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Transformation of a Racemic Mixture by a Chiral Reagent or Catalyst to Give Regioisomeric Products

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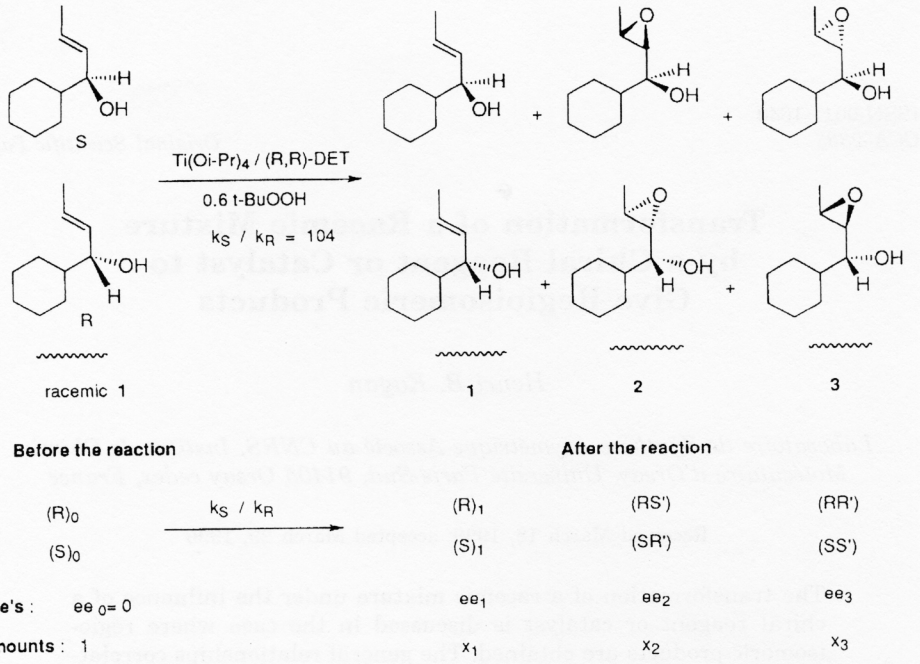
The transformation of a racemic mixture under the influence of a chiral reagent or catalyst is discussed in the case where regioisomeric products are obtained. The general relationships correlating the ee's and the quantities of the various products are given. The special case of asymmetric Baeyer-Villiger oxidation of racemic ketones is taken as an example. Sometimes regioisomeric products are derived from opposite enantiomers, which implies that the regioselectivity of a reaction on an enantiomerically pure starting material will be controlled by the absolute configuration of the chiral reagent or catalyst.

INTRODUCTION

The development of efficient asymmetric reagents or catalysts is extremely useful in asymmetric synthesis (creation of a chiral unit from an achiral precursor). This methodology also applies to kinetic resolution, for example in asymmetric epoxidation of racemic allylic alcohols[1] (Scheme 1) or asymmetric dihydroxylation of racemic olefins.[2] In these cases the partial transformation of the mixture of enantiomers is accompanied by formation of products with additional asymmetric centres, usually but not necessarily, with some stereoselectivity. Scheme 1 presents, an example, the kinetic resolution observed in asymmetric epoxidation of an allylic alcohol, as well as the symbols used here for representation of such general processes.

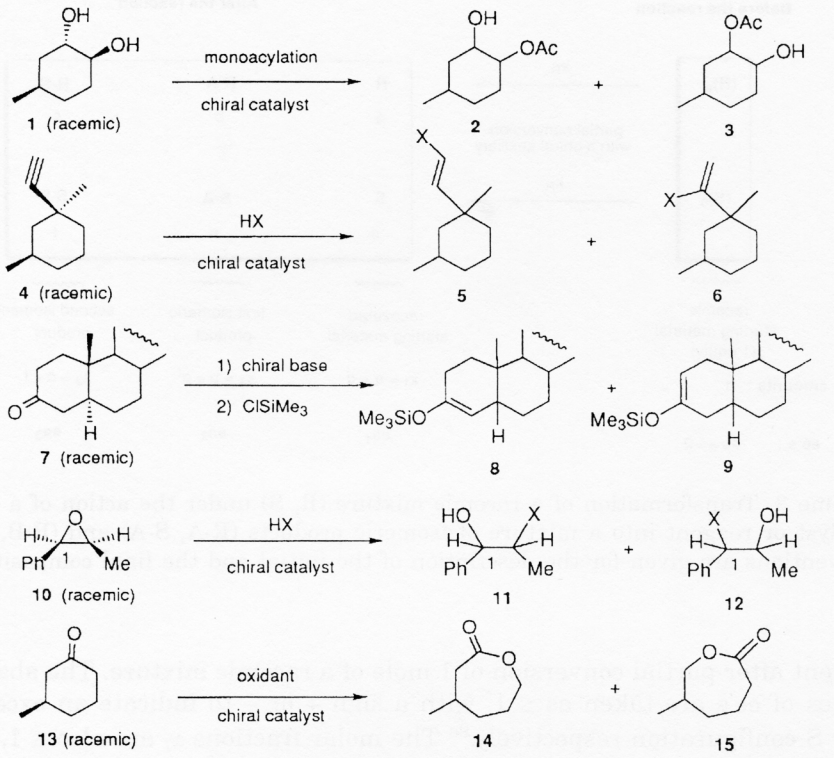
The general relations connecting the relative amounts and the ee's of the various species have been established.[3]



Scheme 1. Partial conversion of a racemic allylic alcohol by asymmetric epoxidation.[1] Symbols represent the general description of such processes.

When there is a complete transformation of the starting racemic compound it may happen that the products are enantiomerically enriched,[4] for example in the full conversion of racemic allylic alcohols. This situation could be taken as an indication of a kinetic resolution. Actually there is no »memory« of a kinetic resolution process, since no starting material remains (for a review on kinetic resolution see Ref. 5). The rate constants ratio (stereoselectivity factor) may well be equal to 1 (no kinetic resolution) even if the diastereomeric products are of high ee's. The presence or absence of a kinetic resolution during the course of the complete conversion of a racemic mixture cannot be deduced from the presence or absence of enantiomeric excess of the products.[5] We want to address a related situation where a chiral reagent or catalyst is involved in partial or total transformation of a racemic mixture giving products without formation of additional chiral units. Some hypothetical examples are listed in Scheme 2 for illustration.

Reactions related to transformation of (dl)-**13** have been described.[6–7] Regioselective deprotonation of ketone **7** with chiral bases has been realized on (5α)-cholestanone (but not on the racemic mixture).[8] According to the ab-



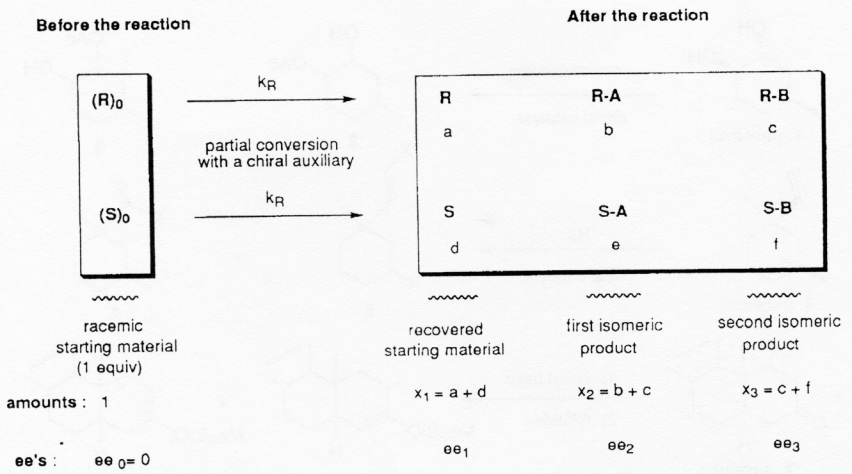
Scheme 2. Hypothetical examples of transformation of racemic mixtures (only one enantiomer shown) by a chiral catalyst or reagent, giving two regioisomeric products (stereochemistry not indicated).

solute configuration of the chiral lithium amide used the kinetic deprotonation occurs either at C_2 or C_4, giving rise to the isomeric TMS enol ethers.

In the next section, the general equation will be established, correlating the various ee's and relative amounts of the chiral species obtained after partial or full transformation of a racemic mixture.

CALCULATIONS

The symbols in Scheme 3 will be used for the general description of the various transformations depicted in Scheme 2. The processes described in Scheme 2 are summarized in Scheme 3 as R $\rightarrow$ R-A + R-B, R-A and R-B being the two products generated from (*R*) enantiomer. Similarly, S $\rightarrow$ S-A + S-B. We call *a*, *b*, *c*, *d*, *e*, *f* relative amounts of the six compounds of the system



Scheme 3. Transformation of a racemic mixture (R, S) under the action of a chiral catalyst or reagent into a mixture of isomeric products (R-A, S-A) and (R-B, S-B). Conventions are given for the description of the initial and the final composition.

present after partial conversion of 1 mole of a racemic mixture. The absolute values of ee's are taken as ≤ 1, with a sign + or − to indicate an excess of R or S configuration respectively.[9a] The molar fractions x_i are also ≤ 1, with $x_1 + x_2 + x_3 = 1$.

Because of the definitions,

$$a + b + c = d + e + f = 0.5 \ .$$

Hence

$$(a - d) + (b - e) + (c - f) = 0$$

$$(ee)_1 = \frac{a-d}{a+d} \qquad (ee)_2 = \frac{b-e}{b+e} \qquad (ee)_3 = \frac{c-f}{c+f} \ .$$

The three above equations are transformed into:

$$(a - d) = (ee)_1 \ (a + d)$$
$$(b - e) = (ee)_2 \ (b + e)$$
$$(c - f) = (ee)_3 \ (c + f) \ .$$

By replacement in the first equation,

$$(a + d) \ (ee)_1 + (b + e) \ (ee)_2 + (c + f) \ (ee)_3 = 0 \ .$$

This equation is transformed into equation (1):

$$x_1\,(\mathrm{ee})_1 + x_2\,(\mathrm{ee})_2 + x_3\,(\mathrm{ee})_3 = 0\ . \qquad (1)$$

If one starts from 1 mole of a mixture of enantiomers with $(\mathrm{ee})_0 \neq 0$, then equation (2) will apply:[9b]

$$x_1\,(\mathrm{ee})_1 + x_2\,(\mathrm{ee})_2 + x_3\,(\mathrm{ee})_3 = \mathrm{ee}_0\ . \qquad (2)$$

When an achiral reagent diverts part of the starting material (with formation of other products), equation (1) remains valid because it has been established only thanks to the material balance of the overall process, without mechanistic hypotheses.

If the achiral reagent competes with the chiral reagent in the formation of the same products, equation (1) is slightly modified.

For example, let us detail the situation where the product (R-A, S-A) of a total amount x_2 and with an enantiomeric excess $(\mathrm{ee})_2$ arises from the racemic mixture (R, S) by a chiral route (giving x'_2, $(\mathrm{ee})'_2$) and by an achiral route (with the set x''_2, $(\mathrm{ee})''_2 = 0$). It follows $x_2 = x'_2 + x''_2$. It is easy to establish that equation (1) is still valid when using the above parameters x_2, $(\mathrm{ee})_2$. If necessary one may use parameters $(\mathrm{ee})'_2$, x'_2 characterizing only the chiral route. One calculates $(\mathrm{ee})_2$ as a function of $(\mathrm{ee})'_2$ in the following way.

We will use the symbols from Scheme 3, only introducing an additional quantity x''_2 of racemic product R-A (amount g) and S-A (amount g). Then, $x''_2 = 2g$ and $x'_2 = b + c$.

By definition $\displaystyle (\mathrm{ee})_2 = \frac{b-e}{b+e+2g}$ and $\displaystyle (\mathrm{ee})'_2 = \frac{b-e}{b+e}$.

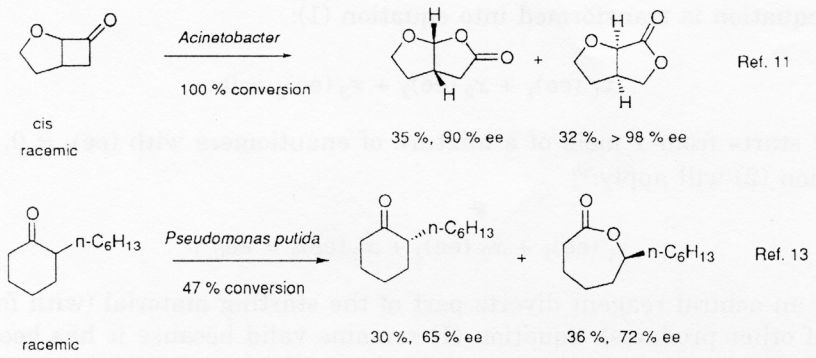
It follows $\displaystyle (\mathrm{ee})_2 = \frac{(\mathrm{ee})'_2}{1+\dfrac{x''_2}{x'_2}} = (\mathrm{ee})'_2\,\frac{x'_2}{x_2}$, hence $(\mathrm{ee})_2\,x_2 = (\mathrm{ee})'_2\,x'_2$. (3)

Equation (1) can now be transformed into equation (4):

$$(\mathrm{ee})_1\,x_1 + (\mathrm{ee})'_2\,x'_2 + (\mathrm{ee})_3\,x_3 = 0\ . \qquad (4)$$

That equation gives access to the term $(\mathrm{ee})'_2 x'_2$ which characterizes the product (R-A, S-A) actually exclusively obtained by the chiral route. With an hypothesis on the amount x'_2 one knows the corresponding $(\mathrm{ee})'_2$ and *vice versa*.

Equations (1) and (2) are similar to the ones that apply to the cases in Scheme 1, where an asymmetric centre is created.[3]

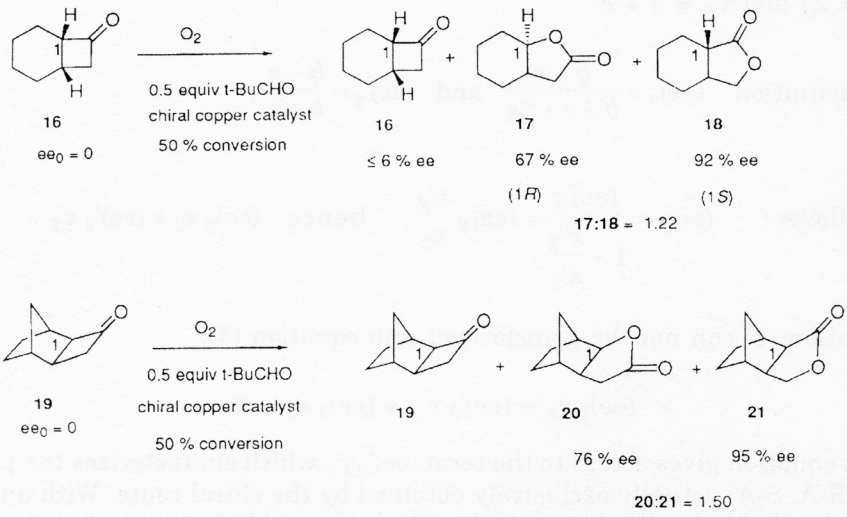


Scheme 4. Examples of enzymatic Baeyer-Villiger oxidation of racemic ketones.[11]

EXAMPLES OF APPLICATION

Asymmetric Baeyer-Villiger enzymatic oxidation of ketones is well documented.[10–13] It can give rise to isomeric lactones if the two adjacent sites of the ketone group are not equivalent (Scheme 4).

Recently, chemical approaches were also discovered.[7,8,14] One set of experiments performed by Bolm *et al.*[8] is described in Scheme 5.



Scheme 5. Asymmetric Baeyer-Villiger oxidation of racemic ketones catalyzed by a chiral copper complex.[15] The absolute configurations of **19–21** are unknown.

Asymmetric oxidation of ketone **16** gives the following values using the above conventions:

$$(ee)_1 \leq 0.06 \qquad (ee)_2 = +0.67 \qquad (ee)_3 = -0.92 \qquad x_2/x_3 = 1.22 \ .$$

If one takes $(ee)_1 \sim 0$, it follows by using equation (1): $0.67\ x_2 - 0.92\ x_3 = 0$, giving $x_2/x_3 = 1.31$, which is not very far from the experimental value 1.22 (measured on the crude product).

Equation (1) may be helpful for discussing some hypotheses. The authors assumed that the high ee for the »abnormal« Baeyer-Villiger product in respect to the »normal« lactone may be the result of competing uncatalyzed pathways introducing some racemic »normal« product. It means that lactone **17** may come from the asymmetric route (amount x'_2 with $(ee)'_2$) and from the racemic route (amount x''_2 with $(ee)''_2 = 0$).

One can use equations (3) and (4) to calculate the term $(ee)'_2\ x'_2$, selecting the experimental values $(ee)_2$ and $(ee)_3$, and taking $(ee)_1 = 0$, as well as the above value $x_2/x_3 = 1.31$. The conversion will be approximated to 50% ($x_1 = 0.5$).

By definition $x_1 + x'_2 + x''_2 + x_3 = 1$, then $x'_2 + x''_2 + x_3 = 0.5$.

Since $(x'_2 + x''_2)/(x_3) = 1.31$, it follows $x_3 = 0.216$ and $x'_2 + x''_2 = 0.284$.

Equation (4) gives:

$$(ee)'_2\ x'_2 = 0.20 \ . \qquad (6)$$

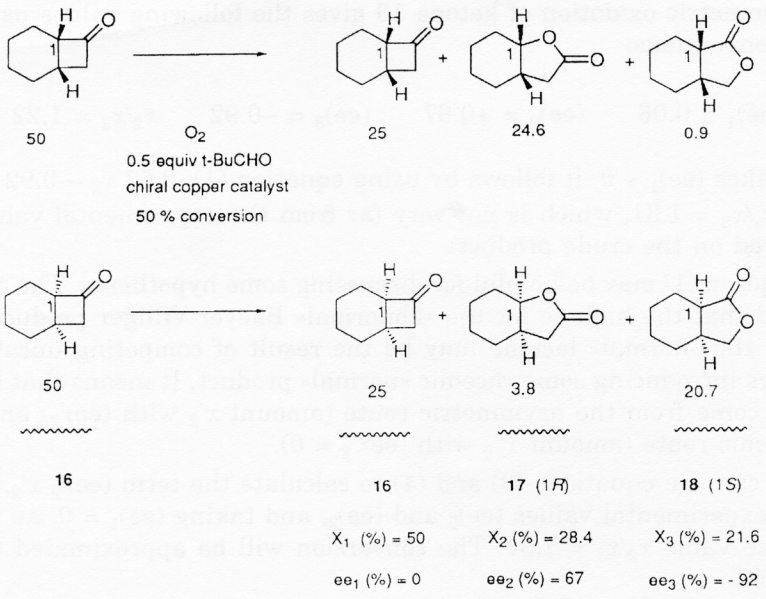
We may learn from Eq. (6) some information on the possible compositions between the chiral and achiral routes leading to **17**. The two extreme situations are as following.

1.) $x''_2 = 0$ (100% *via* the chiral route), $(ee)_2 = (ee)'_2 = 0.67$, $x_2 = x'_2 = 0.284$ (*vide supra*). This situation is summarized in Scheme 6 where the relative amounts of the various components are standardized to 100.

2.) $(ee)'_2 = 1$ (perfect stereoselectivity in the formation of **17**): equation (6) gives $x'_2 = 0.20$. It means that the chiral route will account for $\frac{0.20}{0.284} \times 100 = 70\%$ of the formation of **17**.

In order to fit the experimental data, x'_2 must stay in the following range: $0.20 < x'_2 < 0.284$, defined by the two above situations. One may calculate any intermediate case. For example, if $x'_2 = 0.25$, meaning $\frac{0.25}{0.284} \times 100 = 88\%$ of the chiral route (against 12% of the achiral route), it follows $(ee)'_2 = 0.80$ for lactone **17**.

If one fixes $(ee)'_2 = 0.90$, equation (6) allows calculating $x'_2 : x'_2 = 0.111$, hence, 39% of chiral Baeyer-Villiger oxidation and 61% of achiral oxidation.



Scheme 6. Description of the material balance of an asymmetric Baeyer-Villiger reaction using data of Ref. 15 (Scheme 4), assuming 50% conversion and no kinetic resolution.

In conclusion, the spontaneous Baeyer-Villiger oxidation may indeed account for the low ee of lactone **17**, as postulated by the authors, but in quantities not higher than 30% of the total amount of **17**.

The small discrepancy between the experimental value x_2/x_3 (1.22) and the value (1.31) calculated by equation (1) may be due to neglection of the $x_1(\text{ee})_1$ term. This term is calculated from Eq. (1):

$$x_1\,(\text{ee})_1 + 0.67\,x_2 - 0.92\,x_3 = 0$$

$$\text{giving} \qquad x_1\,(\text{ee})_1 = 0.92\,x_3 - 0.67\,x_2 \qquad \text{or} \qquad (\text{ee})_1 = \frac{0.92\,x_3 - 0.67\,x_2}{x_1}\,.$$

If one takes $x_1 = 0.5 = x_2 + x_3$ and $x_2 / x_3 = 1.22$, one calculates $x_2 = 0.27$ and $x_3 = 0.22$. This gives $(\text{ee})_1 = 0.043$. The values of 4.3% ee for the recovered ketone (*R*-configuration) and a conversion of 50% fully satisfy equation (1), and they are in good agreement with the data of the paper.

The second example of Scheme 5 may be treated similarly: $(\text{ee})_1$ is not specified, $(\text{ee})_2 = -0.76$, $(\text{ee})_3 = +0.95$, $x_2/x_3 = 1.50$. If one takes $(\text{ee})_1 = 0$, it follows by use of equation (1): $x_2/x_3 = 1.25$. This value is, as above, a little

lower than the experimental data of 1.50. The negative sign of **20** was based on the absolute configuration of **20**, arbitrarily depicted in Scheme 4 (absolute configurations of **19–21** are unknown). The ee of **21** must then be taken with a positive sign in order to calculate the positive value of x_2/x_3. With the hypothesis of a conversion of 50%, it is possible to calculate $(ee)_1$ in order to fit $x_2/x_3 = 1.50$. It follows $(ee)_1 = +0.038$, meaning 3.8% ee (1*R* configuration as the major lactone).

In both cases, the kinetic resolution is very low but the two enantiomers of the ketone give opposite regioselectivities in the oxygen insertion.

CONCLUSION

The reactions that we have considered (enzymatic or not) are still quite rare. However, because of the progress of asymmetric synthesis, an increasing importance of racemic mixtures can be expected, as starting material for

Professor V. Prelog (fifth from the left, seating in the first row) at the EUCHEM Conference on Asymmetric Synthesis in La Baule, 1972. It was the first international meeting on that specific topic coorganized by Prof. H. B. Kagan and Prof. A. Horeau. (By courtesy of Prof. Henri B. Kagan)

the preparation of chiral compounds by using an external chirality. If several products are generated from the racemic mixture, the equation (1) will apply and should be useful for handling and analyzing data coming from such transformations.

In the above discussion, there are two possible products issued from each enantiomer. One may address the following question: what are the conditions where one enantiomer is transformed into an excess of one of the two products while the other enantiomer generates the alternate product. This was experimentally found,[6,7] *e.g.* (1*R*)-**16** → (1*R*)-**17** and (1*S*)-**16** → (1*S*)-**18**. The same behaviour may be observed in some enzymatic Baeyer-Villiger oxidations[10–12] and this was considered very characteristic of enzymatic reactions. Later, similar behaviour was found in non enzymatic systems.[6,7]

Let us consider the general description of Scheme 3, assuming that mainly (*R*)o → R-A while (*S*)o → S-B under the influence of the chiral auxiliary. This is a case of stereospecificity (enantiospecificity) as defined for a chiral catalyst, including an enzyme.[15] The respective amounts of products are: $b < c$ and $f < e$. When there is a total transformation of the racemic mixture ($x_1 = 0$) or when there is no kinetic resolution ($(ee)_1 = 0$), it gives $x_1\,(ee)_1 = 0$ and equation (1) collapses to $x_2\,(ee)_2 + x_3\,(ee)_3 = 0$. This expression is verified only if $(ee)_2$ and $(ee)_3$ have opposite signs (since x_2 and x_3 are positive). Full destruction of a racemic mixture or absence of kinetic resolution give two products, which necessarily derive from opposite enantiomers.

When there is a kinetic resolution (x_1 and $(ee)_1 \neq 0$), equation (1) can be written as $x_2\,(ee)_2 + x_3\,(ee)_3 = -x_1\,(ee)_1$. A good enantiospecificity may be expected if $x_1\,(ee)_1 = 0$ (*vide infra*) or if $x_1\,(ee)_1$ is close to zero. This later condition is not incompatible with a kinetic resolution characterized by high $(ee)_1$, but concomitantly with a small x_1 (large conversion of the racemic mixture).

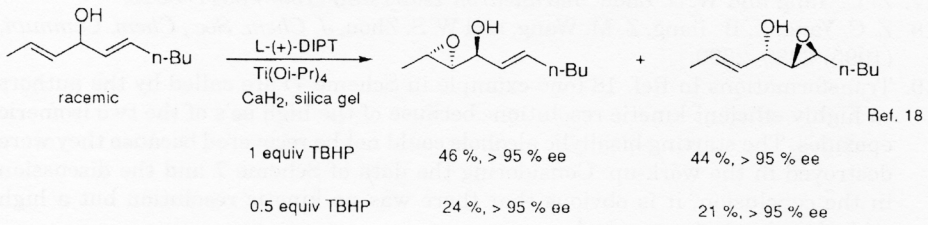
It is interesting to point out that if two products are regioisomers (as the examples in Scheme 2), the key controlling factor is the respective absolute configuration of the substrate and of the reagent or catalyst. In other words the regioselectivity of the transformation of one enantiomer of the substrate is under full control of the configuration of the chiral reagent or catalyst (»chiral reagent control«). For example, in Scheme 5 (1*R*)-**16** provides »normal lactone« **17** while (1*S*)-**16** gave the »abnormal« lactone **18**. Regioselective reactions on chiral substrates using a »chiral reagent control« are still unusual; one good example is the regioselective functionalization of 3-ketosteroids such as **7**.[8]

In conclusion, the present stereochemical analysis may be applied to many asymmetric reactions performed on racemic mixtures. These reactions may involve:

i) creation of a new chiral unit in the products, as previously discussed by us.[3]

ii) formation of two different products because of the control of regioselectivity by the external chirality (regiodivergent reaction on each enantiomer), as discussed here.

iii) a combination of cases i) and ii), as exemplified by recent reports on asymmetric epoxidation of racemic 2-furylmethanols[16,17] or unsymmetrical bisallylic alcohols[18,19] (Scheme 7).[20]



Scheme 7. Asymmetric monoepoxidation of unsymmetrical bis-allylic alcohols.

Acknowledgements – I thank Professor C. Bolm for giving me detailed information on his work on asymmetric Baeyer-Villiger and for discussions which caught my attention on some of the stereochemical problems detailed in the present article. I also acknowledge Professor J.-C. Fiaud for useful suggestions and discussions.

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9. a) Label R or S for the products indicate the chemical correlation to the starting R or S enantiomer. For example, **14** and **15** have both (*R*) configuration if they are generated from (R)-**13**. However, (1*R*)-**10** generates (1*R*)-**11** and (1*S*)-**12** (X = BCl_2). An excess in these two enantiomers in the reaction on (dl)-**10** will define a positive sign for ee's of **11** and **12**. b) Equation (2) is easily obtained by similar calculations using $a + b + c = (1 + (ee)_0)/2$ and $d + e + f = (1 - (ee)_0)/2$.
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19. Transformations in Ref. 18 (one example in Scheme 7) are called by the authors »a highly efficient kinetic resolution« because of the high ee's of the two isomeric epoxides. The starting bisallylic alcohols could not be recovered because they were destroyed in the work-up. Considering the data of Scheme 7 and the discussion in the conclusion, it is obvious that there was no kinetic resolution but a high »chiral regioselective control«.
20. A special case is the recently described intramolecular cyclopropanation of racemic allylic diazoacetates catalyzed by chiral rhodium complexes.[21] There were strong divergent enantiomer differences, one enantiomer gave intramolecular cyclopropanation while the other enantiomer was transformed through hydride abstraction / elimination into two achiral compounds.
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SAŽETAK

Transformacija racemične smjese u različite produkte bez nastajanja novoga kiralnog središta

Henri B. Kagan

Raspravlja se o transformaciji racemične smjese pod utjecajem kiralnih reagensa ili katalizatora kada nastaje više regioizomernih produkata. Dan je općenit odnos između e.v. (enantiomernog viška) i količina različitih dobivenih produkata. Posebni slučaj asimetrične Bayer-Villigerove oksidacije racemičnih ketona uzet je kao primjer. Neki regioizomerni produkti nastaju iz suprotnih enantiomera, što znači da je regioselektivnost reakcije s čistim polaznim materijalom određena apsolutnom konfiguracijom kiralnog reagensa ili katalizatora.