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De-racemization of Enantiomers versus De-epimerization of Diastereomers—Classification of Dynamic Kinetic Asymmetric Transformations (DYKAT)

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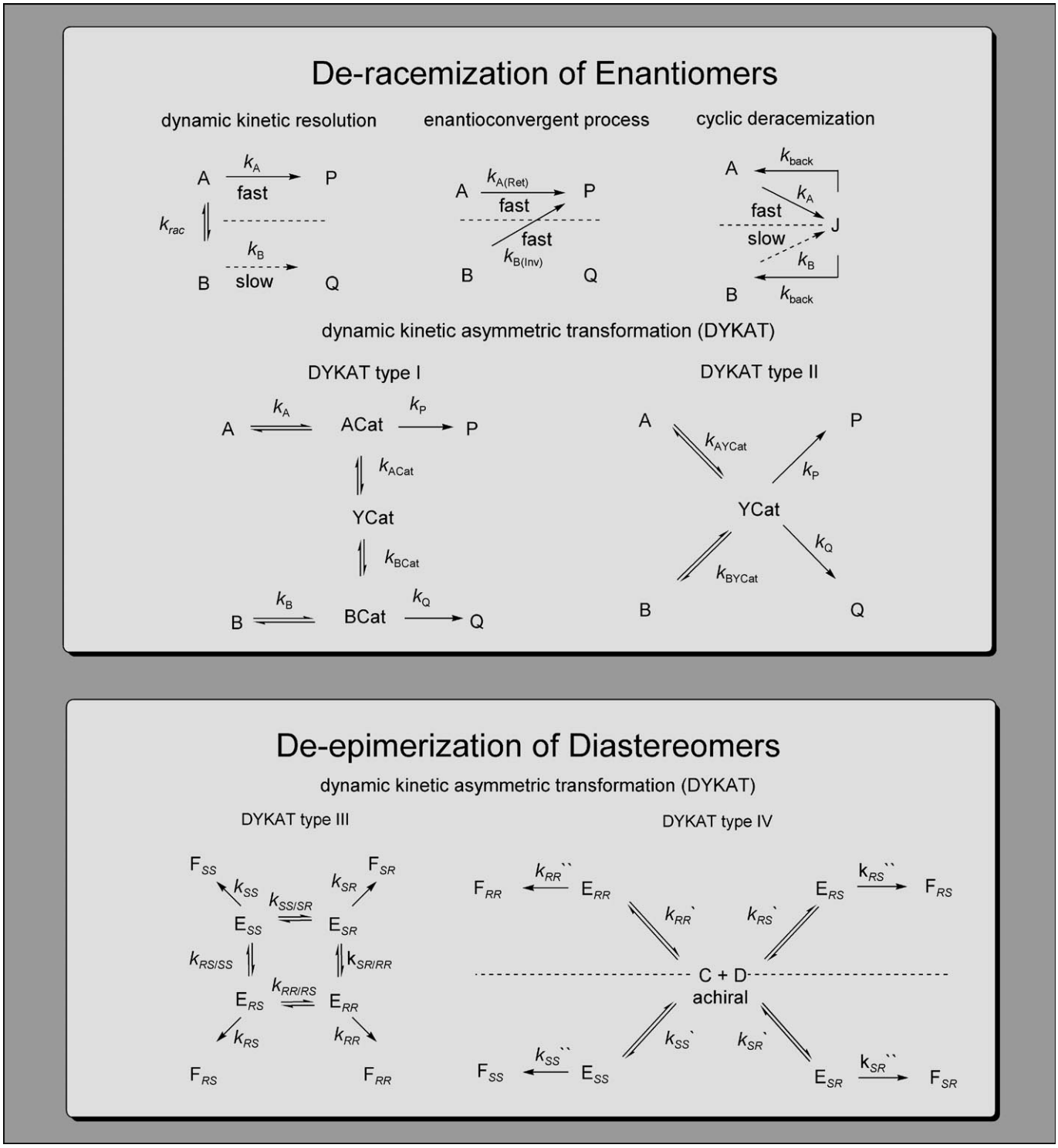

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Abstract: The isolation of single stereoisomers from a racemic (or diastereomeric) mixture by enzymatic or chemical resolution techniques goes in hand with the disposal of 50% (racemate) or more (diastereomeric mixtures) of the "undesired" substrate isomer(s). In order to circumvent this drawback, dynamic systems have been developed for the de-racemization of enantiomers and the de-epimerizations of diastereomers. Key strategies within this area are discussed and are classified according to their underlying kinetics, that is, dynamic kinetic resolution (DKR), dynamic kinetic asymmetric transformations (DYKAT), and hybrids between both of them. Finally, two novel types of DYKAT are defined.

Keywords: asymmetric synthesis · de-epimerization · de-racemization · dynamic kinetic asymmetric transformations · dynamic kinetic resolution

Introduction

To a significant extent, nature formed its complexity through control of chirality. Highly specialized biocatalysts have evolved that are able to control the chirally biased system of life by providing essential regio-, diastereo-, and enantioselectivity. As stereoisomers usually provoke different effects in vivo, rigid stereo-control is a fundamental concern in every synthetic route. However, due to lack of simple methodologies or high costs, industrial processes often have to deal with stereoisomeric mixtures. This paper discusses the key methodologies for the quantitative transformation of diastereomeric and enantiomeric mixtures into a single stereoisomeric product, in particular, the dynamic kinetic resolution of racemates (DKR) and dynamic kinetic asymmetric transformation of diastereomers (DYKATs). Detailed analysis of DYKAT processes requires a more detailed definition. This paper is intended to stimulate the broader use of dynamic processes based on enzymatic and homogeneous (asymmetric) catalysis.

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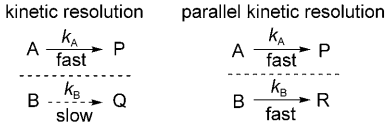
Kinetic Resolution

Due to the fact, that the theoretically possible number of (non-symmetric) racemates is larger than that of (symmetric) prochiral or *meso*-compounds, racemate resolution is the most common way to obtain enantiopure compounds in industry.[1–4] In this context, kinetic resolution (KR) of racemic mixtures provides a widely used protocol by making use of the difference in reactivity of two enantiomers (Scheme 1).[5,6] This as a process in which two enantiomers



Scheme 1. Kinetic and parallel kinetic resolution of a racemate. ––– plane of symmetry. Left-hand side: A,B = substrate enantiomers; P,Q = product enantiomers. Right-hand side: A,B = substrate enantiomers; P,R = products of different chemical structure.

of a racemate are converted to the corresponding product enantiomers at different rates. To obtain an efficient resolution, the reaction rate of one enantiomer has to be much greater than that of the other (e.g., $k_A \gg k_B$).

In KR the enantiomeric excess (*ee*) of both substrate (ee_S) and product (ee_P) varies as the reaction proceeds and hence, *ee* values of KRs are only comparable at the same degree of conversion. To describe the enantioselectivity of KRs by a conversion-independent parameter, the ratio of the (apparent first-order) reaction rates of enantiomers was introduced. It describes the ability of a (bio)catalyst to distinguish between enantiomers under defined reaction conditions (e.g., temperature, water activity, solvent). For biocatalyzed reactions, this value was termed the "enantiomeric ratio" (E)[7–10] and for chemocatalysts it was called the "stereoselectivity factor" (s).[2] The basis for the mathematical treatment of KR was laid by Fajans[11] and subsequently further developed by Sharpless[12] and Sih[7] for chemo- and biocatalytic systems, respectively. In theory, KR represents a competitive reaction system in which two enantiomeric substrates compete for a single chiral catalyst, which is a more complex scenario than that of the single-substrate catalytic network represented by the desymmetrization of prochiral or *meso*-compounds.[13] In biocatalyzed systems, the formation of the enzyme–substrate complex constitutes a unique step, which is absent (or negligible) in chemocatalyzed processes. The kinetics of KRs have been treated as a simplified first-order system and, hence, E and s values are identical and represent synonyms for the annotation of the enantioselectivity of KR. Recently, extended mathematical studies aiming at the improvement of KRs of enantio-enriched substrates[14] and to explain pseudo-first order substrate dependency of some KRs were published.[15] Despite recent advances in the use of metal catalysts for KR,[6,16] biocatalysts play

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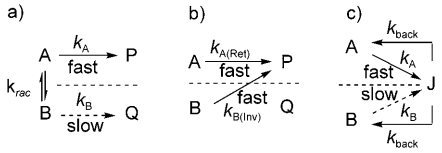
a dominant role in the kinetic resolution of a racemate mainly due to their unparalleled specificity.[17]

To overcome the gradual depletion of ee_P close to (or beyond) 50% conversion, a strategy called "parallel kinetic resolution" (PKR) was introduced by Vedejs and Chen (Scheme 1).[6] To avoid the accumulation of the less reactive substrate enantiomer, it is removed by a parallel reaction (ideally at an identical rate) to yield a different product, thus maintaining a constant 1:1 ratio of substrate enantiomers.[18–21]

De-racemization of Racemic Mixtures

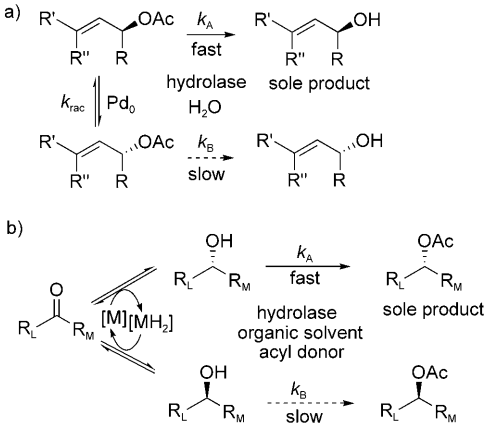
Like KR, PKR is impeded by the fact that theoretical yield of each enantiomer can never exceed a limit of 50% and the remaining 50% of the "wrong" enantiomer have to be separated and discarded (or recycled) in a more or less laborious fashion. Since this sets a low ceiling on the productivity of PKR processes, protocols which allow the complete transformation of a racemate into a single stereoisomeric product, generally denoted as "de-racemization", have been established (Scheme 2).[22,23]



Scheme 2. Conversion of a racemate into a single enantiomeric product: a) dynamic kinetic resolution,[24–30] b) enantio-convergent process,[31–34] and c) cyclic deracemization.[35,36] ––– plane of symmetry; A,B = substrate enantiomers; P,Q = product enantiomers; J = nonchiral intermediate; k_{rac} = substrate racemization; k_{back} = nonselective back reaction.

This can be achieved by either applying dynamic kinetic resolution (DKR, Scheme 2a),[24–30] through enantio-convergent processes (ECP, Scheme 2b)[31–34] or by cyclic deracemization (CycD, Scheme 2c).[35–38]

Dynamic kinetic resolution (DKR): In DKR the substrate is subject to racemization,[26,39,40] which ensures the constant transformation of the less reactive enantiomer into the more reactive one. This allows the transformation of both enantiomers into a single stereoisomeric product in 100% theoretical yield. For an efficient DKR, the rate constants for racemization k_{rac} and the transformation of the more reactive enantiomer (k_A) have to match each other, that is, k_{rac} should be equal (or greater) than k_A (Scheme 2a). If k_{rac} is smaller than k_A, k_{rac} needs to be much greater than the transformation of the less reactive enantiomer k_b ($k_a > k_{rac} \gg k_b$). The mathematical treatment of the kinetics of DKR has been developed by Noyori et al.[41,42] and was recently extended by Andraos.[43] Thermodynamically, racemization is a favorable process that is driven by the increase of entropy when two enantiomers are mixed. According to Eliel, $\Delta G^0 = -T\Delta S^0 = -RT\ln 2 = -0.41$ kcal mol^{-1}.[44] The most widely used racemization processes are thermal, acid- or base-catalyzed racemization, or racemization by Schiff bases or through redox or radical reactions.[39] Interestingly, also enzyme-catalyzed racemization plays an important role.[40] Among these methods, only few are compatible with the presence of a chiral catalyst and thus are suitable for DKR. The simplest DKR is based on the in-situ racemization of stereomerically labile substrate enantiomers combined with stereoselective crystallization of the free substrate (or a diastereomeric salt thereof containing a chiral counterion), denoted as crystallization-induced dynamic resolution (CIDR).[45] In the late 1990s, the combination of biocatalyzed ester-hydrolysis or acyl-transfer with in situ (transition-metal) catalyzed racemization of *sec*-alcohols[46] or (allylic) acetate esters[8] was recognized as a powerful method for the DKR of *sec*-alcohols and esters thereof (Scheme 3).[47] The stereochemical outcome of DKR of *sec*-



Scheme 3. Chemoenzymatic DKR of a) allylic acetate esters,[8] and b) *sec*-alcohols based on (transition) metal-catalyzed substrate racemization.[46] R_M,R_L = medium or large substituents, respectively; [M] = (transition) metal complex.

alcohols can be governed by the choice of the appropriate type of hydrolase: Whereas lipases give access to (*R*)-alcohols ($k_B \ll k_A$), according to the Kazlauskas rule,[48] proteases yield *S* enantiomers in a stereo-complementary fashion ($k_A \ll k_B$).[49,50]

Due to the fact that biosynthetic pathways are usually highly stereospecific, evolution had little need for racemization and consequently, the number of racemases is very limited. A rare example for a bi-enzymatic de-racemization protocol has been verified for α-hydroxycarboxylic acids (Scheme 4).[51,52] Thus, when kinetic resolution catalyzed by lipase-catalyzed *O*-acylation was coupled to enzymatic racemization of the nonreacting substrate enantiomer by using a racemase preparation, the corresponding *O*-acylated product (which was not a substrate for the racemase) was obtained in up to 97% *ee* as the sole product. Since the racemase was inactive in organic solvents, a sequential (rather than a dynamic) protocol had to be applied.[53] Two DKR-

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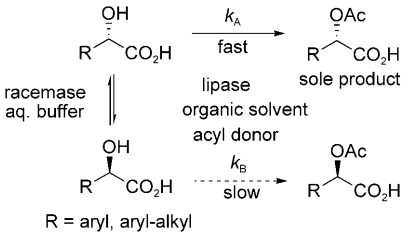
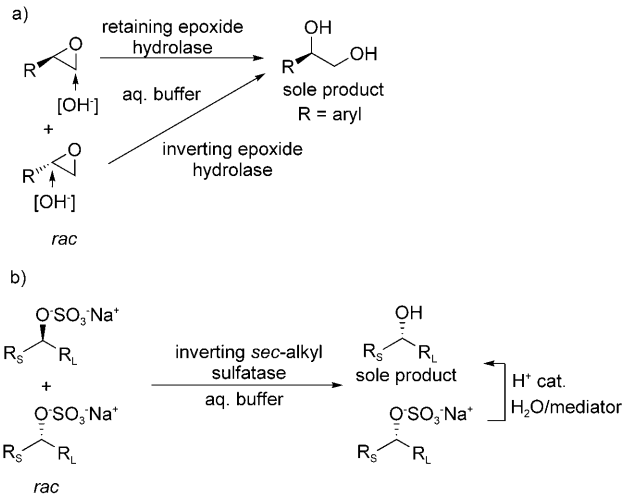


Scheme 4. De-racemization of α-hydroxycarboxylic acids using a sequential two-enzyme (racemase/lipase) protocol.[57]



Scheme 5. De-racemization of a) monosubstituted epoxides by enantioconvergent hydrolysis using two epoxide hydrolases in-situ and b) *sec*-alcohols via their corresponding sulfate esters using inverting sulfatases and acid catalysis in tandem.[53] R_S,R_L = small or large substituents, respectively.

processes were found to proceed in the whole-cell biotransformation of amino acid precursors on an industrial scale; hydrolytic kinetic resolution of a 5-substituted *rac*-hydantoin by a hydantoinase followed by hydrolysis of the *N*-carbamoyl amino acid by a carbamoylase yields the corresponding D-amino acids.[54] Due to the concurrent action of a hydantoin racemase this protocol becomes dynamic. Although this process was introduced already in 1976, it was only recently that the corresponding L-specific enzymes became available; this opened the way to the L-amino acids series.[55] In a related bi-enzymatic dynamic resolution, de-racemization of DL-*N*-acetylamino acids by using a D- or L-specific acylase in combination with an *N*-acylamino acid racemase was accomplished.[55,56]

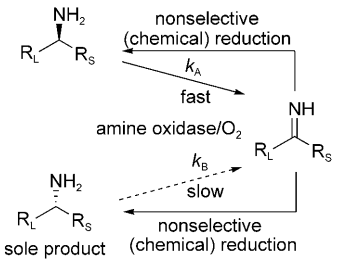
In comparison to *sec*-alcohols, dynamic resolution of chiral amines is still in the state of development, mainly due to the lack of efficient racemization protocols that are compatible with ambient reaction conditions required for an *N*-acylating enzyme.[58–61]

Enantio convergent processes (ECP): To furnish a single stereoisomer from a racemate by ECP, both substrate enantiomers must be transformed through stereochemically matching pathways by proceeding through inversion and retention of configuration, respectively (Scheme 2b). Since the stereochemical prerequisites for the chiral catalysts are rather high—they must show enantioselectivity (by preferring one enantiomer over the other) and stereoselectivity with respect to retention or inversion of configuration during catalysis—ECP processes are rather rare (Scheme 5).

The first two-enzyme ECP comprised the stereo- and enantioselective hydrolysis of styrene-type epoxides using two different epoxide hydrolases employed as whole-cell biocatalysts (Scheme 5). Whereas *Aspergillus niger* hydrolyzed the (*R*)-oxirane with retention of configuration, *Beauveria bassiana* transformed the mirror-image counterpart through stereocomplementary inversion to finally yield a single *R*-configured diol as the sole product.[62] Alternatively, *rac*-oxiranes have been hydrolyzed through ECP by chemoenzymatic[31] and purely enzymatic methods.[63]

A related chemoenzymatic stepwise protocol for the deracemization of *sec*-alcohols via the corresponding sulfate esters was described more recently (Scheme 5).[53] Thus, KR of a *rac-sec*-sulfate ester with an enantioselective sulfatase[64] acting with inversion of configuration furnished a homochiral mixture of *sec*-alcohol and nonreacted *sec*-sulfate ester. Subsequently, an ensuing chemical sulfate ester cleavage proceeding through retention of configuration gave a single enantiomeric *sec*-alcohol as the sole product.

Cyclic de-racemization (CycD): A de-racemization protocol applicable to amino functionalities involves the enantioselective oxidation of an α-aminoacid (or amine) by an amino acid (or amine) oxidase at the expense of molecular oxygen to produce the corresponding imine as a nonchiral intermediate. This imine is reduced back in-situ in a nonselective fashion to furnish both enantiomers of the amine again (Schemes 2c and 6).[35,36] Whereas half of this material (i.e., 25% of total) now consists of the "right" enantiomer, the remaining 25% of the "wrong" stereoisomer has to enter the cycle again to form a 1:1 mixture of enantiomers. When this cyclic process is continued, all of the substrate will eventually end up as "right" enantiomers. This process was



Scheme 6. De-racemization of *rac*-α-amino acids and *rac*-amines through a cyclic redox sequence consisting of an enantioselective (enzymatic) oxidation combined with in-situ nonselective chemical reduction of the intermediate imino species.[35,36] R_S,R_L = small or large substituents, respectively.

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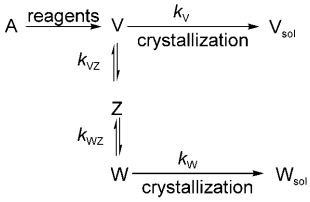
termed cyclic de-racemization (CycD)[22] and not ECP, because the nonreactive stereoisomer is accumulated and serves as the overall "sink" in the enantioselective oxidation/nonselective reduction cycle.

De-epimerization of Diastereomers/Diastereomeric Intermediates

The transformation of a mixture of diastereomers into a single stereoisomer is denoted as "de-epimerization".[22] The fundamental difference between de-racemization and de-epimerization is the difference in reaction enthalpy ΔH. For enantiomers, ΔH equals zero, whereas for diastereomers $\Delta H \neq 0$ due to their difference in physical properties. Consequently, de-epimerization is more facile than de-racemization, since the driving force for the former can be provided by ΔH,[22] and in contrast to racemization, epimerization does not yield an equal mixture of diastereomers. Historically, the first concept of de-epimerization was developed for the selective crystallization of diastereomers from in-situ equilibrating mixtures of epimers (crystallization induced asymmetric transformation CIAT, Scheme 7).[45] The



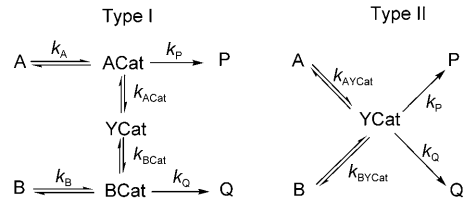
Scheme 7. De-epimerization of a diastereomeric product by a crystallization induced asymmetric transformation (CIAT). A = starting material; V,W = dissolved product diastereomers; Z = chiral intermediate; V_{sol},W_{sol} = solid product diastereomers, k_{VZ},k_{WZ} = product epimerization; k_V,k_W = product crystallization.

diastereomeric ratio of dissolved product diastereomers V_{sol}/W_{sol} depends on the rate constant of the irreversible selective crystallization step (k_V, k_W) and the epimerization constants k_{VZ} and k_{WZ}.

In this context, the concept of de-epimerization is extended to enantiomers that are resolved by making use of diastereomeric intermediates, which are interconverted via different equilibration constants.

Dynamic kinetic asymmetric transformation (DYKAT): Trost et al. have introduced two types of DYKAT[22] for the resolution of racemates using diastereomeric intermediates (Scheme 8), which were classified as type I (cf. Figure 1)[65–68] and II (cf. Scheme 10, below).[66,69]

Although several de-racemization processes were frequently referred to as a DKR,[70–72] they should be properly denoted as dynamic kinetic asymmetric transformation (DYKAT),[65] since they involve the (metal-catalyzed) equilibration of diastereomeric (rather than enantiomeric) intermediates. Trost has defined a DYKAT as follows: "A dynamic kinetic asymmetric transformation has a potential advantage over a resolution (kinetic or dynamic kinetic)—fewer synthetic steps. If the act of converting a racemic mixture into a single enamatiomeric series is combined with one of the structural transformations, the dynamic resolution is not an additional step in the synthesis and thereby saves a step."[73]



Scheme 8. Two types of DYKAT for the de-symmetrization of enantiomers. A,B = substrate enantiomers; P,Q = product enantiomers; Cat = catalyst; ACat,BCat = diastereomeric substrate–catalyst complexes; YCat = complex of chiral catalyst with achiral intermediate Y; k_A,k_B = pre-equilibrium constants for ACat and BCat complex formation; k_{ACat},k_{BCat} = equilibration constants of epimerization of diastereomeric for ACat and BCat complexes with ICat; k_P,k_Q = rate constant of irreversible fomration of product enantiomers P and Q; k_{AYCat},k_{BYCat} = equilibration constants of epimerization of diastereomeric substrates A and B.

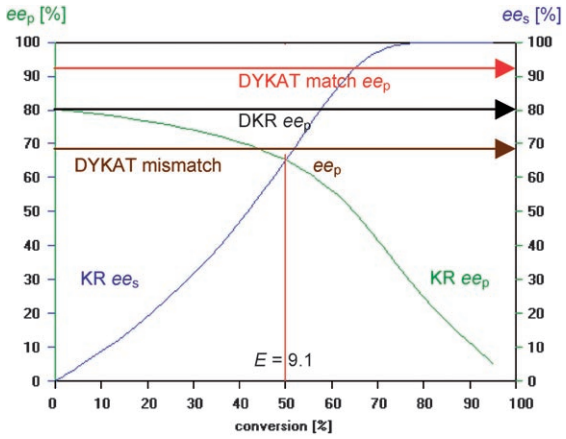


Figure 1. Comparison of the ee_p of KR, DKR and DYKAT (match and mismatch) as function of the conversion with an enantiomeric ratio of E = 9.1.[74]

However, careful literature survey reveals that the principles of DYKAT apply to more processes than is recognized to date. In view of the importance of DYKAT and the lack of a concise definition, we propose a more detailed definition: The de-symmetrization of racemic or diastereomeric mixtures involving interconverting diastereomeric intermediates—implying different equilibration rates of the stereoisomers—is termed dynamic kinetic asymmetric transformation.

This is explained by comparing the kinetics of KR, DKR and DYKAT (Figure 1). In a KR, the enantiomeric excess of the product (ee_p) declines as the reaction proceeds, most dramatically beyond a conversion of 50%. A system can be called dynamic if the equilibration is fast enough to ensure a

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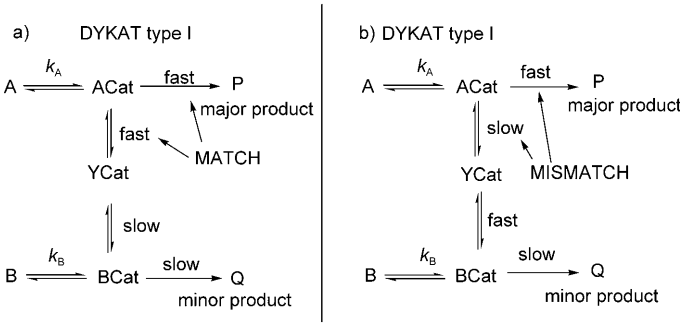
constant ee of the product throughout the reaction proceeds (green line KR ee_p). For DKR, the ee_p remains at the same constant level equivalent to the initial value of a KR (black line DKR ee_p), which is caused by the fact that the ee_s always remains zero, based on the equilibration of substrate enantiomers at a sufficient rate.

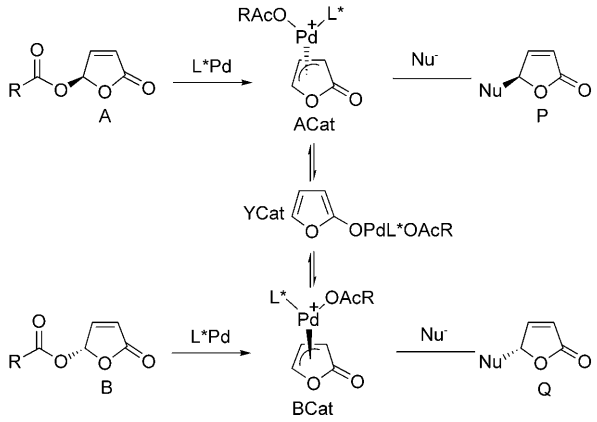
In a DYKAT system, substrates are interconverted through diastereomeric complexes (e.g., for DYKAT type I: ACat/BCat) and thus the substrate isomers are present in unequal amounts, that is, one of the substrate diastereomers is in excess. Two different ("match"/"mismatch") situations can be classified (Scheme 9): If the equilibration step leading to the major product of a DYKAT system (P) is faster than that forming the minor product (Q), the overall selectivity of the process will be higher than that for the KR, because the preferred transformation (ACat→P) matches to the enhanced formation of YCat⇄ACat (Scheme 9a, cf. Figure 1 red line DYKAT match ee_p). In contrast, in a mismatch situation the overall selectivity is decreased, if the equilibration YCat⇄ACat is slower for the major product P (Scheme 9b, cf. Figure 1 brown line DYKAT mismatch ee_p).



Scheme 9. "Match"/"mismatch" situations of DYKAT type I.

De-racemization of enantiomers via diastereomers (DYKAT type I, II): Trost et al. introduced a new approach for asymmetric allylic alkylation (AAA)[66,75,76] through an enantioselective palladium-catalyzed ionization. A racemate of A and B forms the racemate of two diastereomeric η^3-complexes ACat and BCat, which are in rapid equilibrium through the achiral intermediate YCat (Scheme 10).[65,66] Here, the aromaticity of furan serves as a driving force to shift the equilibrium from the diastereomeric η^3- to the nonchiral η^1-complex YCat. If this interconversion is fast relative to the subsequent nucleophilic addition and if one of the diastereomeric η^3-complexes (ACat or BCat) in the presence of a chiral ligand reacts faster than the other, a theoretical yield of 100% of either P or Q can be obtained.

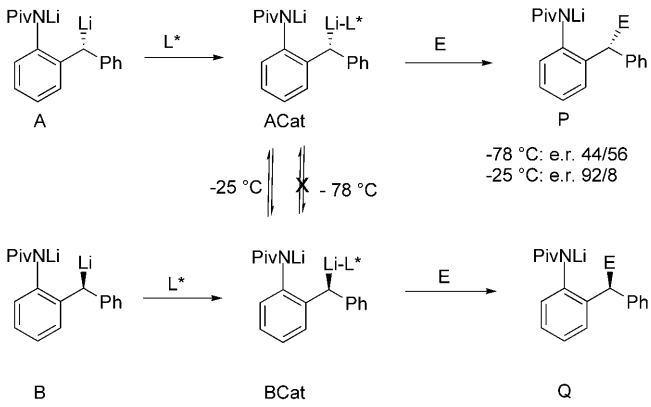
Recently, Bäckvall et al. reported on novel copper-catalyzed DYKAT type I concept.[77] The equilibration of allylic acetates was studied by using an enantiomerically pure allylic acetates and a standard allylic alkylation reagent (BuMgBr) together with a copper catalyst. The equilibration was shown to be strongly dependent on the temperature.



Scheme 10. Palladium-catalyzed DYKAT of enantiomers A and B (type I)[65] (L*: enantiopure ligand, Nu^-: nucleophile).

Having optimized the conditions for the equilibration, the concept suggests the use of chiral catalysts for the irreversible synthesis of stereopure products.

Enantioselective reaction pathways that involve an induced diastereomeric equilibration to intermediates, which are configurationally stable on the timescale of a subsequent reaction, were recently termed dynamic thermodynamic resolution (DTR).[78] Most of these reaction protocols utilize elevated temperatures to obtain thermodynamic control of the equilibrium of diastereomeric intermediates in order to improve the stereoselectivity in the subsequent reaction (Scheme 11).[79] These systems show all properties for a DYKAT type I process and thus, we strongly suggest that they should be termed DYKAT instead of DTR.



Scheme 11. Dynamic Thermodynamic Resolution (L*: enantiopure ligand, E: electrophile).[78]

For DYKAT type II, the intermediate originates from a racemic precursor in which the chiral center is lost and thus, the stereoselectivity solely depends on the subsequent step (i.e., the nucleophilic attack) that is guided by the remaining chiral centers of the substrate and the enantiopure ligand (Scheme 12). Thus, it is a special form of DYKAT in which the equilibration step shows stereoselectivity, but this selectivity is not transferred into the product.

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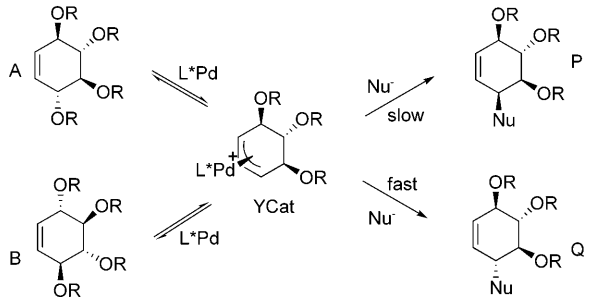
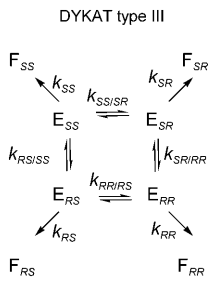


Scheme 12. DYKAT type II[69,80] (L*: enantiopure ligand, Nu^-: nucleophile).

These DYKAT protocols were applied to the asymmetric synthesis of allenes,[81] vinyl epoxides,[73,82] Baylis–Hillman adducts,[83] and natural products.[65,69,80,84–87]

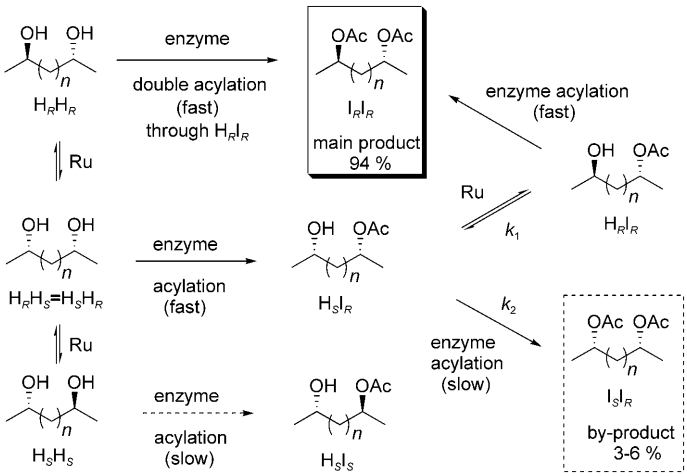


Scheme 13. DYKAT type III with simplified epimerization rates. E_{RS}/E_{SR} & E_{RR}/E_{SS} = enantiomeric pairs of diastereomeric initial products; F_{RS}/F_{SR} & F_{RR}/F_{SS} = enantiomeric pairs of diastereomeric final products; k_{SS}/k_{SR} through k_{RS}/k_{SS} = equilibration rates of formation $E_{SS}/E_{SR}/E_{RR}/E_{RS}$; k_{RR} through k_{SS} = rates of irreversible formation of F_{RS}/F_{SR} & F_{RR}/F_{SS}.

III and IV). Although Bäckvall et al. reports the DYKAT of a racemic diastereomeric mixture of 1,3- and 1,4-diols (type III),[88,89] while Trost et al. employed DYKAT only for racemates (type I and II),[65,69,80] in both cases the equilibration of stereoisomers involves diastereomeric intermediates.

Type III describes the de-epimerization of a diastereomeric mixture of enantiomeric pairs. As all four diastereomers are abundant, this system is much more difficult to analyze than type I and II systems. Since the

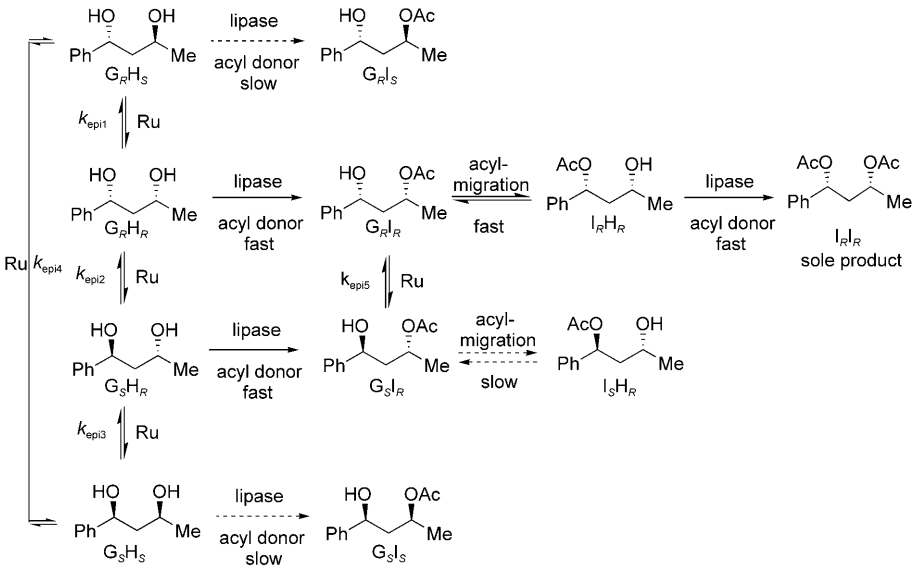
De-epimerization of diastereomers via diastereomers (DYKAT type III, IV): Since the classification of DYKAT types I and II, several novel DYKAT protocols were established for the de-epimerization of diastereomeric mixtures, which we herein classify as type III (cf. Scheme 13) and IV (cf. Scheme 19, later). The most important difference is the overall resolution of enantiomers (type I and II) versus the resolution of diastereomers (type



Scheme 14. DYKATof symmetric 1,4- and 1,3-diols via lipase-catalyzed acyl-transfer in combination with Ru-catalyzed epimerization of hydroxyl groups.[89] H = chiral carbon, convertable for equilibration and for the irreversible step; I = chiral carbon, stable chirality; n = 1,2.

kinetics of a DKR do not apply here the system has to be termed DYKAT.

Recently, symmetric 1,3- and 1,4-diacetates were obtained in high stereopurity starting from *meso*/*rac*-mixtures (1:1) by using an improved epimerization catalyst acting at lower temperature (50 instead of 70 °C), which suppressed acyl-migration (Scheme 14 versus 15) and hence, led to I_RI_R.[89] The intermediate ketones during equilibration are chiral (instead of achiral intermediates in DKR). Hence, the equilibration rate constants are not equal and the interconversion constitutes an epimerization rather than racemization. The ratio of formed enantiomeric diester I_RI_R and *meso*-isomer (I_SI_R)



Scheme 15. DYKAT of 1,3-diols via lipase-catalyzed acyl-transfer in combination with Ru-catalyzed epimerization of hydroxyl groups (DYKAT type III).[88] G = chiral carbon, convertable for equilibration and acyl migration, but not for the irrreversible step; H = chiral carbon, convertable for equilibration, acyl migration and the irrreversible step; I = chiral carbon, convertable for acyl migration, stable chirality.

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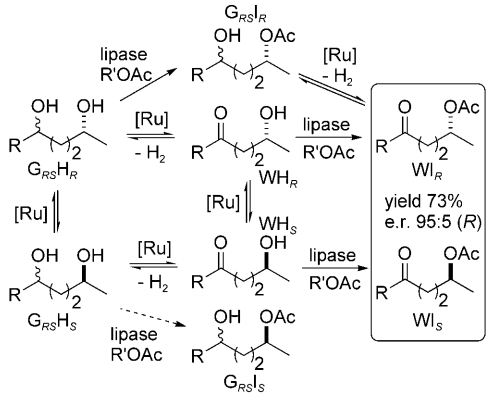
mainly depends on the epimerization rate of H_SI_R and H_RI_R (k_1) versus the *anti*-Kazlauskas acylation rate of H_SI_R (k_2).

For this example, detailed kinetic studies on the intermediates (monoacetates) showed that the second stereocenter indeed influenced the selectivity of the second chiral center. For the *anti* configuration an E value of 94 was obtained, while for the *syn* monoacetate a value of 7 was obtained. It was assumed that the selectivity of the enzyme is significantly influenced by the neighboring group. In contrast to the slow acylation to monoacetate H_SI_S (*anti*-Kazlauskas), the *anti*-Kazlauskas product of I_SI_R is produced much faster.

In the historically first example of a DYKAT type III, the substrates are racemic mixtures of diastereomeric 1,3-diols (Scheme 15).[88] Because of the equilibration between diastereomers, the kinetics of DKR do not apply. For the sake of clarity of this multistep process, only those substrates that are preferentially acylated according to the Kazlauskas rule are depicted.[48]

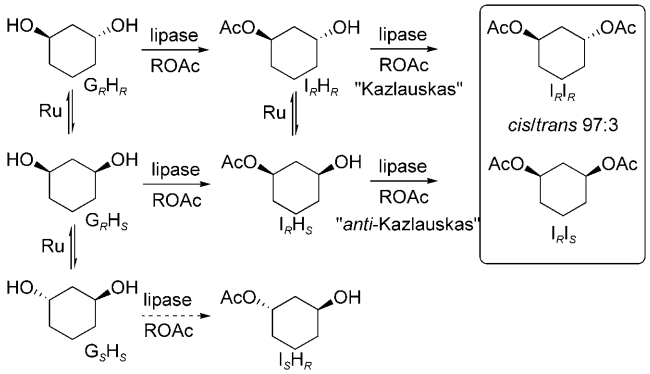
In 1,3-diols occurring as diastereomeric mixture ($G_{RS}H_{RS}$) only the hydroxyl group at the carbon H adjacent to the medium-sized group (i.e., methyl) is accessible for enzymatic transesterification. However, the rate-determining *R*-selective acylation is not significantly influenced by the other stereocenter. Only *syn*-acyl-migration (G_RI_R) occurs fast enough to compete with the dynamic epimerization/acylation process, thereby releasing an accessible (*R*)-alcohol (I_RH_R) to yield the (*R*,*R*)-1,3-diacylated product (I_RI_R). The de-epimerization of 1,2-diols was also achieved applying a similar DYKAT concept yielding one out of four possible stereoisomers in high yield.[90]

Recently, related DYKAT protocols for asymmetric 1,4-diols (Scheme 16)[91] and 1,3-cycloalkanediols (Scheme 17)[92]



Scheme 16. DYKAT (or pseudo-DKR) of asymmetric 1,4-diols via lipase-catalyzed acyl-transfer in combination with Ru-catalyzed epimerization of hydroxyl groups.[91] W = achiral carbon, accessible for reduction.

were published. For asymmetric 1,4-diols with one alcohol not being accessible for the stereoselective acylation it was shown that the stereochemistry of the non-accessible alcohol did not influence the selectivity of the more accessible alcohol,[91] since no diastereoselectivity was observed. Although in a strict sense, diastereomeric intermediates are involved in the Ru-catalyzed epimerization, the second stereocenter seems to have only a minor influence leading to approximately the same kinetic constants. Thus, with this approximation this system may be treated with DKR kinetics and it may be called a "pseudo-DKR".

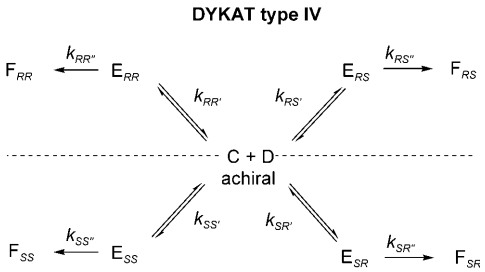


Scheme 17. DYKAT of 1,3-cycloalkanediols via lipase-catalyzed acyl-transfer in combination with Ru-catalyzed epimerization of hydroxyl groups.[92]

In the case of 1,3-cycloalkanediols (Scheme 17),[92] both chiral centers are resolved with high diastereoselectivity (d.r. 97:3). For *Candida antarctica* lipase B, it was shown that the first acylation is less selective ($E=2$) than the second one ($E=48$). Hence, the second chiral center plays an important role for the outcome of the diacetylation and thus this system should be denoted as DYKAT.

In DYKAT type IV, epimerization of diastereomers E_{RR}, E_{SS}, E_{RS}, E_{SR} proceeds through (reversible) destruction of both centers yielding two achiral intermediates C and D (Scheme 18). In comparison to DYKAT type III, all type IV systems so far were simpler, because the epimerization was highly stereoselective; thus, only two out of four diastereoisomers were present in measurable amounts. Nevertheless, all stereoisomers have to be depicted in the model to describe the whole process.

So far, only two examples of DYKAT type IV have been published. As the first example, a one-pot, two-step, polyke-



Scheme 18. DYKAT type IV. C+D = achiral substrates; E_{RS}/E_{SR} & E_{RR}/E_{SS} = enantiomeric pairs of diastereomeric initial products; F_{RS}/F_{SR} & F_{RR}/F_{SS} = enantiomeric pairs of diastereomeric final products; $k_{RR'}$ through $k_{SS'}$ = equilibration rates of formation E_{RS}/E_{SR} & E_{RR}/E_{SS}; $k_{RR''}$ through $k_{SS''}$ = rates of irreversible formation of F_{RS}/F_{SR} & F_{RR}/F_{SS}.

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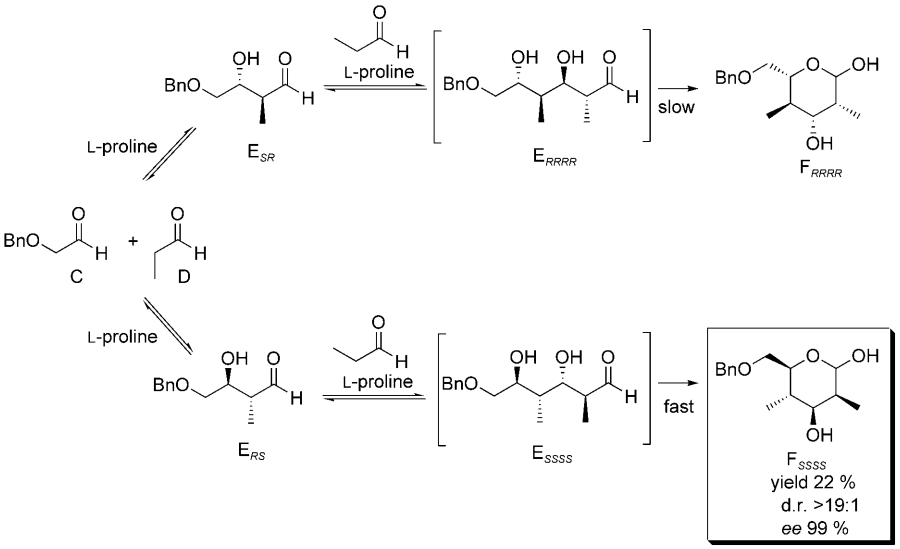
tide sugar synthesis revealed that proline catalyzes the formation of deoxysugars with excellent chemo- and diastereoselectivity by using organocatalysis (Scheme 19).[93]



Scheme 19. One-pot synthesis of polyketide sugars from racemic β-hydroxy aldehydes using an organo-catalyzed DYKAT type IV.[94]

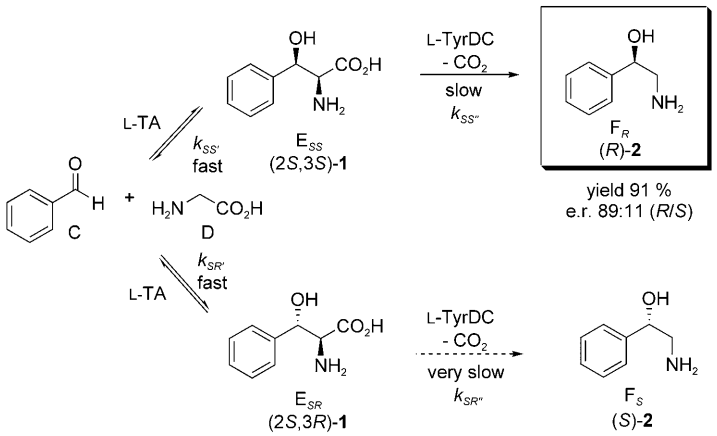
In this type of DYKAT, four stereocenters are formed during the equilibration, whereby an irreversible ring-formation pulls a single stereoisomer out of the equilibrium. For the sake of clarity, only the formation of E_{RS} and E_{SR} are shown due to the high diastereoselectivity of the equilibration.

DYKAT type IV involves epimerization of the β-hydroxyaldehyde (E_{RS}/E_{SR}) intermediates through a cascade comprising reversible retro-aldol reaction ($E_{RS}\Leftrightarrow C+D\Leftrightarrow E_{SR}$), subsequent cross-aldol reaction ($E_{RS}\Leftrightarrow E_{SSSS}$ and $E_{SR}\Leftrightarrow E_{RRRR}$), and final termination by irreversible spontaneous cyclization (preferentially $E_{SSSS}\rightarrow F_{SSSS}$). Overall, polyketide sugar (F_{RRRR}) was obtained in high diastereo- and enantioselectivity but low yield from *rac*-β-hydroxyaldehydes (E_{RS}/E_{SR}).[94] However, the simultaneous resolution of two stereocenters and the stereoselective formation of two additional asymmetric carbons render this approach a very promising protocol for carbohydrate synthesis. Thus it is apparent that simple amino acids catalyze the asymmetric neogenesis of carbohydrates by sequential cross-aldol reactions. The striking simplicity of this dynamic catalytic process suggests a catalytic prebiotic "gluconeogenesis" principle, in which amino acids transfer their stereochemical information onto sugars.[95]

A related DYKAT type IV process was recently reported by us in the context of a one-pot, enzymatic synthesis of amino alcohol F_R starting from glycine and benzaldehyde (C+D) using L-threonine aldolase (L-TA) and L-tyrosine decarboxylase (L-TyrDC) (Scheme 20).[96,97] The low diastereoselectivity[98] and the thermodynamic limitation of L-TA from *Pseudomonas putida*[99] was overcome by pulling one stereoisomer (E_{SS}) out of the equilibrium by means of stereoselective decarboxylation catalyzed by L-TyrDC from *Enterococcus faecalis*[100,101] to furnish enantioenriched F_R.[96]

To the best of our knowledge, this reaction sequence constitutes the first example of a bi-enzymatic de-epimerization of diastereomers. Both stereocenters of the intermediate (E) are interconverted by a reversible aldol/retro-aldol reaction, from which only two (out of four possible) diastereomers (E_{SR}, E_{SS}) are formed due to the excellent stereoselectivity of L-TA. The combination of reversible aldol reaction with irreversible stereoselective decarboxylation of intermediate E furnished amino alcohol F_R as the sole product in good ee and excellent yield (Scheme 20).

During this (formal) aminomethylation of benzaldehyde,



Scheme 20. Bi-enzymatic dynamic kinetic asymmetric transformation based on reversible aldol reaction followed by irreversible decarboxylation (DYKAT type IV).[96,97]

the *sec*-hydroxyl group retains its chirality, while the center at the terminal amino functionality is lost. The moderate C_β-selectivity obtained by the aldolase is drastically enhanced due to the high E_{SS}-selectivity of L-TyrDC. For optimal results regarding stereoselectivities and chemical yield, equilibration (k'_{SR}, k'_{SS}) must be much faster than the irreversible step (k''_{SR}, k''_{SS}).[28,102]

The fundamental differences between the DYKAT of E_{SR}/E_{SS} [(2*S*,3*R*)/(2*S*,3*S*)-**1**] diastereomers via the depicted bi-enzymatic synthesis (Scheme 20)[96] and a parallel kinetic resolution of E_{SR}/E_{RS} [(2*S*,3*R*)/(2*R*,3*S*)-**1**] enantiomers (Scheme 21),[103] have been investigated as follows.

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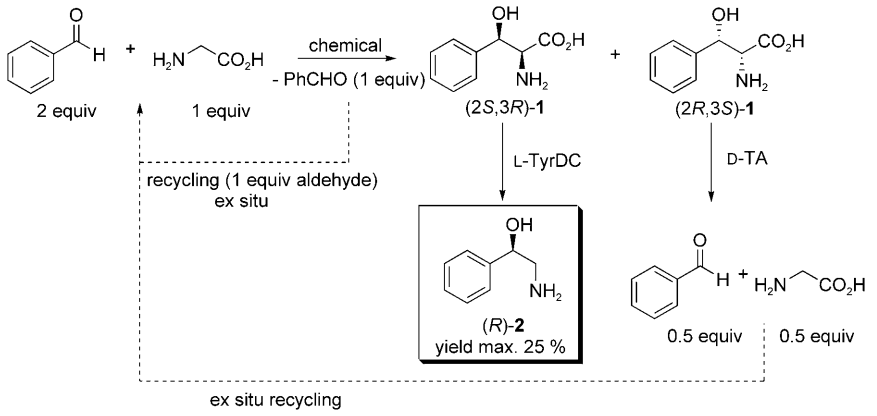


Scheme 21. Production of (*R*)-**2** using a bi-enzymatic parallel kinetic resolution of (chemically synthesized) (2*S*,3*R*)/(2*R*,3*S*)-**1** by simultaneous enantioselective enzymatic decarboxylation and retro-aldol reaction.[103]

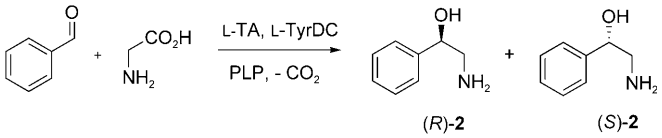
Synthesis of 1,2-Amino Alcohols

PKR versus DYKAT: Although L-amino acid decarboxylases are known to be highly substrate-specific, L-TyrDC tolerates an additional β-hydroxy group and the bulky aromatic substituent to convert L-phenylserine (2*S*,3*R*)-**1** to 2-amino-1-phenylethanol (*R*)-**2** at high rates.[104] Consequently, L-TyrDC was utilized to degrade chemically synthesized (2*S*,3*R*)/(2*R*,3*S*)-**1** to (*R*)-**2** derivatives with a maximum yield of 25% (based on the benzaldehyde), by leaving (2*R*,3*S*)-**1** untouched. To convert the kinetic resolution into a parallel kinetic resolution process, D-TA was utilized to recycle the non-reacting 2R,3S enantiomer by cleaving it to give benzaldehyde and glycine, which can re-enter the resolution process (Scheme 21).[103]

The prerequisite of every dynamic de-epimerization is the fast equilibration of diastereomers at conditions, which are compatible with the irreversible step. In contrast to DKR, the reaction rates of diastereomers are unequal owing to the different physical properties of diastereomers. Hence, stereoselectivity is also generated in the epimerization step. The rate of epimerization catalyzed by L-TA was investigated by using the synthesis reaction of glycine (1 M, in excess) with benzaldehyde or the retro-aldol reaction starting from (2*S*,3*R*)/(2*S*,3*S*)-**1**, (2*S*,3*R*)-**1**, or (2*S*,3*S*)-**1**. After ten minutes, all reactions reached equilibrium at 30% benzaldehyde and 70% of (2*S*,3*R*)-**1** in 20% *de*. This means that the L-TA-catalyzed equilibration of (2*S*,3*R*)/(2*S*,3*S*)-**1** is fast and, thus, should provide a constant ratio of diastereomers throughout the whole dynamic process.[96]

To investigate whether the C_β-selectivity is governed by the relative rates of epimerization versus decarboxylation, both enzymes were employed in different amounts. By using only a tenfold excess of L-TA over L-TyrDC, the *ee* and chemical yield of **2** dropped over time. Enhanced ratios of 48-fold and 86-fold excess gave (*R*)-**2** in high yields and *ee*. These data highlight the importance of an efficient equilibration rate in DYKAT processes.

The equilibrium of benzaldehyde and glycine forming (2*S*,3*R*)/(2*S*,3*S*)-**1** was successfully shifted towards the product side by the irreversible decarboxylation. After 58 h, the conversion of benzaldehyde into the intermediate (2*S*,3*R*)/(2*S*,3*S*)-**1** (8%) and the final amino alcohol (*R*)-**2** (91%) was complete (Scheme 22, Figure 2).[96] Hence, the combination of L-TA and L-TyrDC promises to be suitable for the quantitative conversion of aldehydes into 1,2-amino alcohols. Importantly, the low selectivity at the β-position was improved to 89:11 (*R*/*S*) by the stereoselective decarboxylation. The selectivities of both enzymatic reactions remained constant throughout the time-course of this reaction implying an efficient dynamic nature of the process.



Scheme 22. Synthesis of the intermediate **1** and the final product (*R*)-**2**.[88]

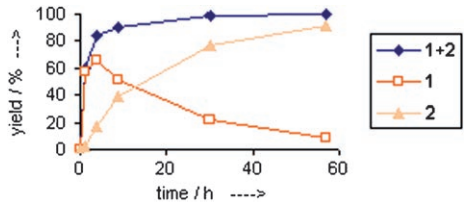


Figure 2. Time course of the synthesis of intermediate **1** and the final product (*R*)-**2**) starting from benzaldehydes and glycene.

To improve the stereoselectivity of this bi-enzymatic process we calculated which enzyme should be improved in future mutagenesis and screening rounds. The enantioselectivity of the bi-enzymatic process was shown to be the product of both independent enzymatic processes (Table 1 entry 1 versus 2). The theoretical enantiomeric excess of the reaction (*ee* 74% assuming a *de* of 15% *anti*-L-TA and a *syn*/*anti*-selectivity for *syn*-L-TyrDC of 9:1 as determined in separate enzymatic reactions) and the experimental data (*ee* 77%) are within statistical error margins (Table1 entries 1 and 2). To reach the limits for industrial production (*ee* > 95%), either L-TA has to be improved to a *de* of 64% (Table1 entry 3) or L-TyrDC has to be evolved to a *de* of 97% (Table1 entry 4). By increasing the diastereoselectivity of L-TA (Figure 3a, curved line) a higher improvement for the overall enantioselectivity was achieved as compared to the amendment of L-TyrDC (Figure 3b, straight line). Hence, L-TA is the limiting factor for the stereoselective synthesis of (*R*)-**2**. Consequently, the main screening activi-

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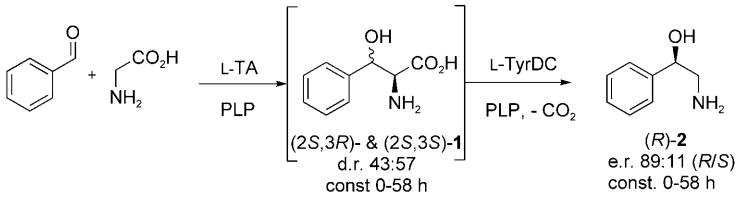
Table 1. Experimental and calculated data: *ee* of (*R*)-**2** for different *de*'s of the involved enzymes.



			L-TA	L-TyrDC	e.r. of **2**[a]	*ee* (*R*)-**2** calcd
1	exptl *ee*	*syn*-**1**	–	–	–	77
		anti-**1**	–	–	–	
2	calcd *ee*	*syn*-**1**	43	90	3870 (*R*)	74
		anti-**1**	57	10	570 (*S*)	
3	L-TA const	*syn*-**1**	43	98.5	4236 (*R*)	96
	altered L-TyrDC	*anti*-**1**	57	1.5	86 (*S*)	
4	L-TyrDC const	*syn*-**1**	82	90	7380 (*R*)	960
	altered L-TA	*anti*-**1**	18	10	180 (*S*)	

[a] e.r. (enantiomeric ratio) = *de*(L-TA) × *de*(L-TyrDC).

ties will be focused on the evolution of L-TA in the near future since it is anticipated that an increase of the low diastereoselectivity to a de of 64% should be more facile.

Combined KR/DYKAT strategy: As long as there are no improved mutants available at present, we succeeded in the synthesis of enantiopure 1,2-amino alcohol by applying a combined KR+DYKAT strategy starting from (2*S*,3*R*)/(2*R*,3*S*)-**1** (Scheme 23).[96]

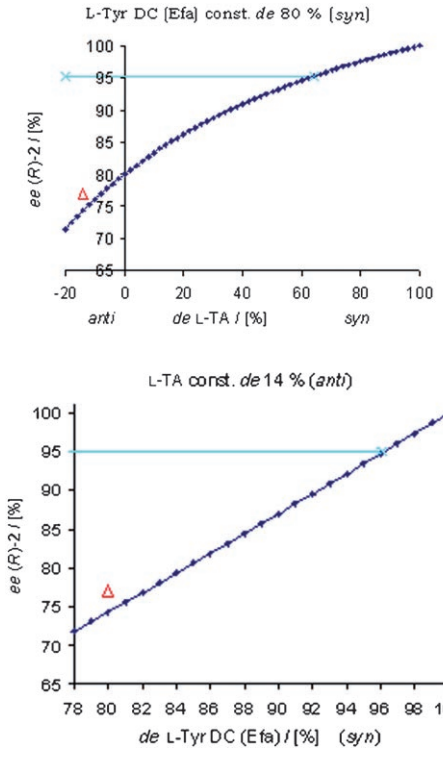
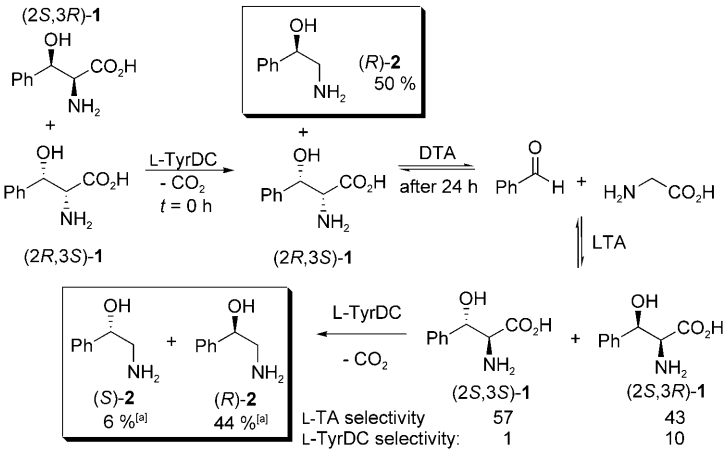


Figure 3. Experimental and calculated data: *ee* of (*R*)-**2** for different *de*'s of the involved enzymes. Top: L-TA const./altered L-TyrDC; bottom: L-TyrDC const./altered L-TA; (Δ experimental *ee* of (*R*)-**2**).

To overcome the 50%-yield limitation of KR while retaining high selectivity, a novel one-pot/three-enzymes protocol was investigated (Scheme 23): In a first step, KR of (2*S*,3*R*)/(2*R*,3*S*)-**1** through enantioselective decarboxylation catalyzed by L-TyrDC gave enantiopure (*R*)-**2** in 50% yield. After 24 h, LTA and D-TA[9] were added. Whereas D-TA catalyzed the retro-aldol cleavage of non-reacting (2*R*,3*S*)-**1** into benzaldehyde and glycine, L-TA recycled this material into (2*S*,3*R*)/(2*S*,3*S*)-**1**. Delayed addition of



Scheme 23. Theoretical outcome for the synthesis of (*R*)-**2** using a KR/DYKAT protocol (94% (*R*)-**2**, 6% (*S*)-**2**); [a] estimated C_β-selectivity of the coupled L-TA/L-TyrDC reaction: 89/11 (*R*/*S*) (see Scheme 22).[96]

L-TA/D-TA (after 24 h) yielded enantiopure (*R*)-**2** (*ee* > 99%) at modest conversion of 67%. The high selectivity shows that all three enzymes collaborate well and with this approach, the kinetic limitation for a low C_β-selectivity in L-TA-catalyzed reactions can be overcome yielding enantiopure (*R*)-**2** at yields beyond 50%.

Conclusion

The main objective of this concept paper is an attempt to combine different elements of dynamic asymmetric catalytic processes dealing with enantiomers or diastereomers—DKR, DYKAT, and dynamic thermodynamic resolution—which have been apparently developed along separate lines with little connection in between and to put these strategies into a broader perspective. By reviewing dynamic processes, the lack of clear definitions became apparent, and is manifested by the fact that DYKAT-systems were sometimes mis-

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leadingly classified as DKRs and that no clear distinction between dynamic thermodynamic resolution and DYKATs exists. By enhancing the understanding of the demands and challenges of dynamic systems for the production of single stereoisomers from racemic or diastereomeric mixtures, we hope to broaden their applicability.

Acknowledgements

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