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1
Introduction: A Survey of How and Why to Separate Enantiomers

Matthew Todd

This book is about the separation of enantiomers by synthetic methods, which is to say methods involving some chemical transformation as part of the separation process. We do not in this book cover chromatographic methods for the separation of enantiomers [1]. Nor do we focus on methods based on crystallizations as these have been amply reviewed elsewhere (see below). We are concerned mainly therefore with resolutions that involve a synthetic component, so mostly with the various flavours of kinetic resolutions through to more modern methods such as divergent reactions of a racemic mixture (DRRM). This introduction briefly clarifies the scope of the book.

The reasons such methods are of continued importance are threefold:

1) *Society: the need for enantiopure compounds.* New molecules as single enantiomers are important to our continued well-being because they are the feedstocks of new medicines, agrochemicals, fragrances and other features of modern society in a chiral world. Of the 205 new molecular entities approved as drugs between 2001 and 2010, 63% were single enantiomers [2]. Nature provides an abundance of enantiopure compounds, but we seek, and need, to exceed this by obtaining useful unnatural molecules as single enantiomers, and we may reasonably want to access both enantiomers of some compounds.
2) *Academia: the basic science involved in the behaviour of chiral compounds.* If we seek the state of the art in our discipline, we cannot help but think that rapid and selective chemical distinction between enantiomers, which results in their facile separation, is something beautiful in itself. There have been many successful methods developed for the synthetic separation of enantiomers, as we shall see, and these are both *de facto* interesting and instructive to consider for the design of future examples of such processes. The relationship between kinetic resolution and asymmetric catalysis is strong, and one can inform the design of the other. It is hoped that the diverse examples described in this book stimulate thoughts in the reader of what is possible next.
3) *Industry: the need for new methods.* There remain many classes of compounds that still cannot be resolved, or where efficiencies are too low for widespread

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adoption. It is still the case that classical resolution techniques are overwhelmingly used over other more complex methods. Of the 128 drug candidate molecules assessed in a recent industry survey, half were being developed as single enantiomers, and the sources of the stereocentres were mainly the chiral pool (55%) with resolution (28%) and asymmetric synthesis (10%) responsible for fewer examples [3]. This is, predictably, a feature of economics as much as science and one must not be too quick to judge new fields like asymmetric catalysis versus older ones like classical resolution. Pasteur added something enantiopure to a racemate in 1853 [4], whereas the catalytic prowess of a metal centre surrounded by chiral ligands was first demonstrated only in 1968 [5]. In addition, many chiral acids and bases have proven to be useful in classical resolutions, while Nature does not seem to be so generous in its supply of molecules that can effect catalytic, asymmetric transformations. The great progress made in synthetic chemistry has not (yet) brought us to the position that allows us to make any enantiopure substance in quantity given that resources are always limited. That leaves us with the synthesis of a racemate from which we pick one enantiomer out. Such a process can be remarkably efficient and cost-effective, if such tools are available, but the great successes described in this book should not hide the fact that we require better separation methods with wide applicability if we are to avoid an overreliance on just using whatever Nature provides.

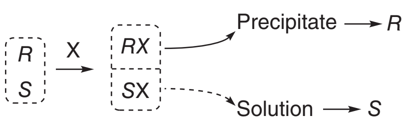
The various methods considered in this book may be classified as follows.

1.1 Classical Methods

A racemate can be resolved with ease if it happens that the enantiomers form separate crystals – a so-called conglomerate. It becomes possible to separate, physically, the enantiomorphic crystals – a process sometimes referred to as *triage*. This is what Pasteur famously achieved in 1848 with a sample of ammonium sodium tartrate [6]. Such good fortune is quite rare and is in any case not a 'synthetic method' in the strictest sense (nor is it practical on a large scale). Other physical processes (alone, without any attendant synthetic process) such as evaporation or sublimation can be used to increase the enantiomeric excess of organic compounds, including amino acids [7].

Another important but non-synthetic method involves harvesting crops of enantioenriched crystals by seeding a supersaturated racemate and is known as *resolution by entrainment*, or *preferential crystallization*. These approaches have been well reviewed and will not be covered here [8]. Rare (but spectacular) examples where crystallizations of conglomerates are observed combined with racemization events in solution, leading to *total spontaneous resolutions* [9], are briefly mentioned in Chapter 7 as there have been interesting recent developments on that front. Included therein are special cases where diastereomeric interactions in solution combined with racemization may yield more than a 50% yield of one enantiomer, often known as a *deracemization*. Racemization is treated as a synthetic process of sorts, but we essentially stop short of processes where stereochemistry is created from prochiral intermediates since such a subject is formally the province of asymmetric catalysis. We will not be covering separations based on physical partitioning of enantiomers using, for example, chiral solvents, macrocycles or membranes [10].

Clearly the best-known non-chromatographic method for the separation of enantiomers, the so-called classical resolution, involves combination of a racemate and an enantiopure compound to form diastereomers that can be separated based on physical properties and the enantiomerically pure compound re-isolated (Scheme 1.1).



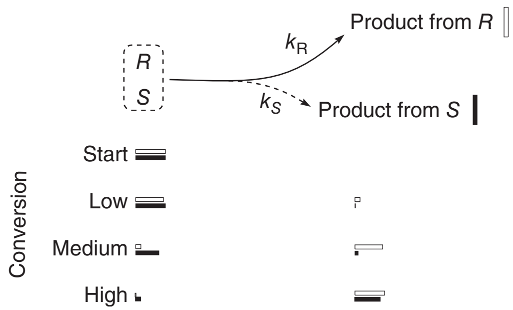
Scheme 1.1 The classical resolution: the separation of intermediate diastereomers differing in their physical properties.

The process is subtle and complex, belying its apparent simplicity on paper. My own experience with obtaining an important drug as a single enantiomer was instructive, and the process was publicly laid out over time as the project was carried out in an open source manner, meaning anyone could contribute to the solution and alter the direction of the research [11]. The project began with an assessment of a number of catalytic, asymmetric synthetic methods but feedback from the community was heavily in favour of moving to a search for a resolution, partly because the drug was needed for a low price. Sure enough a resolution was the solution. Sensitivity to conditions was illustrated by the eventual switch from one resolving agent to another – the structural difference was merely the substitution of the resolving agent's methoxy group for a hydrogen atom – resulting in the opposite enantiomer of the desired compound being isolated in the solid. This important and endlessly surprising area of organic chemistry, now including the so-called Dutch resolution approach of using mixtures of resolving agents, has been widely reviewed [12].

1.2
Kinetic Resolution ('KR')

A conceptually simple and well-known method for the separation of enantiomers is the kinetic resolution. A racemate is subjected to some reaction using a chiral agent and one of the enantiomers of the racemate reacts more quickly than the other (Scheme 1.2). The 'selectivity factor', *s*, is an expression of the difference in the rates of the two reactions.

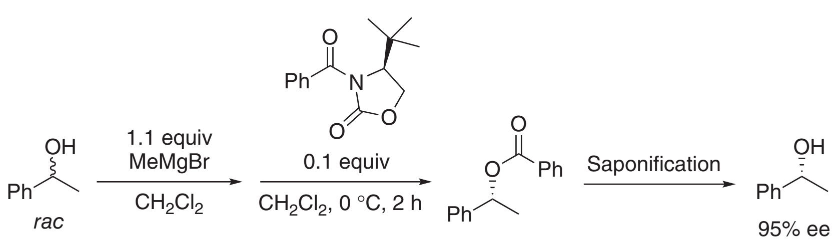
The enantiomer ratio is shown using a formalism borrowed from Ed Vedejs in Chapter 6. As can be seen, the composition varies dynamically as the reaction



Scheme 1.2 Generic kinetic resolution showing the ratio of enantiomers with conversion.

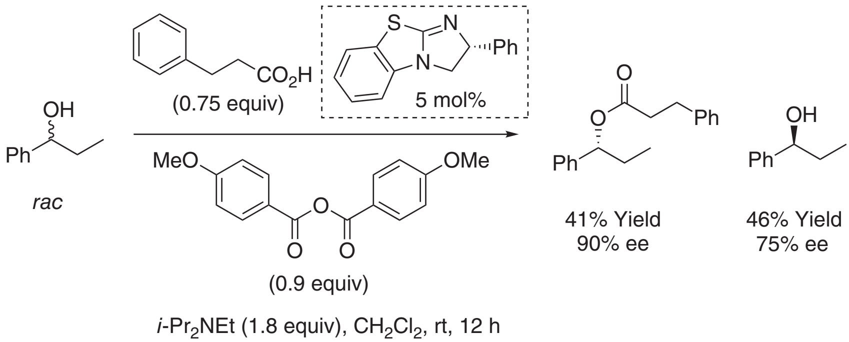
proceeds. At the outset, the system displays its best synthetic selectivity between the enantiomers because an equal amount of each enantiomer is present. As the reaction proceeds, statistics begins to interfere as the fast-reacting enantiomer is depleted. Success is a curse – as the fast-reacting enantiomer concentration reduces it becomes difficult to stop the slow-reacting enantiomer from participating – a 'mass action' problem. This explains the two best-known features of kinetic resolutions – that the maximum yield for the process is necessarily 50%, but that high enantiomeric excesses are found at the extremes of conversion – that is, that the enantioenrichment of the product (whatever that may be) is largest at the start of the reaction while the enantiomeric excess of the starting material left behind is largest just before the end of the reaction. In a kinetic resolution, one cannot usually have one's cake (high enantiomeric excess) and eat it (high yield).

A simple approach to kinetic resolution is to use a stoichiometric *reagent*. In the example shown in Scheme 1.3, an enantioenriched alcohol is obtained from a racemate through the addition of an enantiopure-acylating agent [13]. If 1 equivalent of the reagent were used, a 1 : 1 mixture of diastereomers would result with no kinetic differentiation. Stoichiometric kinetic resolutions thus necessarily employ a sub-stoichiometric amount of the reagent – in the example shown only 0.1 equivalents is used. This method for the separation of enantiomers is described in detail by Maddani, Fiaud and Kagan in Chapter 2.



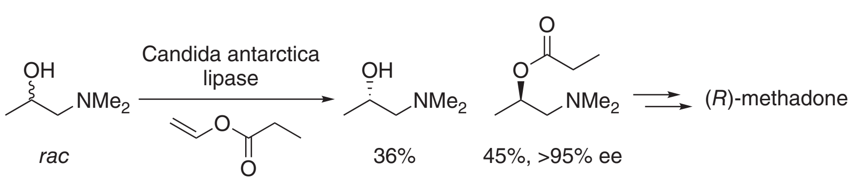
Scheme 1.3 Example of a stoichiometric kinetic resolution: preparation of an enantioenriched alcohol through the addition of an enantiopure-acylating agent.

The obvious alternative is to use a chiral *catalyst* to effect some reaction on the racemate. Frequently, the reaction does not introduce a new stereocentre, and a typical example is shown in Scheme 1.4. This process, developed by Birman, involves an acylation of an alcohol effected by a catalytic quantity of an enantiopure nucleophilic catalyst [14]. Catalytic methods are covered by Hélène Pellissier in Chapter 3.



Scheme 1.4 Example of a catalytic kinetic resolution of a racemic alcohol.

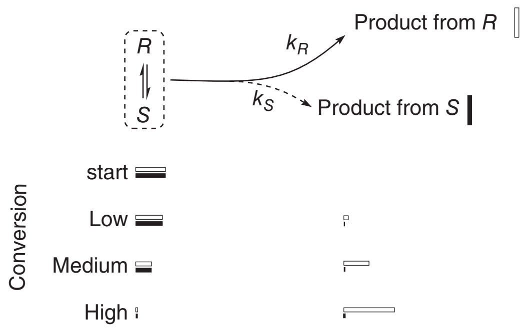
The catalyst can be an enzyme, and some of the most impressive examples have been of this type. In the example shown in Scheme 1.5, a lipase acts on a kilogram of the racemic starting material to generate enantioenriched products that may be separated by distillation after filtration of the enzyme from the reaction mixture [15]. The use of enzymes in kinetic resolutions is covered by Humphrey, Ghanem and Turner in Chapter 4.



Scheme 1.5 Example of catalytic kinetic resolution effected by an enzyme.

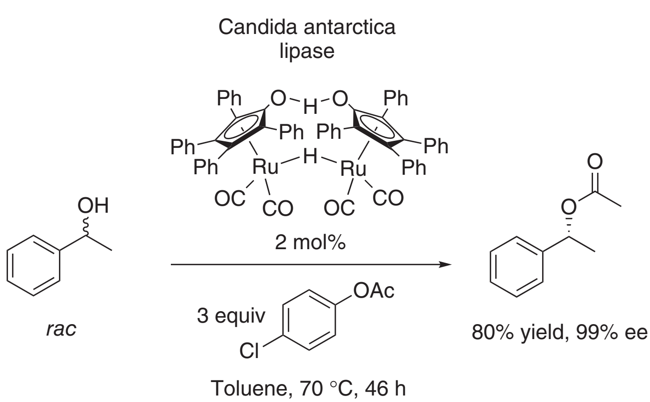
1.3
Dynamic Kinetic Resolution ('DKR')

Kinetic and classical resolutions both suffer from the weakness that the maximum yield of a product is 50%. This limit is removed if the enantiomers of the starting material can be interconverted (Scheme 1.6). The challenge is significant – to run a kinetic resolution in the forward direction and a simultaneous racemization of the starting materials that leaves any compound derived from the starting materials unaffected. The racemization needs to be rapid with respect to the asymmetric transformation, to prevent build-up of the slow-reacting enantiomer.



Scheme 1.6 Generic dynamic kinetic resolution showing the ratio of enantiomers with conversion.

This seemingly insurmountable task has been solved, with several impressive systems having been demonstrated to date, although the number of cases is far lower than those for regular kinetic resolutions. In the example shown in Scheme 1.7, the kinetic resolution of secondary alcohols is achieved with a lipase while the racemization is effected by a ruthenium complex [16]. This example illustrates well the striking effectiveness of two orthogonal chemical processes that might a priori be expected to interfere with each other. Dynamic kinetic resolutions (DKRs) are reviewed by Nakano and Masato Kitamura in Chapter 5. The chapter also includes a description of rarer processes that are frequently confused with DKR but which are mechanistically distinct [17], such as the dynamic kinetic asymmetric transformation (DYKAT); the similarity is that DYKAT and DKR achieve complete conversion of a racemate to one enantioenriched product but the DYKAT product is typically not convertible back to starting material (needed for a separation of

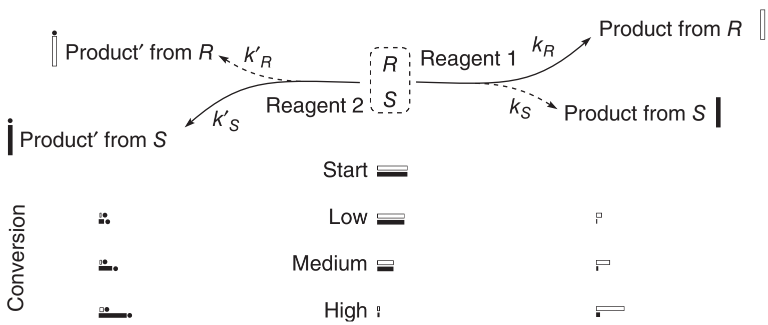


Scheme 1.7 Example of dynamic kinetic resolution.

enantiomers) and involves an intermediate that is chiral, unlike a true DKR that proceeds via an achiral intermediate. Some of these distinctions are covered also in Chapter 7. The role of enzymes in DKR processes is covered also in Chapter 4.

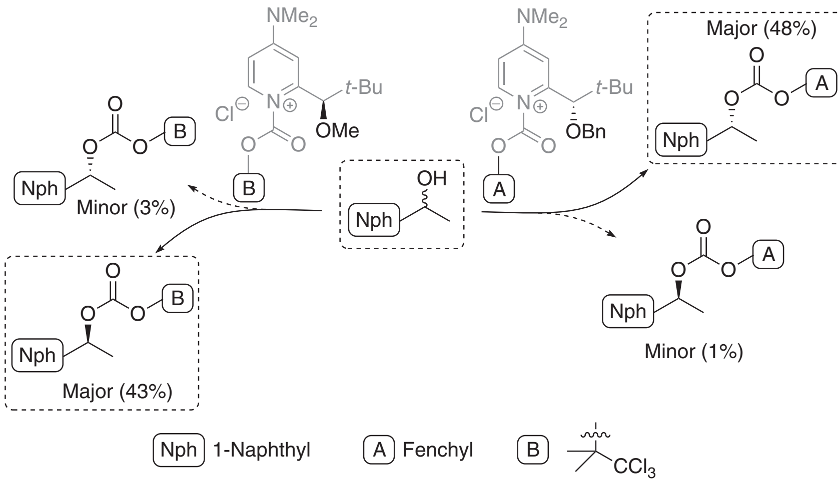
1.4 Divergent Reactions of a Racemic Mixture ('DRRM')

The essential weakness of a simple kinetic resolution is the build-up of the slow-reacting enantiomer of the starting material, a process that may be solved by DKR. There is another solution – to have the slow-reacting enantiomer be consumed by another reaction, to give a second product that may be separated from the first. In other words, to have the enantiomers give distinct (enantioenriched but not enantiomeric) products at similar rates (Scheme 1.8) – known as a *divergent reaction of a racemic mixture*. As for the DKR process, the starting material ideally remains as a racemate throughout, in which case the maximum yield of any given product is 50%. Strictly speaking for the process to be called a *resolution*, there must be a means of separating the products and converting them back to the enantiopure starting materials. The term *DRRM* encompasses processes that involve the addition of one or two chiral reagents to a racemate. The concept is well illustrated by the latter, involving addition of two chiral reagents to a racemate as shown; this subclass of DRRM is frequently referred to as *parallel kinetic resolution* (*PKR*).



Scheme 1.8 Generic divergent reaction of a racemic mixture (note that the *product* from *R* is not the enantiomer of the *product* from *S*).

The specific example shown (Scheme 1.9) involves two pseudo-enantiomeric reagents [18]. One of the reagents reacts rapidly with the (*R*)-enantiomer of the starting alcohol while the other reacts preferentially with the (*S*)-enantiomer. Although a kinetic resolution of the racemate would be possible with either reagent alone, the mass action problem would mean that the reagent's selectivity would need to be very high to match the yield and enantiomeric excess values obtained from the DRRM. This process was discovered by Ed Vedejs, who reviews the field in Chapter 6.

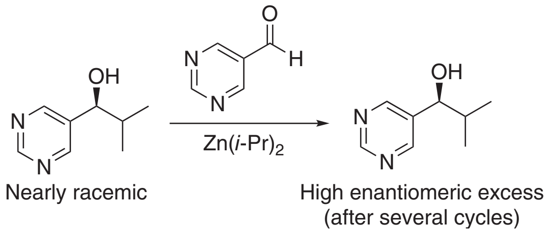


Scheme 1.9 Example of a divergent reaction of a racemic mixture.

1.5 Other Methods

At the end of this book, I summarize a small number of 'neglected' cases not covered elsewhere, such as the use of circularly polarized light, polymerizations, 'ripening' processes, dynamic combinatorial chemistry and even several thermodynamic processes. In some of these cases, the potential for future significance in the synthetic separation of enantiomers is clear but the fields are not yet mature because the methods are young, exhibit recurrent issues, or have been developed for other reasons – in the case of polymerizations the eye of the polymer chemist is typically on the polymer, not on any enantiomeric excess that might be contained in the residual solution. This chapter is a little unusual – it appears that these disparate methods have never previously been collected together; the separate fields typically do not cite each other despite their ultimately sharing a common theme.

One striking example mentioned in this final chapter requires us to bend the term *racemate* to include 'very near racemates' that contain a very small enantiomeric excess. Enrichment of such samples by direct crystallization-based methods would typically only be attempted by committed optimists. In such a situation, we could synthesize more of the excess enantiomer preferentially if we had an appropriately asymmetric autocatalytic reaction – our initial excess enantiomer could replicate at the expense of the other. Preparatively, this is the effective separation of the enantiomers we used at the outset. Such a system has its physical realization in the Soai autocatalysis in which a very small enantiomeric excess of a pyrimidyl alcohol is amplified over several cycles to give an almost enantiopure sample of the alcohol (Scheme 1.10) [19].



Scheme 1.10 The Soai reaction that achieves a form of synthetic separation of enantiomers through selective autocatalysis.

These and other processes are not by any means widespread or generalizable, and they have not yet had an impact on the industrial preparation of enantiopure compounds, but are included as suggestions of where the vibrant and important field of the synthetic separation of enantiomers might go next. Some of these methods also remind us of the 'prototypical' synthetic separation of enantiomers that may have played a role in the origin of life.

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2
Stoichiometric Kinetic Resolution Reactions

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2.1
Introduction

The resolution of a racemic mixture is a basic process, which was discovered by Pasteur in 1848 by the manual separation of the 1 : 1 mixture of enantiomeric crystals of racemic ammonium sodium tartrate [1]. Later Pasteur discovered the resolution of a racemic mixture by the temporary combination with a chiral auxiliary followed by the separation of diastereomers [2]. It was again Pasteur who found that racemic ammonium tartrate in aqueous solution was half-destroyed by *penicillium glaucum* mould, allowing the preparation of 'unnatural' (−)-tartaric acid for the first time [3]. Enzymatic kinetic resolutions (KRs) rapidly became the preferred method to isolate enantioenriched compounds from a racemic mixture, and remained so for many years (see Chapter 4). The first non-enzymatic KR occurred in 1899, when Marckwald and McKenzie [4] realized the partial esterification of racemic mandelic acid by (−)-menthol, releasing a slightly enantioenriched (−)-mandelic acid. (−)-Borneol was also used in a similar reaction [5]. Several examples of KR (in homogeneous conditions) of alcohols or amines by chiral acylating agents were subsequently described. In those days, the isolation and purification of end products were tedious, sometimes with contamination by chiral impurities. Moreover, measurement of the enantiomeric composition was always based on polarimetric measurements (hence the obsolete expression 'optical purity'). Consequently, some reports on KRs until the end of 1960s needed to be considered with caution. Bredig and Fajans [6, 7] were the first to do a detailed kinetic study on the example of partial asymmetric decarboxylation of camphorcarboxylic acid mediated by some alkaloids. Another early kinetic treatment was described by Kuhn [8] during his investigations of photodecomposition of racemic *N,N*'-dimethyl-α-azidopropionamide with circularly polarized light.

We published in 1988 an extended review article on the basis of KR and the main results [9]. A chapter is devoted to KR in the stereochemistry textbook by Eliel *et al*. [10]. Some recent reviews are available on various aspects of non-enzymatic KR [11], for example, practical considerations [12], metal-catalyzed KR processes (Chapter 3) [13], dynamic KR (Chapter 5) [14, 15], parallel KR

Separation of Enantiomers: Synthetic Methods, First Edition. Edited by Matthew Todd.

reactions (Chapter 6) [16, 17] or on various aspects of enantiodivergent reactions (Chapter 6) [18].

This chapter focuses on stoichiometric KR reactions. In Section 2.2, the main kinetic treatments are discussed. In Section 2.3, some examples of the use of chiral reagents in KR are presented. In Sections 2.4 and 2.5, the cases of enantiodivergent and enantioconvergent reactions are discussed. The KR of diastereomers is kinetically similar to KR of enantiomers and is briefly presented in Section 2.6. Finally, some examples of applications of KR are collected in Section 2.7.

2.2 Kinetic Treatment

The expression 'KR' emphasizes that the racemic mixture undergoes a separation under a chiral influence in a kinetically controlled process. In principle, the word 'resolution' refers to the isolation of one of the enantiomers of racemic mixture after a partial transformation of the initial mixture. If the reaction product is chiral, as in the esterification of a racemic alcohol, then the KR will afford a product with some enantiomeric excess. The full transformation of a racemic mixture by coupling with a chiral auxiliary will give a 1 : 1 mixture of diastereomers and is not considered as a KR process, unless the reaction is stopped at an intermediate stage, leaving some enantioenriched starting material.

In an enantioselective reaction, such as an asymmetric hydrogenation of a ketone, the enantiomeric excess of the chiral product (ee_{prod}) is generally constant with conversion. This is not true in a KR, where enantiomeric excess of the recovered starting material (ee_{sm}) and enantiomeric excess of the product (ee_{prod}) change with conversion extent. These points are discussed on a quantitative basis in the next sections.

2.2.1 Reactions First-Order in Substrate

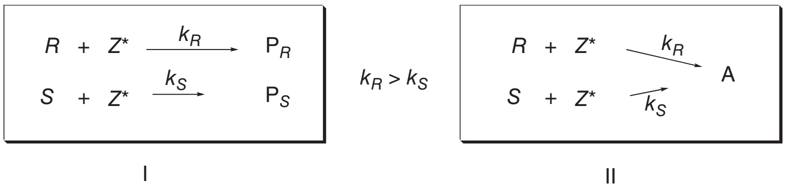
Scheme 2.1 indicates a general presentation of the KR of a racemic compound (*R*, *S*) when the product is chiral (case I) or achiral (case II). In both cases, the KR process is characterized by two competitive reactions going with different rates on the two enantiomers of the racemic mixture. Each rate depends on the concentrations of the reactants, the rate constants and the kinetic law. A common situation is a kinetic law first-order in substrate, here the (*R*) and (*S*) enantiomers (Scheme 2.1).

For an irreversible reaction, the basic set of equations is

$$\frac{d[R]}{dt} = -k_R[R][Z^*] \quad \frac{d[S]}{dt} = -k_S[S][Z^*]$$

The concentration of the chiral auxiliary Z^* will not influence the relative rate, which is expressed as follows.

$$\frac{d[R]/dt}{d[S]/dt} = \left(\frac{k_R}{k_S}\right)\left(\frac{[R]}{[S]}\right) \tag{2.1}$$



Scheme 2.1 Stoichiometric kinetic resolution process under the influence of a chiral reagent Z^* with formation of a chiral product P (case I) or an achiral product A (case II).

Equation 2.1 simplifies into Equation 2.2 by elimination of time t and taking $k_R/k_S = k_{\mathrm{rel}} = s$ (stereoselectivity factor).

$$\frac{\mathrm{d}[R]}{[R]} = s\frac{\mathrm{d}[S]}{[S]} \tag{2.2}$$

Integration of Equation 2.2 gives Equation 2.3 where $[R_0]$ and $[S_0]$ are defined as the initial concentrations of the two enantiomers. This general equation characterizes homocompetitive reactions carried out on two different substrates.

$$s = \frac{\ln([R]/[R_0])}{\ln([S]/[S_0])} \tag{2.3}$$

If one starts from a racemic mixture, then $[R_0] = [S_0]$.

The reaction time t was classically used as the parameter to discuss the course of a KR [6–8, 19]. Conversion extent C gives equations that are easier to handle, especially if taken with values lying between 0 (initial state) and 1 (full transformation) [20, 21]. Conversion C is denoted by $C = 1-([R]+[S])/x_0$, where x_0 is the initial concentration of the racemic mixture. Enantiomeric excess of the remaining starting material ($\mathrm{ee_{sm}}$) is defined as follows.

$$\mathrm{ee_{sm}} = \frac{([S] - [R])}{([S] + [R])} \tag{2.4}$$

In the above equation $[S] > [R]$ because it was assumed that $k_R > k_S$, as in Scheme 2.1.

From Equation 2.4, the values of $[S]$, $[R]$, $[S_0]$ and $[R_0]$ are derived (see Equation 2.5).

$$\begin{aligned} [S] &= 0.5\,(1 + \mathrm{ee_{sm}})\,(1 - C)\,x_0 \\ [R] &= 0.5\,(1 - \mathrm{ee_{sm}})\,(1 - C)\,x_0 \\ [S_0] &= [R_0] = 0.5x_0 \end{aligned} \tag{2.5}$$

By using the values from Equation 2.5, Equation 2.3 gives the stereoselectivity factor s that may be transformed into Equation 2.6.

$$s = \frac{\ln[(1 - \mathrm{ee_{sm}})\,(1 - C)]}{n[(1 + \mathrm{ee_{sm}})\,(1 - C)]} \tag{2.6}$$

Equation 2.6 allows one to compute the curves $\mathrm{ee_{sm}} = \mathrm{f}(C)$ for various values of s. One example is indicated in Figure 2.1 with $s = 10$ and is discussed below. A software is available for the drawing of such curves [22].

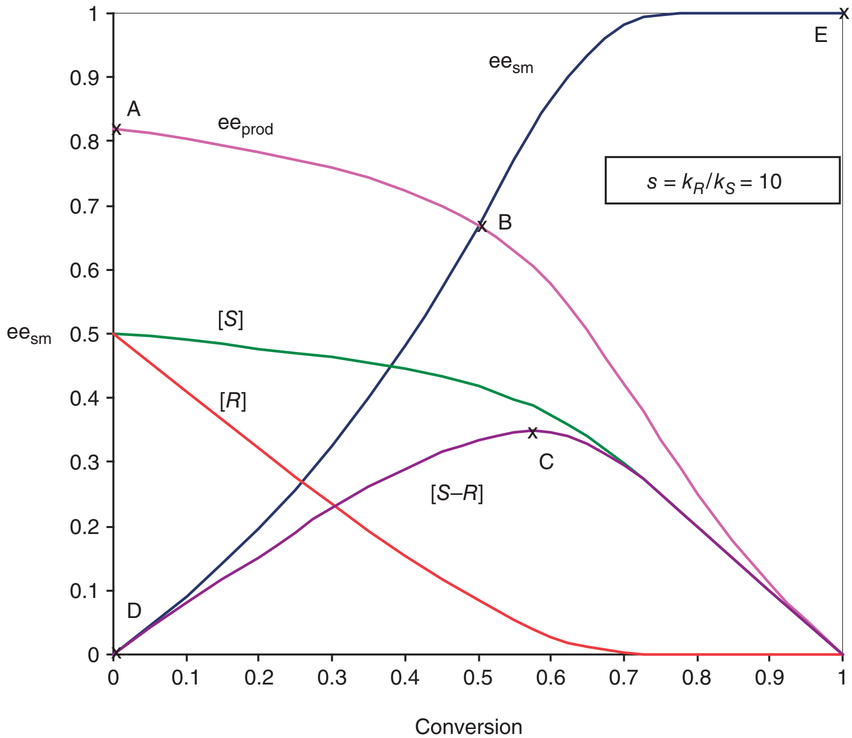


Figure 2.1 Kinetic resolution first-order in substrate ($s = k_{rel} = 10$).

The curve $ee_{sm} = f(C)$ in Figure 2.1 shows that the recovered material has a continuous increase in ee_{sm} with conversion. At 50% conversion, $ee_{sm} = 67\%$. The evolution of [R] and [S] during the KR is given by Equation 2.5 and is plotted in Figure 2.1 (for $x_0 = 1$). The excess in (S) enantiomer expressed by ([S] − [R]) instead of ee_{sm} is also conversion dependent, with an intermediate optimum value as [S] − [R] is equal to zero for $C = 0$ and 1. This maximum occurs because the depletion in the fast-reacting (R)-enantiomer is such that accumulation of the (S)-enantiomer will invert the reaction rates. At the inversion point, the rate of destruction of the both enantiomers are equal, $k_S\,[S] = k_R\,[R]$ or $[S]/[R] = s$. Here, $ee_{sm} = (s-1)/(s+1)$.

If the product is chiral (Scheme 2.1, case II), it is easy to calculate its enantiomeric excess (ee_{prod}) defined by $ee_{prod} = ([\mathrm{Prod}_R] - [\mathrm{Prod}_S])/([\mathrm{Prod}_R] + [\mathrm{Prod}_S])$. There is an excess of Prod_R as $k_R/k_S > 1$. The material balance imposes a relationship between C, ee_{sm} and ee_{prod}. By taking into account that 0.5 mol of (R)-enantiomer of the initial racemic mixture is distributed between the chiral product and the recovered starting material, Equation 2.7 may be derived, which is independent of s.

$$\frac{ee_{sm}}{ee_{prod}} = \frac{C}{(1-C)} \tag{2.7}$$

This allows to modify the fundamental equation (Equation 2.6), by introducing ee_{prod} thanks to Equation 2.7. This leads to the following equation.

$$s = \frac{\ln[1 - C(1 + ee_{prod})]}{\ln[1 - C(1 - ee_{prod})]} \tag{2.8}$$

On Figure 2.1 is also plotted the evolution of ee_{prod} with conversion by using Equation 2.9. There is a progressive decrease of ee_{prod} from the initial value of $(s-1)/(s+1)$ to zero at full conversion of the racemic mixture.

Some following remarkable points are indicated in Figure 2.1.

Point **A**: initial ee_{prod}, equal to $(s+1)/(s-1)$, because $[Prod_R]]/[Prod_S] = s$.
Point **B**: crossing point with $ee_{prod} = ee_{sm}$ and $C = 0.5$ (as calculated using Equation 2.7). Frequently KRs are run to 50% conversion.
Point **C**: inversion rates, where $ee_{sm} = (s-1)/(s+1)$. The conversion value may be calculated from Equation 2.3 by fixing, for example, $x_0 = 1$.
Point **D**: initial enantiomeric excess of the starting material ($ee_{sm} = 0$).
Point **E**: end-point concerning the recovered material. It is close to 100% ee.

The fundamental equation (Equation 2.6) has been obtained by Sharpless *et al.* in 1981 [21] and was inspired by a previous treatment of one of us in 1974 [20] for photoresolution (see Section 2.3). By varying the *s* value, families of curves were plotted as shown in Figure 2.2.

It is interesting to recall that Equation 2.6 applies only for first-order kinetics in substrate but is independent of the order in reagent Z^*. Indeed, Z^* is a common

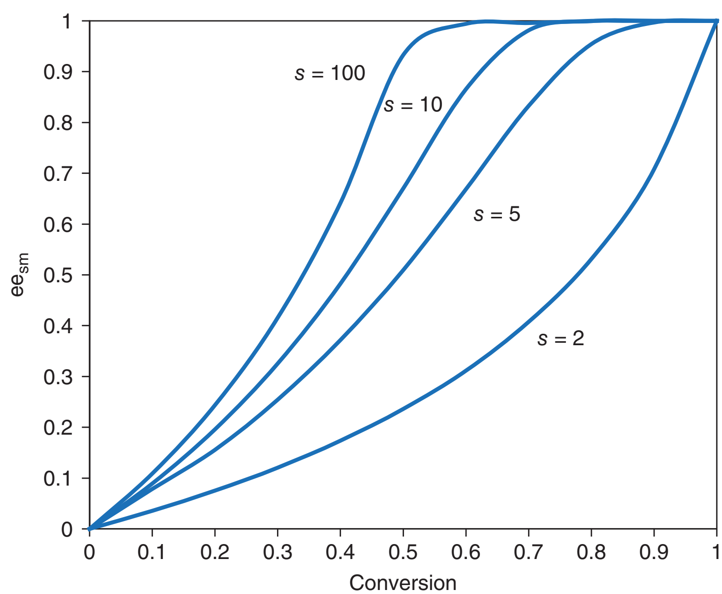


Figure 2.2 Kinetic resolution first-order in substrate for various *s* values.

Table 2.1 Values of ee_{sm} (%) for kinetic resolutions run to 50% conversion.

s	1.1	2.0	3.0	4.0	5.0	10.0	15.0	20.0	50.0	100	150	500	700
ee_{sm}	3.3	23.6	36.4	44.8	50.9	67.0	74.3	78.7	88.7	93.3	95.1	98.1	98.5

Table 2.2 Conversion (%) necessary to recover starting material with $ee_{sm} = 99\%$.

s	2.0	4.0	5.0	10.0	15.0	20.0	50.0	100	150	300	500	700
C (%)	99.7	91.3	86.6	72.1	65.5	61.9	54.9	52.3	51.5	50.6	50.3	50.1

partner in the two parallel reactions of Scheme 2.1 and is eliminated during the establishment of Equation 2.1. A similar situation occurs with a chiral catalyst, the two rate constants representing rate constants of pseudo first-order reactions. The s values are very useful to compare various KR reactions. For example, which is the most efficient process: a KR that gives an ee_{sm} of 50% at 40% conversion, or the one where ee_{sm} is 40% at 30% conversion? The use of Equation 2.6 easily gives an answer to this question, as one calculates $s = 11.4$ and 42.9, respectively; the second process is the best.

From the fundamental equation (Equation 2.6), one can build tables relating s, ee_{sm} and C values. For example, in Table 2.1 are listed couples of s and ee_{sm} values for 50% conversion ($C = 0.5$) of a racemic substrate. In Table 2.2 are similarly indicated some pairs of C and s values necessary to recover the starting material in 99% ee.

Similar calculations apply to the KR of a non-racemic mixture of initial enantiomeric excess $ee_0 = ([S] - [R])/([S] + [R])$, which gives the following.

$$s = \frac{\ln[(1 - ee_{sm})(1 - C)/(1 - ee_0)]}{\ln[(1 + ee_{sm})(1 - C)/(1 - ee_0)]} \tag{2.9}$$

Horeau calculated which conversion (as a function of s) is needed to enhance an initial enantiomeric excess ee_0 to a given final enantiomeric excess ee_{sm} (for example, of 99%) [23].

2.2.1.1 Scope and Validity of Equation 2.6

Equation 2.6 has been established for well-defined conditions: pseudo first-order in substrate (but any order in chiral auxiliary, stoichiometric or catalytic) and no change of mechanism during the course of the reaction, for example, no auto-induction by the products. Reactions with chiral catalysts are especially susceptible to auto-induction. It is then useful to give the calculated s values with an indication of the correspondence between conversion and ee_{sm} or ee_{prod} [11]. We advise running experiments for at least two values of conversion and subsequent verification that the s values obtained are identical or similar. If not, this can indicate a change in the structure of the reagent during the reaction or a non-first-order reaction in substrate. The extrapolation of s at initial conversion is a characteristic value for a