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Computer simulation of asymmetric transformations

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Abstract—In order to obtain the best strategy for organic synthesis, the simulation of the reaction course can be helpful. In this letter we present a facile mathematical system for the simulation of the reaction course based on the reaction kinetics. Reaction courses are described and displayed easily by dividing the whole process into several small intervals. Exemplarily this is demonstrated for kinetic resolutions and desymmetrizations. The Microsoft® Excel tables used for these simulations are available herein.

1. Introduction

The progress of a chemical reaction is determined by its kinetics. The kinetics of a given reaction can be very complicated due to the participation of many components and their mutual relationship. Side reactions, further reactions and reverse reactions in particular have to be considered in a mathematical description and computer simulation of the progress of such reactions. For the correct mathematical description the stoichiometry of all reactions taking place, their rate constants and relationships must be described. Thus, the development of the amounts of the involved reaction participants can be determined by setting up the corresponding differential equations and subsequent integration or equivalent mathematical methods. These and the following calculations require a great deal of computational operations, are time consuming and not easy to survey. The available software for these calculations is often not suitable.[1–3]

Herein, we report a facile mathematical model for the description of reactions, which makes use of dividing the reaction into several small intervals. This concept can be demonstrated with the progress of enantioselectively catalyzed reactions.

Sih et al. have already described the reaction kinetics of asymmetric transformations mathematically.[4,5] In particular the resulting equation

$$c = \mathrm{ee}_{\mathbf{E}}/(\mathrm{ee}_{\mathbf{E}} + \mathrm{ee}_{\mathbf{P}})$$

(c = conversion; ee = enantiomeric excess; **E** = educt; **P** = product) for the resolution of racemates is quoted and applied in almost every article on this subject. Nevertheless, it is often neglected that this equation is only applicable to absolutely irreversible reactions. Since a catalyst sets the equilibrium of a reaction, usually the reverse reaction also takes place. Then, the false application of the above mentioned equation leads to incorrect conclusions concerning the data and in the end, the reaction kinetics, too.

Therefore, we herein report a mathematical simulation of the reaction course, which includes backward reactions. Not only the kinetic resolution of racemates, but also the kinetic resolution of enantiomerically enriched substrates can be simulated. In addition to kinetic resolutions, the desymmetrization of prochiral compounds is also described.

2. Principle of the simulation

Catalysts accelerate the setting up of a chemical equilibrium by lowering the activation energy. In Scheme 1, a typical chemical equilibrium is shown: Educt **E** is converted into product **P** (reaction **R1**). The reverse reaction runs vice versa from product **P** to educt **E** (reaction **R2**).

The reaction partners **E**, **P** and the necessary reagents should be available in excess and are therefore not rate

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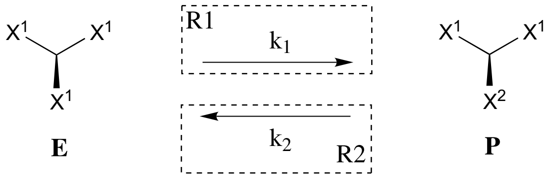


Scheme 1. Chemical equilibrium between **E** and **P**.

limiting. The reaction rate is exclusively determined by the activity of the catalyst used. Since the same catalyst is involved in both reactions **R1** and **R2**, competition takes place. The catalyst with a given activity catalyzes a maximum number of processes *a* within a given time interval. For a better understanding, all simulations in this article are carried out with a constant catalyst activity that means a constant value for *a*. The amounts of the reacting substances [$n(\mathbf{E})$, $n(\mathbf{P})$], their affinities to the catalysts [$A(\mathbf{E})$, $A(\mathbf{P})$] and their conversion constants [$U(\mathbf{R1})$, $U(\mathbf{R2})$] define proportions **T1** and **T2** of reactions **R1** and **R2**. Provided that the reaction conditions remain constant during the transformation, affinities *A* and conversion constants *U* do not change. Hence, rate constants k_1 and k_2 of reactions **R1** and **R2** are given by

$$k_1 = A(\mathbf{E}) \cdot U(\mathbf{R1}) \quad \text{and} \quad k_2 = A(\mathbf{P}) \cdot U(\mathbf{R2}).$$

Since competition takes place, the rate constants k_1 and k_2 are converted into relative constants

$$d = k_1/(k_1 + k_2) \quad \text{and} \quad e = k_2/(k_1 + k_2).$$

Proportions **T1** and **T2** of reactions **R1** and **R2** of the maximum number of catalytic processes *a* can be calculated as

$$\mathbf{T1} = n(\mathbf{E}) \cdot d \quad \text{and} \quad \mathbf{T2} = n(\mathbf{P}) \cdot e.$$

The number of the catalytic processes *a* is defined per time unit. Therefore, only a time interval *i* of a certain length is considered in one calculation step. The changes of the amounts of substances in this interval are

$$\Delta n(\mathbf{E}) = (-\mathbf{T1} + \mathbf{T2}) \cdot a \quad \text{and} \quad \Delta n(\mathbf{P}) = (+\mathbf{T1} - \mathbf{T2}) \cdot a.$$

After subdividing the reaction course into equally long intervals *i*, a value for *a* can be assigned to each of these intervals. The changes of the amounts of substances for each interval *i* are defined as

$$\Delta n(\mathbf{E})_i \quad \text{and} \quad \Delta n(\mathbf{P})_i.$$

Then, the new amounts of substances at the beginning of the next interval are

$$n(\mathbf{E})_{i+1} = n(\mathbf{E})_i + \Delta n(\mathbf{E})_i \quad \text{and} \quad n(\mathbf{P})_{i+1} = n(\mathbf{P})_i + \Delta n(\mathbf{P})_i.$$

The actual reaction course results from calculating the following arithmetic operations for each time interval $i + 1$ using the amounts of substances of the preceding interval:

$$\mathbf{T1}_i = n(\mathbf{E})_i \cdot d, \quad \mathbf{T2}_i = n(\mathbf{P})_i \cdot e,$$
$$\Delta n(\mathbf{E})_i = (-\mathbf{T1}_i + \mathbf{T2}_i) \cdot a, \quad \Delta n(\mathbf{P})_i = (+\mathbf{T1}_i - \mathbf{T2}_i) \cdot a \quad \text{and}$$
$$n(\mathbf{E})_{i+1} = n(\mathbf{E})_i + \Delta n(\mathbf{E})_i, \quad n(\mathbf{P})_{i+1} = n(\mathbf{P})_i + \Delta n(\mathbf{P})_i.$$

These operations are repeated starting with $i = 0$ up to an optional number $i_{\max}$. A modern computer performs these calculations even for $i_{\max} = 10{,}000$ time intervals, within a few milliseconds. Herein all calculations were performed with 10,000 time intervals. The advantage of this mathematical description is the facile programming of the necessary loop in Microsoft® Excel.

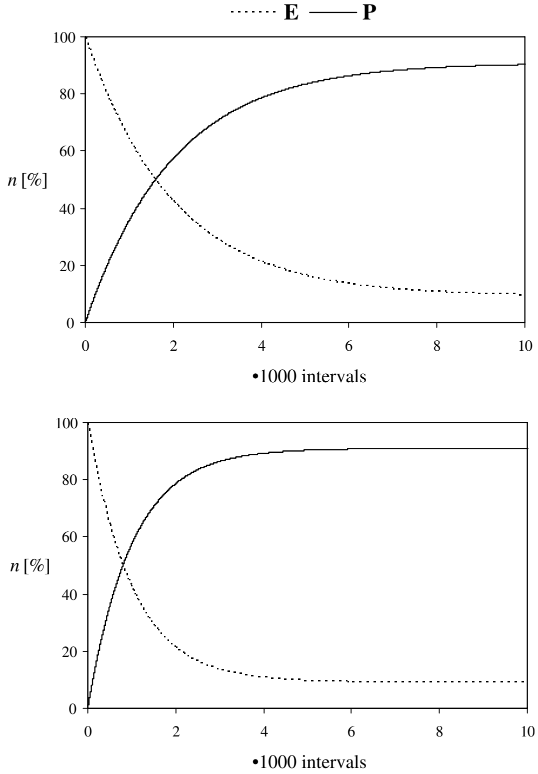


Figure 1. Simulated reaction courses of catalyzed chemical reactions. Amount of substances **E** and **P** (n [%]) during the progress of the reaction rate constants: $k_1 = 10$, $k_2 = 1$; top: $a = 0.0005$; bottom: $a = 0.001$.

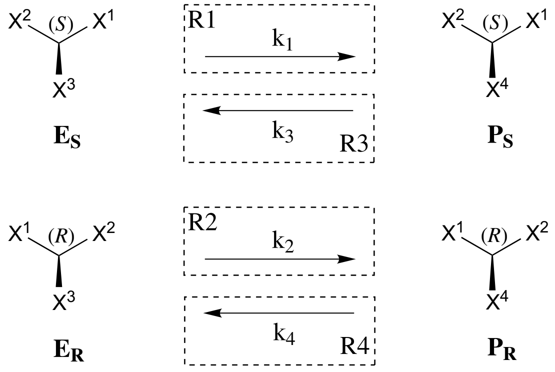
The simulation of the reaction progress is illustrated graphically by plotting the respective amounts of substances against the time intervals. The simulations for different conditions can be calculated by variation of constants k_1, k_2 and *a*. The reaction equilibrium between two components **E** and **P** is the easiest case of a catalytic reaction consisting of only two partial reactions **R1** and **R2**. In Figure 1, it is assumed that **R1** is faster than **R2**. The rate constants k_1 and k_2 are set 10 and 1, respectively. After raising catalyst activity *a*, the equilibrium of the reaction is set faster (Fig. 1 bottom).

Any other reaction course may be calculated and displayed in the same manner by this mathematical system in Microsoft® Excel using the above mentioned operations.

This is shown by simulating the catalytic kinetic resolution, the catalytic desymmetrization of prochiral compounds and the improvement of both processes using multistep strategies.

3. Catalytic kinetic resolution

One possibility for obtaining one enantiomer with a high enantiomeric excess starting with a racemic mixture is the



Scheme 2. Catalytic kinetic resolution.

application of an enantioselective catalyst, which converts one enantiomer faster than the other one. In Scheme 2, the catalytic transformation of enantiomers is shown schematically. Educt **E** consists of a mixture of enantiomers $\mathbf{E_S}$ and $\mathbf{E_R}$ and product **P** of a mixture of enantiomers $\mathbf{P_S}$ and $\mathbf{P_R}$. The catalyst sets the reaction equilibria between $\mathbf{E_S}$ and $\mathbf{P_S}$, as well as between $\mathbf{E_R}$ and $\mathbf{P_R}$.

Thus, four reactions **R1** to **R4** are to be considered. The rate constants for these reactions are given by the following equations:

$$k_1 = A(\mathbf{E_S}) \cdot U(\mathbf{R1}) \quad \text{and} \quad k_2 = A(\mathbf{E_R}) \cdot U(\mathbf{R2}),$$
$$k_3 = A(\mathbf{P_S}) \cdot U(\mathbf{R3}) \quad \text{and} \quad k_4 = A(\mathbf{P_R}) \cdot U(\mathbf{R4}).$$

The relative constants are defined as follows:

$$d = k_1/(k_1 + k_2), \quad e = k_2/(k_1 + k_2),$$
$$f = k_3/(k_3 + k_4), \quad g = k_4/(k_3 + k_4) \quad \text{and}$$
$$h = (k_1 + k_2)/(k_1 + k_2 + k_3 + k_4),$$
$$m = (k_3 + k_4)/(k_1 + k_2 + k_3 + k_4).$$

For reactions **R1** to **R4**, the available catalytic processes a are divided into proportions of

$$\mathbf{T1}_i = n(\mathbf{E_S})_i \cdot d \cdot h, \quad \mathbf{T2}_i = n(\mathbf{E_R})_i \cdot e \cdot h \quad \text{and}$$
$$\mathbf{T3}_i = n(\mathbf{P_S})_i \cdot f \cdot m, \quad \mathbf{T4}_i = n(\mathbf{P_R})_i \cdot g \cdot m.$$

Therefore, the changes of the amounts of substances during a time interval are

$$\Delta n(\mathbf{E_S})_i = (-\mathbf{T1}_i + \mathbf{T3}_i) \cdot a, \quad \Delta n(\mathbf{E_R})_i = (-\mathbf{T2}_i + \mathbf{T4}_i) \cdot a$$
$$\text{and} \quad \Delta n(\mathbf{P_S})_i = (+\mathbf{T1}_i - \mathbf{T3}_i) \cdot a,$$
$$\Delta n(\mathbf{P_R})_i = (+\mathbf{T2}_i - \mathbf{T4}_i) \cdot a.$$

As in the previous example, the amounts of substances at the beginning of the next interval $i + 1$ are the sum of the amounts of substances at the beginning of interval i and the change of the amounts of substances during the time interval i:

$$n(\mathbf{E_S})_{i+1} = n(\mathbf{E_S})_i + \Delta n(\mathbf{E_S})_i,$$
$$n(\mathbf{E_R})_{i+1} = n(\mathbf{E_R})_i + \Delta n(\mathbf{E_R})_i \quad \text{and}$$
$$n(\mathbf{P_S})_{i+1} = n(\mathbf{P_S})_i + \Delta n(\mathbf{P_S})_i,$$
$$n(\mathbf{P_R})_{i+1} = n(\mathbf{P_R})_i + \Delta n(\mathbf{P_R})_i.$$

The reaction progress determined by these parameters was programmed as a Microsoft® Excel table and plotted in a diagram.

Different conditions can be simulated by changing the values for k_1 to k_4 and a. In Figure 2, the development of the amount of substances **E** and **P** (n [%]) is shown on the left and the corresponding development of the enantiomeric excess (% ee) is shown on the right. Each reaction was started with racemic educts. The simulation in Figure 2 (top) is based on the assumption that the reaction equilibrium is shifted to the product sides 10:1 ($k_1/k_3 = k_2/k_4 = 10$). Moreover, it is assumed that the (*S*)-enantiomers are transformed 10 times faster than the (*R*)-enantiomers ($k_1/k_2 = k_3/k_4 = 10$).

The development of the enantiomeric excess (Fig. 2 top, right) indicates only a low enantiomeric purity of **E** and **P**, because backward reactions **R3** and **R4** also take place.

An improvement of the enantiomeric excess is achieved by suppressing the backward reactions. In the middle of Figure 2, a simulation with very low rate constants for the backward reactions ($k_1/k_3 = k_2/k_4 = 10{,}000$) is displayed. Such a quasi irreversible transformation leads to educt **E** in a very high enantiomeric excess (Fig. 2 middle, right), but only a moderate yield (left).

Increasing the enantioselectivity of the catalyst from 10:1 (Fig. 2 top and middle) to 100:1 (Fig. 2 bottom) considerably improved the enantiomeric purity of **E** and **P**.

These examples demonstrate the facile simulation of the kinetic resolution of racemates by changing the ratio of the rate constants k_1 to k_4, which takes into account the reversibility of the transformation (k_1/k_3 and k_2/k_4) and the enantioselectivity of the catalyst (k_1/k_2 and k_3/k_4).

4. Catalytic desymmetrization of prochiral compounds

The catalytic desymmetrization of prochiral compounds represents a further possibility to synthesize chiral compounds in a high enantiomeric excess. In this case, the stereogenic centre in the molecule is established during the catalytic conversion. Conversion of the pro-(*R*) or pro-(*S*) enantiotopic group determines whether the (*R*)- or (*S*)-enantiomer is formed. The conversion of both enantiotopic groups in the same way leads again to a prochiral compound. In Scheme 3, the reactions occurring during the desymmetrization of a prochiral compound are shown schematically. During the first step the prochiral educt **E** is converted into chiral products $\mathbf{P_S}$ and $\mathbf{P_R}$ (reactions **R1** and **R2**). Further transformations of $\mathbf{P_S}$ and $\mathbf{P_R}$ produce the prochiral product **W** (reactions **R3** and **R4**).

As in the previous examples, reactions **R1** to **R4** are part of reaction equilibriums. Their reverse reactions **R5** to **R8** run exactly the opposite way. The rate constants k_1 to k_8 for the corresponding reactions **R1** to **R8** outlined in Scheme 3 are given as follows:

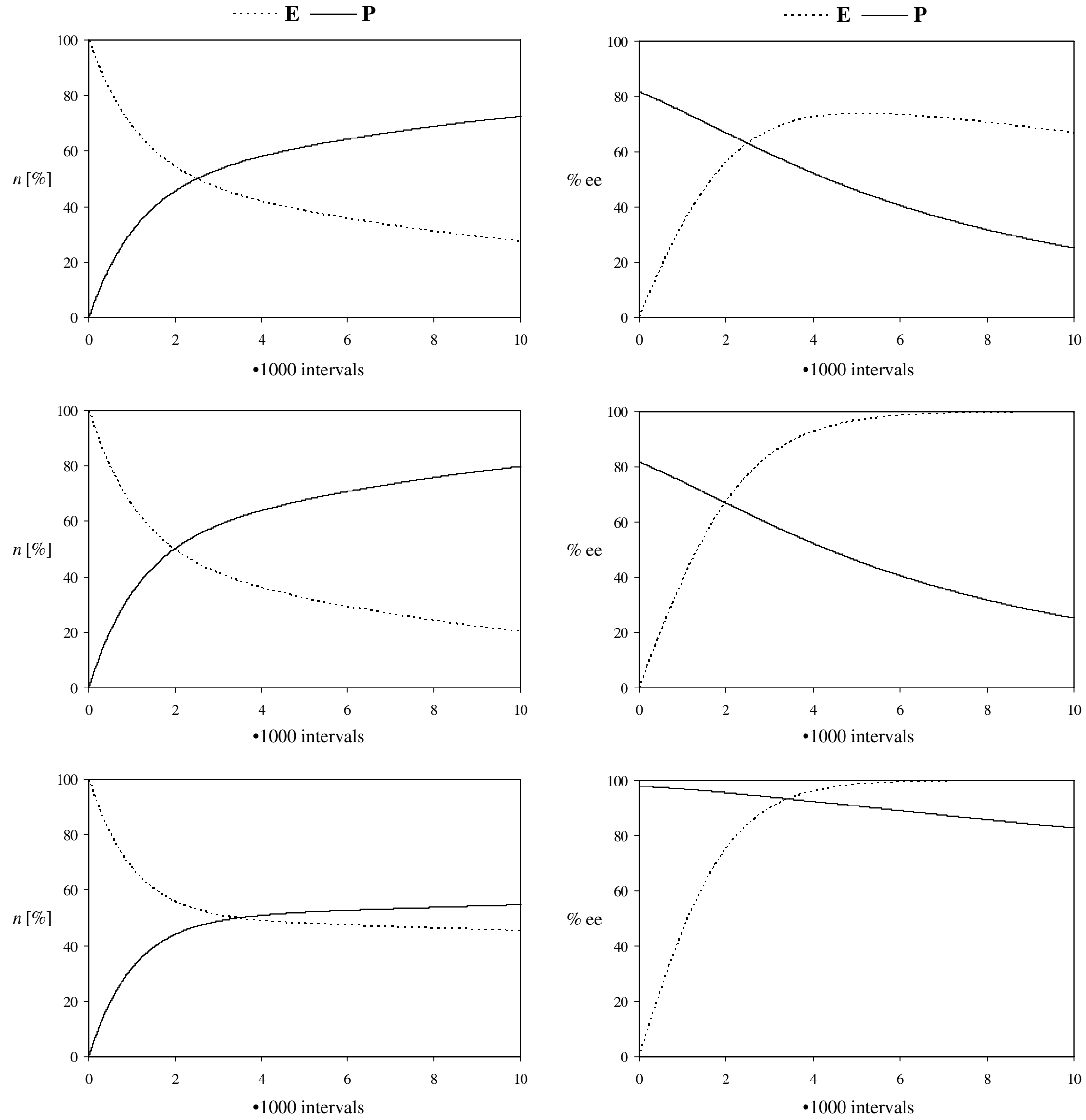


Figure 2. Simulated catalytic kinetic resolutions ($a = 0.001$). Left: Amount of compounds **E** and **P** (n [%]) during the progress of the reaction; right: enantiomeric excess of compounds **E** and **P** (% ee) during the progress of the reaction; top: $k_1 = 10$, $k_2 = 1$, $k_3 = 1$, $k_4 = 0.1$; middle: $k_1 = 10$, $k_2 = 1$, $k_3 = 0.001$, $k_4 = 0.0001$; bottom: $k_1 = 100$, $k_2 = 1$, $k_3 = 0.01$, $k_4 = 0.0001$.

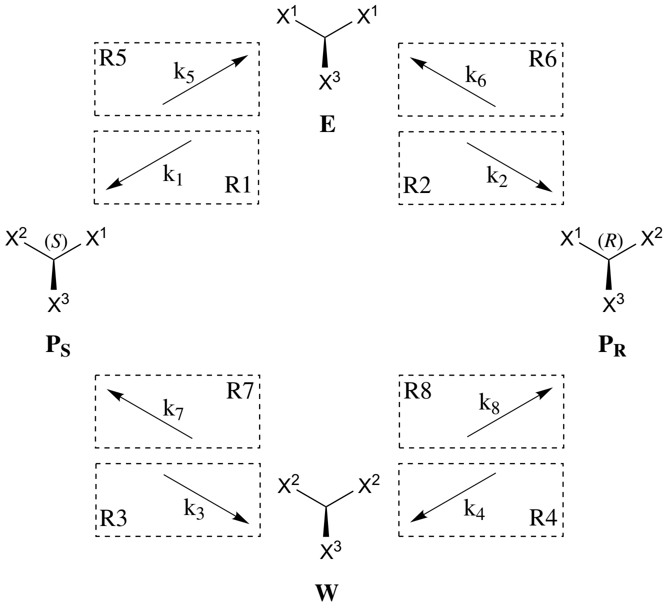
$$k_1 = A(\mathbf{E}) \cdot U(\mathbf{R1}), \quad k_2 = A(\mathbf{E}) \cdot U(\mathbf{R2}),$$
$$k_3 = A(\mathbf{P_S}) \cdot U(\mathbf{R3}), \quad k_4 = A(\mathbf{P_R}) \cdot U(\mathbf{R4}),$$
$$k_5 = A(\mathbf{P_S}) \cdot U(\mathbf{R5}), \quad k_6 = A(\mathbf{P_R}) \cdot U(\mathbf{R6}),$$
$$k_7 = A(\mathbf{W}) \cdot U(\mathbf{R7}), \quad k_8 = A(\mathbf{W}) \cdot U(\mathbf{R8}).$$

The resulting relative constants are

$$d = k_1/(k_1 + k_2), \quad e = k_2/(k_1 + k_2),$$
$$f = k_3/(k_3 + k_4), \quad g = k_4/(k_3 + k_4),$$
$$h = (k_1 + k_2)/(k_1 + k_2 + k_3 + k_4),$$
$$m = (k_3 + k_4)/(k_1 + k_2 + k_3 + k_4),$$
$$o = k_5/(k_5 + k_6), \quad p = k_6/(k_5 + k_6),$$
$$q = k_7/(k_7 + k_8), \quad r = k_8/(k_7 + k_8),$$
$$u = (k_5 + k_6)/(k_5 + k_6 + k_7 + k_8),$$
$$v = (k_7 + k_8)/(k_5 + k_6 + k_7 + k_8),$$
$$x = (k_1 + k_2 + k_3 + k_4)/(k_1 + k_2 + k_3 + k_4 + k_5 + k_6 + k_7 + k_8),$$
$$y = (k_5 + k_6 + k_7 + k_8)/(k_1 + k_2 + k_3 + k_4 + k_5 + k_6 + k_7 + k_8).$$

The maximum number of catalytic processes a is limited by the amount of catalyst. In a competitive situation reactions **R1** to **R8** compete for the catalytic processes. Proportions **T1** to **T8** of reactions **R1** to **R8** are given as follows:

$$\mathbf{T1}_i = n(\mathbf{E})_i \cdot d \cdot h \cdot x, \quad \mathbf{T2}_i = n(\mathbf{E})_i \cdot e \cdot h \cdot x,$$
$$\mathbf{T3}_i = n(\mathbf{P_S})_i \cdot f \cdot m \cdot x, \quad \mathbf{T4}_i = n(\mathbf{P_R})_i \cdot g \cdot m \cdot x,$$
$$\mathbf{T5}_i = n(\mathbf{P_S})_i \cdot o \cdot u \cdot y, \quad \mathbf{T6}_i = n(\mathbf{P_R})_i \cdot p \cdot u \cdot y,$$
$$\mathbf{T7}_i = n(\mathbf{W})_i \cdot q \cdot v \cdot y, \quad \mathbf{T8}_i = n(\mathbf{W})_i \cdot r \cdot v \cdot y.$$



Scheme 3. Catalytic desymmetrization of prochiral compounds.

Hence, within a time interval the changes of the amounts of substances can be calculated:

$$\Delta n(\mathbf{E})_i = (-\mathbf{T1}_i - \mathbf{T2}_i + \mathbf{T5}_i + \mathbf{T6}_i) \cdot a,$$
$$\Delta n(\mathbf{P_S})_i = (+\mathbf{T1}_i - \mathbf{T3}_i - \mathbf{T5}_i + \mathbf{T7}_i) \cdot a,$$
$$\Delta n(\mathbf{P_R})_i = (+\mathbf{T2}_i - \mathbf{T4}_i - \mathbf{T6}_i + \mathbf{T8}_i) \cdot a,$$
$$\Delta n(\mathbf{W})_i = (+\mathbf{T3}_i + \mathbf{T4}_i - \mathbf{T7}_i - \mathbf{T8}_i) \cdot a.$$

The amounts of substances at the beginning of the interval $i+1$ result from the amounts of substances at the beginning of the previous interval i plus the change during the transformation within interval i

$$n(\mathbf{E})_{i+1} = n(\mathbf{E})_i + \Delta n(\mathbf{E})_i,$$
$$n(\mathbf{P_S})_{i+1} = n(\mathbf{P_S})_i + \Delta n(\mathbf{P_S})_i,$$
$$n(\mathbf{P_R})_{i+1} = n(\mathbf{P_R})_i + \Delta n(\mathbf{P_R})_i,$$
$$n(\mathbf{W})_{i+1} = n(\mathbf{W})_i + \Delta n(\mathbf{W})_i.$$

The detailed mathematical description of the catalytic desymmetrization of prochiral compounds is applied to three examples with different parameters (Fig. 3).

Due to the chirality of the catalyst, the enantioselectivities for the conversions of **E** into **P** and **P** into **W** and the corresponding backward reactions are expected to be very similar. The graphics in Figure 3 are calculated by using the same enantioselectivity for both processes. In the first example (Fig. 3 top), the enantioselectivity of the catalyst is set at 5:1 ($k_1/k_2 = k_4/k_3 = k_5/k_6 = k_8/k_7 = 5$) and the ratio of rate constants defining the equilibrium of each partial reaction at 10:1 ($k_1/k_5 = k_2/k_6 = k_3/k_7 = k_4/k_8 = 10$). A catalyst with such properties leads to product **P** with maximal 80% ee and 60% yield.

The charts in the middle of Figure 3 differ from the charts above by suppressing backward reactions **R5** to **R8**. The ratio of the rate constants was set at 10,000:1 ($k_1/k_5 = k_2/k_6 = k_3/k_7 = k_4/k_8 = 10{,}000$) on the product side, indicating almost irreversible transformations. The development of compounds **E**, **P** and **W** (Fig. 3 middle, left) is very similar to that of Figure 3 top, left. However, the enantiomeric purity of **P** increased considerably during the transformation. Moreover, a maximum enantiomeric excess, as seen in Figure 3 top right, does not exist (Fig. 3 middle, right), since racemization is prohibited.

The graphics at the bottom of Figure 3 were calculated with an increased enantioselectivity of the catalyst ($k_1/k_2 = k_4/k_3 = k_5/k_6 = k_8/k_7 = 20$). It clearly shows that the yield of **P** as well as its enantiomeric purity is dramatically increased.

5. Strategies for synthesis

The purpose of enantioselective synthesis is the production of one or both enantiomers with a high yield and enantiomeric purity. The kinetic resolution of racemates as well as the desymmetrization of prochiral compounds as shown in Sections 3 and 4 fulfil this task insufficiently, because the catalysis only runs in one direction due to the reaction conditions: The kinetic resolution of racemates evokes an almost enantiomerically pure educt **E** with only a low yield and a product **P** with a high yield but only a low enantiomeric excess (Section 3). If a prochiral compound is desymmeterized, the enantiomeric excess, as well as the yield of product **P** is high, because the reaction sequence comprises of two enantioselective steps. However, only one enantiomer can be produced with a given catalyst (Section 4).

In order to improve these features, multistep syntheses have been developed.[6] In these cases, the catalytic reaction is stopped after a definite reaction time, the involved compounds are separated and any of these compounds are employed in a second enantioselectively catalyzed reaction.

The production of both enantiomers in a high enantiomeric excess and good yield via such a multistep or cycling reaction sequence, requires a catalyst with opposite enantioselectivity or the reaction equilibriums have to be reversed by changing the reaction conditions. Synthetic catalysts, which work enantioselectively, are often available in the (*S*)- and (*R*)-form, so that generally both enantiomers $\mathbf{P_S}$ and $\mathbf{P_R}$ of the product are easily available. However, natural macromolecular catalysts such as enzymes are normally not available in both enantiomeric forms. Hence, their selectivity to form the (*S*)- or (*R*)-enantiomer is given. An enzymatic reaction with the aim of producing both enantiomers is only possible if the reaction equilibrium can be set on both sides by changing the reaction conditions. This succeeds especially well with quasi-irreversible reactions (compare Sections 3 and 4). In the optimal case of almost complete irreversibility the result corresponds to that, which would be expected by using a catalyst with opposite enantioselectivity. In the following simulations (Sections 5.1 and 5.2) only this case is considered. The employment of lipases as natural catalysts for synthesis represents an

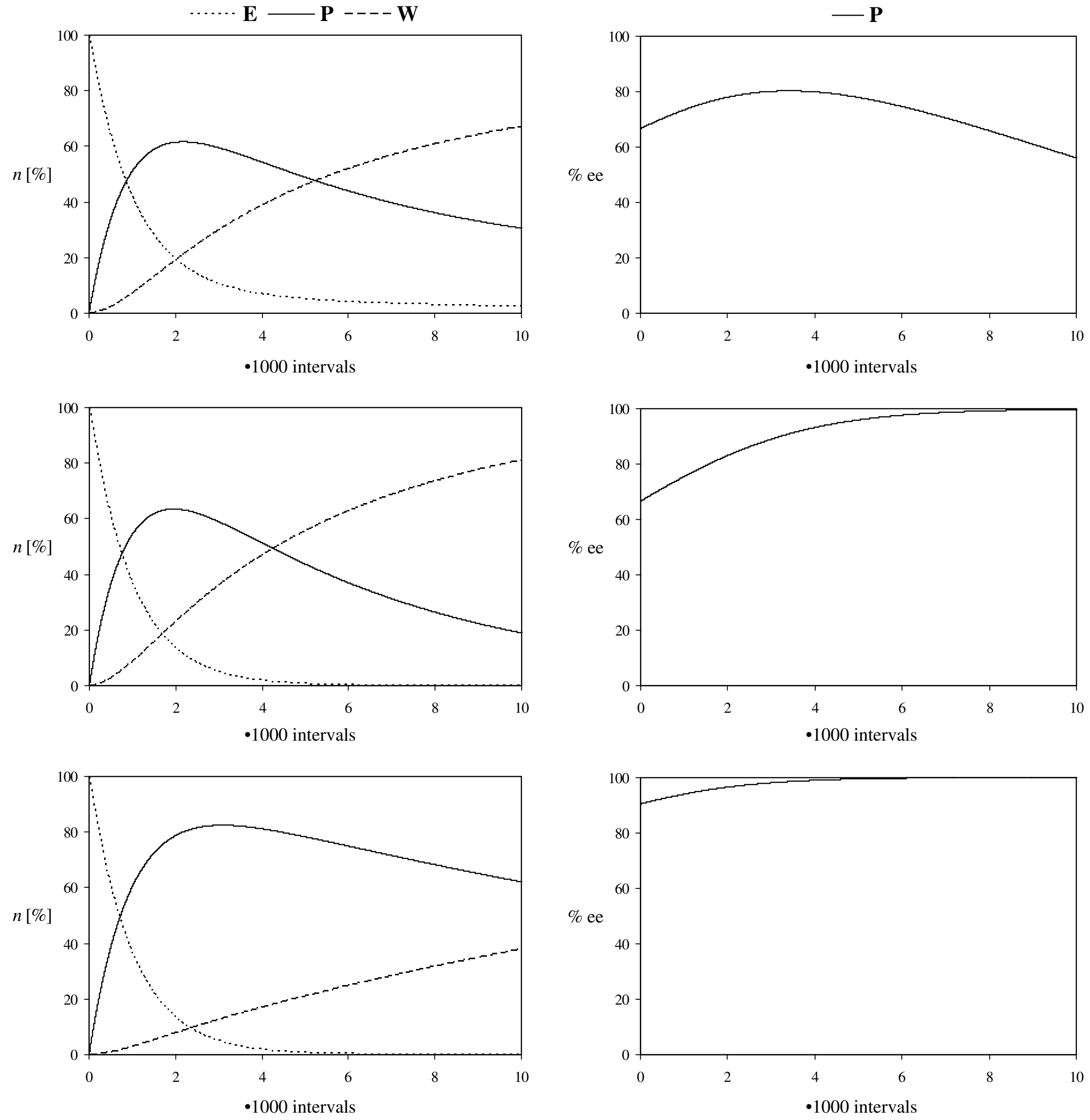


Figure 3. Simulated catalytic desymmetrization of prochiral compounds ($a = 0.002$). Left: Amount of compounds **E**, **P** and **W** (n [%]) during the progress of the reaction; right: enantiomeric excess of compounds **E** and **P** (% ee) during the progress of the reaction; top: $k_1 = 5$, $k_2 = 1$, $k_3 = 1$, $k_4 = 5$, $k_5 = 0.5$, $k_6 = 0.1$, $k_7 = 0.1$, $k_8 = 0.5$; middle: $k_1 = 5$, $k_2 = 1$, $k_3 = 1$, $k_4 = 5$, $k_5 = 0.0005$, $k_6 = 0.0001$, $k_7 = 0.0001$, $k_8 = 0.0005$; bottom: $k_1 = 20$, $k_2 = 1$, $k_3 = 1$, $k_4 = 20$, $k_5 = 0.002$, $k_6 = 0.0001$, $k_7 = 0.0001$, $k_8 = 0.002$.

example of this situation.[7] In an aqueous medium, lipases hydrolyze esters almost irreversibly to alcohols and acids, whereas in non-aqueous organic solvents, lipases catalyze the formation of esters. The corresponding reaction equilibrium is shifted quantitatively towards the ester side by employing enolesters as acylating agents. Both reactions, hydrolysis and esterification, can also be performed non-enantioselectively without a catalyst.

For catalytic kinetic resolutions and catalytic desymmetrizations of prochiral compounds, two different multistep strategies are generally possible. Either the reaction equilibria are set alternately to one and to the other side changing the direction of the catalysis (strategy A), or the catalytic reactions are always carried out in the same direction (strategy B).

5.1. Two step kinetic resolution

For the example shown in Figure 4 it is supposed that a catalyst is available, which sets the reaction equilibrium between the (*S*)-enantiomers $\mathbf{E_S}$ and $\mathbf{P_S}$ 20 times faster than that between the (*R*)-enantiomers $\mathbf{E_R}$ and $\mathbf{P_R}$ ($k_1/k_2 = k_3/k_4 = 20$) (Scheme 2). Two strategies for the synthesis of compounds with a high enantiomeric excess starting from racemate **E** are possible.

Strategy A:
At first, the catalyzed reaction is carried out from **E** in the direction of **P**. Then **E** and **P** are separated and the backward reaction is carried out with enantiomerically enriched product **P** in the direction of **E** (Fig. 4 top and middle) using the same catalyst with the same enantioselectivity.

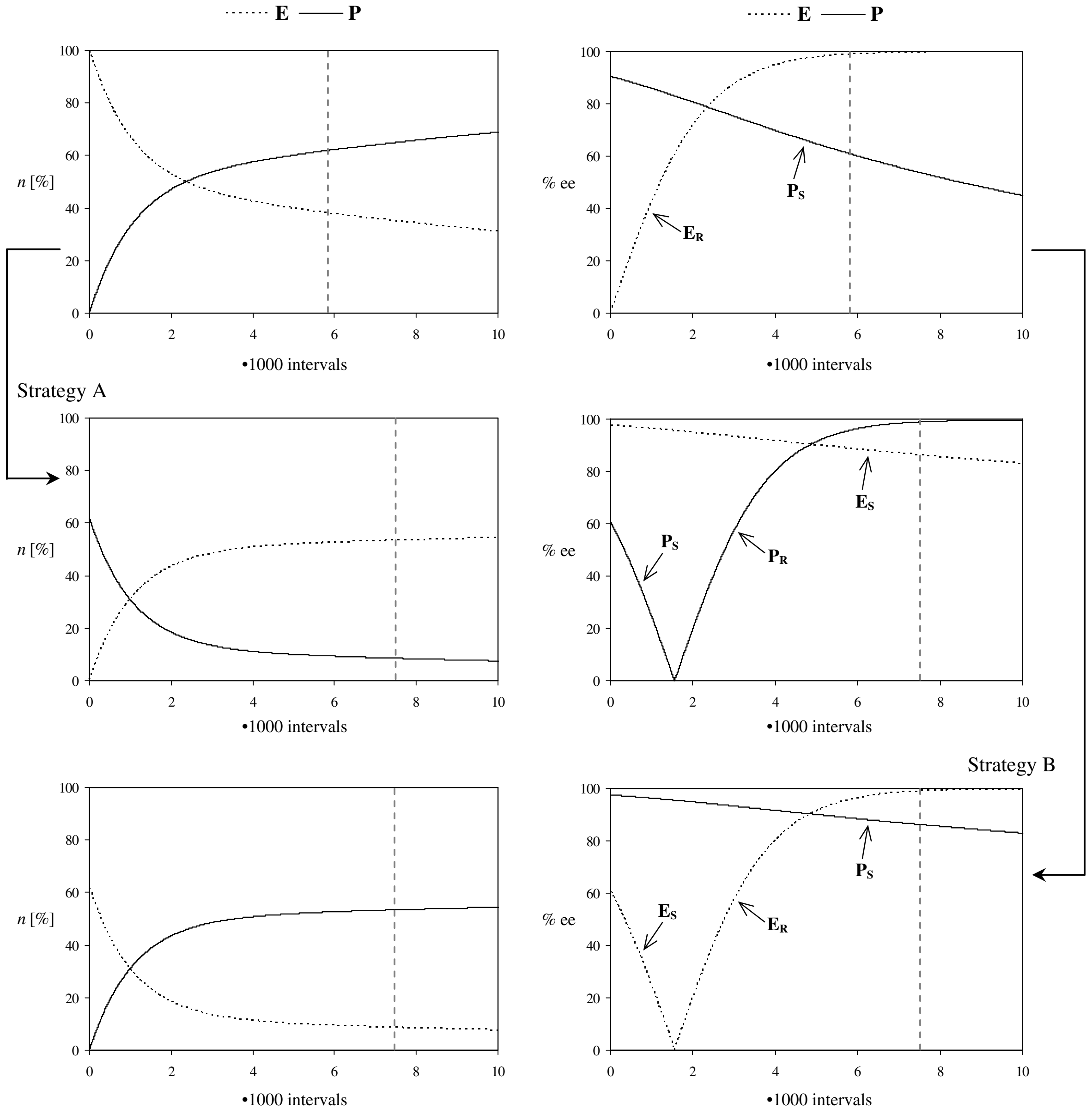


Figure 4. Two-step kinetic resolution of racemates ($a = 0.001$). The grey dotted lines indicate the time when reactions are stopped and the compounds are isolated, since one compound has reached 99.0% ee. Left: Amount of substances **E** and **P** (n [%]) during the progress of the reaction; right: enantiomeric excess of substances **E** and **P** (% ee) during the progress of the reaction; top: first catalytic conversion, $k_1 = 20$, $k_2 = 1$, $k_3 = 0.002$, $k_4 = 0.0001$; middle: *Strategy A*: second catalytic conversion of enantioenriched **P** (60.6% ee $\mathbf{P_S}$) in the reverse reaction, $k_1 = 0.002$, $k_2 = 0.0001$, $k_3 = 20$, $k_4 = 1$; bottom: *Strategy B*: second catalytic conversion of enantioenriched **E** (60.6% ee $\mathbf{E_S}$), which was obtained by the first catalytic conversion and subsequent non-enantioselective transformation of **E**, $k_1 = 20$, $k_2 = 1$, $k_3 = 0.002$, $k_4 = 0.0001$.

Strategy B:
At first, the catalyzed reaction is carried out from **E** to **P** as described in strategy A. Next, enantiomerically enriched product **P** is non-enantioselectively converted into **E** and the catalyzed reaction is repeated with enantiomerically enriched starting material **E** (Fig. 4 top and bottom).

In the examples, the transformations are stopped whenever one compound reaches an enantiomeric excess of 99.0% ee (Fig. 4 indicated by grey dotted lines). The first catalytic transformation results in 38.0% yield of $\mathbf{E_R}$ with 99.0% ee and 62.0% yield $\mathbf{P_S}$ with only 60.6% ee (Fig. 4 top and Table 1).

According to strategy A, the isolated product $\mathbf{P_S}$ is employed in the backward reaction with the same catalyst. The development of the transformation and the enantiomeric excess is shown in Figure 4, middle. It is demonstrated that product $\mathbf{P_R}$ is now produced with 99.0% ee and 8.6% yield. On the other hand 53.4% yield of $\mathbf{E_S}$ is formed with 86.2% ee. These simulations indicate that according to strategy A all four compounds $\mathbf{E_R}$, $\mathbf{E_S}$ and $\mathbf{P_R}$, $\mathbf{P_S}$ are available in an enantioenriched form (see also Table 1 top).

According to strategy B, the isolated amount (62.0%) of the enantiomerically enriched product $\mathbf{P_S}$ (60.6% ee) is

Table 1. Two-step kinetic resolution of racemates ($a = 0.001$)

	E_S		E_R		P_S		P_R	
	n (%)	% ee	n (%)	% ee	n (%)	% ee	n (%)	% ee
Strategy A	50	0	50	0				
First catalytic conversion			38.0	99.0	62.0	60.6		
Second catalytic conversion	53.4	86.2	38.0	99.0			8.6	99.0
Strategy B	50	0	50	0				
First catalytic conversion			38.0	99.0	62.0	60.6		
Second catalytic conversion			46.6	99.0	53.4	86.2		

The yields (n [%]) and % ee values are given for the times indicated by the grey dotted lines in Figure 4.
First catalytic conversion: $k_1 = 20$, $k_2 = 1$, $k_3 = 0.002$, $k_4 = 0.0001$.
Top: *Strategy A*: the second catalytic conversion is the reverse reaction with isolated **P**, $k_1 = 0.002$, $k_2 = 0.0001$, $k_3 = 20$, $k_4 = 1$.
Bottom: *Strategy B*: the second catalytic conversion is another forward reaction with recycled **E**, $k_1 = 20$, $k_2 = 1$, $k_3 = 0.002$, $k_4 = 0.0001$.

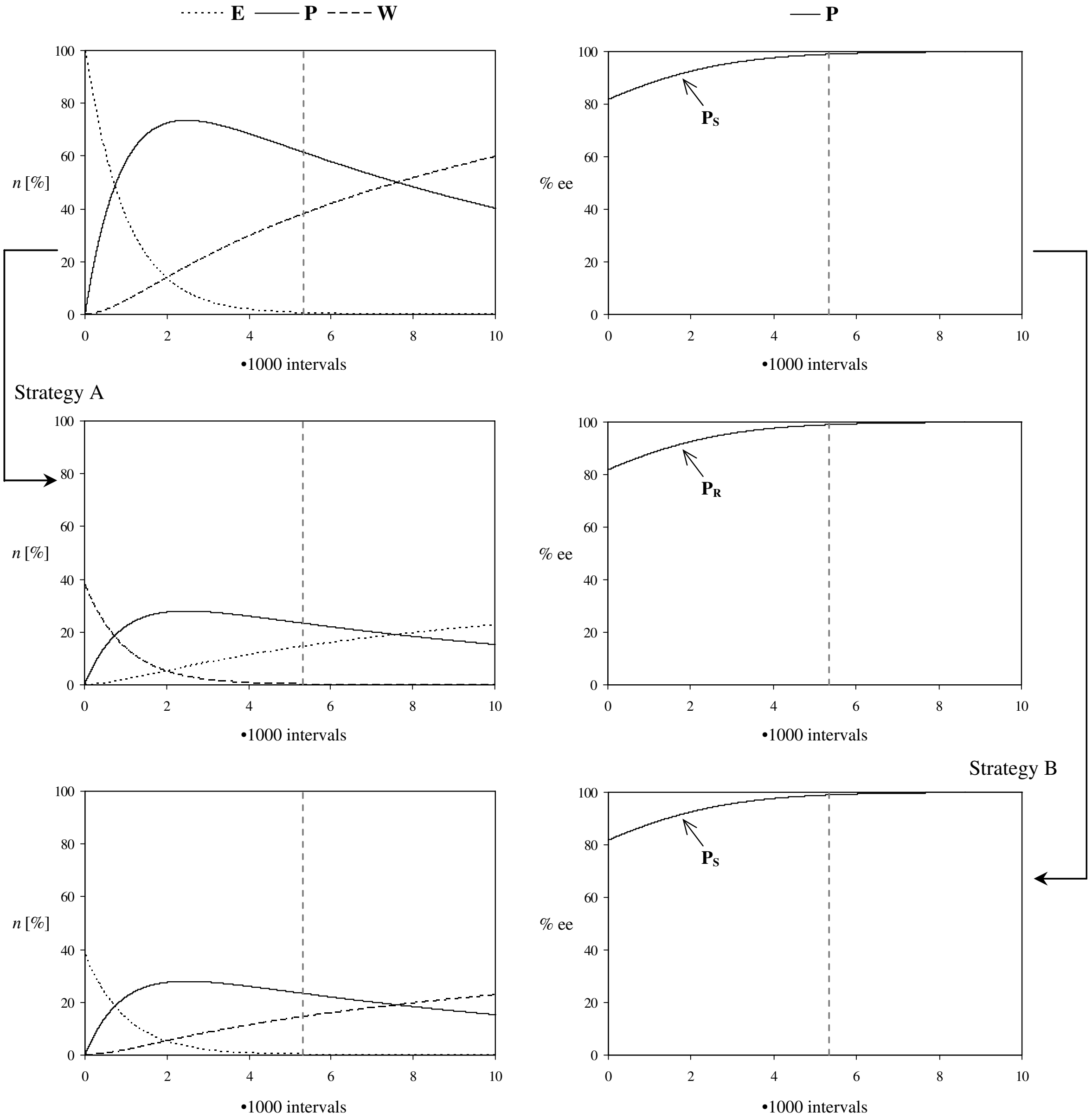


Figure 5. Two-step catalytic desymmetrization of a prochiral compound **E** ($a = 0.002$). The grey dotted lines indicate the time when reactions are stopped and the compounds are isolated, since one compound has reached 99.0% ee. Left: Amount of substances **E**, **P** and **W** (n [%]) during the progress of the reaction; right: enantiomeric excess of substance **P** (% ee) during the progress of the reaction; top: first catalytic conversion, $k_1 = 10$, $k_2 = 1$, $k_3 = 1$, $k_4 = 10$, $k_5 = 0.001$, $k_6 = 0.0001$, $k_7 = 0.0001$, $k_8 = 0.001$; middle: *Strategy A*: second catalytic conversion of produced **W** in a reverse reaction, $k_1 = 0.001$, $k_2 = 0.0001$, $k_3 = 0.0001$, $k_4 = 0.001$, $k_5 = 10$, $k_6 = 1$, $k_7 = 1$, $k_8 = 10$; bottom: *Strategy B*: second catalytic conversion of **E**, upon non-enantioselective transformation of isolated **W**, $k_1 = 10$, $k_2 = 1$, $k_3 = 1$, $k_4 = 10$, $k_5 = 0.001$, $k_6 = 0.0001$, $k_7 = 0.0001$, $k_8 = 0.001$.

Table 2. Two-step desymmetrization of a prochiral compound ($a = 0.002$)

	E	$\mathbf{P_S}$		$\mathbf{P_R}$		**W**
	n (%)	n (%)	% ee	n (%)	% ee	n (%)
Strategy A	100					
First catalytic conversion	0.5	61.5	99.0			38.0
Second catalytic conversion	15.0	61.5	99.0	23.4	99.0	0.2
Strategy B	100					
First catalytic conversion	0.5	61.5	99.0			38.0
Second catalytic conversion	0.2	85.2	99.0			14.7

The yields (n [%]) and % ee values are given for the times indicated by the grey dotted lines in Figure 5.
First catalytic conversion: $k_1 = 10$, $k_2 = 1$, $k_3 = 1$, $k_4 = 10$, $k_5 = 0.001$, $k_6 = 0.0001$, $k_7 = 0.0001$, $k_8 = 0.001$.
Top: *Strategy A*: the second catalytic conversion is the reverse reaction with isolated **W**, $k_1 = 0.001$, $k_2 = 0.0001$, $k_3 = 0.0001$, $k_4 = 0.001$, $k_5 = 10$, $k_6 = 1$, $k_7 = 1$, $k_8 = 10$.
Bottom: *Strategy B*: the second catalytic conversion is another forward reaction with recycled **E**, $k_1 = 10$, $k_2 = 1$, $k_3 = 1$, $k_4 = 10$, $k_5 = 0.001$, $k_6 = 0.0001$, $k_7 = 0.0001$, $k_8 = 0.001$.

converted non-enantioselectively into educt $\mathbf{E_S}$. The development of the following second catalytic conversion carried out with the resulting 62.0% yield of enantioenriched $\mathbf{E_S}$ (60.6% ee) is depicted in Figure 4 bottom. Whereas a further 8.6% yield of $\mathbf{E_R}$ are obtained again with 99.0% ee, product $\mathbf{P_S}$ is enantiomerically enriched to 86.2% ee (see also Table 1 bottom).

The efficiency of both strategies could even be increased by performing more than two catalytic cycles.

5.2. Two step desymmetrization

For the simulation of the two step desymmetrization a catalyst is supposed to exist, setting the equilibrium between a prochiral educt **E** and the (*S*)-configured product $\mathbf{P_S}$ faster than the equilibrium between **E** and the (*R*)-configured product $\mathbf{P_R}$. Due to its chirality this catalyst also prefers the conversions between the (*R*)-configured product $\mathbf{P_R}$ and **W** compared to those between the (*S*)-configured product $\mathbf{P_S}$ and **W**. In order to demonstrate the purpose of the simulation, the ratio of rate constants is set at 10:1 ($k_1/k_2 = k_5/k_6 = k_4/k_3 = k_8/k_7 = 10$) (Scheme 3). Educt **E** and product **P** are transformed into **P** and **W** with the same rate constants, respectively. It is assumed that the reactions are almost irreversible ($k_1/k_5 = k_2/k_6 = k_3/k_7 = k_4/k_8 = 10{,}000$). Two strategies to produce **P** with a high enantiomeric purity are possible.

Strategy A:
At first, the catalyzed reaction is carried out from **E** towards **W**. Then **E**, **P** and **W** are separated and the catalyzed reaction is carried out with isolated **W** in the direction of **E** (Fig. 5 top and middle).

Strategy B:
The reaction is carried out catalytically from **E** to **W** and **E**, **P** and **W** are isolated as detailed in strategy A. Then isolated **W** is non-enantioselectively converted into **E** and the enantioselectively catalyzed reaction is repeated with **E** (Fig. 5 top and bottom).

The simulation of the desymmetrization using the given parameters k_1 to k_8 is shown in Figure 5 (top). Stopping this first catalytic conversion after the enantiomeric excess of $\mathbf{P_S}$ has reached 99.0% ee leads to yields of 61.5% of product $\mathbf{P_S}$, 38.0% of prochiral product **W** and 0.5% of remaining prochiral educt **E** (Fig. 5 top, indicated by grey dotted lines and Table 2). These compounds are isolated and partly transformed again.

According to strategy A, isolated **W** is employed in the backward reaction with the same catalyst. The simulation of the conversion of prochiral product **W** into **P** and **E** is displayed in Figure 5 middle: The reaction is carried out under the conditions mentioned above and stopped after $\mathbf{P_R}$ reached 99.0% ee resulting in 23.4% yield of $\mathbf{P_R}$ (Fig. 5 middle, indicated by grey dotted lines). Hence, both enantiomers $\mathbf{P_S}$ and $\mathbf{P_R}$ are available in a high enantiomeric purity using this two step desymmetrization (see also Table 2 top).

According to strategy B, the isolated amount (38.0%) of prochiral product **W** is converted non-enantioselectively into educt **E**. The now available amount of educt **E** (0.5% + 38.0% = 38.5%) is transformed in a second catalytic conversion carried out under the same reaction conditions as the first one. The development of this reaction is depicted in Figure 5 bottom. This strategy provides a further amount of enantiomerically pure product $\mathbf{P_S}$ (Fig. 5 bottom, indicated by grey dotted lines), whereby the yield is increased from 61.5% to 85.2% yield (see also Table 2, bottom).

The results in Figure 5 and Table 2 clearly indicate that strategy A leads to both enantiomers $\mathbf{P_R}$ and $\mathbf{P_S}$, whereas strategy B affords a high yield of only one enantiomer. Of course, the desymmetrization of a prochiral compound can also be performed in more than two catalytic cycles. Since one desymmetrization cycle already consists of two enantioselective reaction processes anyway ($\mathbf{E} \leftrightarrow \mathbf{P} \leftrightarrow \mathbf{W}$), a multistep synthesis is usually not necessary for the improvement of the enantiomeric excess. Nevertheless, both enantiomers can be produced and the overall yield can be improved by recycling the prochiral compounds and applying multistep strategies.

6. Conclusion

Herein a very simple method for the simulation of the progress of catalyzed reactions is presented. Since the calculations are based on Microsoft® Excel an additional expensive software is not necessary. The principle of the simulations is exemplarily demonstrated with the catalytic kinetic resolution and the catalytic desymmetrization of prochiral compounds. In combination with experimental results these simulations help to find the optimal reaction conditions. In particular the optimal reaction time for stopping the transformation to obtain the desired enantiomer in a high yield and enantiomeric purity is defined by these simulations.

7. Details for the simulations

All diagrams were calculated and plotted with Microsoft® Office Excel 2003. The Excel spreadsheets are available on our group's homepage linked to www.uni-muenster.de/chemie.pz. The Excel spreadsheets are used by entering the catalyst activity into the red cell, the rate constants into the yellow cells and the amounts of starting material into the blue ones. Upon entering the values of interest, the respective diagrams are calculated and shown at once.

7.1. Programming of the Excel spreadsheets

Principle (Fig. 1): *Text cells:* A24 *a*; C24 k_1; D24 k_2; C27 *d*; D27 *e*; A34 Intervals; B34 *n*(**E**) [%]; C34 *n*(**P**) [%]; L34 Int./1000; *Input cells:* A25 Value for *a*; C25 Value for k_1; D25 Value for k_2; B35 Value for *n*(**E**) [%]; C35 Value for *n*(**P**) [%]; *Calculation cells:* C28 = C25/(C25 + D25); D28 = D25/(C25 + D25); A36 = A35 + 1 to A10035 = A10034 + 1; B36 = B35 + (−B35 ∗ \$C\$28 + C35 ∗ \$D\$28) ∗ \$A\$25 to B10035 = B10034 + (−B10034 ∗ \$C\$28 + C10034 ∗ \$D\$28) ∗ \$A\$25; C36 = C35 + (B35 ∗ \$C\$28 − C35 ∗ \$D\$28) ∗ \$A\$25 to C10035 = C10034 + (B10034 ∗ \$C\$28 − C10034 ∗ \$D\$28) ∗ \$A\$25; L35 = A35/1000 to L10035 = A10035/1000; *Diagram:* Rectangle: A1 F1 A22 F22; Axes: X '· 1000 Intervals' 0–10 Y '*n* (%)' 0–100; Data rows: Name 'E' X-Values = Table 1!\$L\$35:\$L\$10035 Y-Values = Table 1!\$B\$35:\$B\$10035 Name 'P' X-Values = Table 1!\$L\$35:\$L\$10035 Y-Values = Table 1!\$C\$35:\$C\$10035.

Kinetic resolution (Figs. 2 and 3): *Text cells:* A24 *a*; C24 k_1; D24 k_2; E24 k_3; F24 k_4; C27 *d*; D27 *e*; E27 *f*; F27 *g*; H27 *h*; I27 *m*; A34 Intervals; B34 *n*(**ES**) [%]; C34 *n*(**ER**) [%]; D34 *n*(**E**) [%]; E34 %ee(**E**); G34 *n*(**PS**) [%]; H34 *n*(**PR**) [%]; I34 *n*(**P**) [%]; J34 %ee(**E**); L34 Int./1000; *Input cells:* A25 Value for *a*; C25 Value for k_1; D25 Value for k_2; E25 Value for k_3; F25 Value for k_4; B35 Value for *n*(**ES**) [%]; C35 Value for *n*(**ER**) [%]; G35 Value for *n*(**PS**) [%]; H35 Value for *n*(**PR**) [%]; *Calculation cells:* C28 = C25/(C25 + D25); D28 = D25/(C25 + D25); E28 = E25/(E25 + F25); F28 = F25/(E25 + F25); H28 = (C25 + D25)/(C25 + D25 + E25 + F25); I28 = (E25 + F25)/(C25 + D25 + E25 + F25); A36 = A35 + 1 to A10035 = A10034 + 1; B36 = B35 + (−B35 ∗ \$C\$28 ∗ \$H\$28 + G35 ∗ \$E\$28 ∗ \$I\$28) ∗ \$A\$25 to B10035 = B10034 + (−B10034 ∗ \$C\$28 ∗ \$H\$28 + G10034 ∗ \$E\$28 ∗ \$I\$28) ∗ \$A\$25; C36 = C35 + (−C35 ∗ \$D\$28 ∗ \$H\$28 + H35 ∗ \$F\$28 ∗ \$I\$28) ∗ \$A\$25 to C10035 = C10034 + (−C10034 ∗ \$D\$28 ∗ \$H\$28 + H10034 ∗ \$F\$28 ∗ \$I\$28) ∗ \$A\$25; D36 = B36 + C36 to D10035 = B10035 + C10035; E36 = ABS((C36/D36 − B36/D36) ∗ 100) to E10035 = ABS((C10035/D10035 − B10035/D10035) ∗ 100); G36 = G35 + (B35 ∗ \$C\$28 ∗ \$H\$28 − G35 ∗ \$E\$28 ∗ \$I\$28) ∗ \$A\$25 to G10035 = G10034 + (B10034 ∗ \$C\$28 ∗ \$H\$28 − G10034 ∗ \$E\$28 ∗ \$I\$28) ∗ \$A\$25; H36 = H35 + (C35 ∗ \$D\$28 ∗ \$H\$28 − H35 ∗ \$F\$28 ∗ \$I\$28) ∗ \$A\$25 to H10035 = H10034 + (C10034 ∗ \$D\$28 ∗ \$H\$28 − H10034 ∗ \$F\$28 ∗ \$I\$28) ∗ \$A\$25; I35 = G35 + H35 to I10035 = G10035 + H10035; J36 = ABS((G36/I36 − H36/I36) ∗ 100) to J10035 = ABS((G10035/I10035 − H10035/I10035) ∗ 100); L35 = A35/1000 to L10035 = A10035/1000; *Diagram1:* Rectangle: A1 F1 A22 F22; Axes: X '· 1000 Intervals' 0–10 Y '*n* (%)' 0–100; Data rows: Name 'E' X-Values = Table 1!\$L\$35:\$L\$10035 Y-Values = Table 1!\$D\$35:\$D\$10035 Name 'P' X-Values = Table 1!\$L\$35:\$L\$10035 Y-Values = Table 1!\$I\$35:\$I\$10035; *Diagram2:* Rectangle: G1 L1 G22 L22; Axes: X '· 1000 Intervals' 0–10 Y '%ee' 0–100; Data rows: Name 'E' X-Values = Table 1!\$L\$35:\$L\$10035 Y-Values = Table 1!\$E\$35:\$E\$10035 Name 'P' X-Values = Table 1!\$L\$35:\$L\$10035 Y-Values = Table 1!\$J\$35:\$J\$10035.

Desymmetrization (Figs. 4 and 5): *Text cells:* A24 *a*; C24 k_1; D24 k_2; E24 k_3; F24 k_4; H24 k_5; I24 k_6; J24 k_7; K24 k_8; C27 *d*; D27 *e*; E27 *f*; F27 *g*; H27 *h*; I27 *m*; C30 *o*; D30 *p*; E30 *q*; F30 *r*; H30 *u*; I30 *v*; K30 *x*; L30 *y*; A34 Intervals; B34 *n*(**E**) [%]; C34 *n*(**PS**) [%]; D34 *n*(**PR**) [%]; E34 *n*(**W**) [%]; G34 *n*(**P**) [%]; H34 %ee (**P**); L34 Int./1000; *Input cells:* A25 Value for *a*; C25 Value for k_1; D25 Value for k_2; E25 Value for k_3; F25 Value for k_4; H25 Value for k_5; I25 Value for k_6; J25 Value for k_7; K25 Value for k_8; B35 Value for *n*(**E**) [%]; C35 Value for *n*(**PS**) [%]; D35 Value for *n*(**PR**) [%]; E35 Value for *n*(**W**) [%]; *Calculation cells:* C28 = C25/(C25 + D25); D28 = D25/(C25 + D25); E28 = E25/(E25 + F25); F28 = F25/(E25 + F25); H28 = (C25 + D25)/(C25 + D25 + E25 + F25); I28 = (E25 + F25)/(C25 + D25 + E25 + F25); C31 = H25/(H25 + I25); D31 = I25/(H25 + I25); E31 = J25/(J25 + K25); F31 = K25/(J25 + K25); H31 = (H25 + I25)/(H25 + I25 + J25 + K25); I31 = (J25 + K25)/(H25 + I25 + J25 + K25); K31 = (C25 + D25 + E25 + F25)/(C25 + D25 + E25 + F25 + H25 + I25 + J25 + K25); L31 = (H25 + I25 + J25 + K25)/(C25 + D25 + E25 + F25 + H25 + I25 + J25 + K25); A36 = A35 + 1 to A10035 = A10034 + 1; B36 = B35 + (−B35 ∗ \$C\$28 ∗ \$H\$28 ∗ \$K\$31 − B35 ∗ \$D\$28 ∗ \$H\$28 ∗ \$K\$31 + C35 ∗ \$C\$31 ∗ \$H\$31 ∗ \$L\$31 + D35 ∗ \$D\$31 ∗ \$H\$31 ∗ \$L\$31) ∗ \$A\$25 to B10035 = B10034 + (−B10034 ∗ \$C\$28 ∗ \$H\$28 ∗ \$K\$31 − B10034 ∗ \$D\$28 ∗ \$H\$28 ∗ \$K\$31 + C10034 ∗ \$C\$31 ∗ \$H\$31 ∗ \$L\$31 + D10034 ∗ \$D\$31 ∗ \$H\$31 ∗ \$L\$31) ∗ \$A\$25; C36 = C35 + (B35 ∗ \$C\$28 ∗ \$H\$28 ∗ \$K\$31 − C35 ∗ \$E\$28 ∗ \$I\$28 ∗ \$K\$31 − C35 ∗ \$C\$31 ∗ \$H\$31 ∗ \$L\$31 + E35 ∗ \$E\$31 ∗ \$I\$31 ∗ \$L\$31) ∗ \$A\$25 to C10035 = C10034 + (B10034 ∗ \$C\$28 ∗ \$H\$28 ∗ \$K\$31 − C10034 ∗ \$E\$28 ∗ \$I\$28 ∗ \$K\$31 − C10034 ∗ \$C\$31 ∗ \$H\$31 ∗ \$L\$31 + E10034 ∗ \$E\$31 ∗ \$I\$31 ∗ \$L\$31) ∗ \$A\$25; D36 = D35 + (B35 ∗ \$D\$28 ∗ \$H\$28 ∗ \$K\$31 − D35 ∗ \$F\$28 ∗ \$I\$28 ∗ \$K\$31 − D35 ∗ \$D\$31 ∗ \$H\$31 ∗ \$L\$31 + E35 ∗ \$F\$31 ∗ \$I\$31 ∗ \$L\$31) ∗ \$A\$25 to D10035 = D10034 + (B10034 ∗ \$D\$28 ∗ \$H\$28 ∗ \$K\$31 − D10034 ∗ \$F\$28 ∗

$I$28 * $K$31 − D10034 * $D$31 * $H$31 * $L$31 + E10034 * $F$31 * $I$31 * $L$31) * $A$25; E36 = E35 + (C35 * $E$28 * $I$28 * $K$31 + D35 * $F$28 * $I$28 * $K$31 − E35 * $E$31 * $I$31 * $L$31 − E35 * $F$31 * $I$31 * $L$31) * $A$25 to E10035 = E10034 + (C10034 * $E$28 * $I$28 * $K$31 + D10034 * $F$28 * $I$28 * $K$31 − E10034 * $E$31 * $I$31 * $L$31 − E10034 * $F$31 * $I$31 * $L$31) * $A$25; G35 = C35 + D35 to G10035 = C10035 + D10035; H36 = ABS((C36/G36 − D36/G36) * 100) to H10035 = ABS((C10035/G10035 − D10035/G10035) * 100); L35 = A35/1000 to L10035 = A10035/1000 *Diagram1:* Rectangle: A1 F1 A22 F22; Axes: X ‘ · 1000 Intervals’ 0–10 Y ‘*n* (%)’ 0–100; Data rows: Name ‘E’ X-Values = Table 1!$L$35:$L$10035 Y-Values = Table 1!$B$35:$B$10035 Name ‘P’ X-Values = Table 1!$L$35:$L$10035 Y-Values = Table 1!$G$35:$G$10035 Name ‘W’ X-Values = Table 1!$L$35:$L$10035 Y-Values = Table 1!$E$35:$E$10035; *Diagram2:* Rectangle: G1 L1 G22 L22; Axes: X ‘ · 1000 Intervals’ 0–10 Y ‘%ee’ 0–100 Data rows: Name ‘P’ X-Values = Table 1!$L$35:$L$10035 Y-Values = Table 1!$H$35:$H$10035.

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