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Application of the Term "Relative Enantioselectivity" as Useful Measure for Comparison of Chiral Catalysts, Demonstrated on Asymmetric Hydrogenation of Amino Acid Precursors *

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In Memory of Günther Snatzke

Abstract: The application of the quotient "relative enantioselectivity" Q = q/q' in which q and q' are enantiomeric ratios R/S (or S/R) for two comparable cases of asymmetric synthesis experiments is recommended for comparison of two or more catalysts or other variables like solvents, substrates and cofactors. The importance of this term Q lies in the possibility to form and compare values of enantioselectivity over the whole range from 99,9 % ee (R) to 99,9 % ee (S) in a mathematically correct way and is demonstrated on multiple examples of asymmetric hydrogenation of partly new N-acyl-dehydroamino acid derivatives with a couple of catalysts [Rh(Ph-ß-glup)(COD)]BF_4 **1** and [Rh(Ph-ß-glup-OH)(COD)]BF_4 **2**. Interesting inversions of Q could be discovered for changes of the type of substrate and in dependence of the polarity of solvents.

The term **enantiomeric excess (% ee)** is widely applied to express the enantioselectivity of an asymmetric process[1]. However, specialists on field of asymmetric catalysis feeling the weakness of this measure often give

$$\% \text{ ee} = \frac{A - B}{A + B} \cdot 100$$

A = amount of the excess enantiomer
B = amount of the other enantiomer

their results as ratio of both enantiomers (A:B) to reach more clarity[2-6]. The measure optical yield (p) equals the value % ee if linear relationship exists between optical rotation and composition of the two pure enantiomers.

* Part IX of the series: Carbohydrate Phosphinites as Chiral Ligands for Asymmetric Syntheses Catalyzed by Complexes, Part VIII see R. Selke, M. Čapka, J. Mol. Catal. **1990**, 63, 319.

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$$p = \frac{[\alpha]_m}{[\alpha]_p} \cdot 100$$

$[\alpha]_m$ = specific rotation of the mixture of enantiomers

$[\alpha]_p$ = specific rotation of one pure enantiomer

The % ee- or p-value gives a good indication of the capability of a chiral catalyst producing the practically important excess part of a wanted enantiomer in the course of an enantioselective process. This part can often easily be separated by simple physical methods from the residual racemate forming part of the same enantiomer being more or less useless for practical utilization if not a racemate resolution follows the separation[7].
However, for comparison of the microscopic behaviour of two catalysts in an asymmetric process or of one catalyst under different conditions the values enantiomeric excess (% ee) and optical yield (p) give a bad indication of the selecting power in the following three cases:
- if the chiral induction differs strongly
- if different enantiomers are favoured
- in a region of very high enantioselectivity.

This difficulties are in practice overcome[2-6] by comparison q of formed enantiomers* A and B:

$$q = \frac{A}{B} = \frac{100 + \%\,ee}{100 - \%\,ee}$$

The term q represents the amount of excess enantiomer A produced in relation to the amount of the minor enantiomer B obtained (or vice versa giving values lower than 1.0) and is a good measure to express the microscopic behaviour of an enantioselective catalyst. It equals the ratio of the enantioface or enantiotopos differentiating reaction rates k_{Re}/k_{Si} or vice versa, respectively. In Table 1 some % ee-values are compared with the corresponding values of the enantiomeric ratio q. This gives an impression of the value of the term q for comparison of the selecting efficiency of catalysts showing largely different % ee and especially in the range of high enantioselectivity - e.g. for enzymes - if sufficiently precise analytical methods are available.
The value q has the advantage that it may be divided by another enantiomeric ratio q' received under different

* In principle q is comparable with the well established measure **enantiomeric ratio E** common in catalytic[8] or enzymatic[9-11] kinetic resolution of both enantiomers A and B from a racemic mixture as a non-dimensional value E:

$$E = \frac{k_{fast}}{k_{slow}} = \frac{k_A}{k_B} = \frac{P}{Q}$$

Kagan and Fiaud[12] named this term "stereoselectivity factor" S. E respectively S represents the quotient of two rate constants indicating the relative rate of the fast reacting enantiomer A and the slow reacting enantiomer B and equals the ratio of both product enantiomers P and Q. The application of the quotients of two formed diastereomers as measure for diastereoselectivity[13] was applied especially for double stereodifferentiating experiments[14-16].

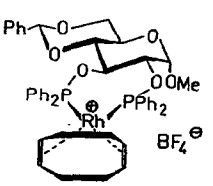
Table 1
Comparison of the values for the enantiomeric excess % ee and enantiomeric ratio $q = \frac{A}{B} = \frac{100 + \%ee}{100 - \%ee}$

% ee	% A		% B	q
0	50	:	50	1
10	55	:	45	1.22
20	60	:	40	1.5
50	75	:	25	3
80	90	:	10	9
90	95	:	5	19
99	99.5	:	0.5	199
99.5	99.75	:	0.25	399
99.9	99.95	:	0.05	1999
99.99	99.995	:	0.005	19999

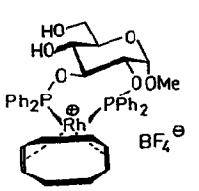
conditions (solvents*, substrates, catalysts and other variables) and gives the possibility to formulate a term **"relative enantioselectivity" Q** :

$$Q = \frac{q}{q'}$$

This term Q seems to be especially important for the comparison of the effectiveness of one or more chiral catalysts with one standard catalyst. Such a comparison should be done with several substrates and only the average value of the relative enantioselectivity Q may give a distinct picture about the suitability of one special catalyst for a particular problem. The relative power of a pair of catalysts may change with the substrate family and sometimes the importance of special parts of the substrate structure for especially high enantioselectivity can be demonstrated more impressively.
We have applied this concept to evaluate the catalytic efficiency of two catalysts which in fact are precatalysts [Rh(Ph-ß-glup)(COD)]BF_4 **1** and [Rh(Ph-ß-glup-OH)(COD)]BF_4 **2** (see Table 2).

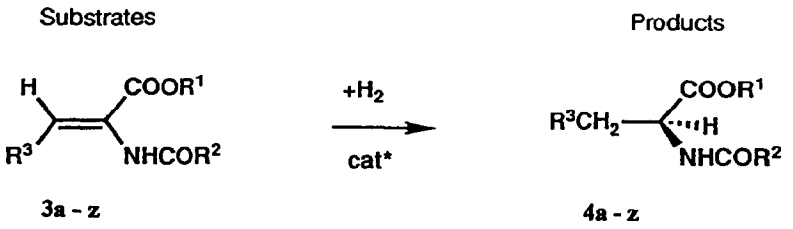


1



2

* The usefulness of the quotient Q for comparison of enantioselectivities in different solvents was shown by us already earlier especially for cases in which the optical induction changes the direction[17].



3a - z 4a - z

Table 2
Asymmetric hydrogenation of 1 mmol of (Z)-2-acylamido-acrylic acid derivatives 3a-z by 0.01 mmol precatalyst 1 or 2 in 15 ml methanol at 25 °C and 0.1 MPa H_2

	Substrate			Catalyst 1			Catalyst 2				
	R^3	R^2	R^1	t/2 min	%ee (S)	q_1	t/2 min	%ee (S)	q_2	$Q = q_2/q_1$	Method
3a	H	Me	H	1	97.7	86.0	1	96.5	56.1	**0.65**	GC a
b	Ph	Me	H	2	96.6	57.8	4	95.1	39.8	**0.69**	GC a
c	Ph	Ph	H	2	95.0	39.0	3	93.7	30.8	**0.79**	GC a
d	3-MeO-4-AcO-C_6H_3	Me	H	10	96.0	49.0	9	95.2	40.7	**0.83**	GC a
e	3-MeO-4-HO-C_6H_3	Ph	H	4	96.9	57.8	4	94.1	32.9	**0.57**	HPLC a,b,c
f	3,4-$(MeO)_2$-C_6H_3	Me	H	6	96.7	59.6	5	94.8	37.5	**0.63**	GC a
g	"	Ph	H	5	95.1	39.8	4	92.0	24.0	**0.60**	HPLC a
h	H	Me	Me	1	90.9	21.0	2	95.2	40.7	**1.9**	GC
i	Ph	Me	Me	6	91.5	22.5	3	94.8	37.5	**1.7**	GC
j	Ph	Me	Et	6	90.6	20.3	3	94.4	34.7	**1.7**	GC
k	Ph	Ph	Me	6	87.3	14.8	3	91.6	22.8	**1.5**	GC
l	Ph	Ph	Et	4	88.5	16.4	3	92.3	25.0	**1.5**	GC
m	3-MeO-4-AcO-C_6H_3	Me	Me	5	92.4	25.3	3	95.6	44.1	**1.8**	GC
n	"	Ph	Me	5	87.2	14.6	4	91.3	22.0	**1.5**	HPLC
o	"	Ph	Et	5	87.2	14.6	5	90.5	20.1	**1.4**	HPLC
p	3,4-$(MeO)_2$-C_6H_3	Me	Me	22	92.4	25.3	12	95,7	45.5	**1.8**	GC
q	"	Me	Et	8	90.6	20.3	5	95.2	40.7	**2.0**	GC
r	"	Me	i-Pr	22	91.3	22.0	11	94.7	36.7	**1.7**	GC
s	"	Ph	Me	8	87.7	15.3	7	91.2	21.7	**1.4**	HPLC
t	"	Ph	Et	10	88.9	17.0	8	90.5	20.1	**1.2**	HPLC c
u	"	Ph	i-Pr	20	89.1	17.4	14	92.7	26.4	**1.5**	HPLC
v	"	Ph	CH_2CH_2OH	10	87.3	14.8	8	89.9	18.8	**1.3**	HPLC b,c
w	3-MeO-4-HO-C_6H_3	Me	Me	12	91.7	23.1	5	95.0	39.0	**1.7**	GC b
x	"	Ph	Me	11	89.0	17.2	6	92.1	24.3	**1.4**	HPLC b
y	"	Me	CH_2CH_2OH	13	91.7	23.1	7	95.5	43.4	**1.9**	HPLC b,c
z	"	Ph	CH_2CH_2OH	16	88.4	16.2	12	90.2	19.4	**1.2**	HPLC b,c

[a] after esterification by diazomethane
[b] in the O-acetylated form
[c] standard deviation $\sigma = \pm 1.0$ %ee, in all other cases $< \pm 0.5$ %ee

The preparation of the complexes and preliminary results of hydrogenation studies have already been reported[18,19]. The chiral precatalysts **1** and **2** constitute an interesting pair for evaluation under such a proposal not only because of their importance for the production of L-DOPA[20] but also because they provide deeper insight into questions connected with the concept of the importance of conformational rigidity of chiral ligands for a high enantioselectivity of their chelates[21]. Table 2 indicates that the enantioselectivity of the complex **2** carrying two hydroxy groups exceeds the conformationally more rigid precatalyst **1** in the hydrogenation of 19 substrate esters (**3h** to **3z**) in all the cases studied. The average of the relative enantioselectivity doubles nearly:

$$\bar{Q}_{ester} = \frac{q_2}{q_1} = 1.6 \pm 0.3.$$

However, all the carboxylic acid substrates investigated (**3a** to **3g**) show the inverse behaviour that means the OH-group carrying catalyst **2** gives - as primarily expected - lower enantioselectivity than the more rigid catalyst **1** :

$$\bar{Q}_{acid} = \frac{q_2}{q_1} = 0.7 \pm 0.1.$$

We think that the catalyst resulting from **2** by loss of cyclooctadiene in the course of hydrogenation may suffer slightly disfavoured or favoured conformational changes due to competitive association of solvent, substrate or product with the free OH-groups in the 4,6-position of the carbohydrate part of the complex which are less probable for the catalyst evolving from **1**.

This change of pyranoside conformation should have an effect on the chiral conformational alignment of the more ore less *quasi*axial/equatorial oriented P-phenyl groups which must be essential in the transition state of hydrogenation for the enantioselectivity[22-24]. We will follow this concept by extended investigation of similar new catalysts with slightly varied structure to select the true explanation especially for the increased relative enantioselectivity Q_{ester}.

In principle it is possible to calculate unknown % ee values for one catalyst under application of Q and the known % ee' for the other catalyst' for instance with one new substrate under identical conditions.

The difference of the free enthalpies of activation in the selectivity of reaction pairs ($\delta\Delta G^{\neq}$) obeys the equation:

$$\delta\Delta G^{\neq} = \Delta G_{cat}^{\neq} - \Delta G_{cat'}^{\neq} = -RT\ln Q = -RT\ln\frac{q}{q'}.$$

From $Q = \frac{q}{q'}$ and $q = \frac{100 + \%ee}{100 - \%ee}$ one receives for the

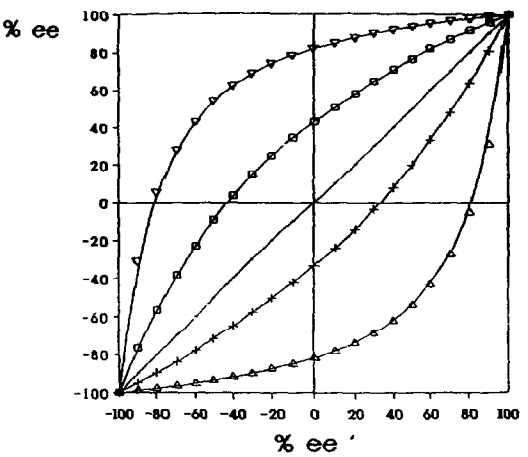
unknown enantiomeric excess:

$$\%ee = \frac{[(Q-1)\times 10000] + [(Q+1)\times 100\%ee']}{[(Q+1)\times 100] + [(Q-1)\times \%ee']}$$

Fig. 1 demonstrates the theoretical relation between % ee and % ee' for some selected Q-values using - % ee for inverted optical induction. Estimation of unknown enantioselectivities in this manner, however, should be used careful and a lot of disturbing effects can be expected, among them differentiating influences of solvents, counterions and tensides on the transition state for two catalysts and in cases of changing enantioselectivity with progression of conversion of the asymmetric reaction[24] and if catalytic enantioselective autoinduction[41] arises. For systems showing a nonlinear influence of temperatureon q and q' as written in detail in a publication about the iso-inversion principle[42] it should give domains for which difficulties can be expected. Generally caution is recommended in valuation of calculated % ee values regarding the relatively high standard deviation of Q.

Fig. 1
Nomogramm, dependence of unknown % ee from known % ee' for selected Q-values at given temperature

symbol	Q
∇	10.0
□	2 5
•	1 0
+	0 5
Δ	0 1



Experiments in low polar solvents with acid substrates are rare in literature in consequence of their low solubility e. g. in pure benzene[25] or toluene. Nevertheless it is possible to hydrogenate (Z)-2-acetamidocinnamic acid **3b** in suspension with acceptable rate* and we could find a pronounced effect of decreasing relative enantioselectivity in comparison of the catalysts 2 and 1:

$$\bar{Q}_{3b} = \frac{q_2}{q_1} = 0.07 \pm 0.02 \quad \text{(see Table 3).}$$

This decrease of $\bar{Q}_{3b}$ by one order of magnitude from 0.7 to 0.07 only by change of the solvent from methanol to aromatic hydrocarbons was higher than expected but seems plausible concerning the decrease of % ee for catalyst 2. However for the unexpected impressive increase of the enantiomeric excess using the catalyst 1 from 96.6 % ee ($q_{MeOH} = 58$) *to more than 98.6 % ee* ($q_{ArH} = 142$) (S)-N-acetyl-phenylalanine

* The additional low solubility of catalyst 2 in toluene causes the extremely slow hydrogenation rate (see Table 3).

$$\overline{Q}_{3b} = \frac{q_{ArH}}{q_{MeOH}} = \frac{142}{58} = 2.5$$

we are still looking for an explanation which includes the inverse effect for catalyst 2 with substrate ester **3i** : % ee decreases from 94.8 in methanol to 91.9 % ee in aromatic solvents[19].

$$\overline{Q}_{3i} = \frac{q_{ArH}}{q_{MeOH}} = \frac{23.7}{37.5} = 0.6.$$

Table 3
Enantioselectivities for hydrogenation of 1 mmol (Z)-2-acetamidocinnamic acid **3b** suspended in low polar solvents (for conditions see Table 2)

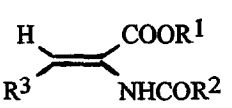
	Catalyst 1			Catalyst 2			
Solvent	t/2 min	% ee (S)	q_1	t/2 min	% ee (S)	q_2	$Q_{3b} = \frac{q_2}{q_1}$
benzene	11	98.6	142	28	85.5	12.8	0.09
toluene	19	98.9	181	480	82.3	10.3	0.06

$\overline{Q}_{3b} = 0.07 \pm 0.02$

The advantage that the term relative enantioselectivity Q contrary to % ee can be averaged for a series of comparable pairs of variables in a mathematically correct way may be used for the estimation of the relative susceptibility of two or more substrates. This can be demonstrated for carboxylic acids and their esters using the experiments from Table 2 by the value $Q = q_{acid} / q_{ester}$. Table 4 clearly shows the higher enantiomeric ratio q_{acid} for the hydrogenation of all acid substrates in methanol by catalyst 1 compared with q_{ester}.
Q_1 distinctly exceeds 2.0 in nearly all cases ($\overline{Q}_1 = 2.8 \pm 0.7$) and this corresponds to the results with most of the known chiral catalysts. However, comparison with data from literature have their limit regarding the different experimental conditions and especially polarimetric estimation of enantioselectivity was used which often has been a source for incorrect values.
Comparable hydrogenation experiments can be taken from a paper of Brunner et al.[26] which contains a lot of enantioselectivities for 4 catalysts and 6 substrates suitable for calculations and giving a sign for exceptions of relative enantioselectivity e. g. $Q_{BPPFA} = q_{acid} / q_{ester} = 0.6 \pm 0.1$ for a ferrocene derived rhodium(I)-complex.
For catalyst 2 the average for the relative enantioselectivity $\overline{Q}_2$ is rather low ($\overline{Q}_2 = 1.2 \pm 0.3$) and two pairs with inverted $Q_2 < 1.0$ exist, both for N-acetylated DOPA-precursors (q_{3d} / q_{3m}, q_{3f} / q_{3p}).
The quotient Q_1/Q_2 gives an impression of the **susceptibility** of the two compared catalysts **1** and **2** in the studied case to changes in substrate structure. This susceptibility is more than twofold for catalyst **1** in comparison with the hydroxy group carrying precatalyst **2**. The latter catalyst indicates only low changes of

Table 4

Relative enantioselectivity $Q = q_{acid}/q_{ester}$ for asymmetric hydrogenation of acid and ester substrates with precatalyts **1** and **2** (for conditions see Table 2)

Substrates 			$Q = \frac{q_{acid}\ (R^1 = H)}{q_{ester}\ (R^1 = Me)}$		
R^3	R^2	numbers	Q_1	Q_2	Q_1 / Q_2
H	Me	**3a / 3h**	4.1	1.4	2.9
Ph	Me	**3b / 3i**	2.6	1.1	2.4
Ph	Ph	**3c / 3h**	2.6	1.4	2.0
3-MeO-4-AcO-C_6H_3	Me	**3d / 3m**	1.9	0.9	2.0
3-MeO-4-HO-C_6H_3	Ph	**3e / 3x**	3.4	1.4	2.5
3,4-$(MeO)_2C_6H_3$	Me	**3f / 3p**	2.4	0.8	2.9
3,4-$(MeO)_2C_6H_3$	Ph	**3g / 3s**	2.6	1.1	2.3
			$\overline{Q_1} = 2.8 \pm 0.7$	$\overline{Q_2} = 1.2 \pm 0.3$	2.4 ± 0.4

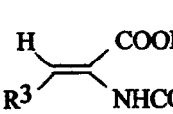
enantioselectivity going from acid to ester substrates. It should be noted that the quotient Q_1/Q_2 in Table 4 is remarkably constant (2.4 ± 0.4). That means extrema for catalyst **1** correspond to similar deviations for catalyst **2** and should be attributed to structural features of the investigated substrates.

Another interesting result emanates from the comparison of N-acetylated and N-benzoylated α-aminoacrylic acids and esters. From Table 5 it can be deduced that both catalysts give a higher optical induction for the N-acetylated compounds in line with earlier reports on other chiral catalysts[21,26-28]. For hydrogenation of the acid substrates **3b,c,f** and **g** with our standard catalyst **1** we overlooked this fact at first, because the enantioselectivities lie very close in the high region of 95.0 to 96.7 % ee. In the beginning we thought we had an especially efficient catalyst for N-benzoylated substrates. These are of particular interest from industrial point of view because the ease of preparation of N-benzoyl-azlactones in high yield via Erlenmeyer condensation make them very attractive[29]. However in fact we only benefit from the strong decrease of the difference % ee in the region of more than 95 % ee ($q > 39$) but the relative enantioselectivity even in our case gives the average value of $\overline{Q_1} = 1.4 \pm 0.2$ corresponding to the first discovery of this difference by Kagan[21]. This is a good example of the worth of the new introduced term Q for comparison of catalysts which provides very high enantioselectivity.

The aforementioned facts clearly focus on the accuracy of the available methods for the estimation of enantiomeric ratio. Regarding our low standard deviation of $\sigma \leq 0.5$ % ee we are sure that the statement of distinctly higher enantioselectivity for N-acetylated in comparison with N-benzoylated substrates is valid also for our catalysts . Deviations of this rule, known from older literature[30,31] seems to be uncertain unless they are checked by chromatographic separation of the product enantiomers.

Table 5

Relative enantioselectivity $Q = q_{Ac} / q_{Bz}$ in asymmetric hydrogenation of N-acetylated and N-benzoylated substrates for precatalyts 1 and 2

Substrates 			$Q = \frac{q_{Ac}\ (R^2 = Me)}{q_{Bz}\ (R^2 = Ph)}$		
R^3	R^2	numbers	Q_1	Q_2	Q_1 / Q_2
Ph	H	**3b / 3c**	1.5	1.3	0.9
Ph	Me	**3i / 3k**	1.5	1.6	1.2
Ph	Et	**3j / 3l**	1.2	1.4	1.2
3,4-$(MeO)_2C_6H_3$	H	**3f / 3g**	1.5	1.6	1.0
3,4-$(MeO)_2C_6H_3$	Me	**3p / 3s**	1.7	2.1	1.3
3,4-$(MeO)_2C_6H_3$	Et	**3q / 3t**	1.2	2.0	1.7
3,4-$(MeO)_2C_6H_3$	i-Pr	**3r / 3u**	1.3	1.4	1.1
3-MeO-4-AcO-C_6H_3	Me	**3m / 3n**	1.7	2.0	1.2
3-MeO-4-HO-C_6H_3	Me	**3w / 3x**	1.3	1.6	1.2
3-MeO-4-HO-C_6H_3	CH_2CH_2OH	**3y / 3z**	1.4	2.2	1.6
			$\bar{Q}_1 = 1.4 \pm 0.2$	$\bar{Q}_2 = 1.7 \pm 0.3$	1.2 ± 0.3

The similar susceptibility of both precatalysts **1** and **2** regarding their relative enantioselectivities $Q = q_{Ac}/q_{Bz}$ against variation of the substrate N-acyl group is indicated by a ratio near one with $Q_1/Q_2 = 1.2 \pm 0.3$ (see Table 5). Please remember that we obtained a distinct deviation from this more or less expected normal case of $Q_1/Q_2 = 1$ for comparison of the relative enantioselectivities $Q = q_{acid}/q_{ester}$ which gave more than the double relative enantioselectivity for precatalyst **1** to this change in substrate structure (Q_1/Q_2 = 2,4 ± 0,4; see Table 4).

CONCLUSION

It is not our intention to substitute the terms enantiomeric excess (% ee) and optical yield (p) which remain their practical importance to express the yield of the usable excess of one interesting enantiomer. However, we feel the importance to propagate the use of the well-known but seldom applied measure enantiomeric ratio (q) as a term which allows to form average values about the whole range of enantioselectivity from 99.9 % ee (R) to 99.9 % ee (S).

The calculation of the relative enantioselectivity Q = q / q' gives a good possibility for comparison of enantioselectivities obtained under special conditions with a standard situation. Q gives especially for classification of the asymmetric efficiency of a new chiral catalyst a much better impression than a comparison

of the non-linear % ee-values for two catalysts.

The possibility to form ratios of two Q-values enables us to compare two catalysts - or other variables - regarding the susceptibility of the relative enantioselectivity against classes of substrates, solvents or other modifiers. Of course this practice to form and apply Q is possible for comparison of all kinds of selectivities, not only enantioselectivities.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

Polarimetric measurements were made with a Polamat A automatic polarimeter from Carl Zeiss, Jena. Melting points are estimated with a Boetius micro-melting point apparatus and are therefore corrected.

^{13}C NMR spectra were recorded on a Tesla BS 587C (20.1 MHz) or on a Bruker AC 250 (62.9 MHz), respectively. For MS we used a mass spectrometer AMD 402 (AMD intectra). ^{1}H NMR spectra and the proof for (Z)-geometry of the new substrates will be given later . IR-spectra were taken on a Specord M80 of Carl Zeiss Jena. Hydrogenation experiments commonly with 1 mmole substrate and 0.01 mmol catalyst in 15 ml solvent at 25 °C and 0.1 MPa H_2 were conducted as described earlier [32].

Enantiomeric ratio of the volatile ester hydrogenation products **4h, i, j** are estimated by GLC on a Hewlett-Packard 5880A gas chromatograph as published[32]. The carboxy group carrying **acid** hydrogenation products **4a-g** have been derived to the methyl ester by diazomethane, and hydroxy group carrying products as **4e** and **4v-z** were acetylated by acetanhydride/triethylamine (1:1) to decrease their polarity. From Table 2 it can be seen, that even for some Dopa-precursors gaschromatographic separation of enantiomers was possible if they were not N-benzoylated. We used 5 m quartz capillary tube (inner diameter 0.2 mm) coated with XE-60 L-valyl-tert.-butylamide for hydrogenation products of **4k** and **4l** (168 °C) and **4m, 4p-r** (170 °C). The enantiomeric ratio of the Dopa-precursors **4e,g,n,o,s-v** and **4x-z** could be estimated by HPLC on a Knauer apparatus after the mentioned derivation to methyl esters of acetoxy compounds. A column 200 x 4 mm i.d. with butanecarbonyl-L-valine-tert.-butylamide on nucleosil 100-5 was applied[33], eluent n-heptane/isopropanol (9:1) flow rate 1 ml/min, detection at 254 nm. For all compounds we reached base-line separation with the exception of the acetylated **4z**: 2-acetoxyethyl (Z)-3-(4-acetoxy-3-methoxyphenyl)-2-benzoylamino-propenoate ($\alpha = 1.05$).

The substrates 2-acetamidoacrylic acid (**3a**) and methyl 2-acetamidoacrylate (**3h**) could be obtained according to the cited literature[34,35]. All other substrates were prepared analogous to the wellknown method of Erlenmeyer[29,36-40]. They were recrystallized up to NMR-purity (^{13}C-NMR-spectra).

2-Hydroxyethyl (Z)-3-(3,4-dimethoxyphenyl)-2-benzoylamino-propenoate (**3v**): 15 g (54.5 mmol) 2-Phenyl-4-(3,4-dimethoxybenzal)-oxazol-5-one[29], 0.5 g Na_2CO_3 and 25 ml ethylene glycol were heated under stirring to 80 °C. Ten minutes later the azlactone is dissolved and the reaction is stopped after further 15 minutes. The mixture was stirred in 100 ml of cold water. The separating grease of the ester crystallized during stirring and kneading, was filtrated, washed with water (18.75 g, 96 % yield) and could be recrystallized from 50 ml ethyl acetate (53 %) m. p. 122 °C; IR (KBr) 3432, 3204 (NH, OH), 1714 (C=O, ester), 1632 (amide I), 1598 (arom), 1516 (amide II), 1284 (C-O, ester), 1250 (Ar-OMe), 1018 (ArO-Me); ^{13}C NMR (20.1 MHz, DMSO-d_6) δ (TMS): 55.1, 55.4 (ArO$\underline{C}H_3$), 59.1 (CH_2OH), 66.5 (COO$\underline{C}H_2$-), 165.1 ($\underline{C}$OOR), 166.1 (NH$\underline{C}$OPh); Anal. found C 64.1; H 5.8; N 3.9: $C_{20}H_{21}NO_6$ requires C 64.7; H 5.7; N 3.8. MS (M^+)371, (M^+-glycol) 309.

Methyl (Z)-3-(4-hydroxy-3-methoxyphenyl)-2-acetylaminopropenoate (**3w**). 30.7 g (0.1 mol) methyl (Z)-3-(4-acetoxy-3-methoxyphenyl)-2-acetylamino-propenoate (**3m**) were suspended in 170 ml absolute methanol, and after addition of 5 ml n/10-sodium methanolate solution in methanol the mixture was boiled on a waterbath up to the clearing of the suspension (30 min) and further 30 min. The success of the transesterification can be controlled by TLC (toluene/acetone = 1:1, Rf 0.40 for **3w**, 0.26 for **3m**). The washed crystalline product (20.9 g, 79 % yield) can be recrystallized from 240 ml acetone (17.4 g), m.p. 135-136 °C, ^{13}C NMR (20.1 MHz, DMSO-d_6) δ (TMS): 22.3 (NHCO$\underline{C}H_3$), 51.8 (COO$\underline{C}H_3$), 55.4 (ArO$\underline{C}H_3$), 165.7 ($\underline{C}$OOR), 169.1 (NH$\underline{C}$OCH$_3$); Anal. found C 59.0; H 5.9; N 5.1: $C_{13}H_{15}NO_5$ requires C 58.9; H 5.7; N 5.3; MS (M^+)265.

Methyl (Z)-3-(4-hydroxy-3-methoxyphenyl)-2-benzoylaminopropenoate (**3x**). In 100 ml absolute methanol 100 g (0.3 mol) 2-phenyl-4-(4-acetoxy-3-methoxybenzal)-oxazol-5-one[40] and 2.4 g NaOH were refluxed under stirring. The thick mass resolves, the solution colours deeply red, and fadenes in the course of the reaction to orange. After filtration from some unsoluble impurities while hot the product quickly cristallizes, yield 70 % light yellow crystals; m.p. 156-157.5 °C (isopropanol); IR(KBr): 3304 (OH,NH), 1718 (C=O,ester), 1644 (amide I), 1602 (arom.), 1520 (amide II), 1284 (C-O, ester), 1258 (Ar-OMe), 1032 (ArO-Me); ^{13}C NMR (20.1 MHz, DMSO-d_6) δ (TMS) 51.9 (COO$\underline{C}H_3$), 55.2 (ArO$\underline{C}H_3$), 165.7 ($\underline{C}$OOCH$_3$), 165.9 (NH$\underline{C}$OPh); Anal. found C 66.0; H 5.3; N 4.0: $C_{18}H_{17}NO_5$ requires C 66.1; H 5.2; N 4.3. MS (M^+) 327, (M^+-OCH_3) 296.

2-Hydroxyethyl (Z)-3-(4-hydroxy-3-methoxyphenyl)-acetylamino-propenoate (**3y**). 61.5 g (0.2 mol) Methyl (Z)-3-(4-acetoxy-3-methoxyphenyl)-2-acetylaminopropenoate (**3m**) was heated in 200 ml ethylene glycol after addition of 5 ml methanolic solution of sodium methanolate (ca 0.04 mol NaOMe) for 6 hours. Added and formed methanol was evaporated twice during the time of reaction. Excess ethylene glycol was distilled under vacuum (10 Torr) at the end of the reaction and the residue (72.7 g) could be recrystallized from 300 ml of water. The solid product becomes colourless by washing with water and a mixture of diethylether / isopropanol. The dry product (33.6 g, 50 %) shows m. p. 148-150 °C. A further crop can be received from the mother liquor. ^{13}C NMR (20.1 MHz, DMSO-d_6) δ (TMS) 22.3 (NHCO$\underline{C}H_3$), 55.4 (ArO$\underline{C}H_3$), 59.0 (CH_2OH), 66.3 (COO$\underline{C}H_2$-), 165.2 ($\underline{C}$OOR), 169.3 (-NH$\underline{C}$OCH$_3$); Anal. found C 57.0; H 5.9; N 5.1: $C_{14}H_{17}NO_6$ requires C 57.0; H 5.8; N 4.7. MS (M^+) 295, (M^+ - CH_2=C=O) 253, M^+ - glycol) 233.

2-Hydroxyethyl (Z)-3-(4-hydroxy-3-methoxyphenyl)-2-benzoylamino-propenoate (**3z**). 17 g (51 mmol) 2-phenyl-4-(4-acetoxy-3-methoxybenzal)-oxazol-5-one[40], 0.5 g Na_2CO_3 and 25 ml ethylene glycol were heated under stirring to 80 °C as described under **3v** and gives a redbrown liquid mass which warm was given to 300 ml of cold H_2O. The ester precipitates at first as a grease which solidifies within 24 hours. 10 g can be recrystallized from 50 ml ethylacetate, m.p. 125 °C. IR(KBr) 3400, 3320, 3136 (NH,OH), 1712 (C=O, ester), 1640 (amide I), 1592 (arom), 1516 (amide II), 1274 (C-O, ester), 1242 (Ar-OMe); ^{13}C NMR (20.1 MHz, DMSO-d_6) δ (TMS) 55.2 (ArO<u>C</u>H_3), 59.1 (CH_2OH), 66.4 (COO<u>C</u>H_2-), 165.2 (<u>C</u>OOR), 166.1 (NH<u>C</u>OPh); Anal. found C 63.9; H 5.4; N 3.9: $C_{19}H_{19}NO_6$ requires C 63.9; H 5.4; N 3.9; MS (M^+) 357, (M^+-glycol) 295.

(S)-2-Hydroxyethyl N-benzoyl-3,4-dimethoxyphenylalaninate (**4v**): Hydrogenation of 2.5 mmol **3v** in 15 ml methanol within 45 min, evaporation, and recrystallization from 4 ml ethyl acetate gives 58 % **4v**, m.p. 94 - 96 °C, $[\alpha]_D^{25}$ + 32.4 (c 2, CH_2Cl_2); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ(TMS) 35.7 (<u>C</u>H_2Ar), 54.4 (CHNH), 55.2, 55.3 (<u>C</u>H_3OAr), 58.8 (CH_2OH), 66.2 (<u>C</u>H_2OCO), 166.4 (COO) ,171.7 (CONH); Anal. found C 63.95; H 6.19; N 3.84: $C_{20}H_{23}NO_6$ requires C 64.33; H 6.21; N 3.75; MS (M^+) 373, (M^+-OCH_2CH_2OH) 312, (M^+-$PhCONH_2$) 252.

(S)-Methyl N-acetyl-4-hydroxy-3-methoxyphenylalaninate (**4w**): Hydrogenation of 2.5 mmol **3w** with 0.01 mmol catalyst **2** in 15 ml methanol within 60 min, evaporated oily substance pretreated with acetone becomes solid, recrystallization from 4 ml isopropanol/n-pentane (1:1) gives 53 % **4w**, m.p. 125-128 °C, $[\alpha]_D^{25}$ 26.9 (c 2, acetone); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (TMS) 23.1 (<u>C</u>H_3CONH), 37.5 (CH_2Ar), 52.3 (<u>C</u>H_3OCO), 53.8 (CHNH), 55.9 (<u>C</u>H_3OAr), 169.7 (COO), 172.2 (CONH); Anal. found C 58.10; H 6.43; N 5.26: $C_{13}H_{17}NO_5$ requires C 58.42; H 6.41; N 5.24; MS (M^+) 267.

(S)-Methyl N-benzoyl-4-hydroxy-3-methoxyphenylalaninate (**4x**): Hydrogenation of 2.5 mmol **3x** with 0.01 mmol catalyst **2** in 15 ml methanol within 60 min, evaporated substance recrystallized from 4 ml ethyl acetate gives 69 % **4x**, m.p. 140-141.5 °C, $[\alpha]_D^{25}$ + 70.6 (c 2, CH_2Cl_2); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ (TMS) 36.8 (<u>C</u>H_2Ar), 51.8 (<u>C</u>H_3OCO), 54.6 (CHNH), 55.3 (<u>C</u>H_3OAr), 166.3 (COO), 172.3 (CONH) ; Anal. found C 65.19; H 5.78; N 4.33; $C_{18}H_{19}NO_5$ requires C 65.64; H 5.81; N 4.25; MS (M^+) 329, (M^+-$PhCONH_2$) 208.

(S)-2-Hydroxyethyl N-acetyl-4-hydroxy-3-methoxyphenylalaninate (**4y**): Hydrogenation of 2.5 mmol **3y** with 0.01 mmol catalyst **2** in 15 ml methanol within 2 h gives 0.75 g of an syrupy product **4y**; $[\alpha]_D^{25}$ + 18 (c 1, acetone); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ (TMS) 22.2 (<u>C</u>H_3CONH), 36.4 (CH_2Ar), 53.8 (CHNH), 55.5 (CH_3OAr), 58.8 (CH_2OH), 66.1 (<u>C</u>H_2OCO), 169.3 (COO), 171.8 (CONH); Anal. found C 55.51; H 6.41; N 4.80; $C_{14}H_{19}NO_6$ requires C 56.56; H 6.44; N 4.71.

(S)-2-Hydroxyethyl N-benzoyl-4-hydroxy-3-methoxyphenylalaninate (**4z**): Hydrogenation of 2.5 mmol **3z** with 0.01 mmol catalyst **2** in 15 ml methanol within 80 min, evaporation, recrystallization from 8 ml ethyl acetate gives 74 % **4z**, m.p. 134.5-136 °C, $[\alpha]_D^{25}$ - 20.8 (c 2, acetone); ^{13}C NMR (62.9 MHz, DMSO-d_6) δ (TMS) 35.9 ($\underline{C}H_2Ar$), 54.6 (CHNH), 55.4 ($\underline{C}H_3OAr$), 58.9 (CH_2OH), 66.3 ($\underline{C}H_2OCO$), 166.4 (COO), 171.9 (CONH); Anal. found C 63.22; H 5.90; N 4.00; $C_{19}H_{21}NO_6$ requires C 63.50; H 5.89; N 3.90; MS (M^+) 359, (M^+- OCH_2CH_2OH) 298, (M^+-$PhCONH_2$) 238.

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