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PARTIAL RESOLUTION THROUGH CHIRAL SYNTHESIS USING A RACEMIC MIXTURE

SANA EL-BABA, JEAN-CLAUDE POULIN and HENRI B. KAGAN

Laboratoire de Synthèse Asymétrique (associé au CNRS LA 255)

Université Paris-Sud 91405 Orsay Cedex, France

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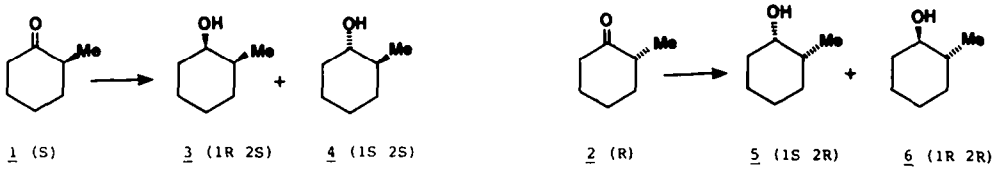
Abstract - A racemic mixture of a compound bearing a reactive prochiral center can partially react with a chiral reagent ; diastereomeric products are formed and the starting material is kinetically resolved. The relationships between the relative amounts and the enantiomeric excesses of reaction products and recovered starting material are discussed. Applications are given for asymmetric hydrogenation of racemic AcΔPheAlaOMe catalyzed by a rhodium-diop complex.

The resolution of a racemic mixture is classically opposed to the creation of an asymmetric center or a chiral unit[1]. Though resolution and chiral synthesis are two processes which seem very different, they do not always exclude each other, as pointed out by Mislow[2]. It is for example possible to envisage an incomplete asymmetric reduction of a racemic mixture such as 1, 2 giving unequal amounts of the four alcohols 3-6.



1 (S) 3 (1R 2S) 4 (1S 2S) 2 (R) 5 (1S 2R) 6 (1R 2R)

3 and 5 : u-diastereomers (cis) 4 and 6 : l-diastereomers (trans)

Example of creation of a new asymmetric center in a racemic mixture of a chiral compound

Scheme 1

An asymmetric reducing agent is thus selecting more or less specifically one antipode of the racemic mixture 1, 2, a typical kinetic resolution. But if one considers the reaction products the reaction could be termed as an asymmetric synthesis of two diastereomers (here the cis and trans isomers). The origin of the optical activity of each diastereomer lies in the differences between four competitive reactions :

$$1 \rightarrow 3 \qquad 1 \rightarrow 4 \qquad 2 \rightarrow 5 \qquad 2 \rightarrow 6$$

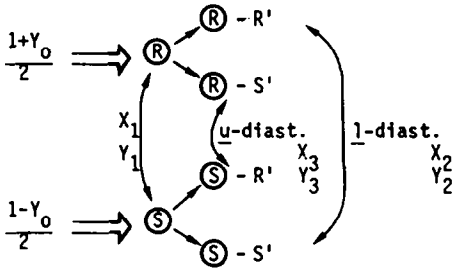
An asymmetric synthesis occurs at the carbonyl group leading to 3 and 4 from 1, and 5 and 6 from 2, the symmetry of the system is such that 3 and 5 form a pair of enantiomers, as do 4 and 6. The situation was fully analyzed by Guetté and Horeau[3] when a racemic mixture R,S is completely transformed into a mixture of two diastereomers l and u. The relative amounts of these diastereomers were found equal the inverse ratio of their optical purities.

We will consider here a more general case (Scheme 2) where a R,S mixture partially reacts with crea-

tion of the stereoisomers R R', S S' (l-diastereomers) and R S', S R' (u-diastereomers)*. If C is defined as the fractional conversion of one mole of the initial mixture the quantity X_1 of recovered starting material will be (1-C).

It exists some general relationships between the initial optical purity Y_o of the R,S mixture, C, the optical purity Y_1 of the recovered starting material, and the optical purities Y_2 and Y_3 and fractional amounts X_2 and X_3 of the l and u-diastereomers. One of these relationships includes the Guetté and Horeau equation[3] as a special case.

Equation [1] has been obtained without any kinetic hypothesis (see in the Appendix) as a direct consequence of the material balance of the system described in Scheme 2.



- Y_o : e.e. of starting material R , S ($Y_o = \frac{R-S}{R+S}$)
- Y_1 : e.e. of R , S after kinetic resolution ($Y_1 = \frac{R-S}{R+S}$)
- Y_2 and Y_3 : e.e. of l and u-diastereomers ($Y_2 = \frac{RR'-SS'}{RR'+SS'}$, $Y_3 = \frac{RS'-SR'}{RS'+SR'}$)
- X_1, X_2, X_3 represent the fractional amounts after partial reaction of one mole of a compound R , S with initial e.e. = Y_o

Scheme 2

$$Y_o = X_1Y_1 + X_2Y_2 + X_3Y_3 \qquad [1]$$

Similar equations (see in the Appendix) are obtained when more than one asymmetric center are created in a racemic mixture or partially resolved compound. In the general case where is creation of N chiral centers, equation [2] applies :

$$Y_o = \sum X_iY_i \qquad (i = 2^N+1) \qquad [2]$$

In the case of formation of one asymmetric center in a racemic mixture ($Y_o = 0$) it could be helpful to know analytical expressions for the diastereomer ratio $\frac{X_2}{X_3} = x$ and for Y_1, Y_2, Y_3.

Equation [1] with $Y_o = 0$ can be changed into the equivalent relations [3] - [6] :

$$\frac{X_2}{X_3} = x = \frac{C(Y_1-Y_3) - Y_1}{C(Y_2-Y_1) + Y_1} \qquad [3]$$

$$Y_1 = \frac{C}{(C-1)(1+x)}(xY_2 + Y_3) \qquad [4]$$

$$Y_2 = \frac{(C-1)}{C}(1+\frac{1}{x})Y_1 - \frac{1}{x}Y_3 \qquad [5]$$

$$Y_3 = \frac{(C-1)}{C}(1+x)Y_1 - xY_2 \qquad [6]$$

Some stereoisomer ratios are independant of C and Y_o. Enantiomer R produces R R' and R S' diastereomers by an asymmetric synthesis at its prochiral center. Hence the ratio $\frac{[R\ R']}{[R\ S']}$ is independent of time, if the structure of the chiral reagent remains constant throughout the reaction. This ratio a measures the enantioselectivity of the process creating a new asymmetric center in antipode R, and is expressed by :

$$\frac{[R\ R']}{[R\ S']} = a = x\frac{(1+Y_2)}{(1+Y_3)} \qquad [7]$$

Similarly

$$\frac{[S\ S']}{[S\ R']} = b = x\frac{(1-Y_2)}{(1-Y_3)} \qquad [8]$$

* l (like) descriptor stands for a diastereomer with two asymmetric centers of R,R' or S,S' configuration and u (unlike) descriptor for R,S' or S,R' configuration, according to a proposal of Seebach and Prelog[4]. Through the present paper the asymmetric centers created are labelled R' or S'.

By dividing equation [7] by equation [8] we find that a relation [9] exists between enantiomeric excesses Y_2 and Y_3 independent of C, Y_o and x :

$$\frac{(1 + Y_2)}{(1 - Y_2)} \cdot \frac{(1 - Y_3)}{(1 + Y_3)} = \text{constant} = \frac{a}{b} \qquad [9]$$

Discussion

i) If the chiral reagent completely destroys the racemic mixture ($Y_o = 0$ and $C = 1$) we have the case previously studied by Guetté and Horeau[3], and equation [1] collapses to $X_2Y_2 + X_3Y_3 = 0$. If the racemic mixture is partially destroyed without kinetic resolution ($Y_o = Y_1 = 0$), the same equation is obtained.

ii) Equations [2] - [7] correlate the variables involved in a partial resolution : enantiomeric excesses Y_o, Y_1, Y_2, Y_3, diastereomeric ratio x and C. If some of these values are not available experimentally they can easily be computed by the use of equations [2] - [7] . The above equations are also useful to detect inconsistancies in experiments. Some examples will be presented later.

To use the above equations conveniently it is necessary to employ the symbols as defined in Scheme 2. The enantiomeric excesses must be taken with a sign in the calculations in agreement with the definitions of Scheme 2. If for example a kinetic resolution ($Y_o = 0$) gives an enrichment in the R-enantiomer ($Y_1 > 0$) by compensation : [SS'] + [SR'] > [RR'] + [RS'] or [SS'] - [RR'] > [RS'] - [SR']. Several combinations of signs of Y_2 and Y_3 can fulfill this requirement.

iii) The various stereoselectivities involved in the process can easily be derived from a few experiments.

If we consider the kinetic resolution of the racemic starting material ($Y_o = 0$) the enantiomer differentiation ability[5] d of the reagent is related to the enantiomeric excess Y_1 :

$$d = \frac{R}{S} = \frac{1 + Y_1}{1 - Y_1}$$

The enantioface differentiation ability in enantiomer R is a (equation [7]).

The enantioface differentiation ability in enantiomer S is b (equation [8]).

iiii) The only kinetic hypothesis introduced was the invariancy of the optical yield when a prochiral centre is transformed into an asymmetric centre. This is a classical assumption in asymmetric synthesis[2] and allows one to elaborate equations [7] - [9] . If the four competitive reactions of Scheme 2 have the same mechanism and same order, with rate constants $K_{RR'}$, $K_{SS'}$, $K_{SR'}$, $K_{RS'}$ along the reaction $\frac{K_{RR'}}{K_{RS'}} = \frac{[RR']}{[RS']} = a$, $\frac{K_{SS'}}{K_{SR'}} = \frac{[SS']}{[SR']} = b$.

At the very beginning of the kinetic resolution of a racemic mixture the concentrations of R and S antipodes are quite similar, then $\frac{[RR']}{[SS']} = \frac{K_{RR'}}{K_{SS'}}$ and $\frac{[SR']}{[RS']} = \frac{K_{SR'}}{K_{RS'}}$

Thus initial optical purities Y_2^o and Y_3^o of diastereomers l and u correlate with $\frac{K_{RR'}}{K_{SS'}}$ and $\frac{K_{SR'}}{K_{RS'}}$:

$$\frac{1 + Y_2^o}{1 - Y_2^o} = \frac{K_{RR'}}{K_{SS'}}$$

$$\frac{1 - Y_3^o}{1 + Y_3^o} = \frac{K_{SR'}}{K_{RS'}}$$

All the ratios of rate constants of Scheme 2 can thus be obtained. Without additional hypotheses it is impossible to calculate the evolution of Y_1, Y_2, Y_3 as a function of C. If the reactions are of first order or pseudo-first order (when an excess of reagent is used) the optical purity Y_1 of residual starting material will increase toward ±1 at the last stage of reaction[6].

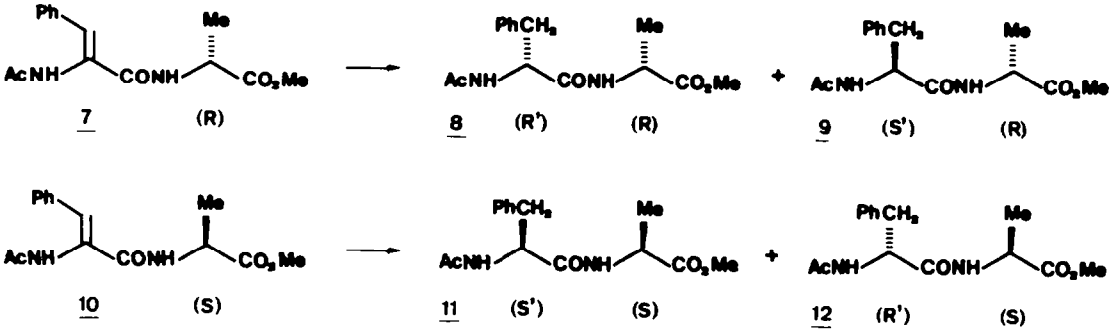
With a chiral reagent of high enantiomer differentiation ability ($K_R/K_S > 100$) it was pointed out that at 60% conversion (c = 0.6) the remaining starting material is optically pure for the presently available methods of enantiomers analysis [7].

EXAMPLES OF APPLICATION

1) Catalytic asymmetric hydrogenation

During the last decade asymmetric hydrogenation catalyzed by chiral rhodium complexes allowed to prepare chiral products with very high enantiomer purity, several reviews are available on this topic[8-10]. By the choice of chiral diphosphines matching at best prochiral substrates optical yields in the range 80-99% are routinely obtained. In contrast, there is no example of kinetic resolution of a racemic mixture using homogeneous asymmetric hydrogenation. We wish to report the first detailed study of kinetic resolution, with the help of a chiral rhodium catalyst, of a racemic mixture containing a reducible prochiral double bond.

Asymmetric hydrogenation was especially useful to prepare various N-acyl α-aminoacids from N-acyl dehydroaminoacids[8-10]. The method was extended to stereoselective synthesis of dipeptides by reduction of monodehydrodipeptides[11-13] or bisdehydrodipeptides[14]. Tripeptides were also produced from monodehydrotripeptides[15].



Scheme 3

Racemic AcΔPheAlaOMe (Scheme 3) was selected for studies of kinetic resolution in presence of [RhCl diop] as chiral catalyst[16]. The reaction was performed at various advancements and each time the stereochemical balance was obtained through a combination of HPLC analysis (which gives the distribution between starting material and the two diastereomeric dipeptides) and glc analysis. This last one was made on a chiral stationary phase after derivatization of the mixture of alanine and phenylalanine coming from quantitative acid hydrolysis of each isolated diastereomer. The enantiomeric purity of the two diastereomeric dipeptides are then obtained. Main results are collected in Table 1.

Table 1

Asymmetric reduction of racemic AcΔPheAlaOMe in presence of RhCl(+)diop[a] (Scheme 3)

% Reduction[b]	Diastereomer ratio (8+11)/(9+12)[b]	Enantiomeric excess (%)[c]		
		7 + 10	8 + 11	9 + 12
39	0.93	6	83.1	83.8
64	0.88	15	79.7	77.7
100	0.92	-	78.7	72.3

a For details see in the experimental section.
b Measured by HPLC.
c Calculated after HPLC isolation of starting material and l and u dipeptides. Each compound was hydrolyzed and its optical purity obtained from the optical purity of recovered alanine and phenylalanine. The predominant enantiomers are 10, 11 and 9 respectively, which means that Y_1, Y_2 have to be taken with a negative sign in calculations while Y_3 is positive.

In the case where the racemic dehydrodipeptide was fully reduced (C = 1.00), equation [3] is obeyed since x = 72.32/78.66 = 0.919 against 0.92 (measured).

For partial conversion of starting material equations [3] - [6] should apply. There are no major discrepancies between experimental data and calculated values from equations [3] - [6] . For example with 64% conversion (C = 0.64) equation [3] leads to x = 0.79 (measured 0.88). It is interesting to consider experimental errors on the data in Table 1. The diastereomer ratio x has been obtained with a good accuracy from HPLC measurements. The optical purities of l and u dipeptides are deduced from enantiomeric excess of phenylalanine and alanine measured by glc are also quite accurate. The more difficult is to evaluate the conversion C and especially the enantiomeric excess Y_1 of the residual starting material (7 + 10) because of the low value. In this situation equation [4] is the most useful since it allows to calculate the missing data Y_1 from other more accurate experimental data (Y_2 = - 0.797, Y_3 = 0.77, x = 0.880, C = 0.64). It comes Y_1 = 0.11 (11% e.e. against 15% e.e. measured). The absolute configuration is in agreement with experimental measurement which had overestimated the e.e. For 39% conversion an enantiomeric excess of 2.2% in (S) configuration is calculated (against 5.9% e.e. (S), measured). A further step in the analysis of the asymmetric reduction of the racemic dehydropeptide (7 + 10) can be done by the use of equations [5] - [7] . These equations are obeyed only if the various steric differentiations involved in the system are constant throughout the reaction course. As stated before, this assumption holds if the structure of the chiral catalyst remains unchanged.

Using equations [7] and [8] the enantioface differentiations a and b on 7 and 10 can be calculated for 39% and 64% conversion. We find a = 0.077 and 0.064, b = 12.72 and 9.86. Since a and b are the ratios of attack on diastereofaces of 7 and 10 it is possible to calculate the enantiomeric excess at the level of the new asymmetric center created from 7 and 10. For 39% and 64% conversion these values are 85.7% e.e. and 87.9% (S configuration) from 7 and 85.4% e.e. and 81.6% (S configuration) from 10. Asymmetric induction for the creation of the new asymmetric center is the result of a "double asymmetric induction"[17] which is definitely different for the enantiomers 7 and 10. Moreover the stereodifferentiations a and b are not perfectly constant between 39% and 64% conversion. This can be confirmed at total conversion (C = 1) since calculations give a = 0.113 and b = 5.93. A strong decrease of the enantioface-differentiations in hydrogenation of 7 and 10 appears between 64% and 100% conversion. It was interesting to confirm this analysis by the study of the hydrogenation of the individual dehydropeptides 7 and 10 in presence of the RhCl(+)diop catalyst. Such a study was performed indeed on 10 using either RhCl(+)diop or RhCl(-)diop, results are in Table 2.

Table 2

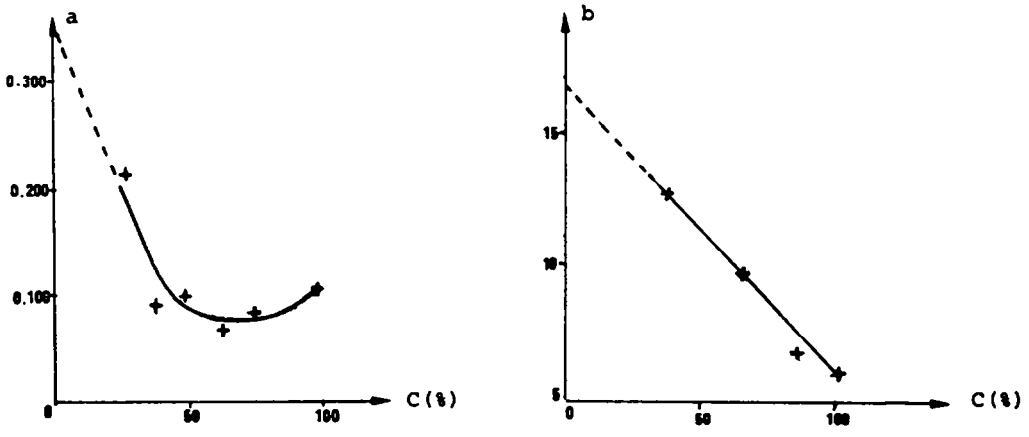
Reduction of AcΔPhe(S)AlaOMe 10 in presence of RhCl(+)diop or RhCl(-)diop[a] (Scheme 3)

Catalyst	% reduction [b]	Ratio of l and u dipeptides[b] (11)/(12)
RhCl(+)diop	85	87.01/12.99 = 6.70
"	100	85.58/14.42 = 5.94
RhCl(-)diop	26	17.41/82.59 = 0.210
"	48	8.54/91.46 = 0.093
"	75	7.62/92.38 = 0.082
"	100	10.21/89.79 = 0.113

a For details see in the experimental section.
b Measured by HPLC.

As hypothetized from the previous discussion it clearly appears that the stereoselectivities are conversion-dependent, especially for the system 10/RhCl(-)diop which is equivalent to 7/RhCl(+)diop. The a value defined in equation [7] is directly measured here by the diastereomer ratio (12/11) ; for a total conversion 0.113 is found which is exactly the value calculated from the total reduction of the racemic dehydrodipeptide. Similarly b is equal to the diastereomer ratio 11/12, in the reduction of 10 with RhCl(+)diop. At total conversion it is measured 5.93 (against 5.93 calculated from the hydrogenation of the racemic dehydrodipeptide). The excellent agreement

between calculations and direct measurements give strong support to the treatment expressed by equations [1] - [9] . It means also in the present case that hydrogenation of racemic AcΔPhe-AlaOMe was appropriately described by independent reductions on each enantiomer (each reduction involving a double asymmetric induction). An important conclusion is the direct confirmation that AcΔPhe(S)AlaOMe is reduced with a stereoselectivity a or b (in presence of RhCl(-)diop or RhCl (+)diop respectively) which changes with conversion. It is possible to get an overview of this evolution by plotting all the data (a or b) versus conversion (scheme 4). The combination



Evolution of stereoselectivities a and b with conversion C
for reactions of scheme 3 with Rh-diop catalyst

Scheme 4

10/RhCl(+)diop shows a continuous decrease of stereoselectivity (b ≈ 17 by extrapolation to 0% conversion, b ≈ 6 for 100% conversion). The situation is more complex for the system (10)/RhCl (-)diop. There is a increase of stereoselectivity from 0% conversion (a extrapolated = 0.35) till 50-60% conversion (b ≈ 0.17) and then a slight decrease till the end of the reaction (a = 0.113). These phenomenon can be interpreted as the indication that several catalytic species are involved in the hydrogenation, in relative quantities changing with time. Diop is a chelating 1,4-diphosphine which in some circumstances behaves as a monodentate ligand[18]. Both the substrate and the product should have also some chelating properties towards rhodium, it is understable that some competition with diop occurs during the whole reaction. We are currently, examining other dehydropeptides for looking to this still undetected phenomenon*, we are also reinvestigating asymmetric reduction of various N-acetyl dehydroaminoacids with RhCl(+)diop in order to see wether the e.e. is conversion-dependent.

2) The kinetic resolution of (±)-2-dimethylaminopropiophenone through asymmetric hydrosilylation was described[19], using one-half equivalent of Ph_2SiH_2 and a rhodium-DIOP catalyst[20]. For 40% conversion it was formed (+)-pseudomethylephedrine (27% e.e. 1S',2S) and (-)-methylephedrine (20% e.e. in 1R',2S) in the ratio 2.083 (based on isolated yields). The unreacted ketone has 23% e.e. in R-(+) configuration. Our conventions give C = 0.40, Y_1 = 0.23, Y_2 = - 0.27, Y_3 = -0.20, x = 50/24 = 2.083.

These values do not fit with equation [3] (a negative value of x = 0.135 is obtained) or equation [4] (a too low value is calculated, Y_1 = 0.165). The most obvious explanation for the discrepancies is the slow racemization of the starting ketone at ambiant temperature as pointed

* We checked that the combination $[Rh(C_2H_4)_2Cl]_2/PPh_3$/Ac(S)Phe(S)AlaOMe (1:1:1) gives a catalyst for reduction of AcΔPheOH. The catalyst remains apparently homogeneous (yellow colour) acetylphenylalanine was recovered as a racemic mixture.

out by the authors[19]. The racemization of the ketone after its recovery doesn't explain adequately the results, it is most probable that partial racemization occurs during the reaction itself (50°C, 2 days), obscuring the stereochemical analysis and the use of formula [3] and [4]. Moreover the yields obtained after isolation involve a poor accuracy on C and x.

3) The Darvon-LAH complex reduces racemic 2-acetoxy tetralone (conversion not stated)[21]. Cis-diol (20% e.e. 1R',2S) and trans-diol (62% e.e. 1R',2R) were isolated (yields : 30% and 5% respectively). Either these values do not reflect the initial composition for 100% conversion (since equation [1] is not obeyed) or a partial resolution of 2-acetoxy tetralone takes place, so that equation [4] relates Y_1 and C. With this latter option and assuming 50% conversion, it is calculated (C = 0.5, Y_2 = 0.62, Y_3 = -0.20, x = 1/6) that the unchanged tetralone would have 8.3% e.e. in (R) configuration. If indeed the reaction is quantitative (C = 1) as it seems implicit from the paper[21] it becomes possible to evaluate the actual diastereomer ratio before the isolation procedure. From equation [1] it comes x = 1/3.1 (instead of 1/6 after purification). Greater losses in the isolation of the minor diastereomer can account for the difference.

4) Enzymatic reactions

Enzymatic reactions are often very stereoselective and can be applied to the resolution of a racemic mixture (for a kinetic treatment see ref.[22]).

In many cases enzyme stereoselectivity is not perfect[22,23], and resolution and product distribution must follow the equations given in this paper. Unfortunately all experimental data are often not available, especially the composition of systems before crystallization of some products.

- Sometimes there is a very good fit with equations developed here. For example reduction by the NADH/HLAD system of the racemic 2-norbornanone in the conditions of ref.[24] gives for a quantitative conversion a mixture of exo and endo norbornanols (in the ration 28/72) with e.e. of 100% (1R, 2R', 4S) and 38% (1S, 2R', 4S) respectively. With our conventions (by labelling the 1R, 2R', 4S) enantiomer as a 1 diastereomer) we have : Y_2 = 1, Y_3 = - 0.38, C = 1, X_2 = 0.28, X_3 = 0.72. The equation [1] is perfectly obeyed with these values. The enantioface differentiation ability in enantiomer (1R, 4S) is a = 1.25 (equation [7]) which corresponds to a ratio of 56/44 = 1.27 in the exo, endo reactivities. The stereoselectivity of the carbonyl reduction in (1S, 4R) norbornanone is given by b (equation [8] ; b = 0 meaning an exclusive formation of the (1S, 2R', 4R) diastereomer (exo attack)).

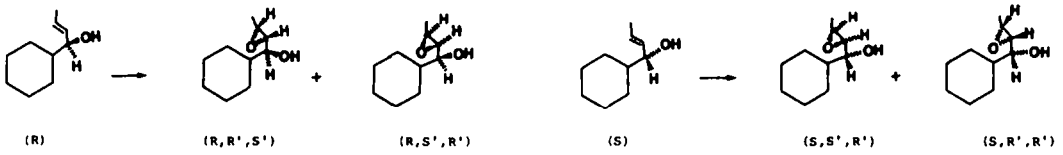
- Often equations [1] - [6] can help to detect inconsistancies in experimental data. For example racemic ketones such as 2-chlorocyclohexanone were resolved by yeast[25]. Thus (S)-2-chlorocyclohexanone (32% yield) was recovered optically pure, and the (R,S') chlorhydrine was the only reduction product. Since X_2 = 0, Y_2 = - 1, Y_3 = 1, equation [4] gives C = 0.5. This means that if the ketone is recovered optically pure (Y_1 = - 1) and the product obtained stereochemically pure the reaction (Y_2 = 1) necessarily went to 50% completion and the observed yields are then greatly underestimated.

5) Spectacular progresses were recently obtained in asymmetric epoxidation with t-BuOOH and a chiral catalyst based on diisopropyl tartrate and $Ti(OiPr)_4$[7]. High enantioselectivities (>95% e.e.) are observed in epoxidation of many prochiral allylic alcohols. A striking feature of this system is its ability to resolve racemic allylic alcohols[7]. In many cases one enantiomer is stereoselectively epoxidized, then the reaction slows down near 50% completion because of the reluctance of the catalyst to react with the remaining antipode. The enantioface differentiation ability is combined here with a high enantiomer differentiation. Such a still uncommun situation with non-enzymatic systems can be discussed in relation with equations [1] - [6]. It means, for example, that x >> 1, X_3 being small and the conversion close to C = 0.5. Another feature is a high enantio-selectivity in the epoxidation of the fast-reacting enantiomer for example a > 100.

In many reports only one diastereomer was detected which means x > 200. The questions arises of the knowledge of the optical purity and quantity of the undetected diastereomer. In this case equation [6] can be simplified since 1 + x ≈ x:

$$\frac{Y_3}{x} = Y_1 \frac{(C-1)}{C} - Y_2$$

The values Y_1,C and Y_2 are known with a good accuracy, then Y_3/x can be calculated. The estimation of a minimum value for the diastereomer ratio x (based for example on glc analysis) leads to the assignment of a limit for the e.e. of the minor diastereomer. In the reported epoxidation of (dl)-cyclohexylbutenol by t-BuOOH catalyzed by (+)-diisopropyl tartrate and $Ti(OiPr)_4$[7], it remains 40% starting material (>96% e.e. in R configuration). Erythro epoxide is formed with e.e. > 95% (in S,S',R' configuration). The reaction is indicated in Scheme 5.



Scheme 5

If the actual values of e.e. are for example 0.99 (R) and 0.06 (S,S',R') respectively, then $Y_1 = 0.39$, $Y_2 = -0.96$, $C = 0.52$. It comes then from calculation $Y_3/x = 0.0046$.

The positive sign means that the u diastereomer (threo product) has necessarily the (R,S',R') stereochemistry.

If $x \simeq 11$ (erythro/threo $\simeq$ 91.5/8.5), $Y_3 \simeq 0.5$ (50 % e.e.). The upper limit of x compatible with the experimental data can be calculated, since $|Y_3| < 1$, hence $x < 21.7$. The tandem values $Y_3 = 1$ (100% e.e.), Erythro/Threo = 95.6/4.4 are the solution for this limit situation.

Conclusion

The detailed analysis of an asymmetric reaction on a racemic mixture for various conversions is a useful source of informations. The equations [1] - [6] applied at any conversion and do not involve kinetic hypotheses and are only the various expressions of the material balance*. They are useful to calculate or to precise a data (e.e. or relative concentration) not easy to measure. They apply to a very large number of chemical or enzymatic asymmetric reactions**. Equations [7] - [9] allow to extract values (a, b) related to various ratios of rate constants (involved in stereodifferentiations). When these values vary with conversion it can be also a useful information as previously discussed in asymmetric hydrogenation.

Acknowledgment

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Experimental section

Instrumental

Proton NMR spectra were recorded on a Perkin Elmer R 32 (at 90 MHz) or a Cameca TSN 250 (at 250 MHz) spectrometer in $CDCl_3$ solution, using TMS as internal standard. HPLC was performed on a 25 cm long column packed with Zorbax ODS (Dupont, Particle size : 5-6 µm). Internal diameter of column are 4.6 mm for analytical work and 9.4 mm for preparative use. Flow rate = 1 ml/min in analytical and 4 = 5 ml/min in preparative scale. Eluent is methanol-water (50/50) and detection was done by UV absorption at 230 nm.

Gas chromatography was performed on a Erba Science apparatus equipped with a 50 m fused silica capillary column coated with XE-60-(S)-Val-(S)-α-phenylethylamide (Chrompack). A temperature programming from 105°C (Ala) to 150°C (Phe) was used.

* If there are some undetected products some cautions are necessary for the use of theses equations (see in Appendix).

** A list of references involving creation of an asymmetric center on a racemic mixture under the influence of a chiral reagent or catalyst is available from the authors.

Chemical and solvents

- (S)-alanine and (R,S)-alanine were purchased from Fluka and Prolabo and used as received.
- Rhodium trichloride is from the "Compagnie des Métaux Précieux".
- (+)-diop and (-)-diop were prepared as described[16] ; methanol was distilled over magnesium powder and stored under nitrogen.
- AcΔPhe(S)AlaOH and AcΔPhe(RS)AlaOH were prepared according to Bergmann[31] by reaction of the sodium salt of alanine with the unsaturated azlactone of N-acetylphenylalanine[26,27].
- AcΔPhe(S)AlaOMe and AcΔPhe(RS)AlaOMe were obtained as in ref.[11] by dissolution of AcΔPheAla-OH in MeOH with concentrated HCl at 0°C and 2 days esterification at room temperature.
- AcΔPhe(RS)AlaOMe was purified by recristallisation from an ethyl acetate-cyclohexane (1/1) solution. Yield 60% ; mp = 146-148°C.

Hydrogenation

In situ catalyst [RhCldiop] was obtained as in ref.[11,16] by introduction of 0.063 mmol (31.5 mg) diop in 0.03 mmol (11.6 mg) $[Rh(C_2H_4)_2Cl]_2$ (ref. [28]) and 5 ml MeOH under nitrogen. After 10 min the catalytic solution was introduced into the hydrogenation flask containing the solution of 1.7 mmol (500 mg) of dehydropeptide in 10 ml MeOH under hydrogen.

Analysis

After hydrogenation, the solvent was distilled off under reduced pressure. Analysis of this mixture was done by ^1H NMR and HPLC.
Optical purity of the non-hydrogenated substrate and the two diastereomeric products were obtained, after a preparative HPLC separation, by a gas chromatography analysis on chiral phase of each sample derivatized according to well-known procedures[29,30].
2 mg of dipeptide or dehydrodipeptide are successirely treated as follows in a pot-one procedure :
a) 4 ml HCl 6N 110°C for 24 h. b) vacuum evaporation of solvents. c) 4 ml iPrOH/HCl 6% 100°C for 1 h. d) vacuum drying. e) 0.2 ml pentafluoropropionic anhydride or 0.2 ml trifluoroacetic anhydride and 1 ml CH_2Cl_2 at room temperature for 1 h. f) vacuum drying. g) dissolution in acetone for glc analysis.

APPENDIX

Demonstration of equation [1]

After partial resolution of one mole of a racemic mixture R,S the composition of the system is as defined in scheme 2.
Equations [10] - [15] relate quantities q,y,z,t,v,w, of compounds R,S,RR',RS',SR',SS' respectively

$$Y_0 = q + z + t - y - v - w \qquad [11]$$

$$Y_1 = \frac{q - y}{q + y} \qquad [12]$$

$$Y_2 = \frac{z - w}{z + w} \qquad [13]$$

$$Y_3 = \frac{t - v}{t + v} \qquad [14]$$

$$X_1 = q + y \quad X_2 = z + w \quad X_3 = t + v \qquad [15]$$

By combining the equations [12] - [15] it is possible to get equations [16].

$$X_1Y_1 = q - y \; ; \; X_2Y_2 = z - w \; ; \; X_3Y_3 = t - v \qquad [16]$$

By combining equations [16] and [11] the equation [1] is obtained :

$$Y_0 = X_1Y_1 + X_2Y_2 + X_3Y_3 \qquad [1]$$

If two new asymmetric centers will appear there will be eight stereoisomers (R R'R", R R' S", ..) leading to four diastereomers with e.e. expressed by Y_2, Y_3, Y_4 and Y_5. By taking the sign conventions as in scheme 2 it is easily found that

$$Y_0 = X_1Y_1 + X_2Y_2 + X_3Y_3 + X_4Y_4 + X_5Y_5$$

Demonstration of equations [3] - [6]

By taking $Y_0 = 0$ and $X_1 = 1 - C$ in equation [1] it comes $Y_1 = (X_2Y_2 + X_3Y_3/(C - 1) = X_3 (xY_2 + Y_3/(C - 1)$.
Since $X_3 = \frac{C}{1 + x}$ equation [4] is immediately obtained. Equations [5] and [6] are found by similar calculations. The diastereomer ratio x can also be expressed as a function of conversion and various enantiomeric excesses.

$$X_1Y_1 + X_2Y_2 + X_3Y_3 = \frac{X_1}{X_3}Y_1 + xY_2 + Y_3 = 0$$

In this equation X_3 can be replaced by $C/(1 + x)$ and X_1 can be replaced by $(1 - C)$. Equation [3] is then obtained.

Cases where by-products are formed

Let assume first that reactants R_0, S_0 of Scheme 2 lead to additional products (P' from R_0,

P" from S_0, with fractional amounts X' and X" respectively).
The material balance established in equation [11] is changed :

$$q + z + t + X' = \frac{1 + Y_0}{2} \quad , \quad y + v + w + X'' = \frac{1 - Y_0}{2}$$

The equations [12] - [15] remain unchanged.
Let name X_i' the fractional amount of the by-products : $X_i' = X' + X''$. Calculations similar to those leading to equation [1] give : $Y_0 = X_1Y_1 + X_2Y_2 + X_3Y_3 + X_i' \left(\frac{X' - X''}{X' + X''}\right)$.

It appears that if X' = X" (formation of by-products in equal amounts from R_0 and S_0, without additional kinetic resolution) then the equation [1] remains valid. Analytical expression of Y_1, Y_2, Y_3 are convenient to obtain from equation [1] as functions of two e.e.'s and two concentration ratios. Thus

$$Y_3 = -\frac{X_1}{X_3} Y_1 - \frac{X_2}{X_3} Y_2 .$$

Equation [3] - [6] cannot be used without modifications involving introduction of X'_1. If X' = X" the equation [1] takes the general form [2] relating e.e. and concentrations of four chiral components.

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