systems show some distinct differences which are:

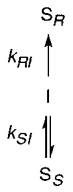
i) The species S_RC^* and S_SC^* are *diastereomers* (rather than enantiomers) and the intermediate SC* during equilibration is chiral (rather than achiral).
ii) As a consequence, $k_{RC^*C^*}$ and $k_{SC^*C^*}$ are *not equal* and the interconversion of S_RC^* and S_SC^* reflects *epimerization* (rather than racemization). Since these facts determine the relative (unequal) population of intermediates S_RC^* and S_SC^*, the kinetics of a dynamic (kinetic) resolution developed by Noyori et al.[17, 37] do not apply.
iii) In contrast to dynamic (kinetic) resolution, which generally depends on two different catalysts, only a single catalytic species is active in DYKAT.

Type II: Product enantiomers P_R and P_S are formed from a single enantiomeric intermediate SC* through a desymmetrization-type process.[32] In this case,

i) the selectivity depends *only* on the ratio of rates of k_{C^*R}/k_{C^*S}, whereas
ii) the rates of formation of the intermediate from substrate enantiomers (k_{RC^*}/k_{SC^*}) and their equilibration through the intermediate controls only the velocity of the process.

Stereoinversion

A special case for the transformation of a racemate S_R/S_S involves the enantio-specific stereochemical inversion of one



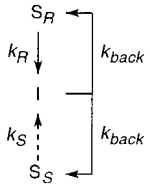
Scheme 4. Principles of the stereoinversion of enantiomers. S_R, S_S = substrate enantiomers; I = achiral intermediate, k_{RI} = irreversible; k_{SI} = in equilibrium; $k_{RI} \approx k_{SI}$.

enantiomer (S_S) via a chemically stable achiral (or prochiral) intermediate I (Scheme 4). This technique may be employed for compounds possessing a *sec*-alcohol or an amine on a *sec*-carbon atom. On the one hand, the reacting enantiomer (S_S) is oxidized to form a ketone or imine I, respectively, which is stereoselectively reduced to the mirror-image *sec*-alcohol (or amine) S_R. Depending on the equilibrium of the redox reactions, the intermediate may be present at an exceedingly small concentration. In order to provide the driving force for the transformation of the racemate into the "uphill"-direction towards a single stereoisomer, at least one of the two reactions has to be irreversible. Various subtypes of stereoinversion processes can be found depending on the equilibria of both reactions. For these processes, the term "stereoinversion" has been proposed by Hafner.[38]

Biocatalytic stereoinversion of *sec*-alcohols via an oxidation–reduction sequence can be achieved by using whole microbial cells.[39–43] Thus, one enantiomer of a racemic mixture (S_S) is selectively oxidized to the corresponding ketone I under catalysis of a dehydrogenase, while the mirror-image counterpart (S_R) remains unaffected. Then, the ketone is reduced again in a subsequent (concurring) step by a different enzyme displaying opposite stereochemical preference. Due to the involvement of two consecutive oxidation–reduction reactions, the net redox balance of the process is zero and (in an ideal case), external cofactor-recycling can be omitted, since the redox equivalents [usually NAD(P)H] are recycled internally by the whole-cell system. The origin of the irreversibility—providing the driving force to cover the entropy-balance—is still unknown and possible explanations are rather speculative.[44]

Cyclic De-racemization

A novel technique for the transformation of both enantiomers of a *sec*-alcohol or an amine linked to a *sec*-carbon atom with a rather awkward appearance has been developed only recently (Scheme 5). It is based on a cyclic oxidation–reduction sequence: In the first step, one enantiomer from the racemic starting material (S_R) is enantioselectively oxidized to form an achiral intermediate I, which constitutes of a ketone or an imine, respectively. In the second step, the latter is nonselectively reduced to give again starting material S_R+S_S in racemic form. Cyclic repetition of this sequence leads to an overall chiral inversion of the faster reacting enantiomer S_R to yield the mirror-image counterpart S_S as the final product in a 100% theoretical chemical and optical yield. The number of cycles required to reach a certain enantiomeric composition of the desired material S_S (and the total turnover of materials associated with it) is a function of the enantioselectivity of the oxidation step. The kinetics of this system has been recently solved.[45]

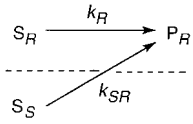


Scheme 5. Cyclic de-racemisation involving an oxidation–reduction sequence. S_R, S_S = substrate enantiomers; I = achiral intermediate. $k_{back} \approx k_R \gg k_S$.

Since this system requires two reactions working simultaneously into opposite directions—that is oxidation and reduction—its feasibility relies mainly on their compatibility in a single reactor. As a consequence, it is not surprising, that such processes have been realized by using a combination of chemo- and bio-catalysts. In practice, cyclic de-racemization has been reported for α-hydroxy- and α-amino acids, where the oxidation was carried out using an α-amino- or α-hydroxyacid oxidase at the expense of molecular oxygen and borohydride as the reducing agent.[46–48] Alternatively, electrochemical cofactor-regeneration is possible.[49]

Enantioconvergent Transformation

A special type of de-racemization technique is making use of two independent concurring reactions depicted in Scheme 6. Thus, each enantiomer is transformed via an independent pathway (k_R, k_{SR}) to give a single stereoisomeric product (P_R). In order to match the requirements for producing the same enantiomeric product, both pathways must exhibit an opposite enantiopreference and therefore must follow an opposite stereochemical course, that is opposite regioselectivity is required. In order to cross the plane of symmetry between S_R and S_S, at least one of the reactions has to proceed with inversion of configuration. The latter is taking place in a direct fashion without occurrence of an achiral intermediate. It is conceivable, that these criteria are rather difficult to meet in practice and, as a consequence, reports on successful enantioconvergent transformations are rather scarce. For instance, depending on the conditions, the hydrolysis of an epoxide may proceed with inversion (generally base catalysis) or retention (generally acid catalysis). This stereochemical flexibility, and the fact that enzymes—epoxide hydrolases[50]—have been found which are able to act in a similar stereo-complementary fashion has led to the development of three types of processes, which allow for the enantioconvergent hydrolysis of epoxides to form a single enantiomeric vicinal diol as the sole product.[51–53]



Scheme 6. Enantioconvergent transformation of a racemate. S_R, S_S = substrate enantiomers; P_R = product enantiomer; k_R via retention; k_{SR} via inversion; ---- plane of symmetry.

When each enantiomer from a racemic substrate is transformed using an asymmetric catalyst (or reactant) to furnish two products, usually product mixtures arise. The latter may constitute i) diastereomers,[54] (ii) regioisomers, iii) constitutional isomers or even iv) non-isomeric compounds. Such processes have been classified as *enantio-divergent*.[55] This term aptly refers to the fact that nature and distribution of products are different depending on the absolute configura-

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tion of the substrate. From a theoretical standpoint, these highly complex processes open a fascinating new area of stereochemistry, however, the number of species formed during the process is equal or higher than that of the starting racemate, and thus the maximum obtainable yield of each of them is below 50%. As a consequence, enantio-divergent processes are of limited value for the preparation of chiral non-racemic materials.

It is an interesting paradox that in order to obtain best results in an enantio-convergent or -divergent process, the enantio-*specificity* [i.e., the selectivity of each enantiomer to react to a (stereo)chemically defined product] must be high, but the enantio-*selectivity* (i.e., the difference in the relative reaction rate of enantiomers) should be low to ensure short reaction times.

De-racemization

Proposal for (re-)definition: After its proposition in 1984,[56] the term "de-racemization" has been used with an increasing frequency over the past few years in various contexts and in ambiguous ways,[57] which deserves some clarification: In a strict sense, "*de-racemization*" would mean the *opposite* of racemization.[58] Thus, it would imply a process, during which two enantiomers are transformed into a single enantiomer of exactly the same compound, that is $S_R+S_S \rightarrow S_R$ (see Scheme 1). When it was proposed, the term de-racemization was defined in this sense. However, since such a process represents a reaction in the energetic "uphill"-direction, it requires some external (chemical) energy to provide the entropy balance. However, the external input of energy into the system is rather difficult to achieve for a transformation which is only dealing with a single chemical species ($S_R+S_S \rightarrow S_R$) where ΔH^0 equals zero.[59] On the contrary, this is more facile for reactions involving the formation of a different species ($S_R+S_S \rightarrow P_R$), because in this case the energy balance for the entropy term can be easily covered by the ΔH^0 of the reaction. Out of these practical considerations, the term de-racemization has been frequently used for the description of processes, which lead to a product P rather than S.[60] After all, the product P_R being formed during the transformation of (S_R+S_S) is always a closely related derivative of the starting material, and chemical interconversion of $S \rightleftharpoons P$ is usually not a problem. This applies to various substrate–product pairs, such as carboxylic ester/acid, hydantoin/*N*-carbamoylamino acid, alcohol/ester and also to diastereomeric salts.[61] In light of this, it is proposed to adopt the more catholic definition:

De-racemization constutites any process during which a racemate is converted into a non-racemic product in 100% theoretical yield without intermediate separation of materials.

According to this definition, dynamic (kinetic) resolution, dynamic (kinetic) asymmetric transformation, dynamic thermodynamic resolution, stereoinversion, and enantioconvergent transformation of a racemate would all constitute subtypes of de-racemization. On the other hand, desymmetrization of prochiral and *meso*-compounds and kinetic resolution of racemates (including subtypes thereof, such as sequential[62] or parallel kinetic resolution[63] and enantio-divergent transformations) are not.

Enantiomeric or optical purification: The term *enantiomeric* or *optical purification* occasionally has been used as a synonym for de-racemization. However, it is linguistically misleading and its use is not recommended for the following reasons: In a general sense, "purification" implies the occurrence of undesired material (resembling an "impurity"), which has to be removed and therefore can be considered as waste. This is definitely not the case for a de-racemization.

De-epimerization: In an analogous sense, the transformation of diastereomers (epimers) into a single (dia)stereoisomer has been denoted as "de-epimerisation"[64] or "de-diastereomerization".[65] Due to the fact that epimers are diastereomers which are different by a single stereocenter, the use of two different terms is not neccessary, thus the more widely used term "de-epimerization" is recommended. Since diastereomers are involved rather than enantiomers, the ΔH^0 of the reaction does not equal zero and, as a consequence, the transformation of diastereomers into a single stereochemical species is considerably more facile than a de-racemization of enantiomers.

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